National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Colon Cancer

V.1.2009

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NCCN Colon Cancer Panel Members

*Paul F. Engstrom, MD/Chair †
Fox Chase Cancer Center

Juan Pablo Arnoletti, MD ¶
University of Alabama at Birmingham Comprehensive Cancer Center

*Al B. Benson, III, MD †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Yi-Jen Chen, MD, PhD §
City of Hope

Michael A. Choti, MD ¶
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Harry S. Cooper, MD ≠
Fox Chase Cancer Center

Anne Covey, MD ϕ
Memorial Sloan-Kettering Cancer Center

Raza A. Dilawari, MD ¶
St. Jude Children's Research Hospital/University of Tennessee Cancer Institute

Dayna S. Early, MD ¤
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Peter C. Enzinger, MD †
Dana-Farber/Brigham and Women's Cancer Center

Marwan G. Fakih, MD †
Roswell Park Cancer Institute

James Fleshman, Jr., MD ¶
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Charles Fuchs, MD †
Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center

Jean L. Grem, MD †
UNMC Eppley Cancer Center at The Nebraska Medical Center

Krystyna Kiel, MD §
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

James A. Knol, MD ¶
University of Michigan Comprehensive Cancer Center

Lucille A. Leong, MD †
City of Hope Cancer Center

Edward Lin, MD †
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Mary F. Mulcahy, MD ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Sujata Rao, MD †
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

*David P. Ryan, MD ¤
Massachusetts General Hospital Cancer Center

Leonard Saltz, MD † ‡ Þ
Memorial Sloan-Kettering Cancer Center

David Shibata, MD ¶
H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida

John M. Skibber, MD ¶
The University of Texas M. D. Anderson Cancer Center

Constantinos Sofocleous, MD, PhD ϕ
Memorial Sloan-Kettering Cancer Center

James Thomas, MD
Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University

Alan P. Venook, MD † ‡
UCSF Comprehensive Cancer Center

Christopher Willett, MD §
Duke Comprehensive Cancer Center

† Medical Oncology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
≠ Pathology
‡ Hematology/Hematology Oncology
Þ Internal medicine
¤ Gastroenterology
ϕ Diagnostic/Interventional Radiology
*Writing Committee Member

NCCN Guidelines Panel Disclosures

Continue

Table of Contents

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This manuscript is being updated to correspond with the newly updated algorithm.

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.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

Summary of the Guidelines updates

Summary changes in the 1.2009 version of the Colon Guidelines from the 3.2008 version include:

COL-3
- The option of 5-FU/leucovorin/oxaliplatin was deleted from the recommended adjuvant therapy options for T3,N0,M0 (no high risk features).
- Link added to new Principles of Survivorship section (COL-G).

COL-4
- Link added to new Principles of Survivorship section (COL-G).

COL-5
- Multidisciplinary team evaluation, including a surgeon with expertise in the resection of hepatobiliary and lung metastases was added to the workup section.
- The recommendation for MRI was deleted and footnote "t" added, describing that MRI should only be considered if the CT with contrast is inadequate.
- Unresectable disease was defined as including "potentially convertible" and "unconvertible". Further guidance and a description of these categories was added to the Principles of Surgery section (COL-B 2 of 3).

COL-6
- The following primary treatment options were added for resectable metastases: FOLFOX or FOLFIRI or CapeOX ± cetuximab (KRAS wild-type gene only).
- The clarification of "2-3 months" was added for neoadjuvant chemotherapy.
- The recommendation for hepatic artery infusion was moved from the body of the algorithm to footnote "x".

COL-7
- The following primary treatment options were added for unresectable metastases: FOLFOX or FOLFIRI or CapeOX ± cetuximab (KRAS wild-type gene only).
- The regimen FOLFOXIRI was added to the primary treatment options with a category 2B designation.
- The recommendation for "re-evaluation for conversion to resectable every 2 mo" was added after primary treatment.
- The recommendation for hepatic artery infusion was moved from the body of the algorithm to footnote "x".

COL-9
- Footnote "z" was added with the recommendation of KRAS gene testing and referral to the Principles of Pathology section.

COL-10
- The recommendation for "re-evaluation for conversion to resectable every 2 mo" was added after primary treatment.
- Footnote "z" was added with the recommendation of KRAS gene testing and referral to the Principles of Pathology section.
- The recommendation for hepatic artery infusion was moved from the body of the algorithm to footnote "x".
- The treatment option of observation was moved from the footnote into the body of the algorithm after primary treatment.
- There is a new footnote "aa" specifying that therapy should be considered for a maximum of 6 months.

COL-11
- The clarification of "2-3 months" was added for neoadjuvant chemotherapy.
- The recommendation for hepatic artery infusion was moved from the body of the algorithm to footnote "x".
- The treatment option of observation was moved from the footnote into the body of the algorithm after primary treatment.
- There is a new footnote "aa" specifying that therapy should be considered for a maximum of 6 months.

Continued

Summary of the Guidelines updates

Summary changes in the 1.2009 version of the Colon Guidelines from the 3.2008 version include:

COL-A 3 of 4
- The KRAS Mutation testing section was added to provide further definition and direction for testing and use of results.

COL-A 4 of 4
- References 34-36 were added to support KRAS information.

COL-B 2 of 3

Liver - the following bullets were added to the page:
- 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.
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization or staged liver resection can be considered.
- 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.

Lung - the following bullets were added to the page:
- 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.

NEW SECTION - There is a new section with recommendations for evaluating a patient for conversion to resectable disease.

COL-B 3 of 3
- References 6, 10-13, and 28-31 were added to support the recommendations on COL-B 2 of 3.

COL-C 1 of 6
- Patients appropriate for therapy - the following options were added for initial therapy: FOLFOX or FOLFIRI or CapeOX ± cetuximab (KRAS wild-type gene only), FOLFOXIRI with a category 2B designation.
- 5FU/leucovorin + bevacizumab was added as a treatment option for patients progressing after FOLFOXIRI. If patients progress on 5FU/leucovorin + bevacizumab, the recommended therapy options are cetuximab or panitumumab.

COL-C 2 of 6
- Cetuximab was added as a treatment option for patients not appropriate for intensive therapy with a category 2B designation.

COL-C 3 of 6
- Footnote 5 is new to the page: Combination therapy involving more than one biologic agent is not recommended.
- Footnote 10 is new to the page: Data are not mature for the addition of biologic agents to FOLFOXIRI.

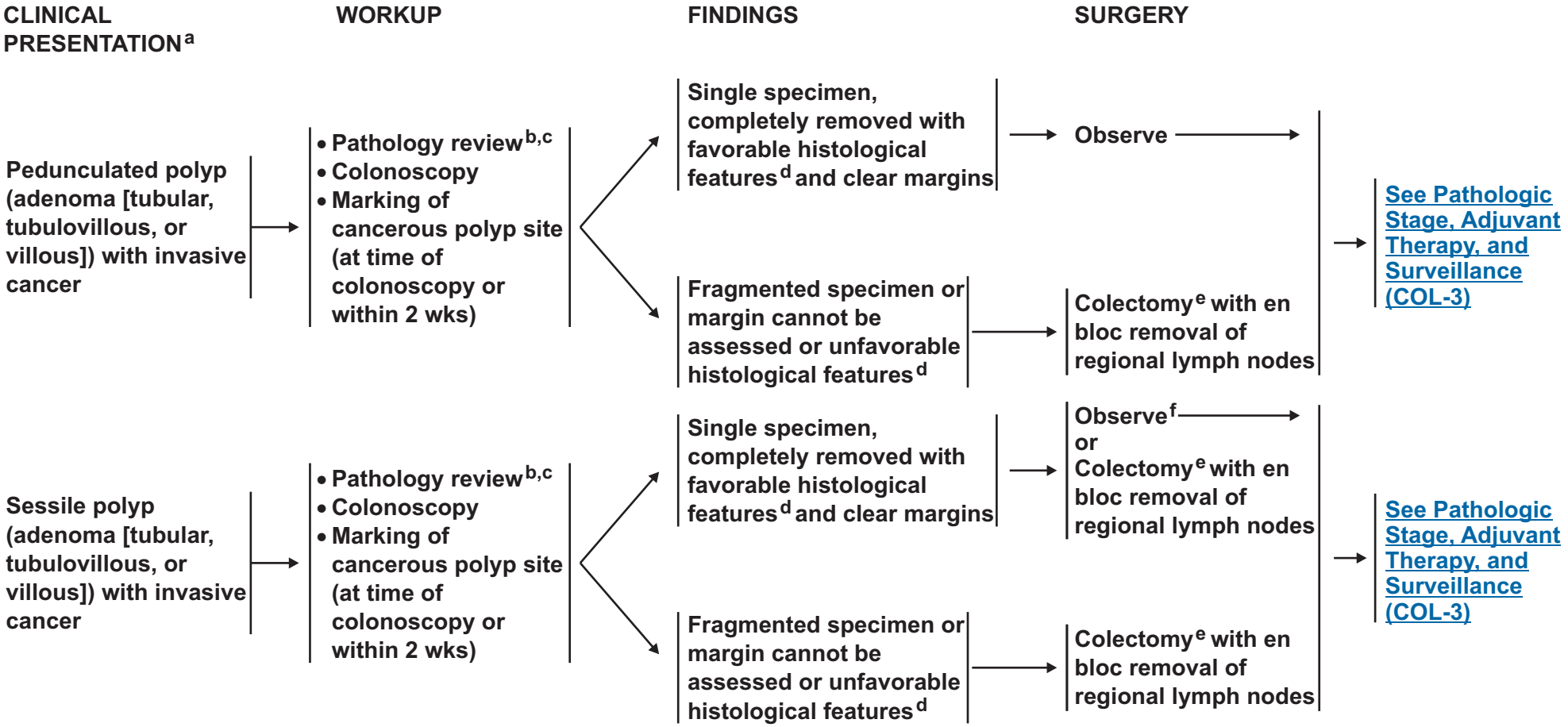
COL-F

The last 2 bullets are new to the page:
- 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.

COL-G
- Principles of Survivorship is a new section to the Guidelines.

Colon Cancer

Guidelines Index
Colon Cancer Table of Contents
Staging, Discussion, References



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

[b] Confirm the presence of invasive cancer (pT1). pTis has no biological 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 (COL-A) - Endoscopically removed malignant polyp.

[e] See Principles of Surgery (COL-B 1 of 3).

[f] Observation may be considered, with the understanding that there is an added 10-15% risk of 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(4):323-8.

Back to Other Clinical Presentations (Table of Contents)

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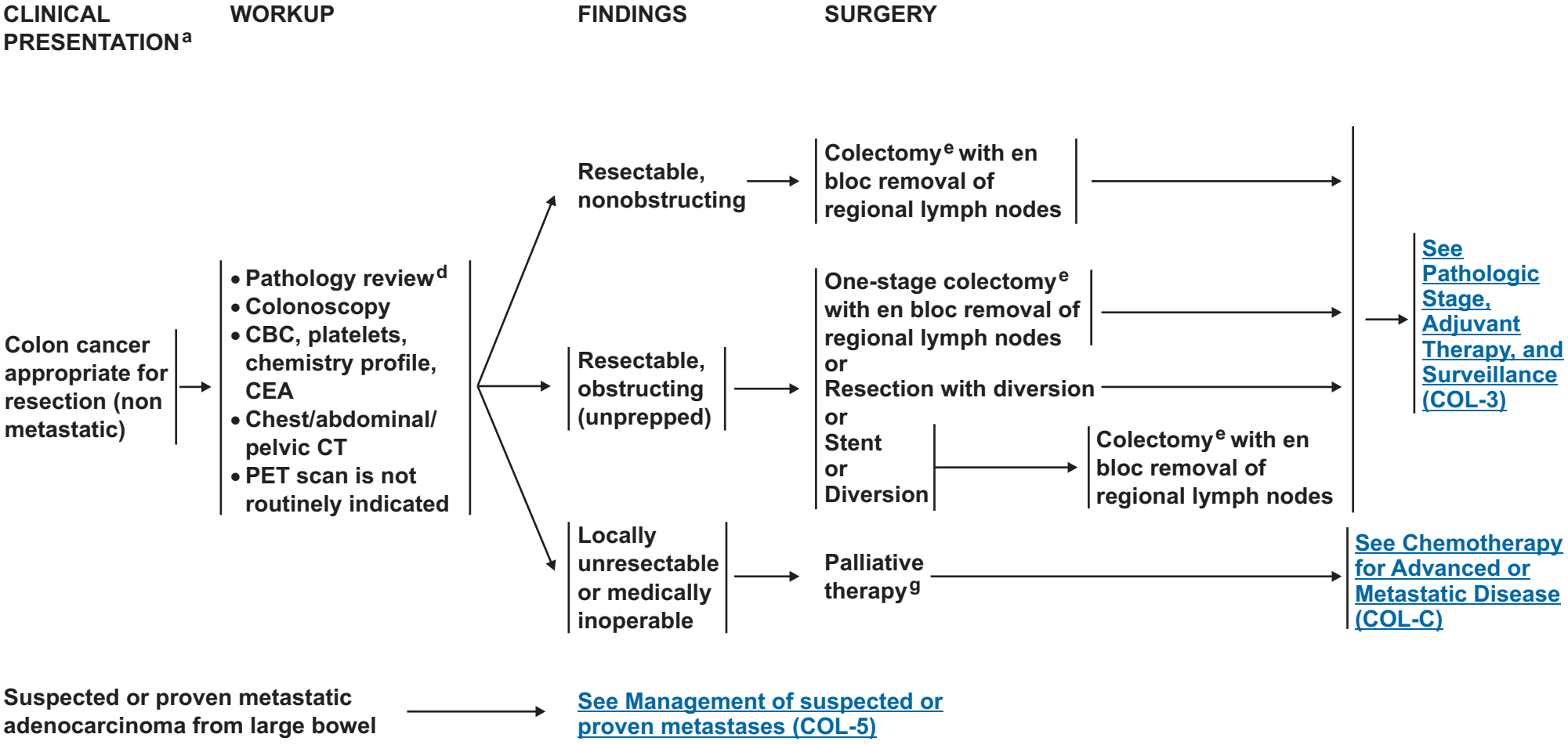
Colon Cancer



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

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

[e] See Principles of Surgery (COL-B 1 of 3).

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

Back to Other Clinical Presentations (Table of Contents)

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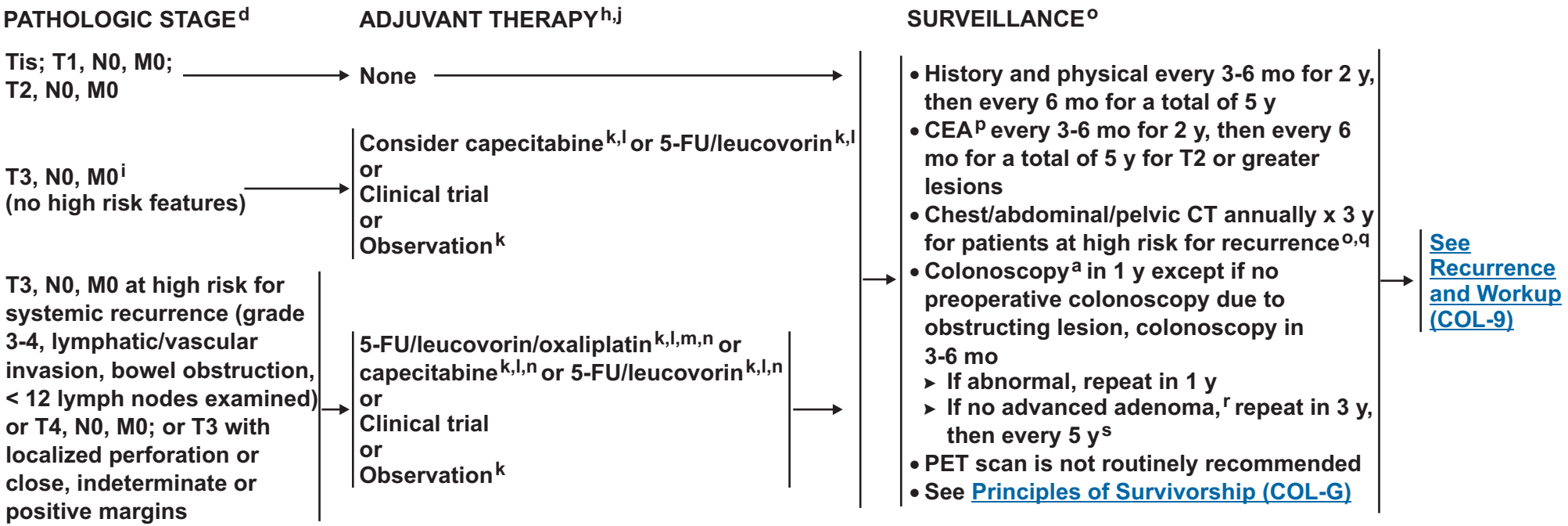

Node positive disease, see page COL-4

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

[d] See Principles of Pathologic Review (COL-A) - Pathological stage.

[h] There are no data to support adjuvant therapy in Stage I disease, however certain high risk Stage II patients (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 (COL-A) - Lymph node evaluation.

[j] There are insufficient data to recommend the use of molecular markers to determine adjuvant therapy.

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

[l] See Principles of Adjuvant Therapy (COL-E).

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

[n] Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy COL-F.

[o] Desch CE, Benson III AB, 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 (eg, lymphatic or venous invasion by 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;130:1865-71.

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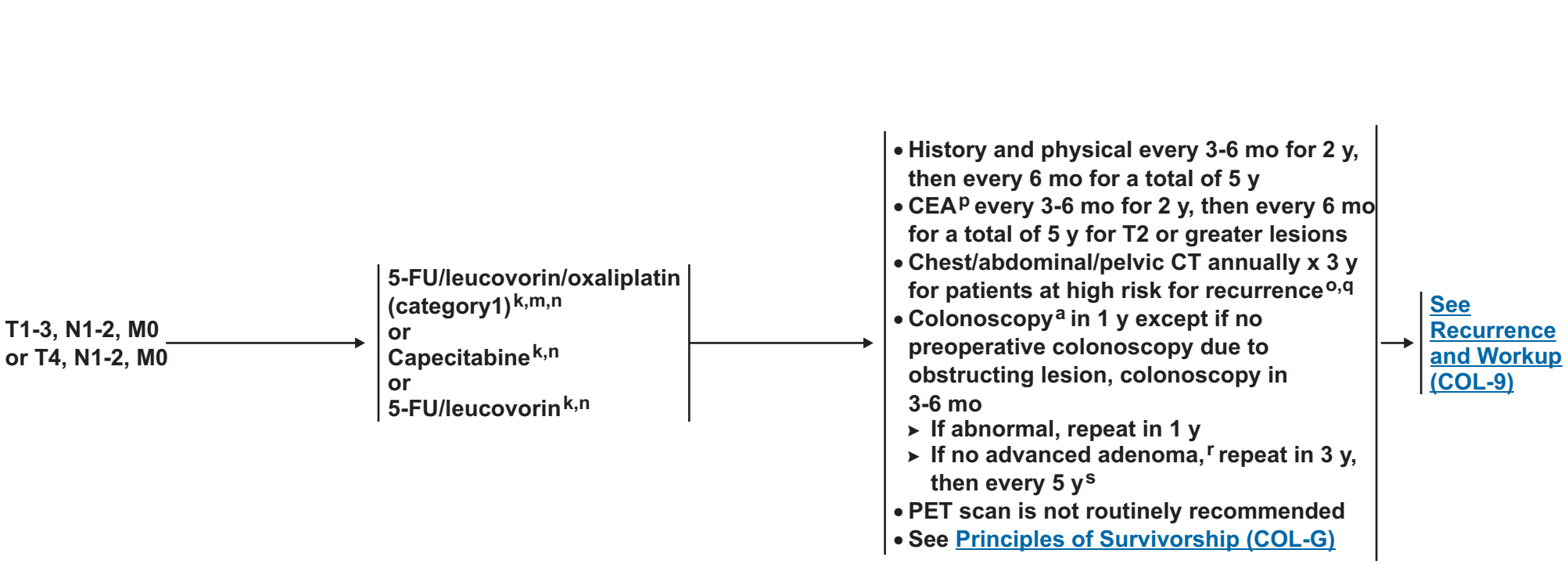

[a] All patients with colon cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP see the NCCN Colorectal Cancer Screening Guidelines.

[d] See Principles of Pathologic Review (COL-A) - Pathological stage.

[j] There are insufficient data to recommend the use of molecular markers to determine adjuvant therapy.

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Guidelines Index
Colon Cancer Table of Contents
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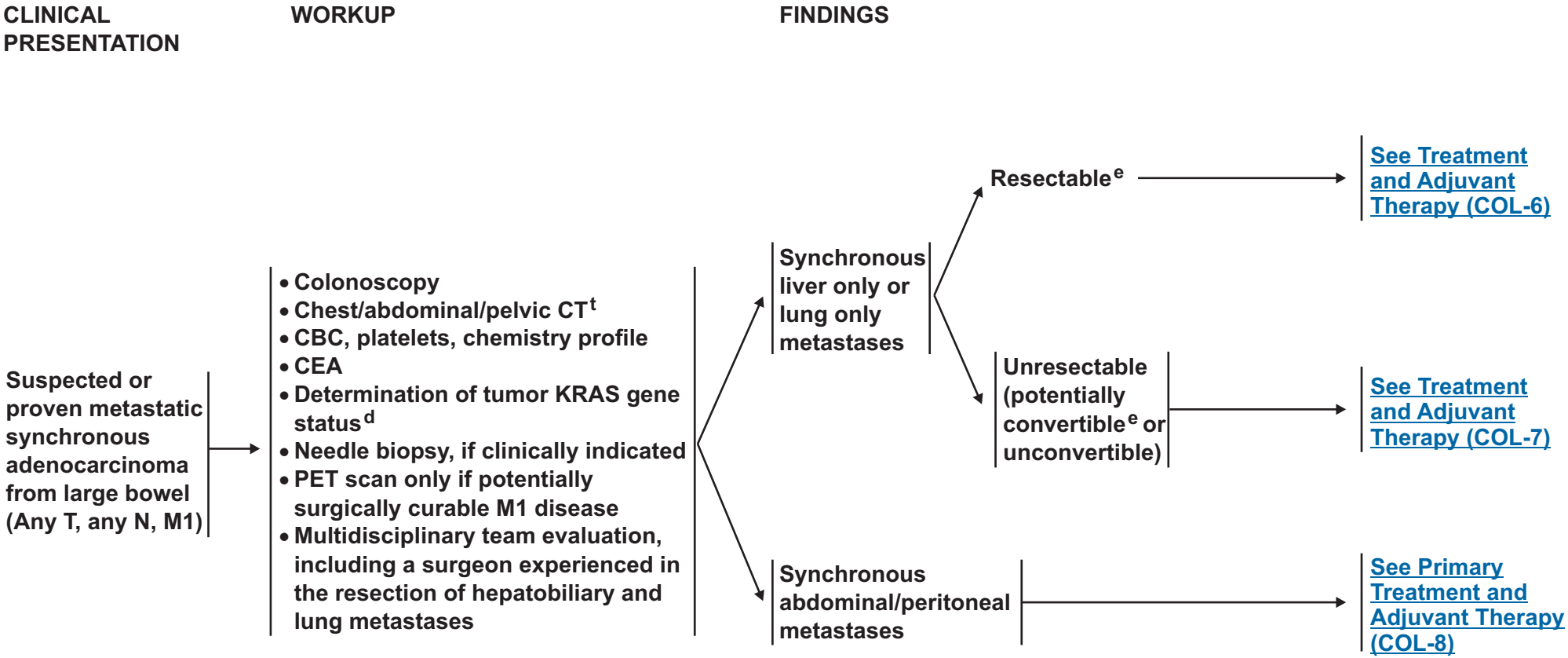

[d] See Principles of Pathologic Review (COL-A 3 of 4) - KRAS Mutation Testing.
[e] See Principles of Surgery (COL-B 2 of 3).
[t] CT should be with contrast. Consider MRI with contrast if CT is inadequate.

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Colon Cancer

TREATMENT

Resectable[e] synchronous liver only or lung only metastases

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

→

ADJUVANT THERAPY
(resected metastatic disease)
(6 mo preferred)

Active chemotherapy regimen for advanced disease (See Chemotherapy for Advanced or Metastatic Disease (COL-C))[x] (category 2B)
or
Consider observation or shortened course of chemotherapy, if patient received neoadjuvant therapy

→

SURVEILLANCE

If patient stage IV, NED:
- **CEA every 3 mo x 2 y, then every 6 mo x 3-5 y**
- **Chest/abdominal/pelvic CT scan every 3-6 mo x 2 y, then every 6-12 mo up to a total of 5 y**
- **Colonoscopy[a] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo**
  - **If abnormal, repeat in 1 y**
  - **If no advanced adenoma,[r] repeat in 3 y, then every 5 y[s]**

→ **Recurrence (See COL-9)**

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

[d] See Principles of Pathologic Review (COL-A 3 of 4) - KRAS Mutation Testing.

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

[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(6):1865-71.

[u] When preoperative therapy is planned, surgical re-evaluation should be planned within 8-10 weeks after initiation of treatment to minimize hepatic toxicity.

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

[w] The safety of administering bevacizumab pre or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6 wk interval between the last dose of bevacizumab and elective surgery and re-initiation of bevacizumab at least 6-8 weeks postoperatively. There is an increased risk of stroke and other arterial events especially in age ≥ 65. The use of bevacizumab may interfere with wound healing.

[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.

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Colon Cancer

Guidelines Index
Colon Cancer Table of Contents
Staging, Discussion, References

TREATMENT

Unresectable synchronous liver only or lung only metastases

- **Systemic therapy[u] (FOLFIRI or FOLFOX or CapeOX[v] ± bevacizumab[w] or FOLFIRI or FOLFOX or CapeOX[v] ± cetuximab [KRAS wild-type gene only][d] or FOLFOXIRI [category 2B])**
- **Consider colon resection[e] only if imminent risk of obstruction or significant bleeding**

→ **Re-evaluate for conversion to resectable[e] every 2 mo[u]**

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

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

ADJUVANT THERAPY (6 mo preferred)

Active chemotherapy regimen for advanced disease (See Chemotherapy for Advanced or Metastatic Disease (COL-C))[x] (category 2B)
or
Consider observation or shortened course of chemotherapy, if patient received neoadjuvant therapy

SURVEILLANCE

If patient stage IV, NED:

- **CEA every 3 mo x 2 y, then every 6 mo x 3-5 y**
- **Chest/abdominal/pelvic CT scan every 3-6 mo x 2 y, then every 6-12 mo up to a total of 5 y**
- **Colonoscopy[a] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo**
  - **If abnormal, repeat in 1 y**
  - **If no advanced adenoma,[r] repeat in 3 y, then every 5 y[s]**

Recurrence (See COL-9)

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

[d] See Principles of Pathologic Review (COL-A 3 of 4) - KRAS Mutation Testing.

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

[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(6):1865-71.

[u] When preoperative therapy is planned, surgical re-evaluation should be planned within 8-10 weeks after initiation of treatment to minimize hepatic toxicity.

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

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[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.

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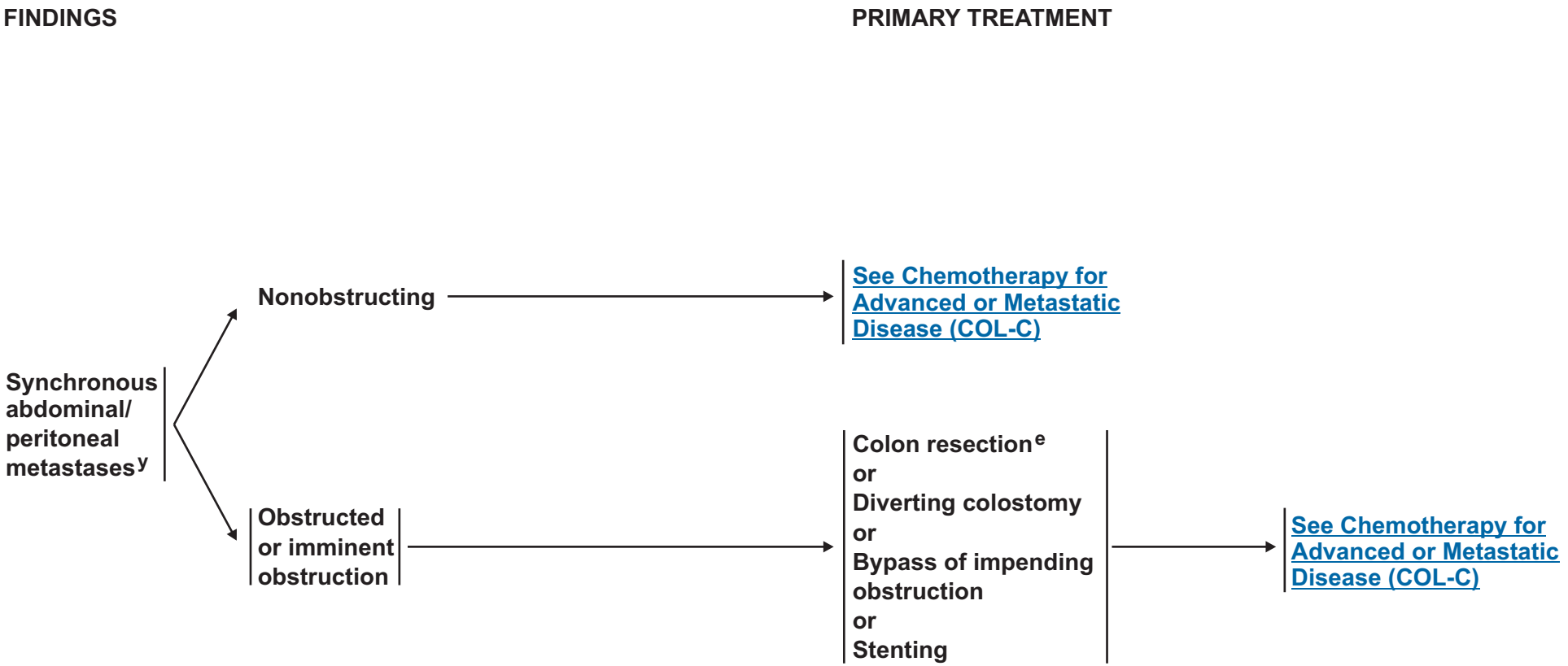

[e] See Principles of Surgery (COL-B 2 of 3).

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

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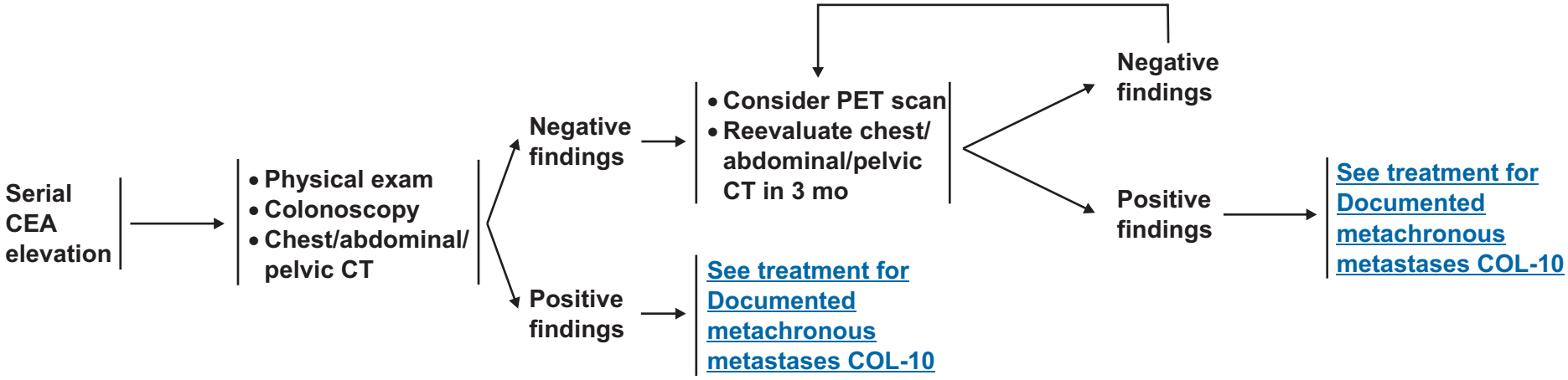
RECURRENCE **WORKUP**



[z]Determination of tumor KRAS gene status. See Principles of Pathologic Review (COL-A 3 of 4) - KRAS Mutation Testing.

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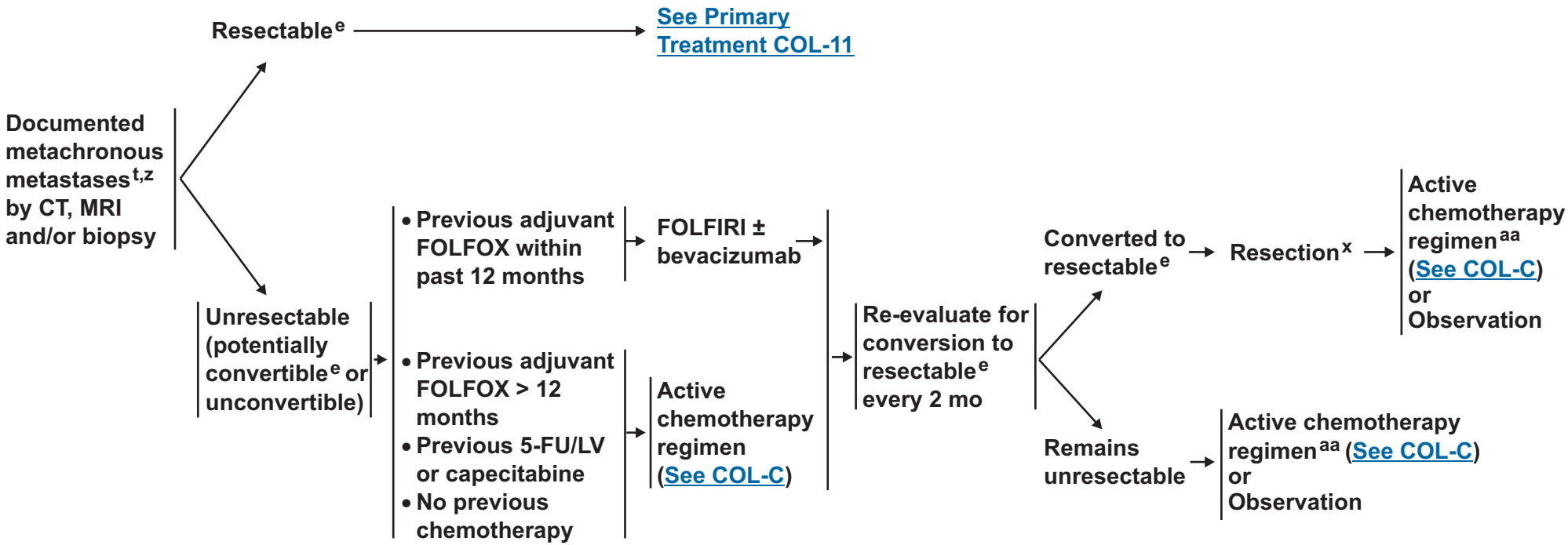
PRIMARY TREATMENT



[e] See Principles of Surgery (COL-B 2 of 3).
[t] Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.
[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 (COL-A 3 of 4) - KRAS Mutation Testing.
[aa] Therapy may be considered for a maximum of 6 months.

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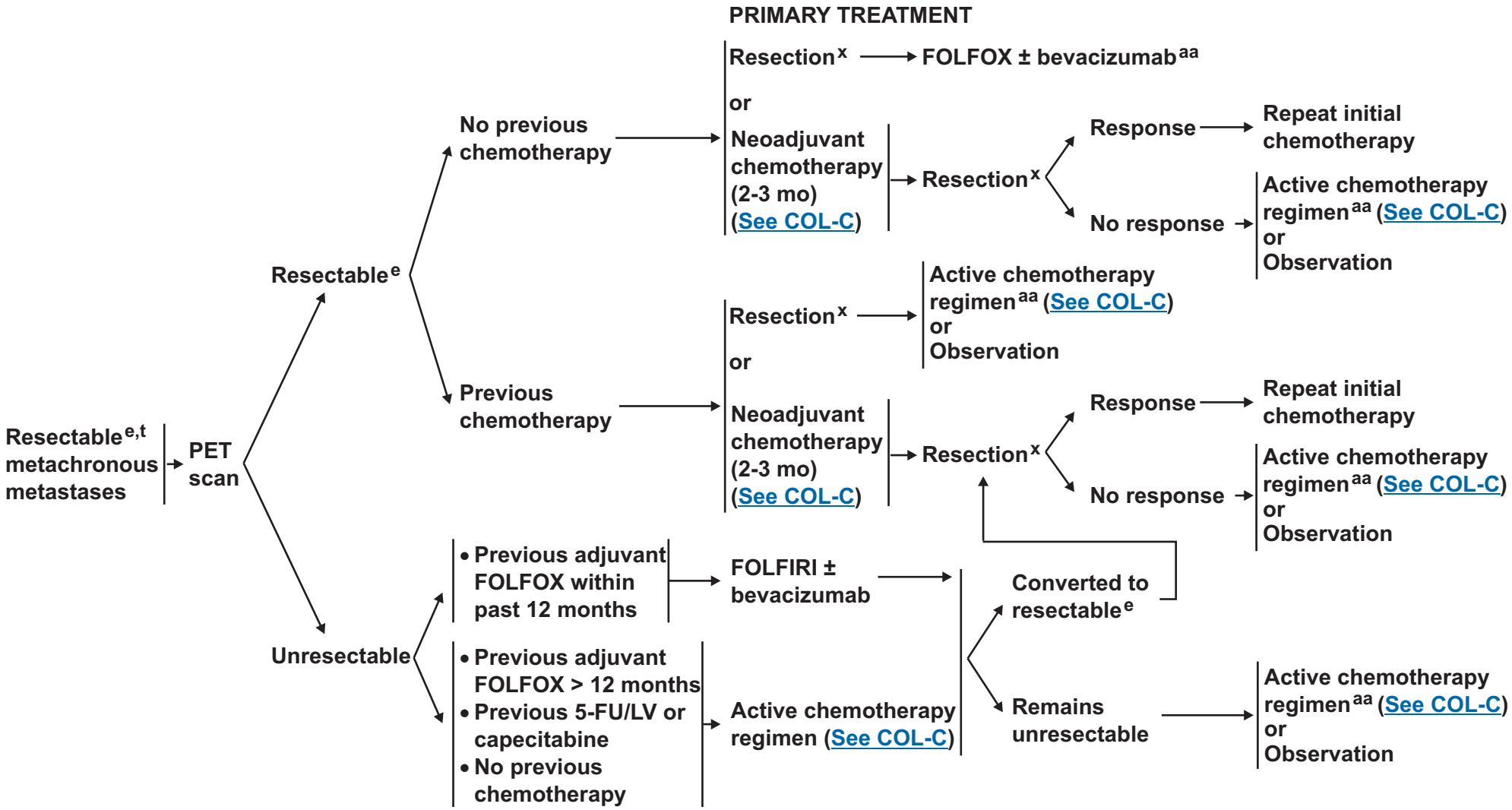
Colon Cancer



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

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

[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] Therapy may be considered for a maximum of 6 months.

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 4)

Endoscopically removed malignant polyps

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

Colon cancer appropriate for resection

- Histological confirmation of primary colonic malignant neoplasm

Pathological stage

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

See Lymph node evaluation and sentinel lymph node on page 2 of 4 COL-A

See KRAS Mutation Testing page 3 of 4 COL-A

See footnotes on page 4 of 4 COL-A

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF PATHOLOGIC REVIEW (2 of 4)

Lymph node evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancers.[8-10] The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, >30.[11-19] The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade and tumor site.[12] For stage II (pN0) colon cancer, if less than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The pathologist should attempt to retrieve as many lymph nodes as possible. It has been shown that the number of negative lymph nodes is an independent prognostic factor for patients with stage IIIB and IIIC colon cancer.[20]

Sentinel lymph node and detection of micrometastasis by immunohistochemistry

- Examination of the sentinal lymph node allows an intense histological and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple H & E sections and/or immunohistochemistry (IHC) to detect cytokeratin positive cells. While studies to date seem promising, there is no uniformity in the definition of what constitutes "true metastatic carcinoma." Confusion arises when isolated tumors cells (ITC) have been considered micrometastatic disease in contraindication to true micrometastasis (tumor aggregates > 0.2 mm to < 2 mm in size). The significance of detection of single cells by IHC alone is controversial. Some studies have considered these to be micrometastasis, however, “consensus” recommends these to be considered ITC and not micrometastatic disease.[21-25] While the 6th edition of the AJCC Cancer Staging[26] manual considers "tumor clusters" < 0.2 mm as isolated tumor cells (pN0) and not metastatic carcinoma, some have challenged this. Some investigators believe that size should not effect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.[27] Hermanek et 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) has a worse prognosis while others have failed to show this survival difference. In these studies, ITC were considered micrometastasis.[29-33]
- At the present time the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and results used with caution in clinical management decisions.[21-25,29-33]

See Malignant polyp, colon cancer appropriate for resection, and pathological stage on page 1 of 4 COL-A

See KRAS Mutation Testing page 3 of 4 COL-A

See footnotes on page 4 of 4 COL-A

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PRINCIPLES OF PATHOLOGIC REVIEW (3 of 4)

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 under the clinical laboratory improvement amendments of 1988 (CLIA – 88) as qualified to perform high complex clinical laboratory (molecular pathology) testing. No specific methodology is recommended (sequencing, hybridization, etc.).**
-
- **The testing can be performed on formalin fixed paraffin embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis as literature has shown that the KRAS mutations are similar in both specimen types.[36]**

See footnotes on page 4 of 4 COL-A

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PRINCIPLES OF PATHOLOGIC REVIEW (4 of 4)

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PRINCIPLES OF SURGERY (1 of 3)

Colectomy

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

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

See footnotes on page 3 of 3 COL-B

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PRINCIPLES OF SURGERY (2 of 3)
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 utilizing preoperative portal vein embolization[12] or staged liver resection[13] can be considered.
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.[14]
- Ablative techniques may be considered alone or in conjunction with resection.[14]
- Solitary lesions have a better prognosis than multiple liver metastases[15]
- 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.[16]

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[17-20]
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.[21-24]
- Re-resection can be considered in selected patients.[25]
- 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

- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.[26-29]
- 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.[30]
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[31]

See footnotes on page 3 of 3 COL-B

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PRINCIPLES OF SURGERY (3 of 3)

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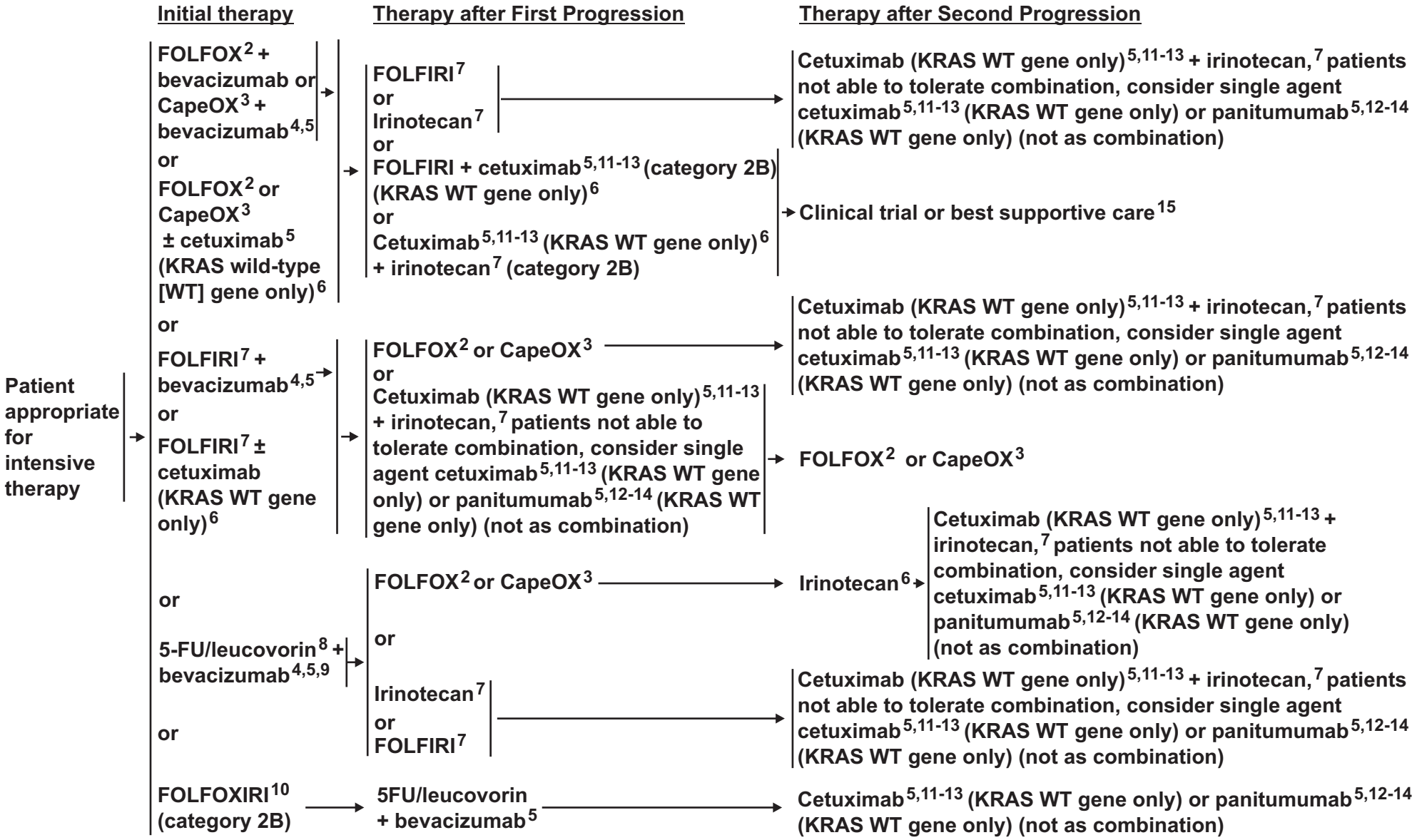
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 6)



Patient not appropriate for intensive therapy, see COL-C 2 of 6

See footnotes on page COL-C 3 of 6

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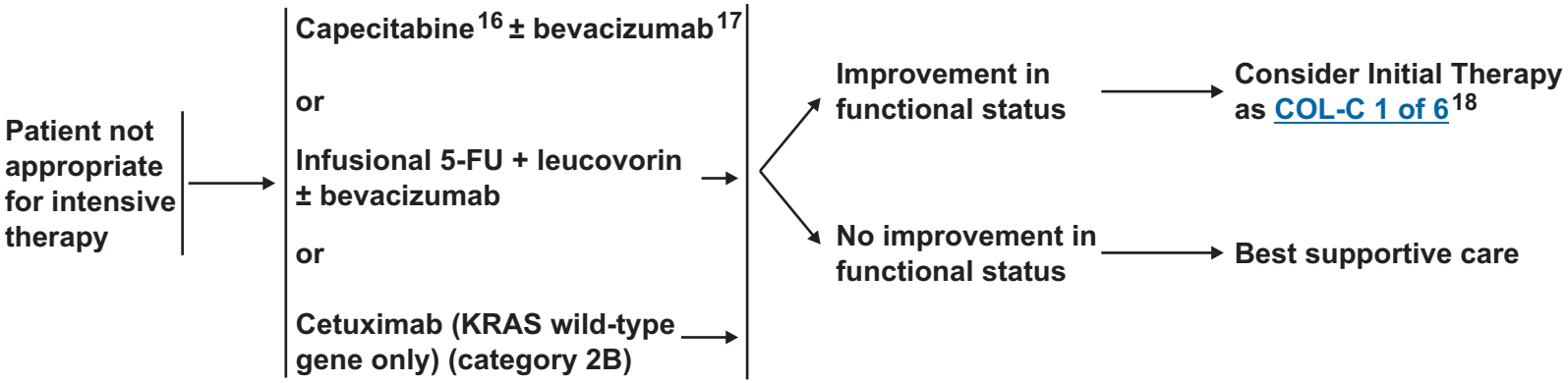
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 2 of 6)

Initial therapy



See footnotes on page COL-C 3 of 6

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 3 of 6)

[1] For chemotherapy references, see Chemotherapy Regimens and References (COL-C pages 4 - 6).

[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.

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

[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). 2008 Gastrointestinal Cancers Symposium. Abstract 273. Punt CJ, Tol J, Rodneburg J. et al randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer, the CAIRO 2 study of the Dutch Colorectal Cancer Group. J Clin Oncol 28:2008 (May 20 suppl; abstract LBA4011).

[6] See Principles of Pathologic Review (COL-A 3 of 4) - KRAS Mutation Testing.

[7] 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.

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

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

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

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

[12] 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.

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

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

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

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

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

[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 this is therefore not recommended.

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 4 of 6)

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/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Repeat every 2 weeks

Bevacizumab + 5-FU containing regimens:[7,8,9]
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 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2/day over 46 hours) to minimize medication errors.

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

See footnotes on page 6 of 6 COL-C

See Additional Chemotherapy Regimens 5 of 6 COL-C

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 5 of 6)

CHEMOTHERAPY REGIMENS

Capecitabine[11]
2000-2500 mg/m^2/day PO in two 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 h infusion
5-FU 500 mg/m^2 bolus administered 1 h after LV infusion
Repeat every week[15]
5-FU 2600 mg/m^2 by 24 h 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 200 mg/m^2 day 1, fluorouracil 3,200 mg/m^2 48 continuous infusion starting on day 1
Repeat every 2 weeks

Irinotecan[18,19]
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

Cetuximab (KRAS wild-type 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/m2 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 wild-type gene only)
Cetuximab 400 mg/m^2 1st infusion, then 250 mg/m^2 IV weekly

Panitumumab[22] **(KRAS wild-type 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 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2/day over 46 hours) to minimize medication errors.

See footnotes on page 6 of 6 COL-C

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 6 of 6)

CHEMOTHERAPY REFERENCES

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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 (eg, T4 lesion, perforation, peritumoral lymphovascular involvement, poorly differentiated histology)**
  - **Assessment of other comorbidities and anticipated life expectancy.**
- **The benefit of adjuvant chemotherapy does not improve survival by more than 5 percent.**

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PRINCIPLES OF ADJUVANT THERAPY (1 of 3)

5-FU/leucovorin

- **Leucovorin 500 mg/m^2 given as a 2 h infusion and repeated weekly x 6**
  5-FU 500 mg/m^2 given bolus 1 h 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 d, every 28 d x 6 cycles[2]**

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

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 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2/day over 46 hours) to minimize medication errors.

See footnotes on page 2 of 3 COL-E

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

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PRINCIPLES OF ADJUVANT THERAPY (2 of 3)

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PRINCIPLES OF ADJUVANT THERAPY (3 of 3)

- **Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in Stage III patients.[1] This is an extrapolation from data available.**
- **FOLFOX appears to be superior for Stage III patients.[2,3] FOLFOX is reasonable for high risk or intermediate risk stage II patients and is not indicated for good or average risk stage II patients. FLOX is an alternative to FOLFOX.[4]**
- **Bolus 5-FU/leucovorin/irinotecan should not be used in adjuvant therapy[5] and infusional 5-FU/leucovorin/irinotecan (FOLFIRI) has not been shown to be superior to 5-FU/LV.[6,7] Data are not yet available for capecitabine combination regimens.**

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PRINCIPLES OF RADIATION THERAPY

- Radiation therapy fields should include the tumor bed, which should be defined by preoperative radiological imaging and/or surgical clips.
- Radiation doses should be:
  - 45-50 Gy in 25-28 fractions.
  - Consider boost for close or positive margins.
  - Small bowel dose should be limited to 45 Gy.
  - 5-fluorouracil based chemotherapy should be delivered concurrently with radiation.
- Intensity modulated radiotherapy (IMRT) or tomotherapy could be considered when there is a high risk of radiation-related normal tissue toxicity. Care should be taken to assure adequate tumor bed coverage.
- Intraoperative radiotherapy (IORT), if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Preoperative radiation is preferred for these patients to aid resectability. If IORT is not available, low dose external beam radiation could be considered, prior to adjuvant chemotherapy.
- 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.

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PRINCIPLES OF SURVIVORSHIP
Colorectal Long-term Follow-up Care (1 of 3)

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:
- 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 (greater than 20% lifetime risk) should get breast MRI and mammogram annually.
  - See NCCN Breast Cancer Screening and Diagnosis Guidelines
- 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 over, 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 over age 70 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 Cervical Cancer Screening Guidelines
- 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 Prostate Cancer Early Detection Guidelines

Continued

[1]American Cancer Society Guidelines for Early Detection of Cancer: http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp, Accessed September 21, 2008.

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PRINCIPLES OF SURVIVORSHIP
Colorectal Long-term Follow-up Care (2 of 3)

Management of Late Sequelae of Disease or Treatment:[2-6]
- **Chronic Diarrhea or Incontinence**
  - ► **Consider anti-diarrheal 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.**
- **Bone Health After Pelvic Radiation**
  - ► **Consider monitoring of bone density or evaluation for pelvic fractures with pelvic pain if previously received pelvic radiation**
- **Sexual Dysfunction After Pelvic Radiation**
  - ► **Screen for erectile dysfunction and dyspareunia in those who received pelvic radiation**
  - ► **Consider referral to urologist or gynecologist for persistent symptoms.**

Immunizations:[7]
- **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**

Continued

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PRINCIPLES OF SURVIVORSHIP
Colorectal Long-term Follow-up Care (3 of 3)

Counseling Regarding Healthy Lifestyle and Wellness:[8-11]
- **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:[12]
- **Include overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received**
- **Describe possible clinical course, including expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment**
- **Include surveillance recommendations**
- **Delineate appropriate timing of transfer of care with specific responsibilities identified for PCP and Oncologist.**

[8] American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention, http://www.cancer.org/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED, Accessed September 21, 2008.

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Staging

Table 1

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

Primary Tumor (T)

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

Regional Lymph Nodes (N)§

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage	T	N	M	Dukes¶	MAC¶
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4	N0	M0	B	B3
IIIA	T1-T2	N1	M0	C	C1
IIIB	T3-T4	N1	M0	C	C2/C3
IIIC	Any T	N2	M0	C	C1/C2/C3
IV	Any T	Any N	M1	-	D

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiatied
G4 Undifferentiated

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

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

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

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

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

Note: The y prefix is to be used for those cancers that are classified after pretreatment, whereas the r prefix is to be used for those cancers that have recurred.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/28/08

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.

Overview

Colorectal cancer is the third most frequently diagnosed cancer in men and women in the United States. In 2008, an estimated 108,070 new cases of colon cancer and approximately 40,780 cases of rectal cancer will occur. During the same year, it is estimated that 49,960 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 because of earlier diagnosis through screening and better treatment modalities.

This manuscript summarizes the NCCN clinical practice guidelines for managing colon cancer. The guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, adjuvant treatment, management of recurrent and metastatic disease, and patient surveillance. When reviewing these guidelines, clinicians should be aware of several things. First, these guidelines adhere to the TNM (tumor/node/metastasis) staging system (Table 1).[2] Furthermore, all recommendations are classified as category 2A except where noted in the text or on the algorithm (see Categories of Evidence and Consensus). The panel unanimously endorses giving priority to treating patients in a clinical trial over standard or accepted therapy. This is especially true for cases of advanced disease and for patients with locally aggressive colorectal cancer who are receiving combined modality treatment.

Risk Assessment

Nearly one-third of cases of colon cancer in the US are associated with familial clustering,[3] and 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 colon cancer patients, especially those 50 years or younger and those with suspected hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), or attenuated FAP be counseled regarding their family history, as detailed in the NCCN Colorectal Cancer Screening Clinical Practice Guidelines.

Staging

The 6th edition of the American Joint Committee on Cancer's AJCC Cancer Staging Manual[2,6] includes several modifications to the colon and rectum staging system (see ST-1). In this version of the staging system, smooth metastatic nodules in the pericolic or perirectal fat are considered lymph node metastases and should be included in N staging. Irregularly contoured metastatic nodules in the peritumoral fat are considered vascular invasion.

Stage II is subdivided into IIA (if the primary tumor is T3) and IIB (for T4 lesions). Stage III is subdivided into 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 four or more positive regional nodes.

An analysis of Surveillance, Epidemiology, and End Results (SEER) data of 119,363 patients with colon cancer from 1991-2000 allowed determination of the following 5-year survival rates by stage: 93.2% (Stage I); 84.7% (Stage 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 (ie, increased survival rates for patients with Stage IIIA disease relative to 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) with Stage IV disease characterized by the presence of one or more distant metastases and designated as M1.[6]

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

Pathology

Colorectal cancers are usually staged after surgical exploration of the abdomen and pathologic examination of the surgical specimen. Some of the criteria which should be included in the report of the pathologic evaluation include the following: grade of the cancer; depth of penetration and extension to adjacent structures (T); number of regional lymph nodes evaluated; number of positive regional lymph nodes (N); an assessment of the presence of distant metastases to other organs, the peritoneum of an abdominal structure, or in nonregional lymph nodes (M),[6,9] and the status of proximal, distal, and peritoneal margins.[6,10]

The AJCC and 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 node(s).[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] While results of some of these studies seem promising, there is no uniformity in the definition of “true” clinically relevant metastatic carcinoma. Some studies have considered detection of single cells by IHC as well as isolated tumor cells (ITC) to be micrometastasis. Presently, the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and the results should be used with caution in clinical management decisions.

Clinical Presentation and Treatment

Workup and Management of the Malignant Polyp

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or villous adenoma, physicians should review pathology and consult with the patient.[24] A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore not considered to be capable of regional nodal metastasis.[6] The panel recommends marking the polyp site at the time of colonoscopy if cancer is suspected or within 2 weeks of the polypectomy when the pathology is known. In patients with invasive cancer and adenoma (tubular, tubulovillous or villous), no additional surgery is required for pedunculated or sessile polyps, if the polyp has been completely resected with favorable histological features.[25] 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.[26] 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 tumor within 1-2 mm from the transected margin and the presence of tumor cells within the diathermy of the transected margin.[24, 27-29] For a pedunculated or sessile polyp with fragmented specimen or margins that cannot be assessed, or with unfavorable pathology, colectomy with en bloc removal of lymph nodes is recommended.[24, 30, 31] Laparoscopic surgery is an option (see section on Workup and Management of Invasive Nonmetastatic Colon Cancer). All patients who have resected polyps should undergo total colonoscopy to rule out other synchronous polyps, as well as appropriate follow-up surveillance endoscopy.[32] Adjuvant chemotherapy is not recommended for patients with Stage I lesions.

Workup and Management of Invasive Nonmetastatic Colon Cancer

Patients who present with invasive colon cancer require a complete staging workup, including pathologic tissue review, total colonoscopy, a complete blood count, platelets, chemistry profile, carcinoembryonic antigen (CEA) determination, and baseline computed tomographic (CT) scans of the chest, abdomen and pelvis.[33] The consensus of the panel is that a positron emission tomography (PET) scan is not routinely indicated at baseline in the absence of evidence of synchronous metastatic disease, 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 of that abnormality. A PET scan is not indicated for assessment of sub-centimeter 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.[34] 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 (ie, apical lymph node) as well as suspicious lymph nodes outside the field of resection, should also be biopsied or removed.

Secondary analyses from the Intergroup INT-0089 trial of patients with high-risk Stage II/III colon cancer receiving adjuvant chemotherapy demonstrated that the accuracy of staging colorectal cancer was

associated the number of nodes removed.[35] Furthermore, these analyses also showed that an increase in the number of lymph nodes examined was associated with increased survival for patients with both -node-negative and node-positive disease,[14] and that the ratio of metastatic to examined lymph nodes (LNR) was a significant prognostic factor for both disease recurrence and overall survival.[36] However, LNR was not shown to be prognostic for patients for whom fewer than 10 lymph nodes were evaluated,[36] and 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 demonstrated an association between improvement in survival and examination of 12 (or 13) or more lymph nodes.[15,18,37] Resection needs to be complete to be considered curative, and positive lymph nodes left behind indicate an incomplete (R2) resection. Patients considered to have N0 disease but for whom <12 nodes have been examined are suboptimally staged and should be considered at higher risk.

Laparoscopic colectomy has been advanced as an approach to the surgical management of colon cancer. A European trial (Barcelona) showed some survival advantage to the laparoscopic approach, but the number of patients enrolled was small.[38] More recently, for patients randomly assigned to either curative surgery with either a conventional open approach or laparoscopically-assisted surgery, no significant differences were observed in 3-year cancer-free survival in a study of 1248 patients with colon cancer (COLOR trial),[39] or in 3-year rates of overall survival, DFS, and local recurrence for 794 patients with colorectal cancer in the CLASICC study.[40] 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.[41,42] After a median of 7 years follow-up, similar 5-year cancer recurrence and 5-year overall survival rates were observed in the two 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. [43-45] However, a subanalysis of results from the COLOR trial evaluating short-term outcomes (eg, conversion rate to open colectomy, number of lymph nodes collected, number of complications) based on hospital case volume indicated that these outcomes were significantly more favorable when laparoscopic surgery was performed at hospitals with high case volumes.[46] Other factors which may confound conclusions drawn from randomized studies comparing open colectomy to laparoscopically-assisted surgery for colon cancer have also been described.[47,48]

The panel recommends that criteria be met when laparoscopic-assisted colectomy is considered; laparoscopically-assisted colorectal operations are performed by an experienced surgeon[49, 50] ; no lesions in rectum, transverse colon, nor prohibitive abdominal adhesions are detected; no advanced local or metastatic disease present; acute bowel obstruction or perforation from cancer is not present; and thorough abdominal exploration is required.[51]

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.[52-54] The European MOSAIC trial has evaluated the efficacy of FOLFOX4 (infusional 5-fluorouracil (5-FU), leucovorin (LV), oxaliplatin) compared to 5-FU/LV in the adjuvant setting in 2246 patients with completely resected Stage II and stage III colon cancer.

Results of this study have been reported with median follow-up of 3 years,[55] 4 years, [56] and 6 years.[57] For Stage III patients, disease-free survival (DFS) at 5 years was 58.9%% in the 5-FU/LV arm and 66.4%% in the FOLFOX4 arm (P=0.005). For Stage II patients, 5-year DFS was 79.9% in the 5-FU/LV arm and 83.7% with the FOLFOX4 regimen (P=0.258). Based on these results, FOLFOX4, or modified FOLFOX 6 is recommended as treatment for stage III colon cancer (category 1). This recommendation is strengthened by results of a recent analysis of individual patient data from 20,898 patients on 18 randomized colon adjuvant clinical trials which suggested that DFS after 2 and 3 years follow-up is an appropriate endpoint for clinical trials involving treatment of colon cancer with 5-FU-based chemotherapy in the adjuvant setting.[58,59] Furthermore, overall survival of patients with stage III disease receiving FOLFOX was significantly increased at 6-year follow up (hazard ratio=0.80; 95% CI, 0.66-0.98; P=0.029) when compared with those receiving 5-FU/LV.[57] While the incidence of grade 3 peripheral sensory neuropathy was 12.4% for patients receiving FOLFOX, long-term safety results demonstrated a gradual recovery for most of these patients. However, neuropathy was present in 12% of this group at 4 years, suggesting that oxaliplatin-induced neuropathy may not be completely reversible in some patients.[57]

Other adjuvant regimens studied for the treatment of early-stage colon cancer include 5-FU-based therapies incorporating irinotecan, 5-FU regimens other than FOLFOX which include oxaliplatin, and single agent capecitabine. The US Intergroup trial CALGB C89803 evaluated irinotecan plus bolus 5-FU/LV (IFL regimen) versus 5-FU/LV alone in Stage III colon cancer.[60] No improvement in either overall survival (P=0.74) or disease-free survival (P=0.85) was observed for patients in the IFL arm compared with those receiving 5-FU/LV. However, IFL was associated with a greater degree of neutropenia, neutropenic fever, and death.[61] In addition, FOLFIRI (infusional 5-fluorouracil, leucovorin, irinotecan), has not been shown to be superior to 5-FU/LV in the adjuvant setting,[62, 63] although a trend toward improvement was seen with addition of irinotecan in one study.[62] A randomized phase III trial (NSABP Protocol C-07) compared the efficacy of FLOX (bolus 5-FU/LV/oxaliplatin) with that of FULV (bolus 5-FU/LV) in prolonging DFS in 2407 patients with Stage II or Stage III colon cancer.[64,65] Three- and 4-year DFS rates were 76.1% and 73.6% for FLOX and 71.8% and 67.0% for FULV, respectively, indicating that the addition of oxaliplatin to weekly FULV significantly improved 4-year DFS in patients with Stage II/Stage III colon cancer (P=0.0034). Grade 3 NCI-Sanofi neurosensory toxicity, diarrhea or dehydration associated with bowel wall thickening was higher with FLOX than with FULV, and, when cross-study comparisons are made, the incidence of grade 3/4 diarrhea was considerably higher with FLOX than FOLFOX. For example, rates of grade 3/4 diarrhea were 10.8% and 6.7% for patients receiving FOLFOX and infusional 5-FU/LV, respectively, in the MOSAIC trial,[57] whereas 38% and 32.2% of patients were reported to have grade 3/4 diarrhea in the NSABP C-07 trial when receiving FLOX and bolus 5-FU/LV, respectively.[65] Single agent oral capecitabine as adjuvant therapy for patients with Stage III colon cancer was shown to be at least equivalent to bolus IV 5-FU/LV (Mayo clinic regimen) with respect to DFS and overall survival with respective hazard ratios of 0.87 (95% CI, 0.75-1.00) and 0.84 (95% CI, 0.69-1.01) when the capecitabine arm was compared to the 5-FU/LV arm.[66]

The impact of adjuvant chemotherapy for patients with Stage II colon cancer has been addressed in several clinical trials and practice-based studies. Results from a meta-analysis of 5 trials in which patients with Stage II and III colon cancer were randomly assigned to receive surgery alone or surgery followed by adjuvant 5-FU/LV demonstrated that most of the benefit of adjuvant therapy was seen in the patients with Stage III disease.[67,68] Similarly, an analysis of pooled data from 7 randomized trials indicated that overall survival of patients with resected early-stage colon cancer treated with 5-FU based adjuvant

therapy was significantly increased in the subset of patients with positive regional lymph nodes but not in patients with N0 disease when compared to patients not receiving chemotherapy, suggesting that the benefit of adjuvant therapy is greater in patients at higher risk due to nodal status.[69] These clinical trial results are supported by data from the community setting. Using the SEER databases, an analysis of outcomes of patients with Stage II disease based on whether patients had or had not received adjuvant chemotherapy showed that there was no significant difference between these 2 groups with respect to 5-year overall survival (eg, 78% vs. 75% respectively), with a hazard ratio for survival of 0.91 (95% CI, 0.77-1.09) when patients receiving adjuvant treatment were compared with untreated patients.[70]

Following primary surgical treatment, the panel recommends 6 months of adjuvant chemotherapy for patients with Stage III (T1-4, N1-2, M0) resected colon cancer. The treatment options are: 5-fluorouracil/leucovorin/oxaliplatin as the standard of care (category 1),[55-57,64,65] or either single agent capecitabine (category 2A),[66] or 5-FU/LV (category 2A) in patients felt to be inappropriate for oxaliplatin therapy.[67, 71, 72] The panel concluded that weekly bolus IFL should not be used as adjuvant therapy in colon cancer. The recently published QUASAR trial indicates a small but statistically significant survival benefit for stage II patients treated with 5-FU/LV.[73] High-risk stage II (T3-T4, N0, M0) patients, defined as those with poor prognostic features including T4 tumors (stage IIB), poor histologic grade (grade 3 or 4 lesions), peritumoral lymphovascular involvement, bowel obstruction at presentation, T3 lesions with localized perforation or close, indeterminate, or positive margins, and inadequately sampled nodes (less than 12 lymph nodes), should be considered for adjuvant chemotherapy[10, 74] with 5-FU/LV/oxaliplatin, single agent 5-FU/LV, or capecitabine (category 2A for all three 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 (hazard ratio=0.84; 95% CI, 0.62-1.14; P-0.258). Nevertheless, subset analyses showed a trend for improved DFS in high-risk stage II patients receiving FOLFOX4 compared to infusional 5-FU/LV (hazard ratio=0.74, 95% CI, 0.52-1.06), suggesting that this patient population may benefit from treatment with FOLFOX.[57] However, no benefit of FOLFOX over 5-FU/LV was seen for patients with low-risk stage II disease in the MOSAIC trial.[57] 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. Decision-making regarding the use of adjuvant therapy for patients with stage II disease should incorporate patient/physician discussions individualized for the patient, and include explanations of the specific characteristics of the disease and the evidence related to the efficacy and possible toxicities associated with treatment, centering on patient choice[74,75] 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. Radiation therapy fields should be defined by preoperative radiological imaging and/or surgical clips. Intensity-modulated radiotherapy (IMRT) which uses computer-imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,[76] can be considered when the risk of such toxicity is high. A summary of ongoing clinical trials in early-stage colon cancer has been presented.[77]

Principles of the Management of Metastatic Disease

Approximately 50%-60% of patients diagnosed with colorectal cancer will develop colorectal metastases.[78, 79] Patients with stage IV (any T, any N, M1) colon cancer or recurrent disease can present with synchronous liver or lung metastases or abdominal peritoneal metastases. Approximately 15%-25% of patients with colorectal cancer present with synchronous liver metastases, although 80%-90% of these

patients are initially evaluated to have unresectable metastatic liver disease.[78, 80-82] Metastatic disease more frequently develops metachronously following treatment for colorectal cancer, with the liver as a common site of involvement.[83] There is some evidence to indicate that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In one retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement (P=0.008) and more bilobar metastases (P=0.016) when compared with patients diagnosed with metachronous liver metastases.[84]

It has been estimated that over one-half of patients who die of colorectal cancer have liver metastases at autopsy, and that metastatic liver disease is the cause of death in the majority of these patients.[85] Results from reviews of autopsy reports of patients dying from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients.[80] Furthermore, rates of 5-year survival for patients with metastatic liver disease not undergoing surgery have been shown to approach 0% in a number of studies.[78, 86] However, studies of selected patients undergoing surgery to remove colorectal liver metastases have demonstrated that cure is possible in this population and should be the goal for many patients with colorectal metastatic liver disease.[78, 87] Recent reports have shown 5-year survival rates following resection of liver metastases exceeding 50%.[88, 89] 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.[90]

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 COL-B).[91-94] Resectability differs fundamentally from endpoints which focus more on palliative measures of treatment, such as response and DFS. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease;[95] resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), since partial liver resection or debulking has not been shown to be beneficial.[79,93] Approaches used in the surgical treatment of liver metastases include preoperative portal vein embolization for the purpose of increasing the volume and function of the portion of the liver which will remain postsurgically, hepatic resection performed in 2 stages for bilobular disease, and the use of ablative methods in combination with resection.[91,96] As with resection, ablative techniques should be considered only when disease is judged to be completely amenable to ablation. Resection of liver metastases should not be performed in the presence of unresectable sites of extrahepatic disease, and hepatic intra-arterial embolization should not routinely be used outside of a clinical trial. The consensus of the panel is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (ie, with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status.

Since the majority of patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease, preoperative chemotherapy is being increasingly employed to downsize colorectal metastases in order to convert these lesions to a resectable status (ie, conversion chemotherapy); it has also been administered to patients with metastatic disease determined to be resectable (ie, neoadjuvant therapy). Potential advantages of this approach include: earlier treatment of micrometastatic disease, determination of

responsiveness to chemotherapy (which can be prognostic and help in the planning of postoperative therapy), and avoidance of local therapy for those patients with early disease progression. Potential disadvantages include: chemotherapy-induced liver injury; and missing the "window of opportunity" for resection through the possibility of either disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.[80, 97] Furthermore, results from a recent study of colorectal cancer patients 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.[98] 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 that a treatment strategy can be developed which optimizes exposure to the preoperative chemotherapy regimen and facilitates an appropriately-timed surgical intervention.[99] When preoperative therapy is planned, the panel recommends that a surgical re-evaluation should be planned within 8-10 weeks after initiation of preoperative therapy.

Certain clinicopathologic factors, such as the presence of extrahepatic metastases and a disease-free interval of < 12 months, have been associated with a poor prognosis in patients with colorectal cancer,[88, 89, 100- 102] although the ability of these factors to predict outcome following resection may be limited.[78] However, decision-making relating to 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 resectable 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 prior chemotherapy in the previous 12 months.

The most important benefit of the preoperative approach is the potential to convert patients with initially unresectable metastatic disease to a resectable state. In the study of Pozzo et al, it was reported that preoperative chemotherapy therapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection.[92] The median time to progression was 14.3 months, with all of these patients alive at a median follow-up of 19 months. In a phase II study conducted by the North Central Cancer Treatment Group (NCCTG),[82] 44 patients with unresectable liver metastases were treated with FOLFOX4. Twenty five patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study of 1439 initially unresectable patients with colorectal liver disease, 1104 patients were treated with chemotherapy and 335 patients (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.[103] The 5-year overall survival rate for these 138 patients was 33%. More recently, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%) were able to undergo curative liver resection following treatment.[104] The median overall survival time in this group was 42.4 months.

Recently, the efficacy of bevacizumab in combination with FOLFOX and FOLFIRI in the treatment of unresectable metastatic disease (see section on Chemotherapy for Advanced or Metastatic Disease) has led to its use in combination with these regimens in the preoperative setting, although the safety of administering bevacizumab pre- or postoperatively, in combination with 5-fluorouracil-based regimens has not been adequately evaluated. A retrospective evaluation of data from 2 randomized trials of 1132 patients receiving chemotherapy with or without bevacizumab as initial therapy for metastatic colorectal cancer indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen when this population was compared to the group receiving chemotherapy alone while undergoing major surgery (13% vs 3.4%, respectively; P=0.28).[105] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to surgery, the incidence of wound healing complications in either group of patients was low (1.3% vs 0.5%; P=0.63). The panel recommends at least a 6 week interval (which corresponds to 2 half-lives of the drug[106]) 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 (ie, bevacizumab excluded from the 6th cycle of therapy).[107] In addition, no significant differences in bleeding, wound, or hepatic complications were observed in a retrospective trial evaluating effects of preoperative bevacizumab stopped ≤ 8 weeks vs. > 8 weeks prior to resection of liver colorectal metastases for patients receiving oxaliplatin- or irinotecan-containing regimens.[108]

Other reported risks associated with the preoperative approach include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.[99] To limit the development of hepatotoxicity, it is therefore recommended that surgery should be performed as soon as possible after the patient becomes resectable and usually not more than 3-4 months following initiation of preoperative treatment.

Colorectal metastatic disease can also occur in the lung.[109] Most of the treatment recommendations discussed for metastatic colorectal liver disease, with the exception of hepatic arterial infusion (HAI), also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in selected cases.[110] The goal of treatment of 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. Nevertheless, the panel recommends administration of a course of an active systemic chemotherapy regimen for metastatic disease for most patients following liver or lung resection to increase the likelihood that residual microscopic disease will be eradicated. Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent administration of chemotherapy directed to the liver metastases through the hepatic artery (i.e. HAI) is listed in the guidelines as an option (category 2B). 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.[80, 111] However, the difference in survival between the 2 arms of the study was not significant at later follow-up periods.[80,112] 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.[80] Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.[87] Limitations on the use of HAI therapy include the potential for biliary toxicity,[80] 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.

Although the benefit of preoperative or postoperative chemotherapy for patients with liver metastases has not yet been validated in randomized clinical trials, a recent European Organization for Research and Treatment of Cancer (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 PFS of 8.1% (P=0.041) and 9.2% (P=0.025) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[113]

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from large bowel (e.g. colorectal liver metastases) is suspected should include total colonoscopy, a complete blood count, platelets, chemistry profile, carcinoembryonic antigen (CEA) determination, a CT scan of the chest, abdomen and pelvis.[33] 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 discussion of KRAS testing on MS-17). The panel recommends a preoperative PET scan at baseline only if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease, and 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 scans be used to assess response to chemotherapy. The criterion of potential surgical cure includes patients with metastatic disease that is not initially resectable or ablatable but for whom a surgical cure may become possible following preoperative chemotherapy. It should be noted that in the overwhelming majority of cases, the presence of extrahepatic disease will preclude the possibility of resection for cure; "conversion to resectability" for the most part refers to a patient with liver-only disease that, due to involvement of critical structures, cannot be resected unless regression is accomplished with chemotherapy. It should be noted that a PET scan can become transiently negative following chemotherapy (eg, in the presence of necrotic lesions)[114] and the panel recommends against using PET scan to evaluate response to chemotherapy. False positive PET scan results can occur in the presence of tissue inflammation following surgery or infection.[114] An MRI with IV contrast can be considered as part of the preoperative evaluation of patients with potentially surgically resectable M1 liver disease. For example, an MRI with contrast may be of use in situations where the PET and CT scan results are inconsistent with respect to the extent of disease in the liver. Close communication between members of the multidisciplinary treatment team is recommended.

Resectable synchronous liver or lung metastases

If a patient is a candidate for surgery and the liver or lung metastases are deemed resectable, the panel recommends the following options: colectomy and synchronous or subsequent liver (or lung) resection,[83, 102] neoadjuvant chemotherapy (eg, choice of FOLFIRI, FOLFOX,[81] or CapeOX [capecitabine, oxaliplatin] chemotherapy with or without bevacizumab) followed by synchronous or staged colectomy with liver or lung resection, or colectomy followed by neoadjuvant chemotherapy

(see above) and a staged resection of metastatic disease. Patients with a solitary lesion in their lungs who can undergo resection should be considered for colectomy followed by staged thoracotomy and pulmonary nodule resection. Biologic waiting period of up to 2-3 months can distinguish patients who would be more likely to benefit from metastasectomy because of indolent disease. Resection of primary colon cancer prior to initiation of chemotherapy is rarely necessary, and should only be done in patients with severe symptoms (eg, complete intestinal obstruction) related to the primary cancer. However, advantages to a neoadjuvant chemotherapy approach include the possibility of downsizing both the primary tumor and metastatic lesions prior to surgery, and a very low rate of complications related to the unresected primary cancer.[81] Patients who have completely resected liver or lung metastases should be offered adjuvant. The panel recommends approximately 6 months as the preferred duration of adjuvant therapy. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B), and, in the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or continuous IV 5-FU infusion. Observation or a shortened course of chemotherapy can be considered for patients who have completed neoadjuvant chemotherapy. Post-treatment follow-up for patients classified as stage IV and no evidence of disease (NED) is described in the section on Post-Treatment Surveillance.

Unresectable synchronous liver or lung metastases

For patients in which the liver or lung disease is deemed to be unresectable, the panel recommends chemotherapy corresponding to initial therapy for metastatic disease (eg, choice of FOLFIRI, FOLFOX, or CapeOX chemotherapy with or without bevacizumab) to attempt to render these patients candidates for resection. Patients with disease converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer followed by adjuvant therapy for a preferred total duration of 6 months. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B), and, in the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or continuous IV 5-FU infusion. Observation or shortened course of chemotherapy can be considered for patients who have completed 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. It should be noted that symptomatic improvement in the primary is often seen with first-line systemic chemotherapy, even within the first one to two weeks, and routine palliate resection of a synchronous primary lesion should not be done in the absence of overt, serious symptoms. Complications from the primary lesion are uncommon in these circumstances, and its removal delays initiation of systemic chemotherapy. An intact primary is not a contraindication to bevacizumab use. The risk of gastrointestinal perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, as large bowel perforations, in general, and perforation of the primary lesion, in particular, are extremely rare.

Ablative therapy[115] of liver metastases using radiofrequency ablation or cryosurgery at the time of colon resection can also be considered when all measurable metastatic disease can be treated (category 2B). Patients with unresectable liver metastases not responding to systemic therapy should receive salvage therapy for advanced or metastatic disease. Post-treatment follow-up for patients classified as stage IV and no evidence of disease (NED) is described in the section on Post-Treatment Surveillance.

Synchronous abdominal/peritoneal metastases

For patients with peritoneal metastases and obstruction, surgical options include colon resection, diverting colostomy, or a bypass of

impending obstruction or stenting, followed by chemotherapy for advanced or metastatic disease. As chemotherapy is 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 (ie, peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy[116,117] 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

Upon documentation 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.[118] 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 discussion of KRAS testing on MS-17).

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 within or before the previous 12 months. For patients who have not received prior chemotherapy and who have resectable metastatic disease, primary treatment options include initial resection followed by chemotherapy, or neoadjuvant chemotherapy followed by resection and additional postoperative chemotherapy. The optimal sequence of therapeutic interventions is less clear for patients who have received prior adjuvant chemotherapy. In particular, the role of preoperative chemotherapy is less clear for patients who exhibit disease recurrence or progression during or within 12 months of receiving prior chemotherapy. Following surgery, adjuvant therapy with an alternative active metastatic chemotherapy regimen is recommended.

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

Chemotherapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colon cancer uses various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine; irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab. [119-134] The putative mechanisms of action of these

agents are varied and include interference with DNA replication, and inhibition of the activities of vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) receptors.[135-138] The choice of therapy is based on consideration of the type and timing of the prior therapy that has been administered and the differing toxicity profiles of the constituent drugs. Although the specific chemotherapy regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[121] For example, if oxaliplatin, administered as a part of an initial treatment regimen, is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the rest of the treatment regimen would still be considered initial therapy. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, as well as plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices following first progression of disease should be based, in part, on the prior therapies received by the patient (ie, exposing patient to a range of cytotoxic agents). Further, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, as well as the potential for surgical cure and the performance status of the patient.

As initial therapy for metastatic disease in a patient with good tolerance to intensive therapy, the panel recommends a choice of 4 chemotherapy regimens: FOLFOX (eg, FOLFOX4 or mFOLFOX6),[122, 130,139-145] CapeOX, [145-147] FOLFIRI,[123,140,144,148] or 5-FU/LV[125,129,148-150]; see COL-C). The panel further recommends that each of these regimens be administered in combination with bevacizumab when used for initial therapy. With respect to the treatment of metastatic disease, the consensus of the panel was that FOLFOX plus bevacizumab and CapeOX plus bevacizumab can be used interchangeably,[145] and that both of these combination regimens, as well as FOLFIRI plus bevacizumab, represent appropriate standard practices for the initial treatment of metastatic colorectal cancer. The infusional 5-FU/LV plus bevacizumab regimen is recommended as initial therapy for patients not able to tolerate oxaliplatin or irinotecan since it has been shown to be associated with lower toxicity.[151-154]

Pooled results from several randomized phase II studies have demonstrated that addition of bevacizumab to first-line 5-FU/LV regimens improved overall survival in patients with metastatic colorectal cancer when compared to survival results for patients receiving these regimens without bevacizumab.[152, 155] A combined analysis of the results of several of these trials showed that addition of bevacizumab to 5-FU/LV-containing regimens was associated with a median survival of 17.9 months versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab.[155] 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.[154] In that pivotal trial a markedly longer survival time was observed with the use of bevacizumab: 20.3 months versus 15.6 months (hazard ratio for death = 0.66; P<0.001). Results from a recent head-to-head randomized, double-blind, placebo-controlled phase III study (N016966) comparing CapeOX (capecitabine dose 1000 mg/m2 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 neither regimen is inferior with respect to the other in terms of toxicity or efficacy endpoints when used in the initial treatment of metastatic colorectal cancer.[145,156,] In this trial, addition of bevacizumab to oxaliplatin-based regimens was associated with an increase in progression-free survival (PFS)

compared to these regimens without bevacizumab (hazard ratio=0.83; 97.5% CI, 0.72-0.95; P=0.0023). However, the significant incremental benefit observed with addition of bevacizumab was more modest than seen in some earlier trials, and it has been suggested that differences observed in cross-study comparisons of NO16966 with other trials might be related to differences in the discontinuation rates and durations of treatment between trials,[157] although such hypotheses are only conjectural. Furthermore, in this 1400 patient randomized study, absolutely no difference in response rates was seen with and without bevacizumab (see below), and this finding would not be potentially influenced by the early withdrawal rates, which occurred after the responses would have occurred. Results of subset analyses evaluating the benefit of adding bevacizumab to either FOLFOX or CapeOX indicated that bevacizumab was associated with improvements in PFS when added to CapeOX but not FOLFOX, although the PFS curves observed for patients receiving either CapeOX plus bevacizumab or FOLFOX plus bevacizumab were nearly identical.[158] An analysis of the ITT population demonstrated no statistically significant increase in median overall survival for patients in the bevacizumab-containing arm of the N016966 trial (21.3 vs. 19 months) (hazard ratio=0.89; 97.5% CI, 0.76-1.03; P=0.0769).[156] 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.[159, 160] Although this trial was closed early and did not meet projected enrollment, a significant increase in PFS was observed for patients receiving first-line FOLFIRI (7.6 months) when compared to PFS results for patients receiving either a modified IFL regimen (5.9 months; P=0.004) or CapeIRI (5.8 months; P=0.015) at a median follow-up of 22.6 months, although 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 significant (P=0.28). However, at a median follow-up of 34.4 months, overall survival was significantly higher for patients receiving FOLFIRI plus bevacizumab (28.0 months) compared with modified IFL plus bevacizumab (19.2 months; P=0.037).[160] Evidence for the comparable efficacy for FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI as initial therapy and were then switched to the other regimen at the time of disease progression.[140] Similar response rates and PFS times were obtained when these 2 regimens were used as first-line therapy. Further support for this conclusion has come from results of a phase III trial comparing the efficacy and toxicity of FOLFOX4 and FOLFIRI regimens in previously untreated patients with metastatic colorectal cancer.[144] No differences were observed in response rate, PFS times, and overall survival in the 2 treatment arms. The results of an ongoing phase III study evaluating the effectiveness of FOLFIRI in combination with bevacizumab in the initial treatment of patients with metastatic disease have not yet been reported.[161]

Convincing, albeit indirect, support for inclusion of bevacizumab in combination with chemotherapeutic agents in the initial treatment of advanced or metastatic colon cancer comes from results of the randomized phase III study E3200, conducted by Eastern Cooperative Oncology Group (ECOG), which demonstrated that bevacizumab in combination with FOLFOX4 improved survival in bevacizumab-naïve patients with previously-treated advanced colorectal cancer. Median overall survival was 12.9 months for patients receiving FOLFOX4 plus bevacizumab compared to 10.8 months for patients receiving FOLFOX4 alone (P=0.0011).[162] Use of single agent bevacizumab is not recommended since it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX plus bevacizumab treatment arms.[162] 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.[106] In addition, use of bevacizumab may interfere with wound healing[105,106,153] (see Principles of Management of Metastatic Disease), and gastrointestinal perforation is a relatively rare, but important, side effect of bevacizumab therapy in patients with colorectal cancer.[105, 153] 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[163]; 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 risk for gastrointestinal perforation.

With respect to the toxicities associated with capecitabine use, the panel noted that patients with diminished creatinine clearance may accumulate levels of the drug,[164] that the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV[153,164] and that North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.[165] Such toxicities may necessitate modifications in the dosing of capecitabine,[153,164,166] and patients on capecitabine should be monitored closely so that dose adjustments can be made at the earliest signs of certain side effects such as hand-foot syndrome. It is currently not known whether the efficacy of CapeOX plus bevacizumab and FOLFOX plus bevacizumab remain comparable when capecitabine doses are lower than the 1000 mg/m2 twice daily dose used in the study of Saltz et al.[156]

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[167,168] 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 decreased dose in patients with Gilbert's disease or elevated serum bilirubin.[169] 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,[168,170] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[170] 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,[169] and a new warning has been added to the label for Camptosar which indicates that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.[167] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[170] although guidelines for the use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on a patient who has experienced irinotecan toxicity is not recommended since that patient will require a dose reduction regardless of the UGT1A1 test result. Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[171] 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.[172] 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).[173] 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=0.0549).

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 (irinotecan, bolus 5-FU/LV) regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial[159] and inferior to FOLFOX in the Intergroup trial[122]) at any point in the therapy continuum and it has been removed from the guidelines. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,[129,148] or capecitabine should be used.[126]

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[148] with or without cetuximab, and irinotecan in combination with cetuximab[132] or as a single agent,[124] for patients who had received a FOLFOX or CapeOX-based regimen for initial therapy. FOLFOX or CapeOX alone is an option for patients who received a FOLFIRI-based regimen as initial treatment. The recommendations regarding use of CapeOX in lieu of FOLFOX after first progression are supported by the results of studies demonstrating comparable efficacy of these 2 agents in initial therapy.[145] Other options for patients initially treated with a FOLFIRI-based regimen include cetuximab plus irinotecan, or single agent cetuximab or panitumumab for those not able to tolerate 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.

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.[140] A combined analysis of data from 7 recent phase III clinical trials in advanced colorectal cancer provided support for a correlation between an increase in median survival and administration of all of the 3 cytotoxic agents (ie, 5-FU/LV, oxaliplatin, and irinotecan) at some point in the continuum of care.[174] Furthermore, overall survival was not found to be associated with the order in which these drugs were received. Single agent irinotecan administered after first progression has been shown to significantly improve overall survival relative to best supportive care[175] or infusional 5-FU/LV.[176] In the study of Rougier et al.,[176] median overall survival was 4.2 months for irinotecan versus 2.9 months for 5-FU (P=0.030) whereas Cunningham et al.[175] reported a surivival rate at 1 year of

36.2% in the group receiving irinotecan versus 13.8% in the supportive-care group (P-0.001). Furthermore, no significant differences in overall survival were observed in the Intergroup N9841 trial when FOLFOX was compared to irinotecan monotherapy following first progression of metastatic colorectal cancer.[177] 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.

A sizable body of literature has demonstrated that the status of the KRAS gene in the tumor is highly predictive of outcome with anti-EGFR therapies.[178-187] Tumors that have a mutation in codon 12 or codon 13 of the KRAS gene are essentially insensitive to EGFR inhibitors such as cetuximab or panitumumab. The panel therefore strongly recommends KRAS genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer. Patients with known codon 12 or 13 KRAS mutations should *not* be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, as there is virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is to be emphasized that KRAS mutations are early events in colorectal cancer formation, and there is a tight correlation between mutation status in the primary and the metastases.[188] For this reason, KRAS genotyping can be done on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of KRAS genotyping if an archived specimen from either the primary tumor or a metastasis is available.

Cetuximab has been studied as both a single agent[132,189] and in combination with irinotecan[132,190] in the treatment of metastatic colorectal cancer. A partial response rate of 9% was observed when single agent cetuximab was administered in an open-label phase II trial to 57 patients with colorectal cancer refractory to prior irinotecan-containing therapy.[189] More recently, cetuximab monotherapy was reported to significantly increase both PFS (hazard ratio=0.68; 95% CI, 0.57-0.80; P<0.001) and overall survival (hazard ratio=0.77; 95% CI, 0.64-0.92; P=0.005) for patients with refractory metastatic colorectal cancer when compared with best supportive care alone.[191] Results from a direct comparison of cetuximab monotherapy and the combination regimen of cetuximab and irinotecan in patients who had progressed following initial therapy with an irinotecan-based regimen indicated that response rates were doubled in the group receiving the combination of cetuximab plus irinotecan when compared with patients receiving cetuximab monotherapy (22.9% versus 10.8% [P-0.007]).[132] Results of a large phase III study of similar design did not demonstrate a difference in overall survival between the 2 treatment arms but also showed significant improvement in response rate, and in median PFS, with the combination of irinotecan and cetuximab compared with irinotecan alone. Toxicity was higher in the cetuximab-containing arm.[192] 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[131]; respective response rates of 10% versus 0% (P<0.0001) for panitumumab plus best supportive care versus best supportive care alone were observed, as well as a significant increase in PFS with panitumumab (hazard ratio=0.54; 95% CI, 0.44-0.66). Results of the PACCE trial showed decreased PFS and increased toxicity of chemotherapy/bevacizumab/panitumumab over

chemotherapy/bevacizumab.[193] 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.[194,195] 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 following progression for patients refractory to irinotecan-based chemotherapy since it has shown activity in this setting.[132] Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[194, 195] Based on case reports, for those patients experiencing severe infusion reactions to cetuximab, administration of panitumumab appears to be feasible.[196,197] 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.[191,198,199]

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.[132] A similar conclusion was drawn with respect to panitumumab.[200] Therefore, routine EGFR testing is not recommended, and no patient should be either considered for or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.

With respect to the treatment continuum for metastatic colorectal cancer, there are no data to support the addition of bevacizumab to a regimen following clinical failure of a previous bevacizumab-containing regimen.[162] Therefore, routine use of cetuximab plus bevacizumab in patients who have experienced clinical failure on a bevacizumab-containing regimen is not recommended.

A recent study of 6,286 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 performance status=2 or ≤ 1 as compared with control groups, although the risks of certain gastrointestinal toxicities were significantly increased for patients with performance status=2.[201] For patients with impaired tolerance to aggressive initial therapy, the guideline includes recommendations for single-agent capecitabine,[126,127] or infusional 5-FU/leucovorin,[128,129] with or without bevacizumab (category 2B for combination with bevacizumab). Although a comparison of capecitabine plus bevacizumab versus capecitabine alone as initial therapy for metastatic cancer has not been done, CapeOX plus bevacizumab has been shown to be superior to CapeOX alone in this setting.[145,153,156,158] 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 (see COL-C). 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 (see COL-C). 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.[202]

Post-Treatment Surveillance

Following curative-intent surgery, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and to identify new metachronous neoplasms at a preinvasive stage. Advantages of more intensive follow-up of Stage II and/or Stage III patients have been demonstrated prospectively in several studies[203-205] and in three recent meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[206-209] Other recent studies impacting on the issue of post-treatment surveillance of colorectal cancer include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials which demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor,[58] and a population-based report indicating increased rates of resectability and survival in patients treated for local recurrence and distant metastases of colorectal cancer, thereby providing support for more intensive post-treatment follow-up in these patients.[210] Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.[211,212]

The following panel recommendations for post-treatment surveillance pertain to patients with Stage I-Stage III disease who have undergone successful treatment (i.e. no known residual disease): history and physical examination every 3-6 months for 2 years, and then every 6 months for a total of 5 years; a carcinoembryonic antigen (CEA) test at baseline and every 3-6 months for 2 years,[213] then every 6 months for the next 5 years if the clinician determines that the patient is a potential candidate for aggressive curative surgery[209,213,214]. Colonoscopy is recommended at approximately 1 year following resection (or at 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. [215] More frequent colonoscopies may be indicated in patients who present with colon cancer before age 50. Chest, abdominal and pelvic CT scan are recommended annually for the first 3 to 5 years in Stage II and III patients [209,212]; 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 a diagnosis of Stage I disease may not need to be seen as frequently (i.e. can be seen once every 6 months). This principle also applies to CEA testing, which is used primarily to monitor for indication of recurrence of disease (see section on Managing an Increasing CEA Level, below), although post-treatment CEA testing is recommended only if the patient is a potential candidate for further intervention.[213] Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps.[215] since data show that patients with a history of colorectal cancer have an increased risk of developing second cancers,[216] particularly in the first 2 years following resection.[215] 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.[215] The recommended frequency of post-treatment surveillance colonoscopies is higher (ie, annually) for patients with HNPCC.[215] CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver.[209] Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases.[209,212] Post-treatment PET scan is not routinely recommended for surveillance of patients with resected early-stage colorectal cancer.[212] Furthermore, PET scan is not routinely recommended to detect metastatic disease in the absence of other evidence of such disease.

Panel recommendations for surveillance of patients with Stage IV NED disease following curative-intent surgery and subsequent adjuvant treatment are similar to those listed for patients with early-stage disease with one exception being that certain evaluations are performed more frequently. Specifically, the panel recommends that these patients undergo CT scan of the chest, abdomen, and pelvis every 3-6 months in the first 2 years following adjuvant treatment and then every 6-12 months for up to a total of 5-7 years, and CEA testing is recommended every 3 months for the first 2 years and then every 6 months in the following 3-5 years.

Managing an Increasing Carcinoembryonic Antigen Level

Managing patients with an elevated CEA level after resection should include colonoscopy, chest, abdominal, and pelvic CT scans, and physical examination (COL-9). If imaging study results are normal in the face of a rising CEA, repeat scans are indicated 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 (ie, 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.[217] 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.[218] The panel does not recommend the use of anti-CEA-radiolabeled scintigraphy.[219] In the event that surgically curable metastatic disease is identified on CT or MRI, the panel does recommend that a PET scan should be obtained before surgical resection to look for evidence of additional metastases that may change the status of patient resectability.

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 three treatment options). A patient with metastatic disease in the liver or lung should be considered for surgical resection if he or she is a candidate for surgery and if complete resection (R0) or ablation can be achieved. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease or when a response to chemotherapy may convert a patient from an unresectable to a resectable state (ie, 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, as well as periodic chest, abdominal and pelvic CT scans, and colonoscopic evaluations. Recommendations for patients with previously untreated disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, including plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy for advanced or metastatic disease includes bevacizumab plus FOLFOX, FOLFIRI, CapeOX or 5-FU/LV. Chemotherapy options for patients with progressive disease are dependent on the choice of initial therapy and, for those able to tolerate intensive therapy, include FOLFIRI, CapeOX, FOLFOX and irinotecan alone or the combination of cetuximab with either irinotecan or FOLFIRI. Monotherapy with either cetuximab or panitumumab is also an option for patients not able to tolerate the combination of irinotecan plus cetuximab after first or second progression of disease. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

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