NCCN National Comprehensive Cancer Network®

The NCCN

Colon Cancer

Clinical Practice Guidelines in Oncology™

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Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2009, an estimated 106,100 new cases of colon and 40,870 cases of rectal cancer will occur. During the same year, it is estimated that 49,920 people will die from colon and rectal cancer.[1] Despite these statistics, mortality from colon cancer has decreased slightly over the past 30 years, possibly due to earlier diagnosis through screening and better treatment modalities.

This manuscript summarizes the NCCN Clinical Practice Guidelines in Oncology for managing colon cancer. The guidelines begin with clinical presentation to the primary care physician or gastroenterologist and address diagnosis, patho-

Colon Cancer Clinical Practice Guidelines in Oncology

Key Words

NCCN Clinical Practice Guidelines, colonic neoplasms, colorectal surgery, adjuvant chemotherapy, 5-fluorouracil, adenocarcinoma, neoplasm staging, neoplasm recurrence, irinotecan, oxaliplatin (*JNCCN* 2009;7:778–831)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

Please Note

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Colon Cancer Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and on-line. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Colon Cancer Guidelines Panel members can be found on page 831. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at www.nccn.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.nccn.org.

logic 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 (available online, in these guidelines, at www.nccn.org [ST-1]).[2] Furthermore, all recommendations are classified as category 2A except where noted in the text or algorithm. 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 colon cancer cases in the United States are associated with familial clustering;[3] first-degree relatives of patients with newly diagnosed colorectal adenomas[4] or invasive colorectal cancer[5] are at increased risk for colorectal cancer. Therefore, it is recommended that all colon cancer patients be counseled regarding their family history, as detailed in the NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening (to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org).

Staging

The 6th edition of the American Joint Committee on

Text continues on p. 803

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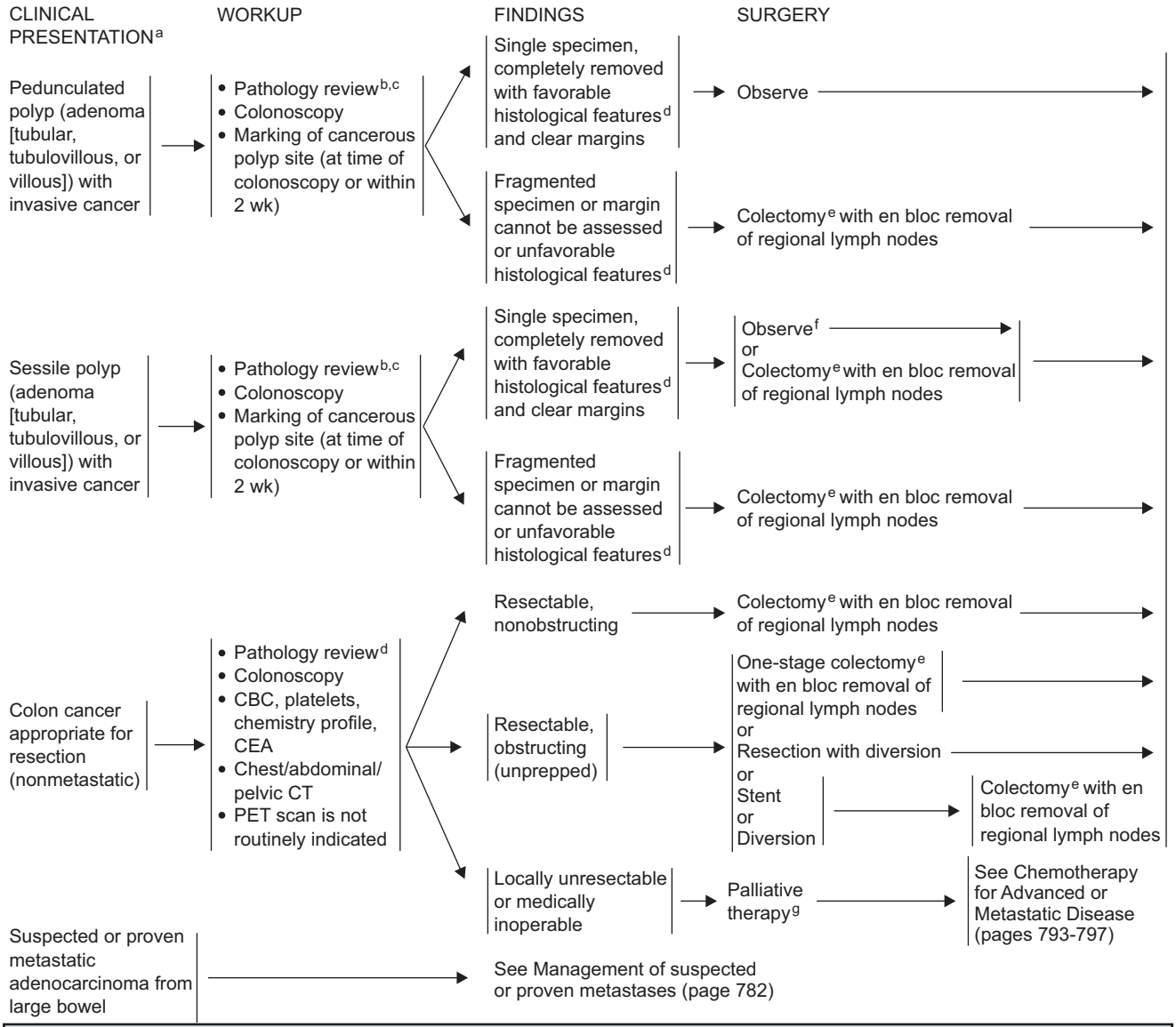

[a] All patients with colon cancer should be counseled for family history. Patients with suspected hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening (to view the most recent version, visit the NCCN Web site at www.nccn.org).

[b] Confirm the presence of invasive cancer (pT1). pTis has no biologic potential to metastasize.

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

[d] See Principles of Pathologic Review: Endoscopically Removed Malignant Polyps (page 788).

[e] See Principles of Surgery (page 791).

[f] Observation may be considered, with the understanding that there is an added 10%-15% risk for lymph node metastases. Nivatvongs S, Rojanasakul A, Reiman HM, et al. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. Dis Colon Rectum 1991;34:323-328.

[g] Palliative therapy may include RT for uncontrolled bleeding, stent for obstruction, and supportive care.

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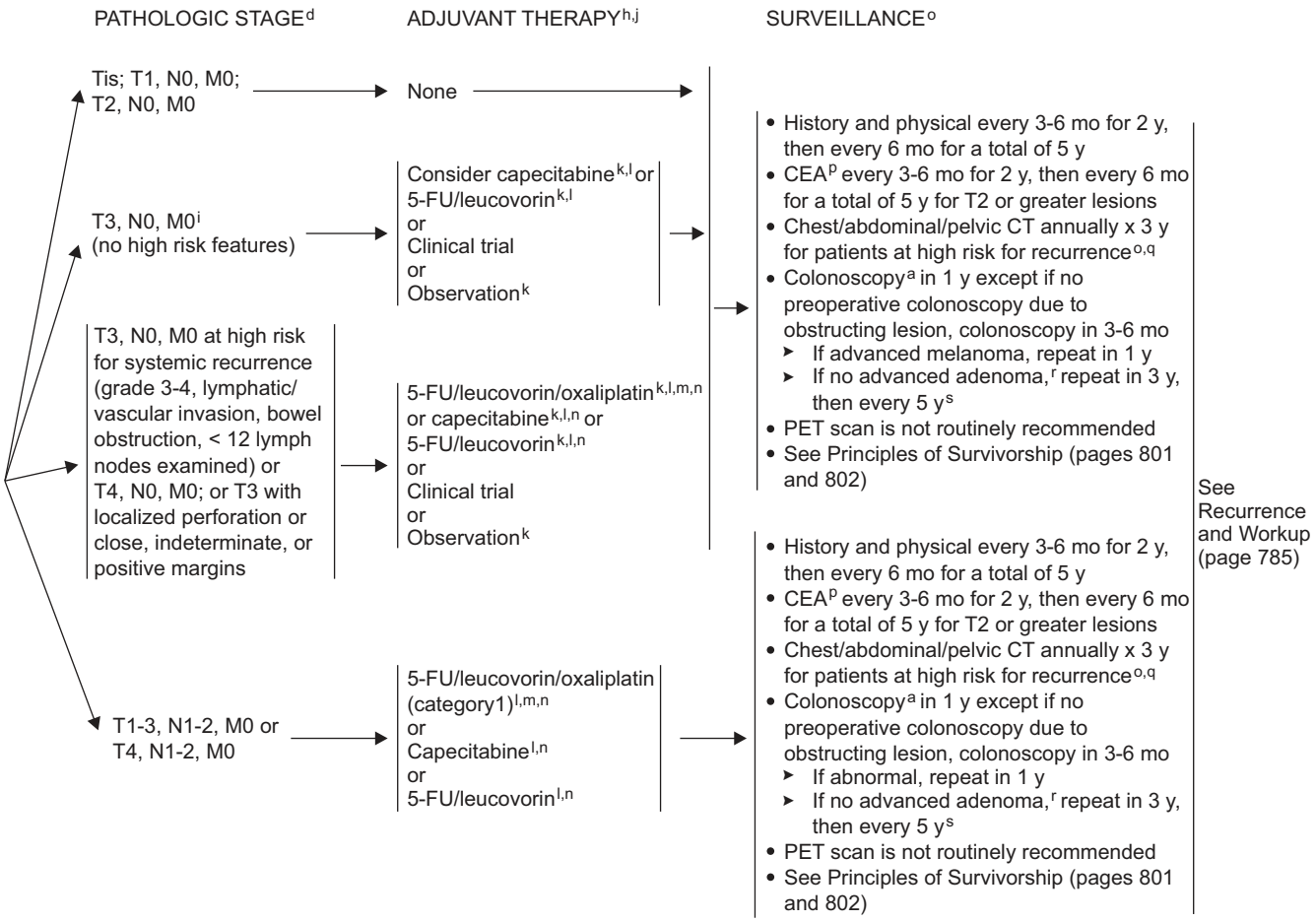
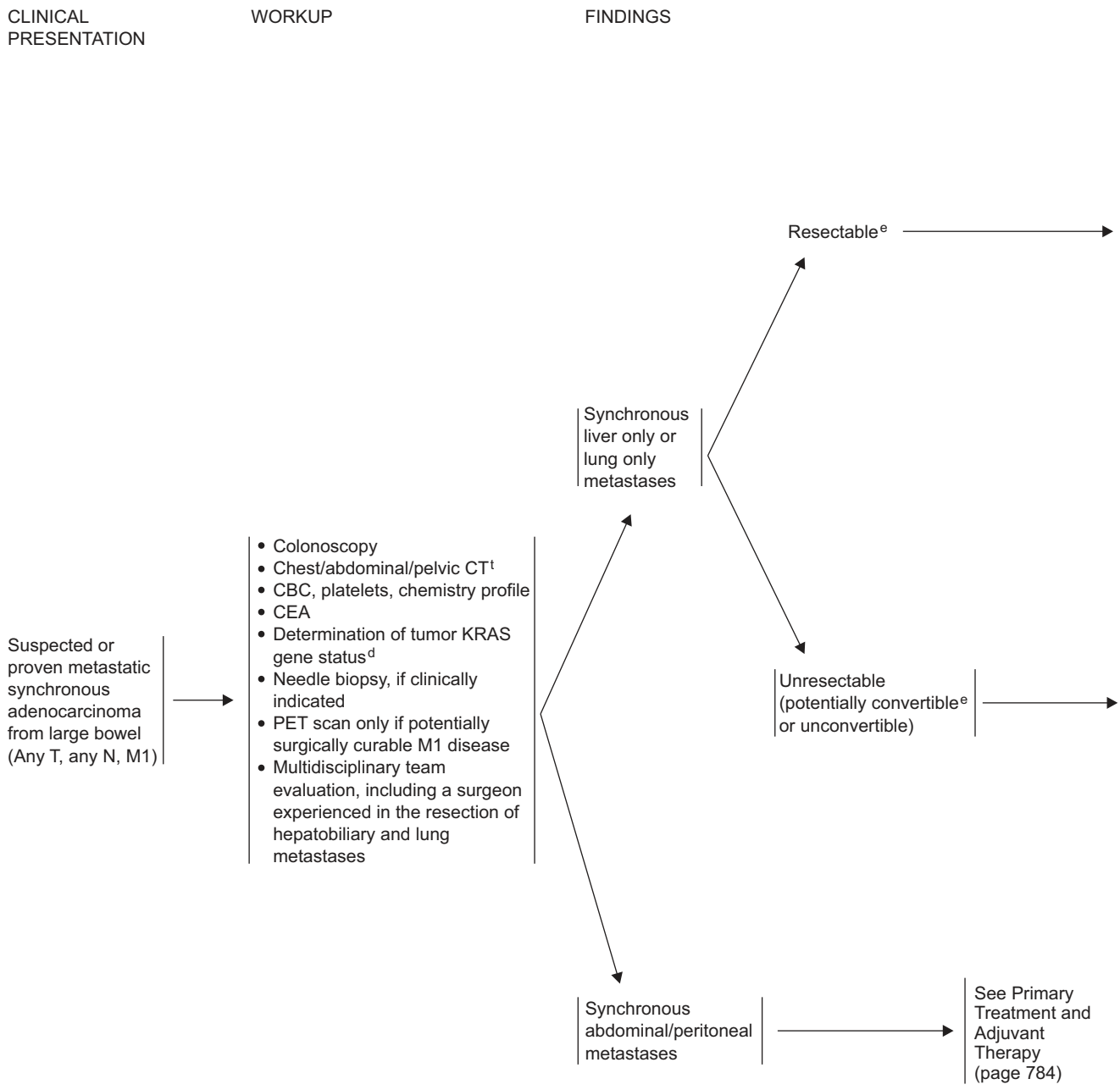


[a] All patients with colon cancer should be counseled for family history. Patients with suspected HNPCC, FAP, and attenuated FAP, see the NCCN Colorectal Cancer Screening Guidelines (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).
[d] See Principles of Pathologic Review: Pathologic Stage (page 788).
[h] No data support adjuvant therapy in stage I disease; however, certain high-risk patients with stage II disease (lymphovascular invasion, poorly differentiated histology, inadequate lymph node sampling) may be considered at higher risk, and a discussion of chemotherapy may be warranted.
[i] 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: Lymph Node Evaluation (page 788).
[j] Data are insufficient to recommend the use of molecular markers to determine adjuvant therapy.
[k] See Principles of Risk Assessment for Stage II Disease (page 798).
[l] See Principles of Adjuvant Therapy (pages 799 and 800).
[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 (page 800).
[o] Desch CE, Benson AB III, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23:8512-8519.
[p] If patient is a potential candidate for further intervention.
[q] CT scan may be useful for patients at high risk for recurrence (e.g., lymphatic or venous invasion of tumor or poorly differentiated tumors).
[r] Villous polyp, polyp > 1 cm, or high-grade dysplasia.
[s] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130:1865-1871.



[d] See Principles of Pathologic Review: KRAS Mutation Testing (page 789).
[e] See Principles of Surgery (page 791).
[t] CT should be with contrast. Consider MRI with contrast if CT is inadequate.

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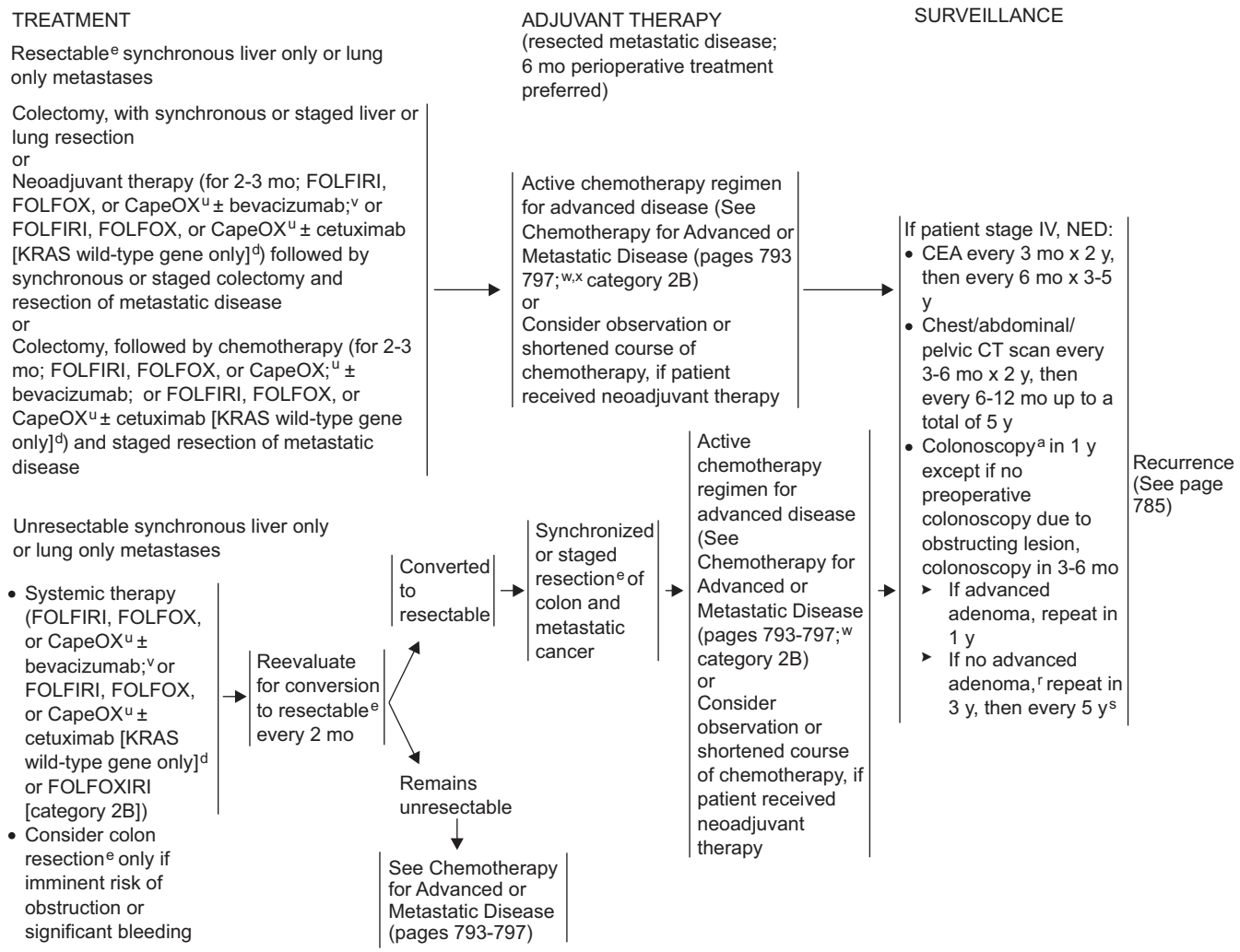

[a] All patients with colon cancer should be counseled for family history. Patients with suspected HNPCC, FAP, and attenuated FAP, see the NCCN Colorectal Cancer Screening Guidelines (to view the most recent version, visit www.nccn.org).

[d] See Principles of Pathologic Review: KRAS Mutation Testing (page 789).

[e] See Principles of Surgery (page 791).

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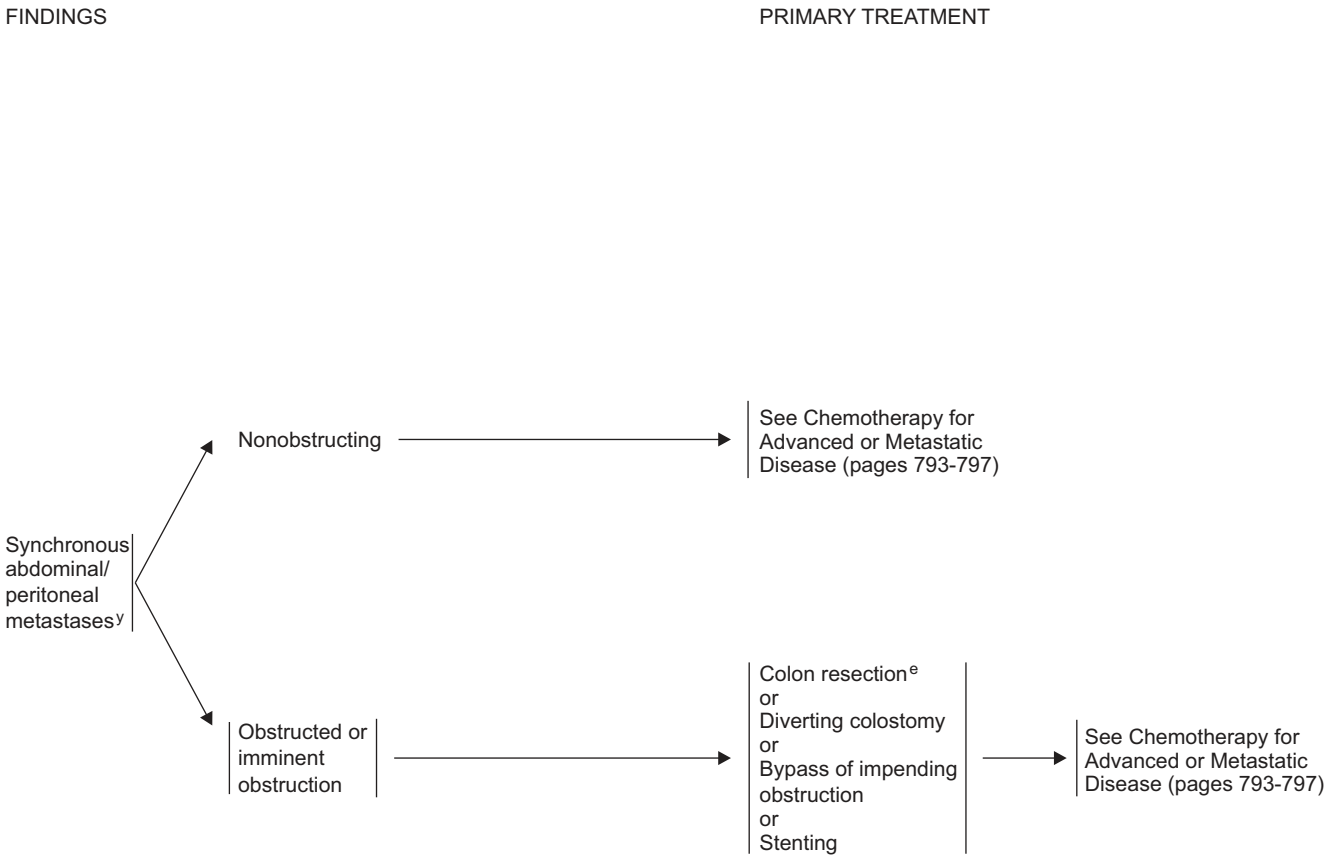
[u] Most safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m^2 twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (and with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large-scale randomized trials.

[v] 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-week interval between the last dose of bevacizumab and elective surgery and reinitiation of bevacizumab at least 6-8 wk postoperatively. There is an increased risk for stroke and other arterial events, especially in patients ≥ 65 years of age. The use of bevacizumab may interfere with wound healing.

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

[x] FOLFOXIRI is not recommended in this setting.



[e] See Principles of Surgery (page 791).
[y] Aggressive cytoreductive debulking and/or intraperitoneal chemotherapy are not recommended outside the setting of a clinical trial.

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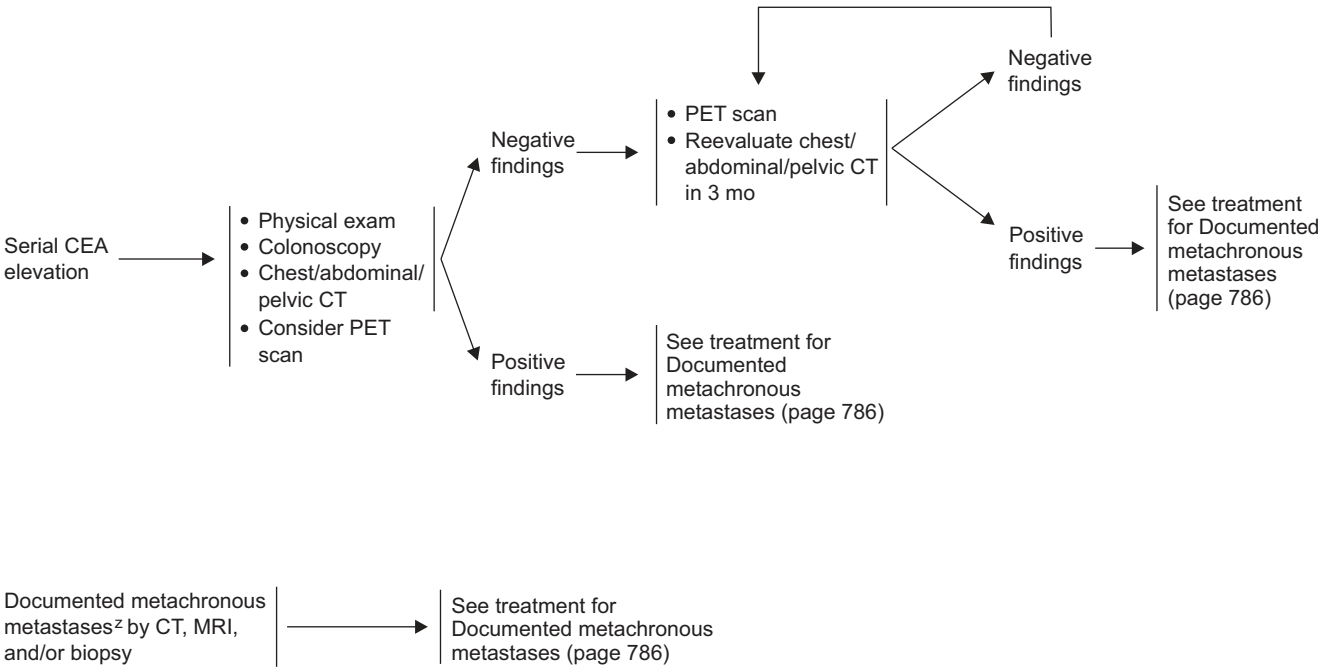
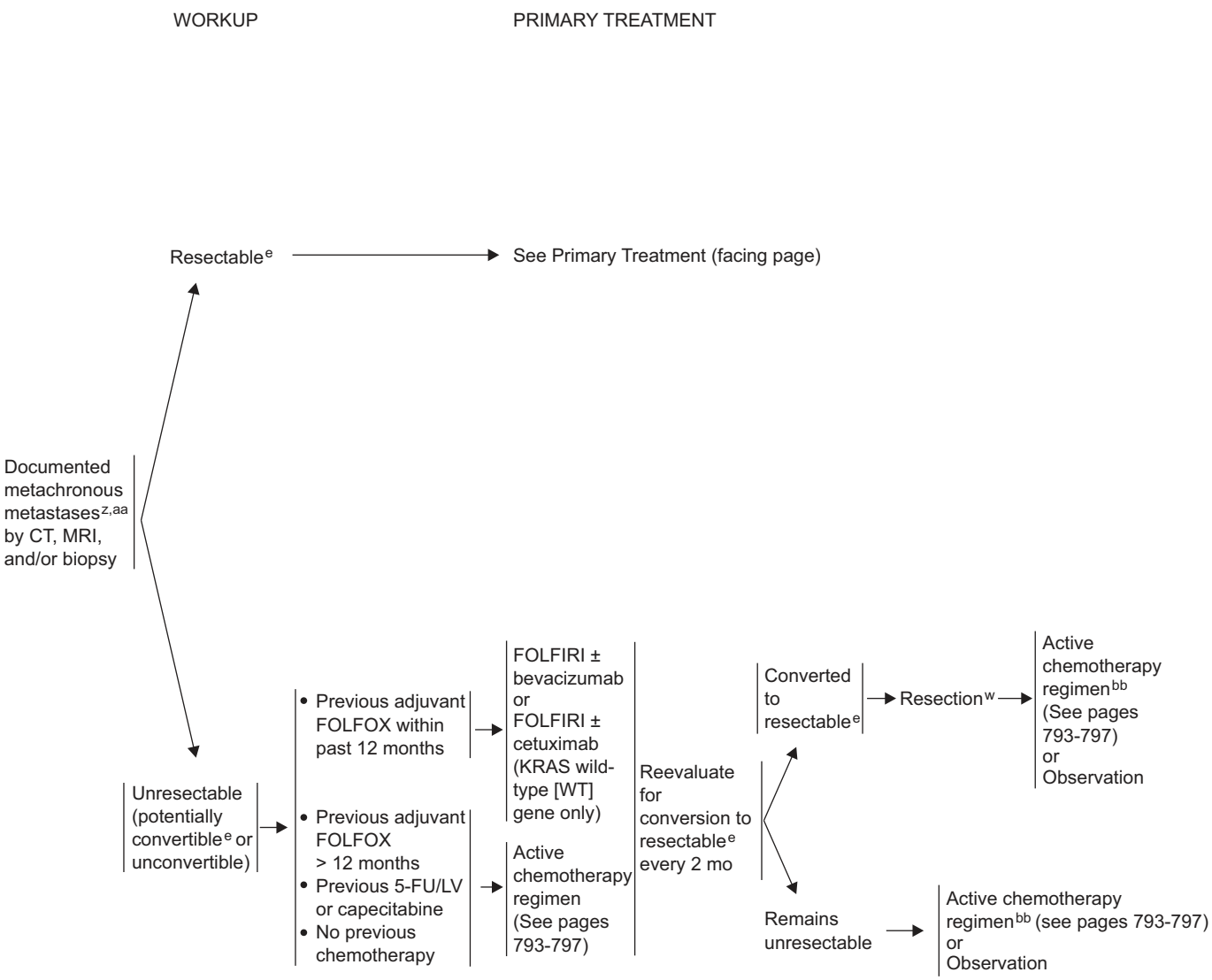
RECURRENCE WORKUP



[z] Determination of tumor KRAS gene status. See Principles of Pathologic Review: KRAS Mutation Testing (page 789)



[e] See Principles of Surgery (page 791).
[x] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[z] Determination of tumor KRAS gene status. See Principles of Pathologic Review: KRAS Mutation Testing (page 789).
[aa] Patients should be evaluated by a multidisciplinary team, including surgical consultation for potentially resectable patients.
[bb] Total perioperative therapy should be considered for a maximum of 6 months.

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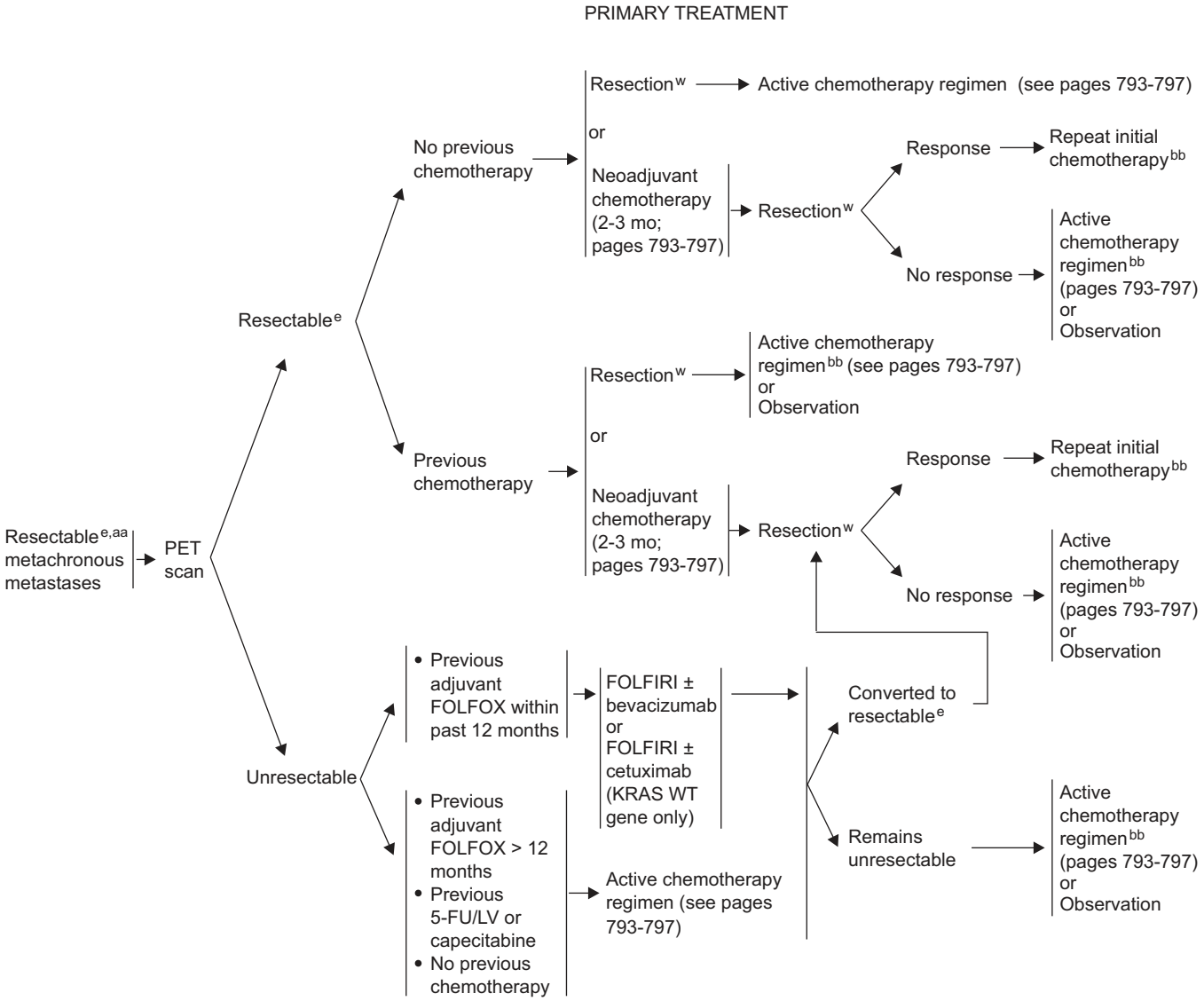

[e] See Principles of Surgery (page 791).
[x] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[aa] Patients should be evaluated by a multidisciplinary team, including surgical consultation for potentially resectable patients.
[bb] Total perioperative therapy should be considered for a maximum of 6 months.

PRINCIPLES OF PATHOLOGIC REVIEW

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 histologic features: grade 1 or 2, no angiolymphatic invasion, and negative margin of resection. No consensus exists 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, or 3) tumor cells present within the diathermy of the transected margin.[1-4]
- Unfavorable histologic features: grade 3 or 4, angiolymphatic invasion, or a "positive margin." See definition of a positive margin above.
- Controversy exists as to whether malignant colorectal polyps with a sessile configuration can be successfully treated with 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, examining the data closely, 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:

- Histologic confirmation of primary colonic malignant neoplasm

Pathologic Stage:

- The following parameters should be reported.
  - Grade of the cancer
  - Depth of penetration (T)
  - Number of lymph nodes evaluated and number positive (N)
  - Status of proximal, distal, and peritoneal margins (radial).[8-9] See Staging Table (available online, in these guidelines, at www.nccn.org [ST-1]).

See footnotes on page 790

PRINCIPLES OF PATHOLOGIC REVIEW

Lymph Node Evaluation:

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately 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, and > 30.[11-19] The number of lymph nodes retrieved can vary with patient age, gender, tumor grade, and tumor site.[12] For stage II (pN0) colon cancer, if < 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. The number of negative lymph nodes has been shown to be an independent prognostic factor for patients with stage IIIB and IIIC colon cancer.[20]

Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry:

- Examination of the sentinal lymph node allows an intense histologic 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. Although 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) are considered micrometastatic disease in contraindication to true micrometastasis (tumor aggregates > 0.2 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] Although the 6th edition of the AJCC Cancer Staging[26] manual considers "tumor clusters" < 0.2 mm to be ITC (pN0) and not metastatic carcinoma, some investigators have challenged this. Some believe that size should not affect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (e.g., glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.[27] Hermanek et al.[28] 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) confers a worse prognosis, whereas others have failed to show a survival difference. In these studies, ITC were considered micrometastasis.[29-33]
- Currently, 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]

KRAS Mutation Testing:

- Mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to therapy with antibodies targeted to the epidermal growth factor receptor.[34,35]
- Testing for mutations in codons 12 and 13 should be performed only in laboratories that are certified according to the clinical laboratory improvement amendments of 1988 (CLIA – 88) as qualified to perform highly complex clinical laboratory (molecular pathology) testing. No specific methodology is recommended (e.g., sequencing, hybridization).
- Testing can be performed on formalin-fixed, paraffin-embedded tissue, and on the primary colorectal cancers and/or metastasis, because literature has shown that the KRAS mutations are similar in both specimen types.[36]

See footnotes on page 790

PRINCIPLES OF PATHOLOGIC REVIEW
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Colon Cancer Version 3:2009

PRINCIPLES OF SURGERY

Colectomy

- Lymphadenectomy
  - Lymph nodes at the origin of feeding vessel should be identified for pathologic exam.
  - Lymph nodes outside the field of resection that are considered suspicious should be biopsied or removed.
  - Positive nodes left behind indicate an incomplete (R2) resection.
  - A minimum of 12 lymph nodes must 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 on the following criteria:[2]
  - Surgeon has 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 required.[5]
  - 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 (available at www.nccn.org).
- Resection must be complete to be considered curative.

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

Liver

- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[6]
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.[7-10] Plan for a debulking resection (less than an R0 resection) is not recommended.[6]
- Patients with resectable metastatic disease and primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.[11]
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches using preoperative portal vein embolization[12] or staged liver resection[13] can be considered.
- Hepatic resection is the preferred treatment for resectable liver metastases from colorectal cancer.[14]
- Ablative techniques may be considered alone or in conjunction with resection.[14]
- Some institutions use intra-arterial embolization in select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, with predominant hepatic metastases (category 3).
- Conformal external beam radiation therapy should not be used unless the patient is symptomatic or in the setting of a clinical trial.
- Re-resection can be considered in selected patients.[15]

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[16-19]
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.[20-23]
- Re-resection can be considered in selected patients.[24]
- Ablative techniques can be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.

Evaluation for conversion to resectable disease

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

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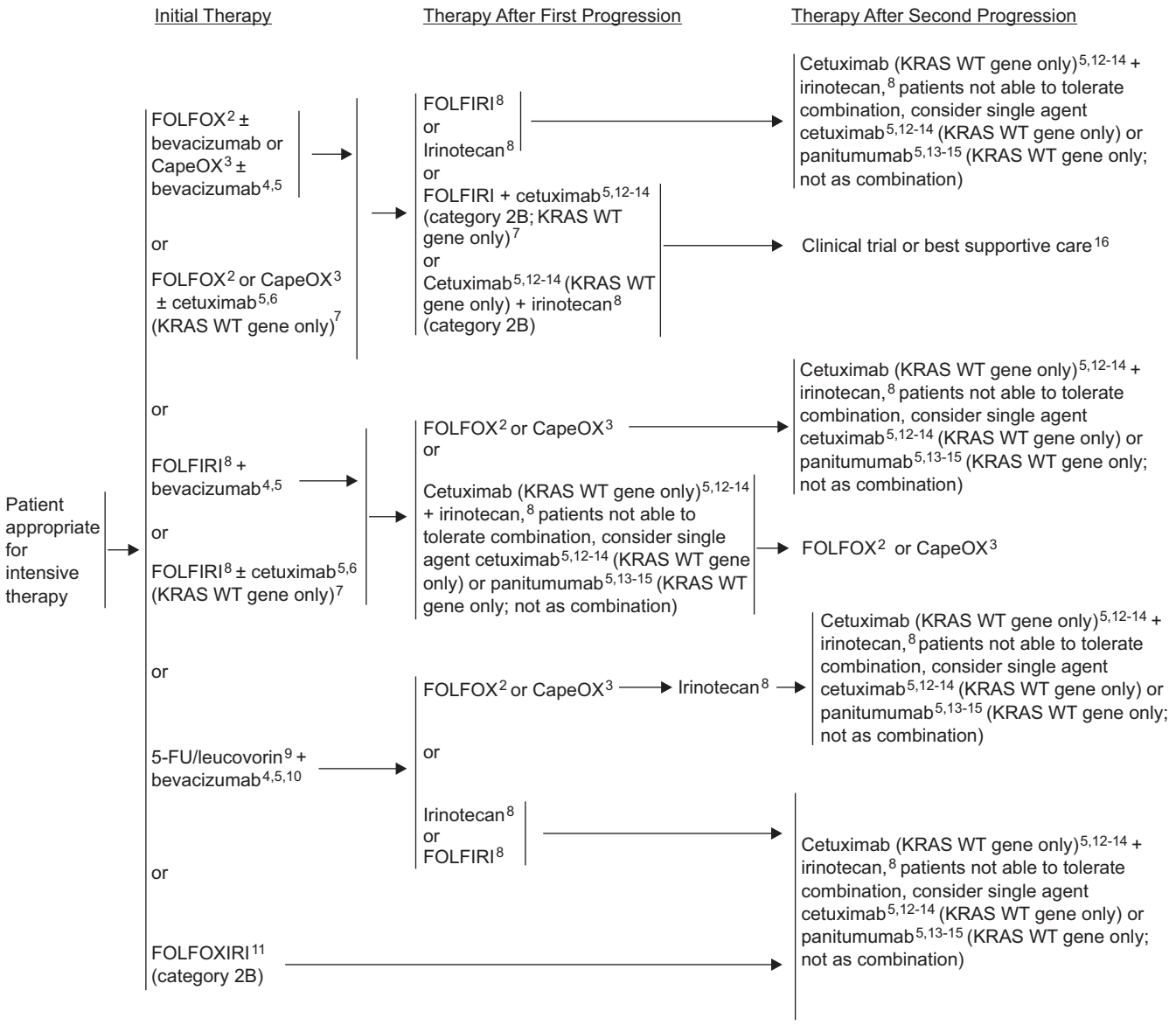
Colon Cancer Version 3:2009

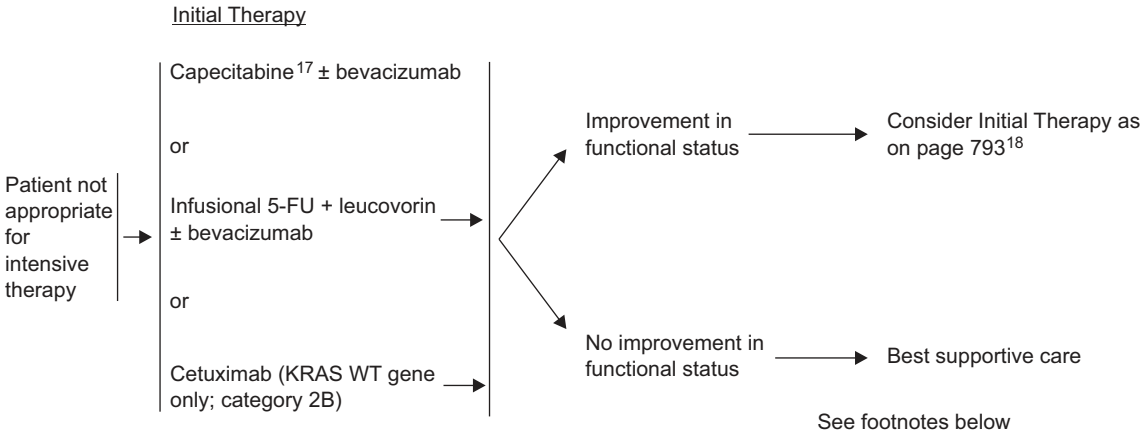
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1]



Patient not appropriate for intensive therapy, see page 794

See footnotes on page 794

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1]



See footnotes below

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

[1]For chemotherapy references, see Chemotherapy Regimens and References (pages 795-797).

[2]Discontinuation of oxaliplatin should be 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. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer - A GERCOR Study. J Clin Oncol 2006;24:394-400.

[3]Most 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 (and with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large scale randomized trials. 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.

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

[5]Combination therapy involving more than one biologic agent is not recommended. Hecht JR, Mitchell T, Chidiac C, et al. An updated analysis of safety and efficacy of oxaliplatin/bevacizumab +/- panitumumab for first-line treatment of metastatic colorectal cancer from a randomized, controlled trial (PACCE) [abstract]. Presented at the 2008 Gastrointestinal Cancers Symposium; Orlando, Florida; January 25-27, 2008. Abstract 273; and Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360:563-572.

[6]If cetuximab is used as initial therapy, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy.

[7]See Principles of Pathologic Review: KRAS Mutation Testing (page 789).

[8]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.

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

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

[11]Data are not mature for the addition of biologic agents to FOLFOXIRI.

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

[13]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.

[14]No data, nor a compelling rationale, 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.

[15]No data support the combination of panitumumab with chemotherapy.

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

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

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

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

CHEMOTHERAPY REGIMENS

FOLFOX

FOLFOX 4
Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1
Leucovorin 200 mg/m^2 IV over 2 hours, days 1 and 2
Followed on days 1 and 2 by 5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours continuous infusion
Repeat every 2 weeks[1]

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

CapeOX[3,4]
Oxaliplatin 130 mg/m^2 day 1, capecitabine 850-1000‡ mg/m^2 twice daily for 14 days
Repeat every 3 weeks

FOLFIRI[5,6]
Irinotecan 180 mg/m^2 IV over 30-120 minutes, day 1
Leucovorin 200 mg/m^2 IV infusion to match duration of irinotecan infusion, days 1 and 2
Followed on days 1 and 2 by 5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours continuous infusion
Repeat every 2 weeks

Irinotecan 180 mg/m^2 IV over 30-120 minutes, day 1
Leucovorin 400* mg/m^2 IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/d x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Repeat every 2 weeks

Bevacizumab + 5-FU containing regimens:[7–9]
Bevacizumab 5 mg/kg IV every 2 weeks +
5-FU and leucovorin
or FOLFOX[10]
or FOLFIRI
Bevacizumab 7.5 mg/kg IV every 3 weeks + CapeOX[4]

*Levoleucovorin dose is 200 mg/m^2. The equivalent dose of leucovorin is 400 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24-hour units (i.e., 1200 mg/m^2/d NOT 2400 mg/m^2/d over 46 hours) to minimize medication errors.

‡Most safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m^2 twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (and with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large-scale randomized trials.

See Additional Chemotherapy Regimens on page 796

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

CHEMOTHERAPY REGIMENS

2000-2500 mg/m^2/day PO in 2 divided doses, days 1-14,
followed by 7 days rest
Repeat every 3 weeks

Bolus or infusional 5-FU/leucovorin
Roswell-Park regimen[12]
Leucovorin 500 mg/m^2 IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m^2 IV bolus 1 hour after start of leucovorin,
days 1, 8, 15, 22, 29, 36
Repeat every 8 weeks

Biweekly[13]
Leucovorin 200 mg/m^2 IV over 2 hours, days 1 and 2
5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours
continuous infusion, days 1 and 2
Repeat every 2 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)[14]
Leucovorin 400* mg/m^2 IV over 2 hours on day 1,
followed by 5-FU bolus 400 mg/m^2 and then 1200 mg/m^2/day x 2
days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Repeat every 2 weeks

Weekly
Leucovorin 20 mg/m^2 as a 2-hour infusion
5-FU 500 mg/m^2 bolus administered 1 hour after LV infusion
Repeat every week[15]
5-FU 2600 mg/m^2 by 24-hour infusion plus leucovorin 500 mg/m^2
Repeat every week[16]

FOLFOXIRI[17]
Irinotecan 165 mg/m^2 IV day 1, oxaliplatin 85 mg/m^2 day 1,
leucovorin 400* mg/m^2 day 1, fluorouracil 3200 mg/m^2 over 48-
hour continuous infusion starting on day 1
Repeat every 2 weeks

Irinotecan 125 mg/m^2 IV over 30-90 minutes, days 1, 8, 15, 22
Repeat every 6 weeks

Irinotecan 300-350 mg/m^2 IV over 30-90 minutes, day 1
Repeat every 3 weeks

(KRAS WT gene only) ± irinotecan[20]
Cetuximab 400 mg/m^2 1st infusion, then 250 mg/m^2 IV weekly
or
Cetuximab 500 mg/m^2 IV every 2 weeks[21]
±
Irinotecan 300-350 mg/m^2 IV every 3 weeks
or
Irinotecan 180 mg/m^2 IV every 2 weeks
or
Irinotecan 125 mg/m^2 every week for 4 weeks
Every 6 weeks

Cetuximab (KRAS WT gene only)
Cetuximab 400 mg/m^2 1st infusion, then 250 mg/m^2 IV weekly

Panitumumab[22] (KRAS WT gene only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

*Levoleucovorin dose is 200 mg/m^2. The equivalent dose of leucovorin is 400 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24-hour units (i.e., 1200 mg/m^2/d NOT 2400 mg/m^2/d over 46 hours) to minimize medication errors.

See footnotes on the facing page

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

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

- 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%.

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PRINCIPLES OF ADJUVANT THERAPY

5-FU/leucovorin
- Leucovorin 500 mg/m^2 given as a 2-hour infusion and repeated weekly x 6
  5-FU 500 mg/m^2 given bolus 1 hour after the start of leucovorin and repeated 6 x weekly
  Every 8 weeks for 4 cycles[1]
- 5-FU 370-400 mg/m^2 + leucovorin 200 mg/m^2 daily x 5 days, every 28 days x 6 cycles[2]

Capecitabine[3]
Capecitabine 1250 mg/m^2 twice daily, days 1-14, every 3 weeks x 24 weeks

FLOX[4] (category 2B)
5-FU 500 mg/m^2 IV bolus weekly x 6 + leucovorin 500 mg/m^2 IV weekly x 6, each 8 week cycle x 3 with oxaliplatin 85 mg/m^2 IV administered on weeks 1, 3, and 5 of each 8-week cycle x 3

FOLFOX 4
Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1
Leucovorin 200 mg/m^2 IV over 2 hours, days 1 and 2
Followed on days 1 and 2 by 5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours continuous infusion
Repeat every 2 weeks[5,6]

mFOLFOX 6
Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1
Leucovorin* 400 mg/m^2 IV over 2 hours, day 1
5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Repeat every 2 weeks[7,8]

*Levoleucovorin dose is 200 mg/m^2. The equivalent dose of leucovorin is 400 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24-hour units (i.e., 1200 mg/m^2/d NOT 2400 mg/m^2/d over 46 hours) to minimize medication errors.

See Additional Principles of Adjuvant Therapy on page 800

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[7] Cheeseman S, Joel S, Chester J, et al. A "modified de Gramont" regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399.
[8] Welles L, Hochster H, Ramanathan R, et al. Preliminary results of a randomized study of safety and tolerability of three oxaliplatin-based regimens as first-line treatment for advanced colorectal cancer ("Tree" study) [abstract]. J Clin Oncol 2004;23:Abstract 3537.

PRINCIPLES OF ADJUVANT THERAPY

- 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 patients with stage III disease.[2,3] FOLFOX is reasonable for patients with high-risk or intermediate-risk stage II disease and is not indicated for patients with good- or average-risk stage II disease. 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.

[1] Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-2704.
[2] Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351.
[3] deGramont A, Boni C, Navarro M, et al. Oxaliplatin/5-FU/LV in adjuvant colon cancer: updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of 6 years [abstract]. J Clin Oncol 2007;25(Suppl 1):Abstract 4007.
[4] Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007;25:2198-2204.
[5] Saltz LB, Niedzwieecki D, Hollis D, et al. Irinotecan plus fluorouracil/leucovorin (IFL) versus fluorouracil/leucovorin alone (FL in stage III colon cancer (intergroup trial CALGB C89803) [abstract]. J Clin Oncol 2004;23(Suppl 1):Abstract 3500.
[6] Van Custem E, Labianca R, Hossfield D, et al. Randomized phase III trial comparing infused irinotecan/5-fluorouracil (5-FU)/folinic acid (IF) versus 5-FU/FA in stage III colon cancer patients (PETACC3) [abstract]. J Clin Oncol 2005;23(Suppl 1):Abstract 8.
[7] Ychou M, Raoul J, Douillard J, et al. A phase III randomized trial of LV5FU2 + CPT-11 versus LV5FU2 alone in high risk colon cancer (FNCLCC Accord02/FFCD9802) [abstract]. J Clin Oncol 2005;23(Suppl 1):Abstract 3502

PRINCIPLES OF RADIATION THERAPY

- Radiation therapy fields should include the tumor bed, which should be defined by preoperative radiologic imaging and/or surgical clips.
- Radiation doses should be:
  - 45-50 Gy in 25-28 fractions.
  - Consider boost for close or positive margins.
  - Small bowel dose should be limited to 45 Gy.
  - 5-FU-based chemotherapy should be delivered concurrently with radiation.
- Intensity-modulated radiotherapy (IMRT) or tomotherapy should only be used in the setting of a clinical trial.
- 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 before adjuvant chemotherapy.
- Some institutions use intra-arterial embolization in select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, and with predominant hepatic metastases (category 3).
- Conformal external beam radiation therapy should not be used unless the patient is symptomatic or in the setting of a clinical trial.

Colon Cancer Version 3:2009

PRINCIPLES OF SURVIVORSHIP
Colorectal Long-Term Follow-up Care

CRC Cancer Surveillance:
- History and physical every 3-6 months for 2 years, then every 6 months for 3 years.
- CEA every 3-6 months for 2 years, then every 6 months for 3 years.
- CT scan of abdomen and pelvis annually for 3 years.
- Colonoscopy at 1 year, then as clinically indicated.

Cancer Screening Recommendations:[1]
- Breast Cancer:
  - Periodic self breast exam (SBE) encouraged (optional).
  - Clinical breast exam (CBE) every 1-3 years between ages 20 and 40.
  - Annual mammogram with clinical breast exam beginning at age 40.
  - Women at high risk (> 20% lifetime risk) should get breast MRI and mammogram annually.
  - See NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis.*
- Cervical Cancer:
  - Annual cervical cytology testing with conventional smears or every 2 years with liquid-based cytology for women up to age 30.
  - After age 30, screening may be every 2-3 years if 3 negative/satisfactory annually cervical cytology tests documented.
  - Alternatively, human papilloma virus (HPV) DNA testing for women age 30 and older, combined with cervical cytology.
  - If cervical cytology and HPV DNA testing both negative, testing may be performed every 3 years.
  - Counseling regarding HPV infection.
  - Women older than 70 years with no abnormal testing in last 10 years and 3 normal tests in a row may discontinue screening.
  - Women without a cervix from a total abdominal hysterectomy do not need to be screened.
  - See NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer Screening.*
- Prostate Cancer:
  - Annual prostate specific antigen (PSA) testing and digital rectal exam (DRE) beginning at age 50.
  - For high risk men (African-American males and those with a family history of prostate cancer): PSA testing and DRE beginning at age 40.
  - See NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection.*

Management of Late Sequelae of Disease or Treatment:[2,3]
- Chronic Diarrhea or Incontinence:
  - Consider antidiarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.
- Oxaliplatin-Induced Neuropathy:
  - Consider the use of gabapentin and/or tricyclic antidepressants for persistent, painful neuropathy.

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

[1]American Cancer Society Guidelines for Early Detection of Cancer. Available at: http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp. Accessed September 21, 2008.
[2]Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer. Cancer 2007;110: 2075-2082.
[3]Sprangers MAG, Taal BG, Aaronson NK, et al. Quality of life inolorectal cancer: stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-369.

PRINCIPLES OF SURVIVORSHIP
Colorectal Long-term Follow-up Care

Immunizations:[4]
- Annual trivalent inactivated influenza vaccination
- Pneumococcal vaccination with revaccination as appropriate

Routine Health Monitoring and Screening:
- Cholesterol, blood pressure, and glucose monitoring
- Bone density testing as appropriate
- Routine dental examinations
- Routine sun protection
- Screening for depression as appropriate

Counseling Regarding Healthy Lifestyle and Wellness:[5-8]
- Screening and counseling to maintain a healthy weight.
- Screening for physical activity and counseling to adopt a physically active lifestyle (recommended activity: at least 30 minutes or more of moderate to vigorous physical activity at least 5 days of the week).
- Screening and counseling for alcohol use.
- Screening and counseling for tobacco use with emphasis on smoking cessation.
- Counseling regarding healthy diet adoption, with emphasis on plant sources.

Prescription for Survivorship and Transfer of Care to Primary Care Physician:[9]
- Include overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received.
- Describe possible clinical course, including expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment.
- Include surveillance recommendations.
- Delineate appropriate timing for transfer of care with specific responsibilities identified for the primary care physician and oncologist.

[4] Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, October 2007–September 2008. Ann Intern Med 2007;147:725-729.
[5] American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention. Available at: http://www.cancer.org/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED. Accessed September 21, 2008.
[6] Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol 2006;24:3535-3541.
[7] Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA 2007;298:754-764.
[8] Dignam JL, Polite BN, Yothers G, et al. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. J Natl Cancer Inst 2006;98:1647-1654.
[9] Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.: The National Academies Press; 2006.

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

Text continued from p. 779

Cancer's (AJCC) Cancer Staging Manual[2,6] includes several modifications to the colon and rectum staging system (available online, in these guidelines, at www.nccn.org [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 IIIA (T1 to T2, N1, M0), IIIB (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 4 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 IIA); 72.2% (stage IIB); 83.4% (stage IIIA); 64.1% (stage IIIB); 44.3% (stage IIIC); and 8.1% (stage IV).[7] It has been proposed that the lack of correlation between stage and prognosis in this study (i.e., increased survival rates for patients with stage IIIA disease vs. those with disease classified as stage IIB) may be associated with a number of factors, including more common use of adjuvant therapy in the former population of patients.[8]

Staging of colon cancer also includes an assessment of the presence or absence of distant metastases (M); stage IV disease is characterized by the presence of 1 or more distant metastases and designated as M1.[6]

The 6th edition of the AJCC staging system suggests 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 that should be included in the report of the pathologic evaluation include 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); assessment of the presence of distant metastases to other organs, the peritoneum of an abdominal structure, or in nonregional lymph nodes (M);[6,9] and status of proximal, distal, and peritoneal margins (see pages 788–790).[6,10]

The AJCC and College of American Pathologists (CAP) recommend evaluation of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancers.[6,11,12] The number of lymph nodes retrieved can vary with age of the patient, gender, and tumor grade or site.[13–15] The extent and quality of surgical resection and pathologic review of the specimen can also have an impact on the node harvest.[16–18]

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 nodes.[19] 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.[19–23] Although 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 (see pages 788–790).

A sizable body of literature has shown that mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to cetuximab or panitumumab therapy.[24–36] Therefore, the panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer at diagnosis of stage IV disease. The recommendation for KRAS testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting. Instead, this early establishment of KRAS

status is appropriate to plan for the treatment continuum, so that the information may be obtained in a non-time–sensitive manner, and the patient and provider can discuss the implications of a KRAS mutation, if present, while other treatment options still exist. KRAS mutations are early events in colorectal cancer formation, and, therefore, a very tight correlation exists between mutation status in the primary tumor and metastases.[35,36] For this reason, KRAS genotyping can be done on archived specimens of either the primary tumor or metastasis. Fresh biopsies should not be obtained solely for the purpose of KRAS genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable. The panel recommends that KRAS gene testing be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing (see pages 788–790).

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 (see page 780).[37] 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 therefore are not considered capable of regional nodal metastasis.[6] The panel recommends marking the polyp site at 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.[38] Favorable histological features include lesions of grade 1 or 2, no angiolymphatic invasion, and a negative resection margin. However, in addition to the option of observation, the panel includes the option of colectomy in patients with a completely-removed, single-specimen, sessile polyp with favorable histological features and clear margins, because it has been reported that patients with sessile polyps have a 10% risk of lymph node metastases.[39] For pedunculated and sessile polyps, unfavorable histopathological features are grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. It should be noted that there is currently no consensus as to the definition of what constitutes a positive margin of resection. A *positive margin* has been defined as the presence of a tumor within 1 to 2 mm from the transected margin and the presence of tumor cells within the diathermy of the transected margin.[37,40–42] For a pedunculated or sessile polyp with fragmented specimen, margins that cannot be assessed, or with unfavorable pathology, colectomy with en bloc removal of lymph nodes is recommended.[37,43,44] Laparoscopic surgery is an option (see following section). All patients who have resected polyps should undergo total colonoscopy to rule out other synchronous polyps, as well as appropriate follow-up surveillance endoscopy.[45] 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, CBC, platelets, chemistry profile, carcinoembryonic antigen (CEA) determination, and baseline CT scans of the chest, abdomen, and pelvis (see page 780).[46] The panel consensus is that a PET scan is not routinely indicated at baseline in the absence of evidence of synchronous metastatic disease and should not be done as a matter of general surveillance. If suspicious abnormalities are seen on CT or MRI scan, then a PET scan may be appropriate for further delineation. A PET scan is not indicated for assessment of subcentimeter lesions, as these are routinely below the level of PET detection.

For resectable colon cancer, the surgical procedure of choice is colectomy with en bloc removal of the regional lymph nodes.[47] 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.[6] Other nodes, such as those at the origin of the vessel feeding the tumor (i.e., apical lymph node) and suspicious lymph nodes outside the

field of resection, should also be biopsied or removed.

Secondary analyses from the Intergroup INT-0089 trial of patients with high-risk stage II or III colon cancer receiving adjuvant chemotherapy showed that the accuracy of staging colorectal cancer was associated with the number of nodes removed.[48] 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 -positive disease.[14] In addition, the ratio of metastatic to examined lymph nodes (LNR) was a significant prognostic factor for both disease recurrence and overall survival,[49] although LNR was not shown to be prognostic for patients for whom fewer than 10 lymph nodes were evaluated.[49] The panel does not consider determination of LNR to be a substitute for an adequate lymph node evaluation. In addition, results from several population-based studies have shown an association between improvement in survival and examination of 12 (or 13) or more lymph nodes.[15,18,50] 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 who have had fewer than 12 nodes 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. Although a small European trial (Barcelona) showed some modest survival advantage to the laparoscopic approach,[51] more recently, for patients randomly assigned to curative surgery with either a conventional open approach or laparoscopically-assisted surgery, an absolute difference of 2.0% (P = not significant) in 3-year disease-free survival (DFS) in favor of open colectomy was observed in a study of 1248 patients with colon cancer (COLOR trial). Although this difference was not statistically significant, noninferiority of the laparoscopic approach could not be established due to study limitations.[52]

In the CLASSIC study of 794 patients with colorectal cancer, no statistically significant differences in 3-year rates of overall survival, DFS, and local recurrence were seen when the 2 surgical approaches were compared.[53] Also reported have been results from another trial of 872 patients with colon cancer (COST study) randomly assigned to undergo open or laparoscopically-assisted colectomy for curable colon cancer.[54,55] After a median of 7 years follow-up, similar 5-year cancer recurrence and overall survival rates were observed in the 2 groups. In addition, several recent meta-analyses have provided support for the conclusion that the 2 surgical approaches provide similar long-term outcomes with respect to local recurrence and survival of patients with colon cancer.[56–58] However, a subanalysis of results from the COLOR trial evaluating short-term outcomes (e.g., conversion rate to open colectomy, number of lymph nodes collected, number of complications) based on hospital case volume indicated that these outcomes were statistically significantly more favorable when laparoscopic surgery was performed at hospitals with high case volumes.[59] Other factors that may confound conclusions drawn from randomized studies comparing open colectomy with laparoscopically-assisted surgery for colon cancer have also been described.[60,61]

The panel recommends that laparoscopically assisted colectomy be considered only by surgeons experienced in the technique. A thorough abdominal exploration is a required part of the procedure. Routine use of laparoscopic-assisted resection is not, at this time, recommended for tumors in the lower and mid rectum or for tumors that are acutely obstructed or perforated or clearly locally invasive into surrounding structures (i.e., T4). Patients at high risk for prohibitive abdominal adhesions should not be approached laparoscopically, and patients who are found to have prohibitive adhesions during laparoscopic exploration should be converted to an open procedure[62–64] (see pages 791 and 792).

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 chemotherapy and/or 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.[65–67] The European MOSAIC trial has evaluated the efficacy of FOLFOX4 (infusional 5-fluorouracil [5-FU], leucovorin [LV], oxaliplatin) compared with 5-FU/LV in the adjuvant setting in 2246 patients with completely resected stage II and III colon cancer.

Results of this study have been reported with median follow-up of 3 years,[68] 4 years,[69] and 6 years.[70] For stage III patients, DFS at 5 years was 58.9% in the 5-FU/LV arm and 66.4% in the FOLFOX4 arm (P = .005). For stage II patients, 5-year DFS differences were not statistically significantly different between the 2 arms. Based on these results, FOLFOX4, or modified FOLFOX6, is recommended as treatment for stage III colon cancer (category 1). Although the initial trials were done with FOLFOX4, modified FOLFOX6 is the control arm for all current National Cancer Institute adjuvant studies.

The recommendation for use of FOLFOX is strengthened by the results of a recent analysis of individual patient data from 20,898 patients on 18 randomized colon adjuvant clinical trials that suggested that DFS after 2 and 3 years follow-up is an appropriate end point for clinical trials involving treatment of colon cancer with 5-FU–based chemotherapy in the adjuvant setting.[71,72] A recent update of this analysis showed that most relapses occur within 2 years after surgery and that recurrence rates were less than 1.5% and less than 0.5% per year after 5 years and 8 years, respectively.[73] Furthermore, overall survival of patients with stage III disease receiving FOLFOX was statistically significantly increased at 6-year follow up (78.5% vs. 76%; hazard ratio [HR] = .80; 95% CI, 0.65–0.97; P = .023) compared with those receiving 5-FU/LV.[74] Although the incidence of grade 3 peripheral sensory neuropathy was 12.4% for patients receiving FOLFOX, long-term safety results showed a gradual recovery for most of these patients. However, neuropathy was present in 15.5% of this group at 4 years, suggesting that oxaliplatin-induced neuropathy may not be completely reversible in some patients.[74]

Other adjuvant regimens studied for the treatment of early-stage colon cancer include 5-FU–based therapies incorporating irinotecan and 5-FU regimens, other than FOLFOX, which include oxaliplatin and single agent capecitabine. The U.S. Intergroup trial CALGB C89803 evaluated irinotecan plus bolus 5-FU/LV (IFL regimen) versus 5-FU/LV alone in stage III colon cancer.[75] No improvement in either overall survival (P = .74) or DFS (P = .85) was seen for patients in the IFL arm compared with those receiving 5-FU/LV. However, IFL was associated with a greater degree of neutropenia, neutropenic fever, and death.[76]

In addition, FOLFIRI (infusional 5-FU, LV, irinotecan), has not been shown to be superior to 5-FU/LV in the adjuvant setting.[77,78] Thus, data do not support the use of irinotecan-containing regimens in the treatment of stage II or III colon cancer. A randomized phase III trial (NSABP C-07) compared the efficacy of FLOX (bolus 5-FU/LV/oxaliplatin) with that of FULV (bolus 5-FU/LV) in prolonging DFS in 2407 patients with stage II or III colon cancer.[79,80] Four-year DFS rates were 73.6% for FLOX and 67.0% for FULV, indicating that the addition of oxaliplatin to weekly FULV statistically significantly improved 4-year DFS in patients with stage II or III colon cancer (P = .0034).

Grade 3 NCI-Sanofi neurosensory toxicity, diarrhea, or dehydration associated with bowel wall thickening was higher with FLOX than FULV, and, when cross-study comparisons are made, the incidence of grade 3/4 diarrhea appears to be considerably higher with FLOX than FOLFOX. For example, rates of grade 3/4 diarrhea were 10.8% and 6.7% for patients receiving FOLFOX and infusional 5-FU/LV, respectively, in the MOSAIC trial,[70] whereas 38% and 32.2% of patients had grade 3/4 diarrhea in the NSABP C-07 trial when receiving FLOX and bolus 5-FU/LV, respectively.[80] Single agent oral capecitabine as adjuvant therapy for patients with stage III colon cancer was shown to be at least equivalent to bolus intravenous 5-FU/LV (Mayo clinic regimen) with respect to DFS and overall survival with respective HRs of 0.87 (95% CI, 0.75–1.00) and 0.84 (95% CI, 0.69–1.01) when the capecitabine arm was compared with the 5-FU/LV arm.[81]

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 showed that most of the benefit of adjuvant therapy was seen in the patients with stage III disease.[82,83] 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 statistically significantly increased in the subset of patients with positive regional lymph nodes but not in patients with N0 disease when compared with patients not receiving chemotherapy. These re-

sults suggest that the benefit of adjuvant therapy is greater in patients at higher risk due to nodal status.[84] These clinical trial results are supported by data from the community setting. Using the SEER databases, an outcome analysis of patients with stage II disease, based on whether patients had or had not received adjuvant chemotherapy, showed that there was no statistically significant difference between these 2 groups with respect to 5-year overall survival (e.g., 78% vs. 75%, respectively), with a HR for survival of 0.91 (95% CI, 0.77–1.09).[85]

After primary surgical treatment, the panel recommends 6 months of adjuvant chemotherapy for patients with stage III (T1-4, N1-2, M0) resected colon cancer (see page 781). The treatment options are: 5-FU/LV/oxaliplatin as the standard of care (category 1),[68–70,79,80] or either single agent capecitabine (category 2A)[81] or 5-FU/LV (category 2A) in patients believed to be inappropriate for oxaliplatin therapy.[82,86,87] The panel concluded that irinotecan-containing regimens should not be used as adjuvant therapy in colon cancer. In contrast to other previously published trials, the QUASAR trial indicates a small but statistically significant survival benefit for stage II patients treated with 5-FU/LV.[88] 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); lymphovascular invasion; bowel obstruction at presentation; lesions with localized perforation or close, indeterminate, or positive margins; and inadequately sampled nodes (< 12 lymph nodes), should be considered for adjuvant chemotherapy[10,89] with 5-FU/LV/oxaliplatin, single agent 5-FU/LV, or capecitabine (category 2A for all 3 regimens). Results of subset analyses of data from the MOSAIC trial did not show a significant DFS benefit of FOLFOX over 5-FU/LV for patients with stage II disease at a follow-up of 6 years (HR = 0.84; 95% CI, 0.62–1.14; P = .258). Nevertheless, subset analyses showed a trend for improved DFS in high-risk stage II patients receiving FOLFOX4 compared with infusional 5-FU/LV (HR = 0.74; 95% CI, 0.52–1.06), suggesting that this patient population may benefit from treatment with FOLFOX.[70] However, no benefit of FOLFOX over 5-FU/LV was seen for patients with low-risk stage II disease in the MOSAIC trial.[70] Based on these results, as well as the possible long-term sequelae of oxaliplatin-based chemotherapy, the panel does not consider FOLFOX to be an appropriate adjuvant therapy option for patients with stage II disease without high-risk features (see page 781). Decision-making regarding use of adjuvant therapy for patients with stage II disease should incorporate patient-physician discussions individualized for the patient and include explanations of disease-specific characteristics and evidence related to the efficacy and possible toxicities associated with treatment, centering on patient choice[89,90] (see page 798).

Radiation therapy delivered concurrently with 5-FU–based chemotherapy may be considered for patients with disease characterized as T4 tumors penetrating to a fixed structure, and locally recurrent disease (see pages 781 and 800). Radiation therapy fields should be defined by preoperative radiologic imaging or surgical clips. Intraoperative radiotherapy, if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Intensity-modulated radiotherapy (IMRT), which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,[91] should only be used in the context of a clinical trial.

A summary of ongoing clinical trials in early-stage colon cancer has been presented.[92]

Principles of the Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with colorectal cancer will develop colorectal metastases.[93,94] 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% to 25% of patients with colorectal cancer present with synchronous liver metastases, although 80% to 90% of these patients are initially evaluated to have unresectable metastatic liver disease.[93,95–97] Metastatic disease more frequently develops metachronously following treatment for colorectal cancer, with the liver as a common site of involvement.[98] 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 = .008) and more bilobar metastases (P = .016) when compared with patients diagnosed with metachronous liver metastases.[99] For patients presenting with synchronous metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver.[100]

It has been estimated that more than 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.[101] Results from reviews of autopsy reports of patients who died from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients.[95] Furthermore, 5-year survival rates for patients with metastatic liver disease not undergoing surgery have been shown to be low in a number of studies.[93,102] However, studies of selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this population and should be the goal for many patients with colorectal metastatic liver disease.[93,103] Recent reports have shown 5-year survival rates after resection of liver metastases exceeding 50%.[104,105] 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.[106]

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 (see pages 791 and 792).[107–110] Resectability differs fundamentally from end points that focus more on palliative measures of treatment, such as response and DFS. Instead, the resectability end point is focused on the potential of surgery to cure the disease;[111] resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), because partial liver resection or debulking has not been shown to be beneficial.[94,109] Approaches used in the surgical treatment of liver metastases include simultaneous resections of colorectal cancer and synchronous liver metastases,[112] preoperative portal vein embolization for the purpose of increasing the volume and function of the portion of the liver which will remain postsurgically,[113] and hepatic resection performed in 2 stages for bilobular disease.[114]

Resection is the standard of care for local treatment of metastatic disease that is initially resectable or converted to a potentially curable status after chemotherapy.[115] However, some patients in this group who cannot undergo resection because of comorbidity, location of metastatic lesions (i.e., adjacent to a major hepatic vein or the vena cava), or an estimate of inadequate liver volume after resection may be candidates for ablation therapy.[116] A number of retrospective studies have compared radiofrequency ablation (RFA) and liver resection in the treatment of liver metastases,[117–119] although RFA has not been well studied in this setting. Most of these studies have shown RFA to be inferior to resection with respect to rates of local recurrence and 5-year overall survival.[115] It is presently unclear whether the differences in outcome seen for patients with liver metastases treated with RFA versus resection alone are due to patient selection bias, technologic limitations of RFA, or a combination.[118] Nevertheless, the panel does not consider RFA to be a substitute for resection in patients with completely resectable disease. In addition, resection or RFA (either alone or in combination with resection) should be reserved for patients whose disease is completely amenable to local therapy. Use of surgery, RFA, or combination with a goal of less than complete resection/ablation of all known sites of disease is not recommended.

The panel consensus is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (i.e., with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status.

Most patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease. For those with liver-limited unresectable disease, however, preoperative chemotherapy is being increasingly employed to downsize colorectal metastases to convert these lesions to a resectable status (i.e., conversion chemotherapy); it has also been administered to patients with metastatic disease determined to be resectable (i.e., neoadjuvant therapy).[120] Potential advantages of this approach include earlier treatment of micrometastatic disease, determination of responsiveness to chemo-

therapy (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 are 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.[95,121]

Furthermore, results from a recent study of patients with colorectal cancer receiving preoperative 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.[122] It is therefore essential that during treatment with preoperative chemotherapy, frequent evaluations are undertaken and close communication is maintained between medical oncologists, radiologists, surgeons, and patients so a treatment strategy can be developed that optimizes exposure to the preoperative chemotherapy regimen and facilitates an appropriately timed surgical intervention.[123] When preoperative chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation should be planned 2 months after initiation of preoperative chemotherapy and that those patients who continue to receive preoperative chemotherapy undergo surgical re-evaluation approximately every 2 months thereafter.[124–127]

Certain clinicopathologic factors, such as the presence of extrahepatic metastases and a disease-free interval of less than 12 months, have been associated with a poor prognosis in patients with colorectal cancer,[104,105,128–130] although the ability of these factors to predict outcome after resection may be limited.[93] However, decision-making regarding whether to offer preoperative 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 downsizing 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 convertible following response to chemotherapy. In addition, preoperative chemotherapy may be more beneficial in patients who have not been exposed to prior chemotherapy or who have not received it 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 by Pozzo et al.,[108] it was reported that preoperative chemotherapy therapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of patients with initially unresectable liver metastases to undergo liver resection. The median time to progression was 14.3 months, with all 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),[97] 44 patients with unresectable liver metastases were treated with FOLFOX4. Twenty-five patients (60%) had tumor reduction and 17 (40%; 68% of responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study of 1439 initially unresectable patients with colorectal liver disease, 1104 patients were treated with chemotherapy and 335 (23%) were able to undergo primary hepatic resection. Of the 1104 patients receiving chemotherapy, 138 patients (12.5%) classified as "good responders" underwent secondary hepatic resection following preoperative chemotherapy, which included oxaliplatin in the majority of cases.[131] The 5-year overall survival rate for these 138 patients was 33%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%) were able to undergo curative liver resection after treatment.[132] The median overall survival time in this group was 42.4 months.

The choice of chemotherapy regimen in the preoperative setting is dependent on a number of factors, including whether the patient has resectable or potentially convertible metastatic disease and the response rates and safety/toxicity issues associated with the regimens. A recent EORTC phase III study evaluating use of perioperative FOLFOX4 (6 cycles before and 6 cycles after surgery) for patients with initially resectable liver metastases demonstrated

absolute improvements in 3-year progression-free survival (PFS) of 8.1% (P = .041) and 9.2% (P = .025) for all eligible and resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[133] The partial response rate after preoperative FOLFOX was 40% and operative mortality was less than 1% in both treatment groups.

There have been recent reports of randomized clinical trials evaluating preoperative FOLFIRI or FOLFOX as conversion therapies in combination with anti-epidermal growth factor receptor (EGFR) inhibitors.[134,135] However, a number of randomized studies have investigated the efficacy and safety of FOLFOX, CapeOX, or FOLFIRI with and without bevacizumab or cetuximab in the first-line treatment of patients with metastatic colorectal cancer (see Chemotherapy for Advanced or Metastatic Disease section). In addition, first-line FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI in 2 randomized clinical trials.[136,137] Significantly improved rates of response and overall survival were reported for patients in the FOLFOXIRI arm of one of the studies,[137] but not the other.[136]

The efficacy of bevacizumab in combination with FOLFOX and FOLFIRI in the treatment of unresectable metastatic disease (see pages 793–797) and section on Chemotherapy for Advanced or Metastatic Disease) has led to its use in combination with these regimens in the preoperative setting, although the safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU–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 compared with the group receiving chemotherapy alone while undergoing major surgery (13% vs. 3.4%, respectively; P = .28).[138] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to surgery, the incidence of wound healing complications in either group of patients was low (1.3% vs. 0.5%; P = .63). The panel recommends at least a 6 week interval (which corresponds to 2 half-lives of the drug[139]) between the last dose of bevacizumab and elective surgery. Further support for this recommendation comes from results of a single center, nonrandomized, phase II trial of patients with potentially resectable liver metastases which showed no increase in bleeding or wound complications when the bevacizumab component of CapeOX plus bevacizumab therapy was stopped 5 weeks prior to surgery (i.e., bevacizumab excluded from the 6th cycle of therapy).[140] In addition, no significant differences in bleeding, wound, or hepatic complications were observed in a retrospective trial evaluating effects of preoperative bevacizumab stopped at 8 weeks or less compared to more than 8 weeks before resection of liver colorectal metastases for patients receiving oxaliplatin- or irinotecan-containing regimens.[141]

Other reported risks associated with the preoperative approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.[123,126,142,143] To limit the development of hepatotoxicity, it is recommended that surgery should be performed as soon as possible after the patient becomes resectable.

As mentioned previously, colorectal metastatic disease can also occur in the lung.[144] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in highly selected cases.[145] The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative.

Only limited data exist regarding the efficacy of adjuvant chemotherapy following resection for metastatic colorectal liver or lung disease. In a pooled analysis of results from 2 randomized clinical trials which closed prematurely involving patients with a potentially curative resection randomly assigned to either systemic chemotherapy with 5-FU/LV or observation, the median PFS was 27.9 months in the chemotherapy arm and 18.8 months for those undergoing surgery alone (HR = 1.32; 95% CI, 1.00–1.76; P = .058) with no difference in overall survival.[146] Nevertheless, the panel recommends administration of a course of an active systemic chemotherapy regimen for metastatic disease, for a total perioperative treatment time of approximately 6 months, for most patients 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) remains an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine (with dexamethasone and with or without LV) by HAI in addition to systemic chemotherapy was shown to be superior to systemic chemotherapy alone with respect to 2-year survival and time to progression of hepatic disease.[95,147] However, the difference in survival between the 2 arms was not significant at later follow-up periods.[95,148] A number of other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy was compared with systemic chemotherapy, although most have not shown a survival benefit of HAI therapy.[95] Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.[103] However, limitations on the use of HAI therapy include the potential for biliary toxicity[95] and the requirement for specific technical expertise. The consensus of the panel is that HAI therapy should be considered only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Finally, a number of liver-directed therapies exist, although their role in the treatment of colorectal metastases is controversial. These therapies include arterial radioembolization with yttrium-90 microspheres,[149,150] arterial chemoembolization,[150] and conformal radiation therapy.[151] Use of intra-arterial embolization is a category 3 recommendation for select patients with predominant hepatic metastases, and conformal external beam radiation therapy should not be used unless the patient is symptomatic or it is used in the setting of a clinical trial (see following sections on Workup and Management of Synchronous Metastatic Disease and Workup and Management of Metachronous Metastatic Disease).

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from large bowel (e.g., colorectal liver metastases) is suspected should include a total colonoscopy, CBC, platelets, chemistry profile, CEA determination, and a CT scan of the chest, abdomen, and pelvis[46] (see page 782). The panel also recommends tumor KRAS gene status testing for all patients with metastatic colon cancer at the time of diagnosis of metastatic disease (see previous discussion of KRAS testing). The panel strongly discourages the routine use of PET scanning for staging, baseline imaging, or routine follow up, and recommends consideration of a preoperative PET scan at baseline only if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease; the purpose of this PET scan is to evaluate for unrecognized metastatic disease that would preclude the possibility of surgical management. Patients with clearly unresectable metastatic disease should not have baseline PET scans, nor should PET be used to assess response to chemotherapy. The criteria for potential surgical cure include metastatic disease that is not initially resectable, but for which surgical cure may become possible after preoperative chemotherapy. It should be noted that in the overwhelming majority of cases, the presence of extrahepatic disease will preclude the possibility of resection for cure; *conversion to resectability* for the most part refers to a patient with liver-only disease that, due to involvement of critical structures, cannot be resected unless regression is accomplished with chemotherapy. It should be noted that a PET scan can become transiently negative following chemotherapy (e.g., in the presence of necrotic lesions)[152] and the panel recommends against using PET scan to evaluate response to chemotherapy. False–positive PET results can occur in the presence of tissue inflammation following surgery or infection.[152] An MRI with intravenous contrast can be considered as part of the preoperative evaluation of patients with potentially surgically resectable M1 liver disease. For example, an MRI with contrast may be of use in situations where PET and CT results are inconsistent with respect to the extent of disease in the liver. Close communication between members of the multidisciplinary treatment team is recommended, including an upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases.

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: colec-

tomy and synchronous or subsequent liver (or lung) resection,[98,130] neoadjuvant chemotherapy for 2 to 3 months (e.g., choice of FOLFIRI, FOLFOX,[96] or CapeOX [capecitabine, oxaliplatin]) with or without bevacizumab, or the same chemotherapy regimens with or without cetuximab (consider in KRAS wild type tumors only) followed by synchronous or staged colectomy with liver or lung resection, or colectomy followed by neoadjuvant chemotherapy (see previous discussion) and a staged resection of metastatic disease (see page 782). 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. Resection of primary colon cancer before initiation of chemotherapy is rarely necessary and should only be done in patients with severe symptoms (e.g., complete intestinal obstruction) related to the primary cancer.

Advantages to a neoadjuvant chemotherapy approach include the possibility of downsizing both the primary tumor and metastatic lesions before surgery, and a very low rate of complications related to the unresected primary cancer.[96] In addition, administration of neoadjuvant chemotherapy for a period of 2 to 3 months may help distinguish patients who are more likely to benefit from metastasectomy because of indolent disease. If bevacizumab is included in the neoadjuvant regimen, there should be at least a 6 week interval between the last dose of bevacizumab and surgery, with a 6 to 8 week postoperative period before re-initiation of bevacizumab. Patients who have completely resected liver or lung metastases should be offered adjuvant chemotherapy. The panel recommends approximately 6 months total duration of pre- and postoperative chemotherapy. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B), with the exception of FOLFOXIRI. In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or a continuous intravenous 5-FU infusion remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure. 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 "Post-Treatment Surveillance." Overall, combined neoadjuvant and adjuvant treatments should not exceed 6 months.

Unresectable Synchronous Liver or Lung Metastases: For patients with liver or lung disease deemed to be unresectable, the panel recommends chemotherapy corresponding to initial therapy for metastatic disease (e.g., choice of FOLFIRI, FOLFOX, or CapeOX with or without bevacizumab, or the same chemotherapy regimens with or without cetuximab [consider in KRAS wild type tumors only]) to attempt to render these patients candidates for resection (see page 783). Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease;[153] these patients should be re-evaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing such therapy. If bevacizumab is included as a component of the conversion therapy, there should be at least a 6 week interval between the last dose of bevacizumab and surgery, with a 6 to 8 week postoperative period before re-initiation of bevacizumab.

Patients with disease converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer including treatment with pre- and postoperative chemotherapy for a preferred total duration of 6 months. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B). In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or continuous intravenous 5-FU infusion remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure. Observation or a shortened course of chemotherapy can be considered for patients who have completed preoperative chemotherapy. Primary treatment of unresectable synchronous liver or lung metastases by palliative colon resection should be considered only if the patient has an unequivocal imminent risk of obstruction or acute significant bleeding.[100] It should be noted that symptomatic improvement in the primary is often seen with first-line systemic chemotherapy, even within the first 1 to 2 weeks, and routine palliative resection of a synchronous primary lesion should not be routinely done in the absence of overt obstruction. Complications from the intact primary lesion are uncommon in these circumstances, and its removal delays initia-

tion of systemic chemotherapy. An intact primary is not a contraindication to bevacizumab use. The risk of gastrointestinal perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, as large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare (see upcoming discussion).

Ablative therapy of metastatic disease, either alone or in combination with resection, can also be considered when all measurable metastatic disease can be treated (see previous section on Principles of the Management of Metastatic Disease). Post-treatment follow-up for patients classified as stage IV and NED is described in "Post-Treatment Surveillance."

Patients with unresectable metastatic disease not responding to preoperative therapy should receive chemotherapy for advanced or metastatic disease as outlined on pages 793–797 with treatment selection based, in part, on whether or not the patient is an appropriate candidate for intensive therapy. Debulking surgery or ablation without curative intent is not recommended.

The panel reached no consensus regarding the use of liver-directed therapies, such as arterial radioembolization therapy and arterial chemoembolization therapy. For select patients, with chemotherapy resistant/refractory disease characterized by predominant liver metastases and no obvious systemic disease, use of these interventions was supported by some panel members but not others (category 3).The consensus of the panel is that conformal external radiation therapy should not be used unless the patient is symptomatic or in a clinical trial.

Synchronous Abdominal/Peritoneal Metastases: For patients with peritoneal metastases and obstruction, surgical options include colon resection, diverting colostomy, or a bypass of impending obstruction or stenting, followed by chemotherapy for advanced or metastatic disease (see page 784). The primary treatment of patients with non-obstructing metastases is chemotherapy for advanced or metastatic disease. The panel currently considers the treatment of disseminated carcinomatosis with cytoreductive surgery (i.e., peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy[154,155] to be investigational and does not endorse such therapy outside of a clinical trial. However, the panel recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities.

Workup and Management of Metachronous Metastatic Disease

Routine use of PET to monitor for disease recurrence is not recommended. It should be noted that the CT that accompanies a PET/CT is a non-contrast CT, and thus not of ideal quality for routine surveillance. Upon documentation on dedicated contrast-enhanced CT or MRI of metachronous metastases in which disease is or may become 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.[156] As with other first identifications of metastatic disease, a tumor sample (metastases or original primary) should be sent for KRAS genotyping in order to define whether anti-EGFR agents can be considered in the list of potential options for this patient (see previous discussion of KRAS testing). Close communication between members of the multidisciplinary treatment team is recommended, including upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases (see page 786).

The management of metachronous metastatic disease is further distinguished from that of synchronous disease by also including an evaluation of the chemotherapy history of the patient and by the absence of colectomy. Resectable patients are classified according to whether they have received no previous chemotherapy or prior chemotherapy (see page 787). For patients who have resectable metastatic disease, primary treatment options include initial resection followed by chemotherapy with an active chemotherapy regimen for 6 months (see pages 793–797) or neoadjuvant chemotherapy for 2 to 3 months followed by resection and additional postoperative chemotherapy for a total duration, including pre- and postoperative chemotherapy, of up to 6 months based on response to the neoadjuvant regimen; observation is also an option for patients without a response to neoadjuvant therapy. For example, the same chemotherapy regimen used in the neoadjuvant setting should be repeated postoperatively for patients with a preoperative disease response to such therapy. However, either an alternative active chemotherapy regimen (see pages 793–797) or observation is an option in the postoperative setting for patients not responding to neoadjuvant therapy.

Patients determined by cross-sectional imaging or PET scan to have unresectable disease (including those considered to potentially convertible or unconvertible) should receive an active chemotherapy regimen based on prior chemotherapy history (see pages 786 and 787). Specifically, patients exhibiting disease progression on FOLFOX administered within the previous 12 months should be switched to a FOLFIRI regimen with the option of including bevacizumab or cetuximab (KRAS wild type only). Patients potentially convertible to resectability should be re-evaluated for disease conversion to a resectable status every 2 months; those with chemotherapy-responsive disease who are converted to a resectable state should undergo resection followed by postoperative therapy as described above for patients with resectable disease and a history of previous chemotherapy. In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or continuous intravenous 5-FU infusion remains an option at centers with experience in this procedure.

Patients with unresectable metastatic disease not responding to preoperative therapy should receive chemotherapy for advanced or metastatic disease as outlined on pages 793–797, with treatment selection based, in part, on whether or not the patient is an appropriate candidate for intensive therapy. Patients receiving palliative chemotherapy should be monitored with CT or MRI scans approximately every 2 to 3 months. PET scans are not recommended for routine monitoring of the progression of metastatic 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.[25,29,31,136,137,153,157–171] The putative mechanisms of action for these agents are varied and include interference with DNA replication and inhibition of the activities of vascular endothelial growth factor (VEGF) receptors and EGFR.[172–175] The choice of therapy is based on consideration of the type and timing of prior therapy that was 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 or therapy after first or second progression, it is important to clarify that these recommendations represent a continuum of care and that the lines of treatment are blurred rather than discrete.[159] For example, if oxaliplatin, administered as 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 prior therapies received by the patient (i.e., exposing patient to a range of cytotoxic agents). Furthermore, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, as well as the potential for surgical cure and the performance status of the patient.

As initial therapy for metastatic disease in a patient appropriate for intensive therapy (i.e., one with a good tolerance for such therapy for whom a high tumor response rate would be potentially beneficial), the panel recommends a choice of 5 chemotherapy regimens: FOLFOX (e.g., mFOLFOX6 or FOLFOX4),[160,168,176–182] CapeOX,[182–184] FOLFIRI,[161,177,181,185] 5-FU/LV,[163,167,185–187] or FOLFOXIRI (see pages 793–797).[136,137] Although use of FOLFOXIRI as initial therapy is a category 2B recommendation, the panel does not consider any of the other regimens (i.e., FOLFOX, CapeOX, and FOLFIRI) to be preferable over the others as initial therapy for metastatic disease. The addition of either bevacizumab or cetuximab (cetuximab only for those with disease characterized by the KRAS wild-type gene only) is an option if FOLFIRI, FOLFOX, or CapeOX is administered.[29,188]

With respect to treatment of metastatic disease, the panel consensus was that FOLFOX and CapeOX can be used interchangeably.[182] Both FOLFIRI and infusional 5-FU/LV regimens are recommended in combination with bevacizumab,[189–191] whereas the option of cetuximab (for KRAS wild-type tumor only) in combination with FOLFIRI is also includ-

ed.[31] If FOLFOXIRI is used (category 2B), it is recommended without the addition of a biologic agent since data regarding the efficacy and safety of such a combination are not yet mature. For those patients not appropriate for intensive therapy (i.e., either due to comorbidity or absence of the need for a therapy associated with a high tumor response rate), initial therapy options include either capecitabine[81] or infusional 5-FU/LV with or without the addition of bevacizumab[190–192] or cetuximab alone (for those with KRAS wild-type gene only).[33]

Pooled results from several randomized phase II studies have demonstrated that the addition of bevacizumab to first-line 5-FU/LV improved overall survival in patients with metastatic colorectal cancer when compared to survival results for patients receiving these regimens without bevacizumab.[191,193] A combined analysis of the results of several of these trials showed that addition of bevacizumab to 5-FU/LV was associated with a median survival of 17.9 months versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab.[193] 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.[194] In that pivotal trial, a longer survival time was observed with the use of bevacizumab (20.3 vs. 15.6 months; HR = 0.66; $P < .001$). Results from a recent head-to-head randomized, double-blind, placebo-controlled phase III study (N016966) 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 over 30 months, results from this study support the conclusion that CapeOx is non-inferior to FOLFOX when used in the initial treatment of metastatic colorectal cancer.[182,188] However, in this large trial of 1400 patients, the addition of bevacizumab to oxaliplatin-based regimens was associated with a more modest PFS increase of 1.4 months compared to these regimens without bevacizumab (HR = 0.83; 97.5% CI, 0.72–0.95; $P = .0023$), and the difference in overall survival, which was also a modest 1.4 months, did not reach statistical significance (HR = 0.89; 97.5% CI, 0.76–1.03; $P = .077$).

Researchers have suggested that differences observed in cross-study comparisons of NO16966 with other trials might be related to differences in the discontinuation rates and durations of treatment between trials, although such hypotheses are only conjectural.[189] Furthermore, in this study, absolutely no difference in response rates was seen with or without bevacizumab (see following discussion), and this finding would not be potentially influenced by the early withdrawal rates, which occurred after the responses would have occurred. Results of subset analyses evaluating the benefit of adding bevacizumab to either FOLFOX or CapeOX indicated that bevacizumab was associated with improvements in 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.[188]

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 CapeIRI (capecitabine plus irinotecan) in terms of efficacy and safety.[195,196] Although this trial was closed early and did not meet projected enrollment, a statistically significant increase in PFS was observed for patients receiving first-line FOLFIRI (7.6 months) when compared to those receiving either a modified IFL regimen (5.9 months; $P = .004$) or CapeIRI (5.8 months; $P = .015$) at a median follow-up of 22.6 months. No significant differences in median overall survival were observed for the modified IFL or CapeIRI regimens compared with the FOLFIRI regimen.

When FOLFIRI or modified IFL was combined with bevacizumab, PFS was shown to increase to 11.2 and 8.3 months, respectively, although this difference was not statistically significant ($P = .28$). However, at a median follow-up of 34.4 months, overall survival was statistically significantly higher for patients receiving FOLFIRI plus bevacizumab (28.0 months) compared with modified IFL plus bevacizumab (19.2 months; $P = .037$).[196] Evidence for the comparable efficacy of 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.[177] 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 FOLF-

OX4 and FOLFIRI regimens in previously untreated patients with metastatic colorectal cancer.[181] No differences were observed in response rate, PFS times, and overall survival. 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.[197]

Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in 2 randomized phase III trials. In one study, statistically significant improvements in PFS (9.8 vs. 6.9 months; HR = 0.63; P = .0006) and median overall survival (22.6 vs. 16.7 months; HR = 0.70; P = .032) were observed in the FOLFOXIRI arm,[137] although there was no overall survival difference between the 2 treatment arms in the other study (median overall survival: 19.5 and 21.5 months, for FOLFIRI and FOLFOXIRI, respectively; P = .337).[136] Both studies showed some increased toxicity in the FOLFOXIRI arm (e.g., significant increases in neurotoxicity and neutropenia;[137] diarrhea, alopecia and neurotoxicity[136]) but no differences in the rate of toxic death were reported.[136] The option of FOLFOXIRI as initial therapy for patients with metastatic colorectal disease has been added to the guidelines as a category 2B option.

The randomized phase III study E3200, conducted by ECOG in patients who had progressed through a first-line non-bevacizumab–containing regimen, demonstrated that the addition of bevacizumab to second-line FOLFOX4 modestly improved survival in these bevacizumab-naïve patients with previously-treated advanced colorectal cancer. Median overall survival was 12.9 months for patients receiving FOLFOX4 plus bevacizumab compared to 10.8 months for patients receiving FOLFOX4 alone (P = .0011).[198] Use of single agent bevacizumab is not recommended since it was shown to have inferior efficacy compared with FOLFOX alone or FOLFOX plus bevacizumab in the treatment arms.[198] 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.[139] In addition, use of bevacizumab may interfere with wound healing[138,139,192] (see previous section on Principles of Management of Metastatic Disease), and gastrointestinal perforation is a rare, but important, side effect of bevacizumab therapy in patients with colorectal cancer.[138,192] Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to gastrointestinal perforation. A small cohort of patients with advanced ovarian cancer had an unacceptably high rate of gastrointestinal perforation when treated with bevacizumab;[199] this illustrates that peritoneal debulking surgery may be a risk factor for gastrointestinal perforation whereas the presence of an intact primary tumor does not appear to increase the risk.

With respect to the toxicities associated with capecitabine use, the panel noted that patients with diminished creatinine clearance may accumulate levels of the drug.[200] The incidence of hand–foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV[192,200] and that North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.[201] Such toxicities may necessitate modifications in the dosing of capecitabine,[192,200,202] and patients should be monitored closely so dose adjustments can be made at the earliest signs of certain side effects, such as hand–foot syndrome. 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/m^2 twice daily dose used in the study of Saltz et al.[188]

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[203,204] 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 hyperbilirubinemias, such as types I and II of Crigler-Najjar syndrome and Gilbert syndrome. Thus, irinotecan should be used with caution and at a decreased dose in patients with Gilbert's disease or elevated serum bilirubin.[205]

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,[204,206] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[206] 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.[205] A warning has been added to the label for Camptosar which indicates that a reduced starting dose should be used in patients known to be homozygous for UGT1A1*28.[203] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[206] although guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on those with irinotecan toxicity is not recommended since that patient will require a dose reduction regardless of the UGT1A1 test result.

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[207] 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.[208] Therefore, the panel recommends adjustments in the schedule/timing of the administration of this drug as a means of limiting this adverse effect. Discontinuation of oxaliplatin from FOLFOX or CapeOX should be strongly considered after 3 months of therapy, or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless there is near-total resolution of that neurotoxicity, but oxaliplatin can be reintroduced if stopped to prevent development of neurotoxicity.

In the phase II OPTIMOX2 trial, patients were randomized to receive an induction FOLFOX regimen (6 cycles) followed by discontinuation of all chemotherapy until tumor progression reached baseline followed by reintroduction of FOLFOX or an OPTIMOX1 approach (discontinuation of oxaliplatin after 6 cycles of FOLFOX [to prevent or reduce neurotoxicity] with continuance of 5-FU/LV followed by reintroduction of oxaliplatin upon disease progression).[209] Results of the study demonstrated a strong trend for improved overall survival for patients receiving the OPTIMOX1 approach compared with patients undergoing an early, pre-planned chemotherapy-free interval (median overall survival 26 vs. 19 months; $P = .0549$).

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 regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial[195] and inferior to FOLFOX in the Intergroup trial[160]) at any point in the therapy continuum. In combination with irinotecan or oxaliplatin, 5-FU should be administered via an infusional biweekly regimen[167,185] or capecitabine should be used.[164]

Recently, cetuximab has been studied in combination with FOLFIRI[31] and FOLFOX[29] as initial therapy options for treatment of metastatic colorectal cancer. A sizable body of recent literature has demonstrated that tumors with a mutation in codon 12 or 13 of the KRAS gene are essentially insensitive to EGFR inhibitors such as cetuximab or panitumumab.[24–32] The panel therefore strongly recommends KRAS genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer (see pages 788–790). Patients with known codon 12 or 13 KRAS mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, as there is virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is implied throughout the guidelines that NCCN recommendations involving cetuximab or panitumumab relate only to patients with KRAS wild type gene.

Use of cetuximab as initial therapy for metastatic disease was investigated in the CRYSTAL trial where patients were randomly assigned to receive FOLFIRI with or without cetuximab.[31] Retrospective analyses of the subset of patients with known KRAS tumor status showed a statistically significant improvement in median PFS with the addition of cetuximab in the group with disease characterized by the KRAS wild-type gene (9.9 vs. 8.7 months; HR = 0.68; 95% CI,

0.50–0.94; P = .02). In a retrospective evaluation of the subset of patients with known tumor KRAS status enrolled in the randomized phase II OPUS trial, addition of cetuximab to FOLFOX was associated with an increased objective response rate (61% vs. 37%; odds ratio = 2.54; P = .011) and a very slightly lower risk of disease progression by 15 days (7.7 vs. 7.2 months; HR = .57; 95% CI, 0.358–0.907; P = .0163) compared with FOLFOX alone.[29]

The recommended therapy options after first progression for patients who have received prior 5-FU/LV-based therapy are dependent on the initial treatment regimen and include FOLFIRI[185] with or without cetuximab,[31] and irinotecan in combination with cetuximab[170] or as a single agent,[162] 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. If cetuximab is used as part of an initial therapy regimen, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy. 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.[182]

Other options for patients initially treated with a FOLFIRI-based regimen include cetuximab plus irinotecan, or single agent cetuximab or panitumumab for those not appropriate for the combination with irinotecan. For patients receiving 5-FU/LV without oxaliplatin or irinotecan as initial therapy, options after first progression include FOLFOX, CapeOX, FOLFIRI, or single agent irinotecan. The recommended option for patients experiencing disease progression on initial therapy with FOLFOXIRI is cetuximab plus irinotecan (for patients with tumors characterized by the wild-type KRAS gene only) or cetuximab or panitumumab alone for those with wild-type KRAS gene only who are not able to tolerate the combination.

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.[177] 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 3 cytotoxic agents (i.e., 5-FU/LV, oxaliplatin, and irinotecan) at some point in the continuum of care.[210] Furthermore, overall survival was not 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[211] or infusional 5-FU/LV.[212]

In the study by Rougier et al.,[212] median overall survival was 4.2 months for irinotecan compared with 2.9 months for 5-FU (P = .030), whereas Cunningham et al.[211] reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive-care group (P = .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.[213] Infusion of calcium and magnesium salts has been suggested as a potential means of limiting the neurotoxic effects of oxaliplatin. Data are limited on this topic but such an approach may be considered.

Cetuximab has been studied as a single agent[33,170,214] and in combination with irinotecan,[170,215] for patients with disease progression on initial therapy for metastatic disease. However, it is important to note that KRAS testing was not done in the earlier studies, unless otherwise specified in the text. 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.[214] In addition, cetuximab monotherapy was reported to significantly increase both PFS (HR = 0.68; 95% CI, 0.57–0.80; P < .001) and overall survival (HR = 0.77; 95% CI, 0.64–0.92; P = .005) for patients with refractory metastatic colorectal cancer when compared with best supportive care alone.[216]

In a retrospective analysis of the subset of patients in this trial with known KRAS tumor status, the benefit of cetuximab versus best supportive care was shown to be enhanced to patients with KRAS wild-type tumors.[33] For those patients, median PFS was 3.7 months compared with 1.9 months (HR = 0.40; 95% CI, 0.30–0.54; P < .001) and median overall survival was 9.5 months compared with 4.8

months (HR = 0.55; 96% CI, 0.41–0.74; $P < .001$) in favor of the cetuximab arm. Results from a direct comparison of cetuximab monotherapy and combination 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% vs. 10.8%; $P = .007$).[170]

Results of a large phase III study of similar design did not show a difference in overall survival between the 2 treatment arms, but showed significant improvement in response rate and median PFS for the combination of irinotecan and cetuximab compared with irinotecan alone. Toxicity was higher in the cetuximab-containing arm.[217] Therefore, it is acceptable to use either irinotecan alone or cetuximab plus irinotecan. For patients receiving irinotecan alone, the combination of cetuximab and irinotecan is preferable to cetuximab alone as therapy after progression on irinotecan for those who can tolerate this combination. For patients not able to tolerate cetuximab plus irinotecan, either single agent cetuximab or single agent panitumumab can be considered.

Panitumumab has been studied as a single agent in the setting of metastatic colorectal cancer for patients with disease progression on both oxaliplatin and irinotecan-based chemotherapy;[169] respective response rates of 10% versus 0% ($P < .0001$) for panitumumab plus best supportive care versus best supportive care alone were observed, as well as a significant increase in PFS with panitumumab (HR = 0.54; 95% CI, 0.44–0.66). In a retrospective analysis of the subset of patients with known KRAS tumor status, the benefit of panitumumab compared with best supportive care was enhanced in patients with KRAS wild-type tumors.[25] PFS was 12.3 versus 7.3 weeks in favor of the panitumumab arm. Response rates to panitumumb were 17% versus 0% in the wild-type and mutant arms, respectively.

Results of the PACCE trial showed decreased PFS and increased toxicity of chemotherapy/bevacizumab/panitumumab over chemotherapy/bevacizumab.[218] Thus, recommendations for the use of panitumumab in the guidelines are currently restricted to single agent use only. The panel allows that panitumumab can be substituted for cetuximab when either drug is used as a single agent following first or second progression. Although no head-to-head studies comparing cetuximab and panitumumab have been undertaken, this recommendation is supported by the similar response rates observed when each agent was studied as monotherapy. One difference between these 2 agents is that panitumumab is a fully human monoclonal antibody whereas cetuximab is a chimeric monoclonal antibody.[219,220] There are no data to support use of either cetuximab or panitumumab after failure of the other drug, and the panel recommends against this practice.

Cetuximab in combination with irinotecan is also indicated after progression for patients refractory to irinotecan-based chemotherapy because it has shown activity in this setting.[170] Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[219,220] Based on case reports, for those patients experiencing severe infusion reactions to cetuximab, administration of panitumumab appears to be feasible.[221,222] Skin toxicity is a side effect of both of these agents and is not considered to be part of the infusion reactions. The incidence and severity of skin reactions with cetuximab and panitumumab appears to be very similar; however, the presence and severity of skin rash in patients receiving either of these drugs has been shown to be predictive of increased response and survival.[31,32,216,223]

Results from 2 randomized phase III trials have demonstrated that combination therapy with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity. In the PACCE trial, addition of panitumumab to a regimen containing oxaliplatin- or irinotecan-based chemotherapy plus bevacizumab was associated with significantly shorter PFS and higher toxicity in both KRAS wild-type and mutant groups.[224] Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab.[225] Therefore, the panel strongly recommends against the use of therapy involving the combination of an anti-EGFR and -VEGF agents.

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.[170] A similar conclusion was drawn with respect to panitumumab.[226] 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 prospective data to support the addition of bevacizumab to a regimen following clinical failure of a previous bevacizumab-containing regimen, and continuation of bevacizumab beyond disease progression is not recommended. If bevacizumab is not used in initial therapy, it may be appropriate to consider adding it to chemotherapy following progression of metastatic disease.[198]

A study of 6286 patients from 9 trials which evaluated the benefits and risks associated with intensive first-line treatment in the setting of metastatic colorectal cancer treatment according to patient performance status showed similar therapeutic efficacy for patients with a performance status of 2 or 1 or less as compared with control groups, although the risks of certain gastrointestinal toxicities were significantly increased for patients with a performance status of 2.[227] For patients with impaired tolerance to aggressive initial therapy, the guideline includes recommendations for single-agent capecitabine,[164,165] infusional 5-FU/LV,[166,167] with or without bevacizumab, or single agent cetuximab for patients with KRAS wild-type tumors only (category 2B). 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.[182,188,189,192]

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, alfa-interferon, taxanes, methotrexate, pemetrexed, sunitinib, sorafinib, erlotinib, or gemcitabine, either as single agents or in combination, as salvage therapy in patients exhibiting disease progression following treatment with standard therapies. These agents have not been shown to be effective in this setting. 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.[228]

Post-Treatment Surveillance

After curative-intent surgery and adjuvant chemotherapy, if administered, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and to identify new metachronous neoplasms at a pre-invasive stage. Advantages of more intensive follow-up of stage II and/or III patients have been demonstrated prospectively in several studies[229–231] and in 3 recent meta-analyses of randomized controlled trials designed to compare low- and high-intensity programs of surveillance.[232–235] Other recent studies impacting 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.[71] A population-based report indicating increased rates of resectability and survival in patients treated for local recurrence and distant metastases of colorectal cancer provides support for more intensive post-treatment follow-up in these patients.[236] Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.[237,238]

The following panel recommendations for post-treatment surveillance pertain to patients with stage I to III disease who have undergone successful treatment (i.e., no known residual disease): history and physical examination every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years; CEA test at baseline and every 3 to 6 months for 2 years,[239] then every 6 months for the next 5 years if the clinician determines that the patient is a potential candidate for aggressive curative surgery.[235,239,240] Colonoscopy is recommended at approximately 1 year after resection (or approximately 3–6 months

post-resection if not performed preoperatively due to obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma (villous polyp, polyp > 1 cm, or high grade dysplasia), in which case colonoscopy should be repeated in 1 year.[240] More frequent colonoscopies may be indicated in patients who present with colon cancer before age 50. Chest, abdominal, and pelvic CT scans are recommended annually for the first 3 to 5 years in stage II and III patients.[235,238] Routine PET scanning is not recommended and should not be obtained either as a routine pre-operative baseline study or for routine surveillance.

Initial follow-up office visits at 3 month intervals for history and physical examination may be more useful for patients diagnosed with stage III disease, whereas patients with 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 indication of recurrence of disease (see following discussion on Managing an Increasing CEA Level), although post-treatment CEA testing is recommended only if the patient is a potential candidate for further intervention.[239] Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps.[240] Data show that patients with a history of colorectal cancer have an increased risk of developing second cancers,[241] particularly in the first 2 years following resection.[240] 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.[240] The recommended frequency of post-treatment surveillance colonoscopies is higher (i.e., annually) for patients with hereditary nonpolyposis colorectal cancer syndrome.[240] CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and liver.[235] Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases.[235,238] Post-treatment PET scan is not routinely recommended for surveillance of patients with resected early-stage colorectal cancer.[238] Furthermore, PET scan is not routinely recommended to detect metastatic disease in the absence of other evidence of such disease.

Post-treatment surveillance also includes a survivorship care plan involving disease preventive measures, such as immunizations against influenza and pneumococcal infections at prescribed intervals and regular dental care, early disease detection through periodic screening for second primary cancers (e.g., breast, cervical, or prostrate cancers), and routine health monitoring to screen for comorbid conditions, including psychosocial distress associated with colon cancer and its treatment (see pages 801 and 802).

Other recommendations include monitoring for late sequelae of colon cancer or treatment of colon cancer, such as chronic diarrhea or incontinence (e.g., patients with stoma);[242] or persistent neuropathy (a well known side effect of oxaliplatin treatment).[74] Specific management interventions to address these side effects are described on pages 801 and 802 and in a recent review.[243]

There is also evidence to indicate that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy body mass index, engaging in regular exercise, and making certain dietary choices, are associated with improved outcomes after treatment for colon cancer. For example, a retrospective study of patients with stage II and III colon cancer enrolled in National Surgical Adjuvant Breast and Bowel Project trials from 1989 to 1994 showed that patients with a body mass index of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[244] In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, DFS was found to be directly correlated with how much exercise these patients received.[245] Furthermore, a diet consisting of more fruits, vegetables, poultry, and fish, and less red meat, as well as diets higher in whole grains and lower in refined grains and concentrated sweets, was found to be associated with an improved outcome in terms of cancer recurrence or death.[246] A discussion of lifestyle characteristics, which may be associated with a decreased risk of colon cancer recurrence, also provides "a teachable moment" for the promotion of overall health and an opportunity to encourage patients to make choices and changes compatible with a healthy lifestyle.

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 contrast-enhanced CT of the chest, abdomen, and pelvis every 3 to 6 months in the first 2 years after adjuvant treatment and then every 6 to 12 months, for up to a total of 5 to 7 years. CEA testing is also recommended every 3 months for the first 2 years and then every 6 months in the following 3 to 5 years. Again, routine use of PET scans for surveillance is not recommended.

Managing an Increasing CEA Level

Managing patients with an elevated CEA level after resection should include colonoscopy; chest, abdominal, and pelvic CT scans; physical examination; and consideration of PET scan (see page 785). If imaging study results are normal in the face of a rising CEA, repeat CT scans are recommended every 3 months until either disease is identified or CEA level stabilizes or declines. The opinion of the panel on the usefulness of PET scan in the scenario of an elevated CEA with negative, good-quality CT scans was divided (i.e., some panel members favored use of PET in this scenario while others noted that the likelihood of PET identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). Use of PET scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called "blind" or "CEA-directed" laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,[247] nor is the use of anti-CEA–radiolabeled scintigraphy

Summary

The NCCN Colon/Rectal/Anal Cancer Guidelines panel believes that a multidisciplinary approach is necessary for managing colorectal cancer. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

The recommended surgical procedure for resectable colon cancer is an en bloc resection and adequate lymphadenectomy. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes. Adjuvant therapy with FOLFOX (category 1), 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 3 treatment options). Patients with metastatic disease in the liver or lung should be considered for surgical resection if they are candidates for surgery and if all original sites of disease are amenable to resection (R0) and/or ablation. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease or when a response to chemotherapy may convert a patient from an unresectable to a resectable state (i.e., conversion therapy). 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; periodic chest, abdominal, and pelvic CT scans; colonoscopic evaluations; and a survivorship plan to manage long-term side effects of treatment, facilitate disease prevention, and promote a healthy lifestyle. Recommendations for patients with 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, including plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy options for advanced or metastatic disease depend on whether or not the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOX, and FOLFOXIRI (category 2B). Addition of a biologic agent (e.g., bevacizumab or cetuximab) is either recommended, or listed as an option, in combination with some of these regimens, depending on available data. Chemotherapy options for patients with progressive disease are dependent on the choice of initial therapy.

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Individual Disclosures for the NCCN Colon Cancer Panel					
Panel Member	**Clinical Research Support**	**Advisory Boards, Speakers Bureau, Expert Witness, or Consultant**	**Patent, Equity, or Royalty**	**Other**	**Date Completed**
J. Pablo Arnoletti, MD	OSI Pharmaceuticals, Inc.	None	None	None	5/19/08
Al B. Benson III, MD	Abbott Laboratories; Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Enzon Pharmaceuticals; Genentech, Inc.; General Electric; Genomic Health, Inc.; ImClone Systems Incorporated; National Cancer Institute; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; Pfizer Inc.; Roche Laboratories, Inc.; sanofi-aventis U.S.; and Taiho Parmaceuticals Co., Ltd.	Abbott Laboratories; Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Enzon Pharmaceuticals; Genentech, Inc.; General Electric; Genomic Health, Inc.; ImClone Systems Incorporated; National Cancer Institute; Novartis Pharmaceuticals Corporation;Onyx Pharmaceuticals, Inc.; Pfizer Inc.; Roche Laboratories, Inc.; sanofi-aventis U.S.; and Taiho Parmaceuticals Co., Ltd.	None	None	7/20/09
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David P. Ryan, MD	None	Genentech, Inc.; and sanofi-aventis U.S.	None	None	12/11/08
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