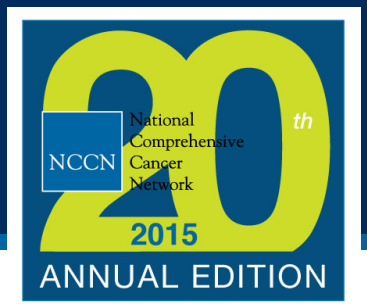

NCCN National Comprehensive Cancer Network®

Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer

Version 2.2015

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NCCN Guidelines Version 2.2015 Panel Members
Colon Cancer

NCCN Guidelines Index
Colon Cancer Table of Contents
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≠ Pathology
‡ Hematology/Hematology oncology
Þ Internal medicine
ϕ Diagnostic/Interventional radiology
¤ Gastroenterology
¥ Patient advocate
*Writing Committee Member

NCCN Guidelines Panel Disclosures

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NCCN Guidelines Version 2.2015 Table of Contents
Colon Cancer

NCCN Guidelines Index
Colon Cancer Table of Contents
Discussion

Clinical Trials: 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 2.2015 Updates Colon Cancer

NCCN Guidelines Index
Colon Cancer Table of Contents
Discussion

Updates in Version 2.2015 of the NCCN Guidelines for Colon Cancer from Version 1.2015 include:

MS-1

- **The discussion section was updated to reflect the changes in the algorithm.**

Updates in Version 1.2015 of the NCCN Guidelines for Colon Cancer from Version 3.2014 include:

COL-1

- **Clinical presentation modified: "Pedunculated or sessile polyp (adenoma ~~[tubular, tubulovillous, or villous]~~) with invasive cancer."**
- **Workup, bullet 3 modified: "Marking of cancerous polyp site (at time of colonoscopy or within 2 weeks *if deemed necessary by the surgeon).*"**

COL-2

- **For patients with resectable, obstructing colon cancer, the option of stent was added in selected cases.**

COL-5

- **Workup, bullet 5 modified: "Determination of tumor ~~RAS (KRAS/NRAS)~~ gene status *for RAS (KRAS exon 2 and non-exon 2, and NRAS) and BRAF* ~~(if RAS non-mutated, consider BRAF testing)~~." (also applies to footnote "jj" on COL-9)**
- **Workup, bullet 7 modified: "*Consider* PET-CT scan ~~only~~ if potentially surgically curable M1 disease *in selected cases*."**
- **Footnote "aa" added with reference, Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA 2014;311:1863-1869. (also applies to COL-9)**
- **The finding "Synchronous unresectable metastases of other sites" was added with link to the treatment recommendations for "Chemotherapy for Advanced or Metastatic Disease (COL-C 1 of 9)."**
- **Footnote "bb" added: "Consider colon resection only if imminent risk of obstruction or significant bleeding."**

COL-6

- **~~Colectomy, with~~ "Synchronous or staged *colectomy with* liver or lung resection."**
- **FOLFOX + cetuximab added as a treatment option with the following footnote "ff": "There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases." (also applies to COL-7)**
- **Footnote "hh" added: "Total duration of perioperative chemotherapy should not exceed 6 months." (also applies to COL-7)**

COL-7

- **FOLFOXIRI ± bevacizumab: category recommendation changed from a 2B to a 2A.**

COL-8

- **Primary treatment: "Diverting colostomy" changed to "Diverting ostomy."**

COL-11

- **First column: CapeOx listed in addition to FOLFOX in previous therapy.**

COL-A 4 of 5

- **KRAS mutation testing, bullet 1 modified: "All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS mutations (KRAS and NRAS). ~~At the very least, exon 2 KRAS mutation status should be determined. Whenever possible, non-exon 2 KRAS mutation status and NRAS mutation status should also be determined.~~ Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab."**
- **Bullets combined for KRAS, NRAS, and BRAF Mutation Testing.**

Updates in Version 1.2015 of the NCCN Guidelines for Colon Cancer from Version 3.2014 include:

COL-C 1 of 9
- **"FOLFOX + cetuximab (KRAS/NRAS WT gene only)" added as a treatment option for Initial therapy.**

COL-C 3 of 9
- **FOLFOXIRI ± bevacizumab: category recommendation changed from a 2B to a 2A.**

COL-C 5 of 9
- **Footnote deleted: "Data are not mature for the addition of biologic agents to FOLFOXIRI."**

COL-C 6 of 9
- **FOLFOX + cetuximab regimen added with reference.**

COL-C 8 of 9
- **The following irinotecan dose added: or Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1. Repeat every 2 weeks.**
- **The following note added to FOLFOXIRI: "The dose of 5-FU listed here was used in European studies. U.S. patients have been shown to have poorer tolerance for 5-FU. A starting dose of 5-FU consistent with the dose recommended in FOLFOX or FOLFIRI should be strongly considered for U.S. patients."**

COL-E 1 of 2
- **Bullet 1 modified: "FOLFOX is superior to *5-FU/leucovorin* ~~fluoropyrimidine therapy alone~~ for patients with stage III colon cancer. *Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin for patients with stage III colon cancer.* ~~FOLFOX is reasonable for high-risk or intermediate-risk stage II patients and is not indicated for good- or average-risk patients with stage II colon cancer.~~ FLOX is an alternative to FOLFOX *or CapeOx but FOLFOX or CapeOx are preferred*."**
- **Bullet 3 modified: "A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. *FOLFOX is reasonable for high-risk stage II patients and is not indicated for good- or average-risk patients with stage II colon cancer."***
- **Bullet 5 deleted: "Bolus 5-FU/leucovorin/irinotecan should not be used in adjuvant therapy, and infusional 5-FU/leucovorin/irinotecan (FOLFIRI) has not been shown to be superior to 5-FU/LV. Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin."**

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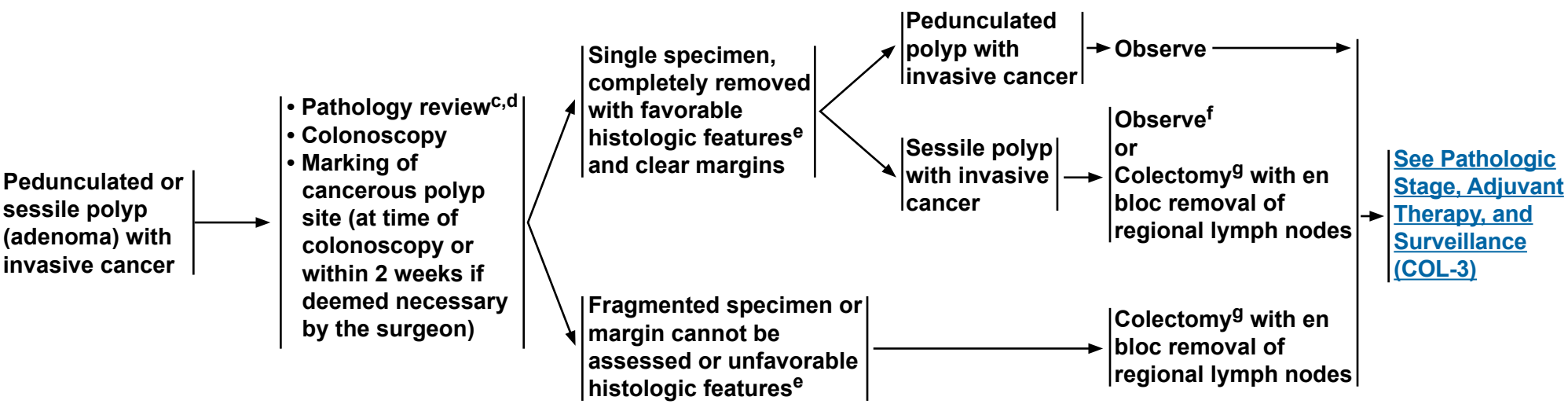

[a]Small bowel and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to the NCCN Guidelines for Colon Cancer. Peritoneal mesothelioma and other extrapleural mesotheliomas may be treated with systemic therapy along NCCN Guidelines for Malignant Pleural Mesothelioma, as outlined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

[b]All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

[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 significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than polypoid malignant polyps. See Principles of Pathologic Review (COL-A) - Endoscopically removed malignant polyp.

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

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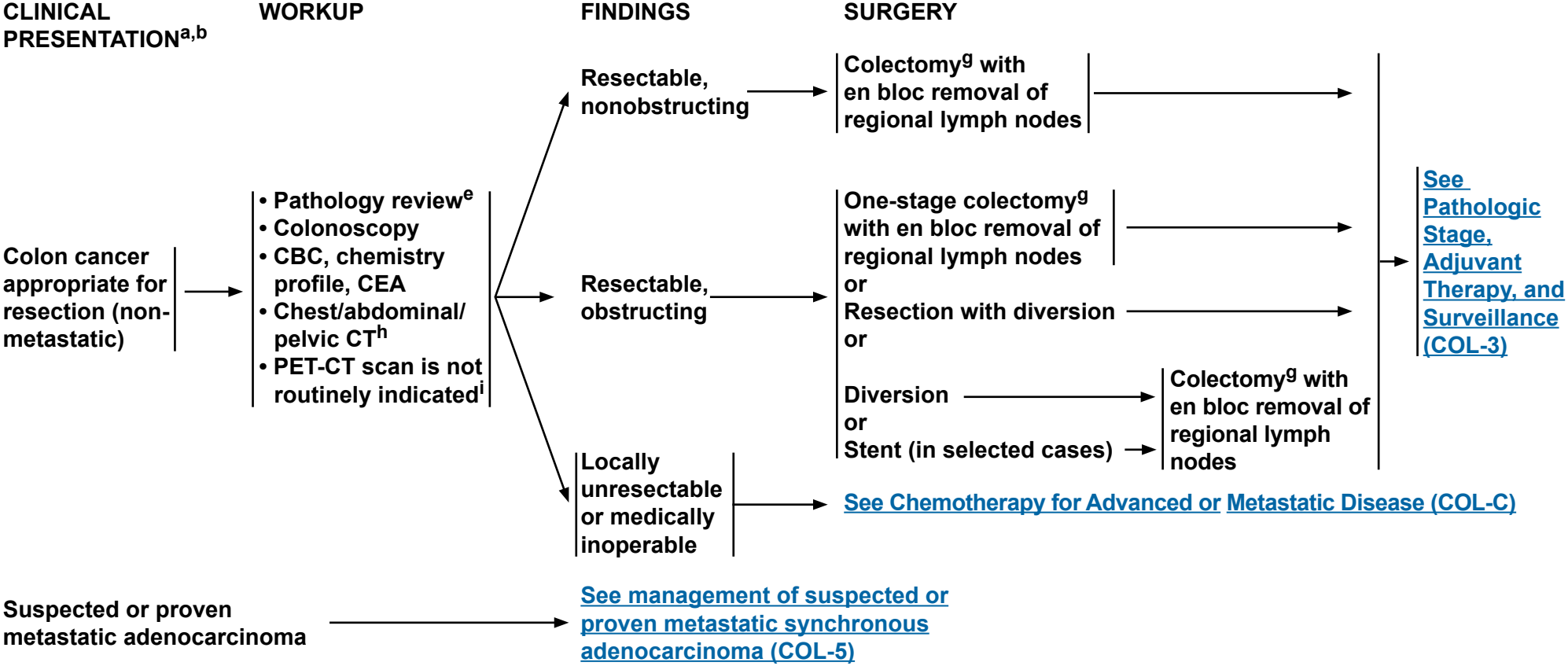

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[e]See Principles of Pathologic Review (COL-A) - Colon cancer appropriate for resection, pathologic stage, and lymph node evaluation.

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

[h]CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

[i]PET-CT does not supplant a contrast-enhanced diagnostic CT scan. PET-CT should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or in patients with strong contraindications to IV contrast.

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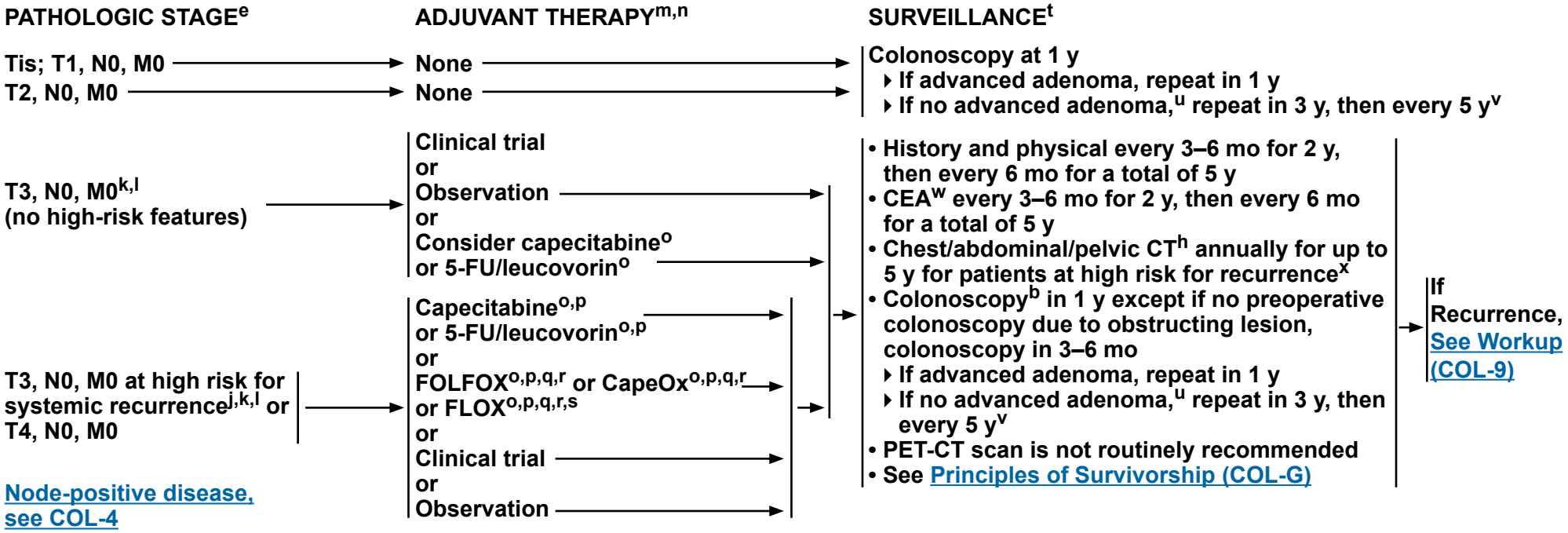

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[e] See Principles of Pathologic Review (COL-A) - Pathologic stage.

[h] CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

[j] High-risk factors for recurrence: poorly differentiated histology (exclusive of those cancers that are MSI-H), lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.

[k] Testing for mismatch repair (MMR) proteins should be considered for all patients <70 years of age or with stage II disease. Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-3226. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20498393.

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

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

[n] 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).

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

[q] A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tournigand C, André T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly (between ages 70 and 75 years) with colon cancer: a subgroup analyses of the Multicenter International Study of oxaliplatin, fluorouracil, and leucovorin in the adjuvant treatment of colon cancer trial. J Clin Oncol 2012; published online ahead of print on August 20, 2012.

[r] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.

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

[t] 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.

[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.

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

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

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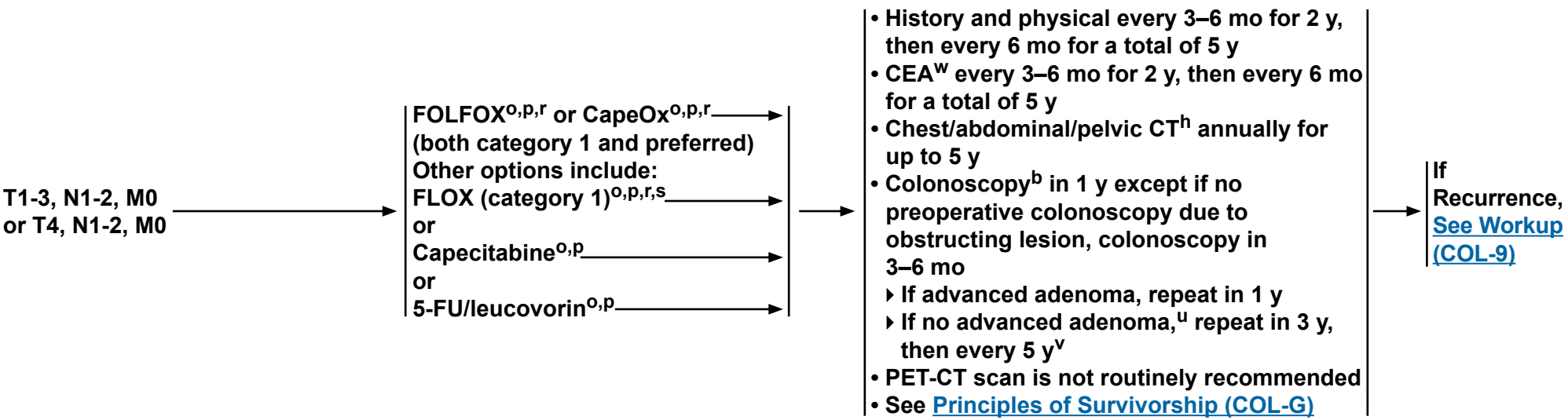

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[e]See Principles of Pathologic Review (COL-A) - Pathologic stage.

[h]CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

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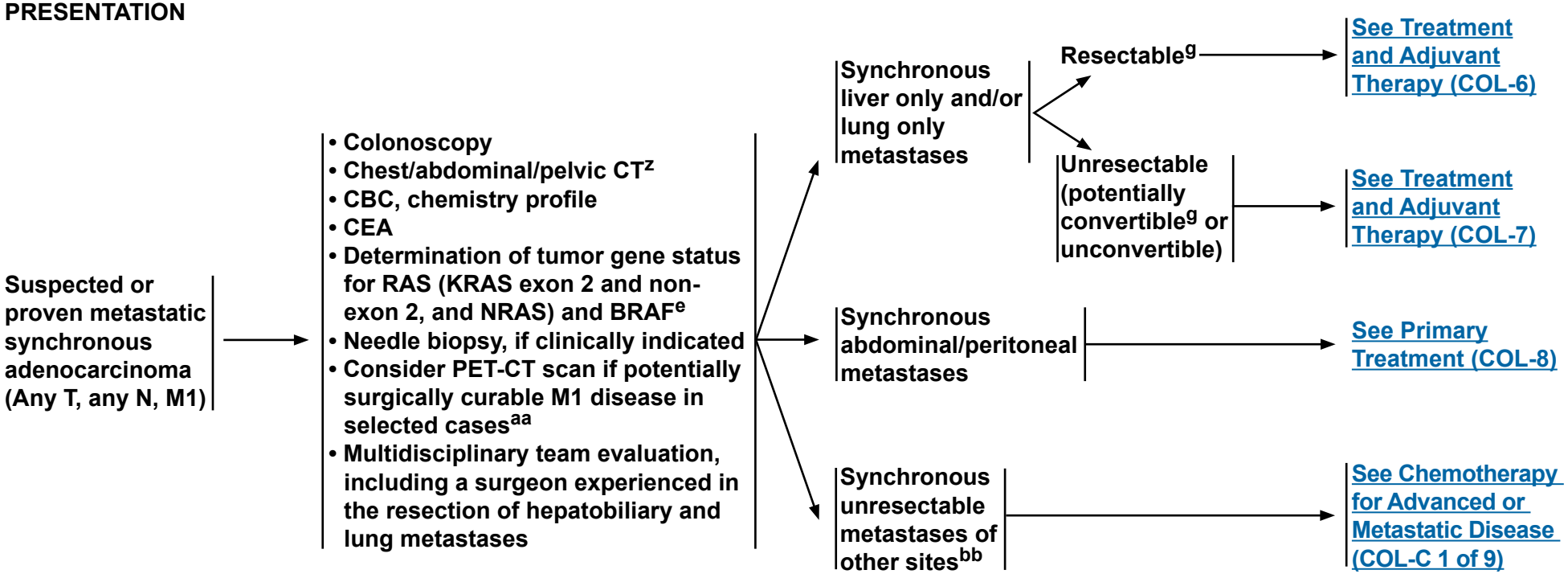

[e] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS and BRAF Mutation Testing.
[g] See Principles of Surgery (COL-B 2 of 3).
[z] CT should be with IV contrast. Consider MRI with IV contrast if CT is inadequate.
[aa] Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA 2014;311:1863-1869.
[bb] Consider colon resection only if imminent risk of obstruction or significant bleeding.

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

Synchronous or staged colectomy[cc] with liver or lung resection
or
Neoadjuvant therapy (for 2–3 months)
FOLFIRI or FOLFOX or CapeOx[dd] ± bevacizumab[ee] or FOLFIRI or FOLFOX ± panitumumab or cetuximab[ff] (KRAS/NRAS wild-type [WT] gene only)[e,gg] followed by synchronous or staged colectomy[cc] and resection of metastatic disease
or
Colectomy,[cc] followed by chemotherapy (for 2–3 months)
FOLFIRI or FOLFOX or CapeOX[dd] ± bevacizumab[ee] or FOLFIRI or FOLFOX ± panitumumab or cetuximab[ff] (KRAS/NRAS WT gene only)[e,gg] and staged resection of metastatic disease

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

FOLFOX/CapeOx preferred

Consider observation or shortened course of chemotherapy

Consider observation or shortened course of chemotherapy

SURVEILLANCE

If patient stage IV, NED:
- **History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y**
- **CEA every 3–6 mo x 2 y, then every 6 mo x 3–5 y**
- **Chest/abdominal/pelvic CT[h] 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]**

If Recurrence, See Workup (COL-9)

[b]All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

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

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[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.

[y]Testing for mismatch repair (MMR) proteins should be considered for all patients <70 years of age.

[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]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.

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

[ff]There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.

[gg]There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status.

[hh]Total duration of perioperative chemotherapy should not exceed 6 months.

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

- **Systemic therapy (FOLFIRI or FOLFOX or CapeOX[dd] ± bevacizumab[ee] or FOLFIRI or FOLFOX ± panitumumab or cetuximab[ff] [KRAS/NRAS WT gene only][e,gg] or FOLFOXIRI ± bevacizumab**
- **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**

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

ADJUVANT THERAPY[y] (6 MO PERIOPERATIVE TREATMENT PREFERRED)[hh]

Active chemotherapy regimen for advanced disease (See COL-C)[cc] (category 2B) or Consider observation or shortened course of chemotherapy

SURVEILLANCE

If patient stage IV, no evidence of disease (NED):

- **History and physical every 3–6 mo x 2 y, then every 6 mo for a total of 5 y**
- **CEA every 3–6 mo x 2 y, then every 6 mo x 3–5 y**
- **Chest/abdominal/pelvic CT[h] 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**
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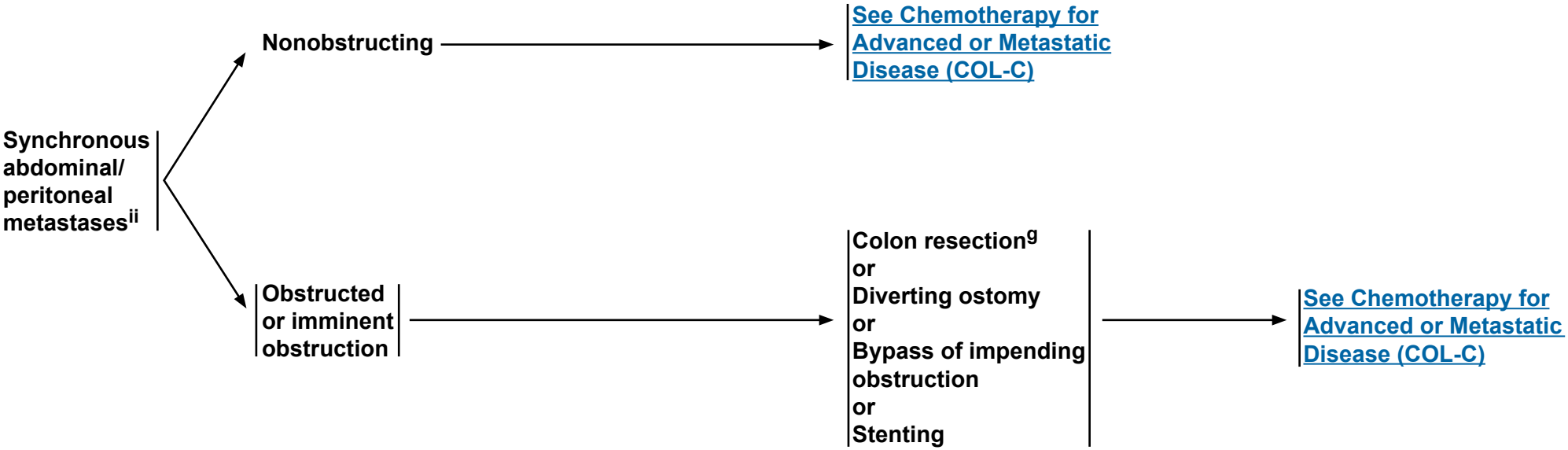
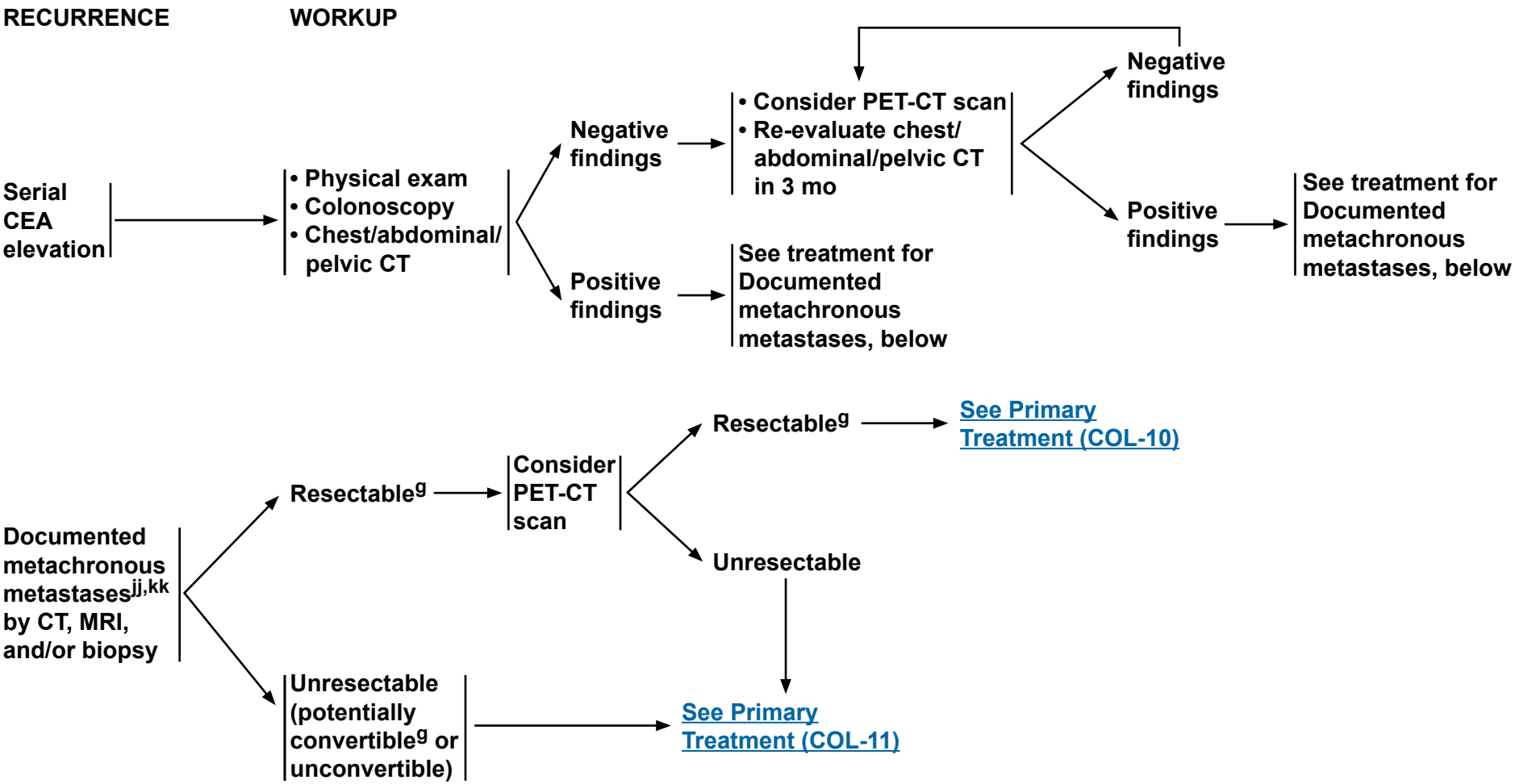
See Recurrence (COL-9)

FINDINGS | **PRIMARY TREATMENT**



[g] See Principles of Surgery (COL-B 2 of 3).
[ii] Aggressive cytoreductive debulking and/or intraperitoneal chemotherapy are not recommended outside the setting of a clinical trial.

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



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

[jj] Determination of tumor gene status for RAS (KRAS exon 2 and non-exon 2, and NRAS) and BRAF. See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS and BRAF Mutation Testing.

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

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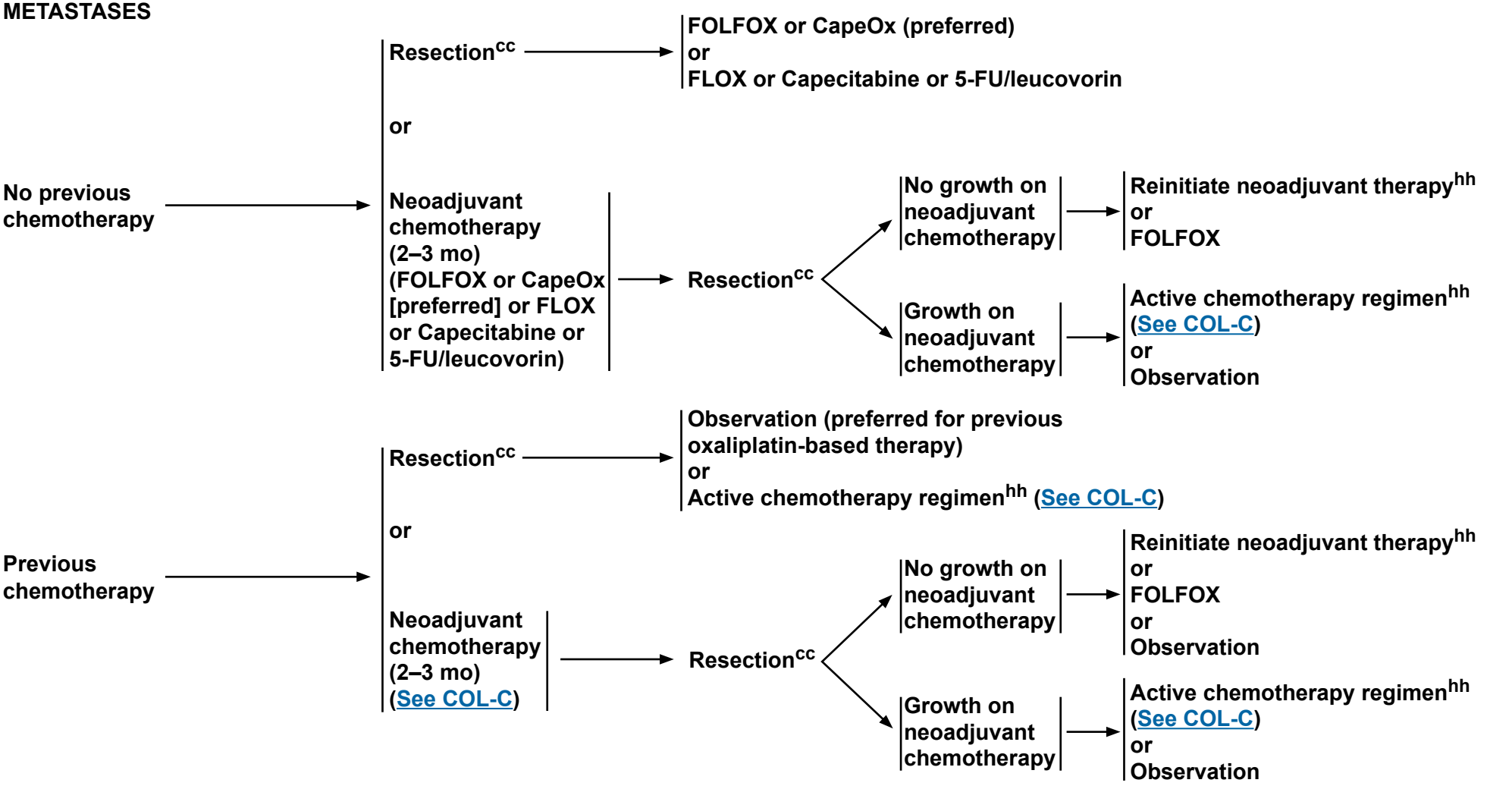

[cc]Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

[hh]Total duration of perioperative chemotherapy should not exceed 6 months..

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UNRESECTABLE METACHRONOUS METASTASES

PRIMARY TREATMENT

- **Previous adjuvant FOLFOX/CapeOx within past 12 months**

→ **FOLFIRI ± bevacizumab**
or
FOLFIRI ± ziv-aflibercept
or
Irinotecan ± bevacizumab
or
Irinotecan ± ziv-aflibercept
or
FOLFIRI + (cetuximab or panitumumab) (KRAS/NRAS WT gene only)[e,ll]
or
(Cetuximab or panitumumab) (KRAS/NRAS WT gene only)[e,ll] + irinotecan

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

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

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

→ **Converted to resectable** → **Resection[cc]** → **Active chemotherapy regimen[hh] (See COL-C)**
or
Observation

→ **Remains unresectable** → **Active chemotherapy regimen (See COL-C)**

[e] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS and BRAF Mutation Testing.
[g] 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] Total duration of perioperative chemotherapy should not exceed 6 months.
[ll] Patients with a V600E BRAF mutation appear to have a poorer prognosis. Limited available data suggest a lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after a 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 histologic 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, and 3) tumor cells present within the diathermy of the transected margin.[1-4]
- Unfavorable histologic features: grade 3 or 4, angiolymphatic invasion, or a "positive margin." See the 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, and 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 margins, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.[3-7]

Colon Cancer Appropriate for Resection

- Histologic confirmation of primary colonic malignant neoplasm.

Pathologic Stage

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

See Pathologic Stage (continued) on COL-A 2 of 5
See Lymph Node Evaluation on COL-A 3 of 5
See KRAS, NRAS, and BRAF Mutation Testing on COL-A 4 of 5
See references on COL-A 5 of 5

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PRINCIPLES OF PATHOLOGIC REVIEW (2 of 5)

Pathologic Stage (continued)

- **Radial (circumferential) margin evaluation - The serosal surface (peritoneal) does not constitute a surgical margin. In colon cancer the circumferential (radial) margin represents the adventitial soft tissue closest to the deepest penetration of tumor, and is created surgically by blunt or sharp dissection of the retroperitoneal aspect. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. The circumferential resection margin corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells, and must be dissected from the retroperitoneum to remove the viscus. On pathologic examination it is difficult to appreciate the demarcation between a 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 the peritoneum.[10-11]**
- **PNI - The presence of PNI 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* = .0005]).[12-14]**
- **Extra nodal tumor deposits - Irregular discrete tumor deposits in pericolic or perirectal fat away 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, PNI. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report. This poorer outcome has also been noted in patients with stage III carcinoma.[15-18]**

See Endoscopically Removed Malignant Polyps and Colon Cancer Appropriate for Resection on COL-A 1 of 5
See Lymph Node Evaluation on COL-A 3 of 5
See KRAS, NRAS, and BRAF Mutation Testing on COL-A 4 of 5
See references on COL-A 5 of 5

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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, and >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 fewer 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 histologic and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple hematoxylin and eosin (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 Manual and Handbook[35] considers “tumor clusters” <0.2 mm to be 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, 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 to be micrometastases.[37-42]
- At the present time the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.[30-34,38-42]

See Endoscopically Removed Malignant Polyp and Colon Cancer Appropriate for Resection on COL-A 1 of 5

See Pathologic Stage on COL-A 2 of 5

See KRAS, NRAS, and BRAF Mutation Testing on COL-A 4 of 5

See references on COL-A 5 of 5

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PRINCIPLES OF PATHOLOGIC REVIEW (4 of 5)

KRAS, NRAS, and BRAF Mutation Testing

- **All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS mutations (KRAS and NRAS). Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab.[43,44,45]**
- **Patients with a V600E BRAF mutation appear to have a poorer prognosis. There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF 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 a patient has progressed on first-line therapy.[46,47]**
- **Testing for KRAS, NRAS, and BRAF mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).**
- **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, NRAS, and BRAF mutations are similar in both specimen types.[48]**

MSI Testing - See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal

- **Lynch syndrome tumors screening (ie, IHC or MSI) should be considered for CRC patients diagnosed at age ≤70 y and also those >70 y who meet the Bethesda guidelines.[49]**

See Endoscopically Removed Malignant Polyps and Colon Cancer Appropriate for Resection on COL-A 1 of 5
See Pathologic Stage on COL-A 2 of 5
See Lymph Node Evaluation on COL-A 3 of 5
See references on COL-A 5 of 5

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF PATHOLOGIC REVIEW - References (5 of 5)

[1]Volk EE, Goldblum JR, Petras RE, et al. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. Gastroenterology 1995;109:1801-1807.
[2]Cooper HS, Deppisch LM, Gourley WK, et al. Endoscopically removed malignant colorectal polyps: clinical pathological correlations. Gastroenterology 1995;108:1657-1665.
[3]Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 2004;127:385-394.
[4]Seitz U, Bohnacker S, Seewald S, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal polyps? Presentation of 114 patients and review of the literature. Dis Colon Rectum 2004;47:1789-1797.
[5]Morson BC, Whiteway JE, Jones EA, et al. Histopathology and prognosis of malignant colorectal polyps treated by endoscopic polypectomy. Gut 1984;25:437-444.
[6]Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology 1985;89:328-336.
[7]Netzer P, Binck J, Hammer B, et al. Significance of histological criteria for the management of patients with malignant colorectal polyps. Scand J Gastroenterol 1997;323:915-916.
[8]Compton CC and Greene FL. The staging of colorectal cancer: 2004 and beyond. Ca Cancer J Clin 2004;54:295-308.
[9]Compton CC, Fielding LP, Burgardt LJ, et al. Prognostic factors in colorectal cancer. College of American pathologists consensus statement. Arch Pathol Lab Med 2000;124:979-994.
[10]Washington MK, Berlin J, Branton P, et al. Protocol for examination of specimens from patients with primary carcinoma of the colon and rectum. Arch Pathol Lab Med 2009;133:1539.
[11]Edge SB, Byrd D, Compton C, et al (eds). AJCC Cancer Staging Manual 7th Edition. Springer NY, 2010.
[12]Liebig C, Ayala G, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clin Oncol 2009;27:5131-5137.
[13]Fujita S, Shimoda T, Yoshimura K, et al. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. J Surg Oncol 2003;84:127-131.
[14]Quah HM. Identification of patients with high risk stage II colon cancer for adjuvant therapy. Dis Colon Rect 2008;51:53-507.
[15]Goldstein NS and Turner JR. Percolonic tumor deposits in patients with T3N+M0: adenocarcinoma. Cancer 2000;88:2228-2238.
[16]Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. J Clin Pathol 2007;117:287-294.
[17]Lo DS, Pollett A, Siu LL, et al. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. Cancer 2008;112:50-54.
[18]Puppa G, Maisonneuve P, Sonzogni A, et al. Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. Mod Pathol 2007;20:843-855.
[19]Sobin HL, and Greene FL. TNM classification. Clarification of number of regional lymph nodes for pN0. Cancer 2001;92:452.
[20]Le Voyer TE, Sigurdson ER, Hamlin AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survery of intergroup trial INT-0089. J Clin Oncol 2003;21:2912-2919.
[21]Sarli L, Bader G, Lusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. European Journal of Cancer 2005;41:272-279.
[22]Swanson RS, Compton CC, Stewart AK, and Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003;10:65-71.
[23]Caplin S, Scerottini G-P, Bosman FT, Konstanda MT, Givel J-C. For patients with Duke's B (TNM stage II) colorectal carcinoma, examination of six or fewer lymph nodes is related to poor prognosis. Cancer 1998;83:666-72.
[24]Maurel J, Launoy G, Grosclaude P, et al. Lymph node harvest reporting in patients with carcinoma of the large bowel. A French population-based study. Cancer 1998;82:1482-6.
[25]Pocard M, Panis Y, Malassagane B, et al. Assessing the effectiveness of mesorectal excision in rectal cancer. Dis Colon Rectum 1998;41:839-845.
[26]Joseph NE, Sigurdson ER, Hamlin AL, et al. Accuracy of determining nodal negativity in colorectal cancer on the basis of number of nodes retrieved on resection. Ann of Surg Oncol 2003;10:213-218.
[27]Goldstein NS. Lymph node recurrences from 2427 pT3 colorectal resection specimens spanning 45 years. Recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. Am J Surg Pathol 2002;26:179-189.
[28]Scott KWM and Grace RH. Detection of lymph node metastasis and colorectal carcinoma before and after fat clearance. Br J Surg 1989;76: 1165-1167.
[29]Johnson PM, Porter GA, Ricciardi R and Baxter NN. Increasing negative lymph node count is independently associated with improved long term survival in stage IIIB and IIIC colon cancer. J Clin Oncol 2006;24:3570-3575.
[30]Turner RR, Nora DT, Trochas D, and Bilchik AJ. Colorectal carcinoma in nodal staging. Frequency and nature of cytokeratin positive cells in sentinal and nonsentinal lymph nodes. Arch Pathol Lab Med 2003;127:673-679.
[31]Saha S, Van AG, Beutler T, et al. Sentinal lymph mapping techniques in colorectal cancer. Sem Oncol 2004;31:374-81.
[32]Wood TF, Nora DT, Morton DL, et al. One hundred consecutive cases of sentinal node mapping in early colorectal carcinoma. Detection of missed micrometastasis. J Gastrointest Surg 2002;6:322-330.
[33]Wiese DA, Sha S, Badin J, et al. Pathological evaluation of sentinel lymph nodes in colorectal carcinoma. Arch Pathol Lab Med 2000;124:1759-1763.
[34]Bertagnolli M, Miedema B, Redstone M, et al. Sentinal node staging of resectable colon cancer. Results of a multicenter study. Ann Surg 2004;240:624-630.
[35]AJCC Cancer Staging Manual, 7th ed. Edge SB, Byrd D, Compton CC, et al. (editors) Springer, New York, 2010.
[36]Jass JB, O'Brien MJ, Riddell RH, Snover DC, on behalf of the Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of surgically resected specimens of colorectal carcinoma. Hum Pathol 2007;38:537-545.
[37]Hermanek P, Hutter RVP, Sobin LH, Wittekind CH. Classification of isolated tumor cells and micrometastasis. Cancer 1999;86:2668-73.
[38]Noura S, Yamamoto H, Ohnishi T, et al. Comparative detection of lymph node micrometastasis of stage II colorectal cancer by reverse transcriptase polymerase chain reaction in immunohistochemistry. J Clin Oncol 2002;20:4232-4241.
[39]Yasuda K, Adachi Y, Shiraishi N, et al. Pattern of lymph node micrometastasis and prognosis of patients with colorectal cancer. Ann Surg Oncol 2001;8:300-304.
[40]Noura S, Yamamoto H, Miyake Y, et al. Immunohistochemical assessment of localization of frequency of micrometastasis in lymph nodes of colorectal cancer. Clin Cancer Research 2002;8: 759-767.
[41]Oberg A, Stenling R, Tavelin B, Lindmark G. Are lymph node micrometastasis of any clinical significance in Duke stages A and B colorectal cancer? Dis Colon Rectum 1998;41:1244-1249.
[42]Greenson JK, Isenhart TCE, Rice R, et al. Identification of occult micrometastasis in pericolonic lymph nodes of Duke's B colorectal cancer. Patient's using monoclonal antibodies against cytokeratin and CC49. Correlation with long term survival. Cancer 1994;73:563-9.
[43]Lievre A, Bachatte J-B, Blige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with Cetuximab. J Clin Oncol 2008;26:374-379.
[44]Amado IG, Wolf M, Peters M, et al. Wild-type KRAS is required for panitunumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-1634.
45Douillard JY, Oliner KS, Siena S, et al. Panitumumab--FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-1034.
[46]Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26:5705-5712.
[47]Bokemeyer C, Cutsem EV, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer 2012;48:1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22446022.
[48]Etienne-Gimeldi M-C, Formenta J-L, Francoual M, et al. KRAS mutations in treatment outcome in colorectal cancer in patients receiving exclusive fluoropyrimidine. Clin Cancer Research 2008;14:4830-4835.
[49]Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308:1555-1565.

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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.**
  - **Clinically positive lymph nodes outside the field of resection that are considered suspicious should be biopsied or removed, if possible.**
  - **Positive nodes left behind indicate an incomplete (R2) resection.**
  - **A minimum of 12 lymph nodes need to be examined to establish N stage.[1]**
- **Laparoscopic-assisted colectomy may be considered based upon the following criteria:[2]**
  - **The surgeon has experience performing laparoscopically assisted colorectal operations.[3,4]**
  - **There is no locally advanced disease.**
  - **It is 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 or clinically suspected HNPCC**
  - **Consider more extensive colectomy for patients with a strong family history of colon cancer or young age (<50 y).**

  See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
- **Resection needs to be complete to be considered curative.**

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

See footnotes on COL-B 3 of 3

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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] Having a plan for a debulking resection (less than an R0 resection) is not recommended.[7]
- Patients with resectable metastatic disease and a 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 (category 3) in highly select patients with chemotherapy-resistant/-refractory disease, without obvious systemic disease, with predominant hepatic metastases.
- Conformal external beam radiation therapy (category 3) 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.
- 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 COL-B 3 of 3

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PRINCIPLES OF SURGERY - REFERENCES (3 of 3)

[1]LeVoyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol 2003;21:2912-2919.
[2]The Clinical Outcomes of Surgical therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050-2059.
[3]Wishner JD, Baker JW, Jr., Hoffman GC, et al. Laparoscopic-assisted colectomy. The learning curve. Surg Endosc 1995;9:1179-1183.
[4]Nelson H, Weeks JC, Wieand HS. Proposed phase III trial comparing laparoscopic-assisted colectomy versus open colectomy for colon cancer. J Natl Cancer Inst Monogr 1995:51-56.
[5]Ota DM, Nelson H, Weeks JC. Controversies regarding laparoscopic colectomy for malignant diseases. Curr Opin Gen Surg 1994:208-213.
[6]Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818-825; discussion 825-7.
[7]Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13:1261-8.
[8]Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. J Clin Oncol 1997;15:938-946.
[9]Nordlinger B, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Surgical resection of liver metastases from colo-rectal cancers. Int Surg 1987;72:70-72.
[10]Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309-318; discussion 318-321.
[11]Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002 Jun;235(6):759-66.
[12]Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol 2007 Dec;14(12):3481-91.
[13]Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 2008 Mar;247(3):451-5.
[14]Adam R, Miller R, Pitombo M, et al. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. Surg Oncol Clin N Am 2007 Jul;16(3):525-36, viii.
[15]Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. Ann Surg 1997;225:51-62.
[16]McAfee MK, Allen MS, Trastek VF, Ilstrup DM, Deschamps C, Pairolero PC. Colorectal lung metastases: results of surgical excision. Ann Thorac Surg 1992;53:780-785; discussion 785-786.
[17]Regnard JF, Grunenwald D, Spaggiari L, et al. Surgical treatment of hepatic and pulmonary metastases from colorectal cancers. Ann Thorac Surg 1998;66:214-218; discussion 218-219.
[18]Inoue M, Kotake Y, Nakagawa K, Fujiwara K, Fukuhara K, Yasumitsu T. Surgery for pulmonary metastases from colorectal carcinoma. Ann Thorac Surg 2000;70:380-383.
[19]Sakamoto T, Tsubota N, Iwanaga K, Yuki T, Matsuoka H, Yoshimura M. Pulmonary resection for metastases from colorectal cancer. Chest 2001;119:1069-1072.
[20]Rena O, Casadio C, Viano F, et al. Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. Eur J Cardiothorac Surg 2002;21:906-912.
[21]Irshad K, Ahmad F, Morin JE, Mulder DS. Pulmonary metastases from colorectal cancer: 25 years of experience. Can J Surg 2001;44:217-221.
[22]Ambiru S, Miyazaki M, Ito H, et al. Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 1998;82:274-278.
[23]Yano T, Hara N, Ichinose Y, Yokoyama H, Miura T, Ohta M. Results of pulmonary resection of metastatic colorectal cancer and its application. J Thorac Cardiovasc Surg 1993;106:875-879.
[24]Hendriks JM, Romijn S, Van Putte B, et al. Long-term results of surgical resection of lung metastases. Acta Chir Belg 2001;101:267-272.
[25]Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8:347-353.
[26]Rivoire M, De Cian F, Meeus P, Negrier S, Sebban H, Kaemmerlen P. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. Cancer 2002;95:2283-2292.
[27]Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006 May 1;24(13):2065-72.
[28]Pawlik TM, Olino K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 2007 Jul;11(7):860-8.
[29]Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol 2006 Aug 20;24(24):3939-45.
[30]Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13:1284-92.

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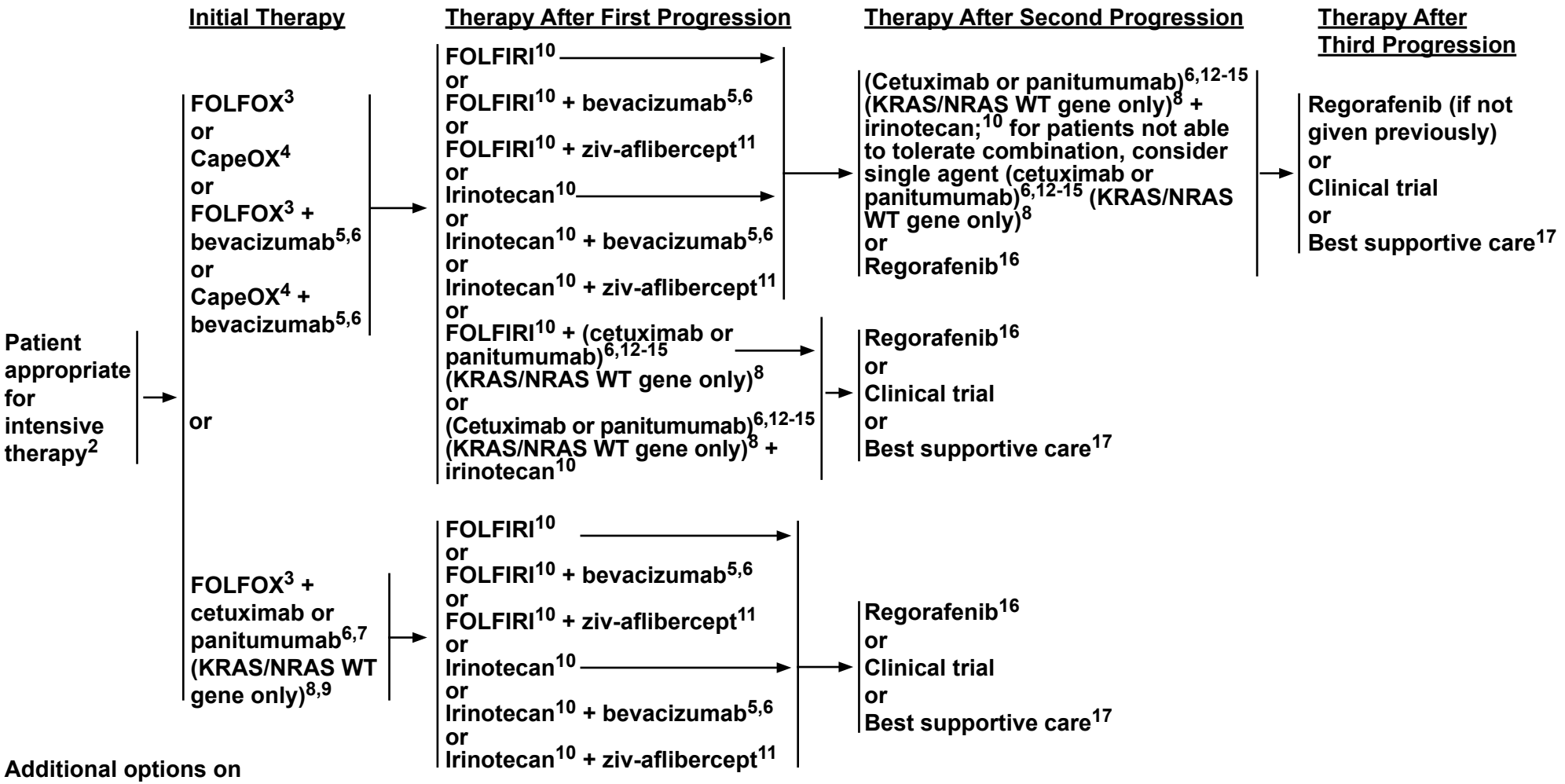
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 9)



Additional options on COL-C 2 of 9 through COL-C 3 of 9

For patients not appropriate for intensive therapy, see COL-C 4 of 9

See footnotes on COL-C 5 of 9

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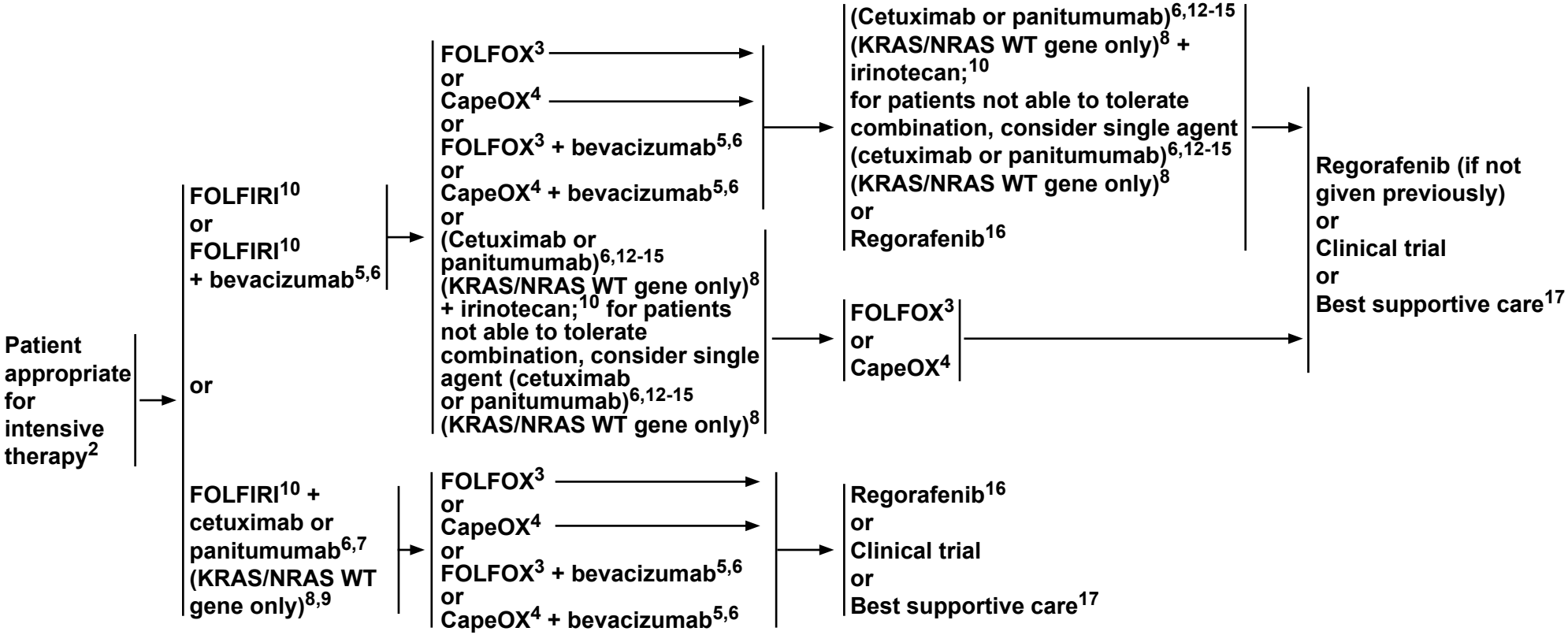
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 2 of 9)



Additional options on COL-C 1 of 9 **through** COL-C 3 of 9

For patients not appropriate for intensive therapy, see COL-C 4 of 9

See footnotes on COL-C 5 of 9

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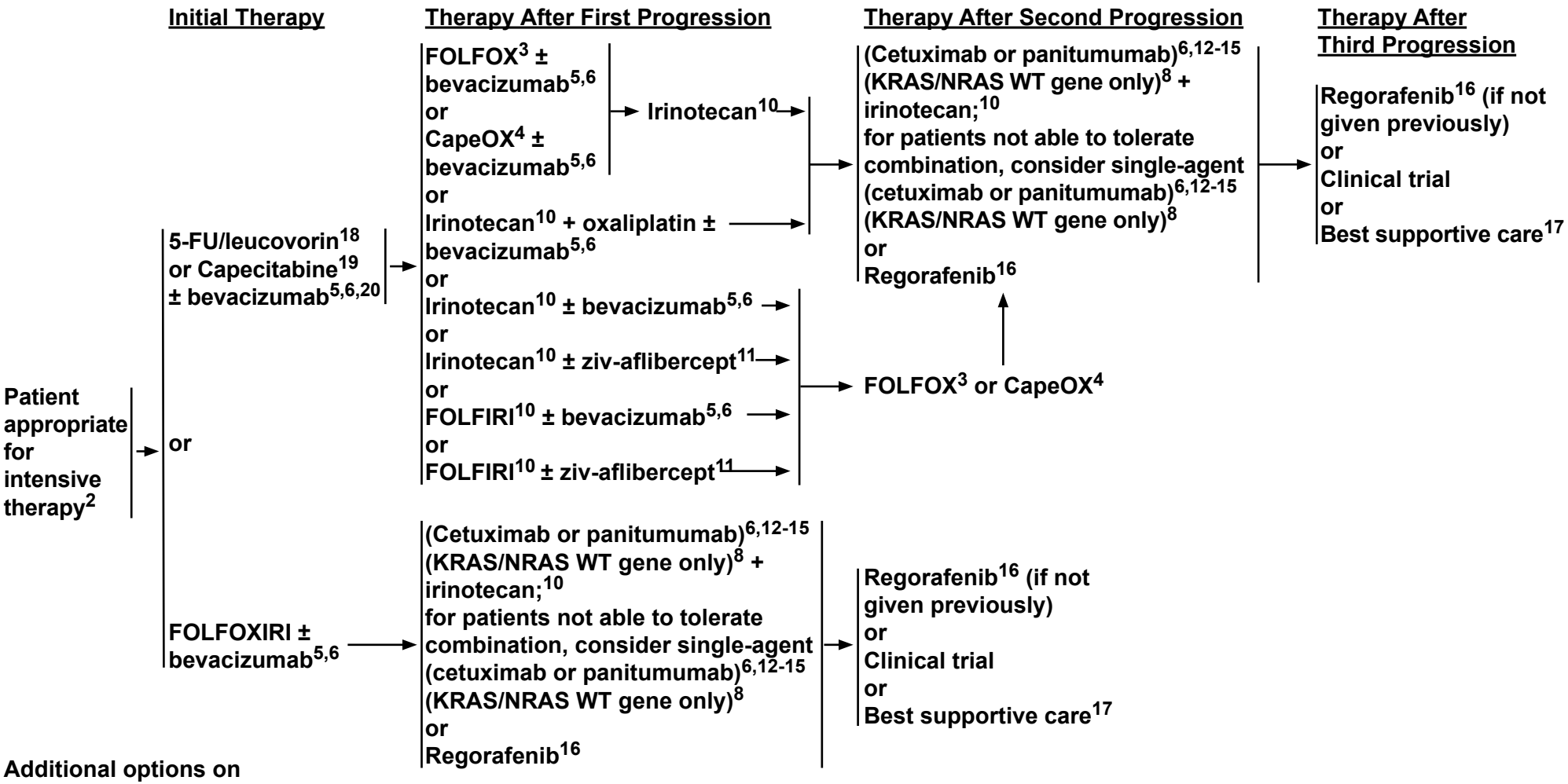
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 3 of 9)



Additional options on COL-C 1 of 9 through COL-C 2 of 9
For patients not appropriate for intensive therapy, see COL-C 4 of 9

See footnotes on COL-C 5 of 9

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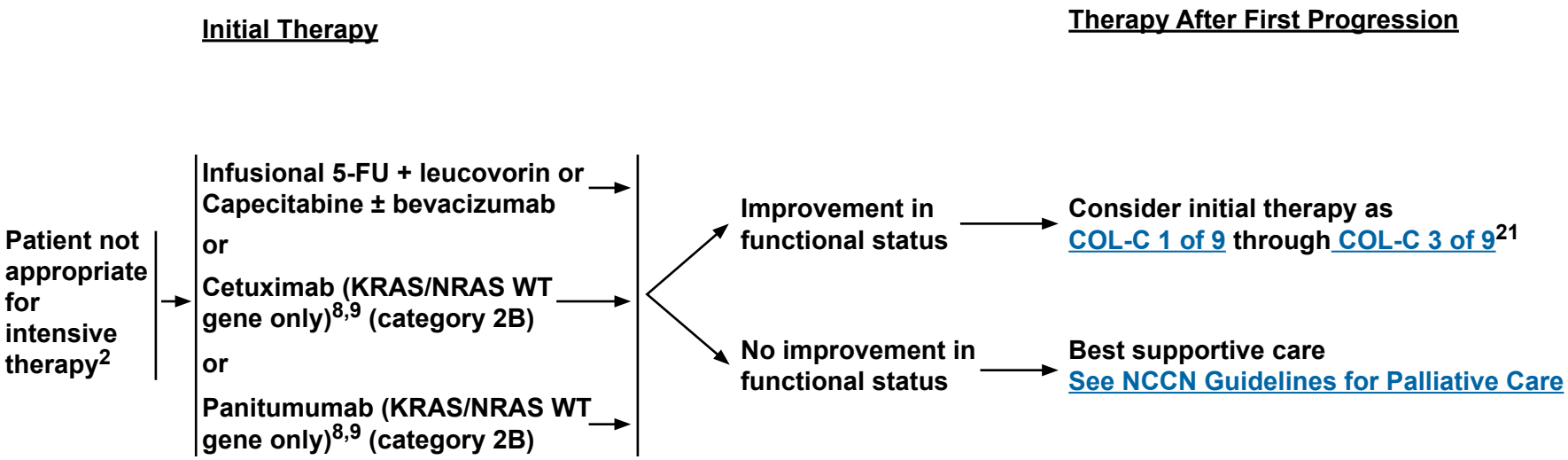
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 4 of 9)



See footnotes on COL-C 5 of 9

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 5 of 9)

[1]For chemotherapy references, see Chemotherapy Regimens and References (COL-C 6-9).

[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 no data to support the routine use of Ca/Mg infusion to prevent oxaliplatin-related neurotoxicity and therefore it should not be done.

[4]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.

[5]There is an increased risk of stroke and other arterial events, especially in those aged ≥ 65 years. 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 is 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, NRAS, and BRAF Mutation Testing.

[9]There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF 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]There are no data to suggest activity of FOLFIRI-ziv-aflibercept in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.

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

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

[14]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.

[15]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 a patient has progressed on first-line therapy.

[16]Regorafenib is a treatment option for patients who have progressed through all available regimens (eg, KRAS/NRAS mutant or KRAS/NRAS WT with previous exposure to anti-EGFR inhibitor.)

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

[18]Infusional 5-FU is preferred.

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

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

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

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 6 of 9)

FOLFOX
mFOLFOX 6
Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Repeat every 2 weeks[1,2,3]

mFOLFOX6 + Bevacizumab[2,4,¶]
Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

mFOLFOX6 + Panitumumab[2,5]
Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFOX + Cetuximab[2,6]
Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m2 IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Repeat every 2 weeks
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks

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

CapeOX[1] + Bevacizumab[7¶]
Oxaliplatin 130 mg/m² IV over 2 hours, day 1
Capecitabine 850–1000‡ mg/m² PO twice daily for 14 days
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

See References on COL-C 9 of 9

*Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
†NCCN recommends limiting chemotherapy orders to 24-h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 hours) to minimize medication errors.
‡The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large-scale randomized trials.
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 7 of 9)

FOLFIRI[8]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion
Repeat every 2 weeks

FOLFIRI[8] + Bevacizumab[9,¶]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFIRI[8] + Cetuximab[10]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Repeat every 2 weeks
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly[11]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[12]

FOLFIRI[8] + Panitumumab[13]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept[14]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion
Ziv-aflibercept 4 mg/kg IV
Repeat every 2 weeks

Capecitabine[15]
850–1250 mg/m² PO twice daily, days 1–14
Repeat every 3 weeks

Capecitabine[15] + Bevacizumab[7¶]
Capecitabine 850–1250 mg/m² PO twice daily, days 1–14
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

See References on COL-C 9 of 9

*Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
†NCCN recommends limiting chemotherapy orders to 24-h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 hours) to minimize medication errors.
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 8 of 9)

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[16]
Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)[8]
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

Weekly
Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV bolus injection 1 hour after the start of leucovorin. Repeat weekly.[17]
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week[18]

IROX[19]
Oxaliplatin 85 mg/m² IV over 2 hours, followed by irinotecan 200 mg/m² over 30-90 minutes every 3 weeks

FOLFOXIRI[20]
Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² day 1, leucovorin 400* mg/m² day 1, fluorouracil 1600 mg/m²/day x 2 days (total 3200 mg/m² over 48 hours)† continuous infusion starting on day 1.
Repeat every 2 weeks
± Bevacizumab[21] 5 mg/kg IV, day 1

The dose of 5-FU listed here was used in European studies. U.S. patients have been shown to have poorer tolerance for 5-FU. A starting dose of 5-FU consistent with the dose recommended in FOLFOX or FOLFIRI should be strongly considered for U.S. patients.

Irinotecan
Irinotecan 125 mg/m² IV over 30-90 minutes, days 1 and 8
Repeat every 3 weeks[22,23]
or Irinotecan 180 mg/m² IV over 30-90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 300-350 mg/m² IV over 30-90 minutes, day 1
Repeat every 3 weeks

Cetuximab (KRAS/NRAS WT gene only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly [24]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[12]

Cetuximab (KRAS/NRAS WT gene only) + irinotecan
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[24]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[12]
Irinotecan 300-350 mg/m² IV over 30-90 minutes, day 1
Repeat every 3 weeks
or Irinotecan 180 mg/m² IV over 30-90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 125 mg/m² IV over 30-90 minutes, days 1 and 8
Repeat every 3 weeks

Panitumumab[25] (KRAS/NRAS WT gene only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib[26]
Regorafenib 160 mg PO daily days 1-21
Repeat every 28 days

See References on COL-C 9 of 9

*Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
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¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES (PAGE 9 of 9)

[1]deGramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced rectal cancer. J Clin Oncol 2000;18:2938-2947.

[2]Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12177775.

[3]Maindrault-Goebel F, deGramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. Ann Oncol 2000;11:1477-1483.

[4]Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. BMC Cancer 2007;7:91.

[5]Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697-4705.

[6]Venook AP, Niedzwiecki D, Lenz H-J, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab or cetuximab for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum [abstract]. ASCO Meeting Abstracts 2014;32:LBA3. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/LBA3.

[7]Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-2019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18421054.

[8]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.

[9]Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17947725.

[10]Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open-label, phase 3 trial. Lancet Oncol 2014. Available: http://www.ncbi.nlm.nih.gov/pubmed/25088940.

[11]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.

[12]Martín-Martorell P, Roselló S, Rodríguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008;99:455-458.

[13]Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:4706-4713. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20921462.

[14]Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen. J Clin Oncol 2012;30:3499-3506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22949147.

[15]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.

[16]Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Protocol C-03. J Clin Oncol 1993;11:1879-1887.

[17]Jäger E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. J Clin Oncol 1996;14:2274-2279.

[18]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.

[19]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.

[20]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.

[21]Loupakis F, Cremolini C, Masi G, et al. FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first-line treatment of metastatic colorectal cancer (MCRC): results of the phase III randomized TRIBE trial. J Clin Oncol 2013;31(Suppl 4): Abstract 336.

[22]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.

[23]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.

[24]Van Cutsem E, Tejpar S, Vanbeckevoort D, et al. Intrapatient Cetuximab Dose Escalation in Metastatic Colorectal Cancer According to the Grade of Early Skin Reactions: The Randomized EVEREST Study. J Clin Oncol 2012;30:2861-2868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22753904.

[25]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.

[26]Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23177514.

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

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

- **Patient/physician discussion regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics, and patient preferences.**
- **When determining if adjuvant therapy should be administered, the following should be taken into consideration:**
  - **Number of lymph nodes analyzed after surgery (<12)**
  - **Poor prognostic features (eg, poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowel obstruction; PNI; localized perforation; close, indeterminate, or positive margins)**
  - **Assessment of other comorbidities and anticipated life expectancy.**
- **The benefit of adjuvant chemotherapy does not improve survival by more than 5%.**
- **MSI Testing - See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.**
  - **Lynch syndrome tumors screening (ie, IHC or MSI) should be considered for CRC patients diagnosed at age ≤70 y and also those >70 y who meet the Bethesda guidelines.[4]**
  - **MMR testing should also be considered for all patients with stage II disease, because stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.[5]**

[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.
[4]Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308:1555-1565.
[5]Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-3226. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20498393.

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PRINCIPLES OF ADJUVANT THERAPY (1 OF 2)

- **FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.[1,2] Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin for patients with stage III colon cancer. FLOX is an alternative to FOLFOX or CapeOx but FOLFOX or CapeOx are preferred.[3]**
- **Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer.[4]**
- **A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer.[5] FOLFOX is reasonable for high-risk stage II patients and is not indicated for good- or average-risk patients with stage II colon cancer.**
- **A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.[5]**
- **Bevacizumab, cetuximab, panitumumab, or irinotecan should not be used in the adjuvant setting for patients with stage II or III colon cancer outside the setting of a clinical trial.**

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

[1]Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-51.
[2]Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trail. J Clin Oncol 2009;27:3109-16. Epub 2009 May 18.
[3]Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007;25:2198-2204.
[4]Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352(26):2696-704.
[5]Tournigand C, André T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly (between ages 70 and 75 years) with colon cancer: a subgroup analyses of the Multicenter International Study of oxaliplatin, fluorouracil, and leucovorin in the adjuvant treatment of colon cancer trial. J Clin Oncol 2012;published online ahead of print on August 20, 2012.

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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.[1,2,3]

FLOX[4]
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[5]
Capecitabine 1250 mg/m² twice daily days 1–14 every 3 wks x 24 wks.

CapeOx[6]
Oxaliplatin 130 mg/m² over 2 hours, day 1. Capecitabine 1000 mg/m² twice daily days 1–14 every 3 weeks x 24 weeks.

5-FU/leucovorin
- **Leucovorin 500 mg/m² given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m² given bolus 1 hour after the start of leucovorin and repeated 6 x weekly. Every 8 weeks for 4 cycles.[7]**
- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)[8]**
  Leucovorin 400* mg/m² IV 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.

*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.

[1]Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351.
[2]Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12177775.
[3]Maindrault-Goebel F, deGramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. Annals of Oncology 2000;11:1477-1483.
[4]Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007;25:2198-2204.
[5]Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-2704.
[6]Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007;25:102-109. Haller DG, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer. J Clin Oncol 2011;29:1465-1471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21383294.
[7]Haller DG, Catalano PJ, Macdonald JS Mayer RJ. Phase III study of fluorouracil, leucovorin and levamisole in high risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol 2005:23:8671-8678.
[8]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.

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PRINCIPLES OF RADIATION THERAPY

- **Radiation therapy fields should include the tumor bed, which should be defined by preoperative radiologic imaging and/or surgical clips.**
- **Radiation doses should be: 45–50 Gy in 25–28 fractions.**
  - **Consider boost for close or positive margins.**
  - **Small bowel dose should be limited to 45 Gy.**
  - **5-FU-based chemotherapy should be delivered concurrently with radiation.**
- **If radiation therapy is to be used, conformal external beam radiation should be routinely used and intensity-modulated radiation therapy (IMRT) should be reserved only for unique clinical situations including re-irradiation of previously treated patients with recurrent disease.**
- **Intraoperative radiation therapy (IORT), if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Preoperative radiation therapy with concurrent 5-FU–based chemotherapy is a consideration for these patients to aid resectability. If IORT is not available, additional 10–20 Gy external beam radiation and/or brachytherapy could be considered to a limited volume.**
- **Some institutions use arterially directed embolization using yttrium-90 microspheres in select patients with chemotherapy-resistant/ refractory disease, without obvious systemic disease, and with predominant hepatic metastases (category 3).**
- **In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, IMRT, or stereotactic body radiation therapy (SBRT) (category 3).**

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PRINCIPLES OF SURVIVORSHIP - Colorectal Long-term Follow-up Care

Colorectal Cancer Surveillance:

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

Management of Late Sequelae of Disease or Treatment:[1-5]

- For chronic diarrhea or incontinence
  - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.

Prescription for Survivorship and Transfer of Care to Primary Care Physician[6] (If primary physician will be assuming cancer surveillance responsibilities):

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

Cancer Screening Recommendations:

These recommendations are for average-risk patients. Recommendations for high-risk individuals should be made on an individual basis.

- Breast Cancer: See the NCCN Guidelines for Breast Cancer Screening
- Prostate Cancer: See the NCCN Guidelines for Prostate Early Detection

Counseling Regarding Healthy Lifestyle and Wellness:[7]

- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (At least 30 minutes of moderate intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy).
- Consume a healthy diet with emphasis on plant sources.
- Limit alcohol consumption.
- Receive smoking cessation counseling as appropriate.

Additional health monitoring and immunizations should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.

[1]Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer. Cancer 2007;110: 2075-82.
[2]Sprangers MAG, Taal BG, Aaronson NK, et al. Quality of life in colorectal cancer: stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-9.
[3]Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther 2003;18:987-94.
[4]DeSnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. Eur J Cancer 2006;15:244-51.
[5]McGough C, Baldwin C, Frost C, Andreyev HJN. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. Br J Cancer 2004;90:2278-87.
[6]Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.:The National Academies Press;2006.
[7]Kushi LH, Byers T, Doyle C, et al and The American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity CA Cancer J Clin 2006;56:254-281.

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NCCN Guidelines Version 2.2015 Staging
Colon Cancer

NCCN Guidelines Index
Colon Cancer Table of Contents
Discussion

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 (eg, 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 through 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 (ie, 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.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2013, an estimated 96,830 new cases of colon cancer and approximately 40,000 cases of rectal cancer will occur. During the same year, an estimated 50,310 people will die of colon and rectal cancer combined.[1,2] Despite these high numbers, the incidence of colon and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005.[3] In fact, from 2006 to 2010, the incidence of colorectal cancer decreased at a rate of 3.3% per year in men and 3.0% in women.[1] The incidence rate for colorectal cancer reported by the CDC for 2010 is 40.4 per 100,000 persons.[4] In addition, mortality from colorectal cancer decreased by almost 35% from 1990 to 2007,[5] and in 2010 was down by 46% from peak mortality rates.[1] These improvements in incidence of and mortality from colorectal cancer are thought to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities.

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing colon cancer. These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, perioperative treatment, patient surveillance, management of recurrent and metastatic disease, and survivorship. When reviewing these guidelines, clinicians should be aware of several things. First, these guidelines adhere to the TNM staging system (Table 1 in the guidelines).[6] Furthermore, all recommendations are classified as category 2A except where noted in the text or algorithm. Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Colon Cancer, an electronic search of the PubMed database was performed to obtain key literature in the field of colorectal cancer published between July 23, 2013 and July 23, 2104, using the following search terms: (colon cancer) OR (colorectal cancer) OR (rectal cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[7]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 519 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Risk Assessment

Approximately 20% of cases of colon cancer are associated with familial clustering,[8,9] and first-degree relatives of patients with newly diagnosed

colorectal adenomas[10] or invasive colorectal cancer[11] are at increased risk for colorectal cancer. Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer)[12,13] and familial adenomatous polyposis.[14] Therefore, it is recommended that all patients with colon cancer be queried regarding their family history and considered for risk assessment, as detailed in the NCCN Guidelines for Colorectal Cancer Screening (available at www.NCCN.org).

Lynch Syndrome

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all colorectal cancer cases.[12,13,15,16] This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Although identifying a germline mutation in an MMR gene through sequencing is definitive for Lynch syndrome, patients usually undergo selection by considering family history and performing an initial test on tumor tissue before sequencing. One of two different initial tests can be performed on colorectal cancer specimens to identify individuals who might have Lynch syndrome: 1) immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation; or 2) analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units.[17] Testing the *BRAF* gene for mutation is indicated when immunohistochemical analysis shows that MLH1 protein expression is absent in the tumor. The presence of a *BRAF* mutation indicates that *MLH1* gene expression is down-regulated through somatic methylation of the promoter region of the gene and not through a germline mutation.[17]

Many NCCN Member Institutions and other comprehensive cancer centers now perform immunohistochemistry (IHC) and sometimes MSI testing on all newly diagnosed colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome.[18-21] The cost effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for colorectal cancer, and this approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the CDC.[22-24] The US Multi-Society Task Force on Colorectal Cancer also recommends universal genetic testing of tumors of all patients with newly diagnosed colorectal cancer.[25] The Cleveland Clinic recently reported on their experiences implementing such a screening approach.[26]

An alternative approach is to test all patients with colorectal cancer diagnosed prior to age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines.[27,28] This approach gave a sensitivity of 95.1% (95% CI, 89.8%–99.0%) and a specificity of 95.5% (95% CI, 94.7%–96.1%). This level of sensitivity was better than that of both the revised Bethesda and Jerusalem recommendations (testing all patients diagnosed with colorectal cancer at age <70 years[29]). While this new selective strategy failed to identify 4.9% of Lynch syndrome cases, it resulted in approximately 35% fewer tumors undergoing MMR testing than a universal approach.[27]

The NCCN Colon/Rectal Cancer Panel endorses this selective approach (testing all patients with colorectal cancer diagnosed ≤70 years plus patients diagnosed at older ages who meet the Bethesda guidelines). MMR testing should also be considered for patients with stage II tumors, as discussed in *Microsatellite Instability*, below. An infrastructure needs to be in place to handle the screening results in either case. A more detailed discussion is available in the NCCN

Guidelines for Colorectal Cancer Screening (available at www.NCCN.org).

Other Risk Factors for Colorectal Cancer

It is well-recognized that individuals with inflammatory bowel disease (ie, ulcerative colitis, Crohn's disease) are at an increased risk for colorectal cancer.[30-32] Other possible risk factors for the development of colorectal cancer include smoking, the consumption of red and processed meats, alcohol consumption, diabetes mellitus, low levels of physical activity, metabolic syndrome, and obesity/high body mass index (BMI).[31,33-47] Some data suggest that consumption of dairy may lower risk for the development of colorectal cancer.[48,49] However, a recent systematic review and metaanalysis of 15 cohort studies (>900,000 subjects; >5200 cases of colorectal cancer) only found an association between risk of colon cancer in men and the consumption of nonfermented milk.[50] No association was seen for rectal cancer in men or for colon or rectal cancer in women, and no association was seen for either cancer in either gender with consumption of solid cheese or fermented milk.

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption are associated with a poor prognosis.[36,51-54] Conversely, a family history of colorectal cancer increases risk while improving prognosis.[55] Data on the effect of dairy consumption on prognosis after diagnosis of colorectal cancer are conflicting.[56,57]

The relationship between diabetes and colorectal cancer is complex. Whereas diabetes and insulin use may increase the risk of developing colorectal cancer, treatment with metformin appears to decrease risk, at least in women.[58-60] In addition, although patients with colorectal cancer and diabetes appear to have a worse prognosis than those without diabetes,[61] patients with colorectal cancer treated with metformin seem to have a survival benefit.[62]

Staging

The 7th edition of the AJCC Cancer Staging Manual includes several modifications to the colon cancer TNM staging system.[6,63,64] The TNM categories reflect very similar survival outcomes for rectal and colon cancer. Therefore, these diseases share the same staging system.[65]

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 the primary tumor was T3 or T4. Stage II disease is now subdivided into IIA (T3 lesions that invade through the muscularis propria into pericolorectal tissues), IIB (T4a lesions that directly penetrate to the surface of the visceral peritoneum), and IIC (T4b lesions where tumor directly invades or is adherent to other organs or structures).[6] These changes are supported by an analysis of 109,953 patients with invasive colon cancer included in the SEER colon cancer database from 1992 to 2004.[66] The relative 5-year survival rate (ie, 5-year survival corrected by age-related morbidity) was considerably higher (79.6%) for node-negative patients with T4 tumors that penetrated the visceral peritoneum compared with patients with tumors that invaded or were adherent to other organs (58.4%).[66]

The definitions of N1 and N2 disease have also been revised to reflect the prognostic impact of the number of involved regional lymph nodes. For example, N1 lesions (1 to 3 positive regional lymph nodes) have been subdivided into N1a (1 positive lymph node) and N1b (2 to 3 positive lymph nodes), whereas N2 tumors (4 or more positive regional nodes) have been split into N2a (4 to 6 positive nodes) and N2b (7 or

more positive nodes). In addition, tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis (ie, satellite tumor nodules) have been classified as N1c.[6] See the *Pathology* section below for a discussion of tumor deposits.

Based on the analyses described above,[66] 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 been revised to more accurately reflect the complex biologic relationship between the extent of tumor invasion and the number of affected lymph nodes. For example, because of the relatively high survival rates observed for patients with lesions with extensive nodal involvement but no tumor penetration beyond the muscularis propria, T1-2, N2 lesions are now classified as either IIIA (T1, N2a) or IIIB (T2, N2a or T1-2, N2b). In addition, T4b, N1 disease, formerly stage IIIB disease, is now included under stage IIIC, because outcomes for these patients were found to be similar to those observed for patients with T3-4, N2 lesions.[66]

Stage IV disease is characterized by the presence of 1 or more distant metastases and is designated as M1.[63] M1 disease is now dichotomized into M1a and M1b according to whether metastasis is confined to 1 or more than 1 organ or site.[6]

Pathology

Colorectal cancers are usually staged after surgical exploration of the abdomen and pathologic examination of the surgical specimen. Some of the criteria that should be included in the report of the pathologic evaluation include the following: grade of the cancer; depth of penetration and extension to adjacent structures (T); number of regional lymph nodes evaluated; number of positive regional lymph nodes (N); an assessment of the presence of distant metastases to other organs, to the peritoneum or an abdominal structure, or in non-regional lymph nodes (M)[63,67]; the status of proximal, distal, and radial margins[63,68]; lymphovascular invasion[6,69,70]; perineural invasion (PNI)[71-73]; and extranodal tumor deposits.[74,75] The prefixes “p” and “yp” used in TNM staging denote “pathologic staging” and “pathologic staging after neoadjuvant therapy and surgery,” respectively.[6]

Margins

In colon cancer, the radial margin (or circumferential resection margin, CRM) represents the adventitial soft tissue closest to the deepest penetration of the tumor. It is created surgically by blunt or sharp dissection of the retroperitoneal aspect, and it corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells.[70] It must be dissected from the retroperitoneum to remove the viscus. The serosal (peritoneal) surface does not constitute a surgical margin. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. In segments of the colon that are completely encased by peritoneum, such as the transverse colon, the mesenteric resection margin is the only relevant radial margin.[70] On pathologic examination, it is difficult to appreciate the demarcation between the peritonealized surface and the non-peritonealized surface. The surgeon is therefore encouraged to mark the area of non-peritonealized surface with a clip or suture.[6] In a study of 608 patients with rectal cancer, a positive radial margin was shown to be a negative prognostic factor for both local recurrence and overall survival (OS).[76] Patients with CRM-positive resections had a 38.2% local recurrence rate, whereas those with CRM-negative resections had a 10.0% local recurrence rate.[76] The 7th edition of the AJCC staging system specifies that the surgeon should score the completeness of resection as R0 for complete tumor resection with all margins being negative; R1 for incomplete tumor resection with microscopic involvement of a margin;

and R2 for incomplete tumor resection with gross residual tumor not resected.[6]

Lymph Nodes

The number of lymph nodes evaluated is important to note on the pathology report. A secondary analysis of patients from the Intergroup Trial INT-0089 showed that an increase in the number of lymph nodes examined was associated with increased survival for patients with both node-negative and node-positive disease.[77] In addition, results from population-based studies show an association between improvement in survival and examination of greater than or equal to12 lymph nodes.[78,79] The mechanism for this correlation is poorly understood. It has been hypothesized that the analysis of more lymph nodes would result in more accurate staging and thus better tailored treatments, but recent results suggest that this idea is not correct.[80-82] Instead it is likely that other factors associated with lymph node harvest are important for the survival advantage. For instance, the extent and quality of surgical resection can have an impact on the node harvest.[83] The number of regional lymph nodes retrieved from a surgical specimen also varies with age of the patient, gender, and tumor grade or site.[77,78,84,85] In addition, it has been suggested that lymph nodes in patients with a strong anti-cancer immune response are easier to find, and that such patients have an improved prognosis.[86] Another possibility is that the underlying tumor biology affects lymph node yield and prognosis in parallel. For instance, MSI and wild-type *KRAS/BRAF* have been associated with both improved prognosis and increased lymph node retrieval.[87,88]

Regardless of the mechanism for the observed correlation, the panel recommends examination of a minimum of 12 lymph nodes. This recommendation is supported by previous statements from the College of American Pathologists (CAP)[70] and recommendations included in the 7th edition of the AJCC Cancer Staging Manual,[6] which specify pathologic examination of a minimum of 10 to 14 lymph nodes. Notably, 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.[70,89] For stage II (pN0) colon cancer, it is recommended that the pathologist go back to the specimen and submit more tissue of potential lymph nodes if fewer than 12 nodes were initially identified. Patients considered to have N0 disease but for whom less than 12 nodes have been examined are suboptimally staged and should be considered to be at higher risk.

The ratio of positive lymph nodes to the total number of lymph nodes examined is also being evaluated for possible prognostic impact. Case series have suggested cutoffs of 0.10 or 0.25 as lymph node ratios that are prognostic for OS or PFS.[90,91] Analysis of the SEER database, however, suggests that the lymph node ratio does not adequately represent the different effects of both the number of positive lymph nodes and the number of lymph nodes examined.[92]

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).[93] Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells and the identification of particular tumor antigens through immunohistochemical analysis have been reported.[93-99] Although results of some of these studies seem promising to some, no uniformity in the definition of “true” clinically relevant metastatic carcinoma exists. The 7th edition of the AJCC Cancer Staging Manual considers “tumor clusters” smaller than 0.2 mm to be isolated tumor cells and not true metastases.[6] However, some

studies have considered detection of single cells through immunohistochemistry to be micrometastases.[100] A recent meta-analysis found that the presence of micrometastases increases the likelihood of disease recurrence, while the presence of isolated tumor cells does not.[101] Overall, the prognostic value of positive cells by immunohistochemistry in stage II (N0 by H&E) colon cancer remains controversial.[95,102,103] Presently, the use of sentinel lymph nodes and detection of cancer cells through immunohistochemistry alone should be considered investigational, and the results should not be given significant weight in clinical management decisions.

There is also potential benefit of assessing regional lymph nodes for isolated tumor cells. One study of 312 consecutive patients with pN0 disease found that positive cytokeratin staining was associated with a higher risk of recurrence.[104] Relapse occurred in 14% of patients with positive nodes compared to 4.7% of those with negative nodes (HR, 3.00; 95% CI, 1.23–7.32; *P* = .013). A recent systematic review and meta-analysis came to a similar conclusion, finding decreased survival in patients with pN0 tumors with immunohistochemical or reverse transcriptase polymerase chain reaction (RT-PCR) evidence of tumor cells in regional nodes.[105] As with sentinel nodes, the molecular detection of cancer cells in regional nodes should be considered investigational, and the results should be used with caution in clinical management decisions.

Extranodal Tumor Deposits

Extranodal tumor deposits, also called peritumoral deposits or satellite nodules, are irregular discrete tumor deposits in the pericolic or perirectal fat that show no evidence of residual lymph node tissue, but are within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor. Most of these tumor deposits are thought to arise from lymphovascular invasion or, occasionally, PNI.[106,107] The number of extranodal tumor deposits should be recorded in the pathology report, because they have been shown to be associated with reductions in disease-free survival (DFS) and OS.[74,75,108] Multivariate survival analysis in one study showed that patients with pN0 tumors without satellite nodules had a 91.5% 5-year survival rate compared with a 37.0% 5-year survival rate for patients with pN0 tumors and the presence of satellite nodules (*P* < .0001).[75]

Perineural Invasion

Several studies have shown that the presence of PNI is associated with a significantly worse prognosis.[71-73,109] For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at one institution found a 4-fold greater 5-year survival in patients without PNI versus patients whose tumors invaded nearby neural structures.[72] Multivariate analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year DFS compared with those without PNI (29% vs. 82%; *P* = .0005).[73] Similar results were seen for patients with stage III disease.[71] PNI is therefore included as a high-risk factor for systemic recurrence.

The Role of Vitamin D in Colorectal Cancer

Prospective studies have suggested that vitamin D deficiency may contribute to colorectal cancer incidence and that vitamin D supplementation may decrease colorectal cancer risk.[110-113] Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with colorectal cancer.[114-116] In fact, a systematic review and meta-analysis of 5 studies totaling 2330 patients with colorectal cancer compared the outcomes of patients in the highest and lowest categories of vitamin D levels and found better OS (HR, 0.71; 95% CI, 0.55–0.91) and disease-specific

mortality (HR, 0.65; 95% CI, 0.49–0.86) in those with higher vitamin D levels.[117] Moreover, in a study of 515 patients with stage IV colorectal cancer, 82% were found to be vitamin D-insufficient (levels <30 ng/mL) and 50% were found to be vitamin D-deficient (levels <20 ng/mL).[118] Nonetheless, no study has yet examined whether vitamin D supplementation improves patient outcomes. In a recent report, the Institute of Medicine concluded that data supporting a role for vitamin D were only conclusive in bone health and not in cancer and other diseases.[119] Citing this report and the lack of level 1 evidence, the panel does not currently recommend routine screening for vitamin D deficiency or supplementation of vitamin D in patients with colorectal cancer.

Adenocarcinomas of the Small Bowel and Appendix

Adenocarcinomas of the small bowel or appendix are rare cancers for which no NCCN Guidelines exist. Localized small bowel adenocarcinomas are treated with surgical resection, but local and distant recurrences are common and optimal perioperative therapy is unknown.[120] The use of perioperative chemotherapy with or without radiation has been addressed mainly with retrospective reports.[121-126] Neoadjuvant chemoradiation was studied in one phase II trial that included patients with duodenal or pancreatic adenocarcinomas.[127] Four of 5 patients with tumors in the duodenum were able to undergo resection. Another small prospective study evaluated neoadjuvant chemoradiation in patients with duodenal or pancreatic adenocarcinomas.[128] All 4 patients with duodenal cancer underwent curative resection and experienced a complete pathologic response.

Data regarding therapy for advanced adenocarcinoma of the small bowel or appendix are also limited mostly to retrospective reports.[129,130] One small prospective phase II study evaluated capecitabine/oxaliplatin (CapeOx) for treatment of advanced adenocarcinomas of the small bowel and ampulla of Vater.[131] The overall response rate (the primary endpoint) was 50%, with 10% achieving complete response. A similar response rate (48.5%) was seen in another small phase II study that assessed the efficacy of FOLFOX (infusional 5-FU, LV, oxaliplatin) in first-line treatment of advanced small bowel cancer.[132] These response rates to CapeOx and FOLFOX were much higher than the 18% response rate seen in another small phase II study that evaluated 5-FU/doxorubicin/mitomycin C in patients with metastatic small bowel adenocarcinomas.[133]

Data on treatment of appendiceal adenocarcinomas are also quite limited. Most patients receive debulking surgery with systemic or intraperitoneal therapy (intraperitoneal therapy is discussed further in *Peritoneal Carcinomatosis*, below). Case series have shown that systemic combination chemotherapy in patients with advanced disease can result in response rates similar to those seen in advanced colorectal cancer.[134-136] A recent analysis of the NCCN Outcomes Database found that fluoropyrimidine-based therapy is the most commonly administered systemic therapy at NCCN Member Institutions.[137] Among 99 patients with a recorded best response, the response rate was 39%, with median PFS of 1.2 years.

Acknowledging the lack of high-level data, the panel recommends that adenocarcinomas of the small bowel or appendix be treated with systemic chemotherapy according to these NCCN Guidelines for Colon Cancer.

Clinical Presentation and Treatment of Nonmetastatic Disease

Workup and Management of the Malignant Polyp

A malignant polyp is defined as one with cancer invading the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated the submucosa and are therefore not considered capable of regional nodal metastasis.[63] The panel recommends marking the polyp site during colonoscopy or within 2 weeks of the polypectomy if deemed necessary by the surgeon.

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or adenoma, physicians should review the pathology and consult with the patient.[138] In patients with invasive cancer in a pedunculated or sessile polyp (adenoma), no additional surgery is required if the polyp has been completely resected and has favorable histologic features.[139,140] Favorable histologic 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 histologic features and clear margins. This option is included because the literature seems to indicate that patients with sessile polyps may have a significantly greater incidence of adverse outcomes, including disease recurrence, mortality, and hematogenous metastasis compared with those with pedunculated polyps. This increased incidence likely occurs because of the high probability of a positive margin after endoscopic removal.[141-143]

If the polyp specimen is fragmented, the margins cannot be assessed, or the specimen shows unfavorable histopathology, colectomy with en bloc removal of lymph nodes is recommended.[138,144,145] Laparoscopic surgery is an option.[146] Unfavorable histopathologic features for malignant polyps include grade 3 or 4, angiolymphatic invasion, or a positive margin of resection.[147,148] Notably, no consensus currently exists 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 to 2 mm of the transected margin or the presence of tumor cells within the diathermy of the transected margin.[138,149-151]

All patients who have resected polyps should undergo total colonoscopy to rule out other synchronous polyps, and should subsequently undergo appropriate follow-up surveillance endoscopy.[152] Adjuvant chemotherapy is not recommended for patients with stage I lesions.

Workup and Management of Invasive Nonmetastatic Colon Cancer

Patients who present with invasive colon cancer appropriate for resection require a complete staging workup, including pathologic tissue review, total colonoscopy, CBC, chemistry profile, carcinoembryonic antigen (CEA) determination, and baseline CT scans of the chest, abdomen, and pelvis.[153] CT should be with IV and oral contrast. If the CT of the abdomen and pelvis is inadequate or if CT with IV contrast is contraindicated, an abdominal/pelvic MRI with contrast plus a non-contrast chest CT should be considered. The consensus of the panel is that a PET/CT scan is not routinely indicated at baseline for preoperative workup. In fact, PET/CT scans are usually done without contrast and multiple slicing and do not obviate the need for a contrast-enhanced diagnostic CT scan. If, however, abnormalities are seen on CT or MRI scan that are considered suspicious but inconclusive for metastases, then a PET/CT scan may be considered to further delineate that abnormality, if this information will change management.

A PET/CT scan is not indicated for assessing subcentimeter lesions, because these are routinely below the level of PET/CT detection.

For resectable colon cancer that is causing overt obstruction, one-stage colectomy with en bloc removal of regional lymph nodes, resection with diversion, or diversion or stent (in selected cases) followed by colectomy are options. Stents are generally reserved for cases of distal lesions in which a stent can allow decompression of the proximal colon with later elective colostomy with primary anastomosis.[154] If the cancer is locally unresectable or the patient is medically inoperable, chemotherapy is recommended, possibly with the goal of converting the lesion to a resectable state.

Surgical Management

For resectable non-metastatic colon cancer, the preferred surgical procedure is colectomy with en bloc removal of the regional lymph nodes.[155,156] The extent of colectomy should be based on the tumor location, resecting the portion of the bowel and arterial arcade containing the regional lymph nodes. Other nodes, such as those at the origin of the vessel feeding the tumor (ie, apical lymph node), and suspicious lymph nodes outside the field of resection, should also be biopsied or removed if possible. Resection must be complete to be considered curative, and positive lymph nodes left behind indicate an incomplete (R2) resection.[6,157]

There has been some recent attention focused on the quality of colectomy.[158] A retrospective observational study found a possible OS advantage for surgery in the mesocolic plane over surgery in the muscularis propria plane.[159] Recently, a comparison of resection techniques by expert surgeons in Japan and Germany showed that complete mesocolic excision with central vascular ligation resulted in greater mesentery and lymph node yields than the Japanese D3 high tie surgery.[160] Differences in outcomes were not reported.

Laparoscopic Colectomy

Laparoscopic colectomy is an option in the surgical management of colon cancer.[161-164] In a small European randomized trial (Barcelona), the laparoscopic approach seemed to be associated with some modest survival advantage, significantly faster recovery, and shorter hospital stays.[165] More recently, a similar larger trial (COLOR trial) of 1248 patients with colon cancer randomly assigned to curative surgery with either a conventional open approach or laparoscopic-assisted surgery showed a nonsignificant absolute difference of 2.0% in 3-year DFS favoring open colectomy.[166] Non-inferiority of the laparoscopic approach could not be established because of study limitations.[166] In the CLASICC study of 794 patients with colorectal cancer, no statistically significant differences in 3-year rates of OS, DFS, and local recurrence were observed between these surgical approaches.[167] Long-term follow-up of participants in the CLASICC trial showed that the lack of differences in outcomes between arms continued over a median 62.9 months.[168]

In another trial (COST study) of 872 patients with colon cancer randomly assigned to undergo either open or laparoscopic-assisted colectomy for curable colon cancer, similar 5-year recurrence and 5-year OS rates were seen after a median of 7 years follow-up.[169,170] A similar randomized controlled trial in Australia and New Zealand also found no differences in disease outcomes.[171] In addition, results of several recent meta-analyses have supported the conclusion that the 2 surgical approaches provide similar long-term outcomes with respect to local recurrence and survival in patients with colon cancer.[172-177] Factors have been described that may confound conclusions drawn from

randomized studies comparing open colectomy with laparoscopic-assisted surgery for colon cancer.[178,179]

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.[180]

In recent years, perioperative care has improved, with reductions in the average length of hospital stay and complication rates after surgery.[181] The multicenter, randomized, controlled EnROL trial therefore compared conventional and laparoscopic colectomy with an enhanced recovery program in place.[182] Outcomes were the same in both arms, with the exception of median length of hospital stay, which was significantly shorter in the laparoscopic group (5 days vs. 7 days; P = .033).

The panel recommends that laparoscopic-assisted colectomy be considered only by surgeons experienced in the technique. A thorough abdominal exploration is required as part of the procedure. Routine use of laparoscopic-assisted colon resection is not currently recommended for tumors that are acutely obstructed or perforated or tumors that are clearly locally invasive into surrounding structures (ie, T4). Patients at high risk for prohibitive abdominal adhesions should not be approached laparoscopically, and those who are found to have prohibitive adhesions during laparoscopic exploration should be converted to an open procedure.[146,183,184]

Adjuvant Chemotherapy for Resectable Colon Cancer

Adjuvant therapy for patients with resected colon cancer has gained considerable interest.[185] Choices for adjuvant therapy for patients with resected, nonmetastatic colon cancer depend on the stage of disease:

- Patients with stage I disease do not require any adjuvant therapy.
- Patients with low-risk stage II disease can be enrolled in a clinical trial, observed without adjuvant therapy, or considered for capecitabine or 5-FU/leucovorin (LV). Based on results of the MOSAIC trial,[186-189] and the possible long-term sequelae of oxaliplatin-based chemotherapy, the panel does not consider FOLFOX (infusional 5-FU, LV, oxaliplatin) to be an appropriate adjuvant therapy option for patients with stage II disease without high-risk features.
- Patients with high-risk stage II disease, defined as those with poor prognostic features, including T4 tumors (stage IIB/IIC); poorly differentiated histology (exclusive of those cancers that are MSI-high [MSI-H]); lymphovascular invasion; PNI; bowel obstruction; lesions with localized perforation or close, indeterminate, or positive margins; or inadequately sampled nodes (<12 lymph nodes), can be considered for adjuvant chemotherapy with 5-FU/LV, capecitabine, FOLFOX, capecitabine/oxaliplatin (CapeOx), or bolus 5-FU/LV/oxaliplatin (FLOX).[68,190] Observation without adjuvant therapy is also an option in this population. The factors in decision making for stage II adjuvant therapy are discussed in more detail below.
- For patients with stage III disease, the panel recommends 6 months of adjuvant chemotherapy after primary surgical

treatment.[191] The treatment options are FOLFOX[186-189,192] or CapeOx[193,194] (both category 1 and preferred); FLOX (category 1)[195]; or single-agent capecitabine[196] or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate.[197-200]

The panel recommends against the use of bevacizumab, cetuximab, panitumumab, or irinotecan in adjuvant therapy for nonmetastatic disease outside the setting of a clinical trial. It was recently shown that patients from the National Cancer Data Base with stage III or high-risk stage II disease treated according to these guidelines had a survival advantage over patients whose treatment did not adhere to these guidelines.[201]

Endpoints for Adjuvant Chemotherapy Clinical Trials

The Adjuvant Colon Cancer End Points (ACCENT) collaborative group evaluated the appropriateness of various endpoints for adjuvant chemotherapy trials in colon cancer. Results of an analysis of individual patient data from 20,898 patients in 18 randomized colon adjuvant clinical trials by the ACCENT group suggested that DFS after 2 and 3 years follow-up are appropriate endpoints for clinical trials involving treatment of colon cancer with 5-FU-based chemotherapy in the adjuvant setting.[202,203] An update of this analysis showed that most relapses occur within 2 years after surgery, and that recurrence rates were less than 1.5% per year and less than 0.5% per year after 5 and 8 years, respectively.[204] More recently, however, a further update of the data suggested that the association between 2- or 3-year DFS and 5-year OS was reduced when patient survival after recurrence was hypothetically prolonged to match the current time to survival from recurrence seen with modern combination therapies (2 years), and that more than 5 years may now be required to evaluate the effect of adjuvant therapies on OS.[205] Further confirmation of this result comes from new analysis by the ACCENT group of data from 12,676 patients undergoing combination therapies from 6 trials.[206] This study determined that 2- and 3-year DFS correlated with 5- and 6-year OS in patients with stage III disease but not in those with stage II disease. In all patients, the correlation of DFS to OS was strongest at 6-year follow-up, suggesting that at least 6 years are required for adequate assessment of OS in modern adjuvant colon cancer trials.[206]

Adjuvant Chemotherapy in Stage II Disease

The impact of adjuvant chemotherapy for patients with stage II colon cancer has been addressed in several clinical trials and practice-based studies. Results from a meta-analysis of 5 trials in which patients with stage II or III colon cancer were randomly assigned to receive surgery alone or surgery followed by adjuvant 5-FU/LV showed that most of the benefit of adjuvant therapy was seen in the patients with stage III disease.[197,207] Similarly, an analysis of pooled data from 7 randomized trials indicated that OS of patients with resected colon cancer treated with 5-FU–based adjuvant therapy was statistically significantly increased with the addition of chemotherapy in the subset of patients with stage III disease but not in those with stage II disease.[208] These results suggest that the benefit of adjuvant therapy is greater in patients at higher risk because of nodal status. In contrast to results from most other trials, the QUASAR trial indicated a small but statistically significant survival benefit for patients with stage II disease treated with 5-FU/LV compared to patients not receiving adjuvant therapy (relative risk of recurrence at 2 years, 0.71; 95% CI, 0.54–0.92; P = .01).[209] In this trial, however, approximately 64% of patients had less than12 lymph nodes sampled, and thus may actually have been patients with higher risk disease who were more likely to benefit from adjuvant therapy.[210]

A recent meta-analysis of 12 randomized controlled trials from 1988 to 2010 in which surgery alone was the control arm found a significant

benefit to adjuvant therapy in patients with stage II colon cancer.[211] The 5-year OS HR was 0.81 (95% CI, 0.71–0.91), and the 5-year DFS HR was 0.86 (95% CI, 0.75–0.98). The trials in this analysis used various chemotherapy regimens, many of which are not currently recommended for this setting. Other limitations of the analysis include the lack of surgical quality control among the studies and the possibility of publication bias. Moreover, the reported differences in outcome are small.

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 or not they had received adjuvant chemotherapy showed no statistically significant difference in 5-year OS between the groups (78% vs. 75%, respectively), with a hazard ratio (HR) for survival of 0.91 (95% CI, 0.77–1.09) when patients receiving adjuvant treatment were compared with untreated patients.[212] Notably, a more recent analysis of more than 24,000 patients with stage II colon cancer from the SEER Medicare database showed no 5-year survival benefit for adjuvant chemotherapy over observation, even in patients with stage II disease with one or more poor prognostic features (HR, 1.03; 95% CI, 0.94–1.13).[213] Although this study was limited to patients older than 65 years and involved a period before the use of oxaliplatin-based therapies,[214] it is still an important piece of data to consider during the decision-making process regarding the use of adjuvant chemotherapy in patients with stage II disease.

The benefit of oxaliplatin in adjuvant therapy for patients with stage II colon cancer has also been addressed. Results from a recent post-hoc exploratory analysis of the MOSAIC trial did not show a significant DFS benefit of FOLFOX over 5-FU/LV for patients with stage II disease at a follow-up of 6 years (HR, 0.84; 95% CI, 0.62–1.14; P = .258).[215] In addition, patients with high-risk stage II disease (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 FOLFOX did not have improved DFS compared with those receiving infusional 5-FU/LV (HR, 0.72; 95% CI, 0.50–1.02; P = .063). Furthermore, no OS benefit was seen in the stage II population overall or in the stage II population with high-risk features. Similar results were seen in the C-07 trial, which compared FLOX to 5-FU/LV in patients with stage II and III disease.[216]

Decision making regarding the use of adjuvant therapy for patients with stage II disease should incorporate patient/physician discussions individualized for the patient, and should include explanations of the specific characteristics of the disease and its prognosis and the evidence related to the efficacy and possible toxicities associated with treatment, centering on patient choice.[190,217] Observation and participation in a clinical trial are options that should be considered. Patients with average-risk stage II colon cancer have a very good prognosis, so the possible benefit of adjuvant therapy is small. Patients with high-risk features, on the other hand, traditionally have been considered more likely to benefit from adjuvant chemotherapy. However, the current definition of high-risk stage II colon cancer is clearly inadequate, because many patients with high-risk features do not have a recurrence while some patients deemed to be average-risk do.[218] Furthermore, no data point to features that are predictive of benefit from adjuvant chemotherapy, and no data correlate risk features and selection of chemotherapy in patients with high-risk stage II disease. Overall, the NCCN Panel supports the conclusion of a 2004 ASCO Panel and believes that it is reasonable to accept the relative benefit of adjuvant therapy in stage III disease as indirect evidence of benefit for stage II disease, especially for those with high-risk features.[190]

Additional information that may influence adjuvant therapy decisions in stage II and/or stage III disease (MSI, multigene assays, and the influence of patient age) is discussed below.

Microsatellite Instability

MSI is an important piece of information to consider when deciding whether to use adjuvant chemotherapy in patients with stage II disease. Evidence shows that MSI is a marker of a more favorable outcome and a predictor of decreased benefit (possibly a detrimental impact) from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease.[219,220] Mutation of MMR genes or modifications of these genes (eg, methylation) can result in MMR protein deficiency and MSI (see *Risk Assessment*, above).[221]

Germline mutations in the MMR genes *MLH1*, *MSH2*, *MSH6*, and/or *PMS2* or *EpCAM* are found in individuals with Lynch syndrome, which is responsible for 2% to 4% of colon cancer cases.[12,13,15,16] Somatic MMR defects have been reported to occur in approximately 19% of colorectal tumors,[222] whereas others have reported somatic hypermethylation of the *MLH1* gene promoter, which is associated with *MLH1* gene inactivation, in as many as 52% of colon tumors.[223] Tumors showing the presence of MSI are classified as either 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).[224] Patients determined to have defective MMR (dMMR) status are biologically the same population as those with MSI-H status.

Data from the PETACC-3 trial showed that tumor specimens characterized as MSI-H are more common in stage II disease than in stage III disease (22% vs. 12%, respectively; $P < .0001$).[225] In another large study, the percentage of stage IV tumors characterized as MSI-H was only 3.5%.[226] These results suggest that MSI-H (ie, dMMR) tumors have a decreased likelihood to metastasize. In fact, substantial evidence shows that in patients with stage II disease, a deficiency in MMR protein expression or MSI-H tumor status is a prognostic marker of a more favorable outcome.[219,220,227] In contrast, the favorable impact of dMMR on outcomes seems to be more limited in stage III colon cancer and may vary with primary tumor location.[228]

Some of these same studies also show that a deficiency in MMR protein expression or MSI-H tumor status may be a predictive marker of decreased benefit (possibly a detrimental impact) from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease.[219,220] A retrospective study involving long-term follow-up of patients with stage II and III disease evaluated according to MSI tumor status showed that those characterized as MSI-L or MSS 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 after surgery, instead exhibiting a lower 5-year survival rate than those undergoing surgery alone.[219] Similarly, results from another retrospective study of pooled data from adjuvant trials by Sargent et al[220] showed that in tumors characterized as dMMR, adjuvant 5-FU chemotherapy seemed to be detrimental in patients with stage II disease, but not in those with stage III disease.

In contrast to the findings of Sargent et al, [Sargent, 2010 #278] however, a recent study of 1913 patients with stage II colorectal cancer from the QUASAR study, half of whom received adjuvant chemotherapy, showed that although dMMR was prognostic (the recurrence rate of dMMR tumors was 11% vs. 26% for MMR-proficient tumors), it did not predict benefit or detrimental impact of chemotherapy.[210] A recent study of patients in the CALGB 9581 and 89803 trials came to a similar conclusion.[229] MMR status was prognostic but not predictive of benefit or detrimental impact of adjuvant therapy

(irinotecan plus bolus 5-FU/LV [IFL regimen]) in patients with stage II colon cancer.

Because patients with stage II MSI-H tumors may have a good prognosis and do not benefit from 5-FU adjuvant therapy, the panel recommends that MMR testing be considered for patients with stage II disease. Poorly differentiated histology is not considered a high-risk feature for patients with stage II disease whose tumors are MSI-H. In addition, MMR testing should be performed for all patients with colorectal cancer diagnosed less than or equal to 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines to assess for the possibility of Lynch syndrome.

Multigene Assays

Several multigene assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer.[218]

Oncotype DX colon cancer assay (Genomic Health, Inc.) quantifies the expression of 7 recurrence-risk genes and 5 reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.[230] Clinical validation in patients with stage II and III colon cancer from QUASAR[231] and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07[232] trials showed that recurrence scores are prognostic for recurrence, DFS, and OS in stage II and III colon cancer, but are not predictive of benefit to adjuvant therapy. For the low, intermediate, and high recurrence risk groups, recurrence at 3 years was 12%, 18%, and 22%, respectively.[231] Multivariate analysis showed that recurrence scores were related to recurrence independently from TNM staging, MMR status, tumor grade, and number of nodes assessed in both stage II and III disease. Similar results were found in a recent prospectively designed study that tested the correlation between recurrence score using the Oncotype DX colon cancer assay and the risk of recurrence in patients from the CALGB 9581 trial (stage II disease).[233] An additional prospectively designed clinical validation study in patients from the NSABP C-07 trial found that the assay results correlated with recurrence, DFS, and OS.[234] This study also found some evidence that patients with higher recurrence scores may derive more absolute benefit from oxaliplatin, although the authors noted that the recurrence score is not predictive of oxaliplatin efficacy in that it does not identify patients who will or will not benefit from oxaliplatin treatment.

ColoPrint (Agendia) quantifies the expression of 18 genes as a prognostic classifier of low versus high recurrence risk.[235] In a set of 206 patients with stage I through III colorectal cancer, the 5-year relapse-free survival rates were 87.6% (95% CI, 81.5%–93.7%) and 67.2% (95% CI, 55.4%–79.0%) for those classified as low and high risk, respectively. In patients with stage II disease in particular, the HR for recurrence between the high and low groups was 3.34 (P = .017).[235] This assay was further validated in a pooled analysis of 320 patients with stage II disease, 227 of whom were assessed as a T3/MSS subset.[236] In the T3/MSS subset, patients classified as low risk and high risk had 3-year recurrence-free survival rates of 91% (86%–96%) and 73% (63%–83%) (P = .002), respectively.[236] As with the Oncotype DX colon cancer assay, recurrence risk determined by ColoPrint is independent of other risk factors, including T stage, perforation, number of nodes assessed, and tumor grade. This assay is being further validated for its ability to predict 3-year relapse rates in patients with stage II colon cancer in a prospective trial.[237]

ColDx (Almac) is a microarray-based multigene assay that uses 634 probes to identify patients with stage II colon cancer at high risk of recurrence.[238] In a 144-sample independent validation set, the HR for

identification of patients with high-risk disease was 2.53 (95% CI, 1.54–4.15; $P < .001$) for recurrence and 2.21 (95% CI, 1.22–3.97; $P = .0084$) for cancer-related death. Similar to the other assays described here, the recurrence risk determined by ColDx is independent of other risk factors.

In summary, the information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, there is no evidence of predictive value in terms of the potential benefit of chemotherapy to any of the available multigene assays. The panel believes that there are insufficient data to recommend the use of multigene assays to determine adjuvant therapy.

Adjuvant Chemotherapy in Elderly Patients

Adjuvant chemotherapy usage declines with the age of the patient.[239] Questions regarding the safety and efficacy of chemotherapy in older patients have been difficult to answer, because older patients are underrepresented in clinical trials. Some data speaking to these questions have been reviewed.[240-242]

Population studies have found that adjuvant therapy is beneficial in older patients. A retrospective analysis of 7263 patients from the linked SEER-Medicare Databases found a survival benefit for the use of 5-FU/LV in patients 65 years or older with stage III disease (HR, 0.70; $P < .001$).[243] Another analysis of 5489 patients aged greater than or equal to 75 years diagnosed with stage III colon cancer between 2004 and 2007 from 4 datasets, including the SEER-Medicare Databases and the NCCN Outcomes Database, showed a survival benefit for adjuvant chemotherapy in this population (HR, 0.60; 95% CI, 0.53–0.68).[239] This study also looked specifically at the benefit of the addition of oxaliplatin to adjuvant therapy in these older stage III patients, and found only a small, non-significant benefit. Analysis of almost 12,000 patients from the ACCENT database also found a reduced benefit to the addition of oxaliplatin to fluoropyrimidines in the adjuvant setting in patients aged greater than or equal to 70 years.[244]

Subset analyses of major adjuvant therapy trials also show a lack of benefit to the addition of oxaliplatin in older patients. Subset analysis of the NSABP C-07 trial showed that the addition of oxaliplatin to 5-FU/LV gave no survival benefit in patients aged greater than or equal to 70 years with stage II or III colon cancer (n=396), with a trend towards decreased survival (HR, 1.18; 95% CI, 0.86–1.62).[216] Similarly, in a subset analysis of the MOSAIC trial, 315 patients aged 70 to 75 years with stage II or III colon cancer derived no benefit from the addition of oxaliplatin (OS HR, 1.10; 95% CI, 0.73–1.65).[215]

Overall, the benefit and toxicities of 5-FU/LV as adjuvant therapy seem to be similar in older and younger patients. However, the panel cautions that a benefit for the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older has not been proven in stage II or stage III colon cancer.

Timing of Adjuvant Therapy

A recent systematic review and meta-analysis of 10 studies involving more than 15,000 patients examined the effect of timing of adjuvant therapy after resection.[245] Results of this analysis showed that each 4-week delay in chemotherapy results in a 14% decrease in OS, indicating that adjuvant therapy should be administered as soon as the patient is medically able. These results are consistent with other similar analyses. However, some critics have pointed out that this type of analysis is biased by confounding factors such as comorbidities, which are likely to be higher in patients with a longer delay before initiation of chemotherapy.[246]

Leucovorin Shortage

A shortage of LV recently existed in the United States. No specific data are available to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levoleucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levoleucovorin is equivalent to 400 mg/m^2 of standard LV. Another option is for practices or institutions to use lower doses of LV for all doses in all patients, because the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg of LV was associated with similar survival and 3-year recurrence rates as 25 mg of LV when given with bolus 5-FU as adjuvant therapy to patients after R0 resections for colorectal cancer.[247] Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m^2) or low-dose (20 mg/m^2) LV.[248] Furthermore, the Mayo Clinic and North Central Cancer Treatment Group (NCCTG) determined that no therapeutic difference was seen between the use of high-dose (200 mg/m^2) or low-dose (20 mg/m^2) LV with bolus 5-FU in the treatment of advanced colorectal cancer, although the 5-FU doses were different in the treatment arms.[249] Finally, if none of the above options is available, treatment without LV would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

FOLFOX and Infusional 5-FU/LV

The European MOSAIC trial compared the efficacy of FOLFOX and 5-FU/LV in the adjuvant setting in 2246 patients with completely resected stage II and III colon cancer. Although this initial trial was performed with FOLFOX4, mFOLFOX6 has been the control arm for all recent and current National Cancer Institute (NCI) adjuvant studies for colorectal cancer, and the panel believes that mFOLFOX6 is the preferred FOLFOX regimen for adjuvant and metastatic treatments. Results of this study have been reported with median follow-ups of 3,[186] 4,[187] and 6 years.[188,189] For patients with stage III disease, DFS at 5 years was 58.9% in the 5-FU/LV arm and 66.4% in the FOLFOX arm (P = .005), and OS of patients with stage III disease receiving FOLFOX was statistically significantly increased at 6-year follow-up (72.9% vs. 68.7%; HR, 0.80; 95% CI, 0.65–0.97; P = .023) compared with those receiving 5-FU/LV.[188] Although the incidence of grade 3 peripheral sensory neuropathy was 12.4% for patients receiving FOLFOX and only 0.2% for patients receiving 5-FU/LV, long-term safety results showed a gradual recovery for most of these patients. However, neuropathy was present in 15.4% of examined patients at 4 years (mostly grade 1), suggesting that oxaliplatin-induced neuropathy may not be completely reversible in some patients.[188]

A recent analysis of 5 observational data sources, including the SEER-Medicare and NCCN Outcomes Databases, showed that the addition of oxaliplatin to 5-FU/LV gave a survival advantage to the general stage III colon cancer population treated in the community.[250] Another population-based analysis found that the harms of oxaliplatin in the medicare population with stage III colon cancer were reasonable, even in patients 75 years or older.[251]

Based on the increases in DFS and OS with FOLFOX in the MOSAIC trial, FOLFOX (mFOLFOX6 preferred) is recommended as a preferred treatment for stage III colon cancer (category 1). Toxicity of this regimen is discussed in *Chemotherapy for Advanced or Metastatic Disease*, below.

FLOX

A randomized phase III trial (NSABP C-07) compared the efficacy of FLOX with that of FULV (bolus 5-FU/LV) in prolonging DFS in 2407 patients with stage II or III colon cancer.[195] Rates of 4-year DFS were 73.2% for FLOX and 67.0% for FULV, with an HR of 0.81 (95% CI, 0.69–0.94; *P* = .005) after adjustment for age and number of nodes, indicating a 19% reduction in relative risk.[195] A recent update of this study showed that the benefit of FLOX in DFS was maintained at 7-year median follow-up (*P* = .0017).[216] However, no statistically significant differences in OS (HR, 0.88; 95% CI, 0.76–1.03; *P* = .1173) or colon-cancer–specific mortality (HR, 0.88; 95% CI, 0.74–1.05; *P* = .1428) were observed when the arms were compared. Furthermore, survival after disease recurrence was significantly shorter in the group receiving oxaliplatin (HR, 1.20; 95% CI, 1.00–1.43; *P* = .0497).[216]

Grade 3 neurotoxicity, diarrhea, and dehydration were higher with FLOX than with 5-FU/LV,[216] and, when cross-study comparisons were made, the incidence of grade 3/4 diarrhea seemed to be considerably higher with FLOX than with FOLFOX. For example, rates of grade 3/4 diarrhea were 10.8% and 6.6% for patients receiving FOLFOX and infusional 5-FU/LV, respectively (*P* < .001), in the MOSAIC trial,[186] whereas 38% and 32% of patients were reported to have grade 3/4 diarrhea in the NSABP C-07 trial when receiving FLOX and bolus 5-FU/LV, respectively (*P* = .003).[195]

Capecitabine and CapeOx

Single-agent oral capecitabine as adjuvant therapy for patients with stage III colon cancer was shown to be at least equivalent to bolus 5-FU/LV (Mayo Clinic regimen) with respect to DFS and OS, with respective HRs of 0.87 (95% CI, 0.75–1.00; *P* < .001) and 0.84 (95% CI, 0.69–1.01; *P* = .07).[196] Final results of this trial were recently reported.[252] After a median follow-up of 6.9 years, the equivalencies in DFS and OS were maintained in all subgroups, including those 70 years of age or older.

Capecitabine was also assessed as adjuvant therapy for stage III colon cancer in combination with oxaliplatin (CapeOx) and showed an improved 3-year DFS rate compared with 5-FU/LV (66.5% vs. 70.9%).[193,194] Based on these data, CapeOx is listed in the guidelines with a category 1 designation as a preferred adjuvant therapy for patients with stage III colon cancer.

Regimens Not Recommended

Other adjuvant regimens studied for the treatment of early-stage colon cancer include 5-FU–based therapies incorporating irinotecan. The CALGB 89803 trial evaluated the IFL regimen versus 5-FU/LV alone in stage III colon cancer.[253] No improvement in either OS (*P* = .74) or DFS (*P* = .84) was observed for patients receiving IFL compared with those receiving 5-FU/LV. However, IFL was associated with a greater degree of neutropenia, neutropenic fever, and death.[253,254] Similar results were observed in a recent randomized phase III trial comparing bolus 5-FU/LV with the IFL regimen in stage II/III colon cancer.[255] In addition, FOLFIRI (infusional 5-FU/LV/irinotecan) has not been shown to be superior to 5-FU/LV in the adjuvant setting.[256,257] Thus, data do not support the use of irinotecan-containing regimens in the treatment of stage II or III colon cancer.

In the NSABP C-08 trial comparing 6 months of mFOLFOX6 with 6 months of mFOLFOX6 with bevacizumab plus an additional 6 months of bevacizumab alone in patients with stage II or III colon cancer, no statistically significant benefit in 3-year DFS was seen with the addition of bevacizumab (HR, 0.89; 95% CI, 0.76–1.04; *P* = .15).[258] Similar results were seen after a median follow-up of 5 years.[259] The results of the phase III AVANT trial evaluating bevacizumab in the adjuvant

setting in a similar protocol also failed to show a benefit associated with bevacizumab in the adjuvant treatment of stage II or III colorectal cancer, and in fact showed a trend toward a detrimental effect to the addition of bevacizumab. Therefore, bevacizumab has no role in the adjuvant treatment of stage II or III colon cancer.[260]

The NCCTG Intergroup phase III trial N0147 assessed the addition of cetuximab to FOLFOX in the adjuvant treatment of stage III colon cancer. In patients with wild-type or mutant *KRAS*, cetuximab provided no added benefit and was associated with increases in grade 3/4 adverse events.[261] In addition, all subsets of patients treated with cetuximab experienced increases in grade 3/4 adverse events. The open-label, randomized, phase 3 PETACC-8 trial also compared FOLFOX with and without cetuximab.[262] Analysis of the wild-type *KRAS* exon 2 subset found that DFS was similar in both arms (HR, 0.99; 95% CI, 0.76–1.28), while adverse events (ie, rash, diarrhea, mucositis, infusion-related reactions) were more common in the cetuximab group. Therefore, cetuximab also has no role in the adjuvant treatment of colon cancer.

Adjuvant Chemoradiation

Radiation therapy delivered concurrently with 5-FU–based chemotherapy may be considered for very select patients with disease characterized as T4 tumors penetrating to a fixed structure or for patients with recurrent disease. Radiation therapy fields should include the tumor bed as defined by preoperative radiologic imaging and/or surgical clips. Intraoperative radiation therapy (IORT), if available, should be considered for these patients as an additional boost.[263,264] If IORT is not available, an additional 10 to 20 Gy of external beam radiation and/or brachytherapy could be considered to a limited volume. Preoperative radiation with concurrent 5-FU–based chemotherapy is also a consideration for these patients to aid resectability. If radiation therapy is to be used, conformal beam radiation should be the routine choice; intensity-modulated radiation therapy (IMRT), which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,[265] should be reserved for unique clinical situations, including reirradiation of previously treated patients with recurrent disease.

Principles of the Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with colorectal cancer develop colorectal metastases,[266-268] and 80% to 90% of these patients have unresectable metastatic liver disease.[267,269-272] Metastatic disease most frequently develops metachronously after treatment for locoregional colorectal cancer, with the liver being the most common site of involvement.[273] However, 20% to 34% of patients with colorectal cancer present with synchronous liver metastases.[272,274] Some evidence indicates that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In a retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement (P = .008) and more bilobar metastases (P = .016) than patients diagnosed with metachronous liver metastases.[275]

It has been estimated that more than half of patients who die of colorectal cancer have liver metastases at autopsy, with metastatic liver disease being the cause of death in most patients.[276] Reviews of autopsy reports of patients who died from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients.[271] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not

undergoing surgery.[267,277] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than 3 tumors, and a disease-free interval of less than 12 months, have been associated with a poor prognosis in patients with colorectal cancer.[274,278-282]

Surgical Management of Colorectal Metastases

Studies of selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this population and should be the goal for a substantial number of these patients.[267,283] Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,[279,282] and a recent meta-analysis reported a median 5-year survival of 38%.[284] In addition, retrospective analyses and meta-analyses have shown that patients with solitary liver metastases have a 5-year OS rate as high as 71% following resection.[285-287] 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 (discussed further in *Determining Resectability*).[288]

Colorectal metastatic disease sometimes occurs in the lung.[266] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.[289,290] Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases.[291-294]

Evidence supporting resection of extrahepatic metastases in patients with metastatic colorectal cancer is limited. In a recent retrospective analysis of patients undergoing concurrent complete resection of hepatic and extrahepatic disease, the 5-year survival rate was lower than in patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence.[295,296] However, a recent international analysis of 1629 patients with colorectal liver metastases showed that 16% of the 171 patients (10.4%) who underwent concurrent resection of extrahepatic and hepatic disease remained disease-free at a median follow-up of 26 months, suggesting that concurrent resection may be of significant benefit in well-selected patients (ie, those with a smaller total number of metastases).[294] A recent systematic review concluded similarly that carefully selected patients might benefit from this approach.[297]

Recent data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken.[298-302] 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.[299] In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year OS and PFS rates were reported to be 73% and 22%, respectively.[298] A recent meta-analysis of 27 studies including greater than 7200 patients found that those with longer disease-free intervals; those whose recurrences were solitary, smaller, or unilobular; and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.[303] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[304]

Patients with a resectable primary colon tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection, as discussed below in *Resectable Synchronous Liver or Lung Metastases*. For patients presenting with unresectable metastases and

an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver (discussed further in *Unresectable Synchronous Liver or Lung Metastases*).[305]

Liver-Directed Therapies

Although the standard of care for patients with resectable metastatic disease is surgical resection, select patients with liver-only or liver-dominant metastatic disease have liver-directed treatment options in addition to or instead of surgical resection.[306,307] The role of non-extirpative liver-directed therapies in the treatment of colorectal metastases is controversial.

Hepatic Arterial Infusion

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (ie, hepatic arterial infusion [HAI]) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAI and intravenous 5-FU with or without LV was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.[271,308] The study was not powered for long-term survival, but a trend (not significant) was seen toward better long-term outcome in the group receiving HAI at later follow-up periods.[271,309] Several 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.[271]

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.[283] Limitations on the use of HAI therapy include the potential for biliary toxicity[271] and the requirement of specific technical expertise. Panel consensus is that HAI therapy should be considered selectively, and only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Arterially Directed Embolic Therapy

Transarterial chemoembolization (TACE) involves hepatic artery catheterization to cause vessel occlusion with locally delivered chemotherapy.[307] A recent randomized trial using HAI to deliver drug-eluting beads loaded with irinotecan (DEBIRI) reported an OS benefit (22 months vs. 15 months; P = .031).[310] A recent meta-analysis identified 5 observational studies and 1 randomized trial and concluded that, although DEBIRI appears to be safe and effective for patients with unresectable colorectal liver metastases, additional trials are needed.[311]

Doxorubicin-eluting beads have also been studied; the strongest data supporting their effectiveness comes from several phase II trials in hepatocellular carcinoma.[312-317] A recent systematic review concluded that data are not strong enough to recommend TACE for the treatment of colorectal liver metastases except as part of a clinical trial.[318] The panel lists arterially directed embolic therapy as a category 3 recommendation for the treatment of colorectal liver metastases.

Liver-Directed Radiation

Liver-directed radiation therapies include arterial radioembolization with microspheres[319-327] and conformal (stereotactic) external beam radiation therapy.[328]

A recent prospective, randomized, phase III trial of 44 patients showed that radioembolization combined with chemotherapy can lengthen time to progression in patients with liver-limited metastatic colorectal cancer

following progression on initial therapy (2.1 vs. 4.5 months; *P* = .03).[329] The effect on the primary endpoint of time to liver progression was more pronounced (2.1 vs. 5.5 months; *P* = .003). Treatment of liver metastases with yttrium-90 glass radioembolization in a prospective, multicenter, phase II study resulted in a median PFS of 2.9 months for patients with colorectal primaries who were refractory to standard treatment.[330] While toxicity with radioembolization is relatively low, the data supporting its efficacy are limited to very small trials and trials with highly selected patients.[331,332] Therefore, the use of arterial-directed therapies, such as radioembolization, in highly selected patients remains a category 3 recommendation based on the limited amount of evidence[333] and different institutional practice patterns.

External beam radiation therapy to the metastatic site can be considered in highly selected cases in which the patient has a limited number of liver or lung metastases or the patient is symptomatic (category 3 recommendation) or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include three-dimensional conformal radiation therapy, stereotactic body radiation therapy (SBRT),[270,334,335] and IMRT, which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.[265,336-339]

Tumor Ablation

Although resection is the standard approach for the local treatment of resectable metastatic disease, some patients who cannot undergo resection because of comorbidity, location of the metastatic lesions, or an estimate of inadequate liver volume after resection may be candidates for tumor ablation therapy.[340] Ablative techniques include radiofrequency ablation (RFA), microwave ablation, cryoablation, percutaneous ethanol injection, and electro-coagulation. Data on these techniques are extremely limited.[341-347]

Several retrospective studies have compared RFA with resection in the treatment of liver or lung metastases.[286,348-351] Most of these studies have shown RFA to be inferior to resection in terms of rates of local recurrence and 5-year OS.[348,352] Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, technologic limitations of RFA, or a combination of these factors, is currently unclear.[350] A 2010 ASCO clinical evidence review determined that RFA has not been well-studied in the setting of colorectal cancer liver metastases, with no randomized controlled trials having been reported at that time.[347] The ASCO panel concluded that a compelling need exists for more research in this area. A 2012 Cochrane Database systematic review recently came to similar conclusions, as did a separate meta-analysis.[345,346] Recently, a trial was reported in which 119 patients were randomized to systemic treatment or systemic treatment plus RFA with or without resection.[353] No difference in OS was seen, but PFS was improved at 3 years in the RFA group (27.6% vs. 10.6%; HR, 0.63; 95% CI, 0.42–0.95; *P* = .025).

The panel does not consider ablation to be a substitute for resection in patients with completely resectable disease. In addition, resection or ablation (either alone or in combination with resection) should be reserved for patients with disease that is completely amenable to local therapy. Use of surgery, ablation, or the combination, with the goal of less-than-complete resection/ablation of all known sites of disease, is not recommended.

Peritoneal Carcinomatosis

Approximately 17% of patients with metastatic colorectal cancer have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis. Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.[354] The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative, and consists of systemic therapy (see *Chemotherapy for Advanced or Metastatic Disease*) with palliative surgery or stenting if needed.[355] The panel cautions that the use of bevacizumab in patients with colon or rectal stents is associated with a possible increased risk of bowel perforation.[356,357]

Several surgical series and retrospective analyses have addressed the role of cytoreductive surgery (ie, peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis without extra-abdominal metastases.[358-365] In the only randomized controlled trial of this approach, Verwaal et al[366] randomized 105 patients to either standard therapy (5-FU/LV with or without palliative surgery) or to aggressive cytoreductive surgery and HIPEC with mitomycin C; postoperative 5-FU/LV was given to 33 of 47 patients. OS was 12.6 months in the standard arm and 22.3 months in the HIPEC arm (P = .032). However, treatment-related morbidity was high, and the mortality was 8% in the HIPEC group, mostly related to bowel leakage. In addition, long-term survival does not seem to be improved by this treatment as seen by follow-up results.[367] Importantly, this trial was performed without oxaliplatin, irinotecan, or molecularly targeted agents. Some experts have argued that the OS difference seen might have been much smaller if these agents were used (ie, the control group would have had better outcomes).[368]

Other criticisms of the Verwaal trial have been published.[368] One important point is that the trial included patients with peritoneal carcinomatosis of appendiceal origin, a group which has seen greater benefit with the cytoreductive surgery/HIPEC approach.[358,362,369] A retrospective multicenter cohort study reported median OS times of 30 and 77 months for patients with peritoneal carcinomatosis of colorectal origin and appendiceal origin, respectively, treated with HIPEC or with cytoreductive surgery and early postoperative intraperitoneal chemotherapy.[362] The median OS time for patients with pseudomyxoma peritonei, which arises from mucinous appendiceal carcinomas, was not reached at the time of publication. A recent retrospective international registry study reported 10- and 15-year survival rates of 63% and 59%, respectively, in patients with pseudomyxoma peritonei from mucinous appendiceal carcinomas treated with cytoreductive surgery and HIPEC.[370] HIPEC was not shown to be associated with improvements in OS in this study, whereas completeness of cytoreduction was. Thus, for patients with pseudomyxoma peritonei, optimal treatment is still unclear.[371]

The individual components of the HIPEC approach have not been well studied. In fact, studies in rats have suggested that the hyperthermia component of the treatment is irrelevant.[372] Results of a retrospective cohort study also suggest that heat may not affect outcomes from the procedure.[359] In addition, significant morbidity and mortality are associated with this procedure. A 2006 meta-analysis of 2 randomized controlled trials and 12 other studies reported morbidity rates ranging from 23% to 44% and mortality rates ranging from 0% to 12%.[365] While the risks are reportedly decreasing with time (ie, recent studies report 1%–5% mortality rates at centers of excellence[363,368]), the benefits of the approach have not been definitively shown. Therefore, the panel currently considers the treatment of disseminated carcinomatosis with

cytoreductive surgery and HIPEC to be investigational and does not endorse this 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.

Determining Resectability

The consensus of the panel is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (ie, with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status. The criteria for determining patient suitability for resection of metastatic disease are the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve.[373-376] When the remnant liver is insufficient in size based on cross-sectional imaging volumetrics, preoperative portal vein embolization of the involved liver can be performed to expand the future liver remnant.[377] It should be noted that size alone is rarely a contraindication to tumor resection. Resectability differs fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease.[378] Resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), because incomplete resection or debulking (R1/R2 resection) has not been shown to be beneficial.[268,373]

The role of PET/CT in determining resectability of patients with metastatic colorectal cancer is discussed in *Workup and Management of Synchronous Metastatic Disease*, below.

Conversion to Resectability

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, chemotherapy is being increasingly considered in highly selected cases in an attempt to downsize colorectal metastases and convert them to a resectable status. Patients presenting with large numbers of metastatic sites within the liver or lung are unlikely to achieve an R0 resection simply on the basis of a favorable response to chemotherapy, as the probability of complete eradication of a metastatic deposit by chemotherapy alone is low. These patients should be regarded as having unresectable disease not amenable to conversion therapy. In some highly selected cases, however, patients with significant response to conversion chemotherapy can be converted from unresectable to resectable status.[352]

Any active metastatic chemotherapeutic regimen can be used in an attempt to convert an unresectable patient to a resectable status, because the goal is not specifically the eradication of micrometastatic disease, but rather the obtaining of optimal size regression of the visible metastases. An important point to keep in mind is that irinotecan- and oxaliplatin-based chemotherapeutic regimens may cause liver steatohepatitis and sinusoidal liver injury, respectively.[379-383] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable. Some of the trials addressing various conversion therapy regimens are discussed below.

In the study of Pozzo et al, it was reported that chemotherapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection.[375] 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 NCCTG,[269] 42 patients with unresectable liver metastases were treated with FOLFOX. Twenty-five

patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study, 1104 patients with initially unresectable colorectal liver metastases were treated with chemotherapy, which included oxaliplatin in the majority of cases, and 138 patients (12.5%) classified as "good responders" underwent secondary hepatic resection.[278] The 5-year DFS rate for these 138 patients was 22%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%; 2 of the 24 had lung metastases) were able to undergo curative resection after treatment.[384] The median OS time in this group was 42.4 months.

In addition, FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI in 2 randomized clinical trials in patients with unresectable disease.[385,386] In both studies, FOLFOXIRI led to an increase in R0 secondary resection rates: 6% versus 15%, $P = .033$ in the Gruppo Oncologico Nord Ovest (GONO) trial[385]; and 4% versus 10%, $P = .08$ in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.[386] In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs. 8%), with a median OS of 23.4 versus 16.7 months ($P = .026$).[387]

More recent favorable results of randomized clinical trials evaluating FOLFIRI or FOLFOX for the purpose of conversion of unresectable disease to resectable disease in combination with anti-epidermal growth factor receptor (EGFR) inhibitors have been reported.[388,389] For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.[388] Retrospective analysis showed that in both treatment arms combined resectability increased from 32% to 60% after chemotherapy in patients with wild-type *KRAS* exon 2 with the addition of cetuximab ($P < .0001$). Final analysis of this trial showed that the median OS of the entire cohort was 35.7 months (95% CI, 27.2–44.2 months), with no difference between the arms.[390] Another recent randomized controlled trial compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable colorectal cancer metastatic to the liver.[391] The primary endpoint was the rate of conversion to resectability based on evaluation by a multidisciplinary team. After evaluation, 20 of 70 (29%) patients in the cetuximab arm and 9 of 68 (13%) patients in the control arm were determined to be eligible for curative-intent hepatic resection. R0 resection rates were 25.7% in the cetuximab arm and 7.4% in the control arm ($P < .01$). In addition, surgery improved the median survival time compared to unresected participants in both arms, with longer survival in patients receiving cetuximab (46.4 vs. 25.7 months; $P = .007$ for the cetuximab arm and 36.0 vs. 19.6 months; $P = .016$ for the control arm). A recent meta-analysis of 4 randomized controlled trials concluded that the addition of cetuximab or panitumumab to chemotherapy significantly increased the response rate, the R0 resection rate (from 11% to 18%; RR, 1.59; $P = .04$), and PFS, but not OS in patients with wild-type *KRAS* exon 2-containing tumors.[392]

The role of bevacizumab in the patient with unresectable disease, whose disease is felt to be potentially convertible to resectability with a reduction in tumor size, has also been studied. Data seem to suggest that bevacizumab modestly improves the response rate to irinotecan-based regimens.[393,394] Thus, when an irinotecan-based regimen is selected for an attempt to convert unresectable disease to resectability, the use of bevacizumab would seem to be an appropriate consideration.

On the other hand, a 1400-patient, randomized, double-blind, placebo-controlled trial of CapeOx or FOLFOX with or without bevacizumab showed absolutely no benefit in terms of response rate or tumor regression for the addition of bevacizumab, as measured by both investigators and an independent radiology review committee.[395] Therefore, arguments for use of bevacizumab with oxaliplatin-based therapy in this "convert to resectability" setting are not compelling. However, because it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

When chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation be planned 2 months after initiation of chemotherapy, and that those patients who continue to receive chemotherapy undergo surgical re-evaluation every 2 months thereafter.[383,396-398] Reported risks associated with chemotherapy include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.[379] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable.

Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

The panel recommends that a course of an active systemic chemotherapy regimen for metastatic disease, administered for a total perioperative treatment time of approximately 6 months, be considered for most patients undergoing liver or lung resection to increase the likelihood that residual microscopic disease will be eradicated. Although systemic therapy can be given before, between, or after resections, the total duration of perioperative chemotherapy should not exceed 6 months. A 2012 meta-analysis identified 3 randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.[399] The pooled analysis showed a benefit of chemotherapy in PFS (pooled HR, 0.75; CI, 0.62–0.91; *P* = .003) and DFS (pooled HR, 0.71; CI, 0.58–0.88; *P* = .001), but not in OS (pooled HR, 0.74; CI, 0.53–1.05; *P* = .088).

The choice of chemotherapy regimen in the pre- and postoperative settings depends on several factors, including the chemotherapy history of the patient and the response rates and safety/toxicity issues associated with the regimens. Regimens recommended for adjuvant therapy and neoadjuvant therapy are the same (see the next section). However, if the tumor grows on neoadjuvant treatment, an active regimen for advanced disease or observation is recommended.

The optimal sequencing of chemotherapy remains unclear. Patients with resectable disease may undergo liver resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) chemotherapy can be used.[400,401]

Potential advantages of preoperative chemotherapy include: earlier treatment of micrometastatic disease, determination of responsiveness to chemotherapy (which can be prognostic and help in planning postoperative therapy), and avoidance of local therapy for those patients with early disease progression. Potential disadvantages include missing the "window of opportunity" for resection because of the possibility of disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.[271,402,403] In fact, results from recent studies of patients with colorectal cancer receiving preoperative chemotherapy indicated that viable cancer was still present in most of the original sites of metastases when these sites were examined pathologically despite achievement of a complete response as evaluated on CT scan.[403-405] Therefore, during

treatment with preoperative chemotherapy, frequent evaluations must be undertaken and close communication must be maintained among medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed that optimizes exposure to the preoperative chemotherapy regimen and facilitates an appropriately timed surgical intervention.[379]

Other reported risks associated with the preoperative chemotherapy approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.[379-383] To reduce the development of hepatotoxicity, the neoadjuvant period is usually limited to 2 to 3 months, and patients should be carefully monitored by a multidisciplinary team.

Chemotherapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colon cancer involves various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, and regorafenib.[198,248,385,386,406-442] 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.[443-446] The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, and the differing toxicity profiles of the constituent drugs. Although the specific chemotherapy regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[422] For example, if oxaliplatin is administered as a part of an initial treatment regimen but is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the remainder of the treatment regimen would still be considered initial therapy.

Principles to consider at the start of therapy include preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive, and plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices after first progression of disease should be based partly on the prior therapies received (ie, exposing the patient to a range of cytotoxic agents). Furthermore, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, and 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 this therapy for whom a high tumor response rate would be potentially beneficial), the panel recommends a choice of 5 chemotherapy regimens: FOLFOX (ie, mFOLFOX6),[430,447] FOLFIRI ,[198] CapeOx,[409,448,449] infusional 5-FU/LV or capecitabine,[198,248,432,442] or FOLFOXIRI.[385,386]

Sequencing and Timing of Therapies

Few studies have addressed the sequencing of therapies in advanced metastatic disease. Prior to the use of targeted agents, several studies randomized patients to different schedules.[447,450-452] The data from these trials suggest that there is little difference in clinical outcomes if intensive therapy is given in first line or if less intensive therapy is given first followed by more intensive combinations.

Results from a randomized study to evaluate the efficacy of FOLFIRI and FOLFOX regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen after first progression showed neither sequence to be significantly superior with respect to PFS or median OS.[447] 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, irinotecan) at some point in the continuum of care.[453] Furthermore, OS was not found to be associated with the order in which these drugs were received.

A study of 6286 patients from 9 trials that evaluated the benefits and risks associated with intensive first-line treatment in the setting of metastatic colorectal cancer treatment according to patient performance status showed similar therapeutic efficacy for patients with performance status of 2 or 1 or less as compared with control groups, although the risks of certain gastrointestinal toxicities were significantly increased for patients with a performance status of 2.[454]

Overall, the panel does not consider one regimen (ie, FOLFOX, CapeOx, FOLFIRI, 5-FU/LV, capecitabine, FOLFOXIRI) to be preferable over the others as initial therapy for metastatic disease. The panel also does not indicate a preference for biologic agents used as part of initial therapy (ie, bevacizumab, cetuximab, panitumumab, none).

Regimens Not Recommended

The consensus of the panel is that infusional 5-FU regimens seem to be less toxic than bolus regimens and that any bolus regimen of 5-FU is inappropriate when administered with either irinotecan or oxaliplatin. Therefore, the panel no longer recommends using the IFL regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial[393,455] and inferior to FOLFOX in the Intergroup trial[456]) at any point in the therapy continuum. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,[198] or capecitabine can be used with oxaliplatin.[440]

The Dutch CAIRO trial showed promising results for the use of capecitabine/irinotecan (CapeIRI) in the first-line treatment of metastatic colorectal cancer.[451] However, in the American BICC-C trial, CapeIRI showed worse PFS than FOLFIRI (5.8 vs. 7.6 months; P = .015), and was considerably more toxic with higher rates of severe vomiting, diarrhea, and dehydration.[393] In this trial, the CapeIRI arm was discontinued. The EORTC study 40015 also compared FOLFIRI with CapeIRI and was discontinued after enrollment of only 85 patients because 7 deaths were determined to be treatment-related (5 in the CapeIRI arm).[457] Several European studies have assessed the safety and efficacy of CapeIRI in combination with bevacizumab (CapeIRI/Bev) in the first-line metastatic setting. A small Spanish study of 46 patients who received CapeIRI/Bev showed encouraging results with good tolerability.[458] Preliminary results from a randomized phase II study conducted in France were presented in 2009, showing a manageable toxicity profile for CapeIRI/Bev in this setting.[459] Additionally, a randomized phase III HeCOG trial compared CapeIRI/Bev and FOLFIRI/Bev in the first-line metastatic setting and found no significant differences in efficacy between the regimens.[460] Despite the differing toxicity profiles reported, the toxicities seemed to be reasonable in both arms. Finally, a randomized phase II study of the AIO colorectal study group compared CapeOx plus bevacizumab with a modified CapeIRI regimen plus bevacizumab and found similar 6-month PFS and similar toxicities.[461] Because of the concerns about the toxicity

of the CapeIRI combination, which may differ between American and European patients, the panel does not recommend CapeIRI or CapeIRI/Bev for the first-line treatment of metastatic colorectal cancer.

Other drug combinations that have produced negative results in phase III trials for the treatment of advanced colorectal cancer include sunitinib plus FOLFIRI, cetuximab plus brivanib, erlotinib plus bevacizumab, and cediranib plus FOLFOX/CapeOx.[462-465] These regimens are not recommended for the treatment of patients with colorectal cancer.

Results from 2 randomized phase III trials have shown that combination therapy with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity.[466,467] In the PACCE trial, the 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* exon 2 wild-type and mutant gene groups.[466] Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab.[467] Therefore, the panel strongly recommends against the use of therapy involving the concurrent combination of an anti-EGFR agent (cetuximab or panitumumab) and an anti-VEGF agent (bevacizumab).

FOLFOX

The phase III EORTC 40983 study, evaluating use of perioperative FOLFOX (6 cycles before and 6 cycles after surgery) for patients with resectable liver metastases, showed absolute improvements in 3-year PFS of 8.1% (P = .041) and 9.2% (P = .025) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[468] The partial response rate after preoperative FOLFOX was 40%, and operative mortality was less than 1% in both treatment groups. However, no difference in OS was seen between the groups, perhaps because second-line therapy was given to 77% of the patients in the surgery-only arm and 59% of the patients in the chemotherapy arm.[469]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[470] Results of the OPTIMOX1 study showed that a “stop-and-go” approach using oxaliplatin-free intervals resulted in decreased neurotoxicity but did not affect OS in patients receiving FOLFOX as initial therapy for metastatic disease.[471] Other trials have also addressed the question of treatment breaks, with or without maintenance therapy, and found that toxicity can be minimized with minimal or no effect on survival.[472] A recent meta-analysis of randomized controlled trials also concluded that intermittent delivery of systemic therapy does not compromise OS compared to continuous treatment.[473] Therefore, the panel recommends adjusting the schedule/timing of the administration of this drug as a means of limiting this adverse effect. Discontinuation of oxaliplatin from FOLFOX or CapeOx should be strongly considered after 3 months of therapy, or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained for the entire 6 months or until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity.

Early data suggested that calcium/magnesium infusion might prevent oxaliplatin-related neurotoxicity.[474-481] However, the phase III randomized, double-blind N08CB study, which randomized 353 patients with colon cancer receiving adjuvant FOLFOX to calcium/magnesium infusion or placebo, found that calcium/magnesium did not reduce cumulative sensory neurotoxicity.[482] The panel therefore recommends against calcium/magnesium infusions for this purpose.

In the phase II OPTIMOX2 trial, patients were randomized to receive either 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 on disease progression) or an induction FOLFOX regimen (6 cycles) followed by discontinuation of all chemotherapy until tumor progression reached baseline, followed by reintroduction of FOLFOX.[483] Results of the study showed no difference in OS for patients receiving the OPTIMOX1 approach compared with those undergoing an early, pre-planned, chemotherapy-free interval (median OS 23.8 vs. 19.5 months; *P* = .42). However, the median duration of disease control, which was the primary endpoint of the study, reached statistical significance at 13.1 months in patients undergoing maintenance therapy and 9.2 months in patients with a chemotherapy-free interval (*P* = .046).[483]

The addition of bevacizumab is an option when FOLFOX is chosen as initial therapy,[395,484] as is the addition of panitumumab or cetuximab for patients with disease characterized by wild-type *KRAS* exon 2 (see discussions on *Bevacizumab, Cetuximab, and Panitumumab*, and *The Role of KRAS, NRAS, and BRAF Status*, below).[418,485,486] With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, panel consensus is that FOLFOX and CapeOx can be used interchangeably. Results from a recent registry-based cohort analysis of greater than 2000 patients support the equivalence of these combinations.[487]

CapeOx

The combination of capecitabine and oxaliplatin, known as CapeOx or XELOX, has been studied as an active first-line therapy for patients with metastatic colorectal cancer.[409,448,449,488,489] In a randomized phase III trial comparing CapeOx and FOLFOX in 2034 patients, the regimens showed similar median PFS intervals of 8.0 and 8.5 months, respectively, and CapeOx was determined to be noninferior to FOLFOX as first-line treatment of metastatic disease.[409] A recent meta-analysis of 3603 patients from 7 randomized controlled trials also showed that CapeOx and FOLFOX had similar benefits for patients with metastatic colorectal cancer.[490]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy (see *FOLFOX*, above).[491] Discontinuation of oxaliplatin from FOLFOX or CapeOx should be strongly considered after 3 months of therapy (the OPTIMOX1 approach[471]), or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until tumor progression. A recent Turkish Oncology Group Trial showed that this stop-and-go approach is safe and effective in first-line with CapeOx/bevacizumab.[492] Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity. The panel recommends against the use of calcium/magnesium infusion to prevent oxaliplatin-related neurotoxicity.[482]

Regarding the toxicities associated with capecitabine use, the panel noted that: 1) patients with diminished creatinine clearance may accumulate levels of the drug, and therefore may require dose modification;[493] 2) the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV;[484,493] and 3) North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.[494] These toxicities may necessitate modifications in the dosing of capecitabine,[484,493,495] 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. Interestingly,

a recent analysis of patients from the AIO's KRK-0104 trial and the Mannheim rectal cancer trial found that capecitabine-related hand-foot skin reactions were associated with an improved OS (75.8 vs. 41.0 months; *P* =.001; HR, 0.56).[496]

The addition of bevacizumab is an option if CapeOx is chosen as initial therapy.[395,484] With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, the consensus of the panel is that FOLFOX and CapeOx can be used interchangeably. Results from a recent registry-based cohort analysis of greater than 2000 patients support the equivalence of these combinations.[487]

FOLFIRI

Evidence for the comparable efficacy for FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI as initial therapy and were then switched to the other regimen at disease progression.[447] Similar response rates and PFS times were obtained when these regimens were used as first-line therapy. Further support for this conclusion has come from results of a phase III trial comparing the efficacy and toxicity of FOLFOX and FOLFIRI regimens in previously untreated patients with metastatic colorectal cancer.[411] No differences were observed in response rate, PFS times, and OS between the treatment arms.

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[497,498] Irinotecan is inactivated by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which is also involved in converting substrates such as bilirubin into more soluble forms through conjugation with certain glycosyl groups. Deficiencies in UGT1A1 can be caused by certain genetic polymorphisms and can result in conditions associated with accumulation of unconjugated hyperbilirubinemias, such as types I and II of the Crigler-Najjar and Gilbert syndromes. Thus, irinotecan should be used with caution and at a decreased dose in patients with Gilbert syndrome or elevated serum bilirubin. Similarly, certain genetic polymorphisms in the gene encoding for UGT1A1 can result in a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in an accumulation of the drug and increased risk for toxicity,[498-500] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[500] Results from a dose-finding and pharmacokinetic study suggest that dosing of irinotecan should be individualized based on UGT1A1 genotype.[501] The maximum tolerated dose of intravenous irinotecan every 3 weeks was 850 mg, 700 mg, and 400 mg in patients with the *1/*1, *1/*/28, and *28/*28 genotypes, respectively.

Commercial tests are available to detect the UGT1A1*28 allele, which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression.[502,503] Also, a warning was added to the label for irinotecan indicating that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.[497] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[500] although guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on patients who experience irinotecan toxicity is not recommended, because they will require a dose reduction regardless of the UGT1A1 test result.

Results from a recent phase IV trial in 209 patients with metastatic colorectal cancer who received bevacizumab in combination with FOLFIRI as first-line therapy showed that this combination was as effective and well-tolerated as bevacizumab with other 5-FU-based therapies.[504] Therefore, the addition of bevacizumab to FOLFIRI is

recommended as an option for initial therapy; alternatively, cetuximab or panitumumab (only for tumors characterized by wild-type *KRAS/NRAS*) can be added to this regimen.[418,429,431,438,505]

Infusional 5-FU/LV and Capecitabine

For patients with impaired tolerance to aggressive initial therapy, the guidelines recommend infusional 5-FU/LV or capecitabine with or without bevacizumab as an option.[198,426,427,437,440,484] Patients with metastatic cancer with no improvement in functional status after this less intensive initial therapy should receive best supportive care. Patients showing improvement in functional status should be treated with one of the options specified for initial therapy for advanced or metastatic disease. Toxicities associated with capecitabine use are discussed earlier (see *CapeOx*).

In a pooled analysis of results from 2 randomized clinical trials involving patients with a potentially curative resection of liver or lung metastases randomly assigned to either postoperative systemic chemotherapy with 5-FU/LV or observation alone after surgery, the median PFS was 27.9 months in the chemotherapy arm and 18.8 months for those undergoing surgery alone (HR, 1.32; 95% CI, 1.00–1.76; *P* = .058), with no significant difference in OS.[506]

Results were recently published from the open-label phase III AVEX trial, in which 280 patients aged 70 years or older were randomized to capecitabine with or without bevacizumab.[507] The trial met its primary endpoint, with the addition of bevacizumab giving a significantly improved median PFS (9.1 vs 5.1 months; HR, 0.53; 95% CI, 0.41–0.69; *P* < .0001).

FOLFOXIRI

FOLFOXIRI is also listed as an option for initial therapy in patients with unresectable metastatic disease.[385,386] Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in 2 randomized phase III trials.[385,386] In the GONO study, statistically significant improvements in PFS (9.8 vs. 6.9 months; HR, 0.63; *P* = .0006) and median OS (22.6 vs. 16.7 months; HR, 0.70; *P* = .032) were observed in the FOLFOXIRI arm,[385] although no OS difference was seen between treatment arms in the HORG study (median OS was 19.5 and 21.5 months for FOLFIRI and FOLFOXIRI, respectively; *P* = .337).[386] Both studies showed some increased toxicity in the FOLFOXIRI arm (eg, significant increases in neurotoxicity and neutropenia,[385] diarrhea, alopecia, and neurotoxicity[386]), but no differences in the rate of toxic death were reported in either study. Long-term outcomes of the GONO trial with a median follow-up of 60.6 months were recently reported.[387] The improvements in PFS and OS were maintained.

For the 2014 version of these guidelines, the panel included the possibility of adding bevacizumab to FOLFOXIRI for initial therapy of patients with unresectable metastatic disease. Results of the GONO group's phase III TRIBE trial found that FOLFOXIRI/bevacizumab significantly increased PFS (12.2 vs. 9.7 months; *P* = .0012) and response rate (65% vs. 53%; *P* = .006) compared to FOLFIRI/bevacizumab in patients with unresectable metastatic colorectal cancer.[508,509] Subgroup analyses indicated that no benefit to the addition of oxaliplatin was seen in patients who received prior adjuvant therapy. Diarrhea, stomatitis, neurotoxicity, and neutropenia were significantly more prevalent in the FOLFOXIRI arm. Results from the randomized phase II OLIVIA trial, which compared mFOLFOX6/bevacizumab to FOLFOXIRI/bevacizumab in patients with unresectable colorectal liver

metastases, were recently reported.[510] Improvement in R0 resection rate was seen in the FOLFOXIRI/bevacizumab arm (49% vs. 23%; *P* = .017). The panel recommends that this aggressive combination only be used in very select patients who could potentially be converted to a resectable state.

Bevacizumab

Bevacizumab[511] is a humanized monoclonal antibody that blocks the activity of VEGF, a factor that plays an important role in tumor angiogenesis. Pooled results from several randomized phase II studies have shown that the addition of bevacizumab to first-line 5-FU/LV improved OS in patients with unresectable metastatic colorectal cancer compared with those receiving these regimens without bevacizumab.[394,512,513] A combined analysis of the results of these trials showed that the addition of bevacizumab to 5-FU/LV was associated with a median survival of 17.9 versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab (*P* = .008).[427] A study of previously untreated patients receiving bevacizumab plus IFL also provided support for the inclusion of bevacizumab in initial therapy.[394] In that pivotal trial, a longer survival time was observed with the use of bevacizumab (20.3 vs. 15.6 months; HR, 0.66; *P* < .001).

Results have also been reported from a large, head-to-head, randomized, double-blind, placebo-controlled, phase III study (NO16966) in which CapeOx (capecitabine dose, 1000 mg/m^2, twice daily for 14 days) with bevacizumab or placebo was compared with FOLFOX with bevacizumab or placebo in 1400 patients with unresectable metastatic disease.[395] The addition of bevacizumab to oxaliplatin-based regimens was associated with a more modest increase of 1.4 months in PFS compared with these regimens without bevacizumab (HR, 0.83; 97.5% CI, 0.72–0.95; *P* = .0023), and the difference in OS, which was also a modest 1.4 months, did not reach statistical significance (HR, 0.89; 97.5% CI, 0.76–1.03; *P* = .077).[395] Researchers have suggested that differences observed in cross-study comparisons of NO16966 with other trials might be related to differences in the discontinuation rates and durations of treatment between trials, although these hypotheses are conjectural.[435] However, in this 1400-patient randomized study, absolutely no difference in response rate was seen with and without bevacizumab, and this finding could not have been influenced by the early withdrawal rates, which would have 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.[395]

The combination of FOLFIRI and bevacizumab in the first-line treatment of advanced colorectal cancer has been studied, although no randomized controlled trials have compared FOLFIRI with and without bevacizumab. A recent systematic review with a pooled analysis (29 prospective and retrospective studies, 3502 patients) found that the combination gave a response rate of 51.4%, a median PFS of 10.8 months (95% CI, 8.9–12.8) and a median OS of 23.7 months (95% CI, 18.1–31.6).[514]

A prospective observational cohort study (ARIES) included 1550 patients who received first-line therapy with bevacizumab with chemotherapy for metastatic colorectal cancer and 482 patients treated with bevacizumab in second-line.[515] Median OS was 23.2 months (95% CI, 21.2–24.8) for the first-line cohort and 17.8 months (95% CI, 16.5–20.7) in the second-line group. A similar cohort study (ETNA) of first-line bevacizumab use with irinotecan-based therapy reported a median OS of 25.3 months (95% CI, 23.3–27.0).[516]

Several meta-analyses have shown a benefit for the use of bevacizumab in first-line therapy for metastatic colorectal cancer.[517-521] A recent meta-analysis of 6 randomized clinical trials (3060 patients) that assessed the efficacy of bevacizumab in first-line treatment of metastatic colorectal cancer found that bevacizumab gave a PFS (HR, 0.72; 95% CI, 0.66–0.78; $P < .00001$) and OS (HR, 0.84; 95% CI, 0.77–0.91; $P < .00001$) advantage.[522] However, subgroup analyses showed that the advantage was limited to irinotecan-based regimens. In addition, a recent analysis of the SEER-Medicare database found that bevacizumab added a modest improvement to OS of patients with stage IV colorectal cancer diagnosed between 2002 and 2007 (HR, 0.85; 95% CI, 0.78–0.93).[523] The survival advantage was not evident when bevacizumab was combined with oxaliplatin-based chemotherapy, but was evident in irinotecan-based regimens. Limitations of this analysis have been discussed,[524,525] but, overall, the addition of bevacizumab to first-line chemotherapy appears to offer a modest clinical benefit.

No data directly address whether bevacizumab should be used with chemotherapy in the perioperative treatment of resectable metastatic disease. Recent data regarding the lack of efficacy of bevacizumab in the adjuvant setting in stage II and III colon cancer[258,526] have prompted some to reconsider the role of bevacizumab in the adjuvant setting of resectable colorectal metastases. The panel does not recommend the use of bevacizumab in the post-resection stage IV adjuvant setting, unless a response to bevacizumab was seen in the neoadjuvant setting.

A recent meta-analysis of randomized controlled trials showed that the addition of bevacizumab to chemotherapy is associated with a higher incidence of treatment-related mortality than chemotherapy alone (relative risk, 1.33; 95% CI, 1.02–1.73; $P = .04$), with hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal perforation (7.1%) being the most common causes of fatality.[527] Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[528] Another meta-analysis showed that bevacizumab was associated with a significantly higher risk of hypertension, gastrointestinal hemorrhage, and perforation, although the overall risk for hemorrhage and perforation is quite low.[529] The risk of stroke and other arterial events is increased in patients receiving bevacizumab, especially in those aged 65 years or older. Gastrointestinal perforation is a rare but important side effect of bevacizumab therapy in patients with colorectal cancer.[484,530] 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.[531] This result illustrated that peritoneal debulking surgery may be a risk factor for gastrointestinal perforation, whereas the presence of an intact primary tumor does not seem to increase the risk for gastrointestinal perforation. The FDA recently approved a safety label warning of the risk for necrotizing fasciitis, sometimes fatal and usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation after bevacizumab use.[532]

Use of bevacizumab may interfere with wound healing.[484,511,530] A retrospective evaluation of data from 2 randomized trials of 1132 patients undergoing chemotherapy with or without bevacizumab as initial therapy for metastatic colorectal cancer indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen compared with the group receiving chemotherapy alone while undergoing major surgery (13% vs. 3.4%, respectively; $P = .28$).[530] However, when chemotherapy plus

bevacizumab or chemotherapy alone was administered before 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* = .63). Similarly, results of a single-center, nonrandomized phase II trial of patients with potentially resectable liver metastases showed no increase in bleeding or wound complications when the bevacizumab component of CapeOx plus bevacizumab therapy was stopped 5 weeks before surgery (ie, bevacizumab excluded from the sixth cycle of therapy).[533] In addition, no significant differences in bleeding, wound, or hepatic complications were seen in a retrospective trial evaluating the effects of preoperative bevacizumab stopped at 8 weeks or less versus at more than 8 weeks before resection of liver colorectal metastases in patients receiving oxaliplatin- or irinotecan-containing regimens.[534] The panel recommends an interval of at least 6 weeks (which corresponds to 2 half-lives of the drug[511]) between the last dose of bevacizumab and elective surgery.

Preclinical studies suggested that cessation of anti-VEGF therapy might be associated with accelerated recurrence, more aggressive tumors on recurrence, and increased mortality. A recent retrospective meta-analysis of 5 placebo-controlled, randomized phase III trials including 4205 patients with metastatic colorectal, breast, renal, or pancreatic cancer found no difference in time to disease progression and mortality with discontinuation of bevacizumab versus discontinuation of placebo.[535] Although this meta-analysis has been criticized,[536,537] the results are supported by recent results from the NSABP Protocol C-08 trial.[258] This trial included patients with stage II and stage III colorectal cancer, and no differences in recurrence, mortality, or mortality 2 years after recurrence were seen between patients receiving bevacizumab versus patients in the control arm. These results suggest that no “rebound effect” is associated with bevacizumab use.

Cetuximab and Panitumumab

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways. Panitumumab is a fully human monoclonal antibody, whereas cetuximab is a chimeric monoclonal antibody.[538,539] Cetuximab and panitumumab have been studied in combination with FOLFIRI and FOLFOX as initial therapy options for treatment of metastatic colorectal cancer. A recent meta-analysis of 14 randomized controlled trials concluded that there is a clear benefit to the use of EGFR inhibitors in patients with *KRAS* exon 2 wild-type metastatic colorectal cancer.[540] Individual trials and the role of *KRAS, NRAS,* and *BRAF* are discussed below.

Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[538,539] Based on case reports and a small trial, administration of panitumumab seems to be feasible for patients experiencing severe infusion reactions to cetuximab.[541-543] Skin toxicity is a side effect of both of these agents and is not considered part of the infusion reactions. The incidence and severity of skin reactions with cetuximab and panitumumab seems to be very similar. Furthermore, the presence and severity of skin rash in patients receiving either of these drugs have been shown to predict increased response and survival.[438,544-549] A recent NCCN task force addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.[550] Cetuximab and panitumumab have also been associated with a risk for venous thromboembolic and other serious adverse events.[551,552]

Based on the results of the PACCE and CAIRO2 trials, the panel strongly advises against the concurrent use of bevacizumab with either cetuximab or panitumumab (see *Bevacizumab*, above).[466,467] A recent

editorial summarizes trials that assessed EGFR inhibitors in combination with various chemotherapy agents.[553] These data are also discussed here.

The Role of KRAS, NRAS, and BRAF Status

The receptor for EGFR has been reported to be overexpressed in 49% to 82% of colorectal tumors.[554-557] EGFR testing of colorectal tumor cells has no proven predictive value in determining likelihood of response to either cetuximab or panitumumab. Data from the BOND study indicated that the intensity of immunohistochemical staining of EGFR in colorectal tumor cells did not correlate with the response rate to cetuximab.[412] A similar conclusion was drawn with respect to panitumumab.[558] Therefore, routine EGFR testing is not recommended, and no patient should be either considered for or excluded from cetuximab or panitumumab therapy based on EGFR test results.

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways, but EGFR status as assessed using immunohistochemistry is not predictive of treatment efficacy.[412,559] Furthermore, cetuximab and panitumumab are only effective in approximately 10% to 20% of patients with colorectal cancer.[412,439,559] The RAS/RAF/MAPK pathway is downstream of EGFR; mutations in components of this pathway are being studied in search of predictive markers for efficacy of these therapies.

A sizable body of literature has shown that tumors with a mutation in codon 12 or 13 of exon 2 of the *KRAS* gene are essentially insensitive to cetuximab or panitumumab therapy (see *KRAS Exon 2 Mutations*, below).[406,438,485,546,560-564] More recent evidence shows mutations in *KRAS* outside of exon 2 and mutations in *NRAS* are also predictive for a lack of benefit to cetuximab and panitumumab (see *NRAS and Other KRAS Mutations, below*).[565,566] The panel therefore strongly recommends *KRAS/NRAS* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer. Patients with known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have 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 *KRAS/NRAS* wild-type genes. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS/NRAS*, this testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see *BRAF V600E Mutations*, below).

The panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer for *RAS* (*KRAS* exon 2 and non-exon 2; *NRAS*) and *BRAF at diagnosis of stage IV disease*. The recommendation for *KRAS/NRAS* testing, at this point, is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *KRAS/NRAS* status is appropriate to plan for the treatment continuum, so that the information may be obtained in a non-time-sensitive manner and the patient and provider can discuss the implications of a *KRAS/NRAS* mutation, if present, while other treatment options still exist. Note that because anti-EGFR agents have no role in the management of stage I, II, or III disease, *KRAS/NRAS* genotyping of colorectal cancers at these earlier stages is not recommended.

KRAS mutations are early events in colorectal cancer formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.[567-569] For this reason, *KRAS/NRAS* genotyping can be performed on archived specimens of either the

primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of *KRAS/NRAS* genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable.

The panel recommends that *KRAS, NRAS, and BRAF* gene testing be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.[570] No specific testing methodology is recommended.[571]

***KRAS* Exon 2 Mutations:** 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.[225,406] A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy,[406,438,485,546,560-564,572] 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.[538,539] Results are mixed as far as the prognostic value of *KRAS* mutations, and the test is not recommended for prognostic reasons.

A recent retrospective study from De Roock et al[573] raised the possibility that codon 13 mutations (G13D) may not be absolutely predictive of non-response. Another recent retrospective study showed similar results.[574] However, as the article by De Roock et al[573] states, these findings are hypothesis-generating only, and prospective studies are needed to determine if patients with *KRAS* G13D mutations can, in fact, benefit from anti-EGFR therapy. Furthermore, a recent retrospective analysis of 3 randomized controlled phase III trials concluded that patients with *KRAS* G13D mutations were unlikely to respond to panitumumab.[575] Currently, use of anti-EGFR agents in patients whose tumors have G13D mutations remains investigational, and is not endorsed by the panel for routine practice.

***NRAS* and Other *KRAS* Mutations:** It was recently reported that 17% of 641 patients from the PRIME trial without *KRAS* exon 2 mutations were found to have mutations in exons 3 and 4 of *KRAS* or mutations in exons 2, 3, and 4 of *NRAS*. A predefined retrospective subset analysis revealed that PFS (HR, 1.31; 95% CI, 1.07–1.60; P = .008) and OS (HR, 1.21; 95% CI, 1.01–1.45; P = .04) were decreased in patients with any *KRAS* or *NRAS* mutation who received panitumumab plus FOLFOX compared to those who received FOLFOX alone.[565] These results show that panitumumab does not benefit patients with *KRAS* or *NRAS* mutations and may even have a detrimental effect in these patients.

Updated analysis of the FIRE-3 trial (discussed in *Cetuximab or Panitumumab vs. Bevacizumab in First-Line,* below) was recently published.[576] When all *RAS* (*KRAS/NRAS*) mutations were considered, PFS was significantly worse in patients with *RAS*-mutant tumors receiving FOLFIRI plus cetuximab than patients with *RAS*-mutant tumors receiving FOLFIRI plus bevacizumab (6.1 months vs. 12.2 months; P = .004). On the other hand, patients with *KRAS/NRAS* wild-type tumors showed no difference in PFS between the regimens (10.4 months vs. 10.2 months; P = .54). This result indicates that cetuximab likely has a detrimental effect in patients with *KRAS* or *NRAS* mutations.

The FDA indication for panitumumab was recently updated to state that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* mutation-positive disease in combination with oxaliplatin-based chemotherapy.[539] The NCCN Colon/Rectal Cancer Panel believes that non-exon 2 *KRAS* mutation status and *NRAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known

KRAS mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab.

***BRAF* V600E Mutations:** Although certain mutations of *KRAS/NRAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *KRAS/NRAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *KRAS/NRAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of colorectal cancers are characterized by a specific mutation in the *BRAF* gene (V600E).[505,577] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.[577,578] Activation of the protein product of the non-mutated *BRAF* gene occurs downstream of the activated KRAS protein in the EGFR pathway; the mutated *BRAF* protein product is believed to be constitutively active,[579-581] thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

The utility of *BRAF* status as a predictive marker is unclear. Limited data from unplanned retrospective subset analyses of patients with metastatic colorectal cancer treated in the first-line setting suggest that although a *BRAF* V600E mutation confers a poor prognosis regardless of treatment, patients with disease characterized by this mutation may receive some benefit from the addition of cetuximab to front-line therapy.[582,583] A planned subset analysis of the PRIME trial also found that mutations in *BRAF* indicated a poor prognosis but were not predictive of benefit to panitumumab added to FOLFOX in first-line treatment of metastatic colorectal cancer.[565] On the other hand, results from the randomized phase III Medical Research Council (MRC) COIN trial suggest that cetuximab may have no effect or even a detrimental one in patients with *BRAF*-mutated tumors treated with CapeOx or FOLFOX in the first-line setting.[578] Overall, the panel believes that there are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on *BRAF* V600E mutation status.

In subsequent lines of therapy, retrospective evidence suggests that mutated *BRAF* is a marker of resistance to anti-EGFR therapy in the non-first-line setting of metastatic disease.[584-586] A retrospective study of 773 primary tumor samples from patients with chemotherapy-refractory disease showed that *BRAF* mutations conferred a significantly lower response rate to cetuximab (2/24; 8.3%) compared with tumors with wild-type *BRAF* (124/326; 38.0%; $P = .0012$).[587] Furthermore, recently reported prospective data from the multicenter randomized controlled PICCOLO trial are consistent with this conclusion, with a detrimental effect seen for the addition of panitumumab to irinotecan in the non-first-line setting in patients with *BRAF* mutations.[588]

Despite uncertainty over its role as a predictive marker, it is clear that mutations in *BRAF* are a strong prognostic marker.[225,578,583,589-593] A recent prospective analysis of tissues from patients with stage II and III colon cancer enrolled in the PETACC-3 trial showed that the *BRAF* mutation is prognostic for OS in patients with MSI-L or MSS tumors (HR, 2.2; 95% CI, 1.4–3.4; $P = .0003$).[225] Moreover, an updated analysis of the CRYSTAL trial showed that patients with metastatic colorectal tumors carrying a *BRAF* mutation have a worse prognosis than those with the wild-type gene.[583] Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (95% CI, 0.33–0.73; $P = .001$).[589] The OS for patients with *BRAF* mutations in the COIN trial was 8.8 months, while those with *KRAS* exon 2 mutations and wild-type *KRAS* exon 2 tumors had OS times of 14.4 months and 20.1 months, respectively.[578] Results from a recent systematic review and meta-analysis of 21 studies, including 9885 patients, suggest that *BRAF* mutation may accompany specific high-risk clinicopathologic characteristics.[594] In particular, an association was observed between

BRAF mutation and proximal tumor location (OR, 5.22; 95% CI, 3.80–7.17; *P* < .001), T4 tumors (OR, 1.76; 95% CI, 1.16–2.66; *P* = .007), and poor differentiation (OR, 3.82; 95% CI, 2.71–5.36; *P* < .001).

The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[595]) at diagnosis of stage IV disease. Testing for the *BRAF* V600E mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed by PCR amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting this mutation.

Cetuximab with FOLFIRI

Use of cetuximab as initial therapy for metastatic disease was investigated in the CRYSTAL trial, in which patients were randomly assigned to receive FOLFIRI with or without cetuximab.[438] Retrospective analyses of the subset of patients with known *KRAS* exon 2 tumor status showed a statistically significant improvement in median PFS with the addition of cetuximab in the group with disease characterized by *KRAS* wild-type exon 2 (9.9 vs. 8.7 months; HR, 0.68; 95% CI, 0.50–0.94; *P* = .02).[438] The statistically significant benefit in PFS for patients with *KRAS* exon 2 wild-type tumors receiving cetuximab was confirmed in a recent publication of an updated analysis of the CRYSTAL data.[583] This recent study included a retrospective analysis of OS in the *KRAS* exon 2 wild-type population and found an improvement with the addition of cetuximab (23.5 vs. 20.0 months, *P* = .009). Importantly, the addition of cetuximab did not affect the quality of life of participants in the CRYSTAL trial.[596]

Panitumumab with FOLFIRI

FOLFIRI with panitumumab is listed as an option for first-line therapy in metastatic colorectal cancer based on extrapolation from data in second-line treatment.[431,588,597,598]

Cetuximab with FOLFOX

Three trials have assessed the combination of FOLFOX and cetuximab in first-line treatment of metastatic colorectal cancer. In a retrospective evaluation of the subset of patients with known tumor *KRAS* exon 2 status enrolled in the randomized phase II OPUS trial, addition of cetuximab to FOLFOX was associated with an increased objective response rate (61% vs. 37%; odds ratio, 2.54; *P* = .011) and a very slightly lower risk of disease progression (7.7 vs. 7.2 months [a 15-day difference]; HR, 0.57; 95% CI, 0.36–0.91; *P* = .016) compared with FOLFOX alone in the subset of patients with *KRAS* exon 2 wild-type tumors.[485] Although data supporting the statistically significant benefits in objective response rate and PFS for patients with tumors characterized by *KRAS* wild-type exon 2 were upheld in a recent update of this study,[599] no median OS benefit was observed for the addition of cetuximab to chemotherapy (22.8 months in the cetuximab arm vs. 18.5 months in the arm undergoing chemotherapy alone; HR, 0.85; *P* = .39).[599]

Furthermore, in the recent randomized phase III MRC COIN trial, no benefit in OS (17.9 vs. 17.0 months; *P* = .067) or PFS (8.6 months in both groups; *P* = .60) was seen with the addition of cetuximab to FOLFOX or CapeOx as first-line treatment of patients with locally advanced or metastatic colorectal cancer and wild-type *KRAS* exon 2.[578] Exploratory analyses of the COIN trial, however, suggest that there may be a benefit to the addition of cetuximab in patients who received FOLFOX instead of CapeOx.[578] Similarly, a recent pooled analysis of the COIN and OPUS studies found that a benefit was suggested in response rate and PFS with the addition of cetuximab to FOLFOX in patients with *KRAS* exon 2 wild-type tumors, although there was no OS benefit.[600]

Notably, more recent trials examining the efficacy of the addition of cetuximab to oxaliplatin-containing regimens in the first-line treatment of patients with advanced or metastatic colorectal cancer and wild-type *KRAS* exon 2 have not shown any benefit. The addition of cetuximab to the Nordic FLOX regimen showed no benefit in OS or PFS in this population of patients in the randomized phase III NORDIC VII study of the Nordic Colorectal Cancer Biomodulation Group.[601]

However, results from the recent randomized phase III CALGB/SWOG 80405 trial of greater than 3000 patients (discussed in *Cetuximab or Panitumumab vs. Bevacizumab in First-Line*, below) showed that the combination of FOLFOX with cetuximab can be effective in first-line treatment of metastatic colorectal cancer.[486] The panel thus added a recommendation for the use of cetuximab with FOLFOX as initial therapy for patients with advanced or metastatic disease to the 2015 version of these guidelines.

The New EPOC trial, which was stopped early because it met protocol-defined futility criteria, found a lack of benefit to cetuximab with chemotherapy in the perioperative metastatic setting (>85% received FOLFOX or CapeOx; patients with prior oxaliplatin received FOLFIRI).[602] In fact, with less than half of expected events observed, PFS was significantly reduced in the cetuximab arm (14.8 vs. 24.2 months; HR, 1.50, 95% CI, 1.00–2.25; $P < .048$). The panel thus cautions that, while the data are not strong enough to prohibit its use, cetuximab in the perioperative setting may harm patients. The panel therefore points out that FOLFOX plus cetuximab should be used with caution in patients with resectable disease and in those with unresectable disease that could potentially be converted to a resectable status.

Panitumumab with FOLFOX

Panitumumab in combination with either FOLFOX[418,603] or FOLFIRI[429] has also been studied in the first-line treatment of patients with metastatic colorectal cancer. Results from the large, open-label, randomized PRIME trial comparing panitumumab plus FOLFOX versus FOLFOX alone in patients with *KRAS/NRAS* wild-type advanced colorectal cancer showed a statistically significant improvement in PFS (HR, 0.72; 95% CI, 0.58–0.90; $P = .004$) and OS (HR, 0.77; 95% CI, 0.64–0.94; $P = .009$) with the addition of panitumumab.[565] Therefore, the combination of FOLFOX and panitumumab remains an option as initial therapy for patients with advanced or metastatic disease. Importantly, the addition of panitumumab had a detrimental impact on PFS for patients with tumors characterized by mutated *KRAS/NRAS* in the PRIME trial (discussed further in *NRAS and Other KRAS Mutations*, above).[565]

Cetuximab or Panitumumab vs. Bevacizumab in First-Line

The randomized, open-label, multicenter FIRE-3 trial from the German AIO group compared the efficacy of FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in first-line, *KRAS* exon 2 wild-type, metastatic disease.[576] This trial did not meet its primary endpoint of investigator-read objective response rate in the 592 randomized patients (62.0% vs. 58.0%; $P = .18$). PFS was nearly identical between the arms of the study, but a statistically significant improvement in OS was reported in the cetuximab arm (28.7 vs. 25.0 months; HR, 0.77; 95% CI, 0.62–0.96; $P = .017$). The panel has several criticisms of the trial, including regarding the lack of third-party review and low rates of second-line therapy. While the rate of adverse events was similar between the arms, more skin toxicity was observed in those receiving cetuximab.

Results of the phase III CALGB/SWOG 80405 trial, comparing FOLFOX/FOLFIRI with cetuximab or bevacizumab, were recently reported.[486] In this study, patients with wild-type *KRAS* exon 2 received either FOLFOX (73%) or FOLFIRI (27%) and were randomized to receive cetuximab or bevacizumab. The primary endpoint of OS was equivalent between the arms, at 29.0 months (95% CI, 25.7–31.2 months) in the bevacizumab arm versus 29.9 months (95% CI, 27.6–31.2 months) in the cetuximab arm (HR, 0.92; 95% CI, 0.78–1.09; *P* =.34).

Results for the randomized multicenter phase II PEAK trial, which compared FOLFOX/panitumumab with FOLFOX/bevacizumab in first-line treatment of patients with wild-type *KRAS* exon 2, were also recently published.[604] In the subset of 170 participants with wild-type *KRAS/NRAS* based on extended tumor analysis, PFS was better in the panitumumab arm (13.0 vs. 9.5 months; HR, 0.65; 95% CI, 0.44–0.96; *P* = .03). A trend towards improved OS was seen (41.3 vs. 28.9 months; HR, 0.63; 95% CI, 0.39–1.02; *P* = .06). Although these data are intriguing, definitive conclusions are hindered by the small sample size and limitations of subset analyses.[605]

Thus, at this time, the panel considers the addition of cetuximab, panitumumab, or bevacizumab to chemotherapy as equivalent choices in the first-line, *RAS* wild-type, metastatic setting.

Therapy After Progression

Decisions regarding therapy after progression of metastatic disease depend on previous therapies. The panel recommends against the use of mitomycin, alfa-interferon, taxanes, methotrexate, pemetrexed, sunitinib, sorafenib, erlotinib, or gemcitabine, either as single agents or in combination, as therapy in patients exhibiting disease progression after treatment with standard therapies. These agents have not been shown to be effective in this setting. Furthermore, no objective responses were observed when single-agent capecitabine was administered in a phase II study of patients with colorectal cancer resistant to 5-FU.[606]

The recommended therapy options after first progression for patients who have received prior 5-FU/LV-based or capecitabine-based therapy are dependent on the initial treatment regimen:

- For patients who received a FOLFOX or CapeOx-based regimen for initial therapy, FOLFIRI or irinotecan alone or with cetuximab or panitumumab (*KRAS/NRAS* wild-type tumor only), bevacizumab, or ziv-aflibercept are recommended options.

- For patients who received a FOLFIRI-based regimen as initial treatment, FOLFOX or CapeOx alone[488] or with bevacizumab; cetuximab or panitumumab plus irinotecan; or single-agent cetuximab or panitumumab (for those not appropriate for the combination with irinotecan) are recommended options.

- For patients who received 5-FU/LV or capecitabine without oxaliplatin or irinotecan as initial therapy, options after first progression include FOLFOX, CapeOx, FOLFIRI, single-agent irinotecan, or irinotecan plus oxaliplatin (IROX). These can be varyingly combined with bevacizumab or ziv-aflibercept.

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

Single-agent irinotecan administered after first progression has been shown to significantly improve OS relative to best supportive care [413] or

infusional 5-FU/LV.[607] In the study of Rougier et al,[607] median PFS was 4.2 months for irinotecan versus 2.9 months for 5-FU (*P* = .030), whereas Cunningham et al[413] reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive-care group (*P* = .0001). Furthermore, no significant differences in OS were observed in the Intergroup N9841 trial when FOLFOX was compared with irinotecan monotherapy after first progression of metastatic colorectal cancer.[608]

A recent meta-analysis of randomized trials found that the addition of a targeted agent after first-line treatment improves outcomes but also increases toxicity.[609] Data relating to specific biologic therapies are discussed below.

Bevacizumab in the Non-First-Line Setting

In the TML (ML18147) trial, patients with metastatic colorectal cancer who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy regimen with or without bevacizumab.[610] This study met its primary endpoint, with patients continuing on bevacizumab having a modest improvement in OS (11.2 months vs. 9.8 months; HR, 0.81; 95% CI, 0.69–0.94; *P* = .0062). Subgroup analyses from this trial found that these treatment effects were independent of *KRAS* exon 2 status.[611]

Similar results were reported from the GONO group's phase III randomized BEBYP trial, in which the PFS of patients who continued on bevacizumab plus a different chemotherapy regimen following progression on bevacizumab was 6.7 months compared to 5.2 months in the control arm (HR, 0.66; 95% CI, 0.49–0.90; *P* = .0072).[612]

The continuation of bevacizumab following progression on bevacizumab was also studied in a community oncology setting through a retrospective analysis of 573 patients from the US Oncology iKnowMed electronic medical record system.[613] Bevacizumab beyond progression was associated with a longer OS (HR, 0.76; 95% CI, 0.61–0.95) and a longer post-progression OS (HR, 0.74; 95% CI, 0.60–0.93) on multivariate analysis. Analyses of the ARIES observational cohort found similar results, with longer post-progression survival with continuation of bevacizumab (HR, 0.84; 95% CI, 0.73–0.97).[614]

Overall, these data (along with data from the VELOUR trial, discussed below) show that the continuation of VEGF blockade in second-line therapy offers a very modest but statistically significant OS benefit. The panel added the continuation of bevacizumab to the second-line treatment options in the 2013 versions of the NCCN Guidelines for Colon and Rectal Cancers. It may be added to any regimen that does not contain an EGFR inhibitor or ziv-aflibercept. The panel recognizes the lack of data suggesting a benefit to bevacizumab with irinotecan alone in this setting, but believes that the option is acceptable, especially in patients whose disease progressed on a 5-FU- or capecitabine-based regimen.

It may also be appropriate to consider adding bevacizumab to chemotherapy after progression of metastatic disease if it was not used in initial therapy.[420] The randomized phase III ECOG E3200 study in patients who experienced progression through a first-line non-bevacizumab–containing regimen showed that the addition of bevacizumab to second-line FOLFOX modestly improved survival.[420] Median OS was 12.9 months for patients receiving FOLFOX plus bevacizumab compared with 10.8 months for patients treated with FOLFOX alone (*P* = .0011).[420] Use of single-agent bevacizumab is not recommended because it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX plus bevacizumab treatment arms.[420]

Cetuximab and Panitumumab in the Non-First-Line Setting

For patients with wild-type *KRAS/NRAS* who experienced progression on therapies *not* containing an EGFR inhibitor, cetuximab or panitumumab plus irinotecan, cetuximab or panitumumab plus FOLFIRI, or single-agent cetuximab or panitumumab[562] is recommended. For patients with wild-type *KRAS/NRAS* progressing on therapies that *did* contain an EGFR inhibitor, administration of an EGFR inhibitor is not recommended in subsequent lines of therapy. Although no head-to-head studies have compared cetuximab and panitumumab, similar response rates have been observed when each agent was studied as monotherapy after progression. No data support switching to either cetuximab or panitumumab after failure of the other drug, and the panel recommends against this practice. If the patient does not experience response to oxaliplatin, irinotecan, and an EGFR inhibitor, the panel recommends best supportive care or enrollment in a clinical trial.

Panitumumab has been studied as a single agent in the setting of metastatic colorectal cancer for patients with disease progression on oxaliplatin/irinotecan-based chemotherapy.[439] In a retrospective analysis of the subset of patients in this trial with known *KRAS* exon 2 tumor status, the benefit of panitumumab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[406] Progression-free survival was 12.3 weeks versus 7.3 weeks in favor of the panitumumab arm. Response rates to panitumumab were 17% versus 0% in the wild-type and mutant arms, respectively.[406]

Panitumumab has also been studied in combination therapy in the setting of progressing metastatic colorectal cancer. Among patients with *KRAS* exon 2 wild-type tumors enrolled in the large Study 181 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 vs. 3.9 months; HR, 0.73; 95% CI, 0.59–0.90; P = .004), although differences in OS between the arms did not reach statistical significance.[431] These results were confirmed in the final results of Study 181.[615] In addition, secondary analysis from the STEPP trial showed that panitumumab in combination with irinotecan-based chemotherapy in second-line therapy has an acceptable toxicity profile.[597] The randomized multicenter PICCOLO trial, which assessed the safety and efficacy of irinotecan/panitumumab, did not meet its primary endpoint of improved OS in patients with wild-type *KRAS/NRAS* tumors.[616]

Cetuximab has been studied both as a single agent[412,545,559,562] and in combination with irinotecan[412,617] in patients experiencing disease progression on initial therapy not containing cetuximab or panitumumab for metastatic disease. Results of a large phase III study comparing irinotecan with or without cetuximab did not show a difference in OS, but showed significant improvement in response rate and in median PFS with irinotecan and cetuximab compared with irinotecan alone.[618] Importantly, *KRAS* status was not determined in this study and toxicity was higher in the cetuximab-containing arm (eg, rash, diarrhea, electrolyte imbalances).[618]

In a retrospective analysis of the subset of patients with known *KRAS* exon 2 tumor status receiving cetuximab monotherapy as second-line therapy,[545] the benefit of cetuximab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[562] For those patients, median PFS was 3.7 versus 1.9 months (HR, 0.40; 95% CI, 0.30–0.54; P < .001) and median OS was 9.5 versus 4.8 months (HR, 0.55; 95% CI, 0.41–0.74; P < .001) in favor of the cetuximab arm.[562]

The recently published randomized, multicenter, open-label, non-inferiority phase 3 ASPECCT trial compared single-agent cetuximab

with single-agent panitumumab in the chemotherapy-refractory metastatic setting.[619] The primary non-inferiority OS endpoint was reached, with a median OS of 10.4 months (95% CI, 9.4–11.6) with panitumumab and 10.0 months (95% CI, 9.3–11.0) with cetuximab (HR 0.97; 95% CI 0.84–1.11). The incidence of adverse events was similar between the groups.

Ziv-Aflibercept

Ziv-aflibercept is a recombinant protein that has part of the human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1.[620] It is designed to function as a VEGF trap to prevent activation of VEGF receptors and thus inhibit angiogenesis. The VELOUR trial tested second-line ziv-aflibercept in patients with metastatic colorectal cancer that progressed after one regimen containing oxaliplatin. The trial met its primary endpoint with a small improvement in OS (13.5 months for FOLFIRI/ziv-aflibercept vs. 12.1 months for FOLFIRI/placebo; HR, 0.82; 95% CI, 0.71–0.94; P = .003).[441] A prespecified subgroup analysis from the VELOUR trial found that median OS in the ziv-aflibercept arm versus the placebo arm was 12.5 months (95% CI, 10.8–15.5) versus 11.7 months (95% CI, 9.8–13.8) in patients with prior bevacizumab treatment and 13.9 months (95% CI, 12.7–15.6) versus 12.4 (95% CI, 11.2–13.5) in patients with no prior bevacizumab treatment.[621]

Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients. No data suggest activity of FOLFIRI plus ziv-aflibercept in patients who progressed on FOLFIRI plus bevacizumab or vice-versa, and no data suggest activity of single-agent ziv-aflibercept. Thus, the panel added ziv-aflibercept as a second-line treatment option in combination with FOLFIRI or irinotecan only following progression on therapy not containing irinotecan.

Adverse events associated with ziv-aflibercept treatment in the VELOUR trial led to discontinuation in 26.6% of patients compared to 12.1% discontinuation in the placebo group.[441] The most common causes for discontinuation were asthenia/fatigue, infections, diarrhea, hypertension, and venous thromboembolic events.

Regorafenib

Regorafenib is a small molecule inhibitor of multiple kinases (including VEGF receptors, fibroblast growth factor [FGF] receptors, platelet-derived growth factor [PDGF] receptors, BRAF, KIT, and RET) that are involved with various processes including tumor growth and angiogenesis.[622] The phase III CORRECT trial randomized 760 patients who progressed on standard therapy to best supportive care with placebo or regorafenib.[424] The trial met its primary endpoint of OS (6.4 months for regorafenib vs. 5.0 months for placebo; HR, 0.77; 95% CI, 0.64–0.94; P = .005). PFS was also significantly but modestly improved (1.9 months vs. 1.7 months; HR, 0.49; 95% CI, 0.42–0.58; P < .000001).

Regorafenib has only shown activity in patients who have progressed on all standard therapy. Therefore, the panel added regorafenib as an additional line of therapy for patients with metastatic colorectal cancer refractory to chemotherapy. For patients with mutant *KRAS/NRAS*, regorafenib can be used in the third-line setting; patients with wild-type *KRAS/NRAS* can receive regorafenib as a third or fourth line of therapy.

The most common grade 3 or higher adverse events in the regorafenib arm of the CORRECT trial were hand-foot skin reaction (17%), fatigue (10%), hypertension (7%), diarrhea (7%), and rash/desquamation (6%).[424] Severe and fatal liver toxicity occurred in 0.3% of 1100 patients treated with regorafenib across all trials.[622] In a meta-analysis of 4 studies that included 1078 patients treated with regorafenib for

colorectal cancer, GIST, renal cell carcinoma, or hepatocellular carcinoma, the overall incidence of all-grade and high-grade hand-foot skin reactions was 60.5% and 20.4%, respectively.[623] In the subset of 500 patients with colorectal cancer, the incidence of all-grade hand-foot skin reaction was 46.6%.

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from the large bowel (eg, colorectal liver metastases) is suspected should include a total colonoscopy, CBC, chemistry profile, CEA determination, needle biopsy if indicated, and CT scan with intravenous contrast of the chest, abdomen, and pelvis.[153] MRI with intravenous contrast should be considered if CT is inadequate. The panel also recommends tumor *KRAS/NRAS* gene status testing at diagnosis of metastatic disease and consideration of *BRAF* genotyping for all patients with *KRAS/NRAS* wild-type metastatic colon cancer (see *The Role of KRAS, NRAS, and BRAF Status*, above).

The panel strongly discourages the routine use of PET/CT scanning for staging, baseline imaging, or routine follow-up, and recommends consideration of a preoperative PET/CT scan at baseline if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease in selected cases. The purpose of this PET/CT scan is to evaluate for unrecognized metastatic disease that would preclude the possibility of surgical management. A recent randomized clinical trial of patients with resectable metachronous metastases assessed the role of PET/CT in the workup of potential curable disease.[624] While there was no impact of PET/CT on survival, surgical management was changed in 8% of patients after PET/CT. For example, resection was not undertaken for 2.7% of patients because additional metastatic disease was identified (bone, peritoneum/omentum, abdominal nodes). In addition, 1.5% of patients had more extensive hepatic resections and 3.4% had additional organ surgery. An additional 8.4% of patients in the PET/CT arm had false-positive results, many of which were investigated with biopsies or additional imaging.

Patients with clearly unresectable metastatic disease should not have baseline PET/CT scans. The panel also notes that PET/CT scans should not be used to assess response to chemotherapy, because a PET/CT scan can become transiently negative after chemotherapy (eg, in the presence of necrotic lesions).[625] False-positive PET/CT scan results can occur in the presence of tissue inflammation after surgery or infection.[625] An MRI with intravenous contrast can be considered as part of the preoperative evaluation of patients with potentially surgically resectable M1 liver disease. For example, an MRI with contrast may be of use when the PET and CT scan results are inconsistent with respect to the extent of disease in the liver.

The criterion of potential surgical cure includes patients with metastatic disease that is not initially resectable but for whom a surgical cure may become possible after preoperative chemotherapy. In most cases, however, 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, because of involvement of critical structures, cannot be resected unless regression is accomplished with chemotherapy (see *Conversion to Resectability*, above).

Close communication among members of the multidisciplinary treatment team is recommended, including an upfront evaluation by a surgeon experienced in the resection of hepatobiliary or lung metastases.

Resectable Synchronous Liver or Lung Metastases

When patients present with colorectal cancer and synchronous liver metastases, resection of the primary tumor and liver can be performed in a simultaneous or staged approach.[626-632] Historically, in the staged approach, the primary tumor was usually resected first. However, the approach of liver resection before resection of the primary followed by adjuvant chemotherapy is now well-accepted.[633] In addition, emerging data suggest that chemotherapy, followed by resection of liver metastases before resection of the primary tumor, might be an effective approach in some patients, although more studies are needed.[634-641]

If a patient with resectable liver or lung metastases is a candidate for surgery, the panel recommends the following options: 1) synchronous or staged colectomy with liver or lung resection,[273,281] followed by adjuvant chemotherapy (FOLFOX or CapeOx preferred[194,468]); 2) neoadjuvant chemotherapy for 2 to 3 months (ie, FOLFIRI, FOLFOX,[272] or CapeOx chemotherapy alone or with bevacizumab; FOLFIRI or FOLFOX regimens with panitumumab; FOLFIRI with cetuximab), followed by synchronous or staged colectomy with liver or lung resection; or 3) colectomy followed by adjuvant chemotherapy (see neoadjuvant options discussed earlier) and a staged resection of metastatic disease. Overall, combined neoadjuvant and adjuvant treatments should not exceed 6 months.

In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure.

Unresectable Synchronous Liver or Lung Metastases

For patients with metastatic disease that is deemed to be potentially convertible (see *Conversion to Resectability*, above),[407] chemotherapy regimens with high response rates should be considered, and these patients should be reevaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing this therapy. If bevacizumab is included as a component of the conversion therapy, an interval of at least 6 weeks between the last dose of bevacizumab and surgery should be applied, with a 6- to 8-week postoperative period before re-initiation of bevacizumab. Patients with disease converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer, including treatment with pre- and postoperative chemotherapy for a preferred total perioperative therapy duration of 6 months. Recommended options for adjuvant therapy for these patients include active chemotherapy regimens for advanced or metastatic disease (category 2B); observation or a shortened course of chemotherapy can also be considered for patients who have completed preoperative chemotherapy. In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure. 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*).

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

For patients with liver-only or lung-only disease that is deemed unresectable (see *Determining Resectability*, above), the panel recommends chemotherapy corresponding to initial therapy for

metastatic disease (eg, FOLFIRI, FOLFOX, or CapeOx chemotherapy alone or with bevacizumab; FOLFIRI or FOLFOX with panitumumab or cetuximab; FOLFOXIRI alone or with bevacizumab).

Results from a recent study suggest that there may be some benefit in both OS and PFS from resection of the primary in the setting of unresectable colorectal metastases.[642] Other retrospective analyses also have shown a potential benefit.[643,644] On the other hand, the prospective, multicenter phase II NSABP C-10 trial showed that patients with an asymptomatic primary colon tumor and unresectable metastatic disease who received mFOLFOX6 with bevacizumab experienced an acceptable level of morbidity without upfront resection of the primary tumor.[645] The median OS was 19.9 months. Notably, symptomatic improvement in the primary is often seen with systemic chemotherapy even within the first 1 to 2 weeks. Furthermore, complications from the intact primary lesion are uncommon in these circumstances,[305] and its removal delays initiation of systemic chemotherapy. In fact, a recent systematic review concluded that resection of the primary does not reduce complications and does not improve OS.[646] However, other systematic reviews and meta-analyses have concluded that, while data are not strong, resection of the primary tumor may provide a survival benefit.[647-649] Another systematic review and meta-analysis identified 5 studies that compared open to laparoscopic palliative colectomies in this setting.[650] The laparoscopic approach resulted in shorter lengths of hospital stays ($P < .001$), fewer postoperative complications ($P = 0.01$), and lower estimated blood loss ($P < .01$).

Overall, the panel believes that the risks of surgery outweigh the possible benefits of resection of asymptomatic primary tumors in the setting of unresectable colorectal metastases. Routine palliative resection of a synchronous primary lesion should therefore only be considered if the patient has an unequivocal imminent risk of obstruction or acute significant bleeding.

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, because large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare.

Synchronous Abdominal/Peritoneal Metastases

For patients with peritoneal metastases causing obstruction or that may cause imminent obstruction, palliative surgical options include colon resection, diverting colostomy, a bypass of impending obstruction, or stenting, followed by chemotherapy for advanced or metastatic disease.

The primary treatment of patients with nonobstructing metastases is chemotherapy. As mentioned above, the panel currently considers the treatment of disseminated carcinomatosis with cytoreductive surgery (ie, peritoneal stripping surgery) and perioperative HIPEC[359,360,651] to be investigational and does not endorse this 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

On documentation of metachronous, potentially resectable, metastatic disease with dedicated contrast-enhanced CT or MRI, characterization of the disease extent using 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 that could preclude surgery.[624,652,653] Specifically, Joyce et al[652] reported that the preoperative PET changed or precluded curative-intent liver

resection in 25% of patients. A recent randomized clinical trial assessed the role of PET/CT in the workup of patients with resectable metachronous metastases.[624] While there was no impact of PET/CT on survival, surgical management was changed in 8% of patients after PET/CT. This trial is discussed in more detail in *Workup and Management of Synchronous Metastatic Disease*, above.

As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) for *KRAS/NRAS* genotype should be performed to define whether anti-EGFR agents can be considered among the potential options. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS/NRAS* genes, this testing is currently optional and not a necessary part of deciding whether to use anti-EGFR agents (see *The Role of KRAS, NRAS, and BRAF Status*).

Close communication between members of the multidisciplinary treatment team is recommended, including upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases. The management of metachronous metastatic disease is distinguished from that of synchronous disease through also including an evaluation of the chemotherapy history of the patient and through the absence of colectomy.

Patients with resectable disease are classified according to whether they have undergone previous chemotherapy. For patients who have resectable metastatic disease, treatment is resection with 6 months of perioperative chemotherapy (pre- or postoperative or a combination of both), with choice of regimens based on previous therapy. For patients without a history of chemotherapy use, FOLFOX or CapeOx is preferred, with FLOX, capecitabine, and 5-FU/LV as additional choices. There are also cases when perioperative chemotherapy is not recommended in metachronous disease. In particular, patients with a history of previous chemotherapy and an upfront resection can be observed or may be given an active regimen for advanced disease. Observation is preferred if oxaliplatin-based therapy was previously administered. In addition, observation is an appropriate option for patients whose tumors grew through neoadjuvant treatment.

Patients determined to have unresectable disease through cross-sectional imaging scan (including those considered potentially convertible) should receive an active chemotherapy regimen based on prior chemotherapy history (see *Therapy After Progression*, above). In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) is an option at centers with experience in the surgical and medical oncologic aspects of this procedure. Patients receiving palliative chemotherapy should be monitored with CT or MRI scans approximately every 2 to 3 months.

Endpoints for Advanced Colorectal Cancer Clinical Trials

In the past few years, there has been much debate over what endpoints are most appropriate for clinical trials in advanced colorectal cancer.[654] Quality of life is an outcome that is rarely measured but of unquestioned clinical relevance.[655] While OS is also of clear clinical relevance, it is often not used because large numbers of patients and long follow-up periods are required.[655] PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.[655,656] In 2011, The GROUP Español Multidisciplinar en Cancer Digestivo (GEMCAD) proposed particular aspects of clinical trial design to be incorporated into trials that use PFS as an endpoint.[657]

A recent study, in which individual patient data from 3 randomized controlled trials were pooled, tested endpoints that take into account subsequent lines of therapy: duration of disease control, which is the sum of PFS times of each active treatment; and time to failure of strategy, which includes intervals between treatment courses and ends when the planned lines of treatment end (because of death, progression, or administration of a new agent).[656] The authors found a better good correlation between these endpoints and OS than between PFS and OS. Another alternative endpoint, time to tumor growth, has also been suggested to predict OS.[658] Further evaluation of these and other surrogate endpoints is warranted.

Posttreatment Surveillance

After curative-intent surgery and adjuvant chemotherapy, if administered, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and identify new metachronous neoplasms at a preinvasive stage. An analysis of data from 20,898 patients enrolled in 18 large, adjuvant, colon cancer, randomized trials showed that 80% of recurrences occurred in the first 3 years after surgical resection of the primary tumor,[204] and a recent study found that 95% of recurrences occurred in the first 5 years.[659]

Advantages of more intensive follow-up of patients with stage II and/or stage III disease have been shown prospectively in several older studies[660-662] and in 3 meta-analyses of randomized controlled trials designed to compare low- and high-intensity programs of surveillance.[663-666] Intensive postoperative surveillance has also been suggested to be of benefit to patients with stage I and IIA disease.[667] Furthermore, a population-based report indicates increased rates of resectability and survival in patients treated for local recurrence and distant metastases of colorectal cancer in more recent years, thereby providing support for more intensive post-treatment follow-up in these patients.[668] Results from a recent randomized controlled trial of 1202 patients with resected stage I to III disease showed that intensive surveillance imaging or CEA screening resulted in an increased rate of curative-intent surgical treatment compared with a minimum follow-up group that only received testing if symptoms occurred, but no advantage was seen in the CEA and CT combination arm (2.3% in the minimum follow-up group, 6.7% in the CEA group, 8% in the CT group, and 6.6% in the CEA plus CT group).[669] In this study, no mortality benefit to regular monitoring with CEA, CT, or both was observed compared with minimum follow-up (death rate, 18.2% vs. 15.9%; difference, 2.3%; 95% CI, −2.6%–7.1%). The authors concluded that any strategy of surveillance is unlikely to provide a large survival advantage over a symptom-based approach. Clearly, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery, and the panel's recommendations are based mainly on consensus. The panel endorses surveillance as a means to identify patients who are potentially curable of metastatic disease with surgical resection.

For patients with stage I disease, the panel believes that a less intensive surveillance schedule is appropriate because of the low risk of recurrence and the harms associated with surveillance. Possible harms include radiation exposure with repeated CT scans, psychological stress associated with surveillance visits and scans, and stress and risks from following up false-positive results. Therefore, for patients with stage I disease, the panel recommends colonoscopy at 1 year. Repeat colonoscopy is recommended at 3 years, and then every 5 years thereafter, unless advanced adenoma (villous polyp, polyp >1 cm, or

high-grade dysplasia) is found. In this case, colonoscopy should be repeated in 1 year.[670]

The following panel recommendations for post-treatment surveillance pertain to patients with stage II/III disease who have undergone successful treatment (ie, no known residual disease). History and physical examination should be given every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years. A CEA test is recommended at baseline and every 3 to 6 months for 2 years,[671] then every 6 months for a total of 5 years for patients with stage III disease and those with stage II disease if the clinician determines that the patient is a potential candidate for aggressive curative surgery.[663,671] Colonoscopy is recommended at approximately 1 year after resection (or at 3–6 months postresection if not performed preoperatively because of an obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia), in which case colonoscopy should be repeated in 1 year.[670] More frequent colonoscopies may be indicated in patients who present with colon cancer before 50 years of age. Chest, abdominal, and pelvic CT scan are recommended annually for up to 5 years in patients with stage III disease and those with stage II disease at a high risk for recurrence.[663,672] Routine CEA monitoring and CT scanning are not recommended beyond 5 years. Routine use of PET/CT to monitor for disease recurrence is not recommended.[672,673] The CT that accompanies a PET/CT is usually a noncontrast CT, and therefore not of ideal quality for routine surveillance.

Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps,[670] because data show that patients with a history of colorectal cancer have an increased risk of developing second cancers, particularly in the first 2 years after resection.[670,674] 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.[670] The recommended frequency of post-treatment surveillance colonoscopies is higher (ie, annually) for patients with Lynch syndrome.[670]

CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and liver.[663] Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases.[663,672]

The ASCO Clinical Practice Guidelines Committee recently endorsed the Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer from Cancer Care Ontario (COO).[675,676] These guidelines differ only slightly from the surveillance recommendations in these NCCN Guidelines for Colon Cancer. While ASCO/COO recommend abdominal and chest CT annually for 3 years in patients with stage II and III disease, the NCCN Panel recommends annual scans for 5 years. The panel bases its recommendation on the fact that approximately 10% of patients will recur after 3 years.[204,659]

Panel recommendations for surveillance of patients with stage IV colorectal cancer with NED after curative-intent surgery and subsequent adjuvant treatment are similar to those listed for patients with stage II/III disease, except that certain evaluations are performed more frequently. Specifically, the panel recommends that these patients undergo contrast-enhanced CT scan of the chest, abdomen, and pelvis every 3 to 6 months in the first 2 years after adjuvant treatment and then every 6 to 12 months for up to a total of 5 years. CEA testing is recommended every 3 to 6 months for the first 2 years and then every 6 months for a total of 5 years, as in early-stage disease. Again, routine use of PET/CT

scans for surveillance is not recommended. A recent analysis of patients with resected or ablated colorectal liver metastases found that the frequency of surveillance imaging did not correlate with time to second procedure or median survival duration.[677] Those scanned once per year survived a median of 54 months versus 43 months for those scanned 3 to 4 times per year (*P* = .08), suggesting that annual scans may be sufficient in this population.

Managing an Increasing CEA Level

Managing patients with an elevated CEA level after resection should include colonoscopy; chest, abdominal, and pelvic CT scans; physical examination; and consideration of PET/CT scan. If imaging study results are normal in the face of a rising CEA, repeat CT scans are recommended every 3 months until either disease is identified or CEA level stabilizes or declines.

In a recent retrospective chart review at Memorial Sloan Kettering Cancer Center, approximately half of elevations in CEA levels after R0 resection of locoregional colorectal cancer were false positives, with most being single high readings or repeat readings in the range of 5 to 15 ng/mL.[678] In this study, false-positive results greater than 15 ng/mL were rare, and all results greater than 35 ng/mL represented true positives.

Panel opinion was divided on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans (ie, some panel members favored use of PET/CT in this scenario whereas others noted that the likelihood of PET/CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). A recent systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT in this setting.[679] The pooled estimates of sensitivity and specificity for the detection of tumor recurrence were 94.1% (95% CI, 89.4–97.1%) and 77.2% (95% CI, 66.4–85.9), respectively. 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,[680] nor does it recommend use of anti-CEA-radiolabeled scintigraphy.

Survivorship

Post-treatment surveillance for all patients also includes a survivorship care plan involving disease-preventive measures, such as immunizations; early disease detection through periodic screening for second primary cancers (eg, breast, cervical, or prostate cancers); and routine good medical care and monitoring (see the NCCN Guidelines for Survivorship, available at www.NCCN.org). Additional health monitoring should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.

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).[681-685] Other long-term problems common to colorectal cancer survivors include peripheral neuropathy, fatigue, insomnia, cognitive dysfunction, and emotional distress.[686,687] Specific management interventions to address these and other side effects are described in a recent review,[688] and a survivorship care plan for patients with colorectal cancer was recently published.[689]

Evidence also indicates that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy BMI, engaging in regular exercise, and making certain dietary choices are associated with improved outcomes and quality of life after treatment for colon cancer. In a prospective observational study of patients with stage III colon

cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, DFS was found to be directly related to how much exercise in which the patients engaged.[690] In addition, a study of a large cohort of men treated for stage I through III colorectal cancer showed an association between increased physical activity and lower rates of colorectal cancer-specific mortality and overall mortality.[691] More recent data support the conclusion that physical activity improves outcomes. In a cohort of more than 2000 survivors of non-metastatic colorectal cancer, those who spent more time in recreational activity had a lower mortality than those who spent more leisure time sitting.[692] In addition, recent evidence suggests that both pre- and post-diagnosis physical activity decreases colorectal cancer mortality. Women enrolled in the Women's Health Initiative study who subsequently developed colorectal cancer had lower colorectal cancer-specific mortality (HR, 0.68; 95% CI, 0.41–1.13) and all-cause mortality (HR, 0.63; 95% CI, 0.42–0.96) if they reported high levels of physical activity.[693] Similar results were seen in recent meta-analyses of prospective studies.[694,695]

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 of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[696] Recent analyses confirm the increased risk for recurrence and death in obese patients.[53] Data from the ACCENT database also found that pre-diagnosis BMI has a prognostic impact on outcomes in patients with stage II/III colorectal cancer undergoing adjuvant therapy.[697] However, a recent analysis of participants in the Cancer Prevention Study-II Nutrition Cohort who subsequently developed colorectal cancer found that pre-diagnosis obesity but not post-diagnosis obesity was associated with higher all-cause and colorectal cancer-specific mortality.[698]

A diet consisting of more fruits, vegetables, poultry, and fish; less red meat; more whole grains; and fewer refined grains and concentrated sweets has been found to be associated with an improved outcome in terms of cancer recurrence or death.[699] There is also some evidence that higher postdiagnosis intake of total milk and calcium may be associated with a lower risk of death in patients with stage I, II, or III colorectal cancer.[57] Recent analysis of the CALGB 89803 trial found that higher dietary glycemic load was also associated with an increased risk of recurrence and mortality in patients with stage III disease.[700] Another analysis of the data from CALGB 89803 found an association between high intake of sugar-sweetened beverages and an increased risk of recurrence and death in patients with stage III colon cancer.[701] The link between red and processed meats and mortality in survivors of non-metastatic colorectal cancer has been further supported by recent data from the Cancer Prevention Study II Nutrition Cohort, in which survivors with consistently high intake had a higher risk of colorectal cancer-specific mortality than those with low intake (RR, 1.79; 95% CI, 1.11–2.89).[51]

A discussion of lifestyle characteristics that may be associated with a decreased risk of colon cancer recurrence, such as those recommended by the American Cancer Society,[702] 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. In addition, a recent trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of colorectal cancer, suggesting that survivors may be open to health behavior change.[703]

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written if the primary physician will be assuming cancer surveillance responsibilities.[704] The prescription

should include an overall summary of treatments received, including surgeries, radiation treatments, and chemotherapy. The possible clinical course should be described, including the expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment. Surveillance recommendations should be included, as should a delineation of the appropriate timing of transfer of care with specific responsibilities identified for the primary care physician and the oncologist.

Summary

The 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 or CapeOx (both category 1, preferred), FLOX (category 1), 5-FU/LV (category 2A), or capecitabine (category 2A) is recommended by the panel for patients with stage III disease. Adjuvant therapy for patients with high-risk stage II disease is also an option; the panel recommends 5-FU/LV with or without oxaliplatin (FOLFOX or FLOX) or capecitabine with or without oxaliplatin (category 2A for all treatment options). Patients with metastatic disease in the liver or lung should be considered for surgical resection if they are candidates for surgery and if all original sites of disease are amenable to resection (R0) and/or ablation. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease. When a response to chemotherapy would likely convert a patient from an unresectable to a resectable state (ie, conversion therapy), this therapy should be initiated. Adjuvant chemotherapy should be considered after resection of liver or lung metastases.

The recommended post-treatment surveillance program includes serial CEA determinations, and periodic chest, abdominal, and pelvic CT scans; colonoscopic evaluations; and a survivorship plan to manage long-term side effects of treatment, facilitate disease prevention, and promote a healthy lifestyle.

Recommendations for patients with disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at initiation 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 the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOx, and FOLFOXIRI. Addition of a biologic agent (eg, bevacizumab, cetuximab, 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 depend on the choice of initial therapy. The panel endorses the concept that treating patients in a clinical trial has priority over standard treatment regimens.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24399786.

2. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin 2014;64:104-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24639052.

3. Cheng L, Eng C, Nieman LZ, et al. Trends in Colorectal Cancer Incidence by Anatomic Site and Disease Stage in the United States From 1976 to 2005. Am J Clin Oncol 2011;34:573-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21217399.

4. Henley SJ, Singh S, King J, et al. Invasive cancer incidence - United States, 2010. MMWR Morb Mortal Wkly Rep 2014;63:253-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24670926.

5. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21685461.

6. Edge SBB, D.R.; Compton, C.C.; Fritz, A.G.; Greene, F.L.; Trotti, A. , ed AJCC Cancer Staging Manual (ed 7th Edition). New York: Springer; 2010.

7. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed July 24, 2014.

8. Hemminki K, Eng C. Clinical genetic counselling for familial cancers requires reliable data on familial cancer risks and general action plans. J Med Genet 2004;41:801-807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15520403.

9. Hemminki K, Chen B. Familial risk for colorectal cancers are mainly due to heritable causes. Cancer Epidemiol Biomarkers Prev 2004;13:1253-1256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15247139.

10. Ahsan H, Neugut AI, Garbowski GC, et al. Family history of colorectal adenomatous polyps and increased risk for colorectal cancer. Ann Intern Med 1998;128:900-905. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9634428.

11. Bonelli L, Martines H, Conio M, et al. Family history of colorectal cancer as a risk factor for benign and malignant tumours of the large bowel. A case-control study. Int J Cancer 1988;41:513-517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3356486.

12. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26:5783-5788. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18809606.

13. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919-932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12621137.

14. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol 2006;101:385-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16454848.

15. Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998;338:1481-1487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9593786.

16. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2005;352:1851-1860. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15872200.

17. Hendriks YM, de Jong AE, Morreau H, et al. Diagnostic approach and management of Lynch syndrome (hereditary nonpolyposis

colorectal carcinoma): a guide for clinicians. CA Cancer J Clin 2006;56:213-225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16870997.

18. Beamer LC, Grant ML, Espenschied CR, et al. Reflex Immunohistochemistry and Microsatellite Instability Testing of Colorectal Tumors for Lynch Syndrome Among US Cancer Programs and Follow-Up of Abnormal Results. J Clin Oncol 2012;30:1058-1063. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22355048.

19. Burt RW. Who should have genetic testing for the lynch syndrome? Ann Intern Med 2011;155:127-128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768586.

20. Ward RL, Hicks S, Hawkins NJ. Population-based molecular screening for Lynch syndrome: implications for personalized medicine. J Clin Oncol 2013;31:2554-2562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23733757.

21. Matloff J, Lucas A, Polydorides AD, Itzkowitz SH. Molecular tumor testing for Lynch syndrome in patients with colorectal cancer. J Natl Compr Canc Netw 2013;11:1380-1385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24225971.

22. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009;11:35-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19125126.

23. Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med 2011;155:69-79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768580.

24. Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 2009;11:42-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19125127.

25. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2014;109:1159-1179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25070057.

26. Heald B, Plesec T, Liu X, et al. Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing lynch syndrome in a large academic medical center. J Clin Oncol 2013;31:1336-1340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23401454.

27. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308:1555-1565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23073952.

28. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14970275.

29. Boland CR, Shike M. Report from the Jerusalem workshop on Lynch syndrome-hereditary nonpolyposis colorectal cancer. Gastroenterology 2010;138:2197 e2191-2197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20416305.

30. Beaugerie L, Svrcek M, Seksik P, et al. Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. Gastroenterology 2013;145:166-175 e168. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23541909.

31. Johnson CM, Wei C, Ensor JE, et al. Meta-analyses of colorectal cancer risk factors. Cancer Causes Control 2013;24:1207-1222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23563998.

32. Lutgens MW, van Oijen MG, van der Heijden GJ, et al. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis 2013;19:789-799. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23448792.

33. Alexander DD, Weed DL, Cushing CA, Lowe KA. Meta-analysis of prospective studies of red meat consumption and colorectal cancer. Eur J Cancer Prev 2011;20:293-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21540747.

34. Cheng J, Chen Y, Wang X, et al. Meta-analysis of prospective cohort studies of cigarette smoking and the incidence of colon and rectal cancers. Eur J Cancer Prev 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24722538.

35. De Bruijn KM, Arends LR, Hansen BE, et al. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. Br J Surg 2013;100:1421-1429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24037561.

36. Esposito K, Chiodini P, Capuano A, et al. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis. Endocrine 2013;44:634-647. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23546613.

37. Fedirko V, Tramacere I, Bagnardi V, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol 2011;22:1958-1972. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21307158.

38. Huxley RR, Ansary-Moghaddam A, Clifton P, et al. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer 2009;125:171-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19350627.

39. Kitahara CM, Berndt SI, de Gonzalez AB, et al. Prospective investigation of body mass index, colorectal adenoma, and colorectal cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. J Clin Oncol 2013;31:2450-2459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23715565.

40. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97:1679-1687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16288121.

41. Levi Z, Kark JD, Barchana M, et al. Measured body mass index in adolescence and the incidence of colorectal cancer in a cohort of 1.1 million males. Cancer Epidemiol Biomarkers Prev 2011;20:2524-2531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22056504.

42. Luo W, Cao Y, Liao C, Gao F. Diabetes mellitus and the incidence and mortality of colorectal cancer: a meta-analysis of 24 cohort studies. Colorectal Dis 2012;14:1307-1312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23046351.

43. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One 2013;8:e53916. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23349764.

44. Magalhaes B, Peleteiro B, Lunet N. Dietary patterns and colorectal cancer: systematic review and meta-analysis. Eur J Cancer Prev 2012;21:15-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21946864.

45. Parajuli R, Bjerkaas E, Tverdal A, et al. The increased risk of colon cancer due to cigarette smoking may be greater in women than men. Cancer Epidemiol Biomarkers Prev 2013;22:862-871. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23632818.

46. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. J Natl Cancer Inst 2014;106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24935969.

47. Yuhara H, Steinmaus C, Cohen SE, et al. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? Am J Gastroenterol 2011;106:1911-1921; quiz 1922. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21912438.

48. Keum N, Aune D, Greenwood DC, et al. Calcium intake and colorectal cancer risk: dose-response meta-analysis of prospective observational studies. Int J Cancer 2014;135:1940-1948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24623471.

49. Murphy N, Norat T, Ferrari P, et al. Consumption of dairy products and colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). PLoS One 2013;8:e72715. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24023767.

50. Ralston RA, Truby H, Palermo CE, Walker KZ. Colorectal cancer and nonfermented milk, solid cheese, and fermented milk consumption: a systematic review and meta-analysis of prospective studies. Crit Rev Food Sci Nutr 2014;54:1167-1179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24499149.

51. McCullough ML, Gapstur SM, Shah R, et al. Association between red and processed meat intake and mortality among colorectal cancer survivors. J Clin Oncol 2013;31:2773-2782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23816965.

52. Phipps AI, Shi Q, Newcomb PA, et al. Associations Between Cigarette Smoking Status and Colon Cancer Prognosis Among Participants in North Central Cancer Treatment Group Phase III Trial N0147. J Clin Oncol 2013;31:2016-2023. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23547084.

53. Sinicrope FA, Foster NR, Yoon HH, et al. Association of obesity with DNA mismatch repair status and clinical outcome in patients with stage II or III colon carcinoma participating in NCCTG and NSABP adjuvant chemotherapy trials. J Clin Oncol 2012;30:406-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22203756.

54. Walter V, Jansen L, Hoffmeister M, Brenner H. Smoking and survival of colorectal cancer patients: systematic review and meta-analysis. Ann Oncol 2014;25:1517-1525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24692581.

55. Morris EJ, Penegar S, Whitehouse LE, et al. A retrospective observational study of the relationship between family history and survival from colorectal cancer. Br J Cancer 2013;108:1502-1507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23511565.

56. Dik VK, Murphy N, Siersema PD, et al. Prediagnostic Intake of Dairy Products and Dietary Calcium and Colorectal Cancer Survival-Results from the EPIC Cohort Study. Cancer Epidemiol Biomarkers Prev 2014;23:1813-1823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24917183.

57. Yang B, McCullough ML, Gapstur SM, et al. Calcium, Vitamin D, Dairy Products, and Mortality Among Colorectal Cancer Survivors: The Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 2014;32:2335-2343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24958826.

58. Bu WJ, Song L, Zhao DY, et al. Insulin therapy and the risk of colorectal cancer in patients with type 2 diabetes: a meta-analysis of observational studies. Br J Clin Pharmacol 2014;78:301-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25099257.

59. Cardel M, Jensen SM, Pottegard A, et al. Long-term use of metformin and colorectal cancer risk in type II diabetics: a population-based case-control study. Cancer Med 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25091592.

60. Karlstad O, Starup-Linde J, Vestergaard P, et al. Use of insulin and insulin analogs and risk of cancer - systematic review and meta-analysis of observational studies. Curr Drug Saf 2013;8:333-348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24215311.

61. Mills KT, Bellows CF, Hoffman AE, et al. Diabetes mellitus and colorectal cancer prognosis: a meta-analysis. Dis Colon Rectum 2013;56:1304-1319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24105007.

62. Mei ZB, Zhang ZJ, Liu CY, et al. Survival benefits of metformin for colorectal cancer patients with diabetes: a systematic review and meta-analysis. PLoS One 2014;9:e91818. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24647047.

63. Compton CC, Greene FL. The staging of colorectal cancer: 2004 and beyond. CA Cancer J Clin 2004;54:295-308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15537574.

64. Jessup JM, Gunderson LL, Greene FL, et al. 2010 staging system for colon and rectal carcinoma. Ann Surg Oncol 2011;18:1513-1517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21445673.

65. Gunderson LL, Jessup JM, Sargent DJ, et al. Revised tumor and node categorization for rectal cancer based on surveillance, epidemiology, and end results and rectal pooled analysis outcomes. J Clin Oncol 2010;28:256-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19949015.

66. Gunderson LL, Jessup JM, Sargent DJ, et al. Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol 2010;28:264-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19949014.

67. Compton CC. Updated protocol for the examination of specimens from patients with carcinomas of the colon and rectum, excluding carcinoid tumors, lymphomas, sarcomas, and tumors of the vermiform appendix: a basis for checklists. Cancer Committee. Arch Pathol Lab Med 2000;124:1016-1025. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10888778.

68. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000;124:979-994. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10888773.

69. Nissan A, Stojadinovic A, Shia J, et al. Predictors of recurrence in patients with T2 and early T3, N0 adenocarcinoma of the rectum treated by surgery alone. J Clin Oncol 2006;24:4078-4084. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16943525.

70. Washington MK, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. Arch Pathol Lab Med 2009;133:1539-1551. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19792043.

71. Fujita S, Shimoda T, Yoshimura K, et al. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. J Surg Oncol 2003;84:127-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14598355.

72. Liebig C, Ayala G, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clin Oncol 2009;27:5131-5137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19738119.

73. Quah HM, Chou JF, Gonen M, et al. Identification of patients with high-risk stage II colon cancer for adjuvant therapy. Dis Colon Rectum 2008;51:503-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18322753.

74. Lo DS, Pollett A, Siu LL, et al. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. Cancer 2008;112:50-54. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18008365.

75. Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. Am J Clin Pathol 2007;127:287-294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17210518.

76. Birbeck KF, Macklin CP, Tiffin NJ, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg 2002;235:449-457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11923599.

77. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol 2003;21:2912-2919. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12885809.

78. Bilimoria KY, Palis B, Stewart AK, et al. Impact of tumor location on nodal evaluation for colon cancer. Dis Colon Rectum 2008;51:154-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18172729.

79. Lykke J, Roikjaer O, Jess P. The relation between lymph node status and survival in Stage I-III colon cancer: results from a prospective nationwide cohort study. Colorectal Dis 2013;15:559-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23061638.

80. Budde CN, Tsikitis VL, Deveney KE, et al. Increasing the number of lymph nodes examined after colectomy does not improve colon cancer staging. J Am Coll Surg 2014;218:1004-1011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24661856.

81. Parsons HM, Tuttle TM, Kuntz KM, et al. Association between lymph node evaluation for colon cancer and node positivity over the past 20 years. JAMA 2011;306:1089-1097. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21917579.

82. Storli K, Sondenaa K, Furnes B, et al. Improved lymph node harvest from resected colon cancer specimens did not cause upstaging from TNM stage II to III. World J Surg 2011;35:2796-2803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21879420.

83. Wong SL, Ji H, Hollenbeck BK, et al. Hospital lymph node examination rates and survival after resection for colon cancer. JAMA 2007;298:2149-2154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18000198.

84. Nedrebo BS, Soreide K, Nesbakken A, et al. Risk factors associated with poor lymph node harvest after colon cancer surgery in a national cohort. Colorectal Dis 2013;15:e301-308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23582027.

85. Sarli L, Bader G, Iusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. Eur J Cancer 2005;41:272-279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15661553.

86. Wong SL. Lymph node evaluation in colon cancer: assessing the link between quality indicators and quality. JAMA 2011;306:1139-1141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21917585.

87. Belt EJ, te Velde EA, Krijgsman O, et al. High lymph node yield is related to microsatellite instability in colon cancer. Ann Surg Oncol 2012;19:1222-1230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21989661.

88. Berg M, Guriby M, Nordgard O, et al. Influence of microsatellite instability, KRAS and BRAF mutations on lymph node harvest in stage I-III colon cancers. Mol Med 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23979710.

89. Gonen M, Schrag D, Weiser MR. Nodal staging score: a tool to assess adequate staging of node-negative colon cancer. J Clin Oncol 2009;27:6166-6171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19901106.

90. Ramos-Esquivel A, Juarez M, Gonzalez I, et al. Prognosis impact of the lymph node ratio in patients with colon adenocarcinoma: a single-centre experience. J Gastrointest Cancer 2014;45:133-136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24382601.

91. Sabbagh C, Mauvais F, Cosse C, et al. A Lymph Node Ratio of 10% Is Predictive of Survival in Stage III Colon Cancer: A French Regional Study. Int Surg 2014;99:344-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25058763.

92. Gleisner AL, Mogal H, Dodson R, et al. Nodal status, number of lymph nodes examined, and lymph node ratio: what defines prognosis after resection of colon adenocarcinoma? J Am Coll Surg 2013;217:1090-1100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24045143.

93. Redston M, Compton CC, Miedema BW, et al. Analysis of micrometastatic disease in sentinel lymph nodes from resectable colon cancer: results of Cancer and Leukemia Group B Trial 80001. J Clin Oncol 2006;24:878-883. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16418493.

94. Bertagnolli M, Miedema B, Redston M, et al. Sentinel node staging of resectable colon cancer: results of a multicenter study. Ann Surg 2004;240:624-628. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15383790.

95. Noura S, Yamamoto H, Miyake Y, et al. Immunohistochemical assessment of localization and frequency of micrometastases in lymph nodes of colorectal cancer. Clin Cancer Res 2002;8:759-767. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11895906.

96. Saha S, Dan AG, Beutler T, et al. Sentinel lymph node mapping technique in colon cancer. Semin Oncol 2004;31:374-381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15190495.

97. Turner RR, Nora DT, Trocha SD, Bilchik AJ. Colorectal carcinoma nodal staging. Frequency and nature of cytokeratin-positive cells in sentinel and nonsentinel lymph nodes. Arch Pathol Lab Med 2003;127:673-679. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12741889.

98. Wiese DA, Saha S, Badin J, et al. Pathologic evaluation of sentinel lymph nodes in colorectal carcinoma. Arch Pathol Lab Med 2000;124:1759-1763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11100053.

99. Wood TF, Nora DT, Morton DL, et al. One hundred consecutive cases of sentinel lymph node mapping in early colorectal carcinoma: detection of missed micrometastases. J Gastrointest Surg 2002;6:322-329; discussion 229-330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12022982.

100. Jass JR, O'Brien MJ, Riddell RH, Snover DC. Recommendations for the reporting of surgically resected specimens of colorectal carcinoma. Hum Pathol 2007;38:537-545. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17270246.

101. Sloothaak DA, Sahami S, van der Zaag-Loonen HJ, et al. The prognostic value of micrometastases and isolated tumour cells in histologically negative lymph nodes of patients with colorectal cancer: a systematic review and meta-analysis. Eur J Surg Oncol 2014;40:263-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24368050.

102. Noura S, Yamamoto H, Ohnishi T, et al. Comparative detection of lymph node micrometastases of stage II colorectal cancer by reverse transcriptase polymerase chain reaction and immunohistochemistry. J Clin Oncol 2002;20:4232-4241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12377967.

103. Yasuda K, Adachi Y, Shiraishi N, et al. Pattern of lymph node micrometastasis and prognosis of patients with colorectal cancer. Ann Surg Oncol 2001;8:300-304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11352302.

104. Mescoli C, Albertoni L, Pucciarelli S, et al. Isolated tumor cells in regional lymph nodes as relapse predictors in stage I and II colorectal cancer. J Clin Oncol 2012;30:965-971. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22355061.

105. Rahbari NN, Bork U, Motschall E, et al. Molecular detection of tumor cells in regional lymph nodes is associated with disease recurrence and poor survival in node-negative colorectal cancer: a systematic review and meta-analysis. J Clin Oncol 2012;30:60-70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22124103.

106. Goldstein NS, Turner JR. Pericolonic tumor deposits in patients with T3N+MO colon adenocarcinomas: markers of reduced disease free survival and intra-abdominal metastases and their implications for TNM classification. Cancer 2000;88:2228-2238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10820343.

107. Puppa G, Maisonneuve P, Sonzogni A, et al. Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. Mod Pathol 2007;20:843-855. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17491597.

108. Ueno H, Mochizuki H. Clinical significance of extrabowel skipped cancer infiltration in rectal cancer. Surg Today 1997;27:617-622. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9306563.

109. Yun JA, Kim HC, Kim SH, et al. Prognostic significance of perineural invasion in stage IIA colon cancer. ANZ J Surg 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25113398.

110. Chung M, Lee J, Terasawa T, et al. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2011;155:827-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22184690.

111. Gorham ED, Garland CF, Garland FC, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. Am J Prev Med 2007;32:210-216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17296473.

112. Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr 2007;85:1586-1591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17556697.

113. Ma Y, Zhang P, Wang F, et al. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. J Clin Oncol 2011;29:3775-3782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21876081.

114. Fedirko V, Riboli E, Tjonneland A, et al. Prediagnostic 25-hydroxyvitamin D, VDR and CASR polymorphisms, and survival in patients with colorectal cancer in western European populations. Cancer Epidemiol Biomarkers Prev 2012;21:582-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22278364.

115. Ng K, Meyerhardt JA, Wu K, et al. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. J Clin Oncol 2008;26:2984-2991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18565885.

116. Zgaga L, Theodoratou E, Farrington SM, et al. Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. J Clin Oncol 2014;32:2430-2439. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25002714.

117. Maalmi H, Ordonez-Mena JM, Schottker B, Brenner H. Serum 25-hydroxyvitamin D levels and survival in colorectal and breast cancer patients: systematic review and meta-analysis of prospective cohort studies. Eur J Cancer 2014;50:1510-1521. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24582912.

118. Ng K, Sargent DJ, Goldberg RM, et al. Vitamin D status in patients with stage IV colorectal cancer: findings from Intergroup trial N9741. J Clin Oncol 2011;29:1599-1606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21422438.

119. Dietary Reference Intakes for Calcium and Vitamin D. Institute of Medicine of the National Academies; 2010. Available at: http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx. Accessed January 27, 2014.

120. Raghav K, Overman MJ. Small bowel adenocarcinomas--existing evidence and evolving paradigms. Nat Rev Clin Oncol 2013;10:534-544. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23897080.

121. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg 2010;199:797-803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20609724.

122. Kelsey CR, Nelson JW, Willett CG, et al. Duodenal adenocarcinoma: patterns of failure after resection and the role of chemoradiotherapy. Int J Radiat Oncol Biol Phys 2007;69:1436-1441. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17689032.

123. Kim K, Chie EK, Jang JY, et al. Role of adjuvant chemoradiotherapy for duodenal cancer: a single center experience. Am J Clin Oncol 2012;35:533-536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21659832.

124. Onkendi EO, Boostrom SY, Sarr MG, et al. Neoadjuvant treatment of duodenal adenocarcinoma: a rescue strategy. J Gastrointest Surg 2012;16:320-324. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21956430.

125. Overman MJ, Kopetz S, Lin E, et al. Is there a role for adjuvant therapy in resected adenocarcinoma of the small intestine. Acta Oncol 2010;49:474-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20397775.

126. Swartz MJ, Hughes MA, Frassica DA, et al. Adjuvant concurrent chemoradiation for node-positive adenocarcinoma of the duodenum. Arch Surg 2007;142:285-288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17372054.

127. Yeung RS, Weese JL, Hoffman JP, et al. Neoadjuvant chemoradiation in pancreatic and duodenal carcinoma. A Phase II Study. Cancer 1993;72:2124-2133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8374871.

128. Coia L, Hoffman J, Scher R, et al. Preoperative chemoradiation for adenocarcinoma of the pancreas and duodenum. Int J Radiat Oncol Biol Phys 1994;30:161-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8083109.

129. Czaykowski P, Hui D. Chemotherapy in small bowel adenocarcinoma: 10-year experience of the British Columbia Cancer Agency. Clin Oncol (R Coll Radiol) 2007;19:143-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17355111.

130. Jigyasu D, Bedikian AY, Stroehlein JR. Chemotherapy for primary adenocarcinoma of the small bowel. Cancer 1984;53:23-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6690001.

131. Overman MJ, Varadhachary GR, Kopetz S, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol 2009;27:2598-2603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19164203.

132. Xiang XJ, Liu YW, Zhang L, et al. A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma. Anticancer Drugs 2012;23:561-566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22481063.

133. Gibson MK, Holcroft CA, Kvols LK, Haller D. Phase II study of 5-fluorouracil, doxorubicin, and mitomycin C for metastatic small bowel adenocarcinoma. Oncologist 2005;10:132-137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15709215.

134. Farquharson AL, Pranesh N, Witham G, et al. A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. Br J

Cancer 2008;99:591-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18682713.

135. Lieu CH, Lambert LA, Wolff RA, et al. Systemic chemotherapy and surgical cytoreduction for poorly differentiated and signet ring cell adenocarcinomas of the appendix. Ann Oncol 2012;23:652-658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21653683.

136. Shapiro JF, Chase JL, Wolff RA, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. Cancer 2010;116:316-322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19904805.

137. Tejani MA, Ter Veer A, Milne D, et al. Systemic Therapy for Advanced Appendiceal Adenocarcinoma: An Analysis From the NCCN Oncology Outcomes Database for Colorectal Cancer. J Natl Compr Canc Netw 2014;12:1123-1130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25099444.

138. Cooper HS, Deppisch LM, Gourley WK, et al. Endoscopically removed malignant colorectal polyps: clinicopathologic correlations. Gastroenterology 1995;108:1657-1665. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7768369.

139. Markowitz AJ, Winawer SJ. Management of colorectal polyps. CA Cancer J Clin 1997;47:93-9112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9074488.

140. Yoshii S, Nojima M, Nosho K, et al. Factors associated with risk for colorectal cancer recurrence after endoscopic resection of T1 tumors. Clin Gastroenterol Hepatol 2014;12:292-302 e293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23962552.

141. Cooper HS. Surgical pathology of endoscopically removed malignant polyps of the colon and rectum. Am J Surg Pathol 1983;7:613-623. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6638257.

142. Cooper HS. Pathologic issues in the treatment of endoscopically removed malignant colorectal polyps. J Natl Compr Canc Netw 2007;5:991-996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17977505.

143. Hassan C, Zullo A, Risio M, et al. Histologic risk factors and clinical outcome in colorectal malignant polyp: a pooled-data analysis. Dis Colon Rectum 2005;48:1588-1596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15937622.

144. Cranley JP, Petras RE, Carey WD, et al. When is endoscopic polypectomy adequate therapy for colonic polyps containing invasive carcinoma? Gastroenterology 1986;91:419-427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3721127.

145. Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology 1985;89:328-336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4007423.

146. Ota DM, Nelson H, Weeks JC. Controversies regarding laparoscopic colectomy for malignant diseases. Curr Opin Gen Surg 1994:208-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7583971.

147. Bosch SL, Teerenstra S, de Wilt JH, et al. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 2013;45:827-834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23884793.

148. Mou S, Soetikno R, Shimoda T, et al. Pathologic predictive factors for lymph node metastasis in submucosal invasive (T1) colorectal cancer: a systematic review and meta-analysis. Surg Endosc 2013;27:2692-2703. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23392988.

149. Seitz U, Bohnacker S, Seewald S, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal adenomas? Presentation of 114 patients and review of the literature. Dis Colon Rectum 2004;47:1789-1796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15622570.

150. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 2004;127:385-394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15300569.

151. Volk EE, Goldblum JR, Petras RE, et al. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. Gastroenterology 1995;109:1801-1807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7498644.

152. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997;112:594-642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9024315.

153. Balthazar EJ, Megibow AJ, Hulnick D, Naidich DP. Carcinoma of the colon: detection and preoperative staging by CT. AJR Am J Roentgenol 1988;150:301-306. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3257314.

154. Huang X, Lv B, Zhang S, Meng L. Preoperative colonic stents versus emergency surgery for acute left-sided malignant colonic obstruction: a meta-analysis. J Gastrointest Surg 2014;18:584-591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24170606.

155. Cohen AM. Surgical considerations in patients with cancer of the colon and rectum. Semin Oncol 1991;18:381-387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1713712.

156. West NP, Hohenberger W, Weber K, et al. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol 2010;28:272-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19949013.

157. Berger AC, Sigurdson ER, LeVoyer T, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol 2005;23:8706-8712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16314630.

158. Madoff RD. Defining quality in colon cancer surgery. J Clin Oncol 2012;30:1738-1740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22473171.

159. West NP, Morris EJ, Rotimi O, et al. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet Oncol 2008;9:857-865. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18667357.

160. West NP, Kobayashi H, Takahashi K, et al. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol 2012;30:1763-1769. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22473170.

161. Lee JK, Delaney CP, Lipman JM. Current state of the art in laparoscopic colorectal surgery for cancer: Update on the multi-centric international trials. Ann Surg Innov Res 2012;6:5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22846394.

162. Morneau M, Boulanger J, Charlebois P, et al. Laparoscopic versus open surgery for the treatment of colorectal cancer: a literature review and recommendations from the Comite de l'evolution des pratiques en oncologie. Can J Surg 2013;56:297-310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24067514.

163. Theophilus M, Platell C, Spilsbury K. Long-term survival following laparoscopic and open colectomy for colon cancer: a meta-analysis of randomized controlled trials. Colorectal Dis 2014;16:O75-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24206016.

164. Wang CL, Qu G, Xu HW. The short- and long-term outcomes of laparoscopic versus open surgery for colorectal cancer: a meta-analysis. Int J Colorectal Dis 2014;29:309-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24445673.

165. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-2229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12103285.

166. Buunen M, Veldkamp R, Hop WCJ, et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol 2009;10:44-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19071061.

167. Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol 2007;25:3061-3068. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17634484.

168. Green BL, Marshall HC, Collinson F, et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 2013;100:75-82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23132548.

169. Laparoscopically assisted colectomy is as safe and effective as open colectomy in people with colon cancer Abstracted from: Nelson H, Sargent D, Wieand HS, et al; for the Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004; 350: 2050-2059. Cancer Treat Rev 2004;30:707-709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15541580.

170. Fleshman J, Sargent DJ, Green E, et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg 2007;246:655-662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17893502.

171. Bagshaw PF, Allardyce RA, Frampton CM, et al. Long-term outcomes of the australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer: the Australasian Laparoscopic Colon Cancer Study trial. Ann Surg 2012;256:915-919. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23154392.

172. Bonjer HJ, Hop WCJ, Nelson H, et al. Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. Arch Surg 2007;142:298-303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17372057.

173. Di B, Li Y, Wei K, et al. Laparoscopic versus open surgery for colon cancer: a meta-analysis of 5-year follow-up outcomes. Surg Oncol 2013;22:e39-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23643698.

174. Jackson TD, Kaplan GG, Arena G, et al. Laparoscopic versus open resection for colorectal cancer: a metaanalysis of oncologic outcomes. J Am Coll Surg 2007;204:439-446. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17324779.

175. Kuhry E, Schwenk W, Gaupset R, et al. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. Cancer Treat Rev 2008;34:498-504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18468803.

176. Ohtani H, Tamamori Y, Arimoto Y, et al. A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and open colectomy for colon cancer. J Cancer 2012;3:49-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22315650.

177. Rondelli F, Trastulli S, Avenia N, et al. Is laparoscopic right colectomy more effective than open resection? A meta-analysis of randomized and nonrandomized studies. Colorectal Dis 2012;14:e447-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22540533.

178. Kienle P, Weitz J, Koch M, Buchler MW. Laparoscopic surgery for colorectal cancer. Colorectal Dis 2006;8 Suppl 3:33-36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16813591.

179. Wagman LD. Laparoscopic and open surgery for colorectal cancer: reaching equipoise? J Clin Oncol 2007;25:2996-2998. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17634477.

180. Kuhry E, Bonjer HJ, Haglind E, et al. Impact of hospital case volume on short-term outcome after laparoscopic operation for colonic cancer. Surg Endosc 2005;19:687-692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15798899.

181. Varadhan KK, Lobo DN, Ljungqvist O. Enhanced recovery after surgery: the future of improving surgical care. Crit Care Clin 2010;26:527-547, x. Available at:

182. Kennedy RH, Francis EA, Wharton R, et al. Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL. J Clin Oncol 2014;32:1804-1811. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24799480.

183. Nelson H, Weeks JC, Wieand HS. Proposed phase III trial comparing laparoscopic-assisted colectomy versus open colectomy for colon cancer. J Natl Cancer Inst Monogr 1995:51-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7577206.

184. Wishner JD, Baker JW, Hoffman GC, et al. Laparoscopic-assisted colectomy. The learning curve. Surg Endosc 1995;9:1179-1183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8553229.

185. Saltz LB. Adjuvant therapy for colon cancer. Surg Oncol Clin N Am 2010;19:819-827. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20883956.

186. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15175436.

187. de Gramont A, Boni C, Navarro M, et al. Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: Efficacy results with a median follow-up of 4 years [abstract]. J Clin Oncol 2005;23 (June 1 suppl):3501. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/3501.

188. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109-3116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19451431.

189. de Gramont A, Boni C, Navarro M, et al. Oxaliplatin/5FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of six years [abstract]. J Clin Oncol 2007;25 (June 20 suppl):4007. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/4007.

190. Benson AB, 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22:3408-3419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15199089.

191. Des Guetz G, Uzzan B, Morere JF, et al. Duration of adjuvant chemotherapy for patients with non-metastatic colorectal cancer. Cochrane Database Syst Rev 2010:CD007046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20091614.

192. Wolmark N, Wieand S, Kuebler JP, et al. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07 [abstract]. J Clin Oncol 2005;23 (June 1 suppl):LBA3500. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/LBA3500.

193. Haller DG, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Folinic Acid As Adjuvant

Therapy for Stage III Colon Cancer. J Clin Oncol 2011;29:1465-1471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21383294.

194. Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007;25:102-109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17194911.

195. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007;25:2198-2204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470851.

196. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-2704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15987918.

197. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet 1995;345:939-944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7715291.

198. Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur J Cancer 1999;35:1343-1347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10658525.

199. Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol 2005;23:8671-8678. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16314627.

200. Wolmark N, Rockette H, Mamounas E, et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. J Clin Oncol 1999;17:3553-3559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10550154.

201. Boland GM, Chang GJ, Haynes AB, et al. Association between adherence to National Comprehensive Cancer Network treatment guidelines and improved survival in patients with colon cancer. Cancer 2013;119:1593-1601. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23280510.

202. Sargent DJ, for the Adjuvant Colon Cancer Endpoints Group. Time-dependent patterns of failure and treatment benefit from adjuvant therapy for resectable colon cancer: Lessons from the 20,800-patient (pt) ACCENT dataset [abstract]. J Clin Oncol 2007;25 (June 20 suppl):4008. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/4008.

203. Sargent DJ, Wieand HS, Haller DG, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2005;23:8664-8670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16260700.

204. Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2009;27:872-877. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19124803.

205. de Gramont A, Hubbard J, Shi Q, et al. Association between disease-free survival and overall survival when survival is prolonged after recurrence in patients receiving cytotoxic adjuvant therapy for colon cancer: simulations based on the 20,800 patient ACCENT data set. J Clin Oncol 2010;28:460-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20008641.

206. Sargent D, Shi Q, Yothers G, et al. Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer

trials with fluoropyrimidines with or without oxaliplatin or irinotecan: Data from 12,676 patients from MOSAIC, X-ACT, PETACC-3, C-06, C-07 and C89803. Eur J Cancer 2011;47:990-996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21257306.

207. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. J Clin Oncol 1999;17:1356-1363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10334519.

208. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15067028.

209. Gray R, Barnwell J, McConkey C, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet 2007;370:2020-2029. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18083404.

210. Hutchins G, Southward K, Handley K, et al. Value of Mismatch Repair, KRAS, and BRAF Mutations in Predicting Recurrence and Benefits From Chemotherapy in Colorectal Cancer. J Clin Oncol 2011;29:1261-1270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21383284.

211. Wu X, Zhang J, He X, et al. Postoperative adjuvant chemotherapy for stage II colorectal cancer: a systematic review of 12 randomized controlled trials. J Gastrointest Surg 2012;16:646-655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22194062.

212. Schrag D, Rifas-Shiman S, Saltz L, et al. Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer. J Clin Oncol 2002;20:3999-4005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12351597.

213. O'Connor ES, Greenblatt DY, Loconte NK, et al. Adjuvant Chemotherapy for Stage II Colon Cancer With Poor Prognostic Features. J Clin Oncol 2011;29:3381-3388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21788561.

214. Meropol NJ. Ongoing Challenge of Stage II Colon Cancer. J Clin Oncol 2011;29:3346-3348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21788557.

215. Tournigand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. J Clin Oncol 2012;30:3353-3360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22915656.

216. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 2011;29:3768-3774. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21859995.

217. Love N, Bylund C, Meropol NJ, et al. How well do we communicate with patients concerning adjuvant systemic therapy? A survey of 150 colorectal cancer survivors [abstract]. J Clin Oncol 2007;25 (June 20 suppl):4020. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/4020.

218. Benson AB, 3rd, Hamilton SR. Path toward prognostication and prediction: an evolving matrix. J Clin Oncol 2011;29:4599-4601. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22067398.

219. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003;349:247-257. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12867608.

220. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based

adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-3226. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20498393.

221. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: Molecular basis of colorectal cancer. N Engl J Med 2009;361:2449-2460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20018966.

222. Halvarsson B, Anderson H, Domanska K, et al. Clinicopathologic factors identify sporadic mismatch repair-defective colon cancers. Am J Clin Pathol 2008;129:238-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18208804.

223. Cunningham JM, Christensen ER, Tester DJ, et al. Hypermethylation of the hMLH1 promoter in colon cancer with microsatellite instability. Cancer Res 1998;58:3455-3460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9699680.

224. Kim GP, Colangelo LH, Wieand HS, et al. Prognostic and predictive roles of high-degree microsatellite instability in colon cancer: a National Cancer Institute-National Surgical Adjuvant Breast and Bowel Project Collaborative Study. J Clin Oncol 2007;25:767-772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17228023.

225. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol 2010;28:466-474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20008640.

226. Koopman M, Kortman GAM, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer 2009;100:266-273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19165197.

227. Tejpar S, Bosman F, Delorenzi M, et al. Microsatellite instability (MSI) in stage II and III colon cancer treated with 5FU-LV or 5FU-LV and irinotecan (PETACC 3-EORTC 40993-SAKK 60/00 trial) [abstract]. J Clin Oncol 2009;27 (May 20 suppl):4001. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/4001.

228. Sinicrope FA, Mahoney MR, Smyrk TC, et al. Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX-based adjuvant chemotherapy. J Clin Oncol 2013;31:3664-3672. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24019539.

229. Bertagnolli MM, Redston M, Compton CC, et al. Microsatellite instability and loss of heterozygosity at chromosomal location 18q: prospective evaluation of biomarkers for stages II and III colon cancer--a study of CALGB 9581 and 89803. J Clin Oncol 2011;29:3153-3162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21747089.

230. O'Connell MJ, Lavery I, Yothers G, et al. Relationship between tumor gene expression and recurrence in four independent studies of patients with stage II/III colon cancer treated with surgery alone or surgery plus adjuvant fluorouracil plus leucovorin. J Clin Oncol 2010;28:3937-3944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20679606.

231. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. J Clin Oncol 2011;29:4611-4619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22067390.

232. O'Connell M, Lee M, Lopatin M, et al. Validation of the 12-gene colon cancer recurrence score (RS) in NSABP C07 as a predictor of recurrence in stage II and III colon cancer patients treated with 5FU/LV (FU) and 5FU/LV+oxaliplatin (FU+Ox) [abstract]. ASCO Meeting Abstracts 2012;30:3512. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/3512.

233. Venook AP, Niedzwiecki D, Lopatin M, et al. Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581.

J Clin Oncol 2013;31:1775-1781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23530100.

234. Yothers G, O'Connell MJ, Lee M, et al. Validation of the 12-gene colon cancer recurrence score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin. J Clin Oncol 2013;31:4512-4519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24220557.

235. Salazar R, Roepman P, Capella G, et al. Gene expression signature to improve prognosis prediction of stage II and III colorectal cancer. J Clin Oncol 2011;29:17-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21098318.

236. Salazar R, Tabernero J, Moreno V, et al. Validation of a genomic classifier (ColoPrint) for predicting outcome in the T3-MSS subgroup of stage II colon cancer patients [abstract]. ASCO Meeting Abstracts 2012;30:3510. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/3510.

237. Salazar R, de Waard JW, Glimelius B, et al. The PARSC trial, a prospective study for the assessment of recurrence risk in stage II colon cancer (CC) patients using ColoPrint [abstract]. ASCO Meeting Abstracts 2012;30:678. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/4_suppl/678.

238. Kennedy RD, Bylesjo M, Kerr P, et al. Development and independent validation of a prognostic assay for stage II colon cancer using formalin-fixed paraffin-embedded tissue. J Clin Oncol 2011;29:4620-4626. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22067406.

239. Sanoff HK, Carpenter WR, Sturmer T, et al. Effect of Adjuvant Chemotherapy on Survival of Patients With Stage III Colon Cancer Diagnosed After Age 75 Years. J Clin Oncol 2012;30:2624-2634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22665536.

240. Dotan E, Browner I, Hurria A, Denlinger C. Challenges in the management of older patients with colon cancer. J Natl Compr Canc Netw 2012;10:213-224; quiz 225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22308516.

241. McCleary NJ, Dotan E, Browner I. Refining the Chemotherapy Approach for Older Patients With Colon Cancer. J Clin Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25071118.

242. Muss HB, Bynum DL. Adjuvant Chemotherapy in Older Patients With Stage III Colon Cancer: An Underused Lifesaving Treatment. J Clin Oncol 2012;30:2576-2578. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22665545.

243. Hanna NN, Onukwugha E, Choti MA, et al. Comparative analysis of various prognostic nodal factors, adjuvant chemotherapy and survival among stage III colon cancer patients over 65 years: an analysis using surveillance, epidemiology and end results (SEER)-Medicare data. Colorectal Dis 2012;14:48-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21689262.

244. McCleary NJ, Meyerhardt JA, Green E, et al. Impact of Age on the Efficacy of Newer Adjuvant Therapies in Patients With Stage II/III Colon Cancer: Findings From the ACCENT Database. J Clin Oncol 2013;31:2600-2606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23733765.

245. Biagi JJ, Raphael MJ, Mackillop WJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA 2011;305:2335-2342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21642686.

246. Sargent D, Grothey A, Gray R. Time to initiation of adjuvant chemotherapy and survival in colorectal cancer. JAMA 2011;306:1199; author reply 1200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21934049.

247. Comparison of flourouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. Lancet 2000;355:1588-1596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10821362.

248. Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. J Clin Oncol 1996;14:2274-2279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8708717.

249. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group study. Cancer 1989;63:1026-1030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2465076.

250. Sanoff HK, Carpenter WR, Martin CF, et al. Comparative effectiveness of oxaliplatin vs non-oxaliplatin-containing adjuvant chemotherapy for stage III colon cancer. J Natl Cancer Inst 2012;104:211-227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22266473.

251. Sanoff HK, Carpenter WR, Freburger J, et al. Comparison of adverse events during 5-fluorouracil versus 5-fluorouracil/oxaliplatin adjuvant chemotherapy for stage III colon cancer: A population-based analysis. Cancer 2012;118:4309-4320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22294436.

252. Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. Ann Oncol 2012;23:1190-1197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21896539.

253. Saltz LB, Niedzwiecki D, Hollis D, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. J Clin Oncol 2007;25:3456-3461. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17687149.

254. Rothenberg ML, Meropol NJ, Poplin EA, et al. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 2001;19:3801-3807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11559717.

255. Papadimitriou CA, Papakostas P, Karina M, et al. A randomized phase III trial of adjuvant chemotherapy with irinotecan, leucovorin and fluorouracil versus leucovorin and fluorouracil for stage II and III colon cancer: a Hellenic Cooperative Oncology Group study. BMC Med 2011;9:10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21281463.

256. Van Cutsem E, Labianca R, Bodoky G, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol 2009;27:3117-3125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19451425.

257. Ychou M, Raoul JL, Douillard JY, et al. A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). Ann Oncol 2009;20:674-680. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19179549.

258. Allegra CJ, Yothers G, O'Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol 2011;29:11-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20940184.

259. Allegra CJ, Yothers G, O'Connell MJ, et al. Bevacizumab in stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial. J Clin Oncol 2013;31:359-364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23233715.

260. de Gramont A, Van Cutsem E, Schmoll HJ, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon

cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol 2012;13:1225-1233. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23168362.

261. Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA 2012;307:1383-1393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22474202.

262. Taieb J, Tabernero J, Mini E, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:862-873. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24928083.

263. Cantero-Munoz P, Urien MA, Ruano-Ravina A. Efficacy and safety of intraoperative radiotherapy in colorectal cancer: A systematic review. Cancer Lett 2011;306:121-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21414718.

264. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. Surg Oncol 2013;22:22-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23270946.

265. Hong TS, Ritter MA, Tome WA, Harari PM. Intensity-modulated radiation therapy: emerging cancer treatment technology. Br J Cancer 2005;92:1819-1824. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15856036.

266. Lee WS, Yun SH, Chun HK, et al. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. Int J Colorectal Dis 2007;22:699-704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17109105.

267. Van Cutsem E, Nordlinger B, Adam R, et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer 2006;42:2212-2221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16904315.

268. Yoo PS, Lopez-Soler RI, Longo WE, Cha CH. Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab. Clin Colorectal Cancer 2006;6:202-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17026789.

269. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. J Clin Oncol 2005;23:9243-9249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16230673.

270. Dawood O, Mahadevan A, Goodman KA. Stereotactic body radiation therapy for liver metastases. Eur J Cancer 2009;45:2947-2959. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19773153.

271. Kemeny N. Management of liver metastases from colorectal cancer. Oncology (Williston Park) 2006;20:1161-1176, 1179; discussion 1179-1180, 1185-1166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17024869.

272. Muratore A, Zorzi D, Bouzari H, et al. Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? Ann Surg Oncol 2007;14:766-770. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17103261.

273. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. J Clin Oncol 1997;15:938-946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9060531.

274. Hayashi M, Inoue Y, Komeda K, et al. Clinicopathological analysis of recurrence patterns and prognostic factors for survival after

hepatectomy for colorectal liver metastasis. BMC Surg 2010;10:27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20875094.

275. Tsai M-S, Su Y-H, Ho M-C, et al. Clinicopathological features and prognosis in resectable synchronous and metachronous colorectal liver metastasis. Ann Surg Oncol 2007;14:786-794. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17103254.

276. Foster JH. Treatment of metastatic disease of the liver: a skeptic's view. Semin Liver Dis 1984;4:170-179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6205450.

277. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet 1994;343:1405-1410. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7515134.

278. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644-657; discussion 657-648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15383792.

279. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-766. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12035031.

280. Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. Ann Surg Oncol 2005;12:900-909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16184442.

281. Fong Y, Salo J. Surgical therapy of hepatic colorectal metastasis. Semin Oncol 1999;26:514-523. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10528899.

282. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 2005;241:715-722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15849507.

283. Venook AP. The Kemeny Article Reviewed Management of Liver Metastases From Colorectal Cancer: Review 2. Oncology 2006;20. Available at: http://www.cancernetwork.com/display/article/10165/108033.

284. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol 2012;4:283-301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23152705.

285. Aloia TA, Vauthey JN, Loyer EM, et al. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg 2006;141:460-466; discussion 466-467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16702517.

286. Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. Am J Surg 2009;197:728-736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18789428.

287. Lee WS, Yun SH, Chun HK, et al. Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. J Clin Gastroenterol 2008;42:945-949. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18438208.

288. Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1261-1268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16947009.

289. Gonzalez M, Poncet A, Combescure C, et al. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a

systematic review and meta-analysis. Ann Surg Oncol 2013;20:572-579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23104709.

290. Onaitis MW, Petersen RP, Haney JC, et al. Prognostic factors for recurrence after pulmonary resection of colorectal cancer metastases. Ann Thorac Surg 2009;87:1684-1688. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19463577.

291. Brouquet A, Vauthey JN, Contreras CM, et al. Improved survival after resection of liver and lung colorectal metastases compared with liver-only metastases: a study of 112 patients with limited lung metastatic disease. J Am Coll Surg 2011;213:62-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21700179.

292. Headrick JR, Miller DL, Nagorney DM, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. Ann Thorac Surg 2001;71:975-979. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11269484.

293. Marin C, Robles R, Lopez Conesa A, et al. Outcome of strict patient selection for surgical treatment of hepatic and pulmonary metastases from colorectal cancer. Dis Colon Rectum 2013;56:43-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23222279.

294. Pulitano C, Bodingbauer M, Aldrighetti L, et al. Liver Resection for Colorectal Metastases in Presence of Extrahepatic Disease: Results from an International Multi-institutional Analysis. Ann Surg Oncol 2011;18:1380-1388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21136180.

295. Carpizo DR, Are C, Jarnagin W, et al. Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. Ann Surg Oncol 2009;16:2138-2146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19495884.

296. Carpizo DR, D'Angelica M. Liver resection for metastatic colorectal cancer in the presence of extrahepatic disease. Ann Surg Oncol 2009;16:2411-2421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19554376.

297. Chua TC, Saxena A, Liauw W, et al. Hepatectomy and resection of concomitant extrahepatic disease for colorectal liver metastases--a systematic review. Eur J Cancer 2012;48:1757-1765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22153217.

298. Andreou A, Brouquet A, Abdalla EK, et al. Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. HPB (Oxford) 2011;13:774-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21999590.

299. de Jong MC, Mayo SC, Pulitano C, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. J Gastrointest Surg 2009;13:2141-2151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19795176.

300. Homayounfar K, Bleckmann A, Conradi LC, et al. Metastatic recurrence after complete resection of colorectal liver metastases: impact of surgery and chemotherapy on survival. Int J Colorectal Dis 2013;28:1009-1017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23371333.

301. Neeff HP, Drognitz O, Holzner P, et al. Outcome after repeat resection of liver metastases from colorectal cancer. Int J Colorectal Dis 2013;28:1135-1141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23468250.

302. Salah S, Watanabe K, Park JS, et al. Repeated resection of colorectal cancer pulmonary oligometastases: pooled analysis and prognostic assessment. Ann Surg Oncol 2013;20:1955-1961. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23334254.

303. Luo LX, Yu ZY, Huang JW, Wu H. Selecting patients for a second hepatectomy for colorectal metastases: An systemic review and meta-

analysis. Eur J Surg Oncol 2014;40:1036-1048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24915859.

304. Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. Ann Surg 1997;225:51-60; discussion 60-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8998120.

305. Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol 2009;27:3379-3384. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19487380.

306. Alsina J, Choti MA. Liver-directed therapies in colorectal cancer. Semin Oncol 2011;38:561-567. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21810515.

307. Johnston FM, Mavros MN, Herman JM, Pawlik TM. Local therapies for hepatic metastases. J Natl Compr Canc Netw 2013;11:153-160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23411382.

308. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med 1999;341:2039-2048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10615075.

309. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. N Engl J Med 2005;352:734-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15716576.

310. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res 2012;32:1387-1395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22493375.

311. Richardson AJ, Laurence JM, Lam VW. Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review. J Vasc Interv Radiol 2013;24:1209-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23885916.

312. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33:41-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19908093.

313. Martin RC, Howard J, Tomalty D, et al. Toxicity of irinotecan-eluting beads in the treatment of hepatic malignancies: results of a multi-institutional registry. Cardiovasc Intervent Radiol 2010;33:960-966. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20661569.

314. Pawlik TM, Reyes DK, Cosgrove D, et al. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol 2011;29:3960-3967. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21911714.

315. Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. Cancer J 2009;15:526-532. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20010173.

316. van Malenstein H, Maleux G, Vandecaveye V, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie 2011;34:368-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21734423.

317. Vogl TJ, Lammer J, Lencioni R, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. AJR Am J Roentgenol 2011;197:W562-570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21940527.

318. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Transarterial (chemo)embolisation versus no intervention or placebo intervention for liver metastases. Cochrane Database Syst Rev 2013;4:CD009498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23633373.

319. Benson A, Mulcahy MF, Siskin G, et al. Safety, response and survival outcomes of Y90 radioembolization for liver metastases: Results from a 151 patient investigational device exemption multi-institutional study [abstract]. Journal of Vascular and Interventional Radiology 2011;22 (suppl):S3. Available at: http://www.jvir.org/article/S1051-0443(11)00003-0/fulltext.

320. Cosimelli M, Golfieri R, Cagol PP, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer 2010;103:324-331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20628388.

321. Gray B, Van Hazel G, Hope M, et al. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 2001;12:1711-1720. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11843249.

322. Hong K, McBride JD, Georgiades CS, et al. Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization. J Vasc Interv Radiol 2009;20:360-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19167245.

323. Lewandowski RJ, Memon K, Mulcahy MF, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. Eur J Nucl Med Mol Imaging 2014;41:1861-1869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24906565.

324. Lim L, Gibbs P, Yip D, et al. A prospective evaluation of treatment with Selective Internal Radiation Therapy (SIR-spheres) in patients with unresectable liver metastases from colorectal cancer previously treated with 5-FU based chemotherapy. BMC Cancer 2005;5:132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16225697.

325. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer 2009;115:1849-1858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19267416.

326. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol 2012;35:1066-1073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21800231.

327. van Hazel GA, Pavlakis N, Goldstein D, et al. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J Clin Oncol 2009;27:4089-4095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652069.

328. Katz AW, Carey-Sampson M, Muhs AG, et al. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. Int J Radiat Oncol Biol Phys 2007;67:793-798. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17197128.

329. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol 2010;28:3687-3694. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20567019.

330. Benson AB, 3rd, Geschwind JF, Mulcahy MF, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. Eur J Cancer 2013;49:3122-3130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23777743.

331. Rosenbaum CE, Verkooijen HM, Lam MG, et al. Radioembolization for treatment of salvage patients with colorectal cancer liver metastases: a systematic review. J Nucl Med 2013;54:1890-1895. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24071510.

332. Saxena A, Bester L, Shan L, et al. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. J Cancer Res Clin Oncol 2014;140:537-547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24318568.

333. Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. Cochrane Database Syst Rev 2009:CD007045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19821394.

334. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol 2009;27:1585-1591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255313.

335. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27:1572-1578. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255321.

336. ACR–ASTRO Practice Guideline for Intensity-Modulated Radiation Therapy (IMRT). The American College of Radiology; 2011. Available at: http://www.acr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality/Radiation-Oncology. Accessed January 24, 2014.

337. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. Cancer 2011;117:4060-4069. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21432842.

338. Meyer J, Czito B, Yin F-F, Willett C. Advanced radiation therapy technologies in the treatment of rectal and anal cancer: intensity-modulated photon therapy and proton therapy. Clin Colorectal Cancer 2007;6:348-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17311699.

339. Topkan E, Onal HC, Yavuz MN. Managing liver metastases with conformal radiation therapy. J Support Oncol 2008;6:9-13, 15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18257395.

340. Abdalla EK, Vauthey J-N, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818-825. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15166961.

341. Bala MM, Riemsma RP, Wolff R, Kleijnen J. Microwave coagulation for liver metastases. Cochrane Database Syst Rev 2013;10:CD010163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24122576.

342. Bala MM, Riemsma RP, Wolff R, Kleijnen J. Cryotherapy for liver metastases. Cochrane Database Syst Rev 2013;6:CD009058. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23740609.

343. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Percutaneous ethanol injection for liver metastases. Cochrane Database Syst Rev 2013;5:CD008717. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23728679.

344. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Electro-coagulation for liver metastases. Cochrane Database Syst Rev 2013;5:CD009497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23728692.

345. Cirocchi R, Trastulli S, Boselli C, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. Cochrane Database Syst Rev 2012;6:CD006317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22696357.

346. Weng M, Zhang Y, Zhou D, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. PLoS One 2012;7:e45493. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23029051.

347. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol 2010;28:493-508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19841322.

348. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg 2009;250:440-448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19730175.

349. Gillams A, Khan Z, Osborn P, Lees W. Survival after radiofrequency ablation in 122 patients with inoperable colorectal lung metastases. Cardiovasc Intervent Radiol 2013;36:724-730. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23070108.

350. Gleisner AL, Choti MA, Assumpcao L, et al. Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. Arch Surg 2008;143:1204-1212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19075173.

351. Reuter NP, Woodall CE, Scoggins CR, et al. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? J Gastrointest Surg 2009;13:486-491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18972167.

352. Abdalla EK. Commentary: Radiofrequency ablation for colorectal liver metastases: do not blame the biology when it is the technology. Am J Surg 2009;197:737-739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18789420.

353. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 2012;23:2619-2626. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22431703.

354. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J Clin Oncol 2012;30:263-267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22162570.

355. Klaver YL, Leenders BJ, Creemers GJ, et al. Addition of biological therapies to palliative chemotherapy prolongs survival in patients with peritoneal carcinomatosis of colorectal origin. Am J Clin Oncol 2013;36:157-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22314003.

356. Cennamo V, Fuccio L, Mutri V, et al. Does stent placement for advanced colon cancer increase the risk of perforation during bevacizumab-based therapy? Clin Gastroenterol Hepatol 2009;7:1174-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19631290.

357. Small AJ, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. Gastrointest Endosc 2010;71:560-572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20189515.

358. Chua TC, Pelz JO, Kerscher A, et al. Critical analysis of 33 patients with peritoneal carcinomatosis secondary to colorectal and appendiceal signet ring cell carcinoma. Ann Surg Oncol 2009;16:2765-2770. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19641972.

359. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric

French study. J Clin Oncol 2010;28:63-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19917863.

360. Esquivel J, Sticca R, Sugarbaker P, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. Ann Surg Oncol 2007;14:128-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17072675.

361. Goere D, Malka D, Tzanis D, et al. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? Ann Surg 2013;257:1065-1071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23299520.

362. Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer 2010;116:5608-5618. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20737573.

363. Haslinger M, Francescutti V, Attwood K, et al. A contemporary analysis of morbidity and outcomes in cytoreduction/hyperthermic intraperitoneal chemoperfusion. Cancer Med 2013;2:334-342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23930210.

364. Tabrizian P, Shrager B, Jibara G, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: outcomes from a single tertiary institution. J Gastrointest Surg 2014;18:1024-1031. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24577736.

365. Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol 2006;24:4011-4019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921055.

366. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737-3743. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14551293.

367. Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15:2426-2432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18521686.

368. Sugarbaker PH, Ryan DP. Cytoreductive surgery plus hyperthermic perioperative chemotherapy to treat peritoneal metastases from colorectal cancer: standard of care or an experimental approach? Lancet Oncol 2012;13:e362-369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22846841.

369. El Halabi H, Gushchin V, Francis J, et al. The role of cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) in patients with high-grade appendiceal carcinoma and extensive peritoneal carcinomatosis. Ann Surg Oncol 2012;19:110-114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21701929.

370. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 2012;30:2449-2456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22614976.

371. Faris JE, Ryan DP. Controversy and consensus on the management of patients with pseudomyxoma peritonei. Curr Treat Options Oncol 2013;14:365-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23934509.

372. Klaver YL, Hendriks T, Lomme RM, et al. Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal

carcinomatosis: an experimental study. Ann Surg 2011;254:125-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21502859.

373. Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. Surg Oncol Clin N Am 2003;12:165-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12735137.

374. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist 2008;13:51-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18245012.

375. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol 2004;15:933-939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15151951.

376. Vauthey J-N, Zorzi D, Pawlik TM. Making unresectable hepatic colorectal metastases resectable--does it work? Semin Oncol 2005;32:118-122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16399448.

377. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 2008;247:451-455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18376189.

378. Folprecht G, Grothey A, Alberts S, et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol 2005;16:1311-1319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15870084.

379. Bilchik AJ, Poston G, Curley SA, et al. Neoadjuvant chemotherapy for metastatic colon cancer: a cautionary note. J Clin Oncol 2005;23:9073-9078. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16361615.

380. Choti MA. Chemotherapy-associated hepatotoxicity: do we need to be concerned? Ann Surg Oncol 2009;16:2391-2394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19554374.

381. Kishi Y, Zorzi D, Contreras CM, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol 2010;17:2870-2876. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20567921.

382. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460-466. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14998849.

383. Vauthey J-N, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065-2072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648507.

384. Delaunoit T, Alberts SR, Sargent DJ, et al. Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. Ann Oncol 2005;16:425-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15677624.

385. 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;25:1670-1676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470860.

386. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). Br J Cancer

2006;94:798-805. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16508637.

387. Masi G, Vasile E, Loupakis F, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. J Natl Cancer Inst 2011;103:21-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21123833.

388. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010;11:38-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19942479.

389. Tan BR, Zubal B, Hawkins W, et al. Preoperative FOLFOX plus cetuximab or panitumumab therapy for patients with potentially resectable hepatic colorectal metastases [abstract]. Gastrointestinal Cancers Symposium 2009:497. Available at: http://meetinglibrary.asco.org/content/10593-63.

390. Folprecht G, Gruenberger T, Bechstein W, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). Ann Oncol 2014;25:1018-1025. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24585720.

391. Ye LC, Liu TS, Ren L, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J Clin Oncol 2013;31:1931-1938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23569301.

392. Petrelli F, Barni S. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. Int J Colorectal Dis 2012;27:997-1004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22358385.

393. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17947725.

394. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-2342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15175435.

395. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-2019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18421054.

396. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8:347-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11352309.

397. Pawlik TM, Olino K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 2007;11:860-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17492335.

398. Rivoire M, De Cian F, Meeus P, et al. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. Cancer 2002;95:2283-2292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12436433.

399. Ciliberto D, Prati U, Roveda L, et al. Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: a systematic review and meta-analysis of randomized controlled trials. Oncol Rep 2012;27:1849-1856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22446591.

400. Araujo R, Gonen M, Allen P, et al. Comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic colorectal cancer. Ann Surg Oncol 2013;20:4312-4321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23897009.

401. Bilchik AJ, Poston G, Adam R, Choti MA. Prognostic variables for resection of colorectal cancer hepatic metastases: an evolving paradigm. J Clin Oncol 2008;26:5320-5321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18936470.

402. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. J Clin Oncol 2005;23:2038-2048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15774795.

403. van Vledder MG, de Jong MC, Pawlik TM, et al. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? J Gastrointest Surg 2010;14:1691-1700. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20839072.

404. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol 2006;24:3939-3945. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921046.

405. Bischof DA, Clary BM, Maithel SK, Pawlik TM. Surgical management of disappearing colorectal liver metastases. Br J Surg 2013;100:1414-1420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24037559.

406. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-1634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18316791.

407. Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1284-1292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16955384.

408. Buroker TR, O'Connell MJ, Wieand HS, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. J Clin Oncol 1994;12:14-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7677801.

409. Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008;26:2006-2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18421053.

410. Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12177775.

411. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol 2005;23:4866-4875. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15939922.

412. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15269313.

413. Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 1998;352:1413-1418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9807987.

414. de Gramont A, Bosset JF, Milan C, et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with

bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol 1997;15:808-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9053508.

415. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938-2947. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10944126.

416. Delaunoit T, Goldberg RM, Sargent DJ, et al. Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: results from Intergroup Trial N9741. Cancer 2004;101:2170-2176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15470715.

417. 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. Lancet 2000;355:1041-1047. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10744089.

418. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697-4705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20921465.

419. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12610178.

420. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539-1544. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17442997.

421. Goldberg RM. Therapy for metastatic colorectal cancer. Oncologist 2006;11:981-987. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17030638.

422. Goldberg RM, Rothenberg ML, Van Cutsem E, et al. The continuum of care: a paradigm for the management of metastatic colorectal cancer. Oncologist 2007;12:38-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17227899.

423. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14665611.

424. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23177514.

425. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18824706.

426. Hurwitz HI, Fehrenbacher L, Hainsworth JD, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. J Clin Oncol 2005;23:3502-3508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15908660.

427. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15867200.

428. Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. J Clin Oncol 2005;23:4553-4560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16002847.

429. Kohne C, Mineur L, Greil R, et al. Primary analysis of a phase II study (20060314) combining first-line panitumumab (pmab) with FOLFIRI in the treatment of patients (pts) with metastatic colorectal cancer (mCRC) [abstract]. J Clin Oncol 2010:414. Available at: http://meetinglibrary.asco.org/content/1456-72.

430. Maindrault-Goebel F, Louvet C, Andre T, et al. Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). GERCOR. Eur J Cancer 1999;35:1338-1342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10658524.

431. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:4706-4713. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20921462.

432. Petrelli N, Herrera L, Rustum Y, et al. A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. J Clin Oncol 1987;5:1559-1565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2443619.

433. Punt CJ, Tol J, Rodenburg CJ, et al. Randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG) [abstract]. J Clin Oncol 2008;26 (May 20 suppl):LBA4011. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/LBA4011.

434. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17602073.

435. Saltz L, Clarke S, Diaz-Rubio E, et al. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Updated efficacy results from XELOX-1/ NO16966, a randomized phase III trial in first-line metastatic colorectal cancer [abstract]. J Clin Oncol 2007;25 (June 20 suppl):4028. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/4028.

436. Van Cutsem E. Challenges in the use of epidermal growth factor receptor inhibitors in colorectal cancer. Oncologist 2006;11:1010-1017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17030643.

437. Van Cutsem E, Hoff PM, Harper P, et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer 2004;90:1190-1197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15026800.

438. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-1417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19339720.

439. Van Cutsem 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470858.

440. Van Cutsem 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11689577.

441. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen. J Clin Oncol 2012;30:3499-3506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22949147.

442. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol 1993;11:1879-1887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8410113.

443. Lentz F, Tran A, Rey E, et al. Pharmacogenomics of fluorouracil, irinotecan, and oxaliplatin in hepatic metastases of colorectal cancer: clinical implications. Am J Pharmacogenomics 2005;5:21-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15727486.

444. O'Dwyer PJ. The present and future of angiogenesis-directed treatments of colorectal cancer. Oncologist 2006;11:992-998. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17030640.

445. Raymond E, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. Semin Oncol 1998;25:4-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9609103.

446. Rothenberg ML, Blanke CD. Topoisomerase I inhibitors in the treatment of colorectal cancer. Semin Oncol 1999;26:632-639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10606256.

447. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229-237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14657227.

448. Cassidy J, Tabernero J, Twelves C, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol 2004;22:2084-2091. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15169795.

449. Porschen R, Arkenau H-T, Kubicka S, et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. J Clin Oncol 2007;25:4217-4223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17548840.

450. Ducreux M, Malka D, Mendiboure J, et al. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. Lancet Oncol 2011;12:1032-1044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21903473.

451. Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. Lancet 2007;370:135-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17630036.

452. Seymour MT, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. Lancet 2007;370:143-152. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17630037.

453. Grothey A, Sargent D, Goldberg RM, Schmoll H-J. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 2004;22:1209-1214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15051767.

454. Sargent DJ, Kohne CH, Sanoff HK, et al. Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer. J Clin Oncol 2009;27:1948-1955. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255311.

455. Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. J Clin Oncol 2008;26:689-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18235136.

456. Goldberg RM, Sargent DJ, Morton RF, et al. Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. J Clin Oncol 2006;24:3347-3353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16849748.

457. Kohne CH, De Greve J, Hartmann JT, et al. Irinotecan combined with infusional 5-fluorouracil/folinic acid or capecitabine plus celecoxib or placebo in the first-line treatment of patients with metastatic colorectal cancer. EORTC study 40015. Ann Oncol 2008;19:920-926. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18065406.

458. Garcia-Alfonso P, Munoz-Martin AJ, Alvarez-Suarez S, et al. Bevacizumab in combination with biweekly capecitabine and irinotecan, as first-line treatment for patients with metastatic colorectal cancer. Br J Cancer 2010;103:1524-1528. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20978503.

459. Ducreux M, Adenis A, Mendiboure J, et al. Efficacy and safety of bevacizumab (BEV)-based combination regimens in patients with metastatic colorectal cancer (mCRC): Randomized phase II study of BEV + FOLFIRI versus BEV + XELIRI (FNCLCC ACCORD 13/0503 study) [abstract]. J Clin Oncol 2009;27 (15s; suppl.):4086. Available at: http://meetinglibrary.asco.org/content/33403-65.

460. Pectasides D, Papaxoinis G, Kalogeras K, et al. XELIRI-bevacizumab versus FOLFIRI-bevacizumab as first-line treatment in patients with metastatic colorectal cancer: a Hellenic Cooperative Oncology Group phase III trial with collateral biomarker analysis. BMC Cancer 2012;12:271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22748098.

461. Schmiegel W, Reinacher-Schick A, Arnold D, et al. Capecitabine/irinotecan or capecitabine/oxaliplatin in combination with bevacizumab is effective and safe as first-line therapy for metastatic colorectal cancer: a randomized phase II study of the AIO colorectal study group. Ann Oncol 2013;24:1580-1587. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23463625.

462. Hoff PM, Hochhaus A, Pestalozzi BC, et al. Cediranib plus FOLFOX/CAPOX versus placebo plus FOLFOX/CAPOX in patients with previously untreated metastatic colorectal cancer: a randomized, double-blind, phase III study (HORIZON II). J Clin Oncol 2012;30:3596-3603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22965965.

463. Siu LL, Shapiro JD, Jonker DJ, et al. Phase III Randomized, Placebo-Controlled Study of Cetuximab Plus Brivanib Alaninate Versus Cetuximab Plus Placebo in Patients With Metastatic, Chemotherapy-Refractory, Wild-Type K-RAS Colorectal Carcinoma: The NCIC Clinical Trials Group and AGITG CO.20 Trial. J Clin Oncol 2013;31:2477-2484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23690424.

464. Carrato A, Swieboda-Sadlej A, Staszewska-Skurczynska M, et al. Fluorouracil, leucovorin, and irinotecan plus either sunitinib or placebo in metastatic colorectal cancer: a randomized, phase III trial. J Clin Oncol 2013;31:1341-1347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23358972.

465. Johnsson A, Hagman H, Frodin JE, et al. A randomized phase III trial on maintenance treatment with bevacizumab alone or in combination with erlotinib after chemotherapy and bevacizumab in metastatic colorectal cancer: the Nordic ACT Trial. Ann Oncol 2013;24:2335-2341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23788755.

466. 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;27:672-680. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19114685.

467. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360:563-572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19196673.

468. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-1016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18358928.

469. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-1215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24120480.

470. Kidwell KM, Yothers G, Ganz PA, et al. Long-term neurotoxicity effects of oxaliplatin added to fluorouracil and leucovorin as adjuvant therapy for colon cancer: results from National Surgical Adjuvant Breast and Bowel Project trials C-07 and LTS-01. Cancer 2012;118:5614-5622. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22569841.

471. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16421419.

472. Seymour M. Conceptual approaches to metastatic disease. Ann Oncol 2012;23 Suppl 10:x77-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22987997.

473. Berry SR, Cosby R, Asmis T, et al. Continuous versus intermittent chemotherapy strategies in metastatic colorectal cancer: a systematic review and meta-analysis. Ann Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25057174.

474. Gamelin L, Boisdron-Celle M, Delva R, et al. Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res 2004;10:4055-4061. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15217938.

475. Gamelin L, Boisdron-Celle M, Morel A, et al. Oxaliplatin-related neurotoxicity: interest of calcium-magnesium infusion and no impact on its efficacy. J Clin Oncol 2008;26:1188-1189; author reply 1189-1190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18309961.

476. Grothey A, Nikcevich DA, Sloan JA, et al. Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer: NCCTG N04C7. J Clin Oncol 2011;29:421-427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21189381.

477. Hochster HS, Grothey A, Childs BH. Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. J Clin Oncol 2007;25:4028-4029. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17664456.

478. Knijn N, Tol J, Koopman M, et al. The effect of prophylactic calcium and magnesium infusions on the incidence of neurotoxicity and clinical outcome of oxaliplatin-based systemic treatment in advanced colorectal cancer patients. Eur J Cancer 2010;47:369-374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21067912.

479. Kurniali PC, Luo LG, Weitberg AB. Role of calcium/ magnesium infusion in oxaliplatin-based chemotherapy for colorectal cancer patients. Oncology (Williston Park) 2010;24:289-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20394142.

480. Wen F, Zhou Y, Wang W, et al. Ca/Mg infusions for the prevention of oxaliplatin-related neurotoxicity in patients with colorectal cancer: a meta-analysis. Ann Oncol 2013;24:171-178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22898039.

481. Wu Z, Ouyang J, He Z, Zhang S. Infusion of calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in colorectal cancer: A systematic review and meta-analysis. Eur J Cancer 2012;48:1791-1798. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22542974.

482. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). J Clin Oncol 2014;32:997-1005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24297951.

483. Chibaudel B, Maindrault-Goebel F, Lledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J Clin Oncol 2009;27:5727-5733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19786657.

484. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 2008;26:3523-3529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18640933.

485. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009;27:663-671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19114683.

486. Venook AP, Niedzwiecki D, Lenz H-J, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC) [abstract]. ASCO Meeting Abstracts 2014;32:LBA3. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/LBA3.

487. Buchler T, Pavlik T, Melichar B, et al. Bevacizumab with 5-fluorouracil, leucovorin, and oxaliplatin versus bevacizumab with capecitabine and oxaliplatin for metastatic colorectal carcinoma: results of a large registry-based cohort analysis. BMC Cancer 2014;14:323. Available at:

488. Cassidy J, Clarke S, Diaz-Rubio E, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br J Cancer 2011;105:58-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21673685.

489. Ducreux M, Bennouna J, Hebbar M, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. Int J Cancer 2011;128:682-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20473862.

490. Zhang C, Wang J, Gu H, et al. Capecitabine plus oxaliplatin compared with 5-fluorouracil plus oxaliplatin in metastatic colorectal cancer: Meta-analysis of randomized controlled trials. Oncol Lett 2012;3:831-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22741002.

491. Product Insert. ELOXATIN (oxaliplatin). Bridgewater, NJ: sanofi-aventis U.S. LLC; 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021759s012lbl.pdf. Accessed January 27, 2014.

492. Yalcin S, Uslu R, Dane F, et al. Bevacizumab + capecitabine as maintenance therapy after initial bevacizumab + XELOX treatment in previously untreated patients with metastatic colorectal cancer: phase III 'Stop and Go' study results--a Turkish Oncology Group Trial. Oncology 2013;85:328-335. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24247559.

493. Package Insert. XELODA® (capecitabine). Nutley, NJ: Roche Pharmaceuticals; 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020896s026lbl.pdf. Accessed January 27, 2014.

494. Haller DG, Cassidy J, Clarke SJ, et al. Potential regional differences for the tolerability profiles of fluoropyrimidines. J Clin Oncol 2008;26:2118-2123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18445840.

495. Schmoll H-J, Arnold D. Update on capecitabine in colorectal cancer. Oncologist 2006;11:1003-1009. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17030642.

496. Hofheinz RD, Heinemann V, von Weikersthal LF, et al. Capecitabine-associated hand-foot-skin reaction is an independent clinical predictor of improved survival in patients with colorectal cancer. Br J Cancer 2012;107:1678-1683. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23033005.

497. Package Insert. Camptosar® (irinotecan hydrochloride injection). New York, NY: Pfizer, Inc.; 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020571s042lbl.pdf. Accessed October 2, 2014.

498. Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004;22:1382-1388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15007088.

499. Liu X, Cheng D, Kuang Q, et al. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians. Pharmacogenomics J 2014;14:120-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23529007.

500. O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. J Clin Oncol 2006;24:4534-4538. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17008691.

501. Innocenti F, Schilsky RL, Ramirez J, et al. Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the UGT1A1 Genotype of Patients With Cancer. J Clin Oncol 2014;32:2328-2334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24958824.

502. The Invader® UGT1A1 Molecular Assay HOLOGIC™; 2011. Available at: http://www.invaderchemistry.com/invader_applications/invader-ugt1a1.html. Accessed August 20, 2014.

503. UGT1A1 for Irinotecan Toxicity: Managing medication dosing and predicting response to treatment of cancer with irinotecan (Camptosar®, CPT-11). LabCorp Laboratory Corporation of America; 2010. Available at: https://www.labcorp.com/wps/portal/!ut/p/c0/04_SB8K8xLLM9MSSzPy8xBz9CP0os_hQV5NgQ09LYwMDS38nAyMv8zAjC6cgI_cAA_2CbEdFABiUI5s!/?WCM_PORTLET=PC_7_UE4S1I9300F7202JNDVEFE2007_WCM&WCM_GLOBAL_CONTEXT=/wps/wcm/connect/labcorp+content/LabCorp/Provider/Resources/Services/Pharmacogenetics. Accessed August 20, 2014.

504. Sobrero A, Ackland S, Clarke S, et al. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. Oncology 2009;77:113-119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19628950.

505. Van Cutsem E, Lang I, Folprecht G, et al. Cetuximab plus FOLFIRI: Final data from the CRYSTAL study on the association of KRAS and BRAF biomarker status with treatment outcome [abstract]. J Clin Oncol 2010;28 (May 20 suppl):3570. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/3570.

506. Mitry E, Fields ALA, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol 2008;26:4906-4911. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18794541.

507. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol 2013;14:1077-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24028813.

508. Falcone A, Cremolini C, Masi G, et al. FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group [abstract]. ASCO Meeting Abstracts 2013;31:3505. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/3505.

509. Loupakis F, Cremolini C, Masi G, et al. FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first-line treatment of metastatic colorectal cancer (MCRC): Results of the phase III randomized TRIBE trial [abstract]. ASCO Meeting Abstracts 2013;31:336. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/4_suppl/336.

510. Gruenberger T, Bridgewater JA, Chau I, et al. Randomized, phase II study of bevacizumab with mFOLFOX6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: Resectability and safety in OLIVIA [abstract]. ASCO Meeting Abstracts 2013;31:3619. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/3619.

511. Package Insert. AVASTIN® (bevacizumab). South San Francisco, C: Genentech, Inc.; 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125085s285lbl.pdf. Accessed August 15, 2014.

512. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003;21:60-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12506171.

513. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol 2005;23:3697-3705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15738537.

514. Petrelli F, Borgonovo K, Cabiddu M, et al. FOLFIRI-bevacizumab as first-line chemotherapy in 3500 patients with advanced colorectal cancer: a pooled analysis of 29 published trials. Clin Colorectal Cancer 2013;12:145-151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23763824.

515. Hurwitz HI, Bekaii-Saab TS, Bendell JC, et al. Safety and effectiveness of bevacizumab treatment for metastatic colorectal cancer: final results from the Avastin((R)) Registry - Investigation of Effectiveness and Safety (ARIES) observational cohort study. Clin Oncol (R Coll Radiol) 2014;26:323-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24686090.

516. Fourrier-Reglat A, Smith D, Rouyer M, et al. Survival outcomes of bevacizumab in first-line metastatic colorectal cancer in a real-life setting: results of the ETNA cohort. Target Oncol 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24307007.

517. Cao Y, Tan A, Gao F, et al. A meta-analysis of randomized controlled trials comparing chemotherapy plus bevacizumab with chemotherapy alone in metastatic colorectal cancer. Int J Colorectal Dis 2009;24:677-685. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19184059.

518. Hurwitz HI, Tebbutt NC, Kabbinavar F, et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: pooled analysis from seven randomized controlled trials. Oncologist 2013;18:1004-1012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23881988.

519. Loupakis F, Bria E, Vaccaro V, et al. Magnitude of benefit of the addition of bevacizumab to first-line chemotherapy for metastatic colorectal cancer: meta-analysis of randomized clinical trials. J Exp Clin

Cancer Res 2010;29:58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20504361.

520. Lv C, Wu S, Zheng D, et al. The efficacy of additional bevacizumab to cytotoxic chemotherapy regimens for the treatment of colorectal cancer: an updated meta-analysis for randomized trials. Cancer Biother Radiopharm 2013;28:501-509. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23768086.

521. Welch S, Spithoff K, Rumble RB, Maroun J. Bevacizumab combined with chemotherapy for patients with advanced colorectal cancer: a systematic review. Ann Oncol 2010;21:1152-1162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19942597.

522. Macedo LT, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. BMC Cancer 2012;12:89. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22414244.

523. Meyerhardt JA, Li L, Sanoff HK, et al. Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. J Clin Oncol 2012;30:608-615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22253466.

524. Hartmann H, Muller J, Marschner N. Is there a difference in demography and clinical characteristics in patients treated with and without bevacizumab? J Clin Oncol 2012;30:3317-3318; author reply 3318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22649139.

525. Hurwitz HI, Lyman GH. Registries and randomized trials in assessing the effects of bevacizumab in colorectal cancer: is there a common theme? J Clin Oncol 2012;30:580-581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22253468.

526. de Gramont A, Cutsem EV, Tabernero J, et al. AVANT: Results from a randomized, three-arm multinational phase III study to investigate bevacizumab with either XELOX or FOLFOX4 versus FOLFOX4 alone as adjuvant treatment for colon cancer [abstract]. J Clin Oncol 2011;29 (suppl 4):362. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/4_suppl/362?sid=0428ab46-122b-408a-9483-34bbabe0636d.

527. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis. JAMA 2011;305:487-494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21285426.

528. Hurwitz HI, Saltz LB, Van Cutsem E, et al. Venous Thromboembolic Events With Chemotherapy Plus Bevacizumab: A Pooled Analysis of Patients in Randomized Phase II and III Studies. J Clin Oncol 2011;29:1757-1764. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21422411.

529. Dai F, Shu L, Bian Y, et al. Safety of bevacizumab in treating metastatic colorectal cancer: a systematic review and meta-analysis of all randomized clinical trials. Clin Drug Investig 2013;33:779-788. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23979925.

530. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol 2005;91:173-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16118771.

531. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 2007;25:5180-5186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024865.

532. Safety: Avastin (bevacizumab). FDA; 2013. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm275758.htm. Accessed January 27, 2014.

533. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. J Clin Oncol

2008;26:1830-1835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18398148.

534. Reddy SK, Morse MA, Hurwitz HI, et al. Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. J Am Coll Surg 2008;206:96-9106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18155574.

535. Miles D, Harbeck N, Escudier B, et al. Disease course patterns after discontinuation of bevacizumab: pooled analysis of randomized phase III trials. J Clin Oncol 2011;29:83-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21098326.

536. Miles DW. Reply to P. Potemski. J Clin Oncol 2011;29:e386. Available at: http://jco.ascopubs.org/content/29/13/e386.full.

537. Potemski P. Is the Postprogression Survival Time Really Not Shortened in the Bevacizumab-Containing Arms of Phase III Clinical Trials? J Clin Oncol 2011;29:e384-385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21422432.

538. Package Insert. Cetuximab (Erbitux®). Branchburg, NJ: ImClone Systems Incorporated; 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125084s242lbl.pdf. Accessed January 27, 2014.

539. Package Insert. Vectibix® (Panitumumab). Thousand Oaks, CA: Amgen Inc.; 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125147s186lbl.pdf. Accessed August 15, 2014.

540. Vale CL, Tierney JF, Fisher D, et al. Does anti-EGFR therapy improve outcome in advanced colorectal cancer? A systematic review and meta-analysis. Cancer Treat Rev 2012;38:618-625. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22118887.

541. Helbling D, Borner M. Successful challenge with the fully human EGFR antibody panitumumab following an infusion reaction with the chimeric EGFR antibody cetuximab. Ann Oncol 2007;18:963-964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17488734.

542. Heun J, Holen K. Treatment with panitumumab after a severe infusion reaction to cetuximab in a patient with metastatic colorectal cancer: a case report. Clin Colorectal Cancer 2007;6:529-531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17553202.

543. Resch G, Schaberl-Moser R, Kier P, et al. Infusion reactions to the chimeric EGFR inhibitor cetuximab--change to the fully human anti-EGFR monoclonal antibody panitumumab is safe. Ann Oncol 2011;22:486-487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239398.

544. Berlin J, Van Cutsem E, Peeters M, et al. Predictive value of skin toxicity severity for response to panitumumab in patients with metastatic colorectal cancer (mCRC): A pooled analysis of five clinical trials [abstract]. J Clin Oncol 2007;25 (June 20 suppl):4134. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/4134.

545. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040-2048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18003960.

546. Lievre A, Bachet J-B, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008;26:374-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18202412.

547. Petrelli F, Borgonovo K, Barni S. The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. Target Oncol 2013;8:173-181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23321777.

548. Stintzing S, Kapaun C, Laubender RP, et al. Prognostic value of cetuximab-related skin toxicity in metastatic colorectal cancer patients and its correlation with parameters of the epidermal growth factor receptor signal transduction pathway: results from a randomized trial of the GERMAN AIO CRC Study Group. Int J Cancer 2013;132:236-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22644776.

549. Van Cutsem E, Tejpar S, Vanbeckevoort D, et al. Intrapatient Cetuximab Dose Escalation in Metastatic Colorectal Cancer According to the Grade of Early Skin Reactions: The Randomized EVEREST Study. J Clin Oncol 2012;30:2861-2868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22753904.

550. Burtness B, Anadkat M, Basti S, et al. NCCN Task Force Report: Management of dermatologic and other toxicities associated with EGFR inhibition in patients with cancer. J Natl Compr Canc Netw 2009;7 Suppl 1:5-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19470276.

551. Petrelli F, Cabiddu M, Borgonovo K, Barni S. Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials. Ann Oncol 2012;23:1672-1679. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22241897.

552. Zhang D, Ye J, Xu T, Xiong B. Treatment related severe and fatal adverse events with cetuximab in colorectal cancer patients: a meta-analysis. J Chemother 2013;25:170-175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23783142.

553. Grothey A, Lenz HJ. Explaining the unexplainable: EGFR antibodies in colorectal cancer. J Clin Oncol 2012;30:1735-1737. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22473160.

554. Antonacopoulou AG, Tsamandas AC, Petsas T, et al. EGFR, HER-2 and COX-2 levels in colorectal cancer. Histopathology 2008;53:698-706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19102009.

555. McKay JA, Murray LJ, Curran S, et al. Evaluation of the epidermal growth factor receptor (EGFR) in colorectal tumours and lymph node metastases. Eur J Cancer 2002;38:2258-2264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12441262.

556. Spano JP, Lagorce C, Atlan D, et al. Impact of EGFR expression on colorectal cancer patient prognosis and survival. Ann Oncol 2005;16:102-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15598946.

557. Yen LC, Uen YH, Wu DC, et al. Activating KRAS mutations and overexpression of epidermal growth factor receptor as independent predictors in metastatic colorectal cancer patients treated with cetuximab. Ann Surg 2010;251:254-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20010090.

558. Hecht JR, Mitchell E, Neubauer MA, et al. Lack of correlation between epidermal growth factor receptor status and response to Panitumumab monotherapy in metastatic colorectal cancer. Clin Cancer Res 2010;16:2205-2213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20332321.

559. Saltz LB, Meropol NJ, Loehrer PJ, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004;22:1201-1208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14993230.

560. Baselga J, Rosen N. Determinants of RASistance to anti-epidermal growth factor receptor agents. J Clin Oncol 2008;26:1582-1584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18316790.

561. De Roock W, Piessevaux H, De Schutter J, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 2008;19:508-515. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17998284.

562. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J

Med 2008;359:1757-1765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18946061.

563. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25:3230-3237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17664471.

564. Tejpar S, Peeters M, Humblet Y, et al. Relationship of efficacy with KRAS status (wild type versus mutant) in patients with irinotecan-refractory metastatic colorectal cancer (mCRC), treated with irinotecan (q2w) and escalating doses of cetuximab (q1w): The EVEREST experience (preliminary data) [abstract]. J Clin Oncol 2008;26 (May 20 suppl):4001. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/4001.

565. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-1034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24024839.

566. Sorich MJ, Wiese MD, Rowland A, et al. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25115304.

567. Artale S, Sartore-Bianchi A, Veronese SM, et al. Mutations of KRAS and BRAF in primary and matched metastatic sites of colorectal cancer. J Clin Oncol 2008;26:4217-4219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18757341.

568. Etienne-Grimaldi M-C, Formento J-L, Francoual M, et al. K-Ras mutations and treatment outcome in colorectal cancer patients receiving exclusive fluoropyrimidine therapy. Clin Cancer Res 2008;14:4830-4835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18676755.

569. Knijn N, Mekenkamp LJ, Klomp M, et al. KRAS mutation analysis: a comparison between primary tumours and matched liver metastases in 305 colorectal cancer patients. Br J Cancer 2011;104:1020-1026. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21364579.

570. Wang HL, Lopategui J, Amin MB, Patterson SD. KRAS mutation testing in human cancers: The pathologist's role in the era of personalized medicine. Adv Anat Pathol 2010;17:23-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20032635.

571. Monzon FA, Ogino S, Hammond MEH, et al. The role of KRAS mutation testing in the management of patients with metastatic colorectal cancer. Arch Pathol Lab Med 2009;133:1600-1606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19792050.

572. Dahabreh IJ, Terasawa T, Castaldi PJ, Trikalinos TA. Systematic review: Anti-epidermal growth factor receptor treatment effect modification by KRAS mutations in advanced colorectal cancer. Ann Intern Med 2011;154:37-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21200037.

573. De Roock W, Jonker DJ, Di Nicolantonio F, et al. Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. JAMA 2010;304:1812-1820. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20978259.

574. Tejpar S, Celik I, Schlichting M, et al. Association of KRAS G13D Tumor Mutations With Outcome in Patients With Metastatic Colorectal Cancer Treated With First-Line Chemotherapy With or Without Cetuximab. J Clin Oncol 2012;30:3570-3577. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22734028.

575. Peeters M, Douillard JY, Van Cutsem E, et al. Mutant KRAS codon 12 and 13 alleles in patients with metastatic colorectal cancer: assessment as prognostic and predictive biomarkers of response to panitumumab. J Clin Oncol 2013;31:759-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23182985.

576. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1065-1075. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25088940.

577. Tol J, Nagtegaal ID, Punt CJA. BRAF mutation in metastatic colorectal cancer. N Engl J Med 2009;361:98-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19571295.

578. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011;377:2103-2114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21641636.

579. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417:949-954. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12068308.

580. Ikenoue T, Hikiba Y, Kanai F, et al. Functional analysis of mutations within the kinase activation segment of B-Raf in human colorectal tumors. Cancer Res 2003;63:8132-8137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14678966.

581. Wan PT, Garnett MJ, Roe SM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 2004;116:855-867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15035987.

582. Bokemeyer C, Cutsem EV, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer 2012;48:1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22446022.

583. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab Plus Irinotecan, Fluorouracil, and Leucovorin As First-Line Treatment for Metastatic Colorectal Cancer: Updated Analysis of Overall Survival According to Tumor KRAS and BRAF Mutation Status. J Clin Oncol 2011;29:2011-2019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21502544.

584. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26:5705-5712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19001320.

585. Laurent-Puig P, Cayre A, Manceau G, et al. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. J Clin Oncol 2009;27:5924-5930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19884556.

586. Loupakis F, Ruzzo A, Cremolini C, et al. KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer. Br J Cancer 2009;101:715-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19603018.

587. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol 2010;11:753-762. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20619739.

588. Seymour MT, Brown SR, Richman S, et al. Addition of panitumumab to irinotecan: Results of PICCOLO, a randomized controlled trial in advanced colorectal cancer (aCRC) [abstract]. ASCO Meeting Abstracts 2011;29:3523. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/3523.

589. Price TJ, Hardingham JE, Lee CK, et al. Impact of KRAS and BRAF Gene Mutation Status on Outcomes From the Phase III AGITG MAX Trial of Capecitabine Alone or in Combination With Bevacizumab and Mitomycin in Advanced Colorectal Cancer. J Clin Oncol

2011;29:2675-2682. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21646616.

590. Safaee Ardekani G, Jafarnejad SM, Tan L, et al. The prognostic value of BRAF mutation in colorectal cancer and melanoma: a systematic review and meta-analysis. PLoS One 2012;7:e47054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23056577.

591. Samowitz WS, Sweeney C, Herrick J, et al. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. Cancer Res 2005;65:6063-6069. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16024606.

592. Saridaki Z, Papadatos-Pastos D, Tzardi M, et al. BRAF mutations, microsatellite instability status and cyclin D1 expression predict metastatic colorectal patients' outcome. Br J Cancer 2010;102:1762-1768. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20485284.

593. Xu Q, Xu AT, Zhu MM, et al. Predictive and prognostic roles of BRAF mutation in patients with metastatic colorectal cancer treated with anti-epidermal growth factor receptor monoclonal antibodies: A meta-analysis. J Dig Dis 2013;14:409-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23615046.

594. Clancy C, Burke JP, Kalady MF, Coffey JC. BRAF mutation is associated with distinct clinicopathological characteristics in colorectal cancer: a systematic review and meta-analysis. Colorectal Dis 2013;15:e711-718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24112392.

595. Santini D, Spoto C, Loupakis F, et al. High concordance of BRAF status between primary colorectal tumours and related metastatic sites: implications for clinical practice. Ann Oncol 2010;21:1565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20573852.

596. Lang I, Kohne CH, Folprecht G, et al. Quality of life analysis in patients with KRAS wild-type metastatic colorectal cancer treated first-line with cetuximab plus irinotecan, fluorouracil and leucovorin. Eur J Cancer 2013;49:439-448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23116683.

597. Mitchell EP, Piperdi B, Lacouture ME, et al. The efficacy and safety of panitumumab administered concomitantly with FOLFIRI or Irinotecan in second-line therapy for metastatic colorectal cancer: the secondary analysis from STEPP (Skin Toxicity Evaluation Protocol With Panitumumab) by KRAS status. Clin Colorectal Cancer 2011;10:333-339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22000810.

598. Sobrero AF, Peeters M, Price TJ, et al. Final results from study 181: Randomized phase III study of FOLFIRI with or without panitumumab (pmab) for the treatment of second-line metastatic colorectal cancer (mCRC) [abstract]. ASCO Meeting Abstracts 2012;30:387. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/4_suppl/387.

599. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Biomarkers predictive for outcome in patients with metastatic colorectal cancer (mCRC) treated with first-line FOLFOX4 plus or minus cetuximab: Updated data from the OPUS study [abstract]. J Clin Oncol 2010:428. Available at: http://meetinglibrary.asco.org/content/1910-72.

600. Taieb J, Maughan T, Bokemeyer C, et al. Cetuximab combined with infusional 5-fluorouracil/folinic acid (5-FU/FA) and oxaliplatin in metastatic colorectal cancer (mCRC): A pooled analysis of COIN and OPUS study data [abstract]. ASCO Meeting Abstracts 2012;30:3574. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/3574.

601. Tveit KM, Guren T, Glimelius B, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. J Clin Oncol 2012;30:1755-1762. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22473155.

602. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver

metastasis: the New EPOC randomised controlled trial. Lancet Oncol 2014;15:601-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24717919.

603. Douillard J, Siena S, Cassidy J, et al. Final results from PRIME: Randomized phase III study of panitumumab (pmab) with FOLFOX4 for first-line metastatic colorectal cancer (mCRC) [abstract]. J Clin Oncol 2011;29(suppl):3510^. Available at: http://meetinglibrary.asco.org/content/84543-102.

604. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: A Randomized, Multicenter Phase II Study of Panitumumab Plus Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab Plus mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type KRAS Exon 2 Metastatic Colorectal Cancer. J Clin Oncol 2014;32:2240-2247. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24687833.

605. Wolpin BM, Bass AJ. Managing Advanced Colorectal Cancer: Have We Reached the PEAK With Current Therapies? J Clin Oncol 2014;32:2200-2202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24934780.

606. Hoff PM, Pazdur R, Lassere Y, et al. Phase II study of capecitabine in patients with fluorouracil-resistant metastatic colorectal carcinoma. J Clin Oncol 2004;22:2078-2083. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15169794.

607. Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998;352:1407-1412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9807986.

608. Kim GP, Sargent DJ, Mahoney MR, et al. Phase III noninferiority trial comparing irinotecan with oxaliplatin, fluorouracil, and leucovorin in patients with advanced colorectal carcinoma previously treated with fluorouracil: N9841. J Clin Oncol 2009;27:2848-2854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19380443.

609. Segelov E, Chan D, Shapiro J, et al. The role of biological therapy in metastatic colorectal cancer after first-line treatment: a meta-analysis of randomised trials. Br J Cancer 2014;111:1122-1131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25072258.

610. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol 2013;14:29-37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23168366.

611. Kubicka S, Greil R, Andre T, et al. Bevacizumab plus chemotherapy continued beyond first progression in patients with metastatic colorectal cancer previously treated with bevacizumab plus chemotherapy: ML18147 study KRAS subgroup findings. Ann Oncol 2013;24:2342-2349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23852309.

612. Masi G, Loupakis F, Salvatore L, et al. Second-line chemotherapy (CT) with or without bevacizumab (BV) in metastatic colorectal cancer (mCRC) patients (pts) who progressed to a first-line treatment containing BV: Updated results of the phase III "BEBYP" trial by the Gruppo Oncologico Nord Ovest (GONO) [abstract]. ASCO Meeting Abstracts 2013;31:3615. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/3615.

613. Cartwright TH, Yim YM, Yu E, et al. Survival outcomes of bevacizumab beyond progression in metastatic colorectal cancer patients treated in US community oncology. Clin Colorectal Cancer 2012;11:238-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22658457.

614. Grothey A, Flick ED, Cohn AL, et al. Bevacizumab exposure beyond first disease progression in patients with metastatic colorectal cancer: analyses of the ARIES observational cohort study.

Pharmacoepidemiol Drug Saf 2014;23:726-734. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24830357.

615. Peeters M, Price TJ, Cervantes A, et al. Final results from a randomized phase 3 study of FOLFIRI {+/-} panitumumab for second-line treatment of metastatic colorectal cancer. Ann Oncol 2014;25:107-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24356622.

616. Seymour MT, Brown SR, Middleton G, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol 2013;14:749-759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23725851.

617. Saltz L, Rubin M, Hochster H, et al. Cetuximab (IMC-C225) Plus Irinotecan (CPT-11) is Active in CPT-11-Refractory Colorectal Cancer (CRC) that Expresses Epidermal Growth Factor Receptor (EGFR) [abstract]. Proc Am Soc Clin Oncol 2001;20:7. Available at:

618. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:2311-2319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18390971.

619. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol 2014;15:569-579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24739896.

620. Package Insert. ZALTRAP® (ziv-aflibercept). Bridgewater, NJ: Regeneron Pharmaceuticals, Inc. / sanofi-aventis U.S. LLC; 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125418s020lbl.pdf. Accessed August 15, 2014.

621. Tabernero J, Van Cutsem E, Lakomy R, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. Eur J Cancer 2014;50:320-331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24140268.

622. Package Insert. STIVARGA (regorafenib) tablets, oral. Wayne, N.J.: Bayer HealthCare Pharmaceuticals; 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203085s001lbl.pdf. Accessed August 15, 2014.

623. Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. Invest New Drugs 2013;31:1078-1086. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23700287.

624. Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA 2014;311:1863-1869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24825641.

625. Delbeke D, Martin WH. PET and PET-CT for evaluation of colorectal carcinoma. Semin Nucl Med 2004;34:209-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15202102.

626. Adam R, Miller R, Pitombo M, et al. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. Surg Oncol Clin N Am 2007;16:525-536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17606192.

627. Chen J, Li Q, Wang C, et al. Simultaneous vs. staged resection for synchronous colorectal liver metastases: a metaanalysis. Int J Colorectal Dis 2011;26:191-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20669024.

628. Lykoudis PM, O'Reilly D, Nastos K, Fusai G. Systematic review of surgical management of synchronous colorectal liver metastases. Br J

Surg 2014;101:605-612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24652674.

629. Mayo SC, Pulitano C, Marques H, et al. Surgical management of patients with synchronous colorectal liver metastasis: a multicenter international analysis. J Am Coll Surg 2013;216:707-716; discussion 716-708. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23433970.

630. Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol 2007;14:3481-3491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17805933.

631. Slesser AA, Simillis C, Goldin R, et al. A meta-analysis comparing simultaneous versus delayed resections in patients with synchronous colorectal liver metastases. Surg Oncol 2013;22:36-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23253399.

632. Worni M, Mantyh CR, Akushevich I, et al. Is there a role for simultaneous hepatic and colorectal resections? A contemporary view from NSQIP. J Gastrointest Surg 2012;16:2074-2085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22972010.

633. Reddy SK, Zorzi D, Lum YW, et al. Timing of multimodality therapy for resectable synchronous colorectal liver metastases: a retrospective multi-institutional analysis. Ann Surg Oncol 2009;16:1809-1819. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18979139.

634. Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? J Am Coll Surg 2010;210:934-941. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20510802.

635. de Jong MC, van Dam RM, Maas M, et al. The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience. HPB (Oxford) 2011;13:745-752. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21929676.

636. De Rosa A, Gomez D, Brooks A, Cameron IC. "Liver-first" approach for synchronous colorectal liver metastases: is this a justifiable approach? J Hepatobiliary Pancreat Sci 2013;20:263-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23325126.

637. Jegatheeswaran S, Mason JM, Hancock HC, Siriwardena AK. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. JAMA Surg 2013;148:385-391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23715907.

638. Lam VW, Laurence JM, Pang T, et al. A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. HPB (Oxford) 2014;16:101-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23509899.

639. Mentha G, Roth AD, Terraz S, et al. 'Liver first' approach in the treatment of colorectal cancer with synchronous liver metastases. Dig Surg 2008;25:430-435. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19212115.

640. Mentha G, Majno P, Terraz S, et al. Treatment strategies for the management of advanced colorectal liver metastases detected synchronously with the primary tumour. Eur J Surg Oncol 2007;33 Suppl 2:S76-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18006267.

641. Van Dessel E, Fierens K, Pattyn P, et al. Defining the optimal therapy sequence in synchronous resectable liver metastases from colorectal cancer: a decision analysis approach. Acta Chir Belg 2009;109:317-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19943586.

642. Faron M, Bourredjem A, Pignon J-P, et al. Impact on survival of primary tumor resection in patients with colorectal cancer and unresectable metastasis: Pooled analysis of individual patients' data from four randomized trials [abstract]. ASCO Meeting Abstracts

2012;30:3507. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/3507.

643. Karoui M, Roudot-Thoraval F, Mesli F, et al. Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study. Dis Colon Rectum 2011;54:930-938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21730780.

644. Venderbosch S, de Wilt JH, Teerenstra S, et al. Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. Ann Surg Oncol 2011;18:3252-3260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21822557.

645. McCahill LE, Yothers G, Sharif S, et al. Primary mFOLFOX6 Plus Bevacizumab Without Resection of the Primary Tumor for Patients Presenting With Surgically Unresectable Metastatic Colon Cancer and an Intact Asymptomatic Colon Cancer: Definitive Analysis of NSABP Trial C-10. J Clin Oncol 2012;30:3223-3228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22869888.

646. Cirocchi R, Trastulli S, Abraha I, et al. Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable Stage IV colorectal cancer. Cochrane Database Syst Rev 2012;8:CD008997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22895981.

647. Ahmed S, Shahid RK, Leis A, et al. Should noncurative resection of the primary tumour be performed in patients with stage iv colorectal cancer? A systematic review and meta-analysis. Curr Oncol 2013;20:e420-441. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24155639.

648. Anwar S, Peter MB, Dent J, Scott NA. Palliative excisional surgery for primary colorectal cancer in patients with incurable metastatic disease. Is there a survival benefit? A systematic review. Colorectal Dis 2012;14:920-930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21899714.

649. Clancy C, Burke JP, Barry M, et al. A Meta-Analysis to Determine the Effect of Primary Tumor Resection for Stage IV Colorectal Cancer with Unresectable Metastases on Patient Survival. Ann Surg Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24849523.

650. Yang TX, Billah B, Morris DL, Chua TC. Palliative resection of the primary tumour in patients with Stage IV colorectal cancer: systematic review and meta-analysis of the early outcome after laparoscopic and open colectomy. Colorectal Dis 2013;15:e407-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23895669.

651. Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol 2009;27:6237-6242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19917862.

652. Joyce DL, Wahl RL, Patel PV, et al. Preoperative positron emission tomography to evaluate potentially resectable hepatic colorectal metastases. Arch Surg 2006;141:1220-1226; discussion 1227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17178965.

653. Pelosi E, Deandreis D. The role of 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) in the management of patients with colorectal cancer. Eur J Surg Oncol 2007;33:1-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17126522.

654. Gill S, Berry S, Biagi J, et al. Progression-free survival as a primary endpoint in clinical trials of metastatic colorectal cancer. Curr Oncol 2011;18 Suppl 2:S5-S10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21969810.

655. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol 2012;30:1030-1033. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22370321.

656. Chibaudel B, Bonnetain F, Shi Q, et al. Alternative end points to evaluate a therapeutic strategy in advanced colorectal cancer: evaluation of progression-free survival, duration of disease control, and time to failure of strategy--an Aide et Recherche en Cancerologie Digestive Group Study. J Clin Oncol 2011;29:4199-4204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21969501.

657. Carrera G, Garcia-Albeniz X, Ayuso JR, et al. Design and endpoints of clinical and translational trials in advanced colorectal cancer. a proposal from GROUP Espanol Multidisciplinar en Cancer Digestivo (GEMCAD). Rev Recent Clin Trials 2011;6:158-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21241233.

658. Claret L, Gupta M, Han K, et al. Evaluation of tumor-size response metrics to predict overall survival in Western and Chinese patients with first-line metastatic colorectal cancer. J Clin Oncol 2013;31:2110-2114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23650411.

659. Seo SI, Lim SB, Yoon YS, et al. Comparison of recurrence patterns between </=5 years and >5 years after curative operations in colorectal cancer patients. J Surg Oncol 2013;108:9-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23754582.

660. Pietra N, Sarli L, Costi R, et al. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. Dis Colon Rectum 1998;41:1127-1133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9749496.

661. Rodriguez-Moranta F, Salo J, Arcusa A, et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. J Clin Oncol 2006;24:386-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16365182.

662. Secco GB, Fardelli R, Gianquinto D, et al. Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. Eur J Surg Oncol 2002;28:418-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12099653.

663. Desch CE, Benson AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2005;23:8512-8519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16260687.

664. Figueredo A, Rumble RB, Maroun J, et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. BMC Cancer 2003;3:26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14529575.

665. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2007:CD002200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17253476.

666. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ 2002;324:813-813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11934773.

667. Tsikitis VL, Malireddy K, Green EA, et al. Postoperative surveillance recommendations for early stage colon cancer based on results from the clinical outcomes of surgical therapy trial. J Clin Oncol 2009;27:3671-3676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19564531.

668. Guyot F, Faivre J, Manfredi S, et al. Time trends in the treatment and survival of recurrences from colorectal cancer. Ann Oncol 2005;16:756-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15790673.

669. Primrose JN, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal

cancer: the FACS randomized clinical trial. JAMA 2014;311:263-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24430319.

670. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. CA Cancer J Clin 2006;56:160-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16737948.

671. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 2006;24:5313-5327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17060676.

672. Pfister DG, Benson AB, 3rd, Somerfield MR. Clinical practice. Surveillance strategies after curative treatment of colorectal cancer. N Engl J Med 2004;350:2375-2382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15175439.

673. Patel K, Hadar N, Lee J, et al. The lack of evidence for PET or PET/CT surveillance of patients with treated lymphoma, colorectal cancer, and head and neck cancer: a systematic review. J Nucl Med 2013;54:1518-1527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23776200.

674. Green RJ, Metlay JP, Propert K, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of Intergroup 0089. Ann Intern Med 2002;136:261-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11848723.

675. Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: american society of clinical oncology clinical practice guideline endorsement. J Clin Oncol 2013;31:4465-4470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24220554.

676. Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer. Cancer Care Ontario; 2012. Available at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=124839. Accessed January 9, 2014.

677. Hyder O, Dodson RM, Mayo SC, et al. Post-treatment surveillance of patients with colorectal cancer with surgically treated liver metastases. Surgery 2013;154:256-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23889953.

678. Litvka A, Cercek A, Segal N, et al. False-positive elevations of carcinoembryonic antigen in patients with a history of resected colorectal cancer. J Natl Compr Canc Netw 2014;12:907-913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24925201.

679. Lu YY, Chen JH, Chien CR, et al. Use of FDG-PET or PET/CT to detect recurrent colorectal cancer in patients with elevated CEA: a systematic review and meta-analysis. Int J Colorectal Dis 2013;28:1039-1047. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23407908.

680. Martin EW, Minton JP, Carey LC. CEA-directed second-look surgery in the asymptomatic patient after primary resection of colorectal carcinoma. Ann Surg 1985;202:310-317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4037904.

681. Desnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. Eur J Cancer Care (Engl) 2006;15:244-251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16882120.

682. Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther 2003;18:987-994. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14616164.

683. McGough C, Baldwin C, Frost G, Andreyev HJ. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy.

Br J Cancer 2004;90:2278-2287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15162154.

684. Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer: patient-reported symptoms 4 years after diagnosis. Cancer 2007;110:2075-2082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17849466.

685. Sprangers MA, Taal BG, Aaronson NK, te Velde A. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7720441.

686. Jansen L, Herrmann A, Stegmaier C, et al. Health-related quality of life during the 10 years after diagnosis of colorectal cancer: a population-based study. J Clin Oncol 2011;29:3263-3269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768465.

687. Mols F, Beijers T, Lemmens V, et al. Chemotherapy-Induced Neuropathy and Its Association With Quality of Life Among 2- to 11-Year Colorectal Cancer Survivors: Results From the Population-Based PROFILES Registry. J Clin Oncol 2013;31:2699-2707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23775951.

688. Denlinger CS, Barsevick AM. The challenges of colorectal cancer survivorship. J Natl Compr Canc Netw 2009;7:883-893; quiz 894. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19755048.

689. Faul LA, Shibata D, Townsend I, Jacobsen PB. Improving survivorship care for patients with colorectal cancer. Cancer Control 2010;17:35-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20010517.

690. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol 2006;24:3535-3541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16822843.

691. Meyerhardt JA, Giovannucci EL, Ogino S, et al. Physical activity and male colorectal cancer survival. Arch Intern Med 2009;169:2102-2108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20008694.

692. Campbell PT, Patel AV, Newton CC, et al. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. J Clin Oncol 2013;31:876-885. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23341510.

693. Kuiper JG, Phipps AI, Neuhouser ML, et al. Recreational physical activity, body mass index, and survival in women with colorectal cancer. Cancer Causes Control 2012;23:1939-1948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23053793.

694. Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: A meta-analysis of prospective cohort studies. Int J Cancer 2013;133:1905-1913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23580314.

695. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. Ann Oncol 2014;25:1293-1311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24644304.

696. Dignam JJ, Polite BN, Yothers G, et al. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. J Natl Cancer Inst 2006;98:1647-1654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17105987.

697. Sinicrope FA, Foster NR, Yothers G, et al. Body mass index at diagnosis and survival among colon cancer patients enrolled in clinical trials of adjuvant chemotherapy. Cancer 2013;119:1528-1536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23310947.

698. Campbell PT, Newton CC, Dehal AN, et al. Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 2012;30:42-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22124093.

699. Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA 2007;298:754-764. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17699009.

700. Meyerhardt JA, Sato K, Niedzwiecki D, et al. Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Natl Cancer Inst 2012;104:1702-1711. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23136358.

701. Fuchs MA, Sato K, Niedzwiecki D, et al. Sugar-sweetened beverage intake and cancer recurrence and survival in CALGB 89803 (Alliance). PLoS One 2014;9:e99816. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24937507.

702. Kushi LH, Byers T, Doyle C, et al. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2006;56:254-281; quiz 313-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17005596.

703. Hawkes AL, Chambers SK, Pakenham KI, et al. Effects of a telephone-delivered multiple health behavior change intervention (CanChange) on health and behavioral outcomes in survivors of colorectal cancer: a randomized controlled trial. J Clin Oncol 2013;31:2313-2321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23690410.

704. Hewitt M, Greenfield S, Stovall E, eds. From Cancer Patient to Cancer Survivor: Lost in Transition. Committee on Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine and National Research Council: National Academy of Sciences; 2006. Available at: http://www.nap.edu/catalog/11468.html.