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### Colon Cancer

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<tr>
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<th><strong>Institution</strong></th>
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<tbody>
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<td>Marwan G. Fakih, MD †</td>
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### Colon Cancer Table of Contents

**NCCN Colon Cancer Panel Members**

**Summary of the Guidelines Updates**

**Clinical Presentations and Primary Treatment:**

- Pedunculated polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer (COL-1)
- Sessile polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer (COL-1)
- Colon cancer appropriate for resection (COL-2)
- Suspected or proven metastatic adenocarcinoma (COL-5)

**Pathologic Stage, Adjuvant Therapy and Surveillance (COL-3)**

**Recurrence and Workup (COL-9)**

**Principles of Pathologic Review (COL-A)**

**Principles of Surgery (COL-B)**

**Chemotherapy for Advanced or Metastatic Disease (COL-C)**

**Principles of Risk Assessment for Stage II Disease (COL-D)**

**Principles of Adjuvant Therapy (COL-E)**

**Principles of Radiation Therapy (COL-F)**

**Principles of Survivorship (COL-G)**

**Staging (ST-1)**

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Summary of changes in the 3.2012 version of the Colon Guidelines from the 2.2012 version include:

**COL-C 6 of 7**
- Capecitabine + bevacizumab: dose and schedule for bevacizumab changed from 5 mg/kg IV weekly to 7.5 mg/kg IV every 3 weeks.

**COL-C 4 of 7, COL-C 6 of 7, COL-C 7 of 7**

Summary of changes in the 2.2012 version of the Colon Guidelines from the 1.2012 version include:

**COL-C 1 of 7**
- The recommendation of cetuximab (KRAS WT only) + irinotecan after progression on first-line FOLFOX ± bevacizumab or CapeOx ± bevacizumab was changed from a category 2B to a category 2A.
- Panitumumab (KRAS WT only) + irinotecan (category 2A) added as an alternate treatment option to cetuximab + irinotecan in advanced or metastatic disease after progression on first- or second-line therapy.

Summary of changes in the 1.2012 version of the Colon Guidelines from the 2.2011 version include:

**COL-1**
- Footnote “a” modified and the following sentence added: Peritoneal mesothelioma and other extrapleural mesotheliomas may be treated with systemic therapy along NCCN guidelines for pleural mesothelioma, as outlined on page MPM-A.
- Footnote “b” modified by adding the consideration of risk assessment. (also applies to other pages)
- Footnote “f” modified, “Observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than polypoid malignant polyps. See Principles of Pathologic Review (COL-A) - Endoscopically removed malignant polyp.

**COL-2**
- Locally unresectable or medically inoperable: Palliative therapy removed along with previous footnote “i”.

**COL-3**
- T3, N0, M0 at high risk for recurrence or T4, N0, M0: The combination regimen of capecitabine + oxaliplatin was added as an option in adjuvant therapy with a category 2A designation.
- Footnote “j” was clarified by adding “exclusive of those cancers that are MSI-H” to grade 3-4.
- Chest/abdominal/pelvic CT recommendation during surveillance changed from 3 y to 3-5 y for patients at high risk for recurrence.

**COL-4**
- The category designation for CapeOx changed from a category 2A to a category 1.

**COL-6**
- FOLFOX + cetuximab removed as a treatment option.
- Adjuvant therapy recommendations following colectomy, with synchronous or staged liver or lung resection: Active chemotherapy regimen for advanced disease (COL-C) changed to adjuvant therapy for stage III disease (COL-4).

**COL-7**
- FOLFOX + cetuximab removed as a treatment option.

**COL-10**
- Response changed to “No progression” and No response changed to “Progression”.
- Adjuvant therapy recommendations following resection and no previous chemotherapy: Active chemotherapy regimen for advanced disease (COL-C) changed to adjuvant therapy for stage III disease (COL-4).

**COL-A 4 of 5**
- BRAF Testing, second bullet: The following sentence was added: Allele-specific PCR is another acceptable method for detecting BRAF V600E mutation.

**COL-B 1 of 3**
- Sub-bullet 2 clarified: Clinically positive lymph nodes outside the field of resection considered suspicious should be biopsied or removed, if possible.
Summary of changes in the 1.2012 version of the Colon Guidelines from the 3.2011 version include:

**COL-C 1 of 7**
- Patient appropriate for intensive therapy: FOLFOX + cetuximab removed as a treatment option for initial therapy of advanced or metastatic disease.

**COL-C 2 of 7**
- Patient not appropriate for intensive therapy: Capecitabine ± bevacizumab added as a treatment option for initial therapy of advanced or metastatic disease.

**COL-C 4 of 7 through COL-C 7 of 7**
- Chemotherapy regimen dosing and references expanded and updated.

**COL-D**
- The following bullet removed: “Ask the patient how much information they would like to know regarding prognosis”
- Prognosis added to patient/physician discussion in the first bullet.
- Perineural invasion added as a poor prognostic feature (sub-bullet 2) in the second bullet describing considerations for adjuvant therapy.

**COL-E 1 of 2**
- Bullet 1: Second sentence removed, “This is an extrapolation from data available.”

**COL-F**
- Bullet 3 modified: Conformal external beam radiation should be routinely used for T4 non-metastatic disease and intensity modulated radiotherapy (IMRT) reserved only for unique clinical situations including re-irradiation of previously treated patients with recurrent disease.
- Bullet 4 modified: 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-fluorouracil based chemotherapy is preferred 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. The ending of “prior to adjuvant chemotherapy” removed.

**COL-G**
- Cancer Surveillance. Previous bullets deleted and the following added:
  - See COL-3 and COL-4.
  - 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 is not recommended beyond 5 years.
- Management of Late Sequelae of Disease or Treatment: The recommendations for Oxaliplatin-induced Neuropathy deleted.
- Cancer Screening Recommendations. Previous bullets deleted and the following added:
  - These recommendations are for average risk patients.
  - Recommendations for high risk individuals should be made on an individual basis.
  - Breast Cancer: See the NCCN Breast Cancer Screening Guidelines
  - Cervical Cancer: See the NCCN Cervical Cancer Screening Guidelines
  - Prostate Cancer: See the NCCN Prostate Early Detection Guidelines
- Counseling Regarding Healthy Lifestyle and Wellness. Previous bullets deleted and the following added:
  - Maintain a healthy body weight throughout life.
  - Adopt a physically active lifestyle (At least 30 minutes of moderate intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (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 primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.
## Clinical Presentation

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>WORKUP</th>
<th>FINDINGS</th>
<th>SURGERY</th>
</tr>
</thead>
</table>
| Pedunculated or sessile polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer | • Pathology review<sup>c,d</sup>  
• Colonoscopy  
• Marking of cancerous polyp site (at time of colonoscopy or within 2 wks) | Single specimen, completely removed with favorable histological features<sup>e</sup> and clear margins | Pedunculated polyp with invasive cancer | Observe |
| Fragmented specimen or margin cannot be assessed or unfavorable histological features<sup>e</sup> | Sessile polyp with invasive cancer | Observe<sup>f</sup> or Colectomy<sup>g</sup> with en bloc removal of regional lymph nodes |

### Discussion

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

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

- **Small bowel and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to the NCCN Colon Cancer Guidelines.** Peritoneal mesothelioma and other extrapleural mesotheliomas may be treated with systemic therapy along NCCN guidelines for pleural mesothelioma, as outlined on page [MPM-A](#).

- **All patients with colon cancer should be counseled for family history and considered for risk assessment.** Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP, see the [NCCN Colorectal Cancer Screening Guidelines](#).

- **Confirm the presence of invasive cancer (pT1).** pTis has no biological potential to metastasize.

- **It has not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis.** College of American Pathologists Consensus Statement 1999. Prognostic factors in colorectal cancer. Arch Pathol Lab Med 2000;124:979-994.

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

- **See [Principles of Pathologic Review (COL-A)](#) - Endoscopically removed malignant polyp.**

- **See [Principles of Surgery (COL-B 1 of 3)](#).**
Colon Cancer

CLINICAL PRESENTATION

WORKUP

FINDINGS

SURGERY

Resectable, nonobstructing

Resectable, obstructing

Locally unresectable or medically inoperable

Colectomy with en bloc removal of regional lymph nodes

One-stage colectomy with en bloc removal of regional lymph nodes or Resection with diversion or Stent or Diversion

Colectomy with en bloc removal of regional lymph nodes

Suspected or proven metastatic adenocarcinoma

See Management of suspected or proven metastases (COL-5)

Colon cancer appropriate for resection (non metastatic)

- Pathology review
- Colonoscopy
- CBC, platelets, chemistry profile, CEA
- Chest/abdominal/pelvic CT
- PET-CT scan is not routinely indicated

Notes:

Small bowel and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to the NCCN Colon Cancer Guidelines. Peritoneal mesothelioma and other extrapleural mesotheliomas may be treated with systemic therapy along NCCN guidelines for pleural mesothelioma, as outlined on page MPM-A.

All patients with colon cancer should be counseled for family history and considered for risk assessment. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP, see the NCCN Colorectal Cancer Screening Guidelines.

See Principles of Pathologic Review (COL-A) - Colon cancer appropriate for resection, pathological stage, and lymph node evaluation.

See Principles of Surgery (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.

See Pathologic Stage, Adjuvant Therapy, and Surveillance (COL-3)

See Chemotherapy for Advanced or Metastatic Disease (COL-C)
## Colon Cancer

### Pathologic Stage

<table>
<thead>
<tr>
<th>Tis; T1, N0, M0; T2, N0, M0</th>
<th>Adjuvant Therapy</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Clinical trial or Observation</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 (no high risk features)</td>
<td>Consider capcitabine or 5-FU/leucovorin</td>
<td>Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo</td>
</tr>
<tr>
<td>T3, N0, M0 at high risk for systemic recurrence or T4, N0, M0</td>
<td>5-FU/leucovorin ± oxaliplatin or Capecitabine ± oxaliplatin</td>
<td>PET-CT scan is not routinely recommended</td>
</tr>
</tbody>
</table>

### Discussion

- **ADJUVANT THERAPY**
  - Tis; T1, N0, M0; T2, N0, M0: None
  - T3, N0, M0 (no high risk features): Consider capcitabine or 5-FU/leucovorin
  - T3, N0, M0 at high risk for systemic recurrence or T4, N0, M0: 5-FU/leucovorin ± oxaliplatin or Capecitabine ± oxaliplatin

- **SURVEILLANCE**
  - History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
  - Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo
  - PET-CT scan is not routinely recommended

### Notes
- All patients with colon cancer should be counseled for family history and considered for risk assessment. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP should be referred to a genetic counselor.
- 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.
- Testing for mismatch repair proteins (MMR) should be considered for all patients < 50 years of age. 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.
- Grade 3-4 diarrhea is considerably higher with FLOX than FOLFOX in cross study comparison.
- If patient is a potential candidate for further intervention.
- CT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor, or poorly differentiated tumors).
- There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.

### Additional Resources
- [See Principles of Pathologic Review (COL-A) - Pathological stage.](#)
- [See Principles of Adjuvant Therapy (COL-E).](#)
- [See Principles of Risk Assessment for Stage II Disease (COL-D).](#)
- [Principles of Survivorship (COL-G).](#)
### Pathologic Stage

| T1-3, N1-2, M0 | T4, N1-2, M0 |

#### Adjuvant Therapy

- **FOLFOX** (category 1) preferred
- Other options include:
  - FLOX (category 1)
  - CapeOx (category 1)
  - Capecitabine
  - 5-FU/leucovorin

#### Surveillance

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/abdominal/pelvic CT annually for 3-5 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
- PET-CT scan is not routinely recommended
- See Principles of Survivorship (COL-G)

### Notes

- If patient is a potential candidate for further intervention.
- Villous polyp, polyp > 1 cm, or high grade dysplasia.
- Testing for mismatch repair proteins (MMR) should be considered for all patients < 50 years of age.
- Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy COL-F.

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**Colon Cancer Table of Contents**

**Discussion**

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

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

WORKUP FINDINGS

<table>
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<tr>
<th>Findings</th>
<th>Action</th>
</tr>
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<td>Synchronous liver only and/or lung only metastases</td>
<td>Resectable → See Treatment and Adjuvant Therapy (COL-6)</td>
</tr>
<tr>
<td>Synchronous abdominal/peritoneal metastases</td>
<td>Unresectable (potentially convertible or unconvertible) → See Treatment and Adjuvant Therapy (COL-7)</td>
</tr>
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</table>

\[6\] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.
\[7\] See Principles of Surgery (COL-B 2 of 3).
\[\] CT should be with IV contrast. Consider MRI with IV contrast if CT is inadequate.
TREATMENT
Resectable synchronous liver and/or lung metastases only

Colectomy, with synchronous or staged liver or lung resection or Neoadjuvant therapy (for 2-3 months)
FOLFIRI or FOLFOX or CapeOx ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± cetuximab (KRAS wild-type [WT] gene only) followed by synchronous or staged colectomy and resection of metastatic disease or Colectomy, followed by chemotherapy (for 2-3 months)
FOLFIRI or FOLFOX or CapeOx ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± cetuximab (KRAS WT gene only) and staged resection of metastatic disease

ADJUVANT THERAPY
(resected metastatic disease)

SURVEILLANCE
(6 MO PERIOPERATIVE TREATMENT PREFERRED)

See adjuvant therapy for stage III disease on COL-4

If patient stage IV, NED:
- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA every 3-6 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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
TREATMENT
Unresectable synchronous liver and/or lung metastases only

- Systemic therapy (FOLFIRI or FOLFOX or CapeOX ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± cetuximab (KRAS WT gene only))
- Consider colon resection only if imminent risk of obstruction or significant bleeding

ADJUVANT THERAPY
(6 MO PERIOPERATIVE TREATMENT PREFERRED)

- Active chemotherapy regimen for advanced disease (See COL-C)
- Synchronized or staged resection of colon and metastatic cancer
- If patient received neoadjuvant therapy, consider observation or shortened course of chemotherapy

SURVEILLANCE

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA every 3-6 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

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The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large scale randomized trials.

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 re-initiation of bevacizumab at least 6-8 weeks postoperatively. There is an increased risk of stroke and other arterial events especially in age ≥ 65. The use of bevacizumab may interfere with wound healing.

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.

See Recurrence (COL-9)
**FINDINGS PRIMARY TREATMENT**

- **Nonobstructing**
  - **Synchronous abdominal/peritoneal metastases**
    - **Obstructed or imminent obstruction**
      - Colon resection or Diverting colostomy or Bypass of impending obstruction or Stenting
      - See Chemotherapy for Advanced or Metastatic Disease (COL-C)

- **Obstructed or imminent obstruction**
  - See Chemotherapy for Advanced or Metastatic Disease (COL-C)

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

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**Aggressive cytoreductive debulking and/or intraperitoneal chemotherapy are not recommended outside the setting of a clinical trial.**

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*See Principles of Surgery (COL-B 2 of 3).*
**Discussion**

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**NCCN Guidelines Version 3.2012**

**Colon Cancer**

**RECURRENCE**

**WORKUP**

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Serial CEA elevation

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

**Negative findings**

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

**Positive findings**

- See treatment for Documented metachronous metastases, below

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Documented metachronous metastases by CT, MRI and/or biopsy

- Resectable
- Consider PET-CT scan

**Resectable**

- See Primary Treatment COL-10

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Unresectable (potentially convertible or unconvertible)

- See Primary Treatment COL-11

---

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

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**See Principles of Surgery (COL-B 2 of 3).**

**ee** Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.

**ff** Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.
RESECTABLE
METACHRONOUS METASTASES

No previous chemotherapy

Resection

See adjuvant therapy for stage III disease on COL-4

or

Neoadjuvant chemotherapy (2-3 mo) (See COL-C)

Resection

No progression

Repeat neoadjuvant therapy or FOLFOX

Progression

Active chemotherapy regimen (See COL-C) or Observation

Previous chemotherapy

Resection (See COL-C)

or Observation

Active chemotherapy regimen (See COL-C) or Observation

No progression

Repeat neoadjuvant therapy or FOLFOX

Progression

Active chemotherapy regimen (See COL-C) or Observation

cc 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.

gg Perioperative therapy should be considered for up to a total of 6 months.

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

### Discussion

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

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

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### UNRESECTABLE METACHRONOUS METASTASES

<table>
<thead>
<tr>
<th>Previous adjuvant FOLFOX within past 12 months</th>
<th>FOLFIRI ± bevacizumab or FOLFIRI ± cetuximab or panitumumab (KRAS WT gene only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous adjuvant FOLFOX &gt; 12 months</td>
<td>Active chemotherapy regimen (See COL-C)</td>
</tr>
<tr>
<td>Previous 5-FU/LV or capecitabine</td>
<td>Re-evaluate for conversion to resectable every 2 mo if conversion to resectability is a reasonable goal</td>
</tr>
<tr>
<td>No previous chemotherapy</td>
<td>HCC 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</td>
</tr>
</tbody>
</table>

- **Active chemotherapy regimen**

See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.

See Principles of Surgery (COL-B 2 of 3).

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.

**Perioperative therapy should be considered for up to a total of 6 months.**

**Patients with a V600E BRAF 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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**Active chemotherapy regimen** (See COL-C) or Observation

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**Active chemotherapy regimen** (See COL-C)

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**Active chemotherapy regimen** (See COL-C)

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**Active chemotherapy regimen** (See COL-C)

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**Active chemotherapy regimen** (See COL-C)

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**Active chemotherapy regimen** (See COL-C)

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**Active chemotherapy regimen** (See COL-C)

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**Active chemotherapy regimen** (See COL-C)
PRINCIPLES OF PATHOLOGIC REVIEW (1 of 5)

Endoscopically removed malignant polyps

- A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTis is not considered a “malignant polyp.”
- Favorable histological features: grade 1 or 2, no angiolymphatic invasion and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as 1) tumor < 1 mm from the transected margin, 2) tumor < 2 mm from the transected margin, 3) tumor cells present within the diathermy of the transected margin.1-4
- Unfavorable histological features: grade 3 or 4, or angiolymphatic invasion, or a “positive margin.” - see positive margin definition above.
- There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated by endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than do polypoid malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable for adverse outcome and endoscopically removed malignant sessile polyps with grade I or II histology, negative margin, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.3-7

Colon cancer appropriate for resection
- Histological confirmation of primary colonic malignant neoplasm.

Pathological stage
- The following parameters should be reported.
  - Grade of the cancer
  - Depth of penetration, (T)
  - Number of lymph nodes evaluated and number positive (N)
  - Status of proximal, distal, and radial margins8-9 See Staging (ST-1)
  - Lymphovascular invasion10,11
  - Perineural invasion12-14
  - Extra Nodal tumor deposits15-18

See Pathological stage (continued) on page 2 of 5 COL-A
See Lymph node evaluation on page 3 of 5 COL-A
See KRAS and BRAF Mutation Testing page 4 of 5 COL-A

Note: All recommendations are category 2A unless otherwise indicated.
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See references on page 5 of 5 COL-A
Pathological stage (continued)

- Radial (circumferential) margin evaluation - The serosal surface (peritoneal) does not constitute a surgical margin. In colon cancer the circumferential (radial) margin represents the adventitial soft tissue closest to the deepest penetration of tumor and is created surgically by blunt or sharp dissection of the retroperitoneal aspect. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. The circumferential resection margin corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells and must be dissected from the retroperitoneum to remove the vissus. On pathological examination it is difficult to appreciate the demarcation between peritonealized surface and non-peritonealized surface. Therefore the surgeon is encouraged to mark the area of non-peritonealized surface with a clip or suture. The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by peritoneum.

- Perineural invasion (PNI) - The presence of perineural invasion is associated with a significantly worse prognosis. In multivariate analysis, PNI has been shown to be an independent prognostic factor for cancer specific and overall disease-free survival. For stage II carcinoma, those with PNI have a significantly worse 5 year disease-free survival compared to those without PNI 29% vs 82% (p=0.0005).

- Extra nodal tumor deposits - Irregular discrete tumor deposits in pericolic or perirectal fat from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered peritumoral deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular or, more rarely, perineural invasion. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report.

In the 7th AJCC staging manual, extra nodal deposits are staged as pN1c. In stage II colon cancer, the presence of extranodal tumor deposits significantly worsens the 5 year disease-free survival 80% vs 50-60% (p<0.01). This poorer outcome has also been noted in patients with stage III carcinoma.
Lymph node evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancers.\(^8\,9\,19\) The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, >30.\(^20\,\text{28}\) The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade and tumor site.\(^\text{21}\) For stage II (pN0) colon cancer, if less than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The pathologist should attempt to retrieve as many lymph nodes as possible. It has been shown that the number of negative lymph nodes is an independent prognostic factor for patients with stage IIIB and IIIC colon cancer.\(^\text{29}\)

Sentinel lymph node and detection of micrometastasis by immunohistochemistry

- Examination of the sentinel lymph node allows an intense histological and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple H & E sections and/or immunohistochemistry (IHC) to detect cytokeratin positive cells.\(^\text{30\text{-}34}\) The significance of detection of single cells by IHC alone is controversial. The 7th edition of the AJCC Cancer Staging\(^\text{35}\) manual considers "tumor clusters" < 0.2 mm as isolated tumor cells (pN0) and not metastatic carcinoma. However, some investigators believe that size should not affect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.\(^\text{36}\)

- Some studies have shown that the detection of IHC cytokeratin positive cells in stage II (N0) colon cancer (defined by H & E) has a worse prognostic value than others have failed to show this survival difference. In these studies, isolated tumor cells were considered micrometastasis.\(^\text{38\text{-}42}\)

- At the present time the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and results used with caution in clinical management decisions.\(^\text{30\text{-}34,38\text{-}42}\)
PRINCIPLES OF PATHOLOGIC REVIEW (4 of 5)

KRAS Mutation Testing
- Mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to therapy with antibodies targeted to the epidermal growth factor receptor.\(^{43,44}\)
- Testing for mutations in codons 12 and 13 should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform high complex clinical laboratory (molecular pathology) testing. No specific methodology is recommended (sequencing, hybridization, etc.).
- The testing can be performed on formalin fixed paraffin embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis as literature has shown that the KRAS mutations are similar in both specimen types.\(^{45}\)

BRAF Mutation Testing
- Patients with a V600E BRAF 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. 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.\(^{46,47}\)
- Testing for the BRAF V600E mutation can be performed on formalin fixed paraffin embedded tissues. This is usually performed by PCR amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting BRAF V600E mutation. This testing should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) and qualified to perform highly complex clinical laboratory (molecular pathology) testing.
PRINCIPLES OF PATHOLOGIC REVIEW - References (5 of 5)


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Colectomy

- Lymphadenectomy
  - Lymph nodes at the origin of feeding vessel should be identified for pathologic exam.
  - Clinically positive lymph nodes outside the field of resection considered suspicious should be biopsied or removed, if possible.
  - Positive nodes left behind indicate an incomplete (R2) resection.
  - A minimum of 12 lymph nodes need to be examined to establish N stage.

- Laparoscopic-assisted colectomy may be considered based upon the following criteria:
  - Surgeon with experience performing laparoscopically-assisted colorectal operations.
  - No disease in rectum or prohibitive abdominal adhesions.
  - No locally advanced disease.
  - Not indicated for acute bowel obstruction or perforation from cancer.
  - Thorough abdominal exploration is required.
  - Consider preoperative marking of small lesions.

- Management of patients with carrier status of known HNPCC
  - Consider more extensive colectomy for patients with a strong family history of colon cancer or young age (< 50 y).

See NCCN Colorectal Cancer Screening Guidelines

- Resection needs to be complete to be considered curative.

See Criteria for Resectability of Metastases and Locoregional Therapies within Surgery on page 2 of 3 COL-B

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See footnotes on page 3 of 3 COL-B
Liver
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.\(^6\)
- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of adequate hepatic function is required.\(^7\)
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.\(^8-11\) Plan for a debulking resection (less than an R0 resection) is not recommended.\(^7\)
- Patients with resectable metastatic disease and primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.\(^12\)
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization\(^13\) or staged liver resection\(^14\) can be considered.
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Some institutions use arterially-directed embolic therapy in highly select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, with predominant hepatic metastases (category 3).
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable (category 3).
- Re-resection can be considered in selected patients.\(^15\)

Lung
- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.\(^16-19\)
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.\(^20-23\)
- Re-resection can be considered in selected patients.\(^24\)
- Ablative techniques can be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable (category 3).

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

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CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE: 

**Initial therapy**

- **FOLFOX³ ± bevacizumab or CapeOX⁴ ± bevacizumab⁵,⁶**
  - or **FOLFOX³ ± panitumumab⁶,⁷ (KRAS wild-type [WT] gene only)⁸,⁹**
  - or **FOLFIRI¹⁰ + bevacizumab⁵,⁶**
  - or **FOLFIRI¹⁰ ± cetuximab or panitumumab⁶,⁷ (KRAS WT gene only)⁸,⁹**
  - or **5-FU/leucovorin¹¹ or Capecitabine¹² ± bevacizumab⁵,⁶,¹³**
  - or **FOLFOXIRI¹⁴ (category 2B)**

**Therapy after First Progression**

- **FOLFIRI⁵,¹⁰**
  - or **Irinotecan¹⁰**
  - or **FOLFIRI + (cetuximab or panitumumab)⁶,¹⁵-¹⁸ (KRAS WT gene only)⁸**
  - or **(Cetuximab or panitumumab)⁶,¹⁵-¹⁸ (KRAS WT gene only)⁸ + irinotecan¹⁰**
  - or **FOLFOX³ or CapeOX⁴,⁵ (Cetuximab or panitumumab)⁶,¹⁵-¹⁸ (KRAS WT gene only)⁸ + irinotecan¹⁰**

**Therapy after Second Progression**

- **Clinical trial or best supportive care¹⁹**
  - or **(Cetuximab or panitumumab)⁶,¹⁵-¹⁸ (KRAS WT gene only)⁸ + irinotecan¹⁰**
  - or **patients not able to tolerate combination, consider single agent (cetuximab or panitumumab)⁶,¹⁵-¹⁸ (KRAS WT gene only)⁸**
  - or **FOLFOX³ or CapeOX⁴ (Cetuximab or panitumumab)⁶,¹⁵-¹⁸ (KRAS WT gene only)⁸ + irinotecan¹⁰**
  - or **patients not able to tolerate combination, consider single agent (cetuximab or panitumumab)⁶,¹⁵-¹⁸ (KRAS WT gene only)⁸**
  - or **Irinotecan¹⁰ (KRAS WT gene only)⁸ + irinotecan¹⁰**
  - or **patients not able to tolerate combination, consider single agent (cetuximab or panitumumab)⁶,¹⁵-¹⁸ (KRAS WT gene only)⁸**

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CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 2 of 7)

**Initial therapy**

- **Patient not appropriate for intensive therapy²**
  - Infusional 5-FU + leucovorin or Capecitabine ± bevacizumab
  - or Cetuximab (KRAS wild-type gene only)⁸,⁹ (category 2B)
  - or Panitumumab (KRAS wild-type gene only)⁸,⁹ (category 2B)

**Therapy after First Progression**

- Improvement in functional status
  - Consider Initial Therapy as COL-C 1 of 7²⁰
- No improvement in functional status
  - Best supportive care
    - See NCCN Palliative Care Guidelines

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See footnotes on page COL-C 3 of 7
CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 3 of 7)

1 For chemotherapy references, see Chemotherapy Regimens and References (COL-C pages 4 - 7).

2 PET-CT should not be used to monitor progress of therapy. CT with contrast or MRI is recommended.

3 Discontinuation of oxaliplatin should be strongly considered from FOLFOX or CapeOX after 3-4 months of therapy (or sooner 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. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer - A GERCOR Study. J Clin Oncol 2008;24:394-400. There are insufficient data to support the routine use of Ca/Mg infusion to prevent oxaliplatin-related neurotoxicity.

4 The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1250 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Some data suggest that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. 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.

5 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 age ≥ 65. The use of bevacizumab may interfere with wound healing.


7 If cetuximab or panitumumab are used as initial therapy, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy.

8 See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.

9 Patients with a V600E BRAF 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.

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

11 Infusional 5-FU is preferred.

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

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

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

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

16 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.

17 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.

18 Patients with a V600E BRAF 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.

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

20 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.

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 4 of 7)

**FOLFOX**

**mFOLFOX 6**

- Oxaliplatin 85 mg/m² IV over 2 hours, day 1
- Leucovorin* 400 mg/m² IV over 2 hours, day 1
- 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)† IV continuous infusion
- Repeat every 2 weeks

**mFOLFOX6 + Bevacizumab**

- Oxaliplatin 85 mg/m² IV over 2 hours, day 1
- Leucovorin* 400 mg/m² IV over 2 hours, day 1
- 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)† IV continuous infusion
- Bevacizumab 5 mg/kg IV, day 1
- Repeat every 2 weeks

**mFOLFOX6 + Panitumumab**

- Oxaliplatin 85 mg/m² IV over 2 hours, day 1
- Leucovorin* 400 mg/m² IV over 2 hours, day 1
- 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)† IV continuous infusion
- Panitumumab 6 mg/kg IV over 60 minutes, day 1
- Repeat every 2 weeks

**CapeOX**

- Oxaliplatin 130 mg/m² IV over 2 hours, day 1
- Capecitabine 850-1000‡ mg/m² twice daily PO for 14 days
- Repeat every 3 weeks

**CapeOX + Bevacizumab**

- Oxaliplatin 130 mg/m² IV over 2 hours, day 1
- Capecitabine 850-1000‡ mg/m² PO twice daily for 14 days
- Bevacizumab 7.5 mg/kg IV, day 1
- Repeat every 3 weeks

**mFOLFOX6 + Bevacizumab**

- Oxaliplatin 85 mg/m² IV over 2 hours, day 1
- Leucovorin* 400 mg/m² IV over 2 hours, day 1
- 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)† IV continuous infusion
- Bevacizumab 5 mg/kg IV, day 1
- Repeat every 2 weeks

**mFOLFOX6 + Panitumumab**

- Oxaliplatin 85 mg/m² IV over 2 hours, day 1
- Leucovorin* 400 mg/m² IV over 2 hours, day 1
- 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)† IV continuous infusion
- Panitumumab 6 mg/kg IV over 60 minutes, day 1
- Repeat every 2 weeks

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

†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 hours) to minimize medication errors.

‡The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. 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/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

IMPORTANT NOTE REGARDING LEUCOVORIN SHORTAGE, PLEASE SEE MS-10

See References on page COL-C 7 of 7
CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 5 of 7)

FOLFIRI\(^7\)
Irinotecan 180 mg/m\(^2\) IV over 30-90 minutes, day 1
Leucovorin 400 mg/m\(^2\) IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m\(^2\) IV bolus day 1, then 1200 mg/m\(^2\)/day x 2 days (total 2400 mg/m\(^2\) over 46-48 hours)† IV continuous infusion
Repeat every 2 weeks

FOLFIRI\(^7\) + Bevacizumab\(^8,\|^\)
Irinotecan 180 mg/m\(^2\) IV over 30-90 minutes, day 1
Leucovorin 400 mg/m\(^2\) IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m\(^2\) IV bolus day 1, then 1200 mg/m\(^2\)/day x 2 days (total 2400 mg/m\(^2\) over 46-48 hours)† IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFIRI\(^7\) + Cetuximab
Irinotecan 180 mg/m\(^2\) IV over 30-90 minutes, day 1
Leucovorin 400 mg/m\(^2\) IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m\(^2\) IV bolus day 1, then 1200 mg/m\(^2\)/day x 2 days (total 2400 mg/m\(^2\) over 46-48 hours)† IV continuous infusion
Cetuximab 400 mg/m\(^2\) IV over 2 hours first infusion, then 250 mg/m\(^2\) IV over 60 minutes weekly\(^9\)
or Cetuximab 500 mg/m\(^2\) IV over 2 hours, day 1, every 2 weeks\(^10\)

FOLFIRI\(^7\) + Panitumumab\(^11\)
Irinotecan 180 mg/m\(^2\) IV over 30-90 minutes, day 1
Leucovorin 400 mg/m\(^2\) IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m\(^2\) IV bolus day 1, then 1200 mg/m\(^2\)/day x 2 days (total 2400 mg/m\(^2\) over 46-48 hours)† IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

*Leucovorin 400 mg/m\(^2\) is the equivalent of levoleucovorin 200 mg/m\(^2\).
†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m\(^2\)/day NOT 2400 mg/m\(^2\) over 48 hours) to minimize medication errors.
‡The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m\(^2\) twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. 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/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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See References on page COL-C 7 of 7
## CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 6 of 7)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capecitabine</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td>850-1250 mg/m² PO twice daily, days 1-14 Repeat every 3 weeks</td>
</tr>
<tr>
<td><strong>Capecitabine + Bevacizumab</strong>&lt;sup&gt;6¶&lt;/sup&gt;</td>
<td>850-1250 mg/m² PO twice daily, days 1-14 Bevacizumab 7.5 mg/kg IV, day 1 Repeat every 3 weeks</td>
</tr>
<tr>
<td><strong>Bolus or infusional 5-FU/leucovorin</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36 5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, 36 Repeat every 8 weeks</td>
</tr>
<tr>
<td><strong>Simplified biweekly infusional 5-FU/LV (sLV5FU2)</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Leucovorin 400 mg/m² IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)&lt;sup&gt;†&lt;/sup&gt; continuous infusion Repeat every 2 weeks Weekly Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV bolus injection 1h after the start of leucovorin. Repeat weekly&lt;sup&gt;13&lt;/sup&gt; 5-FU 2600 mg/m² by 24 h infusion plus leucovorin 500 mg/m² Repeat every week&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>IROX</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Oxaliplatin 85 mg/m² IV over 2 hours, followed by irinotecan 200 mg/m² over 30 or 90 minutes every 3 weeks</td>
</tr>
<tr>
<td><strong>FOLFOXIRI</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² day 1, leucovorin 400 mg/m² day 1, fluorouracil 3,200 mg/m² over 48 h continuous infusion starting on day 1 Repeat every 2 weeks</td>
</tr>
<tr>
<td><strong>Irinotecan</strong></td>
<td>Irinotecan 125 mg/m² IV over 30-90 minutes, days 1, 8 Repeat every 3 weeks&lt;sup&gt;18,19&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Irinotecan</strong></td>
<td>Irinotecan 300-350 mg/m² IV over 30-90 minutes, day 1 Repeat every 3 weeks</td>
</tr>
<tr>
<td><strong>Cetuximab (KRAS wild-type gene only) ± irinotecan</strong>&lt;sup&gt;10,20&lt;/sup&gt;</td>
<td>Cetuximab 400 mg/m² 1st infusion, then 250 mg/m² IV weekly or Cetuximab 500 mg/m² IV every 2 weeks&lt;sup&gt;10&lt;/sup&gt; ± Irinotecan 300-350 mg/m² IV every 3 weeks or Irinotecan 180 mg/m² IV every 2 weeks or Irinotecan 125 mg/m² on days 1, 8 and repeat every 3 weeks</td>
</tr>
<tr>
<td><strong>Cetuximab (KRAS wild-type gene only)</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Cetuximab 400 mg/m² 1st infusion, then 250 mg/m² IV weekly&lt;sup&gt;20&lt;/sup&gt; or Cetuximab 500 mg/m² IV every 2 hours, day 1, every 2 weeks&lt;sup&gt;10&lt;/sup&gt; Panitumumab (KRAS wild-type gene only) Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks</td>
</tr>
</tbody>
</table>

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

†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 hours) to minimize medication errors.

¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).
CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES (PAGE 7 OF 7)


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.


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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE\textsuperscript{1,2,3}

- Patient/physician discussion regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics and patient preferences.
- When determining if adjuvant therapy should be administered, the following should be taken into consideration:
  - Number of lymph nodes analyzed after surgery
  - 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 percent.


Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in Stage III patients.\textsuperscript{1}

FOLFOX is superior to fluoropyrimidine therapy alone for Stage III patients.\textsuperscript{2,3} FOLFOX is reasonable for high risk or intermediate risk stage II patients and is not indicated for good or average risk stage II patients. FLOX is an alternative to FOLFOX.\textsuperscript{4}

Bolus 5-FU/leucovorin/irinotecan should not be used in adjuvant therapy\textsuperscript{5} and infusional 5-FU/leucovorin/irinotecan (FOLFIRI) has not been shown to be superior to 5-FU/LV.\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 stage II or III patients outside the setting of a clinical trial.

\textbf{See Additional Principles of Adjuvant Therapy - Chemotherapy Regimens and References on COL-E 2 of 2}


PRINCIPLES OF ADJUVANT THERAPY - CHEMOTHERAPY REGIMENS AND REFERENCES (2 of 2)

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

FLOX²
5-FU 500 mg/m² IV bolus weekly x 6 + leucovorin 500 mg/m² IV weekly x 6, each 8 week cycle x 3 with oxaliplatin 85 mg/m² IV administered on weeks 1, 3, and 5 of each 8 week cycle x 3.

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

CapeOx⁴
Oxaliplatin 130 mg/m² over 2 hours, day 1. Capecitabine 1000 mg/m² twice daily 1-4 every 3 wks x 24 wks.

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 weeks for 4 cycles.⁵
- Simplified biweekly infusional 5-FU/LV (sLV5FU2)⁶
  Leucovorin 400 mg/m² IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours) † continuous infusion. Repeat every 2 weeks

⁴Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 hours) to minimize medication errors.


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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF RADIATION THERAPY

- Radiation therapy fields should include the tumor bed, which should be defined by preoperative radiological imaging and/or surgical clips.
- Radiation doses should be:
  - Consider boost for close or positive margins.
  - Small bowel dose should be limited to 45 Gy.
  - 5-fluorouracil based chemotherapy should be delivered concurrently with radiation.
- Conformal external beam radiation should be routinely used for T4 non-metastatic disease and intensity modulated radiotherapy (IMRT) reserved only for unique clinical situations including re-irradiation 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-fluorouracil 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 (SBRT). (category 3)

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF SURVIVORSHIP - Colorectal Long-term Follow-up Care

Colorectal Cancer Surveillance:
- See COL-3 and COL-4
- Long term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning are not recommended beyond 5 years.

Management of Late Sequelae of Disease or Treatment: 1-5
- Chronic Diarrhea or Incontinence
  - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.

Prescription for Survivorship and Transfer of Care to Primary Care Physician: 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 patients should be made on an individual basis.
- Breast Cancer: See the NCCN Breast Cancer Screening Guidelines
- Cervical Cancer: See the NCCN Cervical Cancer Screening Guidelines
- Prostate Cancer: See the NCCN Prostate Early Detection Guidelines

Counseling Regarding Healthy Lifestyle and Wellness: 7
- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (At least 30 minutes of moderate intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (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 primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.

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Table 1. Definitions for T, N, M

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumor cannot be assessed</td>
<td>NX Regional lymph nodes cannot be assessed</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>Tis Carcinoma in situ: intraepithelial or invasion of lamina propria</td>
<td>N0 No regional lymph node metastasis</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>T1 Tumor invades submucosa</td>
<td>N1 Metastasis in 1-3 regional lymph nodes</td>
<td>M1a Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)</td>
</tr>
<tr>
<td>T2 Tumor invades muscularis propria</td>
<td>N1a Metastasis in one regional lymph node</td>
<td>M1b Metastases in more than one organ/site or the peritoneum</td>
</tr>
<tr>
<td>T3 Tumor invades through the muscularis propria into the pericolectal tissues</td>
<td>N1b Metastasis in 2-3 regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td>T4a Tumor penetrates to the surface of the visceral peritoneum</td>
<td>N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis</td>
<td></td>
</tr>
<tr>
<td>T4b Tumor directly invades or is adherent to other organs or structures</td>
<td>N2 Metastasis in four or more regional lymph nodes</td>
<td></td>
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</table>
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&n...
Discussion

NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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, it is estimated that 49,380 people will die from colon and rectal cancer combined. Despite these statistics, the incidence per 100,000 population 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 for managing colon cancer. The 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 (tumor / node / metastasis) staging system (Table 1 in the guidelines). Furthermore, all recommendations are classified as category 2A except where noted in the text or on the algorithm (see ‘NCCN Categories of Evidence and Consensus,’ above). While the guidelines are felt 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 cases of colon cancer 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 or HNPCC) and familial adenomatous polyposis (FAP). Therefore, it is recommended that all colon cancer patients be queried regarding their family history and considered for risk assessment as detailed in the NCCN Colorectal Cancer Screening Clinical Practice Guidelines.

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2-4% of all colorectal cancer cases. This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2). While identifying a germline mutation in an MMR gene by sequencing is definitive for Lynch syndrome, patients usually undergo 2
rounds of selection before sequencing: the first based on family history and the second by initial tests on tumor tissue. There are 2 initial tests performed on colorectal cancer specimens to identify individuals who might have Lynch syndrome: immunohistochemical (IHC) analysis for MMR protein expression, which is often diminished due to 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.\textsuperscript{13} Testing the \textit{BRAF} gene for mutation is indicated when \textit{MLH1} expression is absent in the tumor by IHC analysis. The presence of a \textit{BRAF} mutation indicates that \textit{MLH1} expression is down-regulated by somatic methylation of the promoter region of the gene and not by a germline mutation.\textsuperscript{13}

The panel recommends that MMR protein testing should be strongly considered for all colon cancer patients <50 years of age, based on an increased likelihood of Lynch syndrome in this population.\textsuperscript{14} Some centers, however, now perform IHC (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 (CDC).\textsuperscript{15} Please see the NCCN Colorectal Cancer Screening Clinical Practice Guidelines for a more detailed discussion.

**Staging**

The 7\textsuperscript{th} edition of the American Joint Committee on Cancer’s (AJCC) Cancer Staging Manual includes a number of modifications to the colon cancer TNM staging system.\textsuperscript{3, 16, 17} The TNM categories reflect very similar survival outcomes for rectal and colon cancer. Therefore these 2 diseases share the same staging system.\textsuperscript{18}

In the previous version (6\textsuperscript{th} edition) of the AJCC staging system for colon cancer, stage II disease, characterized by full thickness tumor invasion of the bowel wall and the absence of lymph node metastases (ie, N0 disease), was subdivided into IIA and IIB depending on whether the primary tumor was T3 or T4. Stage II disease is now subdivided into IIA (T3 lesions that invade through the muscularis propria into pericolectal tissues), IIB (T4a lesions that directly penetrate to the surface of the visceral peritoneum), and IIC (T4b lesions where tumor directly invades or is adherent to other organs or structures).\textsuperscript{3} These changes are supported by an analysis of 109,953 patients with invasive colon cancer included in the Surveillance Epidemiology and End Results (SEER) colon cancer database from 1992-2004.\textsuperscript{19} The relative 5-year survival rate (ie, 5-year survival corrected by age-related morbidity) for node-negative patients with T4 tumors penetrating the visceral peritoneum was considerably higher (79.6%) compared to patients with tumors that invade or are adherent to other organs (58.4%).\textsuperscript{19}

The definitions of N1 and N2 disease have also been revised to reflect the prognostic impact of the number of involved regional lymph nodes. For example, N1 lesions (1 to 3 positive regional lymph nodes) have been subdivided into N1a (1 positive lymph node) and N1b (2 to 3 positive lymph nodes), whereas N2 tumors (4 or more positive regional nodes) are split into N2a (4 to 6 positive nodes) and N2b (7 or more positive nodes). In addition, tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis (ie, satellite tumor nodules) are classified as N1c.\textsuperscript{3} See the ‘Pathology’ section below for a discussion of tumor deposits.
Based on the analyses described above, stage III disease, previously subdivided into IIIA (T1 to T2, N1, M0), IIIB (T3 to T4, N1, M0), and IIIC (any T, N2, M0), has now been revised to more accurately reflect the complex biologic relationship between the extent of tumor invasion and the number of affected lymph nodes. For example, due to the relatively high survival rates observed for patients with lesions with extensive nodal involvement but no tumor penetration beyond the muscularis propria, T1-2, N2 lesions are now classified as either IIIA (T1, N2a) or IIIB (T2, N2a or T1-2, N2b). In addition, T4b, N1 disease, formerly stage IIIB disease, is now included under stage IIIC, since outcomes for such patients were found to be similar to those observed for patients with T3-4, N2 lesions.

Stage IV disease is characterized by the presence of 1 or more distant metastases and is designated as M1. M1 disease is now dichotomized into M1a and M1b according to whether metastasis is confined to 1 or more than 1 organ or site.

**Pathology**

Colorectal cancers are usually staged after surgical exploration of the abdomen and pathologic examination of the surgical specimen. Some of the criteria that should be included in the report of the pathologic evaluation include the following: grade of the cancer; depth of penetration and extension to adjacent structures (T); number of regional lymph nodes evaluated; number of positive regional lymph nodes (N); an assessment of the presence of distant metastases to other organs, the peritoneum of an abdominal structure, or in non-regional lymph nodes (M); the status of proximal, distal, and radial margins; lymphovascular invasion, perineural invasion, and extra-nodal tumor deposits. The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy and surgery, respectively.

The panel added a discussion of the evaluation of the radial margin in the 2011 Colon Cancer Guidelines. In colon cancer, the radial margin (or circumferential resection margin, CRM) represents the adventitial soft tissue closest to the deepest penetration of the tumor; it is created surgically by blunt or sharp dissection of the retroperitoneal aspect, and it corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells. It must be dissected from the retroperitoneum to remove the viscus. The serosal (peritoneal) surface does not constitute a surgical margin. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. In segments of the colon that are completely encased by peritoneum, such as the transverse colon, the mesenteric resection margin is the only relevant radial margin. On pathological examination, it is difficult to appreciate the demarcation between the peritonealized surface and the non-peritonealized surface. The surgeon is therefore encouraged to mark the area of non-peritonealized surface with a clip or suture. In a study of 608 patients with rectal cancer, a positive radial margin was shown to be a negative prognostic factor for both local recurrence and overall survival (OS). CRM-positive patients had a 38.2% local recurrence rate, while their CRM-negative counterparts had a 10.0% rate of local recurrence.

The 7th edition of the AJCC staging system specifies that the surgeon should score the completeness of resection as R0 for complete tumor resection with all margins negative; R1 for incomplete tumor resection with microscopic involvement of a margin; and R2 for incomplete tumor resection with gross residual tumor not resected.

Extra-nodal tumor deposits, also called peritumoral deposits or satellite nodules, are irregular discrete tumor deposits in the pericolic or
perirectal fat that show no evidence of residual lymph node tissue, but that are within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor. Most of these tumor deposits are thought to be due to lymphovascular invasion or occasionally perineural invasion. The number of extra-nodal tumor deposits should be recorded in the pathology report, since they have been shown to be associated with reductions in disease-free and overall survival. Multivariate survival analysis in one study showed that patients with pN0 tumors without satellite nodules had a 91.5% 5-year survival rate compared to 37.0% for patients with pN0 tumors and the presence of satellite nodules (P<0.0001).

The number of lymph nodes evaluated is important to note on the pathology report. A secondary analysis of patients from the Intergroup Trial INT-0089 showed that an increase in the number of lymph nodes examined was associated with increased survival for patients with both node-negative and node-positive disease. In addition, results from a population-based study demonstrated an association between improvement in survival and examination of ≥12 lymph nodes. The number of regional lymph nodes retrieved from a surgical specimen can vary with age of the patient, gender, and tumor grade or site. The extent and quality of surgical resection and pathologic review of the specimen can also have an impact on the node harvest. The panel recommends examination of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancer. This recommendation is supported by previous statements from CAP, as well as recommendations included in the 7th edition of the AJCC staging manual, which specify pathologic examination of a minimum of 10-14 lymph nodes. Of note, emerging evidence suggests that a greater number of nodes may need to be examined in some situations, particularly for T4 lesions, to provide an adequate assessment of disease stage. For stage II (pN0) colon cancer, it is recommended that the pathologist go back to the specimen and submit more tissue of potential lymph nodes if fewer than 12 nodes were initially identified. Patients considered to have N0 disease but for whom <12 nodes have been examined are suboptimally staged and should be considered at higher risk.

The potential benefit of sentinel lymph node evaluation for colon cancer has mostly been associated with providing more accurate staging of nodal pathology through detection of micrometastatic disease in the sentinel node(s). Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells and the identification of particular tumor antigens through immunohistochemical (IHC) analysis have been reported. While results of some of these studies seem promising to some, there is no uniformity in the definition of “true” clinically relevant metastatic carcinoma. The 7th Edition of the AJCC Cancer Staging Manual considers “tumor clusters” smaller than 0.2 mm to be isolated tumor cells and not true metastases. However, some studies have considered detection of single cells by IHC to be micrometastasis. The prognostic value of IHC-positive cells in stage II (N0 by H&E) colon cancer remains controversial. Presently, the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational, and the results should not be given significant weight in clinical management decisions.

Several studies have demonstrated that the presence of perineural invasion (PNI) is associated with a significantly worse prognosis. For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at one institution found a 4-fold greater 5-year survival in patients without perineural invasion versus patient whose tumors invaded nearby neural structures.
analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year disease-free survival (DFS) compared to those without PNI (29% vs. 82%; P=0.0005). Similar results were seen for patients with stage III disease. Perineural invasion is therefore included as a high risk factor for systemic recurrence.

The Role of Vitamin D in Colorectal Cancer

Prospective studies have suggested that vitamin D deficiency may contribute to colorectal cancer incidence and that vitamin D supplementation may decrease colorectal cancer risk. Furthermore, 2 prospective studies showed that low vitamin D levels were associated with increased mortality of patients with colorectal cancer, especially in stage III and IV disease. Moreover, in a study of 515 patients with stage IV colorectal cancer, 82% of patients were found to be vitamin D insufficient (levels <30 ng/mL) and 50% found to be vitamin D deficient (<20 ng/mL). Nonetheless, no study has yet examined whether vitamin D supplementation improves patient outcomes. In a recent report, the Institute of Medicine concluded that data supporting a role for vitamin D was only conclusive in bone health, not in cancer and other diseases. Citing this report and the lack of level 1 evidence, the panel does not recommend routine screening for vitamin D deficiency or supplementation of vitamin D in patients with colorectal cancer at this time.

Clinical Presentation and Treatment of Nonmetastatic Disease

Workup and Management of the Malignant Polyp

A malignant polyp is defined as one with cancer invading the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore not considered to be capable of regional nodal metastasis. The panel recommends marking the polyp site at the time of 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 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 histological features. Favorable histological 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 histological features and clear margins. The reason for inclusion of this option is that 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 than patients with pedunculated polyps, likely owing to the relatively high probability of a positive margin following endoscopic removal.

If the polyp specimen is fragmented, if the margins cannot be assessed, or if there is unfavorable histopathology, colectomy with en bloc removal of lymph nodes is recommended. Laparoscopic surgery is an option. Unfavorable histopathological features for malignant polyps are grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. It should be noted that there is currently no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as the presence of tumor within 1-2 mm from the transected margin or by 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, as well as 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, a complete blood count, chemistry profile, carcinoembryonic antigen (CEA) determination, and baseline computed tomographic (CT) scans of the chest, abdomen, and pelvis. The consensus of the panel is that a positron emission tomography (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 to be suspicious but inconclusive for metastases, then a PET/CT scan may be considered for further delineation of that abnormality, if such delineation will change management. A PET/CT scan is not indicated for assessment of sub-centimeter lesions, as these are routinely below the level of PET/CT detection.

For resectable non-metastatic colon cancer, the surgical procedure of choice 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 (ie, apical lymph node), as well as suspicious lymph nodes outside the field of resection, should also be biopsied or removed if possible. Resection needs to 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. A small European randomized trial (Barcelona) appeared to show some modest survival advantage, significantly faster recovery, and shorter hospital stays with the laparoscopic approach. More recently, in a similar larger trial for patients randomly assigned to curative surgery with either a conventional open approach or laparoscopically-assisted surgery, a non-significant absolute difference of 2.0% in 3-year disease-free survival in favor of open colectomy was observed in a study of 1,248 patients with colon cancer (COLOR trial). Although this difference was not statistically significant, non-inferiority of the laparoscopic approach could not be established due to study limitations. In the CLASSICC study of 794 patients with colorectal cancer, no statistically significant differences in 3-year rates of overall survival, DFS, and local recurrence were observed when the 2 surgical approaches were compared. Also reported have been results from another trial of 872 patients with colon cancer (COST study) randomly assigned to undergo open or laparoscopically-assisted colectomy for curable colon cancer. After a median of 7 years follow-up, similar 5-year cancer recurrence and 5-year overall survival rates were observed in the 2 groups. In addition, several recent meta-analyses have provided support for the conclusion that the 2 surgical approaches provide similar long-term outcomes with respect to local recurrence and survival of patients with colon cancer. A subanalysis of results from the COLOR trial evaluating short-term outcomes (eg, conversion rate to open colectomy, number of lymph nodes collected, number of complications) based on hospital case volume indicated that these outcomes were statistically significantly...
more favorable when laparoscopic surgery was performed at hospitals with high case volumes. Other factors which may confound conclusions drawn from randomized studies comparing open colectomy to laparoscopically-assisted surgery for colon cancer have been described.

The panel recommends that laparoscopically-assisted colectomy be considered only by surgeons experienced in the technique. A thorough abdominal exploration is a required as part of the procedure. At this time, routine use of laparoscopic-assisted resection is not 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 (ie, T4). Patients at high risk for prohibitive abdominal adhesions should not be approached laparoscopically, and patients 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 aroused considerable interest. Choices for adjuvant therapy for patients with resected nonmetastatic colon cancer are dependent on the stage of disease:

- Stage I patients do not require any adjuvant therapy.
- Low-risk stage II patients can be enrolled in a clinical trial, observed without adjuvant therapy, or considered for capecitabine or 5-FU/LV. Based on results of the MOSAIC trial, as well as the possible long-term sequelae of oxaliplatin-based chemotherapy, the panel does not consider FOLFOX to be an appropriate adjuvant therapy option for patients with stage II disease without high-risk features.
- High-risk stage II patients, 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), lymphovascular invasion, perineural invasion, bowel obstruction, lesions with localized perforation or close, indeterminate, or positive margins, or inadequately sampled nodes (fewer than 12 lymph nodes), should be considered for adjuvant chemotherapy as for stage III patients as detailed below.
- For stage III patients, the panel recommends 6 months of adjuvant chemotherapy following primary surgical treatment. The treatment options are: 5-FU/LV/oxaliplatin (mFOLFOX6) 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 felt to be inappropriate for oxaliplatin therapy.

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 there are no NCCN guidelines, may be treated with systemic chemotherapy according to these NCCN...
Colon Cancer Guidelines. Peritoneal mesothelioma and other extra-pleural mesotheliomas may be treated with systemic therapy along NCCN guidelines for pleural mesothelioma.

Endpoints for Adjuvant Chemotherapy Clinical Trials
The Adjuvant Colon Cancer Endpoints (ACCENT) collaborative group has evaluated the appropriateness of various endpoints for adjuvant chemotherapy trials in colon cancer. Results of an analysis of individual patient data from 20,898 patients in 18 randomized colon adjuvant clinical trials by the ACCENT group suggested that DFS after 2 and 3 years follow-up is an appropriate endpoint 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 following surgery, and that recurrence rates were <1.5%/year and <0.5%/year after 5 years 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 OS in stage III patients but not in stage II patients. In all patients, the DFS-to-OS correlation was strongest at 6-years, suggesting that at least 6 years are required for adequate assessment of OS 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 stage III colon cancer were randomly assigned to receive surgery alone or surgery followed by adjuvant 5-FU/LV demonstrated 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 the stage II subset. These results suggest that the benefit of adjuvant therapy is greater in patients at higher risk due to nodal status. These clinical trial results are supported by data from the community setting. Using the SEER databases, an analysis of outcomes of patients with stage II disease based on whether patients had or had not received adjuvant chemotherapy showed that there was no statistically significant difference between these 2 groups with respect to 5-year overall survival (78% vs. 75% respectively), with a hazard ratio 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 (hazard ratio=0.84; 95% CI, 0.62-1.14; P=0.258), a trend for improved DFS in high-risk stage II patients (ie, disease characterized by at least 1 of the following: T4 tumor; tumor perforation; bowel obstruction; poorly differentiated tumor; venous invasion; <10 lymph nodes examined) receiving FOLFOX compared to infusional 5-FU/LV (hazard ratio=0.72, 95% CI, 0.50-1.02) was observed, 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 stage II patients treated with 5-FU/LV (relative risk of recurrence at 2 years: 0.71; 95% CI 0.54-0.92; P = 0.01).

Of note, a recent analysis of >24,000 stage II colon cancer patients from the SEER Medicare database demonstrated that there was no 5-year survival benefit to the use of adjuvant chemotherapy compared to observation even in stage II patients with 1 or more poor prognostic features (HR, 1.03; 95% CI, 0.94 to 1.13). While this study was limited to patients >65 years of age and involved a time period before the use of oxaliplatin-based therapies, it is still an important piece of data to consider during the decision-making process for the use of adjuvant chemotherapy in stage II patients.

Microsatellite Instability
Another important piece of information to consider during the decision-making process for the use of adjuvant chemotherapy in stage II patients is microsatellite instability. There is evidence that microsatellite instability is a marker of a more favorable outcome and decreased benefit (possibly a detrimental impact) from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease. Mutation of DNA mismatch repair (MMR) genes or modifications of these genes (eg, methylation) can result in MMR protein deficiency and microsatellite instability (see ‘Risk Assessment’ above). Germline mutations in the MMR genes MLH1, MSH2, MSH6, and/or PMS2 are found in individuals with Lynch syndrome, responsible for 2-4% of colon cancer cases. Somatic MMR defects have been reported to occur in approximately 19% of colorectal tumors, while 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. Tumors showing the presence of microsatellite instability are classified as MSI-high (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). 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 tumor specimens characterized as MSI-H to be more common in stage II disease compared with stage III disease (22% vs. 12%, respectively; P<0.0001). In another large study, the percentage of stage IV tumors characterized as MSI-H was only 3.5%. These results suggest that MSI-H (ie, defective MMR) tumors have a decreased likelihood to metastasize. In fact, there is substantial evidence 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.

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 stage II patients.
A retrospective study involving long-term follow-up of stage II and stage III patients evaluated according to MSI tumor status demonstrated that those with low microsatellite instability or stable microsatellites 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 following surgery, instead exhibiting a lower 5-year survival rate compared with those undergoing surgery alone.\textsuperscript{110} Similarly, results from another retrospective study of pooled data from adjuvant trials by Sargent et al showed that in tumors characterized as defective MMR, adjuvant 5-FU chemotherapy appeared to be detrimental in patients with stage II, but not stage III, disease.\textsuperscript{111} In contrast to the findings of Sargent et al, however, a recent study of 1,913 patients with stage II colorectal cancer from the QUASAR study, half of whom received adjuvant chemotherapy, showed that while defective MMR was prognostic (the recurrence rate of defective MMR tumors was 11\% vs. 26\% for MMR-proficient tumors), it did not predict benefit or detrimental impact of chemotherapy.\textsuperscript{119} Overall, while the prognostic power of MMR status is stage II disease seems clear, there is considerable controversy surrounding 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 stage II patients whose tumors are MSI-H.

\textit{Timing of Adjuvant Therapy}
A recent systematic review and meta-analysis of 10 studies involving more than 15,000 patients looked at the effect of timing of adjuvant therapy following 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.

\textit{Leucovorin Shortage}
There is currently a shortage of leucovorin (LV) in the United States. There are no specific data 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\textsuperscript{2} of levo-leucovorin is equivalent to 400 mg/m\textsuperscript{2} of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.\textsuperscript{123} 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/m\textsuperscript{2}) or low dose (20 mg/m\textsuperscript{2}) leucovorin.\textsuperscript{124} Also, the Mayo Clinic and North Central Cancer Treatment (NCTTG) group determined that there was no therapeutic difference between the use of high (200 mg/m\textsuperscript{2}) or low (20 mg/m\textsuperscript{2}) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.\textsuperscript{125} Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10\%) may be considered.
FOLFOX and Infusional 5-FU/LV
The European MOSAIC trial has evaluated the efficacy of FOLFOX (infusional 5-fluorouracil (5-FU), leucovorin (LV), oxaliplatin) compared to 5-FU/LV in the adjuvant setting in 2,246 patients with completely resected stage II and stage III colon cancer. Although this initial trial was done with FOLFOX 4, modified FOLFOX 6 has been the control arm for all recent and the current National Cancer Institute (NCI) adjuvant studies for colorectal cancer, and mFOLFOX6 is felt by the panel to be the FOLFOX regimen of choice in both adjuvant and metastatic treatments. Results of this study have been reported with median follow-up of 3 years,44 4 years,84 and 6 years.85, 86 For stage III patients, disease-free survival (DFS) at 5 years was 58.9% in the 5-FU/LV arm and 66.4% in the FOLFOX arm (P=0.005), 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%; hazard ratio=0.80; 95% CI, 0.65-0.97; P=0.023) when compared with those receiving 5-FU/LV.85 While 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 demonstrated 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.85 Based on the increases in DFS and OS 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 (NSABP Protocol C-07) compared the efficacy of FLOX (bolus 5-FU/LV/oxaliplatin) with that of FULV (bolus 5-FU/LV) in prolonging DFS in 2,407 patients with stage II or stage III colon cancer.90 Four-year DFS rates were 73.2% for FLOX and 67.0% for FULV, with a hazard ratio of 0.81 (95% CI, 0.69-0.94; P=0.005) after adjustment for age and number of nodes, indicating a 19% reduction in relative risk.90 A recent update of this study showed the benefit of FLOX in DFS to be maintained at 7-year median follow-up (P=0.0017).126 However, no statistically significant differences in overall survival (HR, 0.88; 95% CI, 0.76-1.03; P=0.1173) or colon-cancer specific mortality (HR, 0.88; 95% CI, 0.74-1.05; P=0.1428) were observed when the 2 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=0.0497).126

Grade 3 neurotoxicity, diarrhea, and dehydration were higher with FLOX than with 5-FU/LV,126 and, when cross-study comparisons are made, the incidence of grade 3/4 diarrhea appears to be considerably higher with FLOX than 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<0.001), in the MOSAIC trial,83 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=0.003).90

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 hazard ratios of 0.87 (95% CI, 0.75-1.00, P<0.001) and 0.84 (95% CI, 0.69-1.01, P=0.07), when the capecitabine arm was compared to the 5-FU/LV arm.93 Capecitabine has also been assessed as adjuvant therapy for stage III colon cancer in combination with oxaliplatin (CapeOx) and showed improved 3-year DFS compared to 5-FU/LV (66.5% vs. 70.9%).91, 92 CapeOx was shown to have similar efficacy as FOLFOX in the AVANT trial, but it is more toxic.127 With this
new data, CapeOx is now listed in the guidelines with a category 1 designation as adjuvant therapy for stage III patients.

**Regimens Not Recommended**

Other adjuvant regimens studied for the treatment of early-stage colon cancer include 5-FU-based therapies incorporating irinotecan. The Cancer and Leukemia Group B trial CALGB 89803 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=0.74) or disease-free survival (P=0.84) was observed for patients in the IFL arm compared with those receiving 5-FU/LV. However, IFL was associated with a greater degree of neutropenia, neutropenic fever, and death.\(^{129}\) Similar results were observed in a recent randomized phase III comparing bolus 5-FU/LV to 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.

The NSABP C-08 trial comparing 6 months of mFOLFOX6 vs. 6 months of mFOLFOX6 with bevacizumab plus an additional 6 months of bevacizumab alone in patients with stage II or stage III colon cancer did not demonstrate a statistically significant benefit in 3-year DFS with the addition of bevacizumab to FOLFOX (hazard ratio=0.89; 95% CI, 0.76-1.04; P=0.15).\(^{133}\) The results of the phase III AVANT trial evaluating bevacizumab in the adjuvant setting in a similar protocol also failed to show a benefit to bevacizumab in the adjuvant treatment of stage II or III colorectal cancer, and in fact showed a trend towards a detrimental effect to the addition of bevacizumab. Therefore, there is no role for the use of bevacizumab 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 gave 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 showed increases in grade 3/4 adverse events.\(^{135}\) There is therefore no role for the use of cetuximab 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 radiological 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, additional 10-20 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 non-metastatic T4 disease; intensity-modulated radiotherapy (IMRT), 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 re-irradiation of previously treated patients with recurrent disease.
Principles of the Management of Metastatic Disease

Approximately 50%-60% of patients diagnosed with colorectal cancer will develop colorectal metastases, and 80%-90% of these have unresectable metastatic liver disease. Metastatic disease most frequently develops metachronously following treatment for local-regional colorectal cancer, with the liver as the most common site of involvement. However, approximately 20%-34% of patients with colorectal cancer present with synchronous liver metastases. There is some evidence to indicate 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=0.008) and more bilobar metastases (P=0.016) when compared with patients diagnosed with metachronous liver metastases.

It has been estimated that over one-half of patients who die of colorectal cancer have liver metastases at autopsy and that metastatic liver disease is the cause of death in the majority of these patients. Results from reviews of autopsy reports of patients dying from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients. Furthermore, rates of 5-year survival for patients with metastatic liver disease not undergoing surgery have been shown to be quite low in a number of studies. Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than 3 tumors, and a disease-free interval of <12 months, have been associated with a poor prognosis in patients with colorectal cancer.

On the other hand, studies of selected patients undergoing surgery to remove colorectal liver metastases have demonstrated that cure is possible in this population and should be the goal for a substantial number of patients with colorectal metastatic liver disease. Recent reports have shown 5-year disease-free survival rates following resection of liver metastases to be approximately 20%. 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, as discussed further below (see ‘Determining Resectability’). For patients presenting with unresectable metastases and intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver.

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 when compared with patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence. However, in a recent international analysis of 1,629 patients with colorectal liver metastases, 16% of the 171 patients (10.4%) who underwent concurrent resection of extra-hepatic and hepatic disease remained disease-free at a median follow-up of 26 months. This result suggests that concurrent resection may be of significant benefit in well-selected patients (ie, 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} The consensus of the panel 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 (ie, HAI) remains an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone by 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 there was a trend (not significant) towards better long-term outcome in the group receiving HAI at later follow-up periods.\textsuperscript{142, 163} A number of 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 for specific technical expertise. The consensus of the panel 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.

A number of non-extirpative 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{164-168} and conformal external beam radiation therapy.\textsuperscript{169} A recent prospective randomized phase III trial of 44 patients demonstrated that radioembolization combined with chemotherapy can lengthen time to progression in patients with liver-limited metastatic colorectal cancer following progression on initial therapy (2.1 months versus 4.5 months; $P=0.03$).\textsuperscript{170} The effect on the primary endpoint of time to liver progression was more pronounced (2.1 versus 5.5 months; $P=0.003$). Still, the use of arterial-directed therapies such as radioembolization in highly select patients remains a category 3 recommendation based on the relatively limited amount of evidence\textsuperscript{171} 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 3D conformal radiotherapy, stereotactic body radiosurgery (SBRT), and intensity modulated radiotherapy (IMRT), which uses computer-imaging to focus RT to the tumor site and potentially decrease toxicity to normal tissue.\textsuperscript{137, 172-175}

While resection is the standard approach for the local treatment of metastatic disease that is resectable, some patients who cannot undergo resection due to comorbidity, location of the metastatic lesion(s), or an estimate of inadequate liver volume following resection may be candidates for tumor ablation therapy.\textsuperscript{176} A number of retrospective studies have compared radiofrequency ablation (RFA) and liver resection in the treatment of liver metastases.\textsuperscript{177-180} Most of these studies have shown RFA to be inferior to resection with respect to rates of local recurrence and 5-year overall survival.\textsuperscript{177, 181} It is presently unclear whether the differences in outcome observed for
patients with liver metastases treated with RFA versus resection alone are due to patient selection bias, technological limitations of RFA, or a combination of these 2 factors. A recent American Society of Clinical Oncology (ASCO) clinical evidence review determined that RFA has not been well studied in the setting of colorectal cancer liver metastases, with no randomized controlled trials having been reported. The ASCO panel concluded that there is a compelling need for more research in this area.

The NCCN 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 consensus of the panel is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (ie, with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status. The criteria for determining patient suitability for resection of metastatic disease are the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve. It should be noted that size alone is rarely a contraindication to resection of a tumor. Resectability differs fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease. Resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), because incomplete resection or debulking has not been shown to be beneficial.

**Conversion to Resectability**

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

In some highly selected cases, patients with significant response to conversion chemotherapy can be converted from unresectable to resectable status. When initial chemotherapy is planned for patients with unresectable disease that is felt to be potentially convertible to resectability, the panel recommends that a surgical re-evaluation be planned approximately 2 months after initiation of chemotherapy, and that those patients who continue to receive chemotherapy undergo surgical re-evaluation approximately every 2 months thereafter.

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

In the study of Pozzo et al, it was reported that chemotherapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection. The median time to progression was 14.3 months, with all of these patients alive at a median follow-up of 19 months. In a phase II study conducted by the North Central Cancer Treatment Group (NCCTG), 42 patients with unresectable liver metastases were treated with FOLFOX. Twenty-five patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study, 1,104 initially unresectable patients with colorectal liver disease were treated with chemotherapy, which included oxaliplatin in the majority of cases, and 138 patients (12.5%) classified as “good responders” underwent secondary hepatic resection. The 5-year disease-free survival rate for these 138 patients was 22%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%; 2 of the 24 had lung metastases) were able to undergo curative resection following treatment. The median overall survival time in this group was 42.4 months.

There have been more recent favorable reports of randomized clinical trials evaluating FOLFIRI or FOLFOX for the purpose of conversion of unresectable disease to resectable disease in combination with anti-EGFR inhibitors. For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI. Retrospective analysis showed that in both treatment arms combined resectability increased from 32% to 60% following chemotherapy in patients with wild-type KRAS (P < 0.0001) with the addition of cetuximab.

In addition, FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI in 2 randomized clinical trials in unresectable patients. In both studies, FOLFOXIRI led to an increase in R0 secondary resection rates: 6% versus 15%, P = 0.033 in the Gruppo Oncologico Nord Ovest (GONO) trial; and 4% versus 10%, P = 0.08 in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial. In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs. 8%), with a median overall survival of 23.4 vs 16.7 months (P = 0.026).

The role of bevacizumab in the unresectable patient, whose disease is felt to be potentially convertible to resectability with a reduction in tumor size, has also been studied. Data appear to suggest that bevacizumab modestly improves the response rate to irinotecan-based regimens, and so when an irinotecan-based regimen is selected for an attempt to convert unresectable disease to resectability, the use of bevacizumab would seem an appropriate consideration. On the other hand, a 1,400-patient randomized, double-blind, placebo-controlled trial of CapeOx or FOLFOX with or without bevacizumab showed absolutely no benefit in terms of response rate or tumor regression for the addition of bevacizumab, as measured by both investigators and an independent radiology review committee. There would not, therefore, appear to be a compelling argument for use of bevacizumab with oxaliplatin-based therapy in this “covert to resectability” setting.
However, since it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

**Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease**

Chemotherapy is recommended in conjunction with liver resection in those patients who are chemotherapy naïve. 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 the planning of postoperative therapy), and avoidance of local therapy for those patients with early disease progression. Potential disadvantages include: chemotherapy-induced liver injury; and missing the “window of opportunity” for resection through 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 colorectal cancer patients 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. It is therefore essential during treatment with preoperative chemotherapy that frequent evaluations are undertaken and close communication is maintained between medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed which 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 limit the development of hepatotoxicity, the neoadjuvant period is usually limited to 2 to 3 months, and patients should be carefully monitored by a multidisciplinary team.

The panel recommends consideration of administration of a course of an active systemic chemotherapy regimen for metastatic disease, for a total perioperative treatment time of approximately 6 months, 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 post-operative setting is dependent on a number of 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 ‘Chemotherapy for Advanced or Metastatic Disease,’ below).

**Chemotherapy for Advanced or Metastatic Disease**

The current management of disseminated metastatic colon cancer uses 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 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, administered as a part of an initial treatment regimen, is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the rest of the treatment regimen would still be considered initial therapy. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive, as well as plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices following first progression of disease should be based, in part, on the prior therapies received by the patient (ie, exposing the patient to a range of cytotoxic agents). Further, 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, as well as the potential for surgical cure and the performance status of the patient.

As initial therapy for metastatic disease in a patient appropriate for intensive therapy (ie, one with a good tolerance for such therapy for whom a high tumor response rate would be potentially beneficial), the panel recommends a choice of 5 chemotherapy regimens: FOLFOX (ie, mFOLFOX6), FOLFIRI, CapeOx, infusional 5-FU/LV or capecitabine, or FOLFOXIRI. Although use of FOLFOXIRI as initial therapy is a category 2B recommendation, the panel does not consider one of the other regimens (ie, 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 appear 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 (irinotecan, bolus 5-FU/LV) 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 demonstrated worse PFS than infusional 5-FU/leucovorin/irinotecan (FOLFIRI) (5.8 vs 7.6 months; P=0.015), and was considerably more toxic with higher rates of severe vomiting, diarrhea, and dehydration. In this trial, the CapeIRI arm was discontinued. The EORTC study 40015 also compared FOLFIRI to 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 to FOLFIRI/Bev in the first-line metastatic setting and found no significant differences in efficacy between the 2 regimens. Despite the reported differing toxicity profiles, the toxicities seemed to be reasonable in both arms. Due to 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 6,286 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 performance status = 2 or ≤ 1 as compared with control groups, although the risks of certain gastrointestinal toxicities were significantly increased for patients with performance status = 2.

**Leucovorin Shortage**

There is currently a shortage of leucovorin in the United States. Please see the discussion in the section above on 'Adjuvant Chemotherapy for Resectable Colon Cancer' for a detailed discussion.

**FOLFOX**

A recent European Organization for Research and Treatment of Cancer (EORTC) phase III study, evaluating use of perioperative FOLFOX (6 cycles before and 6 cycles after surgery) for patients with resectable liver metastases, demonstrated absolute improvements in 3-year progression-free survival (PFS) of 8.1% (P=0.041) and 9.2% (P=0.025) 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 <1% in both treatment groups.

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy. Results of the OPTIMOX1 study demonstrated that a “stop-and-go” approach employing 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 adjustments in 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 there is near-total resolution of that neurotoxicity, but oxaliplatin can be reintroduced if stopped to prevent development of neurotoxicity. There are insufficient data to support the routine use of calcium/magnesium infusion to prevent oxaliplatin-related neurotoxicity.

In the phase II OPTIMOX2 trial, patients were randomized to receive (1) 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 upon disease progression) or (2) 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 demonstrated no difference in overall survival for patients receiving the OPTIMOX1 approach compared with patients undergoing an early, pre-planned chemotherapy-free interval (median overall survival 23.8 vs. 19.5 months; P=0.42). However, the median duration of disease
control, the primary endpoint of the study, reached statistical significance, at 13.1 months in patients receiving maintenance therapy and 9.2 months in patients with a chemotherapy-free interval (P=0.046).269

The addition of bevacizumab is an option when FOLFOX is chosen as initial therapy,204, 270 as is the addition of panitumumab for those with disease characterized by the wild-type KRAS gene (See discussions on ‘Bevacizumab,’ ‘Cetuximab and Panitumumab,’ and ‘The Role of KRAS and BRAF Status,’ below).222, 271 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.

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.213, 250, 251 In a randomized phase III trial comparing CapeOx and FOLFOX in 2,034 patients, the 2 regimens demonstrated similar median progression-free survival intervals of 8.0 and 8.5 months, respectively, and CapeOx was determined to be non-inferior to FOLFOX as first-line treatment of metastatic disease.213

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy,261 (see ‘FOLFOX,’ above). Discontinuation of oxaliplatin from FOLFOX or CapeOx should be strongly considered after 3 months of therapy (the OPTIMOX1 approach262), or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless there is near-total resolution of that neurotoxicity, but oxaliplatin can be reintroduced if stopped to prevent development of neurotoxicity. There are insufficient data to support the routine use of calcium/magnesium infusion to prevent oxaliplatin-related neurotoxicity.263-268

With respect to the toxicities associated with capecitabine use, the panel noted (1) that patients with diminished creatinine clearance may accumulate levels of the drug, and therefore may require dose modification,272 (2) that the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV.270, 272 and (3) that North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.273 Such toxicities may necessitate modifications in the dosing of capecitabine,270, 272, 274 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.204, 270 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 as initial therapy and were then switched to the other regimen at the time of disease progression.249 Similar response rates and PFS times were obtained when these 2 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, PFS times, and overall survival in the 2 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 hyperbilirubinemas, such as types I and II of Crigler-Najjar syndrome and Gilbert syndrome. Thus, irinotecan should be used with caution and at decreased dose in patients with Gilbert’s disease 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 which indicates 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 the use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on a patient who has experienced irinotecan toxicity is not recommended since that patient will require a dose reduction regardless of the UGT1A1 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 demonstrated that this combination was as effective and well-tolerated as bevacizumab with other 5-FU-based therapies. 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.

Infusional 5-FU/LV and Capecitabine

For patients with impaired tolerance to aggressive initial therapy, the guideline includes recommendations for infusional 5-FU/leucovorin or capecitabine with or without bevacizumab as an option. Metastatic cancer patients 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 above (see ‘CapeOx’).

In a pooled analysis of results from 2 randomized clinical trials involving patients with a potentially curative resection of liver or lung metastases randomly assigned to either postoperative systemic chemotherapy with 5-FU/LV or observation alone following surgery, the median PFS was 27.9 months in the chemotherapy arm and 18.8 months for those undergoing surgery alone (hazard ratio=1.32; 95% CI, 1.00-1.76; P=0.058) with no significant difference in overall survival.

FOLFOXIRI

FOLFOXIRI is also listed as an option for initial therapy in unresectable metastatic patients (category 2B). If FOLFOXIRI is used, the panel recommends that it be without the addition of a biologic agent,
since data regarding the efficacy and safety of such a 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 PFS survival (9.8 months vs. 6.9 months; hazard ratio=0.63; \(P=0.0006\)) and median overall survival (22.6 months vs. 16.7 months; hazard ratio=0.70; \(P=0.032\)) were observed in the FOLFOXIRI arm,\(^{199}\) although there was no overall survival difference between the 2 treatment arms in the other study (median overall survival: 19.5 and 21.5 months, for FOLFIRI and FOLFOXIRI, respectively; \(P=0.337\)).\(^{200}\) Both studies showed some increased toxicity in the FOLFOXIRI arm (eg, significant increases in neurotoxicity and neutropenia\(^{199}\), diarrhea, alopecia and neurotoxicity\(^{200}\)), 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 vascular endothelial growth factor (VEGF), a factor that plays an important role in tumor angiogenesis. Pooled results from several randomized phase II studies have demonstrated that addition of bevacizumab to first-line 5-FU/LV improved overall survival in patients with unresectable metastatic colorectal cancer when compared to patients receiving these regimens without bevacizumab.\(^{203, 283, 284}\) A combined analysis of the results of these trials showed that addition of bevacizumab to 5-FU/LV was associated with a median survival of 17.9 months versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab (\(P=0.008\)).\(^{230}\) A study of previously untreated patients receiving bevacizumab and irinotecan-5-FU chemotherapy (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 months versus 15.6 months (hazard ratio = 0.66; \(P<0.001\)).

Results from a recent head-to-head randomized, double-blind, placebo-controlled phase III study (NO16966) comparing CapeOx (capecitabine dose 1000 mg/m\(^2\) twice daily for 14 days) with bevacizumab or placebo to FOLFOX with bevacizumab or placebo in patients with unresectable metastatic disease have been reported.\(^{204}\) In this large trial of 1,400 patients, the addition of bevacizumab to oxaliplatin-based regimens was associated with a more modest increase of 1.4 months in PFS compared to these regimens without bevacizumab (hazard ratio=0.83; 97.5% CI, 0.72-0.95; \(P=0.0023\)), and the difference in overall survival, which was also a modest 1.4 months, did not reach statistical significance (hazard ratio=0.89; 97.5% CI, 0.76-1.03; \(P=0.077\)).\(^{204}\) It has been 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 such hypotheses are conjectural.\(^{238}\) However, in this 1,400-patient randomized study, absolutely no difference in response rate was seen with and without bevacizumab (see below), 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 PFS when added to CapeOx but not FOLFOX.\(^{204}\) The randomized phase III trial, HEPATICA, comparing capecitabine with and without bevacizumab as adjuvant therapy in patients with liver metastases is currently recruiting patients (clinicaltrials.gov NCT00394992).\(^{285}\)

There are no data that directly address the question of the use of bevacizumab 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 cancer\textsuperscript{127, 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 post-resection 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.\textsuperscript{286} In addition, gastrointestinal perforation is a rare, but important, side effect of bevacizumab therapy in patients with colorectal cancer.\textsuperscript{270, 287} 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,\textsuperscript{288} illustrating that peritoneal debulking surgery may be a risk factor for gastrointestinal perforation whereas the presence of an intact primary tumor does not appear to increase risk for gastrointestinal perforation. A recent meta-analysis of randomized controlled trials demonstrated that the addition of bevacizumab to chemotherapy is associated with a higher incidence of treatment-related mortality than with chemotherapy alone (RR = 1.33, 95% CI, 1.02-1.73; P = 0.04); hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal perforation (7.1%) were the most common causes of fatality.\textsuperscript{289} Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.\textsuperscript{290}

Use of bevacizumab may interfere with wound healing.\textsuperscript{270, 286, 287} A retrospective evaluation of data from 2 randomized trials of 1,132 patients receiving chemotherapy with or without bevacizumab as initial therapy for metastatic colorectal cancer indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen when this population was compared to the group receiving chemotherapy alone while undergoing major surgery (13% vs 3.4%, respectively; P=0.28).\textsuperscript{287} However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to 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=0.63). 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 prior to surgery (ie, bevacizumab excluded from the 6th cycle of therapy).\textsuperscript{291} In addition, no significant differences in bleeding, wound, or hepatic complications were observed in a retrospective trial evaluating effects of preoperative bevacizumab stopped ≤8 weeks vs. >8 weeks prior to resection of liver colorectal metastases for patients receiving oxaliplatin- or irinotecan-containing regimens.\textsuperscript{292} The panel recommends an interval of at least 6 weeks (which corresponds to 2 half-lives of the drug\textsuperscript{286}) 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 upon recurrence, and thus increased mortality. A recent retrospective meta-analysis of 5 placebo-controlled randomized phase III trials including 4,205 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.\textsuperscript{293} Although this meta-analysis has been criticized,\textsuperscript{294, 295} the results are supported by recent results from the
NSABP Protocol C-08 trial. This trial included patients with phase II and phase III colorectal cancer, and no differences in recurrence, mortality, or mortality 2 years following recurrence were seen between patients receiving bevacizumab versus patients in the control arm. These results suggest that there is no ‘rebound effect’ associated with bevacizumab use.

Results from 2 randomized phase III trials have demonstrated that combination therapy with more than 1 biologic agent is not associated with improved outcomes and can cause increased toxicity. In the PACCE trial, addition of panitumumab to a regimen containing oxaliplatin- or irinotecan-based chemotherapy plus bevacizumab was associated with significantly shorter PFS and higher toxicity in both KRAS wild-type and mutant groups. Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab. 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. Recently, cetuximab and panitumumab have been studied in combination with FOLFIRI and FOLFOX as initial therapy options for treatment of metastatic colorectal cancer. A sizable body of recent literature has demonstrated that tumors with a mutation in codon 12 or codon 13 of the KRAS gene are essentially insensitive to EGFR inhibitors such as cetuximab or panitumumab (discussed in more detail in The Role of KRAS and BRAF Status, below). 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, as there is 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, such testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see discussion on KRAS and BRAF testing below).

Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively. Based on case reports and a small trial, for those patients experiencing severe infusion reactions to cetuximab, administration of panitumumab appears to be feasible.

Skin toxicity is a side effect of both of these agents and is not considered to be part of the infusion reactions. The incidence and severity of skin reactions with cetuximab and panitumumab appears to be very similar. Furthermore, the presence and severity of skin rash in patients receiving either of these drugs has been shown to be predictive of increased response and survival. A recent NCCN task force has addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.

Use of cetuximab as initial therapy for metastatic disease was investigated in the CRYSTAL trial where patients were randomly assigned to receive FOLFIRI with or without cetuximab. Retrospective analyses of the subset of patients with known KRAS
tumor status showed a statistically significant improvement in median PFS with the addition of cetuximab in the group with disease characterized by the KRAS wild-type gene (9.9 months vs. 8.7 months; hazard ratio=0.68; 95% CI, 0.50-0.94; P=0.02). The statistically significant benefit in PFS for patients with KRAS wild-type tumors receiving cetuximab was confirmed in a recent publication of an updated analysis of the CRYSTAL data. 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 versus 20.0 months, P=0.0093).

In a retrospective evaluation of the subset of patients with known tumor KRAS status enrolled in the randomized phase II OPUS trial, addition of cetuximab to FOLFOX was associated with an increased objective response rate (61% vs. 37%; odds ratio=2.54; P=0.011) and a very slightly lower risk of disease progression (7.7 months vs. 7.2 months (a 15-day difference); hazard ratio=0.57; 95% CI, 0.35-0.90; P=0.0163) compared with FOLFOX alone in the subset of patients with KRAS wild-type tumors. Whereas data to support the statistically significant benefits in objective response rate and PFS 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 receiving chemotherapy alone (hazard ratio=0.85; P=0.39). 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 OS or PFS in this population of patients in the randomized phase III NORDIC VII study of the Nordic Colorectal Cancer Biomodulation Group. Further, in the recent randomized phase III Medical Research Council (MRC) COIN trial, there was no benefit in OS (17.9 vs. 17.0 months, P = 0.067) or PFS (8.6 months in both groups, P = 0.60) 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 because of the increased incidence of grade 3 adverse events seen in this trial, the panel has removed its 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 PFS with addition of panitumumab (hazard ratio=0.80; 95% CI, 0.67-0.95; P=0.009), although differences in overall survival between the 2 arms were not significant. Therefore, the combination of FOLFOX and panitumumab remains an option as initial therapy for patients with advanced or metastatic disease. It is also important to note that the addition of panitumumab had a detrimental impact on PFS for patients with tumors characterized by mutated KRAS in the PRIME trial.

Based on the results of both the PACCE trial and the CAIRO2 trial, the panel strongly advises against the concurrent use of bevacizumab with either cetuximab or panitumumab (see discussion in ‘Bevacizumab,’ above).
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 by IHC is not predictive of treatment efficacy.\textsuperscript{216, 317} 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 \textit{KRAS} gene.\textsuperscript{116, 210} A sizable body of literature has demonstrated that these \textit{KRAS} mutations predict for lack of response to cetuximab or panitumumab therapy,\textsuperscript{210, 241, 271, 300-305, 318} 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.\textsuperscript{298, 299} There are mixed results as far as the prognostic value of \textit{KRAS} mutations, and the test is not recommended for prognostic reasons. Interestingly, 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.\textsuperscript{319} Another recent retrospective study demonstrated similar results.\textsuperscript{320} However, as stated in the de Roock manuscript, these findings are hypothesis-generating only, and prospective studies are needed to determine if patients with \textit{KRAS} G13D mutations can, in fact, benefit from anti-EGFR therapy. At present, 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 the time of diagnosis of stage IV disease. The recommendation for \textit{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 \textit{KRAS} status is appropriate in order 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 \textit{KRAS} mutation, if present, while other treatment options still exist. Note that since anti-EGFR agents have no role in the management of stage I, II, or III disease, \textit{KRAS} genotyping of colorectal cancers at these earlier stages is not recommended. \textit{KRAS} mutations are early events in colorectal cancer formation, and therefore there is a very tight correlation between mutation status in the primary tumor and the metastases.\textsuperscript{321-323} For this reason, \textit{KRAS} genotyping can be done on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of \textit{KRAS} genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable. The panel recommends that \textit{KRAS} gene testing be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.\textsuperscript{324} No specific testing methodology is recommended.\textsuperscript{325}

Although certain mutations of \textit{KRAS} indicate a lack of response to EGFR inhibitors, many tumors containing wild-type \textit{KRAS} still do not respond to these therapies. Therefore, studies have addressed factors downstream of \textit{KRAS} as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5%-9% of colorectal cancers are characterized by a specific mutation in the \textit{BRAF} gene (V600E).\textsuperscript{281, 326} \textit{BRAF} mutations are, for all practical purposes, limited to those tumors that do not have \textit{KRAS} exon 2 mutations.\textsuperscript{326} Activation of the protein product of the non-mutated \textit{BRAF} gene occurs downstream of activated k-ras protein in the EGFR pathway; the
mutated BRAF protein product is believed to be constitutively active, thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

In fact, there is retrospective evidence that mutated BRAF is another marker of resistance to anti-EGFR therapy in the non-first-line setting of metastatic disease. 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%) when compared to tumors with wild-type BRAF (124/326; 38.0%, P=0.0012). However, data from unplanned retrospective subset analyses of metastatic colorectal cancer patients treated in the first-line setting suggest that although a V600E BRAF 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. Overall, data strongly suggest that BRAF V600E mutations confer resistance to anti-EGFR therapy in the non-first-line setting, while there may be some benefit to the addition of anti-EGFR agents to FOLFOX or FOLFIRI when given to patients with BRAFV600E mutations in the first-line metastatic setting.

A recent prospective analysis of tissues from stage II and III colon cancer patients enrolled in the PETACC-3 trial demonstrated that BRAF mutation is prognostic for overall survival in patients with tumors that have low microsatellite instability or stable microsatellites (hazard ratio 2.2; 95% CI; 1.4-3.4; P=0.0003). Moreover, an updated analysis of the CRYSTAL trial demonstrated that patients with metastatic colorectal tumors carrying a BRAF mutation have a worse prognosis than those with the wild-type gene. Additionally, BRAF mutation status predicted overall survival in the AGITG MAX trial, with a hazard ratio of 0.49 (CI, 0.33 to 0.73; P = 0.001). For patients with KRAS wild-type tumors, the panel includes the option of BRAF genotyping of tumor tissue (either primary tumor or metastasis) at the time of 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 above for KRAS gene testing apply. No specific testing methodology is recommended.

EGFR testing of colorectal tumor cells has no demonstrated 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. A similar conclusion was drawn with respect to panitumumab. Therefore, routine EGFR testing is not recommended, and no patient should be either considered for or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.

Therapy after Progression

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

The recommended therapy options after first progression for patients who have received prior 5-FU/LV-based or capecitabine-based therapy are dependent on the initial treatment regimen:
For patients who received a FOLFOX or CapeOx-based regimen for initial therapy, FOLFIRI with or without cetuximab or panitumumab (KRAS wild type tumor only),234 and irinotecan with or without cetuximab or panitumumab (KRAS wild-type tumor only) are recommended options.216, 223

For patients who received a FOLFIRI-based regimen as initial treatment, FOLFOX or CapeOx alone,339 cetuximab or panitumumab plus irinotecan, or single agent cetuximab or panitumumab (for those not appropriate for the combination with irinotecan) are recommended options.

For patients who received 5-FU/LV or capecitabine without oxaliplatin or irinotecan as initial therapy, options after first progression include FOLFOX, CapeOx, FOLFIRI, single agent irinotecan, or irinotecan plus oxaliplatin (IROX).

For patients who received FOLFOXIRI as initial therapy, cetuximab or panitumumab plus irinotecan or cetuximab or panitumumab alone are recommended options for those with wild-type KRAS gene.

Results from a randomized study to evaluate the efficacy of FOLFIRI and FOLFOX6 regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen following first progression showed neither sequence to be significantly superior with respect to PFS or median overall survival.249 A combined analysis of data from 7 recent phase III clinical trials in advanced colorectal cancer provided support for a correlation between an increase in median survival and administration of all of the 3 cytotoxic agents (ie, 5-FU/LV, oxaliplatin, and irinotecan) at some point in the continuum of care.340 Furthermore, overall survival was not found to be associated with the order in which these drugs were received. Single agent irinotecan administered after first progression has been shown to significantly improve overall survival relative to best supportive care 217 or infusional 5-FU/LV.341 In the study of Rougier et al,341 median progression-free survival was 4.2 months for irinotecan versus 2.9 months for 5-FU (P=0.030), whereas Cunningham et al217 reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive-care group (P=0.0001). Furthermore, no significant differences in overall survival were observed in the Intergroup N9841 trial when FOLFOX was compared to irinotecan monotherapy following first progression of metastatic colorectal cancer.342

Bevacizumab in the Non-First Line Setting
With respect to the treatment continuum for metastatic colorectal cancer, there are no prospective data to support the addition of bevacizumab to a regimen following 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 following progression of metastatic disease.224 The randomized phase III study E3200, conducted by Eastern Cooperative Oncology Group (ECOG) in patients who had progressed through a first line non-bevacizumab-containing regimen, demonstrated that the addition of bevacizumab to second-line FOLFOX modestly improved survival in these patients.224 Median overall survival was 12.9 months for patients receiving FOLFOX plus bevacizumab compared to 10.8 months for patients receiving FOLFOX alone (P=0.0011).224 Use of single agent bevacizumab is not recommended since it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX plus bevacizumab treatment arms.224
Cetuximab and Panitumumab in the Non-First Line Setting
For patients with wild-type KRAS progressing on therapies not containing an EGRF inhibitor, cetuximab or panitumumab plus irinotecan, cetuximab or panitumumab plus FOLFIRI, or single-agent cetuximab or panitumumab are recommended. For patients with wild-type KRAS progressing on therapies that did contain an EGRF inhibitor, administration of an EGFR inhibitor is not recommended in subsequent lines of therapy. Although no head-to-head studies comparing cetuximab and panitumumab have been undertaken, similar response rates have been observed when each agent was studied as monotherapy following progression. There are no data to support switching to use of either cetuximab or panitumumab after failure of the other drug, and the panel recommends against this practice. If the patient has failed oxaliplatin, irinotecan, and an EGFR inhibitor, the panel recommends best supportive care or enrollment on a clinical trial.

Panitumumab has been studied as a single agent 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 with known KRAS tumor status receiving cetuximab monotherapy as second-line therapy, the benefit of cetuximab vs. best supportive care was shown to be enhanced in patients with KRAS wild-type tumors. For those patients, median PFS was 12.3 weeks vs. 7.3 weeks in favor of the panitumumab arm. Response rates to panitumumab were 17% vs. 0% in the wild-type and mutant arms, respectively.

Panitumumab has also been studied in 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 PFS (5.9 months vs. 3.9 months; hazard ratio=0.73; 95% CI, 0.59-0.90; P=0.004), although differences in overall survival between the 2 arms did not reach statistical significance.

Cetuximab has been studied both as a single agent and in combination with irinotecan for patients with 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 demonstrate a difference in overall survival between the 2 treatment arms, but showed significant improvement in response rate and in median PFS with the combination of irinotecan and cetuximab compared with irinotecan alone. It is important to note that KRAS status was not determined in this study and that toxicity was higher in the cetuximab-containing arm (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 vs. best supportive care was shown to be enhanced to patients with KRAS wild-type tumors. For those patients, median PFS was 3.7 months vs. 1.9 months (hazard ratio=0.40; 95% CI, 0.30-0.54; P<0.001) and median overall survival was 9.5 months vs. 4.8 months (hazard ratio=0.55; 95% CI, 0.41-0.74; P<0.001) 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 (eg, colorectal liver metastases) is suspected should include a total colonoscopy, a complete blood count, chemistry profile, carcinoembryonic antigen (CEA) determination, a needle biopsy if indicated, and a CT scan with IV contrast of the chest, abdomen, and pelvis. MRI with IV contrast should be considered if CT
is inadequate. The panel also recommends tumor KRAS gene status testing at the time of diagnosis of metastatic disease and consideration of BRAF genotyping for all patients with KRAS wild-type metastatic colon cancer (see further discussion in ‘The Role of KRAS and BRAF Status,’ above).

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 following chemotherapy (eg, in the presence of necrotic lesions). False positive PET/CT scan results can occur in the presence of tissue inflammation following surgery or infection. An MRI with IV contrast can be considered as part of the preoperative evaluation of patients with potentially surgically resectable M1 liver disease. For example, an MRI with contrast may be of use in situations where 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 following preoperative chemotherapy. It should be noted that in the overwhelming majority of cases, 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, due to involvement of critical structures, cannot be resected unless regression is accomplished with chemotherapy (see ‘Conversion to Resectability,’ above).

Close communication between 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 done 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 done to expand the future liver remnant. As mentioned above, 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 month duration (ie, choice of FOLFIRI, FOLFOX, or CapeOx chemotherapy alone or with bevacizumab; FOLFIRI or FOLFOX regimens 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 above) and a staged resection of metastatic disease. Overall,
combined neoadjuvant and adjuvant treatments should not exceed 6 months.

In the case of liver metastases only, 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,’ above), chemotherapy regimens with high response rates should be considered, and these patients should be re-evaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing such 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 re-initiation of bevacizumab. Patients with disease converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer including treatment with pre- and postoperative chemotherapy for a preferred total perioperative 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 not responding to therapy should receive chemotherapy for advanced or metastatic disease with treatment selection based, in part, on whether the patient is or is not 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 to be unresectable (see ‘Determining Resectability,’ above), the panel recommends chemotherapy corresponding to initial therapy for metastatic disease (eg, 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 by palliative colon resection should be considered only if the patient has an unequivocal imminent risk of obstruction or acute significant bleeding. It should be noted that 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 done 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, as 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’). There was no consensus of the panel 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,’ above).

**Synchronous Abdominal/Peritoneal Metastases**

For patients with peritoneal metastases causing obstruction or felt to be at imminent risk for causing 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 (ie, peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy to be investigational and does not endorse such 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. It should be noted that the CT that accompanies a “PET/CT” is usually a non-contrast CT, and thus not of ideal quality for routine staging. Upon documentation of metachronous potentially resectable metastatic disease by dedicated contrast-enhanced CT or MRI, characterization of the extent of disease by 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 which could preclude surgery. Specifically, Joyce et al reported 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 in order to define whether anti-EGFR agents can be considered in the list of potential options for the patient. Although BRAF genotyping can be considered for patients with tumors characterized by the wild-type KRAS gene, such testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see discussion in ‘The Role of KRAS and BRAF Status’). 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 by also including an evaluation of the chemotherapy history of the patient, and by the absence of colectomy. Patients with resectable disease are classified according to whether or not they have received 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 by cross-sectional imaging scan to have unresectable disease (including those considered potentially convertible) should receive an active chemotherapy regimen based on prior chemotherapy history, as described in ‘Therapy after Progression,’ above. 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.
Post-Treatment Surveillance

Following curative-intent surgery and adjuvant chemotherapy, if administered, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and to identify new metachronous neoplasms at a preinvasive stage. Advantages of more intensive follow-up of stage II and/or stage III patients have been demonstrated prospectively in several studies and in 3 recent meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance. Other recent studies impacting on the issue of post-treatment 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 demonstrated that 80% of recurrences were 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 post-treatment 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 post-treatment surveillance pertain to patients with stage I-stage III disease who have undergone successful treatment (ie, no known residual disease). History and physical examination should be given every 3 to 6 months for 2 years, then every 6 months for a total of 5 years for stage III patients and for stage I/II patients 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 following resection (or at approximately 3 to 6 months post resection if not performed preoperatively due to an obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma (villous polyp, polyp >1 cm or high grade dysplasia), in which case colonoscopy should be repeated in 1 year. More frequent colonoscopies may be indicated in patients who present with colon cancer before age 50. Chest, abdominal, and pelvic CT scan are recommended annually for the first 3 to 5 years in stage III patients and in stage II patients 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 pre-operative baseline study or for routine surveillance.

Initial follow-up office visits at 3 month intervals for history and physical examination may be more useful for patients diagnosed with stage III disease, whereas patients with a diagnosis of stage I disease may not need to be seen as frequently (ie, can be seen once every 6 months). This principle also applies to CEA testing, which is used primarily to monitor for indication of recurrence of disease (see section on ‘Managing an Increasing CEA Level,’ below), 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, since data show that patients with a history of colorectal cancer have an increased risk of developing second cancers, particularly in the first 2 years.
following 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 post-treatment surveillance colonoscopies is higher (ie, annually) for patients with HNPCC. CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver. Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases. Post-treatment 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 such disease.

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

Managing an Increasing Carcinoembryonic Antigen 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. The opinion of the panel on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans was divided (ie, some panel members favored use of PET/CT in this scenario while 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
Post-treatment 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 (eg, 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 (eg, patients with stoma). Specific management interventions to address these and other side effects are described in a recent review. A survivorship care plan for patients with colorectal cancer has recently been 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.
There is also evidence to indicate 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 following treatment for colon cancer. 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 $\geq 35$ kg/m$^2$ had an increased risk of disease recurrence and death. 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. Furthermore, a diet consisting of more fruits, vegetables, poultry, and fish, and less red meat, as well as diets 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. In addition, a recent study of a large cohort of men treated for stage I-stage III colorectal cancer demonstrated an association between increased physical activity and lower rates of colorectal cancer-specific mortality and overall mortality. 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, 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. 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 NCCN Colon/Rectal/Anal Cancer Guidelines 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). A patient with metastatic disease in the liver or lung should be considered for surgical resection if he or she is a candidate for surgery and if 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 (ie, conversion therapy), such therapy should be initiated. Adjuvant chemotherapy should be considered following resection of liver or lung...
metastases. The recommended post-treatment surveillance program for colon cancer patients includes serial CEA determinations, as well as 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 the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, including plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy options for advanced or metastatic disease depend on whether or not 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 (eg, bevacizumab, cetuximab, or 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 are dependent on the choice of initial therapy.
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Discussion


