National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Colon Cancer

Version 2.2011

NCCN.org

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NCCN Guidelines™ Version 2.2011 Panel Members
Colon Cancer

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Discussion

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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

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NCCN Guidelines™ Version 2.2011 Updates Colon Cancer

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Summary changes in the 2.2011 version of the Colon Guidelines from the 1.2011 version include:

The previous footnote related to BRAF was removed and the following footnotes were added to the metastatic section of the Guidelines based on recent presentations:

- **Footnote in the first-line setting: Patients with a V600E BRAF mutation appear to have a poorer prognosis. Retrospective subset analyses suggest potential benefit from anti-EGFR monoclonal antibodies in the first-line setting with active chemotherapy regardless of V600E mutation status. Applies to pages COL-6, COL-7, COL-C 1 of 6 through COL-C 3 of 6.**
- **Footnote after progression on first-line therapy: Patients with a V600E BRAF mutation appear to have a poorer prognosis. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after patient has progressed on first-line therapy. Applies to pages COL-11, COL-C 1 of 6, COL-C 3 of 6.**
- **Information updated in the Principles of Pathologic Review with references on page COL-A 4 of 5.**

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NCCN Guidelines™ Version 2.2011 Updates
Colon Cancer

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Summary changes in the 1.2011 version of the Colon Guidelines from the 3.2010 version include:

COL-1
- Footnote "a" is new to the page: "Small bowel and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to the NCCN Colon Cancer Guidelines."

COL-2
- Resectable, obstructing: "unprepped" removed.

COL-3
- Perineural invasion added as a high risk factor for systemic recurrence.

COL-4
- The term "preferred" added to FOLFOX in the adjuvant setting.
- A category 1 designation added to the FLOX regimen in the adjuvant setting.
- The combination regimen of capecitabine and oxaliplatin added as an option in the adjuvant setting with a category 2A designation.

COL-10
- Patients with resectable metachronous metastases that have a response after neoadjuvant chemotherapy and resection, the recommendation changed from "Repeat initial chemotherapy" to "Repeat neoadjuvant therapy or FOLFOX."

COL-A 2 of 5
- The following parameters were added for reporting of pathologic stage: lymphovascular invasion, perineural invastion, extra nodal tumor deposits.
- Descriptions were added to the following new sections: Radial (circumferential) margin evaluation, Perineural invasion, Extra Nodal Tumor Deposits.

COL-B 1 of 3
- Bullet deleted correlating lymph node ratio to survival.

COL-B 2 of 3

Liver
- Bullet noting that hepatic resection is the treatment of choice moved to the first bullet.
- Bullet 7 - "intra-arterial embolization" changed to "arterially-directed embolic therapy."

COL-B 2 of 3

Lung
- Bullet 7 - "Conformal external beam RT may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable (category 3)." added to principles.

COL-C 1 of 6
- Capecitabine added as an option with bevacizumab for patients appropriate for intensive therapy. This combination was previously included only for patients not appropriate for intensive therapy.
- The combination of irinotecan + oxaliplatin (IROX) added as a treatment option for patients appropriate for intensive therapy.

COL-C 3 of 6
- Footnote 3 - The following sentence was added: "There are insufficient data to support the routine use of Ca/Mg infusion to prevent oxaliplatin-related neurotoxicity."

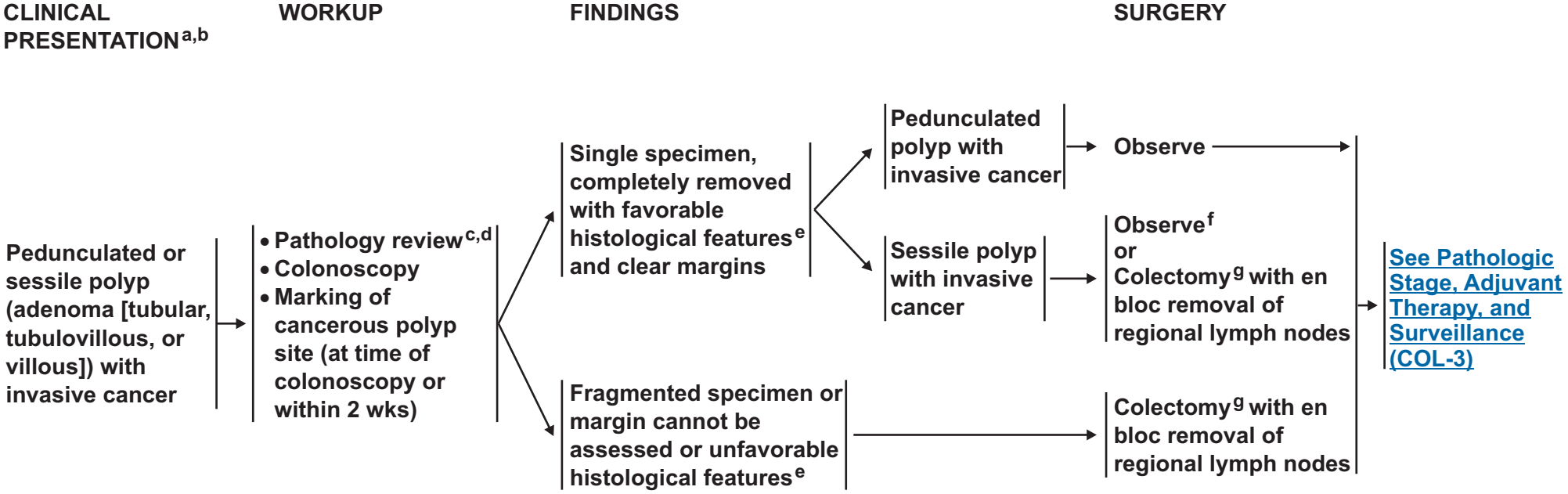
COL-C 5 of 6
- IROX dosing regimen included with reference.

COL-E 2 of 2
- CapeOX dosing regimen included with reference.

COL-F
- Bullet 3 - the statement was clarified that conformal RT should be routinely used *in T4 non-metastatic disease*.
- Bullet 5 - "intra-arterial embolization" changed to "arterially-directed embolic therapy."
- Bullet 6 - "In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3D conformal radiotherapy, IMRT or stereotactic body radiosurgery (SBRT) (category 3)" added to principles.

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[a] Small bowel and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to the NCCN Colon Cancer Guidelines.

[b] 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.

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

[d] 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.

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

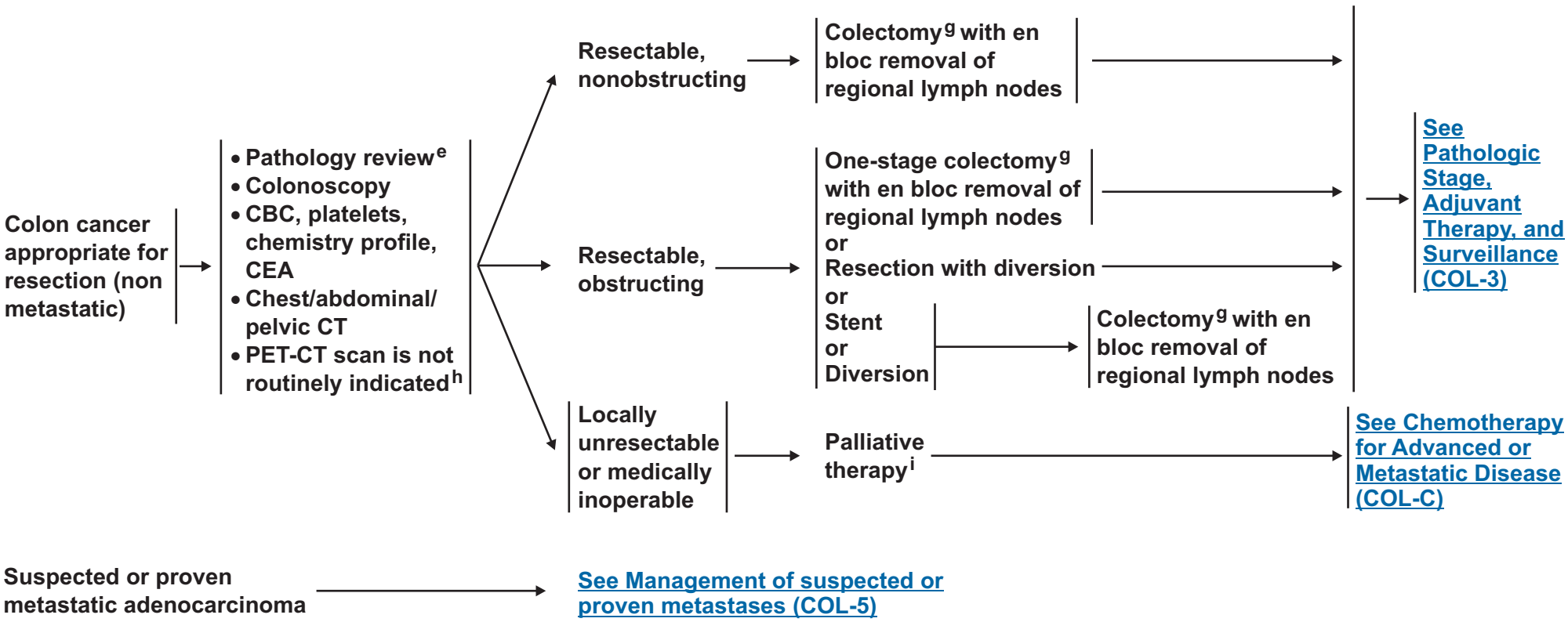
[f] Observation may be considered, with the understanding that there is an added 10-15% risk of lymph node metastases. Nivatvongs S, Rojanasakul A, Reiman HM, et al. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. Dis Colon Rectum 1991;34(4):323-8.

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

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

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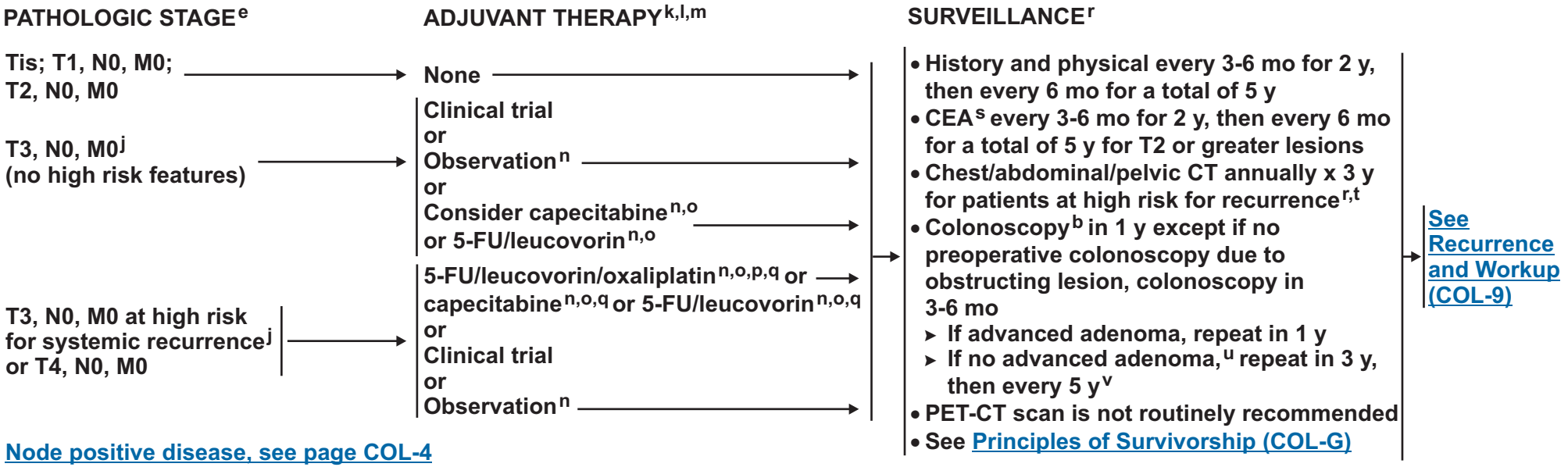


[a] Small bowel and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to the NCCN Colon Cancer Guidelines.
[b] All patients with colon cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP, see the NCCN Colorectal Cancer Screening Guidelines.
[e] See Principles of Pathologic Review (COL-A) - Colon cancer appropriate for resection, pathological stage, and lymph node evaluation.
[g] See Principles of Surgery (COL-B 1 of 3).
[h] PET-CT does not supplant a contrast-enhanced diagnostic CT scan.
[i] Palliative therapy may include RT for uncontrolled bleeding, stent for obstruction, supportive care.

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Node positive disease, see page COL-4

[b] 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.

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

[j] High risk factors for recurrence: grade 3-4, lymphatic/vascular invasion, bowel obstruction, < 12 lymph nodes examined, perineural invasion, localized perforation or close, indeterminate or positive margins.

[k] There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.

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

[m] Testing for mismatch repair proteins (MMR) should be considered for all patients < 50 years of age. Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. Sargent DJ, Marsoni S, Thibodeau SN, et al. Confirmation of deficient mismatch repair (dMMR) as a predictive marker for lack of benefit from 5-FU based chemotherapy in stage II and III colon Cancer (CC): A pooled molecular reanalysis of randomized chemotherapy trials. J Clin Oncol 2008;26(May 20 suppl;abstr 4008).

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

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

[p] 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.

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

[r] 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.

[s] If patient is a potential candidate for further intervention.

[t] CT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor, or poorly differentiated tumors).

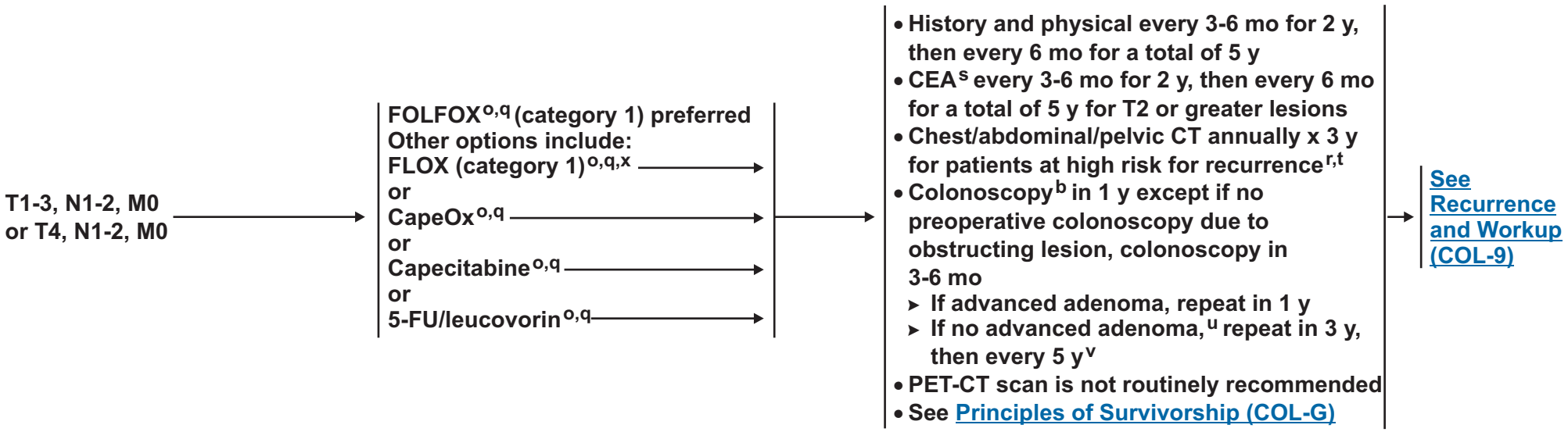
[u] Villous polyp, polyp > 1 cm, or high grade dysplasia.

[v] 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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[b] 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.

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

[k] There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.

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

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

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

[r] 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.

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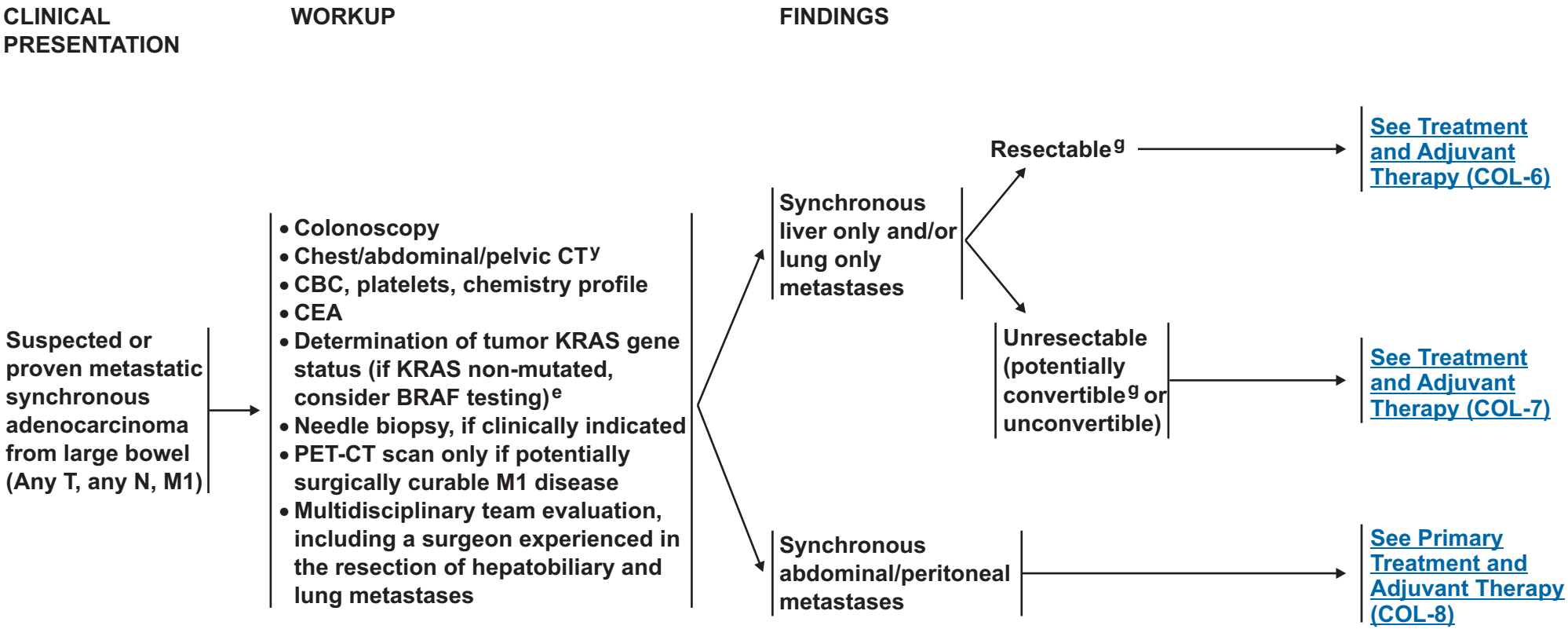
[w] Testing for mismatch repair proteins (MMR) should be considered for all patients < 50 years of age.

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

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[e] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.
[g] See Principles of Surgery (COL-B 2 of 3).
[y] CT should be with IV contrast. Consider MRI with IV contrast if CT is inadequate.

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TREATMENT
Resectable[g] synchronous liver and/or lung metastases only

ADJUVANT THERAPY[w] (resected metastatic disease) (6 MO PERIOPERATIVE TREATMENT PREFERRED)

SURVEILLANCE

Colectomy, with synchronous or staged liver or lung resection
→ **Active chemotherapy regimen for advanced disease (See COL-C)[cc,dd] (category 2B)**

or

Neoadjuvant therapy (for 2-3 months) FOLFIRI or FOLFOX or CapeOx[aa] ± bevacizumab[bb] or FOLFIRI or FOLFOX ± cetuximab or panitumumab (KRAS wild-type [WT] gene only)[e,z] followed by synchronous or staged colectomy and resection of metastatic disease
→ **Consider observation or shortened course of chemotherapy**

or

Colectomy, followed by chemotherapy (for 2-3 months) FOLFIRI or FOLFOX or CapeOX[aa] ± bevacizumab[bb] or FOLFIRI or FOLFOX ± cetuximab or panitumumab (KRAS WT gene only)[e,z] and staged resection of metastatic disease
→ **Consider observation or shortened course of chemotherapy**

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

→ **Recurrence (See COL-9)**

[b] 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.

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

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

[u] Villous polyp, polyp > 1 cm, or high grade dysplasia.

[v] 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.

[w] Testing for mismatch repair proteins (MMR) should be considered for all patients < 50 years of age.

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

[aa] 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.

[bb] 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.

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

[dd] FOLFOXIRI is not recommended in this setting.

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TREATMENT
Unresectable[g] synchronous liver and/or lung metastases only

- **Systemic therapy (FOLFIRI or FOLFOX or CapeOX[aa] ± bevacizumab[bb] or FOLFIRI or FOLFOX ± cetuximab or panitumumab (KRAS WT gene only)[e,z] or FOLFOXIRI [category 2B])**
- **Consider colon resection[g] only if imminent risk of obstruction or significant bleeding**

→ **Re-evaluate for conversion to resectable[g] every 2 mo if conversion to resectability is a reasonable goal**

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

→ **Active chemotherapy regimen for advanced disease (See COL-C)[cc] (category 2B) or If patient received neoadjuvant therapy, consider observation or shortened course of chemotherapy**

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

ADJUVANT THERAPY[w] (6 MO PERIOPERATIVE TREATMENT PREFERRED)

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[b] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo**
  - **If advanced adenoma, repeat in 1 y**
  - **If no advanced adenoma,[u] repeat in 3 y, then every 5 y[v]**

[b] 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.

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

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

[u] Villous polyp, polyp > 1 cm, or high grade dysplasia.

[v] 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.

[w] Testing for mismatch repair proteins (MMR) should be considered for all patients < 50 years of age.

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

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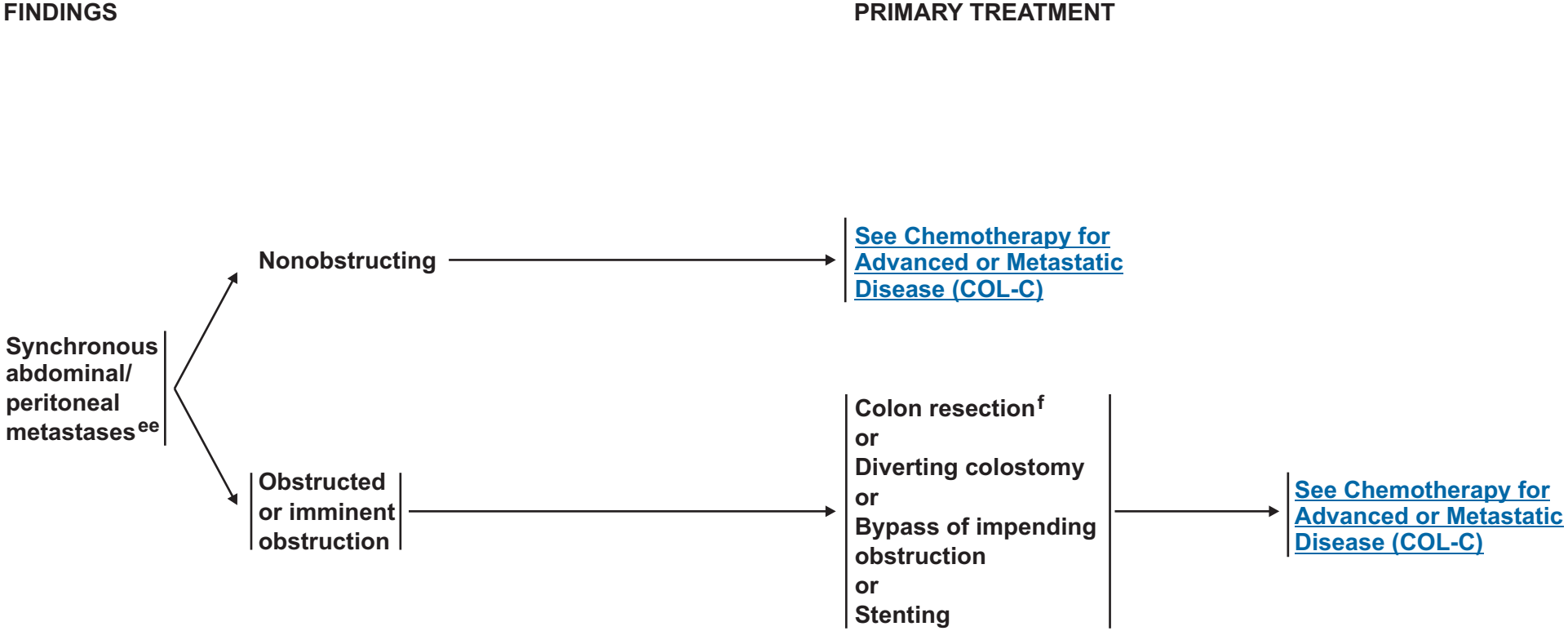
[cc] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

See Recurrence (COL-9)

Note: All recommendations are category 2A unless otherwise indicated.
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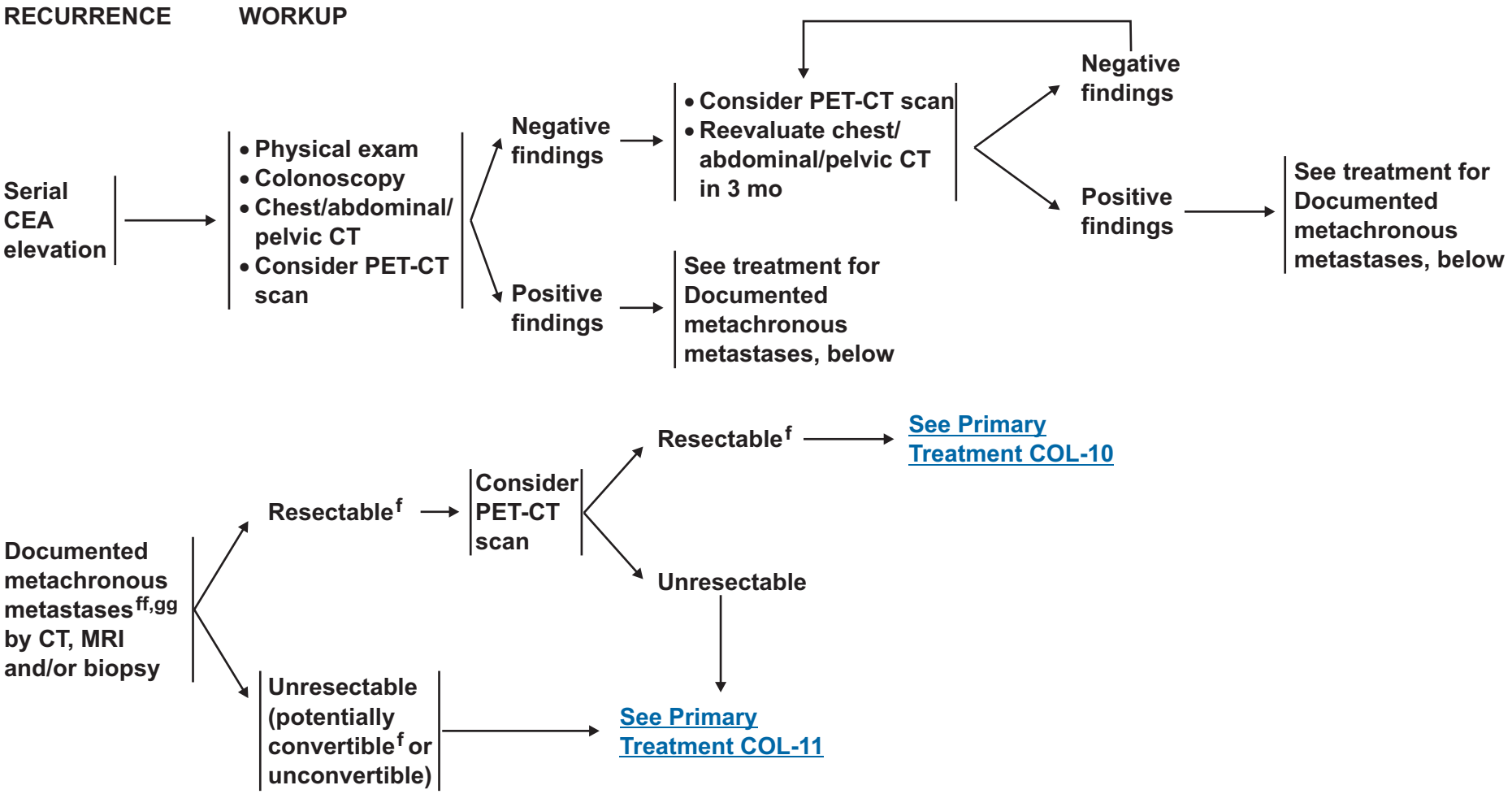
[f] See Principles of Surgery (COL-B 2 of 3).

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

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

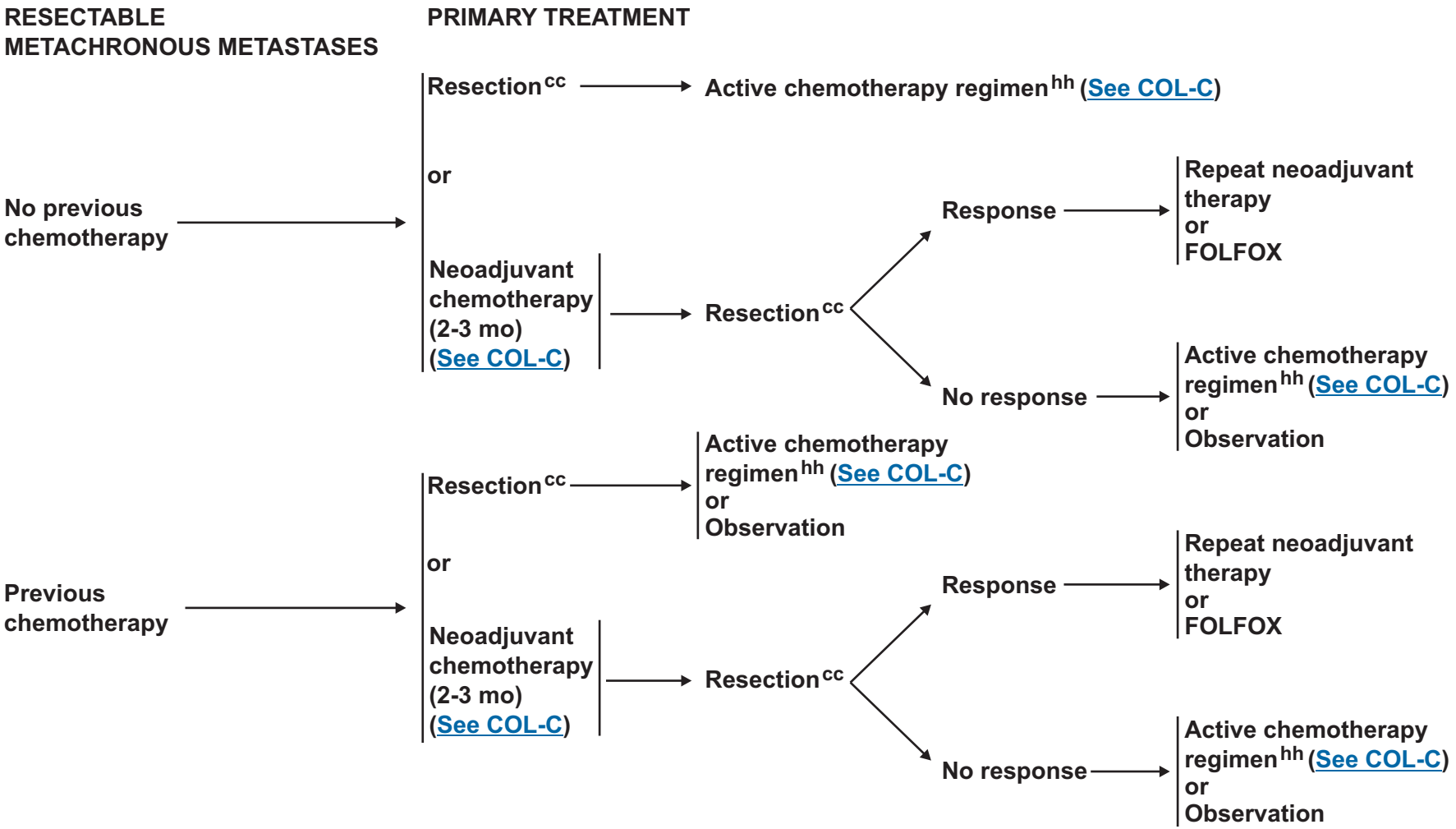
[ff] Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (COL-A 4 of 5) - KRAS and BRAF Mutation Testing.

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

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

[hh] Perioperative therapy should be considered for a up to a total of 6 months.

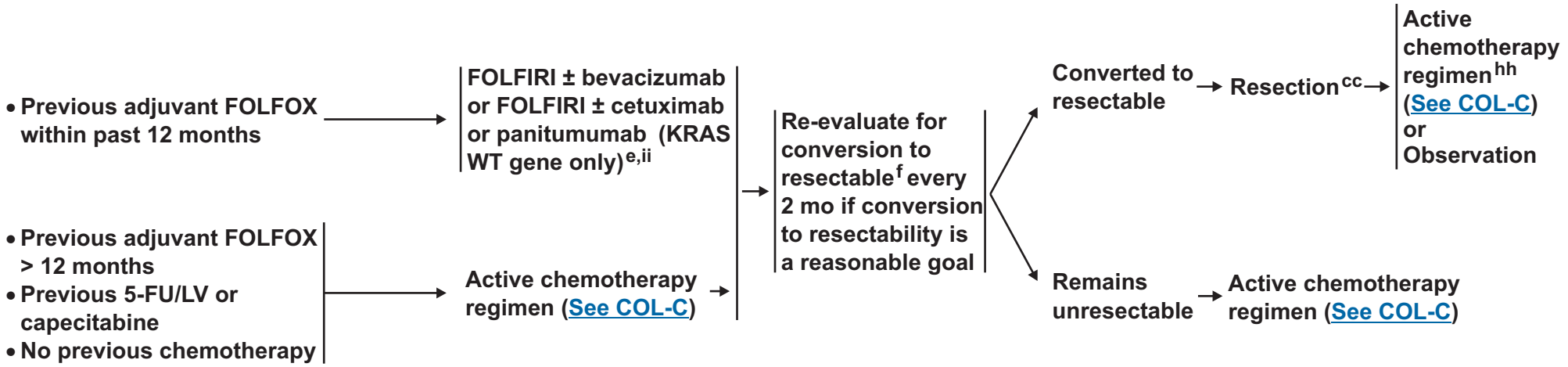
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UNRESECTABLE METACHRONOUS METASTASES

PRIMARY TREATMENT



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

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

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

[hh] Perioperative therapy should be considered for a up to a total of 6 months.

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

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 5)

Endoscopically removed malignant polyps

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

Colon cancer appropriate for resection

- Histological confirmation of primary colonic malignant neoplasm.

Pathological stage

- The following parameters should be reported.
  - Grade of the cancer
  - Depth of penetration, (T)
  - Number of lymph nodes evaluated and number positive (N)
  - Status of proximal, distal, and radial margins[8-9] See Staging (ST-1)
  - Lymphovascular invasion[10,11]
  - Perineural invasion[12-14]
  - Extra Nodal tumor deposits[15-18]

See Malignant polyp and colon cancer appropriate for resection on page 1 of 5 COL-A
See Pathological stage (continued) on page 2 of 5 COL-A
See Lymph node evaluation on page 3 of 5 COL-A
See KRAS and BRAF Mutation Testing page 4 of 5 COL-A
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PRINCIPLES OF PATHOLOGIC REVIEW (2 of 5)

Pathological stage (continued)

- **Radial (circumferential) margin evaluation - The serosal surface (peritoneal) does not constitute a surgical margin. In colon cancer the circumferential (radial) margin represents the adventitial soft tissue closest to the deepest penetration of tumor and is created surgically by blunt or sharp dissection of the retroperitoneal aspect. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. The circumferential resection margin corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells and must be dissected from the retroperioteum to remove the viscus. On pathological examination it is difficult to appreciate the demarcation between peritonealized surface and non-peritonealized surface. Therefore the surgeon is encouraged to mark the area of non-peritonealized surface with a clip or suture. The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by peritoneum.[10-11]**
- **Perineural invasion (PNI) - The presence of perineural invasion is associated with a significantly worse prognosis. In multivariate analysis, PNI has been shown to be an independent prognostic factor for cancer specific and overall disease-free survival. For stage II carcinoma, those with PNI have a significantly worse 5 year disease-free survival compared to those without PNI 29% vs 82% (p=0.0005).[12-14]**
- **Extra nodal tumor deposits - Irregular discrete tumor deposits in pericolic or perirectal fat from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered peritumoral deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular or, more rarely, perineural invasion. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report.**
  In the 7th AJCC staging manual, extra nodal deposits are staged as pN1c. In stage II colon cancer, the presence of extranodal tumor deposits significantly worsens the 5 year disease-free survival 80% vs 50-60% (p<0.01). This poorer outcome has also been noted in patients with stage III carcinoma.[15-18]

See Malignant polyp and colon cancer appropriate for resection on page 1 of 5 COL-A
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See KRAS and BRAF Mutation Testing page 4 of 5 COL-A
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PRINCIPLES OF PATHOLOGIC REVIEW (3 of 5)

Lymph node evaluation

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

Sentinel lymph node and detection of micrometastasis by immunohistochemistry

- Examination of the sentinel lymph node allows an intense histological and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple H & E sections and/or immunohistochemistry (IHC) to detect cytokeratin positive cells.[30-34] The significance of detection of single cells by IHC alone is controversial. The 7th edition of the AJCC Cancer Staging[35] manual considers "tumor clusters" < 0.2 mm as isolated tumor cells (pN0) and not metastatic carcinoma. However, some investigators believe that size should not affect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.[36]
- Some studies have shown that the detection of IHC cytokeratin positive cells in stage II (N0) colon cancer (defined by H & E) has a worse prognosis while others have failed to show this survival difference. In these studies, isolated tumor cells were considered micrometastasis.[38-42]
- At the present time the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and results used with caution in clinical management decisions.[30-34,38-42]

See Malignant polyp and colon cancer appropriate for resection on page 1 of 5 COL-A
See Pathological stage on page 1 of 5 COL-A
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PRINCIPLES OF PATHOLOGIC REVIEW (4 of 5)

KRAS Mutation Testing

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

BRAF Mutation Testing

- Patients with a V600E BRAF mutation appear to have a poorer prognosis. Retrospective subset analyses suggest potential benefit from anti-EGFR monoclonal antibodies in the first-line setting with active chemotherapy regardless of V600E mutation status. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after patient has progressed on first-line therapy.[46,47]
- Testing for the BRAF V600E mutation can be performed on formalin fixed paraffin embedded tissues. This is usually performed by PCR amplification and direct DNA sequence analysis. This testing should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) and qualified to perform highly complex clinical laboratory (molecular pathology) testing.

See Malignant polyp and colon cancer appropriate for resection on page 1 of 5 COL-A
See Pathological stage on page 1 of 5 COL-A
See Lymph node evaluation on page 3 of 5 COL-A
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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 establish N stage.[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 locally advanced 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

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

Lung

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

Evaluation for conversion to resectable disease

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

See footnotes on page 3 of 3 COL-B

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PRINCIPLES OF SURGERY - REFERENCES (3 of 3)

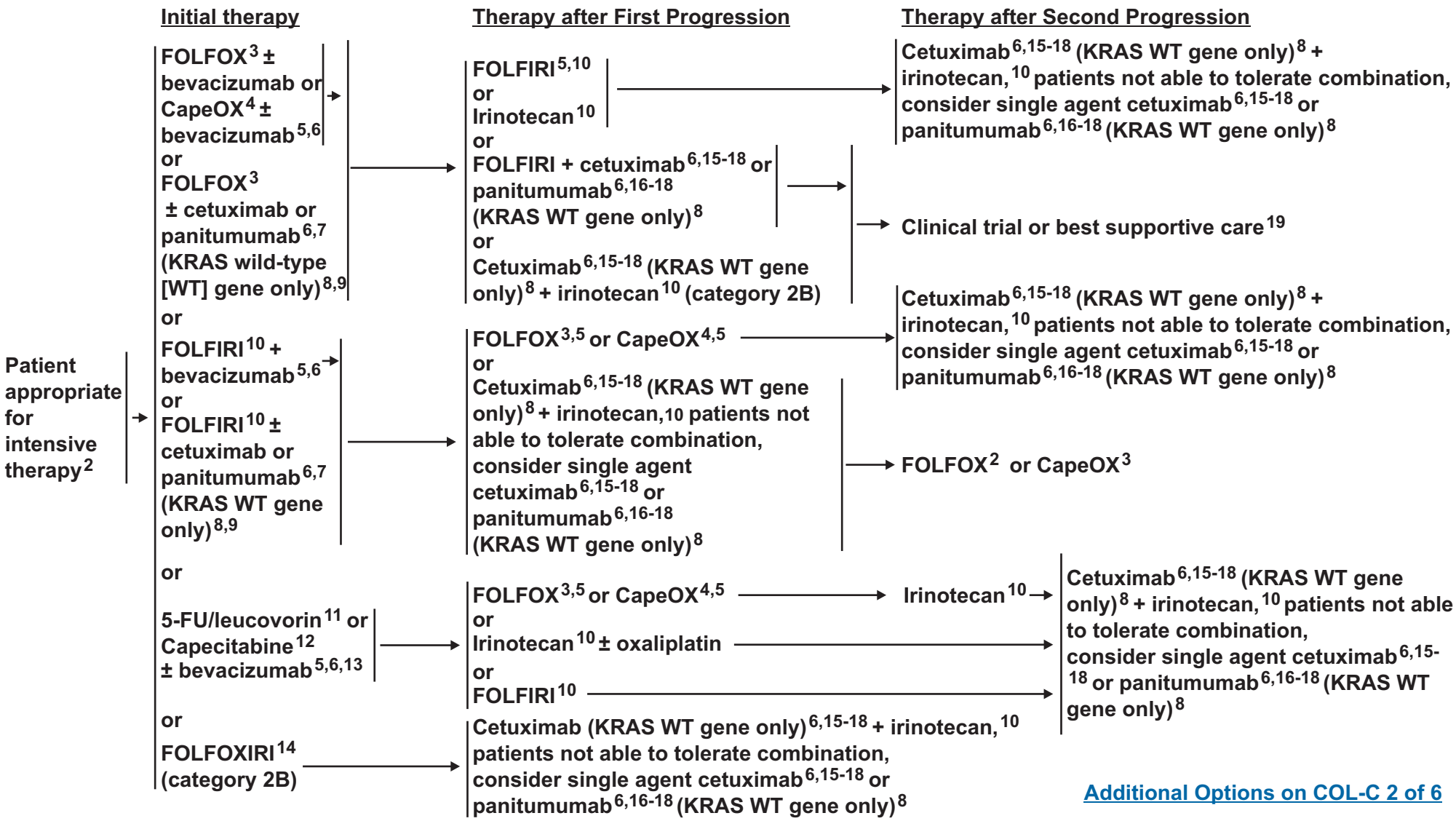
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CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 6)



Additional Options on COL-C 2 of 6

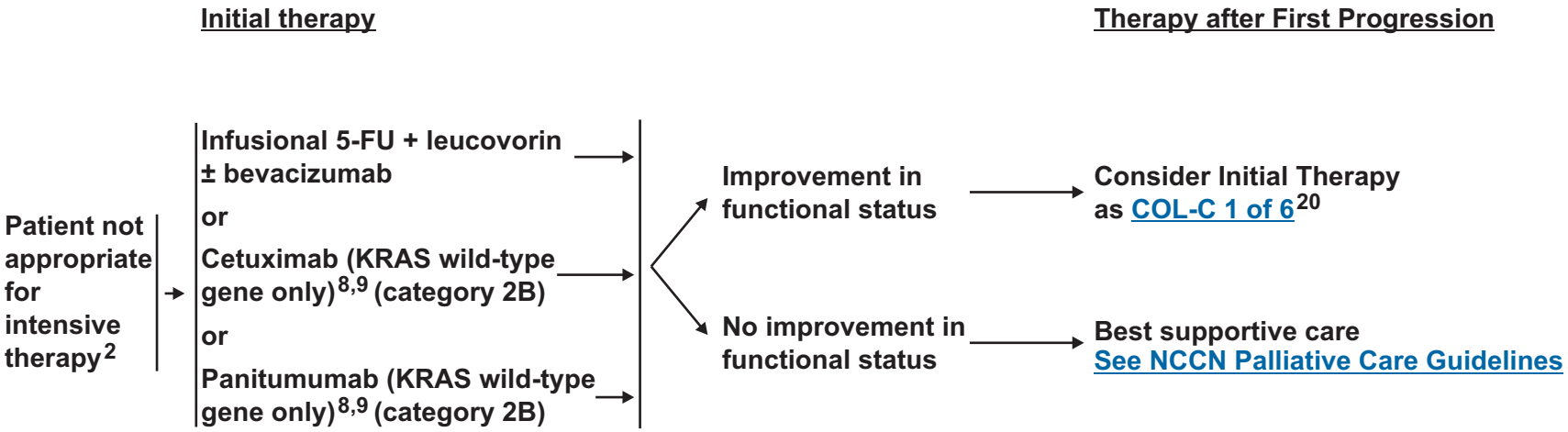
See footnotes on page COL-C 3 of 6

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



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

[3] Discontinuation of oxaliplatin should be strongly considered from FOLFOX or CapeOX after 3-4 months of therapy (or sooner if significant neurotoxicity develops ≥ grade 2) with other drugs maintained (fluoropyrimidine + bevacizumab) until time of tumor progression. Oxaliplatin may be reintroduced if it was discontinued previously for neurotoxicity rather than disease progression. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer - A GERCOR Study. J Clin Oncol 2006;24:394-400. There are insufficient data to support the routine use of Ca/Mg infusion to prevent oxaliplatin-related neurotoxicity.

[4] The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1250 mg/m^2 twice daily for 14 days, repeated every 21 days, is standard. Some data suggest that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large scale randomized trials. For good performance status patients, the 1000 mg/m^2 twice daily dose is the recommended starting dose, with close monitoring in the first cycle for toxicity, and dose adjustments as indicated.

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

[6] Combination therapy involving cytotoxics, anti-EGFRs and anti-VEGFs is not recommended. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009;27:672-80. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360(6):563-572.

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

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

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

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

[11] Infusional 5-FU is preferred.

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

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

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

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

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

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

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

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

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

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

FOLFOX
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 [1]

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

FOLFIRI [3]
Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1
Leucovorin 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Repeat every 2 weeks

Bevacizumab + 5-FU containing regimens: [4-6]
Bevacizumab 5 mg/kg IV every 2 weeks +
5-FU and Leucovorin
or FOLFOX [7]
or FOLFIRI
Bevacizumab 7.5 mg/kg IV every 3 weeks + CapeOX [2]
Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes)

*While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m^2 is the equivalent of levoleucovorin 200 mg/m^2.
†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2 over 48 hours) to minimize medication errors.
‡The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m^2 twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large scale randomized trials.

See Additional Chemotherapy Regimens COL-C 5 of 6

See footnotes on page COL-C 6 of 6

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

Capecitabine[8]
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[9]
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

Simplified biweekly infusional 5-FU/LV (sLV5FU2)[3]
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 IV over 2 hours on day 1, 5-FU 500 mg/m^2 IV bolus injection 1h after the start of leucovorin. Repeat weekly.[10]
5-FU 2600 mg/m^2 by 24 h infusion plus leucovorin 500 mg/m^2
Repeat every week[11]

IROX[12]
Oxaliplatin 85 mg/m^2 IV over 2 hours, followed by irinotecan 200 mg/m^2 over 30 or 90 minutes every 3 weeks

FOLFOXIRI[13]
Irinotecan 165 mg/m^2 IV day 1, oxaliplatin 85 mg/m^2 day 1, leucovorin 400* mg/m^2 day 1, fluorouracil 3,200 mg/m^2 over 48 h continuous infusion starting on day 1
Repeat every 2 weeks

Irinotecan
Irinotecan 125 mg/m^2 IV over 30-90 minutes, days 1, 8
Repeat every 3 weeks[14,15]

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

Cetuximab (KRAS wild-type gene only) ± irinotecan[16]
Cetuximab 400 mg/m^2 1st infusion, then 250 mg/m^2 IV weekly
or
Cetuximab 500 mg/m^2 IV every 2 weeks[16]
±
Irinotecan 300-350 mg/m^2 IV every 3 weeks
or
Irinotecan 180 mg/m^2 IV every 2 weeks
or
Irinotecan 125 mg/m^2 on days 1, 8 and repeat every 3 weeks

Cetuximab (KRAS wild-type gene only)[17]
Cetuximab 400 mg/m^2 1st infusion, then 250 mg/m^2 IV weekly

Panitumumab[18] **(KRAS wild-type gene only)**
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

*While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m^2 is the equivalent of levoleucovorin 200 mg/m^2.
†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2 over 48 hours) to minimize medication errors.

See footnotes on page COL-C 6 of 6

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

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

[3]Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. Eur J Cancer 1999;35(9):1343-7.

[4]Kabbinavar FF, Hambleton J, Mass RD, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol. 2005;23:3706-3712.

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[6]Reidy DL, Chung KY, Timoney JP, et al. Bevacizumab 5 mg/kg can be infused safely over 10 minutes. J Clin Oncol 2007;25:2691-2695.

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[8]VanCutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19:4097-4106.

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[11]Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer:a multicentre randomised trial. The Lancet 2000;355:1041-47.

[12]Haller DG, Rothenberg ML, Wong AO, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single agent fluoropyrimidine therapy for metastatic colorectal carcinoma. J Clin Oncol 2008;26:4544-4550.

[13]Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest. J Clin Oncol 2007;25(13):1670-1676.

[14]Cunningham D, Pyrhonen S, James R, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. The Lancet 1998;352:1413-1418.

[15]Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 2003;21:807-814.

[16]Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.

[17]Van Custem E, Humblet H, Gelderblom J, et al. Cetuximab dose-escalation in patients with metastatic colorectal cancer with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): Pharmacokinetic and efficacy data of a randomized study. 2007 Gastrointestinal Cancers Symposium. Abstract 237.

[18]Van Custem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-1664.

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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.**
- **If considering fluoropyrimidine therapy only, MMR testing recommended. See NCCN Colorectal Screening Guidelines. Stage II MSI-H patients may have a good prognosis and do not benefit from 5FU adjuvant therapy. Sargent DJ, Marsoni S, Thibodeau SN, et al. Confirmation of deficient mismatch repair (dMMR) as a predictive marker for lack of benefit from 5-FU based chemotherapy in stage II and III colon Cancer (CC): A pooled reanalysis of randomized chemotherapy trials. J Clin Oncol 2008;26(May 20 suppl;abstr 4008).**

[1] Benson III AB, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;16:3408-3419.

[2] Figueredo A, Charette ML, Maroun J, et al. Adjuvant therapy for stage II colon cancer: a systematic review from the cancer care ontario program in evidence-based care's gastrointestinal cancer disease site group. J Clin Oncol 2004;16:3395-3407.

[3] Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22:1797-1806.

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PRINCIPLES OF ADJUVANT THERAPY (1 OF 2)

- **Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in Stage III patients.[1] This is an extrapolation from data available.**
- **FOLFOX is superior to fluoropyrimidine therapy alone 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] Mature data are not yet available for capecitabine combination regimens.**
- **Bevacizumab, cetuximab, panitumumab, or irinotecan should not be used in the adjuvant setting for stage II or III patients outside the setting of a clinical trial.**

See Additional Principles of Adjuvant Therapy - Chemotherapy Regimens and References on COL-E 2 of 2

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Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF ADJUVANT THERAPY - CHEMOTHERAPY REGIMENS AND REFERENCES (2 of 2)

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

FLOX[2]
5-FU 500 mg/m² IV bolus weekly x 6 + leucovorin 500 mg/m² IV weekly x 6, each 8 week cycle x 3 with oxaliplatin 85 mg/m² IV administered on weeks 1, 3, and 5 of each 8 week cycle x 3.

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

CapeOx[4]
Oxaliplatin 130 mg/m² over 2 hours, day 1. Capecitabine 1000 mg/m² twice daily days 1-14 every 3 wks x 24 wks.

5-FU/leucovorin
- **Leucovorin 500 mg/m² given as a 2 h infusion and repeated weekly x 6. 5-FU 500 mg/m² given bolus 1 h after the start of leucovorin and repeated 6 x weekly. Every 8 weeks for 4 cycles.[5]**
- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)[6]**
  Leucovorin 400 mg/m² IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m2 over 46-48 hours)† continuous infusion. Repeat every 2 weeks

*While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

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

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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.
- Conformal external beam radiation should be routinely used for T4 non-metastatic disease and intensity modulated radiotherapy (IMRT) reserved only for unique clinical situations.
- Intraoperative radiotherapy (IORT), if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Preoperative radiation therapy with concurrent 5-fluorouracil based chemotherapy is preferred for these patients to aid resectability. If IORT is not available, additional 10-20 Gy external beam radiation could be considered to a limited volume, prior to adjuvant chemotherapy.
- Some institutions use arterially-directed embolization using Yttrium-90 microspheres in select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, and with predominant hepatic metastases. (category 3)
- In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3D conformal radiotherapy, IMRT or stereotactic body radiosurgery (SBRT). (category 3)

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PRINCIPLES OF SURVIVORSHIP - Colorectal Long-term Follow-up Care (1 of 2)

CRC Cancer Surveillance:

- History and Physical every 3-6 months for 2 years, then every 6 months for a total of 5 years.
- CEA every 3-6 months for 2 years, then every 6 months for a total of 5 years.
- CT scan of abdomen and pelvis annually for 3 years.
- Colonoscopy at 1 year, then as clinically indicated.

Cancer Screening Recommendations:[1]

- Breast Cancer:
  - Periodic self breast exam (SBE) encouraged (optional)
  - Clinical breast exam (CBE) every 1-3 years between ages 20 and 40
  - Annual mammogram with clinical breast exam beginning at age 40.
  - Women at high risk (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

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 analgesics or referral to a pain specialist for painful, persistent neuropathy.

Continued

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

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**

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

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

[5] DeSnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. European Journal of Cancer Care 2006;15:244-51.
[6] McGough C, Baldwin C, Frost C, Andreyev HJN. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. British Journal of Cancer 2004;90:2278-87.
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[9] Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.:The National Academies Press;2006.

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National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011 Staging Colon Cancer

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Table 1. Definitions for T, N, M

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[a]
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum[b]
T4b	Tumor directly invades or is adherent to other organs or structures[b,c]

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

Table 2. Anatomic Stage/Prognostic Groups

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	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	Any T	Any N	M1b	-	-

Note : cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (e.g., ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).

*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.

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

[b]Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension thourhg the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

[c]Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN site-specific factor should be used for perineural invasion.

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Discussion – Last updated 05/28/10

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 fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2009, an estimated 106,100 new cases of colon cancer and approximately 40,870 cases of rectal cancer occurred. During the same year, it is estimated that 49,920 people will have died 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 through 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.[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, above). The panel unanimously endorses giving priority to treating patients in a clinical trial over standard or accepted therapy.

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 all colon cancer patients be counseled regarding their family history, as detailed in the NCCN Colorectal Cancer Screening Clinical Practice Guidelines.

Staging

The 7th edition of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual[2,6] includes a number of modifications to the colon cancer staging system . Similar findings were observed in analyses of colon cancer and rectal cancer databases[7]; hence, these 2 cancers share the same staging system.

In the previous version (6th edition) of the AJCC staging system for colon cancer, stage II disease, characterized by full thickness tumor invasion of the bowel wall and the absence of lymph node metastases (ie, N0 disease), was subdivided into IIA and IIB depending on whether

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the primary tumor was T3 or T4. stage II disease is now subdivided into IIA (the primary tumor invades through the muscularis propria into pericolorectal tissues), IIB (T4a lesions which directly penetrate the visceral peritoneum) and IIC (T4b lesions where tumor directly invades or is adherent to other organs or structures).

Other changes relate to the classification of satellite tumor deposits, now defined by the new site-specific prognostic factor "tumor deposits" which includes a description of their texture and number, although consideration of prognostic factors is not required for staging. In addition, satellite nodules are included in the definition of the new N1c category (see below).

These changes are supported by an analysis of 109,953 patients with invasive colon cancer included in the Surveillance Epidemiology and End Results (SEER) colon cancer database from 1992-2004.[8] For example, the relative 5-year survival rate (ie 5-year survival corrected by age-related morbidity) for node-negative patients with T4 tumors penetrating the visceral peritoneum was considerably higher (79.6%) compared with tumors that invade or are adherent to other organs (58.4%).

Based on the analyses described above, stage III disease, previously subdivided into IIIA (T1 to T2, N1, M0), IIIB (T3 to T4, N1, M0), and IIIC (any T, N2, M0), has now been revised (see Table I) to more accurately reflect the complex biologic relationship between the extent of tumor invasion and the number of affected lymph nodes. For example, due to the relatively high survival rates observed for patients with lesions with extensive nodal involvement but no tumor penetration beyond the muscularis propria, T1-2N2 lesions are now classified as either IIIA or IIIB. In addition, T4bN1 disease, formerly stage IIIB disease, is now included under stage IIIC since outcomes for patients with T4bN1 disease were found to be similar to those observed for patients with T3-4,N2 lesions.

The definitions of N1 and N2 disease have also been revised to reflect the prognostic impact of the number of involved regional lymph nodes. For example, N1 lesions (1 to 3 positive regional lymph nodes) have been subdivided into N1a (1 positive lymph node) and N1b (2-3 positive lymph nodes), whereas N2 tumors (4 or more positive regional nodes) is split into N2a (4-6 positive nodes) and N2b (7 or more positive nodes). In addition, tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis is classified as N1c.

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] M1 disease is now dichotomized into M1a and M1b according to whether metastasis is confined to one or more organ(s)/site(s).

The 7th edition of the AJCC staging system specifies that the surgeon should 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

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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 number of regional lymph nodes retrieved from a surgical specimen can vary with age of the patient, gender, and tumor grade or site.[11-13] The extent and quality of surgical resection and pathologic review of the specimen can also have an impact on the node harvest.[14-16] The Panel recommends examination of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancer. This recommendation is supported by previous statements from CAP,[6] as well as recommendations included in the 7th edition of the AJCC staging manual which specifies pathologic examination of a minimum of 10-14 lymph nodes,[2] Of note, emerging evidence suggests that a greater number of nodes may need to be examined in some situations, particularly for T4 lesions, to provide an adequate assessment of disease stage.[17,18]

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.

Approximately 40% of colorectal cancers are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the *KRAS* gene.[24] A sizable body of literature has demonstrated that these *KRAS* mutations predict for lack of response to cetuximab or panitumumab therapy,[25-33] and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of colorectal cancer characterized by these mutations.[34,35] Therefore, the panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer *at the time of diagnosis of stage IV disease.* The recommendation for *KRAS* testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting, but rather, this early establishment of *KRAS* status is appropriate in order to plan for the treatment continuum, so that the information may be obtained in a non-time-sensitive manner, and the patient and provider can discuss the implications of a *KRAS* mutation, if present, while other treatment options still exist. *KRAS* mutations are early events in colorectal cancer formation, and therefore there is a very tight correlation between mutation status in the primary tumor and the metastases.[36,37] 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 unless an archived specimen from either the primary tumor or a metastasis is unavailable. The panel recommends that *KRAS* gene testing be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as

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qualified to perform highly complex molecular pathology testing.[38] No specific testing methodology is recommended.[39]

Approximately 5%-8% of colorectal cancers are characterized by a specific mutation in the *BRAF* gene (V600E).[40,41] *BRAF* mutations are, for all practical purposes, limited to those tumors that do not have *KRAS* exon 2 mutations.[41] There is retrospective evidence that mutated *BRAF* is another marker of resistance to anti-EGFR therapy,[41,42,43] and, as of the date of this writing, all reported patients with tumors characterized by known *BRAF* V600E mutations who have received cetuximab or panitumumab in the chemotherapy-refractory setting have failed to respond. Other data from unplanned retrospective subset analyses suggest, however, that although a V600E *BRAF* mutation confers a poor prognosis regardless of treatment, patients with disease characterized by this mutation received some benefit from the addition of cetuximab to front-line therapy[40]; nevertheless, the data regarding *BRAF* as a predictor of response (or lack thereof) to anti-EGFR therapy remain inconclusive. Although activation of the protein product of the non-mutated *BRAF* gene occurs downstream of activated k-ras protein in the EGFR pathway, the mutated *BRAF* protein product is believed to be constitutively active, thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab. For patients with *KRAS* wild-type tumors, the panel includes the option of *BRAF* genotyping of tumor tissue (either primary tumor or metastasis)[44] at the time of diagnosis of *KRAS* wild-type state IV disease. With respect to technical aspects of *BRAF* gene testing, the specific recommendations regarding tumor tissue sampling described above for *KRAS* gene testing apply. No specific testing methodology is recommended.

DNA mismatch repair (MMR) gene (eg, MLH1, MSH2, MSH6) mutations or modifications (eg, methylation) of these genes can result in MMR protein deficiency.[45] For example, germline mutations in one or more of these genes are found in individuals with HNPCC (ie Lynch syndrome), responsible for 2%-5% of colon cancer cases,[46] and somatic hypermethylation of the MLH1 gene promoter is associated with DNA MMR gene inactivation in sporadic colon cancer tumors in approximately 15%-20% of cases of the disease.[47-49] Immunohistochemical analysis provides an assessment of the level of MMR proteins in tumor tissue.[47] Another marker of MMR protein deficiency, termed “microsatellite instability” (MSI) is detected as an increased or decreased amount of short repeated DNA sequences in tumor tissue caused by the insertion or deletion of repeated units of DNA. Tumors showing the presence of microsatellite instability are classified as MSI-high (MSI-H) or MSI-low (MSI-L), depending on the extent of instability in the markers tested, whereas tumors without this characteristic are classified as microsatellite-stable (MSS).[50]

The Panel recommends that MMR protein testing should be strongly considered for all colon cancer patients < 50 years of age, based on an increased likelihood of HNPCC in this population. Furthermore, the Panel recommends MMR testing for patients with stage II disease being considered for adjuvant therapy with a fluoropyrimidine therapy alone. This recommendation is based on evidence suggesting that MMR protein deficiency is predictive for response to 5-FU chemotherapy in patients with stage II disease[51] (see section on Adjuvant Chemotherapy).

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.[52] A malignant polyp is defined as one with cancer invading through the muscularis mucosae

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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.[53] 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.[54] 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.[52, 55-57] 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.[52, 58, 59] Laparoscopic surgery is an option (see section on Workup and Management of Invasive Nonmetastatic Colon Cancer, below). All patients who have resected polyps should undergo total colonoscopy to rule out other synchronous polyps, as well as appropriate follow-up surveillance endoscopy.[60] 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, chemistry profile, carcinoembryonic antigen (CEA) determination, and baseline computed tomographic (CT) scans of the chest, abdomen and pelvis.[61] The consensus of the panel is that a positron emission tomography (PET)-CT scan is not routinely indicated at baseline, and should not be done as a matter of general surveillance. Furthermore, a PET-CT scan does not obviate the need for a contrast-enhanced diagnostic CT scan. If abnormalities are seen on CT or MRI scan that are considered to be suspicious but inconclusive for metastases, then a PET-CT scan may be considered for further delineation of that abnormality, if such delineation will change management. A PET-CT scan is not indicated for assessment of sub-centimeter lesions, as these are routinely below the level of PET-CT detection.

For resectable colon cancer, the surgical procedure of choice is colectomy with en bloc removal of the regional lymph nodes.[62,63] 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.[64] Furthermore, these

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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.[12] In addition, the ratio of metastatic to examined lymph nodes (LNR) was a significant prognostic factor for both disease recurrence and overall survival,[65] although LNR was not shown to be prognostic for patients for whom fewer than 10 lymph nodes were evaluated.[65] 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.[13,16,66] 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 become an option in the surgical management of colon cancer. Although a small European trial (Barcelona) appeared to show some modest survival advantage to the laparoscopic approach,[67] more recently, for patients randomly assigned to either curative surgery with either a conventional open approach or laparoscopically-assisted surgery, an absolute difference of 2.0% (P=NS) in 3-year disease-free survival in favor of open colectomy was observed in a study of 1248 patients with colon cancer (COLOR trial). Although this difference was not statistically significant, noninferiority of the laparoscopic approach could not be established due to study limitations.[68] In the CLASSIC study of 794 patients with colorectal cancer, no statistically significant differences in 3-year rates of overall survival, DFS and local recurrence were observed when the 2 surgical approaches were compared.[69] 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.[70,71] 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. [72-74] 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 statistically significantly more favorable when laparoscopic surgery was performed at hospitals with high case volumes.[75] Other factors which may confound conclusions drawn from randomized studies comparing open colectomy to laparoscopically-assisted surgery for colon cancer have also been described.[76,77]

The panel recommends that laparoscopically-assisted colectomy be considered only by surgeons experienced in the technique. A thorough abdominal exploration is a required part of the procedure. Routine use of laparoscopic-assisted resection is not, at this time, recommended for tumors in the lower and mid rectum, or for tumors that are acutely obstructed or perforated, or clearly locally invasive into surrounding structures (ie, T4). Patients at high risk for prohibitive abdominal adhesions should not be approached laparoscopically, and patients who are found to have prohibitive adhesions during laparoscopic exploration should be converted to an open procedure[78-80]

For resectable colon cancer that is causing overt obstruction, resection with diversion followed by colectomy or stent insertion followed by colectomy is also an option. If the cancer is locally unresectable or medically inoperable, palliative therapy should be considered and may

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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.[81-83] 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,[84] 4 years, [85] and 6 years.[86] For stage III patients, disease-free survival (DFS) at 5 years was 58.9%% in the 5-FU/LV arm and 66.4%% in the FOLFOX4 arm (P=0.005). For stage II patients, neither 5-year DFS[86] nor overall survival[87] were statistically significantly different between the FOLFOX and 5FU/LV arms. However, overall survival of patients with stage III disease receiving FOLFOX was statistically significantly increased at 6-year follow up (78.5% vs. 76%) hazard ratio=0.80; 95% CI, 0.65-0.97; P=0.023 when compared with those receiving 5-FU/LV.[87] 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 15.5% of this group at 4 years, suggesting that oxaliplatin-induced neuropathy may not be completely reversible in some patients.[87] Based on these results, the modified FOLFOX regimen (mFOLFOX6) is recommended as treatment for stage III colon cancer (category 1). Although the initial trials were done with FOLFOX 4, modified FOLFOX 6 is the control arm for all current National Cancer Institute (NCI) adjuvant studies.

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.[88,89] Four-year DFS rates were 73.6% for FLOX and 67.0% for FULV, respectively, indicating that the addition of oxaliplatin to weekly FULV statistically significantly improved 4-year DFS in patients with stage II/stage III colon cancer (P=0.0034). A recent update of this study showed the benefit in DFS to be maintained at 7-year median follow-up (P=0.0017).[90] However, no statistically significant differences in overall survival (hazard ratio=0.88; 95% CI, 0.76-1.03) or colon-cancer specific mortality (hazard ratio=0.88; 95% CI, 0.74-1.05) were observed when the 2 arms were compared. Furthermore, survival after disease recurrence was significantly shorter in the group receiving oxaliplatin (hazard ratio=1.20; 95% CI, 1.00-1.43).

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 appears to be considerably higher with FLOX than FOLFOX. For example, rates of grade 3/4 diarrhea were 10.8% and 6.7% for patients receiving FOLFOX and infusional 5-FU/LV, respectively, in the MOSAIC trial,[86] 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.[89]

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.[91]

Results of a recent analysis of individual patient data from 20,898 patients on 18 randomized colon adjuvant clinical trials which

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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.[92,93] A more recent update of this analysis showed that most relapses occur within 2 years following surgery, and that recurrence rates were < 1.5%/year and <0.5%/year after 5 years and 8 years, respectively.[94] Very recently, however, a further update of the data suggested that the association between 2- or 3-year DFS and 5-year overall survival is reduced when patient survival after recurrence is prolonged, and that more than 5 years may be required to evaluate the effect of adjuvant therapies on overall survival.[95]

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.[96] 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.[97] In addition, FOLFIRI (infusional 5-fluorouracil, leucovorin, irinotecan), has not been shown to be superior to 5-FU/LV in the adjuvant setting.[98, 99] Thus, data do not support the use of irinotecan-containing regimens in the treatment of stage II or III colon cancer.

The NSABP C-08 trial comparing 6 months of mFOLFOX6 vs. 6 months of mFOLFOX6 with bevacizumab plus an additional 6 months of bevacizumab alone in patients with stage II or stage III colon cancer did not demonstrate a statistically significant benefit in 3-year DFS with the addition of bevacizumab to FOLFOX (hazard ratio=0.89; 95% CI, 0.76-1.04; P=0.15).[100] The ongoing phase III AVANT trial is also evaluating use of bevacizumab in the adjuvant setting in a similar protocol; however, at this time, there is no role for the use of bevacizumab in the adjuvant treatment of stage II or III colorectal cancer.

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.[101,102] Similarly, an analysis of pooled data from 7 randomized trials indicated that overall survival of patients with resected early-stage colon cancer treated with 5-FU based adjuvant therapy was statistically significantly increased in the subset of patients with positive regional lymph nodes but not in patients with N0 disease when compared to patients not receiving chemotherapy, suggesting that the benefit of adjuvant therapy is greater in patients at higher risk due to nodal status.[103] These clinical trial results are supported by data from the community setting. Using the SEER databases, an analysis of outcomes of patients with stage II disease based on whether patients had or had not received adjuvant chemotherapy showed that there was no statistically significant difference between these 2 groups with respect to 5-year overall survival (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.[104]

In contrast to results from most other trials, the QUASAR trial indicated a small but statistically significant survival benefit for stage II patients treated with 5-FU/LV.[105]

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Although results of an 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), a trend for improved DFS in high-risk stage II patients (ie, disease characterized by at least one of the following: T4 tumor; tumor perforation; bowel obstruction; poorly differentiated tumor; venous invasion; < 10 lymph nodes examined) receiving FOLFOX4 compared to infusional 5-FU/LV (hazard ratio=0.74, 95% CI, 0.52-1.06) was observed, suggesting that this patient population may benefit from treatment with FOLFOX.[86] However, no benefit of FOLFOX over 5-FU/LV was seen for patients with low-risk stage II disease in the MOSAIC trial.[86]

There is evidence that in patients with stage II disease, a deficiency in MMR protein expression or MSI-H tumor status (see section on Pathology) is a marker of a more favorable outcome and decreased benefit (possibly a detrimental impact) from adjuvant therapy with a fluoropyrimidine alone.[49,51] A retrospective study involving long-term follow-up of stage II and stage III patients evaluated according to MMR/MSI tumor status, suggested that those with MSI-L or MSS tumor status had improved outcomes with 5-FU adjuvant therapy; however, patients with tumors characterized as MSI-H did not show a statistically significant benefit from 5-FU following surgery, instead exhibiting a lower 5-year survival rate compared with those undergoing surgery alone.[49] Results from another retrospective study of pooled data from adjuvant trials showed that in tumors characterized as MSI-H, adjuvant 5-FU chemotherapy appeared to be detrimental in patients with stage II, but not stage III, disease.[51] Finally, data from a retrospective analysis of patients with stage II and stage III colon cancer enrolled in the PETACC-3 trial suggest that the prognostic impact of the MSI/MMR biomarker is stronger than its ability to predict benefit from adjuvant 5-FU chemotherapy.[106] In that study, MSI-H tumor status was significantly associated with a favorable prognosis in patients with stage II disease. In contrast to the findings of Sargent et al., however, the relapse-free survival rate of patients (either the combined stage II and stage III group or the stage II patients alone) receiving adjuvant 5-FU was significantly better in those with MSI-H tumor status versus MSS tumor status. However, this study was not able to address the impact of adjuvant 5-FU chemotherapy relative to no adjuvant therapy in each subgroup. Finally, there is evidence that MSI-H tumor status is more common in patients with stage II disease. For example, data from the study of Tejpar et al. showed tumor specimens characterized as MSI-H to be more common in stage II disease compared with stage III disease (22% vs. 12%, respectively; P<0.0001). In another large study, the percentage of stage IV tumors characterized as MSI-H was only 3.5%.[107]

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.[108] The treatment options are: 5-fluorouracil/leucovorin/oxaliplatin as the standard of care (category 1),[84-86,88,89] or either single agent capecitabine (category 2A),[91] or 5-FU/LV (category 2A) in patients felt to be inappropriate for oxaliplatin therapy.[101,109,110] The Panel recommends against the use of bevacizumab, cetuximab, panitumumab, or irinotectan in adjuvant therapy, outside the setting of a clinical trial.

High-risk stage II (T3-T4, N0, M0) patients, defined as those with poor prognostic features including T4 tumors (stage IIB), poor histologic grade (grade 3 or 4 lesions), lymphovascular invasion, bowel obstruction at presentation, lesions with localized perforation or close, indeterminate, or positive margins, and inadequately sampled nodes (less than 12 lymph nodes), should be considered for adjuvant

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chemotherapy[10, 111] with 5-FU/LV/oxaliplatin, single agent 5-FU/LV, or capecitabine (category 2A for all three regimens). Based on results of the MOSAIC trial as well as the possible long-term sequelae of oxaliplatin-based chemotherapy, the panel does not consider FOLFOX to be an appropriate adjuvant therapy option for patients with stage II disease without high-risk features. 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.[111,112] The Panel recommends MMR testing for patients with stage II disease, especially if adjuvant therapy with a fluoropyrimidine alone is being considered.

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. Intraoperative radiotherapy (IORT), if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Intensity-modulated radiotherapy (IMRT), which uses computer-imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,[113] should be reserved for unique clinical situations.

Principles of the Management of Metastatic Disease

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.[114.] Metastatic disease more frequently develops metachronously following treatment for colorectal cancer, with the liver as the most common site of involvement.[115] 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.[116] For patients presenting with synchronous metastases and intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver.[117]

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.[118] Results from reviews of autopsy reports of patients dying from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients. Furthermore, rates of 5-year survival for patients with metastatic liver disease not undergoing surgery have been shown to be quite low in a number of studies. [114,119] 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 a substantial number of patients with colorectal metastatic liver disease. [114, 120] Recent reports have shown 5-year survival rates following resection of liver metastases exceeding 50%.[121, 122] 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.[123]

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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.[124-127] 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;[128] 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.[126,129] Approaches used in the surgical treatment of liver metastases include simultaneous resections of colorectal cancer and synchronous liver metastases,[130] preoperative portal vein embolization for the purpose of increasing the volume and function of the portion of the liver which will remain postsurgically,[131] and hepatic resection performed in 2 stages for bilobular disease.[132]

Resection is the standard approach for the local treatment of metastatic disease that is initially resectable or converted to a potentially curable status following chemotherapy.[133] However, some patients in this group who cannot undergo resection due to comorbidity, location of the metastatic lesion(s) (ie, adjacent to a major hepatic vein or the vena cava) or an estimate of inadequate liver volume following resection may be candidates for ablation therapy.[134] A number of retrospective studies have compared radiofrequency ablation (RFA) and liver resection in the treatment of liver metastases,[135-137] although RFA has not been well studied in this setting.[138] Most of these studies have shown RFA to be inferior to resection with respect to rates of local recurrence and 5-year overall survival.[133] It is presently unclear whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are due to patient selection bias, technological limitations of RFA or a combination of these two factors.[136] Nevertheless, the panel does not consider RFA to be a substitute for resection in patients with completely resectable disease. In addition, resection or RFA (either alone or in combination with resection) should be reserved for patients with disease that is completely amenable to local therapy. Use of either surgery, RFA, or the combination of the two "debulking procedures", with a goal of less than complete resection/ablation of all known sites of disease, is not recommended.

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

The majority of patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease. For those with liver-limited unresectable disease, however, preoperative chemotherapy is being increasingly considered to attempt to downsize colorectal metastases in order to attempt to convert these lesions to a resectable status (ie, conversion chemotherapy);

Preoperative chemotherapy has also been administered to patients with metastatic disease determined to be resectable (ie, neoadjuvant therapy).[139] Potential advantages of pre- versus post-operative chemotherapy include: earlier treatment of micrometastatic disease, determination of responsiveness to chemotherapy (which can be prognostic and help in the planning of postoperative therapy), and avoidance of local therapy for those patients with early disease progression. Potential disadvantages include: chemotherapy-induced liver injury; and missing the "window of opportunity" for resection

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through the possibility of either disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.[140, 141] 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.[142] 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.[143] When preoperative chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation should be planned approximately 2 months after initiation of preoperative chemotherapy, and that those patients who continue to receive preoperative chemotherapy undergo surgical re-evaluation approximately every 2 months thereafter.[144-147]

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.[121, 122, 148- 150] 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 convertible following response to chemotherapy. In addition, preoperative chemotherapy may be more beneficial in patients who have not been exposed to prior chemotherapy or who have not received 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.[125] 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)[151] 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.[152] The 5-year overall survival rate for these 138 patients was 33%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%) were able to undergo curative liver resection following treatment.[153] The median overall survival time in this group was 42.4 months.

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The choice of chemotherapy regimen in the preoperative setting is dependent on a number of factors including whether the patient has resectable or potentially convertible metastatic disease, and the response rates and safety/toxicity issues associated with the regimens. A recent 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 progression-free survival (PFS) of 8.1% (P=0.041) and 9.2% (P=0.025) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[154] The partial response rate after preoperative FOLFOX was 40% and operative mortality was <1% in both treatment groups.

There have been recent reports of randomized clinical trials evaluating preoperative FOLFIRI or FOLFOX as conversion therapies in combination with anti-EGFR inhibitors.[155,156] However, a number of randomized studies have investigated the efficacy and safety of FOLFOX, CapeOX, or FOLFIRI with and without bevacizumab or cetuximab in the first-line treatment of patients with metastatic colorectal cancer (see section on Chemotherapy for Advanced or Metastatic Disease). In addition, first-line FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI in 2 randomized clinical trials.[157,158] Significantly improved rates of response and overall survival were reported for patients in the FOLFOXIRI arm of one of the studies,[158] but not in the other.[157]

The efficacy of bevacizumab in combination with FOLFOX or 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. 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 (13% vs 3.4%, respectively; P=0.28).[159] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to surgery, with a delay between bevacizumab administration and surgery of at least 6 weeks, the incidence of wound healing complications in either group of patients was low (1.3% vs 0.5%; P=0.63). The panel recommends an interval of at least 6 weeks (which corresponds to 2 half-lives of the drug[160]) 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).[161] 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.[162]

Other reported risks associated with the preoperative approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.[143,146,163-165] limit the development of hepatotoxicity, it is therefore recommended that

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surgery should be performed as soon as possible after the patient becomes resectable.

As mentioned above, colorectal metastatic disease can also occur in the lung.[166] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases.[167] The goal of treatment of virtually all abdominal/peritoneal metastases is palliative, rather than curative.

Only limited data exist regarding the efficacy of adjuvant chemotherapy following resection for metastatic colorectal liver or lung disease. In a pooled analysis of results from 2 randomized clinical trials involving patients with a potentially curative resection randomly assigned to either systemic chemotherapy with 5-FU/LV or observation, the median PFS was 27.9 months in the chemotherapy arm and 18.8 months for those undergoing surgery alone (hazard ratio=1.32; 95% CI, 1.00-1.76; P=0.058) with no difference in overall survival.[168] Nevertheless, the panel recommends consideration of administration of a course of an active systemic chemotherapy regimen for metastatic disease, for a total perioperative treatment time of approximately 6 months, for most patients following liver or lung resection to increase the likelihood that residual microscopic disease will be eradicated.

In a recent retrospective review of a cohort of 1669 patients from 4 institutions who underwent curative-intent surgery with or without RFA for the treatment of colorectal liver metastasis during the period from 1982 to 2008, 5-year overall survival was 47.3%, the percentage of patients experiencing a recurrence of disease at a median follow-up of 30 months was 56.7%, and median overall recurrence-free survival was 23.0 months.[169] The pattern of recurrence was similarly divided among intrahepatic only, extrahepatic only, or a combination of the 2. Although rates of 5-year overall survival and time to recurrence are substantially higher in this study compared with historical controls from 2 decades earlier, the percentage of patients experiencing disease recurrence is nearly unchanged, suggesting that modern multimodality therapy may prolong recurrence but not increase the number of patients experiencing a cure.

Evidence supporting resection of extrahepatic metastases in patients with metastatic colorectal cancer is extremely limited. In a recent retrospective analysis of patients undergoing concurrent complete resection of hepatic and extrahepatic disease, the 5-year survival rate was lower when compared with patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence.[170,171]

Recent data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken. However, in a retrospective analysis, 5-year survival was shown to decrease with each subsequent curative-intent surgery, and the presence of extrahepatic disease at the time of surgery was independently associated with a poor prognosis.[172] The consensus of the Panel is that re-resection of liver or lung metastases can be considered in carefully selected patients.

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (i.e. HAI) remains an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine (with dexamethasone and with or without LV) by HAI in addition to systemic chemotherapy was shown to be superior to

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systemic chemotherapy alone with respect to 2-year survival and time to progression of hepatic disease.[140,173] However, the difference in survival between the 2 arms of the study was not significant at later follow-up periods.[140,174] 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.[140]. Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.[120] However, limitations on the use of HAI therapy include the potential for biliary toxicity,[140] and the requirement for specific technical expertise. The consensus of the panel is that HAI therapy should be considered only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Finally, a number of liver-directed therapies exist, although their role in the treatment of colorectal metastases is controversial. These therapies include arterial radioembolization with yttrium-90 microspheres,[175,176] and conformal external beam radiation therapy[177] Use of intra-arterial embolization is a category 3 recommendation based on limited evidence[178] and different institutional practice patterns. Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial. (See sections on Workup and Management of Synchronous Metastatic Disease, below, and Workup and Management of Metachronous Metastatic Disease).

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from large bowel (e.g. colorectal liver metastases) is suspected should include a total colonoscopy, a complete blood count, , chemistry profile, carcinoembryonic antigen (CEA) determination, a CT scan of the chest, abdomen and pelvis.[61] The panel also recommends tumor *KRAS* gene status testing and consideration of *BRAF* genotyping (see discussion of *KRAS* testing on MS-3 – MS-4) for all patients with *KRAS* wild-type metastatic colon cancer at the time of diagnosis of metastatic disease

The panel strongly discourages the routine use of PET-CT scanning for staging, baseline imaging, or routine follow up, and recommends consideration of a preoperative PET-CT scan at baseline only if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease; the purpose of this PET-CT scan is to evaluate for unrecognized metastatic disease that would preclude the possibility of surgical management. Patients with clearly unresectable metastatic disease should not have baseline PET-CT scans, nor should PET-CT scans be used to assess response to chemotherapy.

The criterion of potential surgical cure includes patients with metastatic disease that is not initially resectable but for whom a surgical cure may become possible following preoperative chemotherapy. It should be noted that in the overwhelming majority of cases, the presence of extrahepatic disease will preclude the possibility of resection for cure; “conversion to resectability” for the most part refers to a patient with liver-only disease that, due to involvement of critical structures, cannot be resected unless regression is accomplished with chemotherapy.

It should be noted that a PET-CT scan can become transiently negative following chemotherapy (eg, in the presence of necrotic lesions)[179] and the panel recommends against using PET-CT scan to evaluate response to chemotherapy. False positive PET-CT scan results can occur in the presence of tissue inflammation following surgery or infection.[179] 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

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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, including an upfront evaluation by a surgeon experienced in the resection of hepatobiliary or lung metastases.

Resectable synchronous liver or lung metastases

If a patient is a candidate for surgery and the liver or lung metastases are deemed resectable, the panel recommends the following options: colectomy and synchronous or subsequent liver (or lung) resection,[115, 150] neoadjuvant chemotherapy for 2-3 month duration (eg, choice of FOLFIRI, FOLFOX,[180] or CapeOX [capecitabine, oxaliplatin] chemotherapy with or without bevacizumab or FOLFIRI or FOLFOX regimens with or without cetuximab or panitumumab (an EGFR inhibitor should be considered in *KRAS* wild-type tumors only) 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. 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. 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. In addition, administration of neoadjuvant chemotherapy for a period of up to 2-3 months may help distinguish patients who would be more likely to benefit from metastasectomy because of indolent disease. If bevacizumab is included in the neoadjuvant regimen, there should be at least a 6 week interval between the last does of bevacizumab and surgery, with a 6-8 week postoperative period before re-initiation of bevacizumab.

Patients who have completely resected liver or lung metastases should be considered for adjuvant chemotherapy. The panel recommends approximately 6 months total duration of pre- and postoperative chemotherapy. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B) with the exception of FOLFOXIRI. In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) remains at option at centers with experience with the surgical and medical oncologic aspects of this procedure. Observation can be considered, especially for those patients with disease that has progressed or recurred despite fluoropyrimidine and oxaliplatin therapy. 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. Overall, combined neoadjuvant and adjuvant treatments should not exceed 6 months.

Unresectable synchronous liver or lung metastases

For patients with liver or lung disease that 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 or FOLFOX or FOLFIRI regimens with or without cetuximab or panitumumab (an EGFR inhibitor should be considered in *KRAS* wild-type tumors only) or FOLFOXIRI alone (category 2B) to attempt to render these patients candidates for resection. Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially

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convertible disease,[181] and these patients should be re-evaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing such therapy. If bevacizumab is included as a component of the conversion therapy, there should be at least a 6 week interval between the last dose of bevacizumab and surgery, with a 6-8 week postoperative period before re-initiation of bevacizumab. Patients with disease converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer including treatment with pre- and postoperative chemotherapy for a preferred total perioperative duration of 6 months. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B). In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) remains an option at centers with experience with the surgical and medical oncologic aspects of this procedure. 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.[117] 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 palliative resection of a synchronous primary lesion should not be routinely done in the absence of overt obstruction. Complications from the intact primary lesion are uncommon in these circumstances, and its removal delays initiation of systemic chemotherapy. An intact primary is not a contraindication to bevacizumab use. The risk of gastrointestinal perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, as large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare.

Ablative therapy of metastatic disease, either alone or in combination with resection, can also be considered when all measurable metastatic disease can be treated (see Principles of the Management of Metastatic Disease). 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.

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

There was no consensus of the panel regarding the use of liver-directed therapies such as arterial radioembolization therapy. For select patients, with chemotherapy resistant/refractory disease characterized by predominant liver metastases and no obvious systemic disease, use of these interventions was supported by some panel members but not others (category 3).The consensus of the panel is that conformal external radiation therapy may be considered in highly selected cases or in the setting of a clinical trial; it should not be used indiscriminately in patients with potentially respectable disease.

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.

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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[182,183] to be investigational and does not endorse such therapy outside of a clinical trial. However, the panel recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities.

Workup and Management of Metachronous Metastatic Disease

Routine use of PET-CT to monitor for disease recurrence is not recommended. It should be noted that the CT that accompanies a "PET-CT" is a non-contrast CT, and thus not of ideal quality for routine staging. Upon documentation on dedicated contrast-enhanced CT or MRI of metachronous metastases that disease either is or may become resectable, characterization of the extent of disease by PET-CT scan should be considered. PET-CT is used at this juncture to promptly characterize the extent of metastatic disease, and to identify possible sites of extrahepatic disease which could preclude surgery.[184] 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. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS* gene, such testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see discussion of *KRAS* and *BRAF* testing on MS-3 – MS-4). Close communication between members of the multidisciplinary treatment team is recommended, including upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases.

The management of metachronous metastatic disease is 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. Patients with resectable disease are classified according to whether they have received no previous chemotherapy or prior chemotherapy. For patients who have resectable metastatic disease, primary treatment options include initial resection followed by chemotherapy with an active chemotherapy regimen for 6 months or neoadjuvant chemotherapy for 2-3 months followed by resection and consideration of additional postoperative chemotherapy for a total duration of pre- plus postoperative chemotherapy of 6 months based on response to the neoadjuvant regimen; observation is also an option for patients without a response to neoadjuvant therapy. For example, the same chemotherapy regimen used in the neoadjuvant setting should be repeated postoperatively for patients with a preoperative disease response to such therapy. However, either an alternative active chemotherapy regimen or observation is an option in the postoperative setting for patients not responding to neoadjuvant therapy.

Patients determined by cross-sectional imaging or PET-CT scan to have unresectable (including those considered to potentially convertible or unconvertible) disease should receive an active 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, or cetuximab or panitumumab (an EGFR inhibitor should be considered for *KRAS* wild type tumors only). Patients potentially convertible to resectability should be re-evaluated for disease conversion to a resectable status every 2 months; those with chemotherapy-responsive disease who are converted to a resectable state should undergo resection followed by postoperative

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therapy as described above for patients with resectable disease and a history of previous chemotherapy. In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) remains at option at centers with experience with the surgical and medical oncologic aspects of this procedure.

Patients with unresectable metastatic disease not responding to preoperative therapy should receive chemotherapy for advanced or metastatic disease, with treatment selection based, in part, on whether the patient is or is not an appropriate candidate for intensive therapy. Patients receiving palliative chemotherapy should be monitored with CT or MRI scans approximately every 2-3 months. PET-CT scans are not recommended for routine monitoring of the progression of metastatic disease.

Chemotherapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colon cancer uses various active drugs, either in combination or as single agents: 5-FU/ LV, capecitabine; irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab.[24,29,31,157,158,181,185-209] 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.[210,211,212,213] The choice of therapy is based on consideration of the goals of therapy, 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.[188] For example, if oxaliplatin, administered as a part of an initial treatment regimen, is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the rest of the treatment regimen would still be considered initial therapy. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive, as well as plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices following first progression of disease should be based, in part, on the prior therapies received by the patient (ie, exposing patient to a range of cytotoxic agents). Further, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, as well as the potential for surgical cure and the performance status of the patient.

As initial therapy for metastatic disease in a patient appropriate for intensive therapy (ie, one with a good tolerance for such therapy for whom a high tumor response rate would be potentially beneficial), the panel recommends a choice of 5 chemotherapy regimens: FOLFOX (ie, mFOLFOX6),[197,214] CapeOX,[206,215,216] FOLFIRI,[185] infusional 5-FU/LV[185,192,217, 218] or FOLFOXIRI.[157,158] Although use of FOLFOXIRI as initial therapy is a category 2B recommendation, the panel does not consider one of the other regimens (ie, FOLFOX, CapeOX, and FOLFIRI) to be preferable over the others as initial therapy for metastatic disease. Biologic agents used as part of initial therapy include bevacizumab, cetuximab, or panitumumab. For FOLFIRI-containing initial therapy, the addition of bevacizumab is recommended; alternatively, cetuximab or panitumumab (for tumor characterized by *KRAS* wild-type tumor only) can be added to this chemotherapy regimen.[31,40,207-209] Furthermore, addition of bevacizumab is an option if

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either FOLFOX or CapeOX is chosen as initial therapy. The addition of cetuximab or panitumumab (only for those with disease characterized by the *KRAS* wild-type gene) is also an option if FOLFOX is administered as initial therapy.[29,207,219] With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, the consensus of the panel was that FOLFOX and CapeOX can be used interchangeably. Infusional 5-FU/LV regimens in combination with bevacizumab[220-222] and FOLFOXIRI alone[157,158] are also listed as options. If FOLFOXIRI is used (category 2B), it is recommended without the addition of a biologic agent since data regarding the efficacy and safety of such a combination are not yet mature. For those patients not appropriate for intensive therapy (ie, either due to comorbidity or absence of the need for a therapy associated with a high tumor response rate), initial therapy options include either capecitabine[193,194] or infusional 5FU/LV with or without the addition of bevacizumab;[221-223] cetuximab or panitumuab alone (category 2B) are also included as initial therapy options for those with disease characterized by the *KRAS* wild-type gene only.[33]

Based on the results of both the PACCE trial and the CAIRO-2 trial, the panel strongly advises against the concurrent use of bevacizumab with either cetuximab or panitumumab.

Pooled results from several randomized phase II studies have demonstrated that addition of bevacizumab to first-line 5-FU/LV improved overall survival in patients with metastatic colorectal cancer when compared to survival results for patients receiving these regimens without bevacizumab.[222,224] A combined analysis of the results of several of these trials showed that addition of bevacizumab to 5-FU/LV was associated with a median survival of 17.9 months versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab.[224] 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.[225] In that pivotal trial a longer survival time was observed with the use of bevacizumab: 20.3 months versus 15.6 months (hazard ratio = 0.66; P<0.001). Results from a recent head-to-head randomized, double-blind, placebo-controlled phase III study (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 CapeOx is non-inferior to FOLFOX when used in the initial treatment of metastatic colorectal cancer.[206,219] However in this large trial of 1400 patients, the addition of bevacizumab to oxaliplatin-based regimens was associated with a more modest increase of 1.4 months in PFS compared to these regimens without bevacizumab (hazard ratio=0.83; 97.5% CI, 0.72-0.95; P=0.0023), and the difference in overall survival, which was also a modest 1.4 months, did not reach statistical significance (hazard ratio=0.89; 97.5% CI, 0.76-1.03; P=0.077). It has been suggested that differences observed in cross-study comparisons of NO16966 with other trials might be related to differences in the discontinuation rates and durations of treatment between trials, although such hypotheses are conjectural.[220]. 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).[219]

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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.[226, 227] Although this trial was closed early and did not meet projected enrollment, a statistically significant increase in PFS was observed for patients receiving first-line FOLFIRI (7.6 months) when compared to 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 statistically significant (P=0.28). However, at a median follow-up of 34.4 months, overall survival was statistically significantly higher for patients receiving FOLFIRI plus bevacizumab (28.0 months) compared with modified IFL plus bevacizumab (19.2 months; P=0.037).[227] 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.[214] 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.[205] 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.[228]

Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in 2 randomized phase III trials. In one study, statistically significant improvements in PFS survival (9.8 months vs. 6.9 months; hazard ratio=0.63; P=0.0006) and median overall survival (22.6 months vs. 16.7 months; hazard ratio=0.70; P=0.032) were observed in the FOLFOXIRI arm,[158] although there was no overall survival difference between the 2 treatment arms in the other study (median overall survival: 19.5 and 21.5 months, for FOLFIRI and FOLFOXIRI, respectively; P=0.337).[157] Both studies showed some increased toxicity in the FOLFOXIRI arm (eg, significant increases in neurotoxicity and neutropenia,[158] diarrhea, alopecia and neurotoxicity[157] but no differences in the rate of toxic death were reported.[157] FOLFOXIRI as initial therapy for patients with metastatic colorectal disease has been added to the guidelines as a category 2B option.

The randomized phase III study E3200, conducted by Eastern Cooperative Oncology Group (ECOG) in patients who had progressed through a first line non-bevacizumab-containing regimen, demonstrated that the addition of bevacizumab to second-line FOLFOX4 modestly improved survival in these bevacizumab-naïve patients with previously-treated advanced colorectal cancer. Median overall survival was 12.9 months for patients receiving FOLFOX4 plus bevacizumab compared to 10.8 months for patients receiving FOLFOX4 alone (P=0.0011).[229] 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.[229] Because 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

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if they have progressed on a bevacizumab-containing regimen. If bevacizymab is not used in intial therapy, it may be appropriate to consider following first progression of disease.

The risk of stroke and other arterial events is increased in elderly patients receiving bevacizumab.[160] In addition, use of bevacizumab may interfere with wound healing[159,160,223] (see Principles of Management of Metastatic Disease), and gastrointestinal perforation is a rare, but important, side effect of bevacizumab therapy in patients with colorectal cancer.[159, 223] 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,[230] illustrating that peritoneal debulking surgery may be a risk factor for gastrointestinal perforation whereas the presence of an intact primary tumor does not appear to increase risk for gastrointestinal perforation.

With respect to the toxicities associated with capecitabine use, the panel noted that patients with diminished creatinine clearance may accumulate levels of the drug,[231] 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[223, 231] and that North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.[232] Such toxicities may necessitate modifications in the dosing of capecitabine, [223,231,233] 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.[219]

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[234,235] 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.[236] 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,[235,237] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[237] 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,[236] and a warning has been added to the label for Camptosar which indicates that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.[234] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[237] 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.

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Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[238] 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.[239] 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).[240] 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[226] and inferior to FOLFOX in the Intergroup trial[189]) 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,[185] or capecitabine should be used.[193]

Recently, cetuximab and panitumumab have been studied in combination with FOLFIRI[31, 209] and FOLFOX[29,207] as initial therapy options for treatment of metastatic colorectal cancer. A sizable body of recent literature has demonstrated that 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.[25-32] The panel therefore strongly recommends *KRAS* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer. Patients with known codon 12 or 13 *KRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, as there is virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is implied throughout the guidelines that NCCN recommendations involving cetuximab or panitumumab relate only to patients with disease characterized by the *KRAS* wild type gene. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS* gene, such testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see discussion on MS-3-MS-4).

Use of cetuximab as initial therapy for metastatic disease was investigated in the CRYSTAL trial where patients were randomly assigned to receive FOLFIRI with or without cetuximab.[31] Retrospective analyses of the subset of patients with known *KRAS*

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tumor status showed a statistically significant improvement in median PFS with the addition of cetuximab in the group with disease characterized by the *KRAS* wild-type gene (9.9 months vs. 8.7 months; hazard ratio=0.68; 95% CI, 0.50-0.94; P=0.02). The statistically significant benefit in PFS for patients with KRAS wild-type tumors receiving cetuximab was confirmed in a recent presentation of the final analysis of the CRYSTAL data.[40] In a retrospective evaluation of the subset of patients with known tumor *KRAS* status enrolled in the randomized phase II OPUS trial, addition of cetuximab to FOLFOX was associated with an increased objective response rate (61% vs. 37%; odds ratio=2.54; P=0.011) and a very slightly lower risk of disease progression by 15 days (7.7 months vs. 7.2 months; hazard ratio=0.57; 95% CI, 0.358-0.907; P=0.0163) compared with FOLFOX alone in the subset of patients with *KRAS* wild-type tumors.[29] Whereas data to support the statistically significant benefits in objective response rate and PFS for patients with tumors characterized by the *KRAS* wild –type gene were upheld in a recent update of this study, no median overall survival benefit was observed for the addition of cetuximab to chemotherapy (22.8 months in the cetuximab arm vs. 18.5 months in the arm receiving chemotherapy alone (hazard ratio=0.855; P=0.3854).[241]

Panitumumab in combination with either FOLFOX[207] or FOLFIRI[209] has been studied in the first-line treatment of patients with metastatic colorectal cancer. Results from a large, open-label, randomized trial comparing panitumumab plus FOLFOX versus FOLFOX alone in patients with *KRAS* wild-type advanced colorectal cancer showed a statistically significant improvement in progression-free survival with addition of panitumumab (hazard ratio=0.80; 95% CI, 0.66-0.97; P=0.02), although differences in overall survival between the 2 arms were not significant.[207] Furthermore, addition of panitumumab had a detrimental impact on PFS for patients with tumors characterized by mutated *KRAS*.

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 with or without cetuximab or panitumumab (*KRAS* wild type tumor only),[31,208] and irinotecan in combination with cetuximab[199] (*KRAS* wild-type tumor only) or as a single agent,[191] for patients who had received a FOLFOX or CapeOX-based regimen for initial therapy. Among patients with *KRAS* wild-type tumors enrolled in a large trial comparing FOLFIRI alone versus FOLFIRI plus panitumumab as second-line therapy for metastatic colorectal cancer, addition of the biologic agent was associated with improvement in median PFS (5.9 months vs. 3.9 months; hazard ratio=0.73; 95% CI, 0.59-0.90; P=0.004), although differences in overall survival between the 2 arms did not reach statistical significance.[208]

FOLFOX or CapeOX alone is an option for patients who received a FOLFIRI-based regimen as initial treatment. If cetuximab or panitumumab is used as part of an initial therapy regimen, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy. The recommendations regarding use of CapeOX in lieu of FOLFOX after first progression are supported by the results of studies demonstrating comparable efficacy of these 2 agents in initial therapy.[206] Other options for patients initially treated with a FOLFIRI-based regimen include cetuximab plus irinotecan, or single agent cetuximab or panitumumab for those not appropriate for the combination with irinotecan. For patients receiving 5-FU/LV without oxaliplatin or irinotecan as initial therapy, options after first progression include: FOLFOX, CapeOX, FOLFIRI or single agent irinotecan. The recommended option for patients experiencing disease progression on initial therapy with FOLFOXIRI is cetuximab plus irinotecan (for patients

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with tumors characterized by the wild-type *KRAS* gene only) or cetuximab or panitumumab alone for those with wild-type *KRAS* gene only who are not able to tolerate the combination.

Results from a randomized study to evaluate the efficacy of FOLFIRI and FOLFOX6 regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen following first progression showed neither sequence to be significantly superior with respect to PFS or median overall survival.[214] 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.[242] 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[48] or infusional 5-FU/LV.[243] In the study of Rougier et al.,[243] median overall survival was 4.2 months for irinotecan versus 2.9 months for 5-FU (P=0.030) whereas Cunningham et al.[244] reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive-care group (P-0.001). Furthermore, no significant differences in overall survival were observed in the Intergroup N9841 trial when FOLFOX was compared to irinotecan monotherapy following first progression of metastatic colorectal cancer.[245] Infusion of calcium and magnesium salts has been suggested as a potential means of limiting the neurotoxic effects of oxaliplatin. Data are limited on this topic but such an approach may be considered.

Cetuximab has been studied both a single agent,[33,199,246] and in combination with irinotecan,[199,247] for patients with disease progression on initial therapy for metastatic disease. However, it is important to note that *KRAS* testing was not done in the earlier studies; and unless otherwise specified in the text, it was not performed. 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.[246] In addition, 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.[248] In a retrospective analysis of the subset of patients in this trial with known *KRAS* tumor status, the benefit of cetuximab vs. best supportive care was shown to be enhanced to patients with *KRAS* wild-type tumors.[33] For those patients, median PFS was 3.7 months vs. 1.9 months (hazard ratio=0.40; 95% CI, 0.30-0.54; P<0.001) and median overall survival was 9.5 months vs. 4.8 months (hazard ratio=0.55; 96% CI, 0.41-0.74; P<0.001) in favor of the cetuximab arm. 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]).[199] 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.[249] 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

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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 the setting of metastatic colorectal cancer for patients with disease progression on both oxaliplatin and irinotecan-based chemotherapy[198]; 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). In a retrospective analysis of the subset of patients in this trial with known *KRAS* tumor status, the benefit of panitumumab vs. best supportive care was shown to be enhanced in patients with *KRAS* wild-type tumors.[24] PFS was 12.3 weeks vs. 7.3 weeks in favor of the panitumumab arm. Response rates to panitumumb were 17% vs. 0% in the wild-type and mutant arms, respectively.

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.[34,35] 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.[199] Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[34,35] Based on case reports, for those patients experiencing severe infusion reactions to cetuximab, administration of panitumumab appears to be feasible.[250,251] Skin toxicity is a side effect of both of these agents and is *not* considered to be part of the infusion reactions. The incidence and severity of skin reactions with cetuximab and panitumumab appears to be very similar; however, the presence and severity of skin rash in patients receiving either of these drugs has been shown to be predictive of increased response and survival.[31,32,248,252] A recent NCCN task force has addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.[253]

Results from 2 randomized phase III trials have demonstrated that combination therapy with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity. In the PACCE trial, addition of panitumumab to a regimen containing oxaliplatin- or irinotecan-based chemotherapy plus bevacizumab was associated with significantly shorter PFS and higher toxicity in both *KRAS* wild-type and mutant groups.[254] Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab.[255] Therefore, the panel strongly recommends against the use of therapy involving the concurrent combination of an anti-EGFR agent and an anti-VEGF agent.

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.[199] A similar conclusion was drawn with respect to panitumumab.[256] Therefore, routine EGFR testing is not recommended, and no patient should be either considered for or

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excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.

With respect to the treatment continuum for metastatic colorectal cancer, there are no prospective data to support the addition of bevacizumab to a regimen following clinical failure of a previous bevacizumab-containing regimen, and continuation of bevacizumab beyond disease progression is not recommended. If bevacizumab is not used in initial therapy, it may be appropriate to consider adding it to chemotherapy following progression of metastatic disease.[229]

A 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.[257] For patients with impaired tolerance to aggressive initial therapy, the guideline includes recommendations for single-agent capecitabine,[193,194] infusional 5-FU/leucovorin,[185] with or without bevacizumab, or single agent cetuximab or panitumumab for patients with *KRAS* wild-type tumors only (category 2B). Although a comparison of capecitabine plus bevacizumab versus capecitabine alone as initial therapy for metastatic cancer has not been done, CapeOX plus bevacizumab has been shown to be superior to CapeOX alone in this setting.[206,219, 220,223]

Metastatic cancer patients with no improvement in functional status should receive best supportive care. Patients showing improvement in functional status should be treated with one of the options specified for therapy after first progression as described above.

The panel recommends that progression of disease following treatment with an EGFR inhibitor alone or a regimen including cetuximab and irinotecan should be followed by either best supportive care or enrollment in a clinical trial. The panel recommends against the use of capecitabine, mitomycin, alfa-interferon, taxanes, methotrexate, pemetrexed, sunitinib, sorafinib, erlotinib, or gemcitabine, either as single agents or in combination, as salvage therapy in patients exhibiting disease progression following treatment with standard therapies. These agents have not been shown to be effective in this setting. No objective responses were observed when single agent capecitabine was administered in a phase II study of patients with colorectal cancer resistant to 5-FU.[258]

Post-Treatment Surveillance

Following curative-intent surgery and adjuvant chemotherapy, if administered, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and to identify new metachronous neoplasms at a preinvasive stage. Advantages of more intensive follow-up of stage II and/or stage III patients have been demonstrated prospectively in several studies[259-261] and in three recent meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[262-265] 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,[92] 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

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for more intensive post-treatment follow-up in these patients.[266] Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.[267,268]

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,[269] then every 6 months for the next 5 years if the clinician determines that the patient is a potential candidate for aggressive curative surgery.[265,269,270] 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.[270] 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. [265,268] Routine PET-CT scanning is not recommended and should not be obtained either as a routine pre-operative baseline study or for routine surveillance.

Initial follow-up office visits at 3 month intervals for history and physical examination may be more useful for patients diagnosed with stage III disease, whereas patients with a diagnosis of stage I disease may not need to be seen as frequently (ie, can be seen once every 6 months). This principle also applies to CEA testing, which is used primarily to monitor for indication of recurrence of disease (see section on Managing an Increasing CEA Level), although post-treatment CEA testing is recommended only if the patient is a potential candidate for further intervention.[269] Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps,[270] since data show that patients with a history of colorectal cancer have an increased risk of developing second cancers,[271] particularly in the first 2 years following resection.[270] 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.[270] The recommended frequency of post-treatment surveillance colonoscopies is higher (ie, annually) for patients with HNPCC.[270] CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver.[265] Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases.[265,268] Post-treatment PET-CT scan is not routinely recommended for surveillance of patients with resected early-stage colorectal cancer.[268] Furthermore, PET-CT scan is not routinely recommended to detect metastatic disease in the absence of other evidence of such disease.

Post-treatment surveillance also includes a survivorship care plan involving disease preventive measures such as immunizations against influenza and pneumococcal infections at prescribed intervals and regular dental care, and early disease detection through periodic screening for second primary cancers (eg, breast, cervical, or prostrate cancers) and routine health monitoring to screen for comorbid conditions including psychosocial distress associated with colon cancer and its treatment. A survivorship care plan for patients with colorectal cancer has recently been published.[272]

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Other recommendations include monitoring for late sequelae of colon cancer or the treatment of colon cancer, such as: chronic diarrhea or incontinence (eg, patients with stoma)[273]; persistent neuropathy - a well known side effect of oxaliplatin treatment.[87].Specific management interventions to address these side effects are described in a recent review.[274]

There is also evidence to indicate that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy body mass index (BMI), engaging in regular exercise, and making certain dietary choices are associated with improved outcomes following treatment for colon cancer. For example, a retrospective study of patients with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI ≥35 kg/m2 had an increased risk of disease recurrence and death.[275] In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, disease-free survival was found to be directly correlated with how much exercise these patients received.[276] Furthermore, a diet consisting of more fruits, vegetables, poultry and fish, and less red meat, as well as diets higher in whole grains and lower in refined grains and concentrated sweets, was found to be associated with an improved outcome in terms of cancer recurrence or death.[277] In addition, a recent study of a large cohort of men treated for stage I-stage III colorectal cancer demonstrated an association between increased physical activity and lower rates of colorectal cancer-specific mortality and overall mortality.[278] A discussion of lifestyle characteristics which may be associated with a decreased risk of colon cancer recurrence also provides “a teachable moment” for the promotion of overall health, and an opportunity to encourage patients to make choices and changes compatible with a healthy lifestyle.

Panel recommendations for surveillance of patients with stage IV NED disease following curative-intent surgery and subsequent adjuvant treatment are similar to those listed for patients with early-stage disease with one exception being that certain evaluations are performed more frequently. Specifically, the panel recommends that these patients undergo contrast-enhanced CT 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. Again, routine use of PET-CT scans for surveillance is not recommended.

Managing an Increasing Carcinoembryonic Antigen Level

Managing patients with an elevated CEA level after resection should include colonoscopy, chest, abdominal, and pelvic CT scans, physical examination, and consideration of PET-CT scan. If imaging study results are normal in the face of a rising CEA, repeat CT scans recommended every 3 months until either disease is identified or CEA level stabilizes or declines. The opinion of the panel on the usefulness of PET-CT scan in the scenario of an elevated CEA with negative, good-quality CT scans was divided (ie, some panel members favored use of PET-CT in this scenario while others noted that the likelihood of PET-CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). Use of PET-CT scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called "blind” or “CEA-directed” laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,[279] nor is the use of anti-CEA-radiolabeled scintigraphy

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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 all original sites of disease are amenable to resection (R0) and/or ablation. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease or when a response to chemotherapy may convert a patient from an unresectable to a resectable state (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, as well as a survivorship plan to manage long-term side effects of treatment, facilitate disease prevention, and promote a healthy lifestyle. Recommendations for patients with disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, including plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy options for advanced or metastatic disease depend on whether or not the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOX, and FOLFOXIRI (category 2B). Addition of a biologic agent (eg, bevacizumab, cetuximab, or panitumumab) is either recommended, or listed as an option, in combination with some of these regimens, depending on available data. Chemotherapy options for patients with progressive disease are dependent on the choice of initial therapy.

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Discussion update in progress