Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2011, an estimated 101,340 new cases of colon cancer and approximately 39,870 cases of rectal cancer will occur. During the same year, an estimated 49,380 people will die of colon and rectal cancer combined. Despite these statistics, the incidence per 100,000 of colon and rectal cancers has decreased from 60.5 in 1976 to 46.4 in 2005. In addition, mortality from colorectal cancer has decreased by almost 35% from 1990 to 2007, possibly because of earlier diagnosis through screening and better treatment modalities.

This manuscript summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer. These NCCN Guidelines begin with NCCN Colon Cancer Clinical Practice Guidelines in Oncology

Al B. Benson III, MD; J. Pablo Arnoletti, MD; Tanios Bekaii-Saab, MD; Emily Chan, MD, PhD; Yi-Jen Chen, MD, PhD; Michael A. Choti, MD, MBA; Harry S. Cooper, MD; Raza A. Dilawari, MD; Paul F. Engstrom, MD; Peter C. Enzinger, MD; James W. Fleshman, Jr., MD; Charles S. Fuchs, MD, MPH; Jean L. Grem, MD; James A. Knol, MD; Lucille A. Leong, MD; Edward Lin, MD; Killian Salerno May, MD; Mary F. Mulcahy, MD; Kate Murphy, BA; Eric Rohren, MD, PhD; David P. Ryan, MD; Leonard Saltz, MD; Sunil Sharma, MD; David Shibata, MD; John M. Skibber, MD; William Small, Jr., MD; Constantinos T. Sofocleous, MD, PhD, FSIR; Alan P. Venook, MD; and Christopher Willett, MD

Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2011, an estimated 101,340 new cases of colon cancer and approximately 39,870 cases of rectal cancer will occur. During the same year, an estimated 49,380 people will die of colon and rectal cancer combined. Despite these statistics, the incidence per 100,000 of colon and rectal cancers has decreased from 60.5 in 1976 to 46.4 in 2005. In addition, mortality from colorectal cancer has decreased by almost 35% from 1990 to 2007, possibly because of earlier diagnosis through screening and better treatment modalities.

This manuscript summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer. These NCCN Guidelines begin with...
the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, adjuvant treatment, management of recurrent and metastatic disease, patient surveillance, and survivorship. When reviewing these guidelines, clinicians should be aware of several things. First, these guidelines adhere to the TNM staging system (see the staging table, available online, in these guidelines, at www.NCCN.org [ST-1]). 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.

Risk Assessment

Approximately 20% of colon cancer cases are associated with familial clustering, and first-degree relatives of patients with newly diagnosed colorectal adenomas or invasive colorectal cancer are at increased risk for colorectal cancer. Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC]) and familial adenomatous polyposis (FAP). 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 Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colorectal Can-

NCCN Colon Cancer Panel Members

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Text continues on p. 1255
Pedunculated or sessile polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer

Pedunculated polyp with invasive cancer → Observe

Suspected or proven metastatic adenocarcinoma

Observer or proven metastases (page 1242)

CLINICAL PRESENTATION

WORKUP

FINDINGS

SURGERY

Single specimen, completely removed with favorable histologic features and clear margins

Pedunculated polyp with invasive cancer → Observe

Suspected or proven metastases (page 1242)

See Principles of Pathologic Review: Endoscopically Removed Malignant Polyps (available online, in these guidelines, at [COL-A]).

See Principles of Surgery (available online, in these guidelines, at [COL-B 1 of 3]).

PET-CT does not supplant a contrast-enhanced diagnostic CT scan.

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Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
### Colon Cancer Version 1:2012

<table>
<thead>
<tr>
<th>PATHOLOGIC STAGE</th>
<th>ADJUVANT THERAPY</th>
<th>SURVEILLANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis; T1, N0, M0; T2, N0, M0</td>
<td>None</td>
<td>- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y</td>
</tr>
<tr>
<td>T3, N0, M0 at high risk for systemic recurrence or T4, N0, M0</td>
<td>Clinical trial or Observation or Consider capecitabine or 5-FU/leucovorin</td>
<td>- CEA every 3-6 mo for 2 y, then every 6 mo for a total of 5 y</td>
</tr>
<tr>
<td>T3, N0, M0</td>
<td>5-FU/leucovorin 0.0-0.1 g or oxaliplatin 0.0 Ig (FOLFOX or FLOX) or CapeOx (category 1)</td>
<td>- Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo</td>
</tr>
<tr>
<td></td>
<td>or FOLFOX preferred if oxaliplatin-based regimen used or Clinical trial or Observation</td>
<td>» If no advanced adenoma, repeat in 1 y</td>
</tr>
<tr>
<td>T1-3, N1-2, M0 or T4, N1-2, M0</td>
<td>FOLFOX (category 1) preferred or FLOX (category 1) or CapeOx (category 1)</td>
<td>- PET scan is not routinely recommended</td>
</tr>
<tr>
<td></td>
<td>or Capecitabine or 5-FU/leucovorin</td>
<td>» If advanced adenoma, repeat in 1 y</td>
</tr>
</tbody>
</table>

---

1. All patients with colon cancer should be counseled for family history and considered for risk assessment. Patients with suspected hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP should be counseled for family history and considered for risk assessment. Patients with indicated family history and risk assessment should be referred to a genetic counselor for counseling and genetic testing.

2. See Principles of Pathologic Review: Pathological Stage (available online, in these guidelines, visit the NCCN Web site at www.NCCN.org).

3. High risk factors for recurrence: grade 3-4 (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.

4. Testing for mismatch repair proteins (MMR) should be considered for all patients aged < 50 y. Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. (Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-3226.)

5. See Principles of Risk Assessment for Stage II Disease (page 1252).

6. There are insufficient data to recommend the use of multigene assay panels to determine adjuvant therapy.

7. Bevacizumab, cetuximab, panitumumab, or irinotecan should not be used in the adjuvant setting for patients with stage II or III disease outside the setting of a clinical trial.

8. See Principles of Adjuvant Therapy (pages 1252 and 1253).

9. Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy (page 1253).

10. Grade 3-4 diarrhea is considerably higher with FLOX than FOLFOX in cross study comparison.

11. CT scan may be useful for patients at high risk for recurrence (e.g., lymphatic or venous invasion by tumor, or poorly differentiated tumors).

12. Villous polyp, polyp > 1 cm, or high-grade dysplasia.


14. Testing for mismatch repair proteins (MMR) should be considered for all patients aged < 50 y.

15. Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy (page 1253).
Suspected or proven metastatic synchronous adenocarcinoma (any T, any N, M1)

- Colonoscopy
- Chest/abdominal/pelvic CT
- CBC, platelets, chemistry profile
- CEA
- Determination of tumor KRAS gene status (if KRAS non-mutated, consider BRAF testing)
- Needle biopsy, if clinically indicated
- PET/CT scan only if potentially surgically curable M1 disease
- Multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary and lung metastases

Synchronous liver only and/or lung only metastases

Resectable

Synchronous abdominal/peritoneal metastases

Unresectable (potentially convertible or unconvertible)

See Primary Treatment and Adjuvant Therapy (page 1244)

---

8 See Principles of Pathologic Review (available online, in these guidelines, at www.NCCN.org [COL-A 4 of 5]) - KRAS and BRAF Mutation Testing.
9 See Principles of Surgery (available online, in these guidelines, at www.NCCN.org [COL-B 2 of 3]).

Y CT should be with IV contrast. Consider MRI with IV contrast if CT is inadequate.
Colon Cancer Version 1:2012

TREATMENT
Resectable synchronous liver and/or lung metastases only

- Colectomy, followed by chemotherapy or neoadjuvant therapy (for 2-3 mo)
  - FOLFIRI or FOLFOX or CapeOx± bevacizumab or FOLFIRI or FOLFOX ± panitumumab (KRAS wild-type WT gene only) followed by synchronous or staged colectomy and resection of metastatic disease or
  - FOLFIRI or FOLFOX or CapeOx± bevacizumab or FOLFIRI or FOLFOX ± panitumumab (KRAS WT gene only) and staged resection of metastatic disease

Unresectable synchronous liver and/or lung metastases only

- Systemic therapy FOLFIRI or FOLFOX or CapeOx± bevacizumab or FOLFIRI or FOLFOX ± panitumumab (KRAS WT gene only) or FOLFOXIRI (category 2B)
  - Consider colon resection only if imminent risk of obstruction or significant bleeding

ADJUVANT THERAPY
(6-mo perioperative treatment preferred)

SURVEILLANCE
See adjuvant therapy for stage III disease on page 1241

- Consider observation or shortened course of chemotherapy
- Consider observation or shortened course of chemotherapy
- If patient stage IV, NED:
  - CEA every 3 mo x 2 y, then every 6 mo x 3-5 y
  - Chest/abdominal/pelvic CT scan every 3-6 mo x 2 y, then every 6-12 mo up to a total of 5 y
  - Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo
  - > If advanced adenoma, repeat in 1 y
  - > If no advanced adenoma, repeat in 3 y, then every 5 y

If recurrence, see workup (page 1245)

2 All patients with colon cancer should be counseled for family history and considered for risk assessment. Patients with suspected hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP see the NCCN Guidelines for colorectal cancer screening (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

3 See principles of pathologic review: KRAS and BRAF mutation testing (available online, in these guidelines, at [COL-A 4 of 5]).

4 See Principles of Surgery (available online, in these guidelines, at www.NCCN.org [COL-B 2 of 3]).

5 Villous polyp, polypl > 1 cm, or high-grade dysplasia.


7 Testing for mismatch repair proteins (MMR) should be considered for all patients aged < 50 y.

8 Patients with a BRAF V600E mutation seem to have a poorer prognosis. Retrospective subset analyses suggest potential benefit from anti-EGFR monoclonal antibodies in the first-line setting with active chemotherapy regardless of V600E mutation status.

9 Most 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 d, repeated every 21 d, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (and with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large-scale randomized trials.

10 The safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6-wk interval between the last dose of bevacizumab and elective surgery, and bevacizumab should be reinitiated at least 6-8 weeks postoperatively. Bevacizumab is associated with an increased risk of stroke and other arterial events, especially in patients aged > 65 y. The use of bevacizumab may interfere with wound healing.

11 Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
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Colon Cancer Version 1:2012

**Recurrence**

- Serial CEA elevation
  - Physical exam
  - Colonoscopy
  - Chest/abdominal/pelvic CT
  - Consider PET-CT scan

**Workup**

- Positive findings
  - Consider PET-CT scan
  - Reevaluate chest/abdominal/pelvic CT in 3 mo

- Negative findings
  - See treatment for Documented metachronous metastases, below

- Documented metachronous metastases by CT, MRI, and/or biopsy
  - Resectable
    - Consider PET-CT scan
    - See Primary Treatment (page 1246)
  - Unresectable
    - (potentially convertible or unconvertible)
    - See Primary Treatment (page 1246)

**Notes:**
- See Principles of Surgery (available online, in these guidelines, at www.NCCN.org [COL-B 2 of 3]).
- Determination of tumor KRAS (if KRAS nonmutated, consider BRAF testing). See Principles of Pathologic Review: KRAS and BRAF Mutation Testing (available online, in these guidelines, at www.NCCN.org [COL-A 4 of 5]).
- Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.
Primary Treatment

Resectable Metachronous Metastases

No previous chemotherapy

- Resection\(\text{cc}\)
  - See adjuvant therapy for stage III disease on page 1241

- Neoadjuvant chemotherapy (2-3 mo) (pages 1247-1251)
  - No progression
    - Repeat neoadjuvant therapy or FOLFOX
  - Progression
    - Active chemotherapy regimen\(^9\) (see pages 1247-1251) or Observation

Previous chemotherapy

- Neoadjuvant chemotherapy (2-3 mo) (pages 1247-1251)
  - No progression
    - Repeat neoadjuvant therapy or FOLFOX
  - Progression
    - Active chemotherapy regimen\(^9\) (see pages 1247-1251) or Observation

Unresectable Metachronous Metastases

- Previous adjuvant FOLFOX within past 12 mo
  - FOLFIRI ± bevacizumab or FOLFIRI ± cetuximab or panitumumab (KRAS WT gene only)\(^e,h\)
    - Reevaluate for conversion to resectable\(^d\) every 2 mo if conversion to resectability is a reasonable goal
    - Converted to resectable
      - Resection\(\text{cc}\)
      - Active chemotherapy regimen\(^9\) (see pages 1247-1251) or Observation
    - Remains unresectable
      - Active chemotherapy regimen (see pages 1247-1251)

- Previous adjuvant FOLFOX > 12 mo
  - Active chemotherapy regimen (pages 1247-1251)
  - No previous chemotherapy

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\(^e\) See Principles of Pathologic Review: KRAS and BRAF Mutation Testing (available online, in these guidelines, at www.NCCN.org [COL-A 4 of 5]).

\(^f\) See Principles of Surgery (available online, in these guidelines, at www.NCCN.org [COL-B 2 of 3]).

\(^g\) 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.

\(^h\) Perioperative therapy should be considered for up to a total of 6 mo.

\(^d\) Patients with a BRAF V600E mutation appear to have a poorer prognosis. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after patient has progressed on first-line therapy.

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### CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:

<table>
<thead>
<tr>
<th>Initial therapy</th>
<th>Therapy after First Progression</th>
<th>Therapy after Second Progression</th>
</tr>
</thead>
</table>
| FOLFOX³ ± bevacizumab or CapeOx⁴ ± bevacizumab or FOLFOX³ ± panitumumab (KRAS WT gene only)⁸,⁹ or FOLFIRI¹⁰ ± bevacizumab or FOLFIRI ± cetuximab or panitumumab (KRAS WT gene only)⁸,⁹ or 5-FU/leucovorin or Capecitabine or bevacizumab or FOLFOXIRI (category 2B) | FOLFIRI⁵,¹⁰ or Irinotecan¹⁰ or FOLFIRI + cetuximab (KRAS WT gene only)⁸ or Cetuximab (KRAS WT gene only)⁸ or Irinotecan¹⁰ (category 2B) or FOLFOX²,³,⁵ or CapeOx⁴,⁵ or Cetuximab (KRAS WT gene only)⁸ + irinotecan¹⁰ or Cetuximab (KRAS WT gene only)⁸ or Irinotecan¹⁰ (category 2B) or Irinotecan¹⁰ or Oxa³,⁵ or FOLFIRI¹⁰ | Cetuximab (KRAS WT gene only)⁸ + irinotecan¹⁰ patients not able to tolerate combination, consider single-agent cetuximab (KRAS WT gene only)⁸ or panitumumab (KRAS WT gene only)⁸ or Clinical trial or best supportive care¹⁹ or Cetuximab (KRAS WT gene only)⁸ or panitumumab (KRAS WT gene only)⁸ or FOLFOX³ or CapeOx⁴ or Cetuximab (KRAS WT gene only)⁸ or panitumumab (KRAS WT gene only)⁸ or Irtínecan¹⁰ or Cetuximab (KRAS WT gene only)⁸ or panitumumab (KRAS WT gene only)⁸ or Irtínecan¹⁰ or Cetuximab (KRAS WT gene only)⁸ or panitumumab (KRAS WT gene only)⁸ or Clinical trial or best supportive care¹⁹ |}

**Patient appropriate for intensive therapy²**

<table>
<thead>
<tr>
<th>Initial therapy</th>
<th>Therapy after First Progression</th>
<th>Therapy after Second Progression</th>
</tr>
</thead>
</table>
| Infusional 5-FU + leucovorin or Capecitabine ± bevacizumab or Cetuximab (KRAS WT gene only)⁸,⁹ (category 2B) or Panitumumab (KRAS WT gene only)⁸,⁹ (category 2B) | Improvement in functional status | Cetuximab (KRAS WT gene only)⁸ + irinotecan¹⁰ patients not able to tolerate combination, consider single-agent cetuximab (KRAS WT gene only)⁸ or panitumumab (KRAS WT gene only)⁸ or Clinical trial or best supportive care¹⁹ |}

**Patient not appropriate for intensive therapy**

<table>
<thead>
<tr>
<th>Initial therapy</th>
<th>Therapy after First Progression</th>
<th>Therapy after Second Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in functional status</td>
<td>Consider Initial Therapy as above²⁰</td>
<td>Best supportive care See NCCN Guidelines for Palliative Care (to view the most recent version of these guidelines, visit the NCCN Web site at <a href="http://www.NCCN.org">www.NCCN.org</a>).</td>
</tr>
</tbody>
</table>
PET/CT should not be used to monitor progress of therapy. CT with chemotherapy references, there are insufficient data to support continuation of bevacizumab beyond progression is not recommended. If significant neurotoxicity develops grade 2) with other drugs maintained (fluoropyrimidine + bevacizumab) until time of tumor progression. Oxaliplatin may be reintroduced if it was discontinued previously for neurotoxicity rather than disease progression. For good performance status, patients with a KRAS mutation appear to have a poorer prognosis. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of KRAS and BRAF mutation.

Combination therapy involving cytotoxics, anti-EGFRs and anti-VEGFs is not recommended. (Hecht JR, Mitchell E, Chidac T, et al. A randomized phase II/IIb trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009;27:672-680; and Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360:563-572.) Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 min and 7.5 mg/kg over 15 min). Patients with a BRAF V600E mutation appear to have a poorer prognosis. Retrospective subset analyses suggest potential benefit from anti-EGFR monoclonal antibodies in the first-line setting with active chemotherapy regardless of V600E mutation status.

Irinotecan should be used with caution and with decreased doses in patients with Gilbert disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established. Infusional 5-FU is preferred.

Patients with diminished creatinine clearance may require dose modification of capecitabine.

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

Data are not mature for the addition of biologic agents to FOLFIRI.

Cetuximab is indicated in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.

EGFR testing has no demonstrated predictive value, and therefore routine EGFR testing is not recommended. No patient should be included or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.

There are no data, nor is there a compelling rationale, to support the use of panitumumab after clinical failure on cetuximab, or the use of cetuximab after clinical failure on panitumumab. As such, the use of one of these agents after therapeutic failure on the other is not recommended.

Patients with a BRAF V600E mutation appear to have a poorer prognosis. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after patient has progressed on first-line therapy.

Single-agent or combination therapy with capecitabine, mitomycin, or gemcitabine has not been shown to be effective in this setting.

The use of single-agent capecitabine as a salvage therapy after failure on a fluoropyrimidine-containing regimen has been shown to be ineffective, and this is therefore not recommended.

For chemotherapy references, see pages 1249-1251.

Discontinuation of oxaliplatin should be strongly considered from FOLFIRI or CapeOX after 3-4 mo of therapy (or sooner if significant neurotoxicity develops ≥ grade 2) with other drugs maintained (fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large-scale randomized trials. For good performance status patients, the 1000 mg/m² twice daily dose is the recommended starting dose, with close monitoring in the first cycle for toxicity, and dose adjustments as indicated.

There are insufficient data to support continuation of bevacizumab with a second-line regimen after progression on a bevacizumab-containing first line regimen, and such continuation of bevacizumab beyond progression is not recommended. If bevacizumab is not used in initial therapy, it may be appropriate to consider, if there is no contraindication to therapy. There is an increased risk of stroke and other arterial events especially in patients aged ≥ 65 y. The use of bevacizumab may interfere with wound healing.

Combination therapy involving cytotoxics, anti-EGFRs and anti-VEGFs is not recommended. (Hecht JR, Mitchell E, Chidac T, et al. A randomized phase II/IIb trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009;27:672-680; and Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360:563-572.) If cetuximab or panitumumab are used as initial therapy, then neither cetuximab nor panitumumab should be used in second-line or subsequent lines of therapy.
### CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

<table>
<thead>
<tr>
<th>Regimen Description</th>
<th>Dose Schedule</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFOX6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin, 85 mg/m² IV over 2 h, day 1</td>
<td>Leucovorin*, 400 mg/m² IV bolus on day 1, then 1200 mg/m²/d x 2 d (total 2400 mg/m² over 46-48 h)† IV continuous infusion</td>
<td>Repeat every 2 wk</td>
</tr>
<tr>
<td>FOLFIRI*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan, 180 mg/m² IV over 30-90 min, day 1</td>
<td>Leucovorin, 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1</td>
<td>5-FU, 400 mg/m² IV bolus day 1, then 1200 mg/m²/d x 2 d (total 2400 mg/m² over 46-48 h)† IV continuous infusion</td>
</tr>
<tr>
<td>mFOLFOX6 + bevacizumab‡∥</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin, 85 mg/m² IV over 2 h, day 1</td>
<td>Bevacizumab, 5 mg/kg IV, day 1</td>
<td>Repeat every 2 wk</td>
</tr>
<tr>
<td>FOLFIRI* + bevacizumab‡∥</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan, 180 mg/m² IV over 30-90 min, day 1</td>
<td>Bevacizumab, 5 mg/kg IV, day 1</td>
<td>Repeat every 2 wk</td>
</tr>
<tr>
<td>mFOLFOX6 + panitumumab‡∥</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin, 85 mg/m² IV over 2 h, day 1</td>
<td>Repeat every 2 wk</td>
<td></td>
</tr>
<tr>
<td>CapeOX†,‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin, 130 mg/m² IV over 2 h, day 1</td>
<td>Capecitabine, 850-1000 mg/m² twice daily PO for 14 d</td>
<td>Repeat every 3 wk</td>
</tr>
<tr>
<td>CapeOX + bevacizumab†,‡∥</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin, 130 mg/m² IV over 2 h, day 1</td>
<td>Bevacizumab, 7.5 mg/kg IV, day 1</td>
<td>Repeat every 3 wk</td>
</tr>
<tr>
<td>CapeOX + panitumumab†,‡∥</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin, 130 mg/m² IV over 2 h, day 1</td>
<td>Panitumumab, 6 mg/kg IV over 60 min, day 1</td>
<td>Repeat every 2 wk</td>
</tr>
</tbody>
</table>

*Leucovorin, 400 mg/m², is the equivalent of levo-leucovorin, 200 mg/m².
†NCCN recommends limiting chemotherapy orders to 24-h units (i.e., 1200 mg/m²/d NOT 2400 mg/m² over 48 h) to minimize medication errors.
‡Most 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 d, repeated every 21 d, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (and with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large-scale randomized trials.
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 min and 7.5 mg/kg over 15 min).
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

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

Capecitabine + bevacizumab
850-1250 mg/m² PO twice daily, days 1-14
Repeat every 3 wk

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

Simplified biweekly infusional 5-FU_leucovorin (sLV5FU2)
Leucovorin, 400 mg/m² IV over 2 h on day 1, followed by 5-FU, 400 mg/m² and then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 48-48 h) continuous infusion
Repeat every 2 wk

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

IROX
Oxaliplatin, 85 mg/m² IV over 2 h, followed by irinotecan, 200 mg/m² over 30 or 90 min every 3 wk

FOLFOXIRI
Irinotecan, 165 mg/m² IV day 1, oxaliplatin, 85 mg/m² day 1, leucovorin, 400* mg/m² day 1, fluorouracil, 3200 mg/m² over 48-h continuous infusion starting on day 1
Repeat every 2 wk

Irinotecan
Irinotecan, 125 mg/m² IV over 30-90 min, days 1, 8
Repeat every 3 wk
Irinotecan, 300-350 mg/m² IV over 30-90 min, day 1
Repeat every 3 wk

Cetuximab (KRAS WT gene only) + irinotecan
Cetuximab, 400 mg/m² first infusion, then 250 mg/m² IV weekly or cetuximab, 500 mg/m² IV every 2 wk
Irinotecan, 300-350 mg/m² IV every 3 wk
or irinotecan, 180 mg/m² IV every 2 wk
or irinotecan, 125 mg/m² on days 1, 8 and repeat every 3 wk

Cetuximab (KRAS WT gene only)
Cetuximab, 400 mg/m² first infusion, then 250 mg/m² IV weekly
or cetuximab, 500 mg/m² IV over 2 h, day 1, every 2 wk

Panitumumab (KRAS WT gene only)
Panitumumab, 6 mg/kg IV over 60 min every 2 wk

*Leucovorin, 400 mg/m², is the equivalent of levo-leucovorin, 200 mg/m².
†NCCN recommends limiting chemotherapy orders to 24-h units (i.e., 1200 mg/m²/d NOT 2400 mg/m² over 48 h) to minimize medication errors.
‡Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 min and 7.5 mg/kg over 15 min).
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

REFERENCES


5 European studies showing equivalent efficacy for CapeOX used at a higher dose; however, European patients consistently tolerate capecitabine with less toxicity than American patients.


PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE\textsuperscript{1,2,3}

- Patient/physician discussion regarding the potential risks of therapy compared with 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
  - Poor prognostic features (e.g., T4 lesion, perforation, peritumoral lymphovascular involvement, poorly differentiated histology, perineural invasion)
  - Assessment of other comorbidities and anticipated life expectancy
- The benefit of adjuvant chemotherapy does not improve survival by more than 5%.
- If considering fluoropyrimidine therapy only, MMR should be considered. See NCCN Guidelines for Colorectal Screening (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. (Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-3226.)

PRINCIPLES OF ADJUVANT THERAPY

- Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III disease.\textsuperscript{1}
- FOLFOX is superior to fluoropyrimidine therapy alone for patients with stage III disease.\textsuperscript{2,3} FOLFOX is a reasonable option for patients with high- or intermediate-risk stage II disease and is not indicated for those with good- or average-risk stage II disease. FLOX is an alternative to FOLFOX.\textsuperscript{4}
- Bolus 5-FU/leucovorin/irinotecan should not be used in adjuvant therapy\textsuperscript{3} and infusional 5-FU/leucovorin/irinotecan (FOLFIRI) has not been shown to be superior to 5-FU/leucovorin.\textsuperscript{6,7} Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin.\textsuperscript{8}
- Bevacizumab, cetuximab, panitumumab, or irinotecan should not be used in the adjuvant setting for patients with stage II or III disease outside the setting of a clinical trial.

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PRINCIPLES OF ADJUVANT THERAPY

mFOLFOX 6
Oxaliplatin, 85 mg/m² IV over 2 h, day 1. Leucovorin⁴, 400 mg/m² IV over 2 h, day 1. 5-FU, 400 mg/m² IV bolus on day 1, then 1200 mg/m²/d x 2 d (total 2400 mg/m² over 46-48 h) continuous infusion. Repeat every 2 wk.¹

FOLFOX²
5-FU, 500 mg/m² IV bolus weekly x 6 + leucovorin, 500 mg/m² IV weekly x 6, each 8-wk cycle x 3 with oxaliplatin, 85 mg/m² IV administered on weeks 1, 3, and 5 of each 8-wk cycle x 3.

Capecitabine³
Capecitabine, 1250 mg/m² twice daily days 1-14 every 3 wk x 24 wk.

CapeOx⁴
Oxaliplatin, 130 mg/m² over 2 h, day 1. Capecitabine, 1000 mg/m² twice daily days 1-14 every 3 wk x 24 wk.

5-FU/leucovorin
• Leucovorin, 500 mg/m² given as a 2-h infusion and repeated weekly x 6. 5-FU, 500 mg/m² given bolus 1 h after the start of leucovorin and repeated 6 x weekly. Every 8 wk for 4 cycles.⁵
• Simplified biweekly infusional 5-FU/LV (slV5FU2)⁶
  Leucovorin, 400 mg/m² IV over 2 h on day 1, followed by 5-FU, bolus 400 mg/m² and then 1200 mg/m²/d x 2 d (total 2400 mg/m² over 46-48 h) continuous infusion. Repeat every 2 wk.

¹Leucovorin, 400 mg/m², is the equivalent of levo-leucovorin, 200 mg/m².
²NCCN recommends limiting chemotherapy orders to 24-h units (i.e., 1200 mg/m²/d NOT 2400 mg/m² over 48 h) to minimize medication errors.

PRINCIPLES OF RADIATION THERAPY

• 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
  - Small bowel dose should be limited to 45 Gy
  - 5-FU-based chemotherapy should be delivered concurrently with radiation
• Conformal external beam radiation should be routinely used for T4 nonmetastatic disease and intensity modulated radiotherapy (IMRT) reserved only for unique clinical situations including reirradiation of previously treated patients with recurrent disease.
• Intraoperative radiotherapy (IORT), if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Preoperative radiation therapy with concurrent 5-FU-based chemotherapy is a consideration for these patients to aid resectability. If IORT is not available, additional 10-20 Gy external beam radiation and/or brachytherapy could be considered to a limited volume.
• Some institutions use arterially directed embolization using yttrium-90 microspheres in select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, and with predominant hepatic metastases (category 3).
• In patients with a limited number of liver or lung metastases, radiotherapy 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 3D conformal radiotherapy, IMRT or stereotactic body radiation therapy (category 3).
PRINCIPLES OF SURVIVORSHIP - Colorectal Long-Term Follow-Up Care

Colorectal Cancer Surveillance:
- See page 1241.
- 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 y.
- Chronic diarrhea or incontinence
  - Consider antidiarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.
- Management of Late Sequelae of Disease or Treatment:1-5

Prescription for Survivorship and Transfer of Care to Primary Care Physician (PCP)6 (if primary physician will be assuming cancer surveillance responsibilities):
- Include overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received
- Describe possible clinical course, including expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment
- Include surveillance recommendations
- Delineate appropriate timing of transfer of care with specific responsibilities identified for PCP and oncologist.

Cancer Screening Recommendations:
These recommendations are for average-risk patients.
Recommendations for high-risk individuals should be made on an individual basis.
- Breast cancer: See the NCCN Guidelines for Breast Cancer Screening
- Cervical cancer: See the NCCN Guidelines for Cervical Cancer Screening
- Prostate cancer: See the NCCN Guidelines for Prostate Early Detection

Counseling Regarding Healthy Lifestyle and Wellness:7
- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (≥30 min of moderate intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (i.e., ostomy, neuropathy).
- Consume a healthy diet with emphasis on plant sources.
- Limit alcohol consumption.
- Smoking cessation counseling as appropriate.

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

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all colorectal cancer cases.8,9,11,12 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 2 rounds of selection before sequencing: the first based on family history and the second based on initial tests on tumor tissue. Two initial tests are performed on colorectal cancer specimens to identify individuals who might have Lynch syndrome: immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation, and analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as an altered amount of short repeated DNA sequences in tumor tissue caused by the insertion or deletion of repeated units.13 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.13

The panel recommends that MMR protein testing be strongly considered for all patients younger than 50 years with colon cancer, based on an increased likelihood of Lynch syndrome in this population.14 Some centers, however, now perform immunohistochemistry (and sometimes MSI) testing on all colorectal tumors to determine which patients should have genetic testing for Lynch syndrome. The cost-effectiveness of this so-called reflex testing approach has been confirmed for colorectal cancer, and this approach was endorsed by the Evaluation of Genomic Applications in Prevention and Practice (EGAPP) working group at the Centers for Disease Control and Prevention (CDC).15 A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening (available online at www.NCCN.org).
Colon Cancer

The panel recommends marking the polyp site during colonoscopy if cancer is suspected, or within 2 weeks of the polypectomy when the pathology is known.

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. In patients with invasive cancer or adenoma (tubular, tubulovillous, or villous), no additional surgery is required if the polyp has been completely resected and has favorable histologic features. 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 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, probably because of the high probability of a positive margin after endoscopic removal.

If the polyp specimen is fragmented, the margins cannot be assessed, or the specimen shows unfavorable histopathology, colectomy with en bloc removal of lymph nodes is recommended. Laparoscopic surgery is an option. Unfavorable histopathologic features for malignant polyps are grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. 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.

All patients who have resected polyps 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 pathologic tissue review, total colonoscopy, CBC, chemistry profile, carcinoembryonic antigen (CEA) determination, and baseline CT scans of the chest, abdomen, and pelvis. The consensus of the panel is that a PET/CT scan is not routinely indicated at baseline and should not be performed as a matter of general surveillance. Furthermore, a PET/CT scan does not obviate the need for a contrast-enhanced diagnostic CT scan. If 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 nonmetastatic colon cancer, the preferred surgical procedure is colectomy with en bloc removal of the regional lymph nodes. 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 (i.e., 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.

Laparoscopic colectomy has become an option in the surgical management of colon cancer. 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. More recently, a similar 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 disease-free survival (DFS) favoring open colectomy. Although this difference was not statistically significant, non-inferiority of the laparoscopic approach could not be established because of study limitations. In the CLASICC study of 794 patients with colorectal cancer, no statistically significant differences in 3-year rates of overall survival, DFS, and local recurrence were observed between these surgical approaches.

In another trial of 872 patients with colon cancer (COST study) randomly assigned to undergo ei-
ther open or laparoscopic-assisted colectomy for curable colon cancer, similar 5-year recurrence and 5-year overall survival rates were seen after a median of 7 years follow-up. 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.

A subanalysis of results from the COLOR trial evaluating short-term outcomes (e.g., 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. Other factors have been described that may confound conclusions drawn from randomized studies comparing open colectomy with laparoscopic-assisted surgery for colon cancer.

The panel recommends that laparoscopic-assisted colectomy be considered only by surgeons experienced in the technique. A thorough abdominal exploration is required as part of the procedure. Routine use of laparoscopic-assisted resection is not currently recommended for tumors in the lower and mid-rectum, for tumors that are acutely obstructed or perforated, nor for tumors clearly locally invasive into surrounding structures (i.e., T4). Patients at high risk for prohibitive abdominal adhesions should not be approached laparoscopically, and those who are found to have prohibitive adhesions during laparoscopic exploration should be converted to an open procedure.

For resectable colon cancer that is causing overt obstruction, resection with diversion, stent insertion followed by colectomy, or diversion followed by colectomy are options. If the cancer is locally unresectable or medically inoperable, chemotherapy is recommended with the goal of converting the lesion to a resectable state.

Adjuvant Chemotherapy for Resectable Colon Cancer

Adjuvant therapy for patients with resected colon cancer has gained considerable interest. Choices for adjuvant therapy for patients with resected nonmetastatic colon cancer depend on the stage of disease:

• Patients with stage I disease do not require any adjuvant therapy.

• Patients with low-risk stage II disease can be enrolled in a clinical trial, observed without adjuvant therapy, or considered for capecitabine or 5-FU/leucovorin (LV). Based on results of the MOSAIC trial, and the possible long-term sequelae of oxaliplatin-based chemotherapy, the panel does not consider FOLFOX (infusional 5-FU, LV, oxaliplatin) to be an appropriate adjuvant therapy option for patients with stage II disease without high-risk features.

• Patients with high-risk stage II disease, defined as those with poor prognostic features, including T4 tumors (stage IIB/IIC); poor histologic grade (grade 3 or 4 lesions, exclusive of those cancers that are MSI-high [MSI-H]); lymphovascular invasion; perineural invasion; bowel obstruction; lesions with localized perforation or close, indeterminate, or positive margins; or inadequately sampled nodes (< 12 lymph nodes), should be considered for adjuvant chemotherapy the same as patients with stage III disease, detailed below.

• For patients with stage III disease, the panel recommends 6 months of adjuvant chemotherapy after primary surgical treatment. The treatment options are 5-FU/LV/oxaliplatin (modified FOLFIRI) as the standard of care (category 1); bolus 5-FU/LV/oxaliplatin (FLOX, category 1); capecitabine/oxaliplatin (CapeOx, category 1); or single-agent capecitabine or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate.

The panel recommends against the use of bevacizumab, cetuximab, panitumumab, or irinotecan in adjuvant therapy for nonmetastatic disease outside the setting of a clinical trial. Adenocarcinomas of the small bowel or appendix, for which no NCCN Guidelines exist, may be treated with systemic chemotherapy according to these NCCN Guidelines. Peritoneal mesothelioma and other extrapleural mesotheliomas may be treated with systemic therapy according to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Malignant Pleural Mesothelioma (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

End Points for Adjuvant Chemotherapy Clinical Trials: The Adjuvant Colon Cancer End Points (ACCENT) Collaborative Group evaluated the appropriateness of various end points 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 is an appropriate end point for clinical trials involving treatment of colon cancer with 5-FU–based chemotherapy in the adjuvant setting. 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. More recently, however, a further update of the data suggested that the association between 2- or 3-year DFS and 5-year overall survival is 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 overall survival. Further confirmation of this result comes from new analysis by the ACCENT group of data from 12,676 patients undergoing combination therapies from 6 trials. This study determined that 2- and 3-year DFS correlated with 5- and 6-year overall survival in patients with stage III disease but not in those with stage II. In all patients, the correlation of DFS to overall survival was strongest at 6 years, suggesting that at least 6 years are required for adequate assessment of overall survival in modern adjuvant colon cancer trials.

**Adjuvant Chemotherapy in Stage II Disease:** 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. Observation and participation in a clinical trial are options that can be considered.

The impact of adjuvant chemotherapy for patients with stage II colon cancer has been addressed in several clinical trials and practice-based studies. Results from a meta-analysis of 5 trials in which patients with stage II or III colon cancer were randomly assigned to receive surgery alone or surgery followed by adjuvant 5-FU/LV showed that most of the benefit of adjuvant therapy was seen in the patients with stage III disease. Similarly, an analysis of pooled data from 7 randomized trials indicated that overall survival of patients with resected colon cancer treated with 5-FU–based adjuvant therapy was statistically significantly increased with the addition of chemotherapy in the subset of patients with stage III disease but not in those with stage II. These results suggest that the benefit of adjuvant therapy is greater in patients at higher risk because of nodal status. These clinical trial results are supported by data from the community setting. Using the SEER Medicare database, an 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 overall survival between the groups (78% vs. 75%, respectively), with a hazard ratio (HR) for survival of 0.91 (95% CI, 0.77–1.09) when patients receiving adjuvant treatment were compared with untreated patients.

Similar results were seen in the MOSAIC trial. Although results of a subset analysis of data from 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), a trend toward improved DFS was seen in patients with high-risk stage II disease (i.e., 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 compared with infusional 5-FU/LV (HR, 0.72; 95% CI, 0.50–1.02), suggesting that this patient population may benefit from treatment with FOLFOX. 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 (relative risk of recurrence at 2 years, 0.71; 95% CI, 0.54–0.92; P = .01).

Notably, a recent analysis of more than 24,000 patients with stage II colon cancer from the SEER Medicare database showed no 5-year survival benefit for adjuvant chemotherapy over observation, even in patients with stage II disease with one or more poor prognostic features (HR, 1.03; 95% CI, 0.94–1.13). Although this study was limited to patients older than 65 years and involved a period before the use of oxaliplatin-based therapies, it is still an important piece of data to consider during the decision-making process regarding the use of adjuvant chemotherapy in patients with stage II disease.
MSI: MSI is another important piece of information to consider when deciding whether to use adjuvant chemotherapy in patients with stage II disease. Evidence shows that MSI is a marker of a more favorable outcome and a predictor of decreased benefit (possibly a detrimental impact) from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease.\textsuperscript{110,111} Mutation of DNA MMR genes or modifications of these genes (e.g., methylation) can result in MMR protein deficiency and MSI (see Risk Assessment, page 1252).\textsuperscript{112}

Germline mutations in the MMR genes MLH1, MSH2, MSH6, and/or PMS2 are found in individuals with Lynch syndrome, which is responsible for 2% to 4% of colon cancer cases.\textsuperscript{8,9,11,12} Somatic MMR defects have been reported to occur in approximately 19% of colorectal tumors,\textsuperscript{113} 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.\textsuperscript{114} 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 microsatellite-stable (MSS).\textsuperscript{115} Patients determined to have defective MMR status (dMMR) are biologically the same population as those with MSI-H status.

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; \(P < .0001\)).\textsuperscript{116} In another large study, the percentage of stage IV tumors characterized as MSI-H was only 3.5%.\textsuperscript{117} These results suggest that MSI-H (i.e., 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.\textsuperscript{110,111,118}

However, 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 (possibly a detrimental impact) from adjuvant therapy with a fluoropyrimidine alone in patients with stage II.\textsuperscript{110,111} 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.\textsuperscript{110} Similarly, results from another retrospective study of pooled data from adjuvant trials by Sargent et al.\textsuperscript{111} 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.,\textsuperscript{111} however, a recent study of 1913 patients with stage II colorectal cancer from the QUASAR study, half of whom received adjuvant chemotherapy, showed that although dMMR was prognostic (the recurrence rate of dMMR tumors was 11% vs. 26% for MMR-proficient tumors), it did not predict benefit or detrimental impact of chemotherapy.\textsuperscript{119} Overall, although the prognostic power of MMR status in stage II disease seems clear, considerable controversy surrounds the predictive power of MMR status.\textsuperscript{120,121}

The panel recommends that MMR testing be considered for patients with stage II disease and planned adjuvant therapy with a fluoropyrimidine alone. Grade 3 or 4 (poorly differentiated) is not considered a high-risk feature for patients with stage II disease whose tumors are MSI-H.

**Timing of Adjuvant Therapy:** A recent systematic review and meta-analysis of 10 studies involving more than 15,000 patients examined the effect of timing of adjuvant therapy after resection.\textsuperscript{122} Results of this analysis showed that each 4-week delay in chemotherapy results in a 14% decrease in overall survival, indicating that adjuvant therapy should be administered as soon as the patient is medically able. These results are consistent with other similar analyses.

**LV Shortage:** A shortage of LV currently exists 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 levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m\(^2\) of levo-leucovorin is equivalent to 400 mg/m\(^2\) of standard 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 efficac-
CapeOx was shown to be 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 colorectal cancer. Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m²) or low-dose (20 mg/m²) LV. 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/m²) or low-dose (20 mg/m²) LV with bolus 5-FU in the treatment of advanced colorectal cancer, although the 5-FU doses were different in the arms. Finally, if none of the above options are available, treatment without LV would be reasonable. For patients who tolerate this without grade 2 or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

**FOLFOX and Infusional 5-FU/LV:** The European MOSAIC trial compared the efficacy of FOLFOX and 5-FU/LV in the adjuvant setting in 2246 patients with completely resected stage II and III colon cancer. Although this initial trial was performed with FOLFOX4, mFOLFOX6 has been the control arm for all recent and current NCI adjuvant studies for colorectal cancer, 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 3, 4, and 6 years. 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 overall survival of patients with stage III disease receiving FOLFOX was statistically significantly increased at 6-year follow-up (72.9% vs. 68.7%; HR, 0.80; 95% CI, 0.65–0.97; P = .023) compared with those receiving 5-FU/LV. 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 this group at 4 years (mostly grade 1), suggesting that oxaliplatin-induced neuropathy may not be completely reversible in some patients. Based on the increases in DFS and overall survival with FOLFOX in the MOSAIC trial, FOLFOX (mFOLFOX6 preferred) is recommended as treatment for stage III colon cancer (category 1).

**FLOX:** A randomized phase III trial (National Surgical Adjuvant Breast and Bowel Project [NSABP] Protocol C-07) compared the efficacy of FLOX with that of 5-FU/LV (bolus 5-FU/LV) in prolonging DFS in 2407 patients with stage II or III colon cancer. Rates of 4-year DFS were 73.2% for FLOX and 67.0% for FULV, with an HR of 0.81 (95% CI, 0.69–0.94; P = .005) after adjustment for age and number of nodes, indicating a 19% reduction in relative risk. A recent update of this study showed the benefit of FLOX in DFS was maintained at 7-year median follow-up (P = .0017). However, no statistically significant differences in overall survival (HR, 0.88; 95% CI, 0.76–1.03; P = .1173) or colon cancer–specific mortality (HR, 0.88; 95% CI, 0.74–1.05; P = .1428) 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). Grade 3 neurotoxicity, diarrhea, and dehydration were higher with FLOX than with 5-FU/LV, and, when cross-study comparisons are made, the incidence of grade 3/4 diarrhea seems 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, respectively (P < .001), in the MOSAIC trial 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, respectively (P = .003).

**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 overall survival, 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). Capecitabine has also been assessed as adjuvant therapy for stage III colon cancer in combination with oxaliplatin (CapeOx) and showed an improved 3-year DFS rate compared with 5-FU/LV (66.5% vs. 70.9%). CapeOx was shown to have similar efficacy to FOLFOX in the AVANT trial, but it is more toxic. With this new data,
CapeOx is now listed in the guidelines with a category 1 designation as adjuvant therapy for patients with stage III colon cancer. **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 irinotecan plus bolus 5-FU/LV (IFL regimen) versus 5-FU/LV alone in stage III colon cancer.\(^{128}\) No improvement in either overall survival (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.\(^ {128,129}\) Similar results were observed in a recent randomized phase III trial comparing bolus 5-FU/LV with the IFL regimen in stage II/III colon cancer.\(^ {130}\) In addition, FOLFIRI (infusional 5-FU/LV/irinotecan) has not been shown to be superior to 5-FU/LV in the adjuvant setting.\(^ {131,132}\) Thus, data do not support the use of irinotecan-containing regimens in the treatment of stage II or III colon cancer. In the NSABP C-08 trial comparing 6 months of mFOLFOX6 with 6 months of mFOLFOX6 with bevacizumab plus an additional 6 months of bevacizumab alone in patients with stage II or III colon cancer, no statistically significant benefit in 3-year DFS was seen with the addition of bevacizumab (HR, 0.89; 95% CI, 0.76–1.04; P = .15).\(^ {133}\) 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 colorectal cancer, and in fact showed a trend toward a detrimental effect to the addition of bevacizumab. Therefore, bevacizumab has no role in the adjuvant treatment of stage II or III colon cancer.\(^ {127}\)

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 KRAS, cetuximab provided no added benefit and was associated with increases in grade 3/4 adverse events.\(^ {134}\) The subset of patients in this trial with mutant KRAS treated with cetuximab had worse DFS than those with mutant KRAS treated with FOLFOX alone, and also experienced increases in grade 3/4 adverse events.\(^ {135}\) Therefore, cetuximab also has no role in the adjuvant treatment of colon cancer.

**Adjuvant Chemoradiation:** 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. Radiation therapy fields should include the tumor bed as defined by preoperative radiologic imaging and/or surgical clips. Intraoperative radiotherapy (IORT), if available, should be considered for these patients as an additional boost.\(^ {136}\) If IORT is not available, an additional 10- to 20-Gy external beam radiation and/or brachytherapy could be considered to a limited volume. Preoperative radiation with concurrent 5-FU-based chemotherapy is also a consideration for these patients to aid resectability. Conformal beam radiation should be routinely used for nonmetastatic T4 disease; intensity-modulated radiotherapy, which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,\(^ {137}\) should be reserved for unique clinical situations, including reirradiation of previously treated patients with recurrent disease.

**Principles of the Management of Metastatic Disease**

Approximately 50% to 60% of patients diagnosed with colorectal cancer will develop colorectal metastases,\(^ {138–140}\) and 80% to 90% of these have unresectable metastatic liver disease.\(^ {139,141–143}\) Metastatic disease most frequently develops metachronously after treatment for locoregional colorectal cancer, with the liver the most common site of involvement.\(^ {144}\) However, 20% to 34% of patients with colorectal cancer present with synchronous liver metastases.\(^ {143,145}\) 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.\(^ {146}\)

It has been estimated that more than one-half of patients who die of colorectal cancer have liver metastases at autopsy, with metastatic liver disease the
cause of death in most patients.\textsuperscript{147} Reviews of autopsy reports of patients dying of colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients.\textsuperscript{142} Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.\textsuperscript{139,148} Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than 3 tumors, and a disease-free interval of less than 12 months, have been associated with a poor prognosis in patients with colorectal cancer.\textsuperscript{143,149–153} However, 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.\textsuperscript{139,154} Recent reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases.\textsuperscript{150,151} 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, available online, in these guidelines, at www.NCCN.org [MS-15]). For patients presenting with unresectable metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver.\textsuperscript{156}

Evidence supporting resection of extrahepatic metastases in patients with metastatic colorectal cancer is extremely 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.\textsuperscript{157,158} 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\textsuperscript{159} suggesting that concurrent resection may be of significant benefit in well-selected patients (i.e., those with smaller total number of metastases).

Recent data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken. However, in a retrospective analysis, 5-year survival was shown to decrease with each subsequent curative-intent surgery, and the presence of extrahepatic disease at the time of surgery was independently associated with a poor prognosis.\textsuperscript{160} Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.\textsuperscript{161}

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 (i.e., hepatic artery infusion [HAI]) remains an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of fluorouracil with dexamethasone through HAI 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.\textsuperscript{142,162} The study was not powered for long-term survival, but a trend (not significant) was seen toward better long-term outcome in the group receiving HAI at later follow-up periods.\textsuperscript{142,161} Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy was compared with systemic chemotherapy, although most have not shown a survival benefit of HAI therapy.\textsuperscript{142} Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.\textsuperscript{154} Limitations on the use of HAI therapy include the potential for biliary toxicity\textsuperscript{142} and the requirement of specific technical expertise. Panel consensus is that HAI therapy should be considered selectively, and only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Several nonextirpative liver-directed therapies exist, although their role in the treatment of colorectal metastases is controversial. These therapies include arterial radioembolization with yttrium-90 microspheres\textsuperscript{164–166} and conformal external beam radiation therapy.\textsuperscript{169} A recent, prospective, randomized phase III trial of 44 patients showed that radioembolization combined with chemotherapy can lengthen time to progression in patients with liver-limited metastatic colorectal cancer after progression on initial therapy (2.1 vs. 4.5 months; \(P = .03\)).\textsuperscript{170} The effect on the primary end point of time to liver progression was more pronounced (2.1 vs. 5.5 months;
Conversion to Resectability

The latest version of this section of the guidelines manuscript can be found in the full NCCN Guidelines for Colon Cancer, available online, at www.NCCN.org.

Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

Chemotherapy is recommended in conjunction with liver resection in patients who are chemotherapy-naive. However, the optimal sequencing of chemotherapy remains unclear. Patients with resectable disease may undergo liver resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) chemotherapy can be used. This question is the subject of an ongoing NCI-sponsored cooperative trial (NSABP C-11).

Potential advantages of preoperative chemotherapy include earlier treatment of micrometastatic disease, determination of responsiveness to chemotherapy (which can be prognostic and help in planning postoperative therapy), and avoidance of local therapy for patients with early disease progression. Potential disadvantages include chemotherapy-induced liver injury and 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. In fact, results from a recent study of patients with colorectal cancer receiving preoperative chemotherapy indicated that viable cancer was still present in most of the original sites of metastases when these sites were examined pathologically, despite achievement of a complete response as evaluated on CT scan. Therefore, during treatment with preoperative chemotherapy, frequent evaluations must be undertaken and close communication maintained among medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed that optimizes exposure to the preoperative chemotherapy regimen and facilitates an appropriately timed surgical intervention.

Other reported risks associated with the preoperative chemotherapy approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively. To reduce the development of hepatoxicity, the neoadjuvant period is usually limited.

P = .003). Still, the use of arterial-directed therapies, such as radioembolization, in highly selected patients remains a category 3 recommendation based on the limited amount of evidence and different institutional practice patterns.

Radiotherapy can be considered in highly selected cases in which the patient has a limited number of liver or lung metastases (category 3 recommendation) 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 3-dimensional conformal radiotherapy, stereotactic body radiosurgery, and intensity-modulated radiotherapy, which uses computer-imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.

Although resection is the standard approach for the local treatment of resectable metastatic disease, some patients who cannot undergo resection because of comorbidity, location of the metastatic lesions, or an estimate of inadequate liver volume after resection may be candidates for tumor ablation therapy. Several retrospective studies have compared radiofrequency ablation (RFA) and liver resection in the treatment of liver metastases. Most of these studies have shown RFA to be inferior to resection in terms of rates of local recurrence and 5-year overall survival. Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, technological limitations of RFA, or a combination of these factors is currently unclear. The ASCO panel concluded that a compelling need exists for more research in this area.

The panel does not consider ablation to be a substitute for resection in patients with completely resectable disease. In addition, resection or ablation (either alone or in combination with resection) should be reserved for patients with disease that is completely amenable to local therapy. Use of either surgery, ablation, or the combination, with the goal of less-than-complete resection/ablation of all known sites of disease, is not recommended.

Determining Resectability

The latest version of this section of the guidelines manuscript can be found in the full NCCN Guidelines for Colon Cancer, available online, at www.NCCN.org.
to 2 to 3 months, and patients should be carefully monitored by a multidisciplinary team.

The panel recommends a course of an active systemic chemotherapy 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. The choice of chemotherapy regimen in the pre- and postoperative settings depends on several factors, including the response rates and safety/toxicity issues associated with the regimens. Regimens recommended for adjuvant therapy and neoadjuvant therapy are the same (see the next section).

Chemotherapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colon cancer involves various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab. The putative mechanisms of action of these agents are varied and include interference with DNA replication and inhibition of the activities of vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) receptors.

The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, and the differing toxicity profiles of the constituent drugs. Although the specific chemotherapy regimens listed in the NCCN 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. For example, if oxaliplatin is administered as a part of an initial treatment regimen but is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the remainder of the treatment regimen would still be considered initial therapy.

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

As initial therapy for metastatic disease in a patient appropriate for intensive therapy (i.e., 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 5 chemotherapy regimens: FOLFOX (i.e., mFOLFOX6), infusional FOLFIRI, CapeOx, infusional 5-FU/LV or capecitabine, or FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, and irinotecan). Although use of FOLFOXIRI as initial therapy is a category 2B recommendation, the panel does not consider one of the other regimens (i.e., FOLFOX, CapeOx, FOLFIRI, or 5-FU/LV or capecitabine) to be preferable over the others as initial therapy for metastatic disease. Biologic agents used as part of initial therapy include bevacizumab, cetuximab, or panitumumab.

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

The Dutch CAIRO trial showed promising results for the use of capecitabine/irinotecan (CapeIRI) in the first-line treatment of metastatic colorectal cancer. However, in the American BICC-C trial, CapeIRI showed worse progression-free survival than infusional FOLFIRI (5.8 vs. 7.6 months; \( P = .015 \)), and was considerably more toxic with higher rates of severe vomiting, diarrhea, and dehydration. In this trial, the CapeIRI arm was discontinued. The EORTC 40015 study also compared FOLFIRI with...
CapeIRI and was discontinued after enrollment of only 85 patients because 7 deaths were determined to be treatment-related (5 in the CapeIRI arm). 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. Preliminary results from a randomized phase II study conducted in France were presented in 2009, showing a manageable toxicity profile for CapeIRI/Bev in this setting. Finally, a randomized phase III HeCOG trial compared CapeIRI/Bev with FOLFIRI plus bevacizumab in the first-line metastatic setting and found no significant differences in efficacy between the regimens. Despite the differing toxicity profiles reported, the toxicities seemed to be reasonable in both arms. Because of the concerns about the toxicity of the capecitabine/irinotecan combination, which may differ between American and European patients, the panel does not recommend CapeIRI or CapeIRI/Bev for the first-line treatment of metastatic colorectal cancer.

A study of 6286 patients from 9 trials that evaluated the benefits and risks associated with intensive first-line treatment in the setting of metastatic colorectal cancer treatment according to patient performance status showed similar therapeutic efficacy for patients with a performance status of 2, or 1 or less compared with control groups, although the risks of certain gastrointestinal toxicities were significantly increased for patients with performance status of 2. Leucovorin: A shortage of leucovorin currently exists in the United States (see Leucovorin Shortage, page 1259).

FOLFOX: A recent EORTC phase III 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 progression-free survival 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. The partial response rate after preoperative FOLFOX was 40%, and operative mortality was less than 1% in both treatment groups.

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy. Results of the OPTIMOX1 study showed that a "stop-and-go" approach using oxaliplatin-free intervals resulted in decreased neurotoxicity but did not affect overall survival in patients receiving FOLFOX as initial therapy for metastatic disease. 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, but it can be reintroduced if stopped. Data are insufficient supporting the routine use of calcium/magnesium infusion to prevent oxaliplatin-related 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. Results of the study showed no difference in overall survival for patients receiving the OPTIMOX1 approach compared with those undergoing an early, preplanned chemotherapy-free interval (median overall survival 23.8 vs. 19.5 months; P = .42). However, the median duration of disease control, which was the primary end point 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).

The addition of bevacizumab is an option when FOLFOX is chosen as initial therapy, as is the addition of panitumumab for patients with disease characterized by the wild-type KRAS gene (see discussions on Bevacizumab [page 1267], Cetuximab and Panitumumab [page 1269], and The Role of KRAS and BRAF Status, page 1270). With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemothera-
therapy without an additional biologic agent, panel consensus is that FOLFOX and CapeOx can be used interchangeably.

**CapeOx:** The combination of capecitabine and oxaliplatin, known as CapeOx or XELOX, has been studied as an active first-line therapy for patients with metastatic colorectal cancer. In a randomized phase III trial comparing CapeOx and FOLFOX in 2034 patients, the regimens showed similar median progression-free survival 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.

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy (see FOLFOX, page 1265). Discontinuation of oxaliplatin from FOLFOX or CapeOx should be strongly considered after 3 months of therapy (the OPTIMOX approach), or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity, but it can be reintroduced if stopped. Data are insufficient to support the routine use of calcium/magnesium infusion to prevent oxaliplatin-related neurotoxicity.

Regarding the toxicities associated with capecitabine use, the panel noted that 1) patients with diminished creatinine clearance may accumulate levels of the drug, and therefore may require dose modification; 2) the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV; and 3) North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries. These toxicities may necessitate modifications in the dosing of capecitabine and 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.

The addition of bevacizumab is an option if CapeOx is chosen as initial therapy. 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.

**FOLFIRI:** Evidence for the comparable efficacy for FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI initially and were then switched to the other regimen at disease progression. Similar response rates and progression-free survival times were observed 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 metastatic colorectal cancer. No differences were observed in response rate, progression-free survival times, and overall survival between the treatment arms.

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia. 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 hyperbilirubinemia, 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, although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms. Commercial tests are available to detect the UGT1A1*28 allele, which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression and a warning has been added to the label for Camptosar indicating that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28. A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented, although guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on patients who experienced irinotecan-related toxicity.

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notecan toxicity is not recommended because they will require a dose reduction regardless of the UG-T1A1 test result.

Results from a recent phase IV trial in 209 patients with metastatic colorectal cancer 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.\(^{260}\) Therefore, the addition of bevacizumab to FOLFIRI is recommended as an option for initial therapy; alternatively, cetuximab or panitumumab (only for tumors characterized by wild-type KRAS) can be added to this regimen.\(^{222,232,234,241,281}\)

**Infusional 5-FU/LV and Capecitabine:** 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.\(^{95,229,230,240,241,270}\)

Patients with metastatic cancer with no improvement in functional status after such 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, page 1266).

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 progression-free survival 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 overall survival.\(^{282}\)

**FOLFOXIRI:** FOLFOXIRI is also listed as an option for initial therapy in patients with unresectable metastatic colon cancer (category 2B).\(^{199,200}\) If FOLFOXIRI is used, the panel recommends that it be without the addition of a biologic agent, because data regarding the efficacy and safety of this combination are not yet mature.

Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in 2 randomized phase III trials.\(^{199,200}\) In one study, statistically significant improvements in progression-free survival (9.8 vs. 6.9 months; HR, 0.63; \(P = .0006\)) and median overall survival (22.6 vs. 16.7 months; HR, 0.70; \(P = .032\)) were observed in the FOLFOXIRI arm,\(^{199}\) although no overall survival difference was seen between treatment arms in the other study (median overall survival, 19.5 and 21.5 months, for FOLFIRI and FOLFOXIRI, respectively; \(P = .337\)).\(^{220}\) Both studies showed some increased toxicity in the FOLFOXIRI arm (e.g., significant increases in neurotoxicity and neutropenia,\(^{199}\) diarrhea, alopecia, and neurotoxicity\(^ {202}\)), but no differences in the rate of toxic death were reported in either study.

**Bevacizumab:** Bevacizumab is a humanized monoclonal antibody that blocks the activity of VEGF, a factor that plays an important role in tumor angiogenesis. Pooled results from several randomized phase II studies have shown that the addition of bevacizumab to first-line 5-FU/LV improved overall survival in patients with unresectable metastatic colorectal cancer compared with those receiving these regimens without bevacizumab.\(^{203,283,284}\) 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 IFL without bevacizumab (\(P = .008\)).\(^{230}\) A study of previously untreated patients receiving bevacizumab and IFL also provided support for the inclusion of bevacizumab in initial therapy.\(^{203}\)

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 been reported from a recent 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.\(^{204}\) The addition of bevacizumab to oxaliplatin-based regimens was associated with a more modest increase of 1.4 months in progression-free survival compared with these regimens without bevacizumab (HR, 0.83; 97.5% CI, 0.72–0.95; \(P = .0023\)), and the difference in overall survival, which was also a modest 1.4 months, did not reach statistical significance (HR, 0.89; 97.5% CI, 0.76–1.03; \(P = .077\)).\(^{204}\) 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. However, in this 1400-patient randomized study, absolutely no difference in response rate was seen with and without bevacizumab (see later discussion), and this finding would not be potentially influenced by the early withdrawal rates, which 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 progression-free survival when added to CapeOx but not FOLFOX. The randomized phase III trial HEPATICA, which is comparing capecitabine with and without bevacizumab as adjuvant therapy in patients with liver metastases, is currently recruiting patients (ClinicalTrials.gov identifier: NCT00394992).

No data directly address whether bevacizumab should be used with chemotherapy in the perioperative treatment of resectable metastatic disease. Recent data regarding the lack of efficacy of bevacizumab in the adjuvant setting in stage II and III colon cancer127,133 have prompted some to reconsider the role of bevacizumab in the adjuvant setting of resectable colorectal metastases. The panel does not recommend the use of bevacizumab in the postsection stage IV adjuvant setting, unless a response to bevacizumab was seen in the neoadjuvant setting.

The risk of stroke and other arterial events is increased in elderly patients receiving bevacizumab. In addition, gastrointestinal perforation is a rare but important side effect of bevacizumab therapy in patients with colorectal cancer. Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to gastrointestinal perforation. A small cohort of patients with advanced ovarian cancer had an unacceptably high rate of gastrointestinal perforation when treated with bevacizumab, illustrating 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. A recent meta-analysis of randomized controlled trials showed that the addition of bevacizumab to chemotherapy is associated with a higher incidence of treatment-related mortality than chemotherapy alone (relative risk, 1.33; 95% CI, 1.02–1.73; P = .04), with hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal perforation (7.1%) the most common causes of fatality. Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.

Use of bevacizumab may interfere with wound healing. A retrospective evaluation of data from 2 randomized trials of 1132 patients undergoing chemotherapy with or without bevacizumab as initial therapy for metastatic colorectal cancer indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen compared with the group receiving chemotherapy alone (13% vs. 3.4%, respectively; P = .28). 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 (i.e., bevacizumab excluded from the sixth cycle of therapy). In addition, no significant differences in bleeding, wound, or hepatic complications were seen in a retrospective trial evaluating the effects of preoperative bevacizumab stopped 8 weeks or less versus more than 8 weeks before resection of liver colorectal metastases in patients receiving oxaliplatin or irinotecan-containing regimens. The panel recommends an interval of at least 6 weeks (which corresponds to 2 half-lives of the drug) between the last dose of bevacizumab and elective surgery.

Preclinical studies suggested that cessation of anti-VEGF therapy might be associated with accelerated recurrence, more aggressive tumors on recurrence, and therefore 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. Although this meta-analysis has been criticized, the results are supported by recent results from the NSABP protocol C-08 trial. This trial included...
patients with stage II and III colorectal cancer, 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.

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.\(^{296,297}\) In the PACCE trial, the addition of panitumumab to a regimen containing oxaliplatin- or irinotecan-based chemotherapy plus bevacizumab was associated with significantly shorter progression-free survival and higher toxicity in both KRAS wild-type and mutant gene groups.\(^{296}\) Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab.\(^{297}\) 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-VEGF agent (bevacizumab).

**Cetuximab and Panitumumab:** 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.\(^{298,299}\) Cetuximab and panitumumab were recently studied in combination with FOLFIRI\(^{312,313}\) and FOLFOX\(^{222,271}\) as initial therapy options for treatment of metastatic colorectal cancer. A sizable body of recent literature has shown that tumors with a mutation in codon 12 or 13 of the KRAS gene are essentially insensitive to EGFR inhibitors, such as cetuximab or panitumumab.\(^{210,241,271,300–305}\) (see The Role of KRAS and BRAF Status, page 1270). The panel therefore strongly recommends KRAS genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer. Patients with known codon 12 or 13 KRAS mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is implied throughout the guidelines that NCCN recommendations involving cetuximab or panitumumab relate only to patients with disease characterized by the KRAS wild-type gene. Although BRAF genotyping can be considered for patients with tumors characterized by the wild-type KRAS gene, this testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see The Role of KRAS and BRAF Status, page 1270).

Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.\(^{298,299}\) Based on case reports and a small trial, administration of panitumumab seems to be feasible for patients experiencing severe infusion reactions to cetuximab.\(^{306–308}\) 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.\(^{241,304,309,310}\) A recent NCCN Task Force addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.\(^{311}\)

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.\(^{311}\) Retrospective analyses of the subset of patients with known KRAS tumor status showed a statistically significant improvement in median progression-free survival with the addition of cetuximab in the group with disease characterized by the KRAS wild-type gene (9.9 vs. 8.7 months; HR, 0.68; 95% CI, 0.50–0.94; \(P = .02\)).\(^{311}\) The statistically significant benefit in progression-free survival for patients with KRAS wild-type tumors receiving cetuximab was confirmed in a recent publication of an updated analysis of the CRYSTAL data.\(^{312}\) This recent study included a retrospective analysis of overall survival in the KRAS wild-type population and found an improvement with the addition of cetuximab (23.5 vs. 20.0 months; \(P = .0093\)).

In a retrospective evaluation of the subset of patients with known tumor KRAS status enrolled in the randomized phase II OPUS trial, the 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, 0.358–0.907; P = .0163) compared with FOLFOX alone in the subset of patients with KRAS wild-type tumors. Although data supporting the statistically significant benefits in objective response rate and progression-free survival for patients with tumors characterized by the KRAS wild-type gene were upheld in a recent update of this study, no median overall survival 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). 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 metastatic colorectal cancer and wild-type KRAS have not shown any benefit. The addition of cetuximab to the Nordic FLOX regimen showed no benefit in overall or progression-free survival in this population of patients in the randomized phase III NORDIC VII study of the Nordic Colorectal Cancer Biomodulation Group. Furthermore, in the recent randomized phase III Medical Research Council (MRC) COIN trial, no benefit in overall survival (17.9 vs. 17.0 months; P = .067) or progression-free survival (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 metastatic colorectal cancer and wild-type KRAS. Because of this lack of benefit and the increased incidence of grade 3 adverse events seen in this trial, the panel removed the recommendation for the use of cetuximab with FOLFOX as initial therapy for patients with advanced or metastatic disease.

Panitumumab in combination with either FOLFOX or FOLFIRI has also been studied in the first-line treatment of patients with metastatic colorectal cancer. Results from the large, open-label, randomized PRIME trial comparing panitumumab plus FOLFOX versus FOLFOX alone in patients with KRAS wild-type advanced colorectal cancer showed a statistically significant improvement in progression-free survival with the addition of panitumumab (HR, 0.80; 95% CI, 0.67–0.95; P = .009), although differences in overall survival between the arms were not significant. 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 progression-free survival for patients with tumors characterized by mutated KRAS in the PRIME trial.

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, page 1267).

The Role of KRAS and BRAF Status: Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways, but EGFR status as assessed using immunohistochemistry is not predictive of treatment efficacy. 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.

Approximately 40% of colorectal cancers are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene. A sizable body of literature has shown that these KRAS mutations are predictive of lack of response to cetuximab or panitumumab therapy, and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of colorectal cancer characterized by these mutations. Results are mixed as far as the prognostic value of KRAS mutations, and the test is not recommended for prognostic reasons. A recent retrospective study from De Roock et al. raised the possibility that codon 13 mutations (G13D) may not be absolutely predictive of non-response. Another recent retrospective study showed similar results. However, as the article by De Roock et al. states, these findings are hypothesis-generating only, and prospective studies are needed to determine if patients with KRAS G13D mutations can, in fact, benefit from anti-EGFR therapy. Currently, use of anti-EGFR agents in patients whose tumors have G13D mutations remains investigational and is not endorsed by the panel for routine practice.

The panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer at diagnosis of stage IV disease. The recommendation for KRAS testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting, but rather this early establishment of KRAS status is appropriate to plan for the treatment continuum.
so that the information may be obtained in a non–time-sensitive manner, and the patient and provider can discuss the implications of a KRAS mutation, if present, while other treatment options still exist. Note that because anti-EGFR agents have no role in the management of stage I, II, or III disease, KRAS genotyping of colorectal cancers at these earlier stages is not recommended. KRAS mutations are early events in colorectal cancer formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.\(^{321-323}\) For this reason, KRAS genotyping can be performed on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of KRAS genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable. The panel recommends that KRAS gene testing be performed only in laboratories that are certified under the CLIA regulations of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.\(^{324}\) No specific testing methodology is recommended.\(^{325}\)

Although certain mutations of KRAS indicate a lack of response to EGFR inhibitors, many tumors containing wild-type KRAS still do not respond to these therapies. Therefore, studies have addressed factors downstream of KRAS as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of colorectal cancers are characterized by a specific mutation in the KRAS gene (V600E).\(^ {320,326}\) BRAF mutations are, for all practical purposes, limited to tumors that do not have KRAS exon 2 mutations.\(^ {326}\) Activation of the protein product of the nonmutated BRAF gene occurs downstream of the activated KRAS protein in the EGFR pathway; the mutated BRAF protein product is believed to be constitutively active,\(^ {327-329}\) thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

In fact, retrospective evidence exists that mutated BRAF is another marker of resistance to anti-EGFR therapy in the non–first-line setting of metastatic disease.\(^ {330-332}\) A retrospective study of 773 primary tumor samples from chemotherapy-refractory patients 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%; \(P = .0012\)).\(^ {333}\) However, data from unplanned retrospective subset analyses of patients with metastatic colorectal cancer treated in the first-line setting suggest that although a BRAF V600E mutation confers a poor prognosis regardless of treatment, patients with disease characterized by this mutation may receive some benefit from the addition of cetuximab to front-line therapy.\(^ {312,334}\) Overall, data strongly suggest that BRAF V600E mutations confer resistance to anti-EGFR therapy in the non–first-line setting, whereas some benefit may be derived from the addition of anti-EGFR agents to FOLFOX or FOLFIRI when given to patients with BRAF V600E mutations in the first-line metastatic setting.\(^ {281}\)

A recent prospective analysis of tissues from patients with stage II and III colon cancer enrolled in the PETACC-3 trial showed that the BRAF mutation is prognostic for overall survival in patients with MSI-L or MSS tumors (HR, 2.2; 95% CI, 1.4–3.4; \(P = \text{.0003}\)).\(^ {116}\) 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.\(^ {312}\) Additionally, BRAF mutation status predicted overall survival in the AGITG MAX trial, with an HR of 0.49 (CI, 0.33–0.73; \(P = .001\)).\(^ {335}\) For patients with KRAS wild-type tumors, the panel includes the option of BRAF genotyping of tumor tissue (either primary tumor or metastasis)\(^ {336}\) at diagnosis of KRAS wild-type stage IV disease. With respect to technical aspects of BRAF gene testing, the specific recommendations regarding tumor tissue sampling described earlier for KRAS gene testing apply. No specific testing methodology is recommended.

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.\(^ {216}\) A similar conclusion was drawn with respect to panitumumab.\(^ {337}\) Therefore, routine EGFR testing is not recommended, and no patient should be either considered for or excluded from cetuximab or panitumumab therapy based on EGFR test results.

**Therapy After Progression**

The latest version of this section of the guidelines manuscript can be found in the full NCCN Guidelines for Colon Cancer, available online, at www.NCCN.org.
Bevacizumab in the Non–First-Line Setting

With respect to the treatment continuum for metastatic colorectal cancer, no prospective data support the addition of bevacizumab to a regimen after clinical failure of a previous bevacizumab-containing regimen, and continuation of bevacizumab beyond disease progression is not recommended.

If bevacizumab is not used in initial therapy, it may be appropriate to consider adding it to chemotherapy after progression of metastatic disease. 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. Median overall survival was 12.9 months for patients receiving FOLFOX plus bevacizumab compared with 10.8 months in patients treated with FOLFOX alone (P = .0011). 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.

Cetuximab and Panitumumab in the Non–First-Line Setting

For patients with wild-type KRAS who experienced progression on therapies not containing an EGFR inhibitor, cetuximab plus irinotecan (category 2B), cetuximab or panitumumab plus FOLFIRI, or single-agent cetuximab or panitumumab is recommended. If the patient does not experience response to oxaliplatin, irinotecan, and an EGFR inhibitor, the panel recommends best supportive care or enrollment on a clinical trial.

Although no head-to-head studies have compared cetuximab and panitumumab, similar response rates have been observed when each agent was studied as monotherapy after progression. 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 metastatic colorectal cancer for patients with disease progression on oxaliplatin/irinotecan-based chemotherapy. In a retrospective analysis of the subset of patients in this trial with known KRAS tumor status, the benefit of panitumumab versus best supportive care was shown to be enhanced in patients with KRAS wild-type tumors. Progression-free survival was 12.3 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.

Panitumumab has also been studied as combination therapy in the setting of progressing metastatic colorectal cancer. Among patients with KRAS wild-type tumors enrolled in a large trial comparing FOLFIRI alone versus FOLFIRI plus panitumumab as second-line therapy for metastatic colorectal cancer, addition of the biologic agent was associated with improvement in median progression-free survival (5.9 vs. 3.9 months; HR, 0.73; 95% CI, 0.59–0.90; P = .004), although differences in overall survival between the arms did not reach statistical significance.

Cetuximab has been studied both as a single agent and in combination with irinotecan 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 overall survival but showed significant improvement in response rate and in median progression-free survival with irinotecan and cetuximab compared with irinotecan alone. Importantly, KRAS status was not determined in this study and toxicity was higher in the cetuximab-containing arm (e.g., rash, diarrhea, electrolyte imbalances).

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

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from large bowel (e.g., colorectal liver metastases) is suspected should include a total colonoscopy, CBC, chemistry profile, CEA determination, needle biopsy if indicated, and CT scan with intravenous contrast of the chest, abdomen, and pelvis. MRI with intravenous contrast...
should be considered if CT is inadequate. The panel also recommends tumor KRAS gene status testing at diagnosis of metastatic disease and consideration of BRAF genotyping for all patients with KRAS wild-type metastatic colon cancer (see The Role of KRAS and BRAF Status, page 1270).

The panel strongly discourages the routine use of PET/CT scanning for staging, baseline imaging, or routine follow-up, and recommends consideration of a preoperative PET/CT scan at baseline only 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. 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 (e.g., in the presence of necrotic lesions). False-positive PET/CT scan results can occur in the presence of tissue inflammation after surgery or infection. 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, available online, in these guidelines, at www.NCCN.org [MS-15]).

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 colorectal cancer and synchronous liver metastases, resection of the primary tumor and liver can be performed in a simultaneous or staged approach.

When the remnant liver is insufficient in size based on cross-sectional imaging volumetrics, preoperative portal vein embolization of the involved liver can be performed to expand the future liver remnant. Colorectal metastatic disease can also occur in the lung. Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases.

If a patient with resectable liver or lung metastases is a candidate for surgery, the panel recommends the following options: 1) colectomy and synchronous or subsequent liver (or lung) resection, followed by adjuvant chemotherapy (following the options for stage III adjuvant therapy, FOLFOX preferred); 2) neoadjuvant chemotherapy for 2 to 3 months (i.e., choice of FOLFIRI, FOLFOX, or CapeOx chemotherapy alone or with bevacizumab; FOLFIRI or FOLFIRI with panitumumab; or FOLFIRI with cetuximab), followed by synchronous or staged colectomy with liver or lung resection; or 3) colectomy followed by adjuvant chemotherapy (see neoadjuvant options discussed earlier) 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, HAI therapy 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, available online, in these guidelines, at www.NCCN.org [MS-15]) chemotherapy regimens with high response rates should be considered, and these patients should be reevaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing this therapy. If bevacizumab is included as a component of the conversion therapy, there should be at least a 6-week interval between the last dose of bevacizumab and surgery, with a 6- to 8-week postoperative period before reinitiation 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 duration of 6 months. Recommended options for adjuvant therapy for these patients include active chemotherapy regimens for advanced or metastatic disease (category 2B); 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, HAI therapy 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.

Patients with potentially convertible metastatic disease that is not responding to therapy should receive chemotherapy 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, available online, in these guidelines, at www.NCCN.org [MS-15]), the panel recommends chemotherapy corresponding to initial therapy for metastatic disease (e.g., choice of FOLFIRI, FOLFOX, or CapeOx chemotherapy alone or with bevacizumab; or FOLFIRI or FOLFOX with panitumumab; FOLFIRI with cetuximab; or FOLFOXIRI alone [category 2B]).

Primary treatment of unresectable synchronous liver or lung metastases with palliative colon resection should be considered only if the patient has an unequivocal imminent risk of obstruction or acute significant bleeding. Notably, symptomatic improvement in the primary is often seen with systemic chemotherapy even within the first 1 to 2 weeks, and routine palliative resection of a synchronous primary lesion should not be routinely performed in the absence of overt obstruction. Complications from the intact primary lesion are uncommon in these circumstances, and its removal delays initiation of systemic chemotherapy. 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.

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 Principles of the Management of Metastatic Disease, page 1261). The panel did not reach consensus regarding the use of liver-directed therapies, such as arterial radioembolization therapy and conformal external radiation therapy (see discussion in Principles of the Management of Metastatic Disease, page 1261).

**Synchronous Abdominal/Peritoneal Metastases:**
For patients with peritoneal metastases causing obstruction or that are believed may cause obstruction, palliative surgical options include colon resection, diverting colostomy, a bypass of impending obstruction, or stenting, followed by chemotherapy for advanced or metastatic disease.

The primary treatment of patients with non-obstructing metastases is chemotherapy. The panel currently considers the treatment of disseminated carcinomatosis with cytoreductive surgery (i.e., peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy to be investigational and does not endorse this therapy outside of a clinical trial. However, the panel recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities.

**Workup and Management of Metachronous Metastatic Disease**
Routine use of PET/CT to monitor for disease recurrence is not recommended. The CT that accompanies a PET/CT is usually a noncontrast CT, and therefore not of ideal quality for routine staging. 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. 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. Specifically, Joyce et al. reported that the preoperative PET changed or precluded curative-intent liver resection in 25% of patients.

As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) for KRAS genotype should be performed to define whether anti-EGFR agents can be considered among the list of potential options.
Although BRAF genotyping can be considered for patients with tumors characterized by the wild-type KRAS gene, this testing is currently optional and not a necessary part of deciding whether to use anti-EGFR agents (see The Role of KRAS and BRAF Status, page 1270). 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 including an evaluation of the chemotherapy history of the patient and 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, primary treatment options include initial resection with 6 months of perioperative chemotherapy (postoperative or a combination of pre- and postoperative).

Patients determined to have unresectable disease through cross-sectional imaging scan (including those considered potentially convertible) should receive an active chemotherapy regimen based on prior chemotherapy history (see Therapy After Progression, available online, in these guidelines, at www.NCCN.org [MS-27]). In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) is an option at centers with experience in the surgical and medical oncologic aspects of this procedure. Patients receiving palliative chemotherapy should be monitored with CT or MRI scans approximately every 2 to 3 months.

**Posttreatment Surveillance**

After curative-intent surgery and adjuvant chemotherapy, if administered, posttreatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and identify new metachronous neoplasms at a preinvasive stage. Advantages of more-intensive follow-up of patients with stage II and/or III disease have been shown prospectively in several studies and in 3 recent meta-analyses of randomized controlled trials designed to compare low- and high-intensity programs of surveillance. Other recent studies impacting the issue of posttreatment surveillance of colorectal cancer include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials that showed that 80% of recurrences occurred in the first 3 years after surgical resection of the primary tumor. Intensive postoperative surveillance has also been shown to benefit patients with stage I and IIA disease. Furthermore, a population-based report indicates increased rates of resectability and survival in patients treated for local recurrence and distant metastases of colorectal cancer in more recent years, thereby providing support for more intensive posttreatment follow-up in these patients. Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.

The following panel recommendations for posttreatment surveillance pertain to patients with stage I through III disease who have undergone successful treatment (i.e., 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 is recommended at baseline and every 3 to 6 months for 2 years, then every 6 months for a total of 5 years for patients with stage III disease, and those with stage I/II disease with T2 or greater lesions if the clinician determines that the patient is a potential candidate for aggressive curative surgery. 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. More frequent colonoscopies may be indicated in patients who present with colon cancer before 50 years of age. Chest, abdominal, and pelvic CT scans are recommended annually for the first 3 to 5 years in patients with stage III disease and those with stage II disease at a high risk for recurrence. Routine CEA monitoring and CT scanning are not recommended beyond 5 years. Routine PET/CT scanning is not recommended and should not be obtained either as a routine preoperative baseline study or for routine surveillance.
Initial follow-up office visits at 3-month intervals for history and physical examination may be more useful in patients diagnosed with stage III disease, whereas patients diagnosed with stage I disease may not need to be seen as frequently (i.e., once every 6 months). This principle also applies to CEA testing, which is used primarily to monitor for indication of recurrence of disease (see Managing an Increasing CEA Level, page 1276), although post-treatment CEA testing is recommended only if the patient is a potential candidate for further intervention. Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps, because data show that patients with a history of colorectal cancer have an increased risk of developing second cancers, particularly in the first 2 years after resection. Furthermore, use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original colorectal cancer. The recommended frequency of posttreatment surveillance colonoscopies is higher (i.e., annually) for patients with HNPCC. CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and liver. Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases. Posttreatment PET/CT scan is not routinely recommended for surveillance of patients with resected early-stage colorectal cancer. Furthermore, PET/CT scan is not routinely recommended to detect metastatic disease in the absence of other evidence of this disease.

Panel recommendations for surveillance of patients with stage IV colorectal cancer with no evidence of disease (NED) after curative-intent surgery and subsequent adjuvant treatment are similar to those listed for patients with early-stage 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, and then every 6 to 12 months for up to a total of 5 years, and CEA testing is recommended every 3 months for the first 2 years and then every 6 months in the following 3 to 5 years. Again, routine use of PET/CT scans for surveillance is not recommended.

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. Panel opinion was divided on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans (i.e., 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). 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, nor do they recommend use of anti–CEA-radiolabeled scintigraphy.

Survivorship
Posttreatment surveillance for all patients also includes a survivorship care plan involving disease-preventive measures, such as immunizations; early disease detection through periodic screening for second primary cancers (e.g., breast, cervical, or prostate cancers); and routine good medical care and monitoring. Other recommendations include monitoring for late sequelae of colon cancer or the treatment of colon cancer, such as chronic diarrhea or incontinence (e.g., patients with stoma). Specific management interventions to address these and other side effects are described in a recent review, and a survivorship care plan for patients with colorectal cancer was recently published. 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.

Evidence also indicates that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy body mass index (BMI), engaging in regular exercise, and making certain dietary choices, are associated with improved outcomes after treatment. For example, a retrospective study of patients...
with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI of 35 kg/m² or greater had an increased risk of disease recurrence and death.³³⁰ In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, disease-free survival was found to be directly correlated with how much exercise these patients received.³³¹ Furthermore, a diet consisting of more fruits, vegetables, poultry, and fish, and less red meat, and higher in whole grains and lower in refined grains and concentrated sweets, was found to be associated with an improved outcome in terms of cancer recurrence or death.³³² In addition, a recent study of a large cohort of men treated for stage I through III colorectal cancer showed an association between increased physical activity and lower rates of colorectal cancer–specific mortality and overall mortality.³³³ 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,³³⁴ 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.

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written if the primary physician will be assuming cancer surveillance responsibilities.³³⁵ The prescription should include an overall summary of treatments received, including surgeries, radiation treatments, and chemotherapy. The possible clinical course should be described, including the expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment. Surveillance recommendations should be included, as should a delineation of the appropriate timing of transfer of care with specific responsibilities identified for the primary care physician and the oncologist.

Summary

The panel believes that a multidisciplinary approach is necessary for managing colorectal cancer. 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 therapy with FOLFOX (category 1, preferred), FLOX (category 1), CapeOx (category 1), 5-FU/LV (category 2A), or capecitabine (category 2A) is recommended by the panel for patients with stage III disease. Adjuvant therapy for patients with high-risk stage II disease is also an option; the panel recommends 5-FU/LV with or without oxaliplatin (FOLFOX or FLOX) or capecitabine with or without oxaliplatin (category 2A for all treatment options). 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. Preoperative chemotherapy can be considered as initial therapy in 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 (i.e., conversion therapy), this therapy should be initiated. Adjuvant chemotherapy should be considered after resection of liver or lung metastases.

The recommended posttreatment surveillance program includes serial CEA determinations and 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 preplanned 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 (category 2B). Addition of a biologic agent (e.g., bevacizumab, cetuximab, panitumumab) is either recommended or listed as an option in combination with some of these regimens, depending on available data. Chemotherapy options for patients with progressive disease depend on the choice of initial therapy.
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