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Summary of the Guidelines updates

Summary changes in the 1.2008 version of the Colon Guidelines from the 2.2007 version include:

**COL-3**
- Footnote "r" defining advanced adenoma is new to the page, "Villous polyp, polyp > 1 cm, or high grade dysplasia".

**COL-5**
- Footnote "t" is new to the page, emphasizing the role of a multidisciplinary team approach for patients with synchronous liver or lung metastases.

**COL-6**
- The recommendation for bevacizumab in combination with chemotherapy was changed from "+" to "±" for resectable synchronous metastases.
- Footnote "u" was modified to include a surgical evaluation 8-10 weeks after the initiation of therapy due to the risk of steatohepatitis.

**COL-7**
- The recommendation for bevacizumab in combination with chemotherapy was changed from "+" to "±" for unresectable synchronous metastases.

**COL-8**
- Footnote "y" - "Aggressive cytoreductive debulking and/or intraperitoneal chemotherapy are not recommended outside the setting of a clinical trial" was added to synchronous abdominal/pertitoneal metastases.

**COL-10**
- Footnote "x" clarifying the setting for HAI therapy is new to the page, "Should be performed at institutions with experience in both the surgical and medical oncologic aspects of this procedure".

**COL-A 2 of 3**
- Under "Lymph node evaluation", the sentences beginning with "For stage II (pN0) colon cancer..." and ending "for patients with stage IIIB and IIIC colon cancer" are new to the bullet.
- Under "Sentinel lymph node", the sentences beginning with "While the 6th Edition of the AJCC..." and ending "...invasion of the vessel (lymphatic) wall" are new to the first bullet.

**COL-B 3 of 4** - Principles of Surgery:
- The bullet "Plans for a debulking resection (< R0 resection) is not recommended" was added.
- "All original sites of disease need to be resectable" was added to the bullet "Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant therapy."
- Ablative techniques "may" be considered "when all known disease is amenable to ablation."

**COL-C** - Chemotherapy for Advanced or Metastatic Disease:
- A clarifying statement was added that cetuximab or panitumumab single agent therapy is for patients not able to tolerate cetuximab + irinotecan. (COL-C 1 of 5)
- A bi-weekly schedule for the administration of cetuximab at 500 mg/m² was added (COL-C 4 of 5)

**COL-E 3 of 3** - Principles of Adjuvant Therapy:
- Bullet 2 - The following statement was added "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."
- Bullet 3 - The statement was modified to include "infusional 5-FU/leucovorin/irinotecan (FOLFIRI) has not been shown to be superior to 5-FU/LV".

Footnote "r" defining advanced adenoma is new to the page, "Villous polyp, polyp > 1 cm, or high grade dysplasia".

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**Colon Cancer**

**CLINICAL PRESENTATION**

- **Pedunculated polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer**
  - **WORKUP**
    - Pathology review
    - Colonoscopy
    - Marking of cancerous polyp site (at time of colonoscopy or within 2 wks)
  - **FINDINGS**
    - Single specimen, completely removed with favorable histological features and clear margins
    - Fragmented specimen or margin cannot be assessed or unfavorable histological features
  - **SURGERY**
    - Observe
    - Colectomy with en bloc removal of regional lymph nodes

- **Sessile polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer**
  - **WORKUP**
    - Pathology review
    - Colonoscopy
    - Marking of cancerous polyp site (at time of colonoscopy or within 2 wks)
  - **FINDINGS**
    - Single specimen, completely removed with favorable histological features and clear margins
    - Fragmented specimen or margin cannot be assessed or unfavorable histological features
  - **SURGERY**
    - Observe
    - Colectomy with en bloc removal of regional lymph nodes

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**Staging, MS, References**

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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.
### Colon Cancer

#### CLINICAL PRESENTATION

**Colon cancer appropriate for resection (non metastatic)**

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

#### WORKUP

- Suspected or proven metastatic adenocarcinoma from large bowel

<table>
<thead>
<tr>
<th>FINDINGS</th>
<th>SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable, nonobstructing</td>
<td>Colectomy(^e) with en bloc removal of regional lymph nodes</td>
</tr>
<tr>
<td>Resectable, obstructing (unprepped)</td>
<td>One-stage colectomy(^e) with en bloc removal of regional lymph nodes or Resection with diversion or Stent or Diversion</td>
</tr>
<tr>
<td>Locally unresectable or medically inoperable</td>
<td>Palliative therapy(^g)</td>
</tr>
</tbody>
</table>

#### SURGERY

- Colectomy\(^e\) with en bloc removal of regional lymph nodes
- One-stage colectomy\(^e\) with en bloc removal of regional lymph nodes or Resection with diversion or Stent or Diversion
- Colectomy\(^e\) with en bloc removal of regional lymph nodes

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

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

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

### Notes

- All patients with colon cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP, see the NCCN Colorectal Cancer Screening Guidelines.
- Colon cancer appropriate for resection, pathological stage, and lymph node evaluation.
- See Principles of Pathologic Review (COL-A).
- Colon cancer appropriate for resection, pathological stage, and lymph node evaluation.
- See Principles of Surgery (COL-B).
- Palliative therapy may include RT for uncontrolled bleeding, stent for obstruction, supportive care.

**Back to Other Clinical Presentations (Table of Contents)**

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### PATHOLOGIC STAGE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Adjuvant Therapy</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis; T1, N0, M0; T2, N0, M0</td>
<td>None</td>
<td>None</td>
<td>History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y</td>
</tr>
<tr>
<td>T3, N0, M0</td>
<td>Consider capecitabine or 5-FU/leucovorin or 5-FU/leucovorin/oxaliplatin (category 2B for all options)</td>
<td>Clinical trial or Observation</td>
<td>Chest/abdominal/pelvic CT may be considered annually x 3 y for patients at high risk for recurrence</td>
</tr>
<tr>
<td>T3, N0, M0 at high risk for systemic recurrence (grade 3-4, lymphatic/vascular invasion, bowel obstruction, &lt; 12 lymph nodes examined) or T4, N0, M0; or T3 with localized perforation or close, indeterminate or positive margins</td>
<td>5-FU/leucovorin/oxaliplatin or capcitabine or 5-FU/leucovorin</td>
<td>Clinical trial or Observation</td>
<td>Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo if abnormal, repeat in 1 y if advanced adenoma, repeat in 3 y, then every 5 y</td>
</tr>
</tbody>
</table>

### Node positive disease, see page COL-4

- All patients with colon cancer should be counseled for family history. 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) - Pathological stage.
- There are no data to support adjuvant therapy in Stage I disease, however certain high risk Stage II patients (perivascular invasion, poorly differentiated histology, inadequate lymph node sampling) may be considered at higher risk and a discussion of chemotherapy may be warranted.
- Patients considered to be N0 but who have < 12 nodes examined are suboptimally staged and should be considered in the high risk group. See Principles of Pathologic Review (COL-A) - Lymph node evaluation.
- There are insufficient data to recommend the use of molecular markers to determine adjuvant therapy.
- See Principles of Risk Assessment for Stage II Disease (COL-D).
- See Principles of Adjuvant Therapy (COL-E).

### 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 for T2 or greater lesions
- Chest/abdominal/pelvic CT may be considered annually x 3 y for patients at high risk for recurrence
- Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo if abnormal, repeat in 1 y if advanced adenoma, repeat in 3 y, then every 5 y
- PET scan is not routinely recommended

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### Pathologic Stage

<table>
<thead>
<tr>
<th>ADJUVANT THERAPY</th>
<th>SURVEILLANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-3, N1-2, M0</td>
<td>5-FU/leucovorin/oxaliplatin (category 1)(^k,m,n) or Capecitabine(^k,n) or 5-FU/leucovorin(^k,n)</td>
</tr>
<tr>
<td>or T4, N2-2, M0</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></td>
<td>• CEA(^q) every 3-6 mo for 2 y, then every 6 mo for a total of 5 y for T2 or greater lesions</td>
</tr>
<tr>
<td></td>
<td>• Chest/abdominal/pelvic CT annually x 3 y for patients at high risk for recurrence(^o,p)</td>
</tr>
<tr>
<td></td>
<td>• Colonoscopy(^q) in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo</td>
</tr>
<tr>
<td></td>
<td>▶ If abnormal, repeat in 1 y</td>
</tr>
<tr>
<td></td>
<td>▶ If advanced adenoma,(^r) repeat in 3 y, then every 5 y(^s)</td>
</tr>
<tr>
<td></td>
<td>• PET scan is not routinely recommended</td>
</tr>
</tbody>
</table>

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

\(^d\)See Principles of Pathologic Review (COL-A) - Pathological stage.

\(^j\)There are insufficient data to recommend the use of molecular markers to determine adjuvant therapy.

\(^k\)See Principles of Risk Assessment for Stage II Disease (COL-D).

\(^m\)Treatment options include FOLFOX (infusional 5-FU, leucovorin, oxaliplatin or FLOX (bolus 5-FU, leucovorin, oxaliplatin). Grade 3-4 diarrhea is considerably higher with FLOX than FOLFOX in cross study comparison.

\(^n\)Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy COL-F.


\(^p\)CT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion of tumor or poorly differentiated tumors).

\(^q\)If patient is a potential candidate for further intervention.

\(^r\)Villous polyp, polyp > 1 cm, or high grade dysplasia.

Suspected or proven metastatic synchronous adenocarcinoma from large bowel (Any T, any N, M1)

- Colonoscopy
- Chest/abdominal/pelvic CT
- CBC, platelets, chemistry profile
- CEA
- Needle biopsy, if clinically indicated
- PET scan only if potentially surgically curable M1 disease
- Consider MRI with IV contrast for preoperative evaluation, if potentially resectable M1 liver disease

CLINICAL PRESENTATION

WORKUP

FINDINGS

Synchronous liver only or lung only metastases

Resectable → See Treatment and Adjuvant Therapy (COL-6)

Unresectable → See Treatment and Adjuvant Therapy (COL-7)

Abdominal/peritoneal metastases

Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

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See Principles of Surgery (COL-B)

See Primary Treatment and Adjuvant Therapy (COL-8)
Colon Cancer

TREATMENT

Resectable synchronous liver only or lung only metastases → Colectomy, with synchronous or subsequent liver or lung resection or
Neoadjuvant therapy
(FOLFIRI or FOLFOX or CapeOX ± bevacizumab) followed by synchronous or staged colectomy and resection of metastatic disease or
Colectomy, followed by chemotherapy (FOLFIRI or FOLFOX or CapeOX ± bevacizumab) and staged resection of metastatic disease

ADJUVANT THERAPY

(resected metastatic disease)

(6 mo preferred)

Active chemotherapy regimen for advanced disease (See Chemotherapy for Advanced or Metastatic Disease (COL-C)) or
Hepatic artery infusion therapy ± systemic 5-FU/leucovorin (category 2B) or continuous IV 5-FU - liver metastases only or
Consider observation or shortened course of chemotherapy, if patient received neoadjuvant therapy

SURVEILLANCE

If patient stage IV, NED:
• CEA every 3 mo × 2 y, then every 6 mo × 3-5 y
• Chest/abdominal/pelvic CT scan every 3-6 mo × 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 abnormal, repeat in 1 y
  ▶ If advanced adenoma, repeat in 3 y, then every 5 y

Recurrent (See COL-9)

All patients with colon cancer should be counseled for family history. 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 Surgery (COL-B).

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


When preoperative therapy is planned, surgical evaluation should be planned within 8-10 weeks after initiation of treatment due to concerns related to an increased risk of steatohepatitis.

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. There is an increased risk of stroke and other arterial events especially in age ≥ 65. The use of bevacizumab may interfere with wound healing.

Should be performed at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

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FINDINGS

Synchronous abdominal/peritoneal metastases

Obstructed or imminent obstruction

Nonobstructing

PRIMARY TREATMENT

Colon resection or Diverting colostomy or Bypass of impending obstruction or Stenting

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

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

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**Colon Cancer**

**Recurrence Workup**

- **Serial CEA elevation**
  - **Negative findings**
    - Physical exam
    - Colonoscopy
    - Chest/abdominal/pelvic CT
  - **Positive findings**
    - Consider PET scan
    - Reevaluate chest/abdominal/pelvic CT in 3 mo
    - See treatment for Documented metachronous metastases COL-10

- **Documented metachronous metastases by CT, MRI and/or biopsy**
  - See treatment for Documented metachronous metastases COL-10

---

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**Resectable**

- **Documented metachronous metastases by CT, MRI and/or biopsy**

\[\text{See Primary Treatment COL-11}\]

**Unresectable**

- **Previous adjuvant FOLFOX within past 12 months**
  - FOLFIRI ± bevacizumab
  - Converted to resectable

- **Previous adjuvant FOLFOX > 12 months**
  - Previous 5-FU/LV or capecitabine
  - No previous chemotherapy
  - Active chemotherapy regimen (See COL-C)
  - Active chemotherapy regimen

- **Active chemotherapy regimen**

\[\text{Resection or Resection + hepatic artery infusion therapy (category 2B) - liver metastases only}\]

**Active chemotherapy regimen**

\[\text{See COL-C}\]

\[\text{See Principles of Surgery (COL-B)}\]

- Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.
- Should be performed at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
- If patient has seen all active chemotherapy regimens, observation is an option.

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Resectable\textsuperscript{e, t} or Resection + hepatic artery infusion therapy\textsuperscript{x} (category 2B)
- liver metastases only

No previous chemotherapy
Previous chemotherapy > 12 mo

Pet scan

Resectable\textsuperscript{e, t}

Previous chemotherapy within past 12 mo

Resectable\textsuperscript{e, t}

Previous adjuvant FOLFOX within past 12 months

Previous adjuvant FOLFOX > 12 months
Previous 5-FU/LV or capecitabine
No previous chemotherapy

FOLFIRI ± bevacizumab

Converted to resectable\textsuperscript{e}

Active chemotherapy regimen\textsuperscript{z} (See COL-C)

Unresectable

Active chemotherapy regimen\textsuperscript{z} (See COL-C)

Active chemotherapy regimen\textsuperscript{z} (See COL-C)

Active chemotherapy regimen\textsuperscript{z} (See COL-C)

Active chemotherapy regimen\textsuperscript{z} (See COL-C)

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\textsuperscript{e}See Principles of Surgery (COL-B).
\textsuperscript{t}Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.
\textsuperscript{x}Should be performed at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
\textsuperscript{z}If patient has seen all active chemotherapy regimens, observation is an option.
PRINCIPLES OF PATHOLOGIC REVIEW (1 of 3)

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 angiolympathic 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 angiolympathic 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 peritoneal margins (radial)8-9 See Staging (ST-1)

See Lymph node evaluation and sentinel lymph node on page 2 of 3 COL-A
See footnotes on page 3 of 3 COL-A

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Lymph node evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancers.8-10 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, >30.11-19 The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade and tumor site.12 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 IIIIB and IIIC colon cancer.20

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. While studies to date seem promising, there is no uniformity in the definition of what constitutes "true metastatic carcinoma." Confusion arises when isolated tumors cells (ITC) have been considered micrometastatic disease in contraindication to true micrometastasis (tumor aggregates > 0.2 mm to < 2 mm in size). The significance of detection of single cells by IHC alone is controversial. Some studies have considered these to be micrometastasis, however, "consensus" recommends these to be considered ITC and not micrometastatic disease.21-25 While the 6th edition of the AJCC Cancer Staging26 manual considers "tumor clusters" < 0.2 mm as isolated tumor cells (pN0) and not metastatic carcinoma, some have challenged this. Some investigators believe that size should not effect 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.27 Hermanek et al28 proposed isolated tumor cells to be defined as single tumor cells or small clusters (never more than a few cells clumped together) without evidence of extrasinusoidal stromal proliferation or reaction and no contact with or invasion of the vessel (lymphatic) wall.

- Some studies have shown that the detection of IHC cytokeratin positive cells in stage II (N0) colon cancer (defined by H & E) has a worse prognosis while others have failed to show this survival difference. In these studies, ITC were considered micrometastasis.29-33

- 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.21-25,29-33
PRINCIPLES OF PATHOLOGIC REVIEW (3 of 3)

References


Colectomy

- Lymphadenectomy
  - Lymph nodes at the origin of feeding vessel should be identified for pathologic exam.
  - Lymph nodes outside the field of resection considered suspicious should be biopsied or removed.
  - Positive nodes left behind indicate an incomplete (R2) resection.
  - A minimum of 12 lymph nodes need to be examined to clearly establish stage II (T 3-4, N0) colon cancer.
  - Even for Stage III disease, the number of lymph nodes correlates with survival.¹
- Laparoscopic-assisted colectomy may be considered based upon the following criteria:²
  - Surgeon with experience performing laparoscopically-assisted colorectal operations.³,⁴
  - No disease in rectum or prohibitive abdominal adhesions.
  - No advanced local or metastatic disease.
  - Not indicated for acute bowel obstruction or perforation from cancer.
  - Thorough abdominal exploration is required⁵
  - 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 on page 3 of 4 COL-B

See footnotes on page 2 of 4 COL-B
Liver
- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of adequate hepatic function is required.1,2
- Plan for a debulking resection (less than an R0 resection) is not recommended.
- There should be no unresectable extrahepatic sites of disease.3,4,5
- Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant therapy.6,7 All original sites of disease need to be resectable.
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.8
- Ablative techniques may be considered when all known disease is amenable to ablation.8
- Solitary lesions have a better prognosis than multiple liver metastases9
- Intra-arterial embolization should not be routinely used outside the setting of a clinical trial.
- The primary tumor must have been resected for cure (R0).
- Re-resection can be considered in selected patients.10

Lung
- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.11-14
- Resectable extrapulmonary metastases do not preclude resection.15-18
- The primary tumor must have been resected for cure (R0).
- Re-resection can be considered in selected patients.19

See footnotes on page 4 of 4 COL-B


CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 1 of 5)

Initial therapy

Patient can tolerate intensive therapy

FOLFOX² + bevacizumab or CapeOX³ + bevacizumab⁴

or

FOLFIRI⁵ + bevacizumab⁴

or

5-FU/leucovorin⁶ + bevacizumab⁴,⁷

Patient cannot tolerate intensive therapy

Capecitabine⁸ ± bevacizumab⁹ (category 2B for combination with bevacizumab)

or

Infusional 5-FU + leucovorin ± bevacizumab

Therapy after First Progression

FOLFIRI⁵ or Irinotecan⁵

or

FOLFIRI + cetuximab¹⁰,¹¹,¹² (category 2B)

or

Cetuximab¹⁰,¹¹,¹² + irinotecan⁵ (category 2B)

or

FOLFOX² or CapeOX³

or

Cetuximab¹⁰,¹¹,¹² + irinotecan⁵

or

Cetuximab¹⁰,¹¹,¹² or panitumumab¹¹,¹²,¹³ (not as combination)

Improveemnt in functional status

No improvement in functional status

Consider Initial Therapy as above¹⁵

Therapy after Second Progression

Cetuximab¹⁰,¹¹,¹² + irinotecan⁵

For patients not able to tolerate cetuximab + irinotecan, consider single agent cetuximab¹⁰,¹¹,¹² or panitumumab¹¹,¹²,¹³ (not as combination)

Clinical trial or best supportive care¹⁴

Cetuximab¹⁰,¹¹,¹² + irinotecan⁵

For patients not able to tolerate cetuximab + irinotecan, consider single agent cetuximab¹⁰,¹¹,¹² or panitumumab¹¹,¹²,¹³ (not as combination)

FOLFOX² or CapeOX³

Cetuximab¹⁰,¹¹,¹² + irinotecan⁵

For patients not able to tolerate cetuximab + irinotecan, consider single agent cetuximab¹⁰,¹¹,¹² or panitumumab¹¹,¹²,¹³ (not as combination)

Irinotecan⁵

Cetuximab¹⁰,¹¹,¹² + irinotecan⁵

For patients not able to tolerate cetuximab + irinotecan, consider single agent cetuximab¹⁰,¹¹,¹² or panitumumab¹¹,¹²,¹³ (not as combination)

Best supportive care

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.

See footnotes on page COL-C 2 of 5
For chemotherapy references, see Chemotherapy Regimens and References (COL-C pages 3 - 5).

Discontinuation of oxaliplatin is strongly considered from FOLFOX or CapeOX after 3 months of therapy or sooner if significant neurotoxicity develops (> grade 3) 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. Tourniag 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 2006;24:394-400. Ca/Mg infusions should not be used to reduce neurotoxicity because treatment reduces rate of response to FOLFOX.

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. 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/m^2 twice daily dose is the recommended starting dose, with close monitoring in the first cycle for toxicity, and dose adjustments as indicated.

There are no prospective data to support continuation of bevacizumab with a second-line regimen after first progression on a bevacizumab-containing regimen and such use is not routinely recommended. If bevacizumab 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.

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.

Infusional 5-FU is preferred. Bolus regimens of 5-FU are inappropriate as combination regimens with oxaliplatin or irinotecan.

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

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

Routine use of bevacizumab + cetuximab is not recommended in patients with prior bevacizumab progression.

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

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

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

There are no data to support the combination of panitumumab with chemotherapy.

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

The use of single agent capecitabine as a salvage therapy after failure on a fluoropyrimidine-containing regimen has been shown to be ineffective, and this is therefore not recommended.
### CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 3 of 5)

#### CHEMOTHERAPY REGIMENS

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Details</th>
</tr>
</thead>
</table>
| **FOLFOX** | Oxaliplatin 85 mg/m² IV over 2 hours, day 1  
Leucovorin 200 mg/m² IV over 2 hours, days 1 and 2  
Followed on days 1 and 2 by 5-FU 400 mg/m² IV bolus, then  
600 mg/m² IV over 22 hours continuous infusion  
Repeat every 2 weeks |
| **FOLFIRI** | Irinotecan 180 mg/m² IV over 30-120 minutes, day 1  
Leucovorin 200 mg/m² IV infusion to match duration of irinotecan  
infusion, days 1 and 2  
Followed on days 1 and 2 by 5-FU 400 mg/m² IV bolus, then 600  
mg/m² IV over 22 hours continuous infusion  
Repeat every 2 weeks |
| **FOLFOX 4** | 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 weeks²,³ |
| **CapeOX** | Oxaliplatin 130 mg/m² day 1, Capecitabine 850-1000 mg/m²  
twice daily for 14 days  
Repeat every 3 weeks |

*Leucovorin dose in Europe is 200 mg/m² of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m².

†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m²/day over 46 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.

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See footnotes on page 5 of 5 COL-C

**See Additional Chemotherapy Regimens 4 of 5 COL-C**
### CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 4 of 5)

**CHEMOTHERAPY REGIMENS**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2000-2500 mg/m²/day PO in two divided doses, days 1-14, followed by 7 days rest. Repeat every 3 weeks.</td>
</tr>
<tr>
<td>Bolus or infusional 5-FU/leucovorin</td>
<td></td>
</tr>
<tr>
<td>Roswell-Park regimen&lt;sup&gt;12&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>Biweekly&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Leucovorin 200 mg/m² IV over 2 hours, days 1 and 2. 5-FU 400 mg/m² IV bolus, then 600 mg/m² IV over 22 hours continuous infusion, days 1 and 2. Repeat every 2 weeks.</td>
</tr>
<tr>
<td>Biweekly infusional 5-FU/LV (sLV5FU2)&lt;sup&gt;14&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)† continuous infusion. Repeat every 2 weeks.</td>
</tr>
<tr>
<td>Weekly</td>
<td>Leucovorin 20 mg/m² as a 2 h infusion. 5-FU 500 mg/m² bolus administered 1 h after LV infusion. Repeat every week&lt;sup&gt;15&lt;/sup&gt;. 5-FU 2600 mg/m² by 24 h infusion plus leucovorin 500 mg/m². Repeat every week&lt;sup&gt;16&lt;/sup&gt;.</td>
</tr>
</tbody>
</table>

<sup>1</sup>Leucovorin dose in Europe is 200 mg/m² of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m².

<sup>†</sup>NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m²/day over 46 hours) to minimize medication errors.

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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.*
CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 5 of 5)

CHEMOTHERAPY REFERENCES


4. 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

- Ask the patient how much information they would like to know regarding prognosis.
- Patient/physician discussion regarding the potential risks of therapy compared to potential benefits. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk prognostic 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)
  - Assessment of other comorbidities and anticipated life expectancy.
- The benefit of adjuvant chemotherapy does not improve survival by more than 5 percent.

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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.
### PRINCIPLES OF ADJUVANT THERAPY (1 of 3)

<table>
<thead>
<tr>
<th>5-FU/leucovorin</th>
<th>FOLFOX 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Leucovorin 500 mg/m² given as a 2 h infusion and repeated weekly x 6</td>
<td>Oxaliplatin 85 mg/m² IV over 2 hours, day 1</td>
</tr>
<tr>
<td>5-FU 500 mg/m² given bolus 1 h after the start of leucovorin and repeated 6 x weekly.</td>
<td>Leucovorin 200 mg/m² IV over 2 hours, days 1 and 2</td>
</tr>
<tr>
<td>Every 8 weeks for 4 cycles¹</td>
<td>Followed on days 1 and 2 by 5-FU 400 mg/m² IV bolus, then</td>
</tr>
<tr>
<td>• 5-FU 370-400 mg/m² + leucovorin 200 mg/m² daily x 5 d, every 28 d x 6 cycles²</td>
<td>600 mg/m² IV over 22 hours continuous infusion</td>
</tr>
<tr>
<td>Capecitabine³</td>
<td>Repeat every 2 weeks⁵,⁶</td>
</tr>
<tr>
<td>Capecitabine 1250 mg/m² twice daily days 1-14 every 3 wks x 24 wks</td>
<td>mFOLFOX 6</td>
</tr>
<tr>
<td>FLOX⁴ (category 2B)</td>
<td>Oxaliplatin 85 mg/m² IV over 2 hours, day 1</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Leucovorin⁹ 400 mg/m² IV over 2 hours, day 1</td>
<td>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</td>
</tr>
</tbody>
</table>

*Leucovorin dose in Europe is 200 mg/m² of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m².

**NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m²/day over 46 hours) to minimize medication errors.

See footnotes on page 2 of 3 COL-E

See Additional Principles of Adjuvant Therapy on page 3 of 3 COL-E

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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.
PRINCIPLES OF ADJUVANT THERAPY (2 of 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 ADJUVANT THERAPY (3 of 3)

- Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in Stage III patients.\(^1\) This is an extrapolation from data available.
- FOLFOX appears to be superior for Stage III patients.\(^2,3\) 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.\(^4\)
- Bolus 5-FU/leucovorin/irinotecan should not be used in adjuvant therapy\(^5\) and infusional 5-FU/leucovorin/irinotecan (FOLFIRI) has not been shown to be superior to 5-FU/LV.\(^6,7\) Data are not yet available for capecitabine combination regimens.

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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.
- Intensity modulated radiotherapy (IMRT) or tomotherapy could be considered when there is a high risk of radiation-related normal tissue toxicity. Care should be taken to assure adequate tumor bed coverage.
- Intraoperative radiotherapy (IORT), if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Preoperative radiation is preferred for these patients to aid resectability. If IORT is not available, low dose external beam radiation could be considered, prior to adjuvant chemotherapy.
- Intra-arterial radioembolization or chemoembolization should not be routinely used outside the setting of a clinical trial.

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.
## Staging

### Table 1

**American Joint Committee on Cancer (AJCC) TNM Staging System for Colorectal Cancer***

#### Primary Tumor (T)
- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma *in situ*: intraepithelial or invasion of lamina propria †
- **T1**: Tumor invades submucosa
- **T2**: Tumor invades muscularis propria
- **T3**: Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
- **T4**: Tumor directly invades other organs or structures, and/or perforates visceral peritoneum ‡

#### Regional Lymph Nodes (N) §
- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Metastasis in 1 to 3 regional lymph nodes
- **N2**: Metastasis in 4 or more regional lymph nodes

#### Distant Metastasis (M)
- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis

#### Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Dukes §</th>
<th>MAC §</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>A</td>
<td>B1</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>B</td>
<td>B2</td>
</tr>
<tr>
<td>IIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>B</td>
<td>B3</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-T2</td>
<td>N1</td>
<td>M0</td>
<td>C</td>
<td>C1</td>
</tr>
<tr>
<td>IIIIB</td>
<td>T3-T4</td>
<td>N1</td>
<td>M0</td>
<td>C</td>
<td>C2/C3</td>
</tr>
<tr>
<td>IIIIC</td>
<td>Any T</td>
<td>N2</td>
<td>M0</td>
<td>C</td>
<td>C1/C2/C3</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>-</td>
<td>D</td>
</tr>
</tbody>
</table>

### Histologic Grade (G)
- **GX**: Grade cannot be assessed
- **G1**: Well differentiated
- **G2**: Moderately differentiated
- **G3**: Poorly differentiated
- **G4**: Undifferentiated

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit [www.cancerstaging.net](http://www.cancerstaging.net).) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.

†Tis includes cancer cells confined within the glandular basement membrane (*intraepithelial*) or lamina propria (*intramucosal*) with no extension through the muscularis mucosae into the submucosa.

‡Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum. Tumor that is adherent to other organs or structures macroscopically is classified T4. However, if no tumor is present in the adhesion microscopically the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

§A tumor nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion.

*Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

**Note:** The y prefix is to be used for those cancers that are classified after pretreatment, whereas the r prefix is to be used for those cancers that have recurred.
Manuscript
This manuscript is being updated to correspond with the newly updated algorithm. Last update 04/19/07

NCCN Categories of Evidence and Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Colorectal cancer is the third most frequently diagnosed cancer in men and women in the United States. In 2007, an estimated 112,340 new cases of colon cancer will occur. During the same year, it is estimated that 52,180 people will die from colon and rectal cancer. Despite these statistics, mortality from colon cancer has decreased over the past 30 years, 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, and patient surveillance. 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). Furthermore, all recommendations are classified as category 2A except where noted in the text or on the algorithm (see Categories of Consensus). The panel unanimously endorses giving priority to treating patients in a clinical trial over standard or accepted therapy. This is especially true for cases of advanced disease and for patients with locally aggressive colorectal cancer who are receiving combined modality treatment.

Risk Assessment

Nearly one-third of cases of colon cancer in the US 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. Therefore, it is recommended that colon cancer patients, especially those 50 years or younger and those with suspected hereditary nonpolyposis colon cancer (HNPPC), familial adenomatous polyposis (FAP), or attenuated FAP be counseled regarding their family history, as detailed in the NCCN Colorectal Cancer Screening Clinical Practice Guidelines.

Staging

The 6th edition of the American Joint Committee on Cancer’s AJCC Cancer Staging Manual includes several modifications to the colon and rectum staging system (see ST-1). In this version of the staging system, smooth metastatic nodules in the pericolic or perirectal fat are considered lymph node metastases and should be included in N staging. Irregularly contoured metastatic nodules in the peritumoral fat are considered vascular invasion.

Stage II is subdivided into IIA (if the primary tumor is T3) and IIB (for T4 lesions). Stage III is subdivided into IIA (T1 to T2, N1, M0), IIB (T3 to T4, N1, M0), and IIIC (any T, N2, M0). The difference between N1 and
N2 disease is in the number of nodes involved: N1 lesions have 1 to 3 positive regional lymph nodes, whereas N2 tumors have four or more positive regional nodes.

An analysis of Surveillance, Epidemiology, and End Results (SEER) data of 119,363 patients with colon cancer from 1991-2000 allowed determination of the following 5-year survival rates by stage: 93.2% (Stage I); 84.7% (Stage II); 72.2% (Stage II); 83.4% (Stage II); 64.1% (Stage II); 44.3% (Stage II); and 8.1% (Stage IV). It has been proposed that the lack of correlation between stage and prognosis in this study (ie, increased survival rates for patients with Stage III disease relative to those with disease classified as Stage II) may be associated with a number of factors including more common use of adjuvant therapy in the former population of patients.

Staging of colon cancer also includes an assessment of the presence or absence of distant metastases (M) with Stage IV disease characterized by the presence of one or more distant metastases and designated as M1.

The 6th edition of the AJCC staging system includes the suggestion that the surgeon mark the area of the specimen with the deepest tumor penetration so that the pathologist can directly evaluate the radial margin. The surgeon is encouraged to score the completeness of the resection as (1) R0 for complete tumor resection with all margins negative; (2) R1 for incomplete tumor resection with microscopic involvement of a margin; and (3) R2 for incomplete tumor resection with gross residual tumor not resected.

Pathology

Colorectal cancers are usually staged after surgical exploration of the abdomen and pathologic examination of the surgical specimen. Some of the criteria which 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 nonregional lymph nodes (M); and the status of proximal, distal, and peritoneal margins.

The AJCC and CAP recommend evaluation of a minimum of 12 lymph nodes to accurately identify Stage II colorectal cancers. The number of lymph nodes retrieved can vary with age of the patient, gender, and tumor grade or site. The extent of surgical resection can also have an impact on the node harvest. The apical lymph node is the most proximal node within 1 cm of vessel ligation at the apex of vascular pedicle. Apical lymph node involvement is significantly associated with adverse outcome.

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, or identification of particular tumor antigens through immunohistochemical (IHC) analysis have been reported. While results of some of these studies seem promising, there is no uniformity in the definition of “true” clinically relevant metastatic carcinoma. Some studies have considered detection of single cells by IHC as well as isolated tumor cells (ITC) to be micrometastasis. Presently, the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and the results should be used with caution in clinical management decisions.
Clinical Presentation and Treatment

Workup and Management of the Malignant Polyp

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or villous adenoma, physicians should review pathology and consult with the patient.  

A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into 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. In patients with invasive cancer and adenoma (tubular, tubulovillous or villous), no additional surgery is required for pedunculated or sessile polyps, if the polyp has been completely resected with favorable histological features. Favorable histological features include lesions of grade 1 or 2, no angiolympathic 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, fragmented specimen or margins that cannot be assessed, or with unfavorable pathology, colectomy with en bloc removal of lymph nodes is recommended. For pedunculated or sessile polyp with unfavorable histopathological features are: grade 3 or 4, angiolympathic 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 and the presence of tumor cells within the diathermy of the transected margin. For a pedunculated or sessile polyp with fragmented specimen or margins that cannot be assessed, or with unfavorable pathology, colectomy with en bloc removal of lymph nodes is recommended. Laparoscopic surgery is an option (see section on Workup and Management of Invasive Nonmetastatic Colon Cancer).

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 require a complete staging workup, including pathologic tissue review, total colonoscopy, a complete blood count, platelets, 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) scan is not routinely indicated at baseline in the absence of evidence of synchronous metastatic disease. For resectable 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. Examination of a minimum of 12 lymph nodes is necessary to establish Stage II colon cancer. 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.

Secondary analyses from the Intergroup INT-0089 trial of patients with high-risk Stage II/III colon cancer receiving adjuvant chemotherapy demonstrated that the accuracy of staging colorectal cancer was associated the number of nodes removed. Furthermore, these analyses also 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, and that the ratio of metastatic to examined lymph nodes was a significant prognostic factor.
for both disease recurrence and overall survival.\textsuperscript{34} Resection needs to be complete to be considered curative, and positive lymph nodes left behind indicate an incomplete (R2) resection. Patients considered to have N0 disease but for whom <12 nodes have been examined are suboptimally staged and should be considered at higher risk.

Laparoscopic colectomy has been advanced as an approach to the surgical management of colon cancer. A European trial has shown some survival advantage to the laparoscopic approach, but the number of patients enrolled was small.\textsuperscript{35} Recently, initial results from a US trial comparing laparoscopically assisted and open surgery for curable colon cancer were reported.\textsuperscript{36} A total of 872 patients with adenocarcinoma of colon (no advanced disease) were randomly assigned to undergo open or laparoscopically assisted colectomy. After a median of 4.4 years follow-up, similar cancer recurrence rates were observed in the two groups. However, results from a subanalysis of results from this 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 significantly more favorable when laparoscopic surgery was performed at hospitals with high case volumes.\textsuperscript{37, 38}

The panel recommends that the following criteria be met when laparoscopic-assisted colectomy is considered: laparoscopically-assisted colorectal operations are performed by an experienced surgeon\textsuperscript{39, 40}; no lesions in rectum, transverse colon, nor prohibitive abdominal adhesions are detected; no advanced local or metastatic disease present; acute bowel obstruction or perforation from cancer is not present; and thorough abdominal exploration is required.\textsuperscript{41}

For resectable colon cancer that is causing obstruction, resection with diversion followed by colectomy or stent insertion followed by colectomy is also recommended. If the cancer is locally unresectable or medically inoperable, palliative therapy should be considered and may include radiation therapy for uncontrolled bleeding, stent for obstruction or supportive care.

**Adjuvant Chemotherapy for Resectable Colon Cancer**

Adjuvant therapy for patients with resected colon cancer has aroused considerable interest.\textsuperscript{42-44} The European MOSAIC trial has evaluated the efficacy of FOLFOX4 (infusional 5-fluorouracil (5-FU), leucovorin (LV), oxaliplatin) compared to 5-FU/LV in the adjuvant setting in 2246 patients with completely resected Stage II and stage III colon cancer. For Stage III patients, disease-free survival (DFS) at 4 years was 61.0\% in the 5-FU/LV arm and 69.7\% in the FOLFOX4 arm. For Stage II patients, 4-year DFS was 81.3\% in the 5-FU/LV arm and 85.1\% with the FOLFOX4 regimen. Results of this study have been reported with median follow-up of three years\textsuperscript{45, 46} and follow-up is ongoing for a minimum of 5 years. Based on these results, FOLFOX4 is recommended as treatment for early-stage colon cancer. This recommendation is strengthened by results of a recent analysis of individual patient data from 20,898 patients on 18 randomized colon adjuvant clinical trials which suggested that DFS after 3 years follow-up is an appropriate endpoint for adjuvant colon clinical trials involving 5-FU-based chemotherapy.\textsuperscript{47}

Other adjuvant regimens studied for the treatment of early-stage colon cancer include 5-FU-based therapies incorporating irinotecan, 5-FU regimens other than FOLFOX which include oxaliplatin, and single agent capcitabine. The US Intergroup trial CALGB C89803 evaluated irinotecan plus bolus 5-FU/LV (IFL regimen) versus 5-FU/LV alone in Stage III colon cancer.\textsuperscript{48} The preliminary results presented in 2004 indicated no improvement in terms of either overall survival (P=0.88) or failure free survival (P=0.84) for IFL, as compared to 5-FU/LV. However, IFL has been associated with a greater degree of neutropenia, neutropenic fever, and death.\textsuperscript{49} In addition, FOLFIRI (infusional 5-fluorouracil, leucovorin, irinotecan), has not been shown to
be superior to 5-FU/LV in the adjuvant setting, although a trend toward improvement was seen with addition of irinotecan. 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 3-year DFS in 2407 patients with Stage II or Stage III colon cancer. Median follow-up was 34 months. Three-year DFS was 76.5% vs. 71.6% for FLOX and FULV respectively, indicating that the addition of oxaliplatin to weekly FULV significantly improved 3-year DFS in patients with Stage II or Stage III colon cancer (P=0.004). Grade 3 NCI-Sanofi neurosensory toxicity, diarrhea or dehydration associated with bowel wall thickening was higher with FLOX than with FULV, and, when cross-study comparisons are made, the incidence of grade 3/4 diarrhea was considerably higher with FLOX than FOLFOX. For example, rates of grade 3/4 diarrhea were 10.8% and 6.7% for patients receiving FOLFOX and infusional 5-FU/LV, respectively, in the MOSAIC trial, whereas 38% and 32.3% 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. Single agent oral capecitabine as adjuvant therapy for patients with Stage III colon cancer was shown to be at least equivalent to bolus IV 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) and 0.84 (95% CI, 0.69-1.01) when the capecitabine arm was compared to the 5-FU/LV arm.

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 and 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 early-stage colon cancer treated with 5-FU based adjuvant therapy was significantly increased in the subset of patients with positive regional lymph nodes but not in patients with NO disease when compared to patients not receiving chemotherapy, suggesting 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 significant difference between these 2 groups with respect to 5-year overall survival (eg, 78% vs. 78% for survival of 0.91 (95% CI, 0.77-1.09) when patients receiving adjuvant treatment were compared with untreated patients.

Following primary surgical treatment, the panel recommends 6 months of adjuvant chemotherapy for patients with Stage III (T1-4, N1-2, M0) resected colon cancer. The treatment options are: 5-fluorouracil/leucovorin/oxaliplatin as the standard of care (category 1), single agent capecitabine (category 2A), or 5-FU/LV (category 2A). The panel concluded that weekly bolus IFL should not be used as adjuvant therapy in colon cancer. All 3 of the postoperative adjuvant therapy regimens listed above are designated as category 2B recommendations for patients with stage II (T3, N0, M0) disease with no high risk features. These patients should be entered in a clinical trial, if possible, or may also be observed. High-risk stage II (T3-T4, N0, M0) patients, defined as those with poor prognostic features including T4 tumors (stage IIB), poor histologic grade (grade 3 or 4 lesions), peritumoral lymphovascular involvement, bowel obstruction at presentation, T3 lesions with localized perforation or close, indeterminate, or positive margins, and inadequately sampled nodes (less than 12 lymph nodes), should be considered for adjuvant chemotherapy with 5-FU/LV, single agent capecitabine, or 5-FU/LV/oxaliplatin (category 2A for all three regimens). It should be noted, however, that there is currently no evidence to indicate that
patients with high-risk stage II disease are more likely to respond to chemotherapy than patients with stage II disease without these high-risk features (ie, factors associated with a poorer prognosis are not necessarily predictive of response to treatment). Furthermore, the benefit of chemotherapy in this population has not been shown to improve overall survival by more than 5%.54, 55 Decision-making regarding the use of adjuvant therapy for patients with stage II disease should incorporate patient/physician discussions individualized for the patient, and include explanations of the specific characteristics of the disease and the evidence related to the efficacy and possible toxicities associated with treatment, centering on patient choice.59 Radiation therapy delivered concurrently with 5-FU-based chemotherapy should be considered for patients with disease characterized as T4 tumors penetrating to a fixed structure, and recurrent disease. Radiation therapy fields should be defined by preoperative radiological imaging and/or surgical clips. Intensity-modulated radiotherapy (IMRT) which uses computer-imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,60 can be considered when the risk of such toxicity is high.

### Principles of the Management of Metastatic Disease

Approximately 50%-60% of patients diagnosed with colorectal cancer will develop colorectal metastases.61, 62 Patients with stage IV (any T, any N, M1) colon cancer or recurrent disease can present with synchronous liver or lung metastases or abdominal peritoneal metastases. Approximately 15%-25% of patients with colorectal cancer present with synchronous liver metastases, although 80%-90% of these patients are initially evaluated to have unresectable metastatic liver disease.61, 63-65 Metastatic disease more frequently develops metachronously following treatment for colorectal cancer, with the liver as a common site of involvement.66 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 one 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.67

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.68 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.63 Furthermore, rates of 5-year survival for patients with metastatic liver disease not undergoing surgery have been shown to approach 0% in a number of studies.61, 69 However, 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 many patients with colorectal metastatic liver disease.61, 70 Recent reports have shown 5-year survival rates following resection of hepatic colorectal metastases exceeding 50%.71, 72 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.73

The criteria for determining patient suitability for resection, or surgical cure, of metastatic disease are evolving, with the emphasis being increasingly placed on the likelihood of achieving negative surgical margins while maintaining adequate liver reserve, as opposed to other criteria, such as the number of liver metastases present.74, 75 Resectability differs fundamentally from endpoints which focus more on palliative measures of treatment, such as response and DFS. Instead, the resectability endpoint is focused on the potential of surgery to cure
the disease,\textsuperscript{76} since partial liver resection or debulking has not been shown to be beneficial.\textsuperscript{62} Approaches used in the surgical treatment of liver metastases include preoperative portal vein embolization for the purpose of increasing the volume and function of the portion of the liver which will remain postsurgically, hepatic resection performed in 2 stages for bilobular disease, and the use of ablative methods in combination with resection.\textsuperscript{74} The panel does not recommend the use of ablative techniques without resection or in patients for whom negative margins can be achieved with resection alone.\textsuperscript{77} Resection of liver metastases should not be performed in the presence of unresectable sites of extrahepatic disease, and hepatic intra-arterial embolization should not routinely be used outside of a clinical trial.

Since the majority of patients diagnosed with metastatic colorectal disease are initially classified as unresectable, neoadjuvant chemotherapy is being increasingly employed to downsize colorectal metastases. Potential advantages of this approach 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 either disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.\textsuperscript{63, 78} Furthermore, results from a recent study of colorectal cancer patients receiving neoadjuvant chemotherapy indicated that cancer cells were 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.\textsuperscript{79} It is therefore essential that during treatment with neoadjuvant chemotherapy, 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 neoadjuvant regimen and facilitates an appropriately-timed surgical intervention.\textsuperscript{80}

Certain clinicopathologic factors, such as the presence of extrahepatic metastases and a disease-free interval of < 12 months, have been associated with a poor prognosis in patients with colorectal cancer,\textsuperscript{71, 72, 81-83} although the ability of these factors to predict outcome following resection may be limited.\textsuperscript{61} However, decision-making relating to whether to offer neoadjuvant therapy begins with an initial evaluation of the degree of resectability of metastatic disease. Benefits of initial surgery in patients with clearly resectable disease characterized by generally favorable prognostic characteristics may outweigh the benefits of down sizing the disease with neoadjuvant chemotherapy. Alternatively, preoperative chemotherapy would be more appropriate in patients with borderline resectable disease or disease that is initially unresectable but potentially resectable following response to chemotherapy. In addition, neoadjuvant chemotherapy may be more beneficial in patients who have not been exposed to prior chemotherapy or who have not received prior chemotherapy in the previous 12 months.

The most important benefit of the preoperative approach is the potential to convert patients with initially unresectable metastatic disease to a resectable state. In the study of Pozzo et al, it was reported that neoadjuvant therapy 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.\textsuperscript{75} 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),\textsuperscript{65} 44 patients with unresectable liver metastases were treated with FOLFOX4. 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 of 1104 initially unresectable patients with colorectal liver disease, 335 patients (23%) were able to undergo primary hepatic resection and 138 patients (12.5%) classified as “good responders” underwent secondary hepatic resection following neoadjuvant treatment which included oxaliplatin in the majority of cases. The 5-year survival rate for these 138 patients overall was 33%. More recently, 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%) were able to undergo curative liver resection following treatment. The median overall survival time in this group was 42.4 months.

Recently, the efficacy of bevacizumab in combination with FOLFOX and FOLFIRI in the treatment of unresectable metastatic disease (see section on Chemotherapy for Advanced or Metastatic Disease) has led to its use in combination with these regimens in the neoadjuvant setting, although the safety of administering bevacizumab pre- or postoperatively, in combination with 5-fluorouracil-based regimens has not been adequately evaluated. A retrospective evaluation of data from 2 randomized trials of 1132 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). However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to surgery, the incidence of wound healing complications in either group of patients was low (1.3% vs 0.5%; P=0.63). The panel recommends at least a 6 week interval (which corresponds to 2 half-lives of the drug) between the last dose of bevacizumab and elective surgery.

Other reported risks associated with the neoadjuvant approach include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered. To limit the development of hepatotoxicity, it is therefore recommended that surgery should be performed as soon as possible after the patient becomes resectable and usually not more than 3-4 months following initiation of preoperative treatment.

Colorectal metastatic disease can also occur in the lung. Most of the treatment recommendations discussed for metastatic colorectal liver disease, with the exception of hepatic arterial infusion (HAI), also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in selected cases. The goal of treatment of most abdominal/peritoneal metastases is palliative, rather than curative. The panel does not recommend cytoreductive resection of disseminated carcinomatosis with hyperthermia and intraperitoneal chemotherapy outside of a clinical trial.

Although only limited data exist regarding the efficacy of adjuvant chemotherapy following resection for metastatic colorectal liver or lung disease, administration of a course of an active systemic chemotherapy regimen for metastatic disease is recommended by the panel for most patients following liver or lung resection to increase the likelihood that residual microscopic disease will be eradicated. Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent administration of chemotherapy directed to the liver metastases through the hepatic artery (i.e. HAI) is listed in the guidelines as an option (category 2B). After hepatic resection, administration of fluorodeoxyuridine (FUDR) by HAI in addition to systemic chemotherapy was shown to be superior to systemic...
chemotherapy alone with respect to survival and time to hepatic progression but not time to extrahepatic progression. An investigation of the current role of HAI with FUDR in conjunction with oxaliplatin and capecitabine in the treatment of metastatic colorectal liver disease is underway in the NSABP C-09 trial. Some of the uncertainties regarding patient selection for neoadjuvant chemotherapy are also relevant to the application of HAI. Limitations on the use of HAI therapy include the potential for biliary toxicity and the requirement for specific technical expertise.

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from large bowel (e.g. colorectal liver metastases) is suspected should include total colonoscopy, a complete blood count, platelets, chemistry profile, carcinoembryonic antigen (CEA) determination, a CT scan of the chest, abdomen and pelvis, and a needle biopsy, if clinically indicated. The panel recommends a preoperative PET scan at baseline only if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease. The criterion of potential surgical cure includes patients with metastatic disease that is not initially resectable or ablable but for whom a surgical cure may become possible following neoadjuvant chemotherapy. A PET scan which utilizes a radioactive derivative of glucose (i.e., (18) F-fluorodeoxyglucose PET imaging) to detect tissues associated with increased metabolic activity can become transiently negative following chemotherapy (e.g., in the presence of necrotic lesions) and the panel recommends against using PET scan to evaluate response to chemotherapy. False positive PET 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. Close communication between members of the multidisciplinary treatment team is recommended.

Resectable synchronous liver or lung metastases

If a patient is a candidate for surgery and the liver or lung metastases are deemed resectable, the panel recommends the following options: neoadjuvant chemotherapy (e.g., bevacizumab plus choice of FOLFIRI, FOLFOX, or CapeOX [capecitabine, oxaliplatin]) followed by synchronous or staged colectomy with liver or lung resection, or colectomy followed by neoadjuvant chemotherapy (see above) and a staged resection of metastatic disease. Patients with a solitary lesion in their lungs who can undergo resection should be considered for colectomy followed by staged thoracotomy and pulmonary nodule resection. Biologic waiting period of up to 2 months can distinguish patients who would be more likely to benefit from metastasectomy because of indolent disease. Resection of primary colon cancer prior to initiation of chemotherapy is necessary in patients with moderate or severe symptoms (e.g., intestinal obstruction) related to the primary cancer. However, advantages to a neoadjuvant chemotherapy approach include the possibility of downsizing both the primary tumor and metastatic lesions prior to surgery, and a very low rate of complications related to the unresected primary cancer. Patients who have completely resected liver or lung metastases should be offered adjuvant chemotherapy. The panel recommends 6 months as the preferred duration of adjuvant therapy. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B), and, in the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or continuous IV 5-FU infusion. Observation or a shortened course of chemotherapy can be considered for patients who have completed neoadjuvant chemotherapy. Post-treatment follow-up
for patients classified as stage IV and no evidence of disease (NED) is described in the section on Post-Treatment Surveillance.

Unresectable synchronous liver or lung metastases

For patients in which the liver or lung disease is deemed to be unresectable but potentially convertible to a resectable state, the panel recommends preoperative chemotherapy corresponding to initial therapy for metastatic disease (e.g., bevacizumab plus choice of FOLFIRI, FOLFOX, or CapeOX.) to attempt to render these patients candidates for resection. Patients with lesions converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer followed by adjuvant therapy for a preferred total duration of 6 months. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B), and, in the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or continuous IV 5-FU infusion. Observation or shortened course of chemotherapy can be considered for patients who have completed neoadjuvant chemotherapy. Primary treatment of unresectable synchronous liver or lung metastases by palliative colon resection should be considered if the patient has an imminent risk of obstruction or significant bleeding. Ablative therapy of liver metastases using radiofrequency ablation or cryosurgery at the time of colon resection can also be considered when all measurable metastatic disease can be treated (category 2B). Patients with unresectable liver metastases not responding to systemic therapy should receive salvage therapy for advanced or metastatic disease. Post-treatment follow-up for patients classified as stage IV and no evidence of disease (NED) is described in the section on Post-Treatment Surveillance.

Synchronous abdominal/peritoneal metastases

For patients with peritoneal metastases and an impending obstruction, surgical options include colon resection, diverting colostomy, or a bypass of impending obstruction or stenting, followed by chemotherapy for advanced or metastatic disease. Primary treatment of patients with non-obstructing metastases is chemotherapy for advanced or metastatic disease. The panel does not recommend cytoreductive surgery of disseminated carcinomatosis outside of a clinical trial.

Workup and Management of Metachronous Metastatic Disease

Upon documentation of metachronous metastases in which disease is or may become potentially resectable, characterization of the extent of disease by PET scan is recommended. PET 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. Two other factors further distinguish the management of metachronous metastatic disease from that of synchronous disease: an evaluation of the chemotherapy history of the patient; and the absence of colectomy. Resectable patients are classified according to whether they have received no previous chemotherapy or prior chemotherapy within or before the previous 12 months. For patients who have not received prior chemotherapy and who have resectable metastatic disease, primary treatment options include neoadjuvant chemotherapy followed by resection and additional postoperative chemotherapy, or initial resection followed by chemotherapy. The optimal sequence of therapeutic interventions is less clear for patients who have received prior adjuvant chemotherapy. In particular, the role of neoadjuvant chemotherapy is less clear for patients who exhibit disease recurrence or progression during or within 12 months of receiving prior chemotherapy. Following surgery, adjuvant therapy with an alternative active metastatic chemotherapy regimen is recommended.

Patients determined by cross-sectional imaging or PET scan to be unresectable should receive an active metastatic chemotherapy regimen based on prior chemotherapy history. Specifically, patients exhibiting disease progression on FOLFOX administered within the
previous 12 months should be switched to a FOLFIRI regimen with the option of inclusion of bevacizumab. Patients with chemotherapy-responsive disease who are converted to a resectable stage should undergo resection, with the option of HAI therapy to treat liver metastases (category 2B for HAI therapy), followed by adjuvant treatment with an active chemotherapy regimen. If metastatic lesions remain unresectable subsequent treatment is dependent, in part, on the performance status (PS) of the patient. Treatment with an active chemotherapy regimen for advanced or metastatic disease is the treatment of choice for patients with PS 0-2. Patients with PS ≥ 3 are given best supportive care. Best supportive care is an option for patients diagnosed with metachronous metastases who have previously received all active chemotherapy regimens in cases of both resectable and unresectable disease.

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 type and timing of the prior therapy that has been administered 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 in both the presence and absence of disease progression, 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 (i.e., exposing 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 with good tolerance to intensive therapy, the panel recommends a choice of 4 chemotherapy regimens: FOLFOX (eg, FOLFOX4 and mFOLFOX6), CapeOX, CapeOX, or 5-FU/LV. The panel further recommends that each of these regimens be administered in combination with bevacizumab when used for initial therapy. With respect to the treatment of metastatic disease, the consensus of the panel was that FOLFOX plus bevacizumab and CapeOX plus bevacizumab can be used interchangeably, and that both of these combination regimens, as well as FOLFIRI plus bevacizumab, represent standards of care for the initial treatment of metastatic colorectal cancer. The infusional 5-FU/LV plus bevacizumab regimen is recommended as initial therapy for patients not able to tolerate oxaliplatin or irinotecan since it has been shown to be associated with lower toxicity but also lower overall survival than the combination chemotherapy regimens.

Results from several phase II studies have demonstrated that addition of bevacizumab to first-line 5-FU/LV regimens improved overall survival.
in patients with metastatic colorectal cancer when compared to survival results for patients receiving these regimens without bevacizumab. A combined analysis of the results of several of these trials showed that addition of bevacizumab to 5-FU/LV-containing regimens 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. 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. In that pivotal trial a markedly longer survival time was observed with the use of bevacizumab: 20.3 months versus 15.6 months (hazard ratio for death = 0.66; P<0.001). Addition of bevacizumab to initial therapy with FOLFOX, bolus 5-FU/LV, or CapeOX significantly improved response rate and time to tumor progression in the TREE 1 & 2 studies which evaluated the safety and efficacy of oxaliplatin/fluoropyrimidine regimens (FOLFOX; CapeOX; and bolus 5-FU/LV plus oxaliplatin) with and without bevacizumab. Although the final analysis of the TREE studies was a historical comparison of 2 sequential cohorts in a single protocol without randomization of patients to plus/minus bevacizumab treatment arms, addition of bevacizumab was shown to increase response rate by approximately 10% and time to tumor progression by 2 months when results for all patients, regardless of 5-FU backbone regimen, were evaluated. In a pooled analysis of patients enrolled in all 3 treatment arms, median survival time associated with administration of a 5-FU backbone regimen without bevacizumab was 18.2 months (95% CI, 14.5-21.6) and 24.4 months (95% CI, 21.4-26.8) when bevacizumab was added to these regimens. No significant differences in activity between the 3 different 5-FU-based regimens were observed in the TREE study although this analysis was limited by small sample sizes. Nevertheless, the bolus 5-FU/LV regimen may be the least efficacious since overall survival for patients in the 3 arms (without and with bevacizumab) were reported to be 19.2 months and 26.0 months for FOLFOX, 17.2 months and 27.0 months for CapeOX, and 17.9 months and 20.7 months for bolus 5-FU/LV. Although addition of bevacizumab to these regimens was associated with an increase in grade 3-4 hypertension, impaired wound healing, and bowel perforation in each arm, the overall tolerability of these regimens in combination with bevacizumab was considered to be acceptable and an increase in the toxicity of chemotherapy-related events was not observed. Of note, the grade 3-4 toxicity associated with bevacizumab plus oxaliplatin-based chemotherapy in the TREE study was significantly less than that reported in the pivotal study involving IFL plus bevacizumab. Very recently, results from a head-to-head phase III study comparing CapeOX (capecitabine dose 1000 mg/m^2 twice daily for 14 days) with FOLFOX have been reported. With a median follow-up period of 18.6 months, results from this study support the conclusion that neither regimen is inferior with respect to the other in terms of toxicity or efficacy endpoints when used in the initial treatment of metastatic colorectal cancer. Although a combined analysis of results observed with CapeOX plus bevacizumab and FOLFOX plus bevacizumab showed that the addition of bevacizumab was associated with an increase in progression-free survival (PFS) compared to these regimens without bevacizumab, the significant incremental benefit observed with addition of bevacizumab was more modest than seen in some earlier trials. 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, although the PFS curves observed for patients receiving either CapeOX plus bevacizumab or FOLFOX plus bevacizumab were nearly identical. The results of the phase III BICC-C study evaluating the effectiveness of 3 irinotecan-containing regimens with and without bevacizumab demonstrated that, for first-line treatment of advanced colorectal cancer, FOLFIRI is superior to a modified IFL regimen or CapIRI (capecitabine plus irinotecan) in terms of efficacy and safety. In that study, a significant increase in PFS was observed for patients receiving first-line FOLFIRI (7.6 months) when compared to
PFS results for patients receiving either a modified IFL regimen (5.8 months; P=0.007) or CapIRI (5.7 months; P=0.03). Furthermore, when FOLFIRI was combined with bevacizumab, PFS was shown to increase to 9.0 months. 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. 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 FOLFOX4 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. The results of an ongoing phase III study evaluating the effectiveness of FOLFIRI in combination with bevacizumab in the initial treatment of patients with metastatic disease have not yet been reported.

Convincing, albeit indirect, support for inclusion of bevacizumab in combination with chemotherapeutic agents in the initial treatment of advanced or metastatic colon cancer comes from results of the randomized phase III study E3200, conducted by Eastern Cooperative Oncology Group (ECOG), which demonstrated that bevacizumab in combination with FOLFOX4 improved survival in bevacizumab-naïve patients with previously-treated advanced colorectal cancer. Median overall survival was 12.5 months for patients receiving FOLFOX4 plus bevacizumab compared to 10.7 months for patients receiving FOLFOX4 alone. 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. Although this study involved patients with previously-treated disease, the results cannot be used to support use of bevacizumab in patients after first or second progression if they have progressed on a bevacizumab-containing regimen.

The risk of stroke and other arterial events is increased in elderly patients receiving bevacizumab. In addition, use of bevacizumab may interfere with wound healing (see Principles of Management of Metastatic Disease), and gastrointestinal perforation is a relatively rare, but important, side effect of bevacizumab therapy in patients with colorectal cancer.

With respect to the toxicities associated with capecitabine use, the panel noted that patients with diminished creatinine clearance may accumulate levels of the drug, 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 and that North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries. Such toxicities may necessitate modifications in the dosing of capecitabine, and patients on capecitabine should be monitored closely so that dose adjustments can be made at the earliest signs of certain side effects such as hand-foot syndrome. For example, the capecitabine dose was reduced from 1000 mg/m² twice daily to 850 mg/m² twice daily on days 1-14 in the TREE studies. It is currently not known whether the efficacy of CapeOX plus bevacizumab and FOLFOX plus bevacizumab remain comparable when capecitabine doses are lower than the 1000 mg/m² twice daily dose used in the study of Cassidy et al.

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia. Irinotecan is metabolized by the enzyme uridine diphosphate-glucuronyl transferase 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.\textsuperscript{140} 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,\textsuperscript{139,141} although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.\textsuperscript{141} A commercial test is available to detect the UGT1A1*28 allele which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression,\textsuperscript{140} and a new 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.\textsuperscript{138} A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,\textsuperscript{141} although guidelines for the use of this test in clinical practice have not been established.

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.\textsuperscript{142} 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.\textsuperscript{143} Discontinuation of oxaliplatin from FOLFOX or CapeOX should be strongly considered after 3 months of therapy or sooner for unacceptable neurotoxicity (eg, > grade 3) with other drugs in the regimen maintained until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy but oxaliplatin can subsequently be reintroduced if stopped to prevent development of neurotoxicity.

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\textsuperscript{132} and FOLFOX in the Intergroup trial\textsuperscript{97}) at any point in the therapy continuum and it has been removed from the guidelines. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,\textsuperscript{104,123} or the oral route (i.e. capecitabine).\textsuperscript{101}

The recommended therapy after first progression for patients who have received prior 5-FU/LV-based therapy includes irinotecan as a single agent\textsuperscript{99} or in combination with cetuximab.\textsuperscript{107} Other options are dependent on the initial treatment regimen and include FOLFIRI\textsuperscript{123} with or without cetuximab for patients who had received a FOLFOX or CapeOX-based regimen for initial therapy. FOLFOX or CapeOX alone is an option for patients who received a FOLFIRI-based regimen as initial treatment. The recommendations regarding use of CapeOX in lieu of FOLFOX after first progression are supported by the results of studies demonstrating comparable efficacy of these 2 agents in initial therapy.\textsuperscript{120} Other options to consider after first progression include: FOLFOX, CapeOX, or FOLFIRI for patients receiving 5-FU/LV without oxaliplatin or irinotecan as initial therapy; and single agent cetuximab or panitumumab for patients initially treated with a FOLFIRI-based regimen.

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.\textsuperscript{115} 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. 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 or infusional 5-FU/LV. In the study of Rougier et al., median overall survival was 4.2 months for irinotecan versus 2.9 months for 5-FU (P=0.030) whereas Cunningham et al. reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive-care group (P=0.001). 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.

Cetuximab has been studied as both a single agent and in combination with irinotecan in the treatment of metastatic colorectal cancer. A partial response rate of 9% was observed when single agent cetuximab was administered in an open-label phase II trial to 57 patients with colorectal cancer refractory to prior irinotecan-containing therapy. Results from a direct comparison of cetuximab monotherapy and the combination regimen of cetuximab and irinotecan in patients who had progressed following initial therapy with an irinotecan-based regimen indicated that response rates were doubled in the group receiving the combination of cetuximab plus irinotecan when compared with patients receiving cetuximab monotherapy (22.9% versus 10.8% [P=0.007]). Therefore, combination therapy with cetuximab and irinotecan is preferable to cetuximab alone as therapy after first progression for patients who can tolerate this combination regimen. Panitumumab, however, has only been studied as a single agent in the setting of metastatic colorectal cancer for patients with disease progression on initial chemotherapy; respective response rates of 8% versus 0% for panitumumab plus best supportive care versus best supportive care alone were observed, as well as a significant increase in PFS with panitumumab (hazard ratio=0.54; 95% CI, 0.44-0.66).

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 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.
With respect to the treatment continuum for metastatic colorectal cancer, there are no data to support the addition of bevacizumab to a regimen following clinical failure of a previous bevacizumab-containing regimen. Therefore, routine use of cetuximab plus bevacizumab in patients who have experienced clinical failure on a bevacizumab-containing regimen is not recommended.

For patients with impaired tolerance to aggressive initial therapy, the guideline recommends single-agent capecitabine or bolus or infusional 5-FU/leucovorin with or without bevacizumab (category 2B for combination with bevacizumab). Although a comparison of capecitabine plus bevacizumab versus capecitabine alone as initial therapy for metastatic cancer has not been done, CapeOX plus bevacizumab has been shown to be superior to CapeOX alone in this setting. Metastatic cancer patients with no improvement in functional status should receive best supportive care. Patients showing improvement in functional status should be treated with one of the options specified for therapy after first progression as described above.

The panel recommends that progression of disease following treatment with an EGFR inhibitor alone or a regimen including cetuximab and irinotecan should be followed by either best supportive care or enrollment in a clinical trial. The panel recommends against the use of capecitabine, mitomycin, or gemcitabine, either as single agents or in combination, as salvage therapy in patients exhibiting disease progression following treatment with a fluoropyrimidine-containing regimen. These agents have not been shown to be effective in this setting, and 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.

Post-Treatment Surveillance

Following curative-intent surgery, 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, identify new metachronous neoplasms at a preinvasive stage, and reassure the patient. Advantages of more intensive follow-up of Stage II and/or Stage III patients have been demonstrated prospectively in several studies and in three 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 which demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor, and a population-based report indicating increased rates of resectability and survival in patients treated for local recurrence and distant metastases of colorectal cancer, 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 (i.e. no known residual disease): history and physical examination every 3-6 months for 2 years, then every 6 months for the next 5 years if the clinician determines that the patient is a potential candidate for aggressive curative surgery; colonoscopy within 1 year of resection (or 3 to 6 months if not performed preoperatively due to obstructing lesion), repeated in 3 years if the colon is free of polyps followed by colonoscopic surveillance every 5 years, or, if first follow-up...
Colonoscopy is abnormal, repeat colonoscopy after 1 year and, if negative for polyps, repeat colonoscopic surveillance in 3 years and then every 5 years; chest, abdominal and pelvic CT scan are recommended annually every 3 years in Stage III patients at high risk or recurrence (ie, those with perineural or venous invasion of tumor or poorly differentiated tumors) and may be considered annually for 3 years for patients with Stage II disease at high risk for recurrence.\textsuperscript{159, 165} PET scan is not routinely recommended.

Initial follow-up office visits at 3 months 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 (i.e. can be seen once every 6 months). This principle also applies to CEA testing, which is used primarily to monitor for recurrence of the original disease (see section on Managing an Increasing CEA Level), although post-treatment CEA testing is recommended only if the patient is a potential candidate for further intervention.\textsuperscript{162} 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.\textsuperscript{164} 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.\textsuperscript{164} The recommended frequency of post-treatment surveillance colonoscopies is higher (ie, annually) for patients with HNPCC.\textsuperscript{164} CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver.\textsuperscript{159} Hence, CT scan is not routinely recommended in patients who are not candidates for potentially curative resection of liver or lung metastases.\textsuperscript{159} Post-treatment PET scan is not routinely recommended for surveillance of patients with resected early-stage colorectal cancer to detect recurrence of the original cancer. Furthermore, PET 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 NED disease following curative-intent surgery and subsequent adjuvant treatment are similar to those listed for patients with early-stage disease with one exception being that certain evaluations are performed more frequently. Specifically, the panel recommends that these patients undergo CT scan of the chest, abdomen, and pelvis every 3-6 months in the first 2 years following adjuvant treatment and then every 6-12 months for up to a total of 5 years, and CEA testing is recommended for those with informative levels (preoperatively elevated) every 3 months for the first 2 years and then every 6 months in the following 3-5 years.

**Managing an Increasing Carcinoembryonic Antigen Level**

Managing patients with an elevated CEA level after resection should include colonoscopy, chest, abdominal, and pelvic CT scans, and physical examination. If imaging study results are normal in the face of a rising CEA, repeat scans are indicated every 3 months if symptoms occur. In addition, PET scan may be used to determine if isolated metastases can be demonstrated if CT scan results are negative.\textsuperscript{167} 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.\textsuperscript{168} The panel does not recommend the use of anti-CEA-radiolabeled scintigraphy.\textsuperscript{169} PET scan should be considered before surgical resection for patients with a suspected recurrence or those with documented metastases by CT, MRI and/or biopsy. In the case of local recurrence or resectable organ-confined lesion, curative surgery may be possible. Likewise, isolated lesions in the liver or lung may be resected for cure.
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 when possible. Adjuvant therapy with FOLFOX (category 1), 5-FU/LV (category 2A), or capecitabine (category 2A) is recommended by the panel for patients with Stage III disease, and as an option for patients with high-risk Stage II disease (category 2A for all three 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 complete resection (R0) or ablation can be achieved. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease (neoadjuvant) or when a response to chemotherapy can convert a patient from an unresectable to a resectable state. 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, and colonoscopic evaluations. Recommendations for patients with previously untreated 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, as well as plans for adjusting therapy for patients who experience certain toxicities.

Recommended initial therapy for advanced or metastatic disease includes bevacizumab plus FOLFOX, FOLFIRI, CapeOX or 5-FU/LV.

Patients with progressive disease who have received a 5-FU-based or capecitabine-based regimen as initial therapy should be treated with second or third-line chemotherapy consisting of FOLFIRI, CapeOX, FOLFOX or irinotecan alone or, in the case of irinotecan and FOLFIRI, in combination with cetuximab. Monotherapy with either cetuximab or panitumumab is also an option after first or second progression.

Disclosures for the NCCN Colon Cancer Guidelines Panel

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