National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Colon Cancer

V.1.2008

Continue

www.nccn.org

End User License Agreement

Colon Cancer Table of Contents
Staging, MS, References

National Comprehensive Cancer Network, Inc.

End User License Agreement for the NCCN Clinical Practice Guidelines in Oncology

IMPORTANT READ CAREFULLY: This End User License Agreement (the "Agreement") is a legal agreement between you (either an individual or an entity) and the National Comprehensive Cancer Network, Inc. ("NCCN") covering your use of one (1) PDF version of the NCCN Clinical Practice Guidelines in Oncology, which, together with any updates thereto, are hereinafter referred to collectively as the "Guidelines." BY VIEWING OR OTHERWISE ACCESING THE DATA CONTAINED IN THIS PDF, YOU AGREE TO BE BOUND BY THE TERMS AND CONDITIONS OF THIS LICENSE AGREEMENT. IF YOU DO NOT AGREE WITH THE TERMS OF THIS LICENSE AGREEMENT, DO NOT VIEW, ACCESS, OR USE THIS PDF AND RETURN THE PDF TO NCCN.

1. Grant of License. NCCN hereby grants to you a non-transferable, non-exclusive, limited license to access and use the Guidelines subject to the terms set forth in this License Agreement.

2. Proprietary Rights. You acknowledge that, as between you and NCCN, NCCN is the owner of all right, title and interest in and to the Guidelines, including, without limitation, all copyrights, trademarks, goodwill, derivative works, and other intellectual property and proprietary rights related thereto. Except for the limited rights expressly enumerated herein, you are not granted any rights relating to copyrights, trade names, trademarks (whether registered or unregistered) or any other rights, franchises or licenses with respect to the Guidelines or NCCN. You hereby agree that you shall not at any time dispute, challenge, or contest, directly or indirectly, NCCN's right, title and interest in and to the Guidelines, or assist or aid others to do so.

3. Restrictions on Use. You may not copy, transfer, reproduce, or create derivative works from, any part of the Guidelines for any reason. You may make and retain file copies of "Insubstantial Portions" of the Guidelines solely for your internal purposes. "Insubstantial Portions" means a quantity of data from the Guidelines that would not reasonably substitute for a comprehensive copy of the Guidelines and would not prejudice or diminish NCCN's advantage in licensing the Guidelines for commercial gain. Notwithstanding the foregoing, you may include Insubstantial Portions of the Guidelines in materials prepared in the ordinary course of your business for re-distribution to patients in connection with the delivery of your principal services. Any such materials shall cite NCCN as the source of the Guidelines and provide notice of NCCN's copyrights and other proprietary rights, as follows: © National Comprehensive Cancer Network, Inc. 2005/2006/2007. NCCN and NATIONAL COMPREHENSIVE CANCER NETWORK are registered trademarks of National Comprehensive Cancer Network, Inc. You shall provide NCCN with examples of re-distributed materials including any portion of the Guidelines upon NCCN's reasonable request, but shall not be required to provide confidential information to NCCN. You agree to immediately cease any such re-distribution on receipt of notice from NCCN that, in NCCN's reasonable judgment, such re-distribution involves more than an Insubstantial Portion of the Guidelines or is otherwise in violation of this Agreement.

4. Limited Warranty; Disclaimers; Limitation of Damages. The Guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

NCCN MAKES NO WARRANTIES CONCERNING THE GUIDELINES OR ANY ELECTRONIC DELIVERY MEDIA SUPPLIED BY NCCN, WHICH ARE PROVIDED "AS IS." NCCN DISCLAIMS ALL WARRANTIES, EXPRESS OR IMPLIED INCLUDING, WITHOUT LIMITATION, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. NCCN DOES NOT WARRANT THE ACCURACY OR COMPLETENESS OF THE GUIDELINES AND DOES NOT WARRANT OR GUARANTEE OR MAKE ANY REPRESENTATION REGARDING THE USE OR THE RESULTS OF THE USE OF THE GUIDELINES. IN NO EVENT SHALL NCCN OR ITS MEMBERS BE LIABLE FOR ANY INCIDENTAL, INDIRECT, SPECIAL, PUNITIVE OR CONSEQUENTIAL DAMAGES ARISING OUT OF OR IN CONNECTION WITH THE LICENSE GRANTED UNDER THIS AGREEMENT OR USE OF THE GUIDELINES INCLUDING, WITHOUT LIMITATION, LOSS OF LIFE, LOSS OF DATA, LOSS OF INCOME OR PROFIT, OR OTHER LOSSES SUSTAINED AS A RESULT OF INJURY TO ANY PERSON, OR LOSS OR DAMAGE TO PROPERTY, OR CLAIMS OF THIRD PARTIES, EVEN IF NCCN HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

SOME JURISDICTIONS DO NOT ALLOW THE LIMITATION OF IMPLIED WARRANTIES OR LIABILITY FOR INCIDENTAL, INDIRECT, SPECIAL, PUNITIVE OR CONSEQUENTIAL DAMAGES, SO THE ABOVE LIMITATIONS MAY NOT APPLY.

FOR ANY CLAIM YOU MAY HAVE AGAINST NCCN UNDER THIS AGREEMENT, YOUR EXCLUSIVE REMEDY AND NCCN'S ENTIRE LIABILITY SHALL BE TO PROVIDE REPLACEMENT GUIDELINES TO YOU.

5. Trademarks. NCCN and the NATIONAL COMPREHENSIVE CANCER NETWORK are trademarks (the "Marks") of the National Comprehensive Cancer Network, Inc. and nothing in this Agreement shall constitute a license with respect to such trademarks. You shall not use the Marks or any confusingly similar Marks for any purpose, including, without limitation, for purposes of marketing or promoting your services, without the prior written approval of NCCN, which approval may be withheld in NCCN's sole discretion. Each approved use of the Marks shall require the independent written approval of NCCN.

6. General. This Agreement contains the entire agreement between NCCN and you relating to its subject matter. No amendment, change, or modification of this Agreement shall be binding on either party unless mutually agreed to by the parties in writing. If any provision of this Agreement is held to be invalid or unenforceable by a court of competent jurisdiction, the validity and enforceability of the remaining provisions shall not be affected thereby. This Agreement will be governed by and construed in accordance with the laws of the Commonwealth of Pennsylvania without giving any effect to the conflict of law provisions thereof, and each party agrees to submit to personal jurisdiction in the federal and state courts of Pennsylvania and waives any objection to venues in said courts. This Agreement will not be governed by the United Nations Conventions of Contracts for the International Sale of goods, the application of which is expressly excluded. You agree that the Guidelines will not be shipped, transferred or exported into any country or used in any manner prohibited by the United States Export Administration Act, or any other export laws, restrictions. This Agreement will terminate automatically upon failure by you to comply with its terms.

BY ACCESSING THE DATA CONTAINED IN THIS PDF, YOU ACKNOWLEDGE THAT YOU HAVE READ THIS AGREEMENT, UNDERSTAND IT, AND AGREE TO BE BOUND BY ITS TERMS AND CONDITIONS.

Click Here to Continue

NCCN Colon Cancer Panel Members

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

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

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

Yi-Jen Chen, MD, PhD §
City of Hope

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

Harry S. Cooper, MD ≠
Fox Chase Cancer Center

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

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

Marwan G. Fakih, MD †
Roswell Park Cancer Institute

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

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

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

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

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

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

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

Kirk A. Ludwig, MD ¶
Duke Comprehensive Cancer Center

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

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

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

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

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

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

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

Continue

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

Table of Contents

For help using these documents or for more information about the NCCN Guidelines and the Complete Library of Clinical Practice Guidelines in Oncology, please click here

Staging
Manuscript
References

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

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

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

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

See NCCN Categories of Evidence and Consensus

Print the Colon Cancer Guideline

Order the Patient Version of the Colon Cancer Guideline

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.

Summary of the Guidelines updates

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

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

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

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

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

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

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

COL-A - Principles of Pathologic Review:
- COL-A 1 of 3
  - Bullet 4 under "Endoscopically removed polyps" is new.
- COL-A 2 of 3
  - Under "Lymph node evaluation", the sentences beginning with "For stage II (pN0) colon cancer..." and ending "for patients with stage IIIB and IIIC colon cancer" are new to the bullet.
  - Under "Sentinel lymph node", the sentences beginning with "While the 6th Edition of the AJCC..." and ending "...invasion of the vessel (lymphatic) wall" are new to the first bullet.

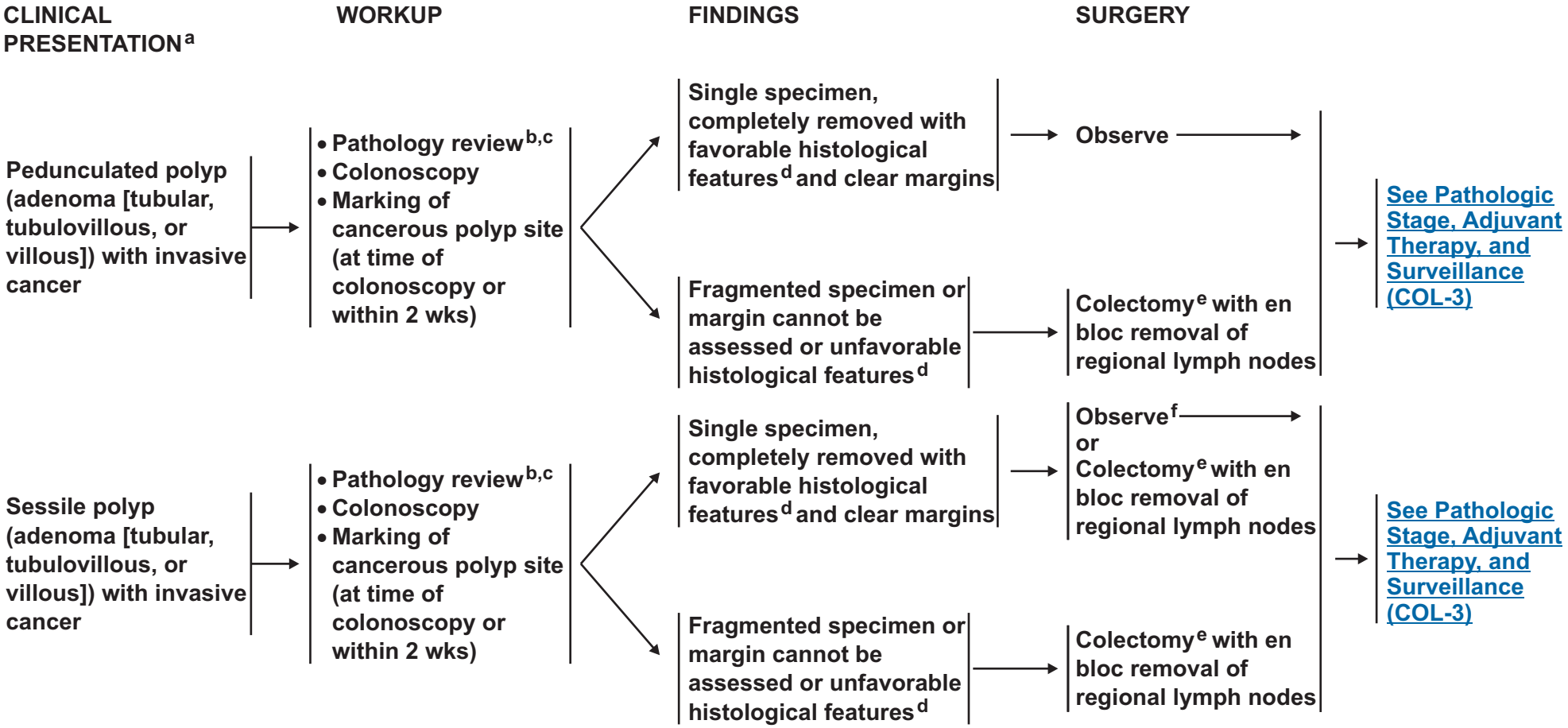
COL-B 3 of 4 - Principles of Surgery:
- The bullet "Plans for a debulking resection (< R0 resection) is not recommended" was added.
- "All original sites of disease need to be resectable" was added to the bullet "Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant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

COL-C - Chemotherapy for Advanced or Metastatic Disease:
- A clarifying statement was added that cetuximab or panitumumab single agent therapy is for patients not able to tolerate cetuximab + irinotecan. (COL-C 1 of 5)
- A bi-weekly schedule for the administration of cetuximab at 500 mg/m^2 was added (COL-C 4 of 5)

COL-E 3 of 3 - Principles of Adjuvant Therapy:
- Bullet 2 - The following statement was added "FOLFOX is reasonable for high risk or intermediate risk stage II patients and is not indicated for good or average risk stage II patients. FLOX is an alternative to FOLFOX."
- Bullet 3 - The statement was modified to include "infusional 5-FU/leucovorin/irinotecan (FOLFIRI) has not been shown to be superior to 5-FU/LV".

Colon Cancer

Colon Cancer Table of Contents
Staging, MS, References



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

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

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

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

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

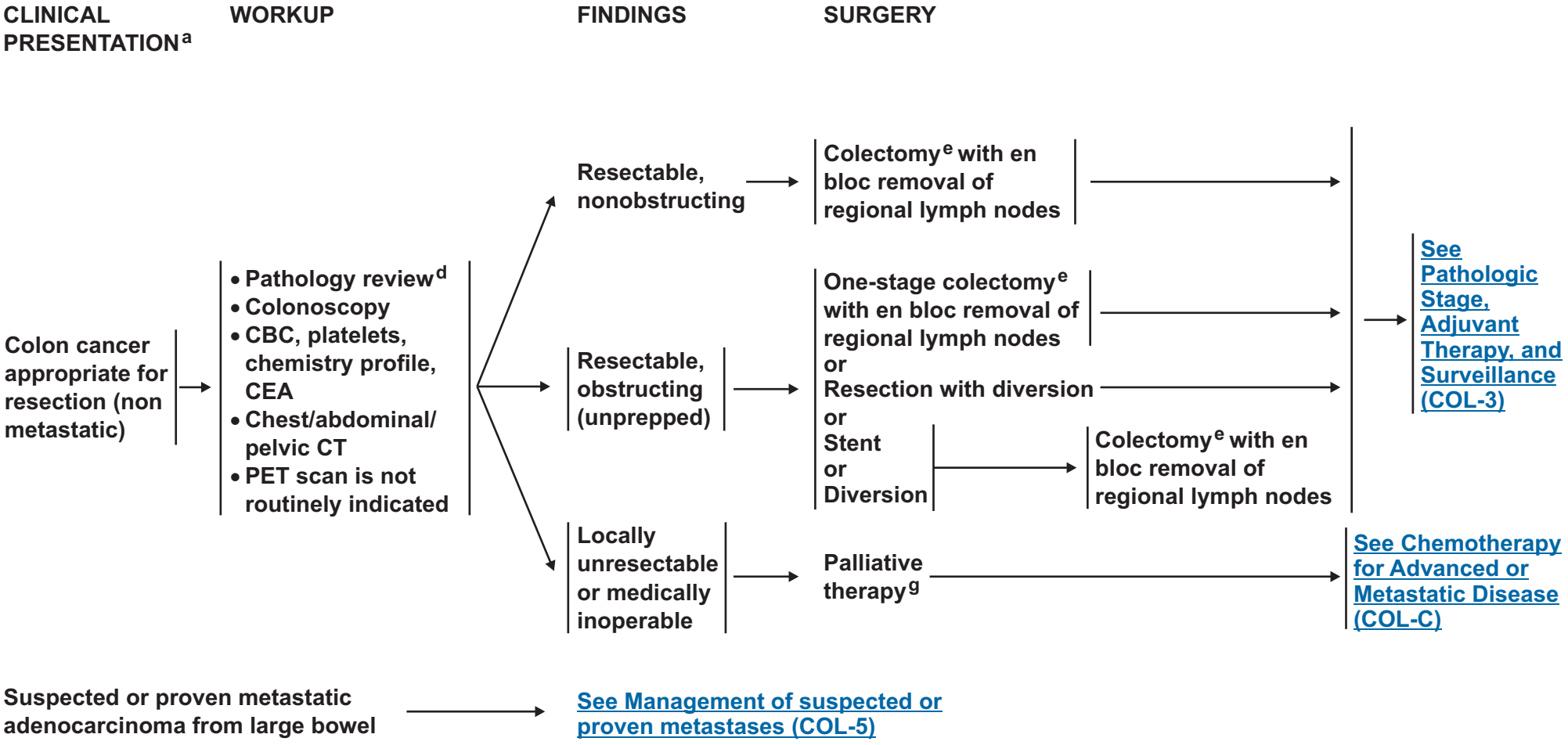
[f] Observation may be considered, with the understanding that there is an added 10-15% risk of lymph node metastases. Nivatvongs S, Rojanasakul A, Reiman HM, et al. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. Dis Colon Rectum 1991;34(4):323-8.

Back to Other Clinical Presentations (Table of Contents)

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

Colon Cancer

Colon Cancer Table of Contents
Staging, MS, References



Suspected or proven metastatic adenocarcinoma from large bowel → [See Management of suspected or proven metastases (COL-5)]

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

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

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

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

Back to Other Clinical Presentations (Table of Contents)

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.

Colon Cancer

Colon Cancer Table of Contents
Staging, MS, References

PATHOLOGIC STAGE[d]	ADJUVANT THERAPY[h,j]	SURVEILLANCE[o]
Tis; T1, N0, M0; T2, N0, M0	None	• History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y • CEA[q] every 3-6 mo for 2 y, then every 6 mo for a total of 5 y for T2 or greater lesions • Chest/abdominal/pelvic CT may be considered annually x 3 y for patients at high risk for recurrence[o,p] • Colonoscopy[a] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo ▸ If abnormal, repeat in 1 y ▸ If advanced adenoma,[r] repeat in 3 y, then every 5 y[s] • PET scan is not routinely recommended
T3, N0, M0[i] (no high risk features)	Consider capecitabine[k,l] or 5-FU/leucovorin[k,l] or 5-FU/leucovorin/oxaliplatin[k,l,m] (category 2B for all options) or Clinical trial or Observation[k]	
T3, N0, M0 at high risk for systemic recurrence (grade 3-4, lymphatic/vascular invasion, bowel obstruction, < 12 lymph nodes examined) or T4, N0, M0; or T3 with localized perforation or close, indeterminate or positive margins	5-FU/leucovorin/oxaliplatin[k,l,m,n] or capecitabine[k,l,n] or 5-FU/leucovorin[k,l,n] or Clinical trial or Observation[k]	

See Recurrence and Workup (COL-9)

Node positive disease, see page COL-4

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

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

[h] There are no data to support adjuvant therapy in Stage I disease, however certain high risk Stage II patients (perivascular invasion, poorly differentiated histology, inadequate lymph node sampling) may be considered at higher risk and a discussion of chemotherapy may be warranted.

[i] Patients considered to be N0 but who have < 12 nodes examined are suboptimally staged and should be considered in the high risk group. See Principles of Pathologic Review (COL-A) - Lymph node evaluation.

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

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

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

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

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

[o] Desch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23:8512-8519.

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

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

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

[s] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130:1865-71.

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.

PATHOLOGIC STAGE[d]	ADJUVANT THERAPY[j]	SURVEILLANCE[o]
T1-3, N1-2, M0 or T4, N1-2, M0	5-FU/leucovorin/oxaliplatin (category1)[k,m,n] or Capecitabine[k,n] or 5-FU/leucovorin[k,n]	• History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y • CEA[q] every 3-6 mo for 2 y, then every 6 mo for a total of 5 y for T2 or greater lesions • Chest/abdominal/pelvic CT annually x 3 y for patients at high risk for recurrence[o,p] • Colonoscopy[a] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo ► If abnormal, repeat in 1 y ► If advanced adenoma,[r] repeat in 3 y, then every 5 y[s] • PET scan is not routinely recommended

See Recurrence and Workup (COL-9)

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

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

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

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

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

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

[o] Desch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23:8512-8519.

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

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

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

[s] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130:1865-71.

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.

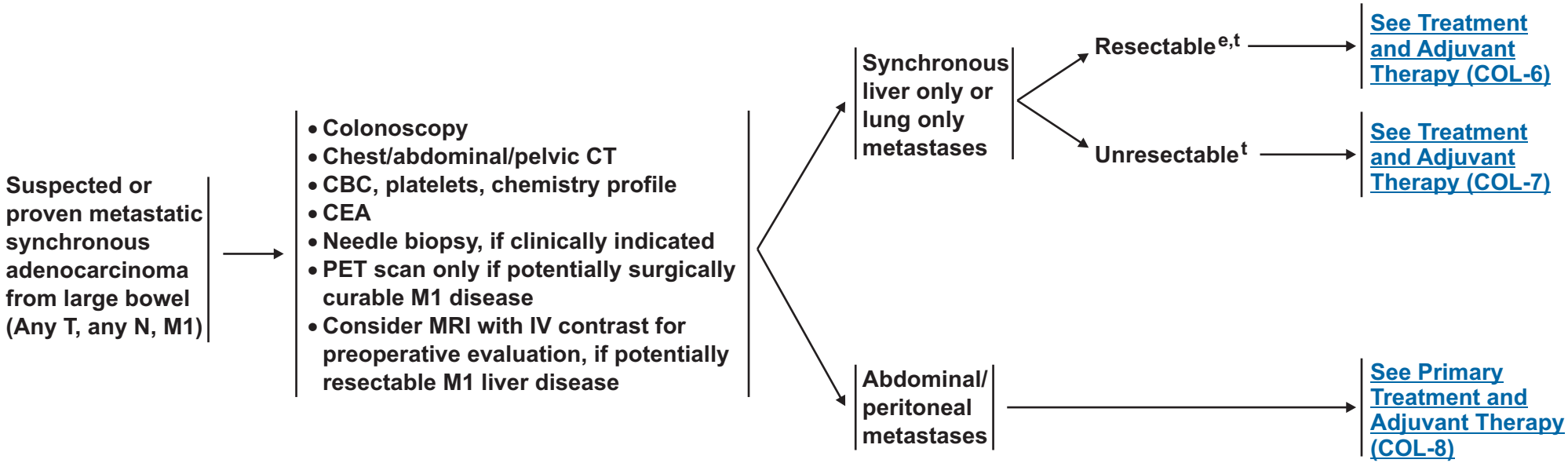
Colon Cancer

Colon Cancer Table of Contents
Staging, MS, References

CLINICAL PRESENTATION

WORKUP

FINDINGS



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

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

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

Colon Cancer

Colon Cancer Table of Contents
Staging, MS, References

TREATMENT	ADJUVANT THERAPY (resected metastatic disease) (6 mo preferred)	SURVEILLANCE
Resectable[e] synchronous liver only or lung only metastases → **Colectomy, with synchronous or subsequent liver or lung resection or Neoadjuvant therapy[u] (FOLFIRI or FOLFOX or CapeOX[v] ± bevacizumab[w]) followed by synchronous or staged colectomy and resection of metastatic disease or Colectomy, followed by chemotherapy[u] (FOLFIRI or FOLFOX or CapeOX[v] ± bevacizumab[w]) and staged resection of metastatic disease**	**Active chemotherapy regimen for advanced disease (See Chemotherapy for Advanced or Metastatic Disease (COL-C)) (category 2B) or Hepatic artery infusion therapy[x] ± systemic 5-FU/leucovorin (category 2B) or continuous IV 5-FU - liver metastases only or Consider observation or shortened course of chemotherapy, if patient received neoadjuvant therapy**	**If patient stage IV, NED:** • **CEA every 3 mo x 2 y, then every 6 mo x 3-5 y** • **Chest/abdominal/pelvic CT scan every 3-6 mo x 2 y, then every 6-12 mo up to a total of 5 y** • **Colonoscopy[a] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo** ▸ **If abnormal, repeat in 1 y** ▸ **If advanced adenoma,[r] repeat in 3 y, then every 5 y[s]** → **Recurrence (See COL-9)**

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

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

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

[s] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130(6):1865-71.

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

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

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

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

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.

Colon Cancer

Colon Cancer Table of Contents
Staging, MS, References

TREATMENT

Unresectable synchronous liver only or lung only metastases

- Systemic therapy[u] (FOLFIRI or FOLFOX or CapeOX[v] ± bevacizumab[w])
  - Converted to resectable → Synchronized or staged resection[e] of colon and metastatic cancer
  - Remains unresectable → See Chemotherapy for Advanced or Metastatic Disease (COL-C)
- Consider colon resection only if imminent risk of obstruction or significant bleeding
- Consider colon resection and ablative therapy[e] (category 2B) - liver metastases only

ADJUVANT THERAPY (6 mo preferred)

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

SURVEILLANCE

If patient stage IV, NED:

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

Recurrence (See COL-9)

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

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

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

[s] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130(6):1865-71.

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

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

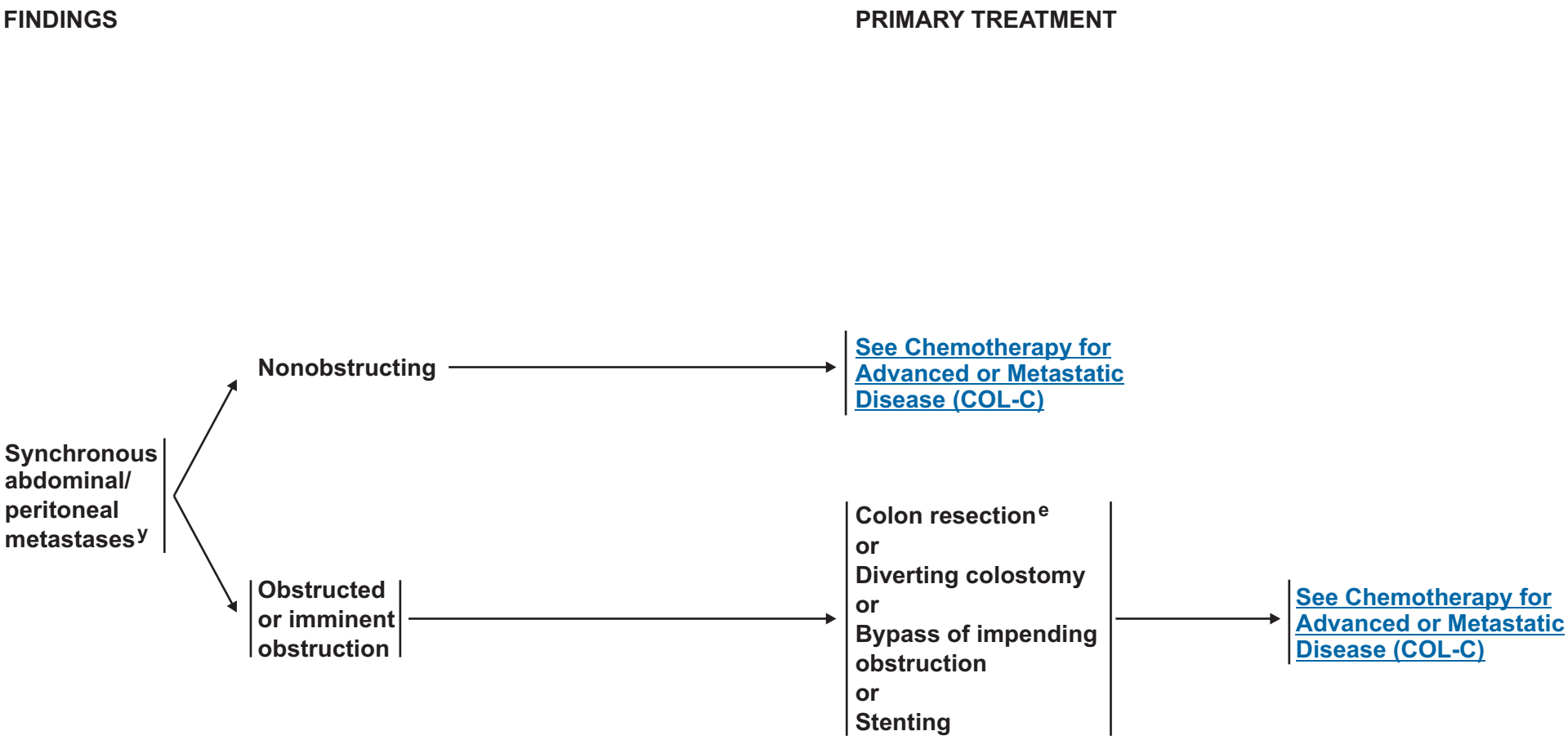
[w] The safety of administering bevacizumab pre or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6 wk interval between the last dose of bevacizumab and elective surgery. There is an increased risk of stroke and other arterial events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

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

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.

Colon Cancer

Colon Cancer Table of Contents
Staging, MS, References

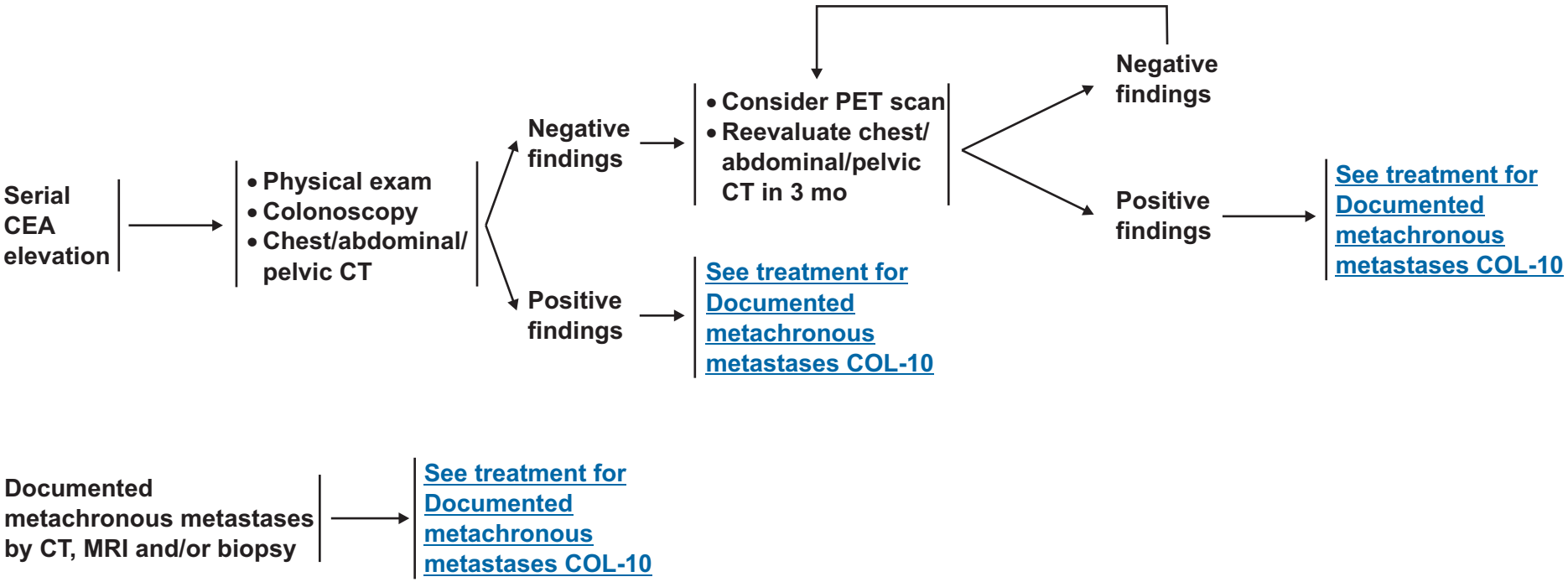


[e] See Principles of Surgery (COL-B).

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

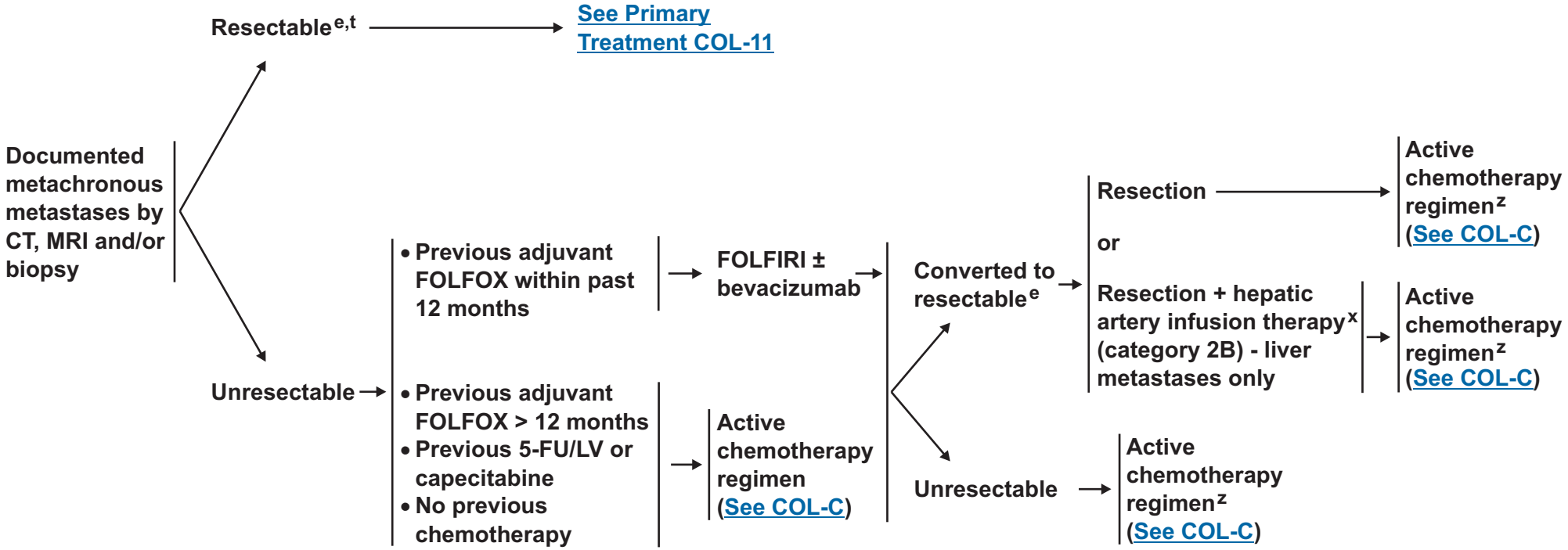
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RECURRENCE **WORKUP**



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.

PRIMARY TREATMENT

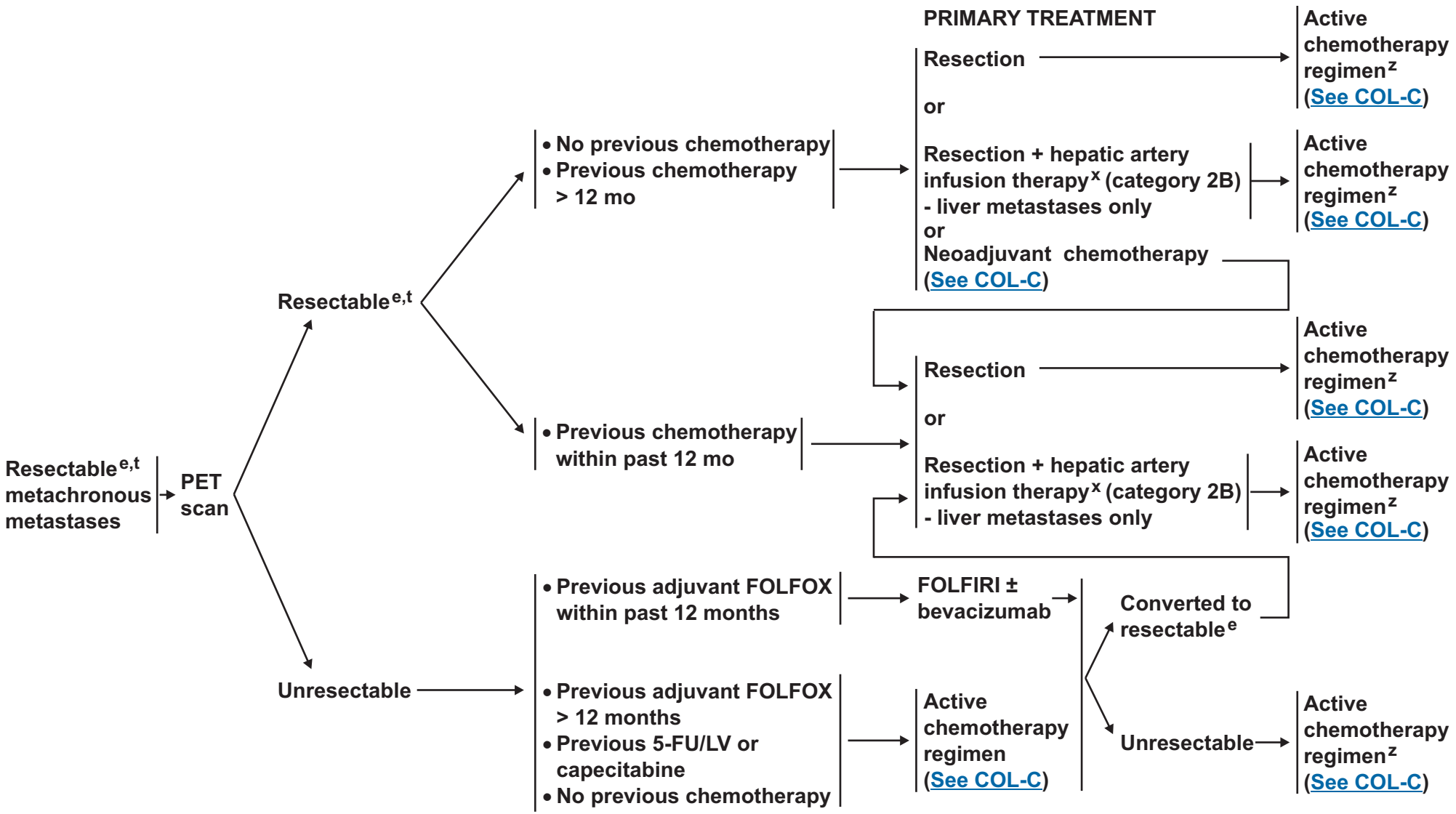


[e] See Principles of Surgery (COL-B).
[t] Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.
[x] Should be performed at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[z] If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

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.

Colon Cancer

Colon Cancer Table of Contents
Staging, MS, References



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

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

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

[z] If patient has seen all active chemotherapy regimens, observation is an option.

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 PATHOLOGIC REVIEW (1 of 3)

Endoscopically removed malignant polyps

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

Colon cancer appropriate for resection

- Histological confirmation of primary colonic malignant neoplasm

Pathological stage

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

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

See footnotes on page 3 of 3 COL-A

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 PATHOLOGIC REVIEW (2 of 3)

Lymph node evaluation

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

Sentinel lymph node and detection of micrometastasis by immunohistochemistry

- Examination of the sentinal lymph node allows an intense histological and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple H & E sections and/or immunohistochemistry (IHC) to detect cytokeratin positive cells. While studies to date seem promising, there is no uniformity in the definition of what constitutes "true metastatic carcinoma." Confusion arises when isolated tumors cells (ITC) have been considered micrometastatic disease in contraindication to true micrometastasis (tumor aggregates > 0.2 mm to < 2 mm in size). The significance of detection of single cells by IHC alone is controversial. Some studies have considered these to be micrometastasis, however, “consensus” recommends these to be considered ITC and not micrometastatic disease.[21-25] While the 6th edition of the AJCC Cancer Staging[26] manual considers "tumor clusters" < 0.2 mm as isolated tumor cells (pN0) and not metastatic carcinoma, some have challenged this. Some investigators believe that size should not effect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.[27] Hermanek et al[28] proposed isolated tumor cells to be defined as single tumor cells or small clusters (never more than a few cells clumped together) without evidence of extrasinusoidal stromal proliferation or reaction and no contact with or invasion of the vessel (lymphatic) wall.
- Some studies have shown that the detection of IHC cytokeratin positive cells in stage II (N0) colon cancer (defined by H & E) has a worse prognosis while others have failed to show this survival difference. In these studies, ITC were considered micrometastasis.[29-33]
- At the present time the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and results used with caution in clinical management decisions.[21-25,29-33]

See Malignant polyp, colon cancer appropriate for resection, and pathological stage on page 1 of 3 COL-A

See footnotes on page 3 of 3 COL-A

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 PATHOLOGIC REVIEW (3 of 3)
References

[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]Sobin HL, and Greene FL. TNM classification. Clarification of number of regional lymph node for pN0. Cancer 2001;92(2):452.

[11]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.

[12]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.

[13]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.

[14]Chaplin 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.

[15]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.

[16]Procard M, Panis Y, Malassagane B, et al. Assessing the effectiveness of mesorectal excision in rectal cancer. Dis Colon Rectum 1998;41:839-845.

[17]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.

[18]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.

[19]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.

[20]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.

[21]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.

[22]Saha S, Van AG, Beutler T, et al. Sentinal lymph mapping techniques in colorectal cancer. Sem Oncol 2004;31:374-81.

[23]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.

[24]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.

[25]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.

[26]AJCC Cancer Staging Manual, 6th ed. Greene FL, Page D, Balch C, et al (editors) Springer, New York, 2002:227.

[27]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.

[28]Hermanek P, Hutter RVP, Sobin LH, Wittekind CH. Classification of isolated tumor cells and micrometastasis. Cancer 1999;86:2668-73.

[29]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.

[30]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.

[31]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.

[32]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.

[33]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.

PRINCIPLES OF SURGERY (1 of 4)

Colectomy

- **Lymphadenectomy**
  - Lymph nodes at the origin of feeding vessel should be identified for pathologic exam.
  - Lymph nodes outside the field of resection considered suspicious should be biopsied or removed.
  - Positive nodes left behind indicate an incomplete (R2) resection.
  - A minimum of 12 lymph nodes need to be examined to clearly establish stage II (T 3-4, N0) colon cancer.
  - Even for Stage III disease, the number of lymph nodes correlates with survival.[1]
- **Laparoscopic-assisted colectomy may be considered based upon the following criteria:**[2]
  - Surgeon with experience performing laparoscopically-assisted colorectal operations.[3,4]
  - No disease in rectum or prohibitive abdominal adhesions.
  - No advanced local or metastatic disease.
  - Not indicated for acute bowel obstruction or perforation from cancer.
  - Thorough abdominal exploration is required[5]
  - Consider preoperative marking of small lesions.
- **Management of patients with carrier status of known HNPCC**
  - Consider more extensive colectomy for patients with a strong family history of colon cancer or young age (< 50 y). See NCCN Colorectal Cancer Screening Guidelines
- **Resection needs to be complete to be considered curative.**

See Criteria for Resectability of Metastases on page 3 of 4 COL-B

See footnotes on page 2 of 4 COL-B

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 SURGERY (2 of 4)
REFERENCES

[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.

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 SURGERY (3 of 4)
CRITERIA FOR RESECTABILITY OF METASTASES

Liver

- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of adequate hepatic function is required.[1,2]
- Plan for a debulking resection (less than an R0 resection) is not recommended.
- There should be no unresectable extrahepatic sites of disease.[3,4,5]
- Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant therapy.[6,7] All original sites of disease need to be resectable.
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.[8]
- Ablative techniques may be considered when all known disease is amenable to ablation.[8]
- Solitary lesions have a better prognosis than multiple liver metastases[9]
- Intra-arterial embolization should not be routinely used outside the setting of a clinical trial.
- The primary tumor must have been resected for cure (R0).
- Re-resection can be considered in selected patients.[10]

Lung

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

See footnotes on page 4 of 4 COL-B

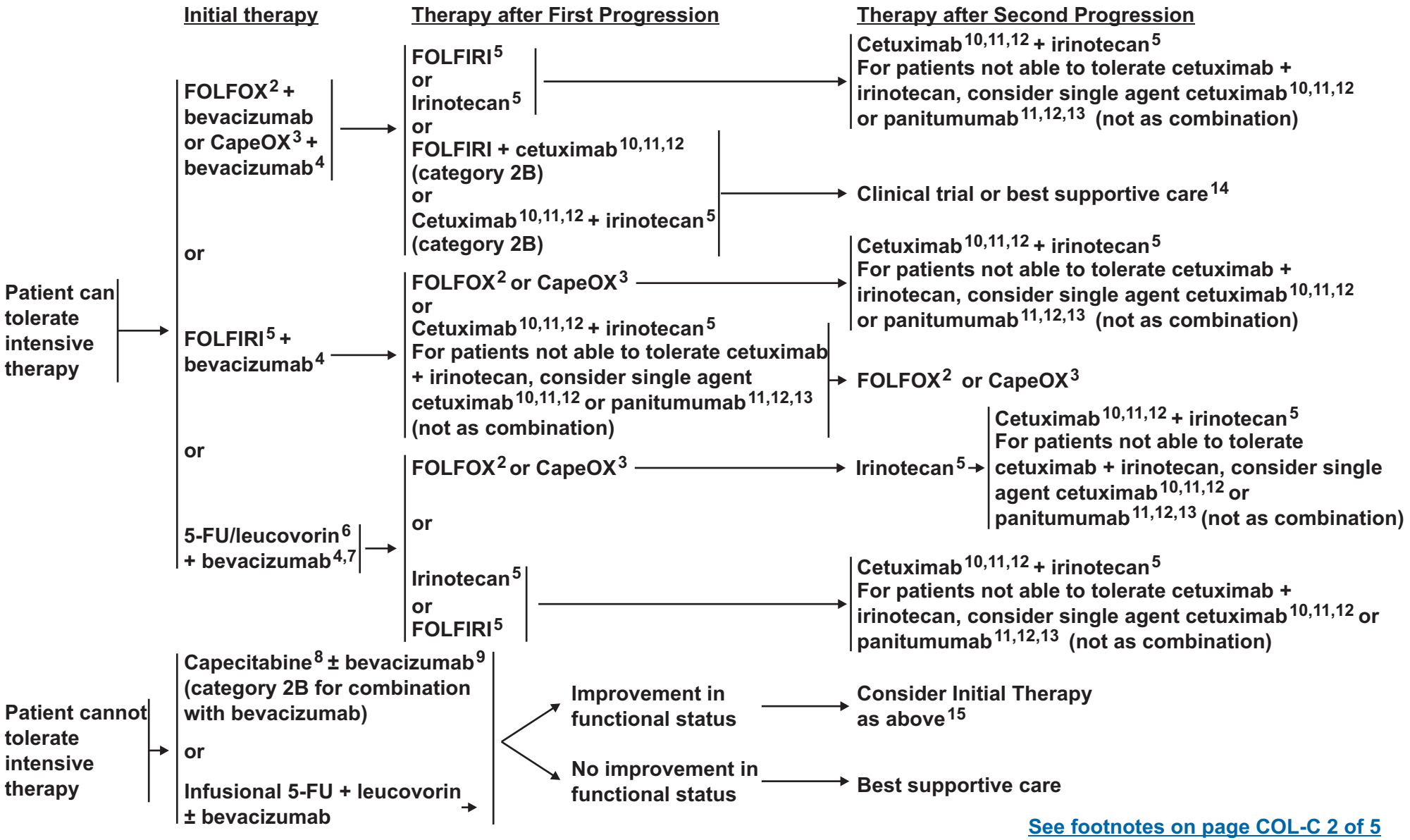
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SURGERY (4 of 4)
CRITERIA FOR RESECTABILITY OF METASTASES - REFERENCES

[1]Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. Registry of Hepatic Metastases. Surgery 1988;103:278-288.
[2]Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. Surgery 1986;100:278-284.
[3]Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. J Clin Oncol 1997;15:938-946.
[4]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.
[5]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.
[6]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.
[7]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.
[8]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.
[9]Goldberg RM, Fleming TR, Tangen CM, et al. Surgery for recurrent colon cancer: strategies for identifying resectable recurrence and success rates after resection. Eastern Cooperative Oncology Group, the North Central Cancer Treatment Group, and the Southwest Oncology Group. Ann Intern Med 1998;129:27-35.
[10]Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. Ann Surg 1997;225:51-62.
[11]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.
[12]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.
[13]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.
[14]Sakamoto T, Tsubota N, Iwanaga K, Yuki T, Matsuoka H, Yoshimura M. Pulmonary resection for metastases from colorectal cancer. Chest 2001;119:1069-1072.
[15]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.
[16]Irshad K, Ahmad F, Morin JE, Mulder DS. Pulmonary metastases from colorectal cancer: 25 years of experience. Can J Surg 2001;44:217-221.
[17]Ambiru S, Miyazaki M, Ito H, et al. Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 1998;82:274-278.
[18]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.
[19]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.

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.

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



See footnotes on page COL-C 2 of 5

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.

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 2 of 5)

[1] For chemotherapy references, see Chemotherapy Regimens and References (COL-C pages 3 - 5).

[2] Discontinuation of oxaliplatin is strongly considered from FOLFOX or CapeOX after 3 months of therapy or sooner if significant neurotoxicity develops (> grade 3) with other drugs maintained (fluoropyrimidine + bevacizumab) until time of tumor progression. Oxaliplatin may be reintroduced if it was discontinued previously for neurotoxicity rather than disease progression. 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. Ca/Mg infusions should not be used to reduce neurotoxicuty because treatment reduces rate of response to FOLFOX.

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

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

[5] 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.

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

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

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

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

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

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

[12] 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.

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

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

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

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.

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 3 of 5)

CHEMOTHERAPY REGIMENS

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

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

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

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

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

Bevacizumab + 5-FU containing regimens:[7,8,9]
Bevacizumab 5 mg/kg IV every 2 weeks +
5-FU and Leucovorin
or FOLFOX[10]
or FOLFIRI
Bevacizumab 7.5 mg/kg IV every 3 weeks + CapeOX[4]

*Leucovorin dose in Europe is 200 mg/m^2 of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2/day over 46 hours) to minimize medication errors.

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

See footnotes on page 5 of 5 COL-C

See Additional Chemotherapy Regimens 4 of 5 COL-C

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.

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 4 of 5)

CHEMOTHERAPY REGIMENS

Capecitabine[11]
2000-2500 mg/m^2/day PO in two divided doses, days 1-14, followed by 7 days rest
Repeat every 3 weeks

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

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

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

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

Irinotecan[17,18]
Irinotecan 125 mg/m^2 IV over 30-90 minutes, days 1, 8, 15, 22
Repeat every 6 weeks

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

Cetuximab ± irinotecan[19]
Cetuximab 400 mg/m^2 1st infusion, then 250 mg/m^2 weekly
or
Cetuximab 500 mg/m^2 every 2 weeks[20]
±
Irinotecan
300-350 mg/m^2 IV every 3 weeks
or
180 mg/m^2 IV every 2 weeks
or
125 mg/m^2 every week for 4 weeks
Every 6 weeks

Panitumumab[21]
Panitumumab 6 mg/kg IV administered over 60 minutes every 2 weeks

*Leucovorin dose in Europe is 200 mg/m^2 of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2/day over 46 hours) to minimize medication errors.

See footnotes on page 5 of 5 COL-C

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.

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

CHEMOTHERAPY REFERENCES

[1] Goldberg R, 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.

[2] Cheeseman S, Joel S, Chester J, et al. A "modified de Gramont" regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Brit J Cancer 2002;87:393-399.

[3] Cassidy J, Clarke S, Diaz Rubio E, et al. First efficacy and safety results from Xelox-1/NO16966, a randomized 2 x 2 factorial phase III trial of Xelox vs Folfox4 + bevacizumab or placebo in first-line metastatic colorectal cancer. Ann Oncol;17(suppl 9):late breaking abstract #3.

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

[5] Douillard J, Cunningham D, Roth A 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;355:1041-1047.

[6] 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.

[7] 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.

[8] 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.

[9] 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.

[10] Giantonio BJ, Catalano PJ, Meropol NJ, et al. High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200. 2005 ASCO Gastrointestinal Cancers Symposium;Abstract 169a.

[11] 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.

[12] 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.

[13] 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.

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

[15] 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.

[16] 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.

[17] 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.

[18] 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.

[19] 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.

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

[21] 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.

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]

- **Ask the patient how much information they would like to know regarding prognosis.**
- **Patient/physician discussion regarding the potential risks of therapy compared to potential benefits. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk prognostic characteristics and patient preferences.**
- **When determining if adjuvant therapy should be administered, the following should be taken into consideration:**
  - **Number of lymph nodes analyzed after surgery**
  - **Poor prognostic features (eg, T4 lesion, perforation, peritumoral lymphovascular involvement, poorly differentiated histology)**
  - **Assessment of other comorbidities and anticipated life expectancy.**
- **The benefit of adjuvant chemotherapy does not improve survival by more than 5 percent.**

[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.

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

PRINCIPLES OF ADJUVANT THERAPY (1 of 3)

5-FU/leucovorin

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

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

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

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

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

*Leucovorin dose in Europe is 200 mg/m^2 of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m^2.

**NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2/day over 46 hours) to minimize medication errors.

See footnotes on page 2 of 3 COL-E

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

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

PRINCIPLES OF ADJUVANT THERAPY (2 of 3)

[1]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.

[2]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.

[3]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.

[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]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.

[6]deGramont A, Boni C, Navarro M, et al. Oxaliplatin/5-FU/LV in adjuvant colon cancer: updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of 6 years. J Clin Oncol 2007;25:18S (June 20 suppl). Abstract 4007.

[7]Cheeseman S, Joel S, Chester J, et al. A “modified de Gramont” regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Brit J Cancer 2002;87:393-399.

[8]Welles L, Hochster H, Ramanathan R et al. Preliminary results of a randomized study of safety and tolerability of three oxaliplatin-based regimens as first-line treatment for advanced colorectal cancer (”Tree” study). J Clin Oncol 2004;23:Abstract 3537.

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

PRINCIPLES OF ADJUVANT THERAPY (3 of 3)

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

[1] 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.
[2] Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-51.
[3] deGramont A, Boni C, Navarro M, et al. Oxaliplatin/5-FU/LV in adjuvant colon cancer: updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of 6 years. J Clin Oncol 2007;25:18S (June 20 suppl). Abstract 4007.
[4] Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007;25:2198-2204.
[5] Saltz LB, Niedzwieecki D, Hollis D, et al. Irinotecan plus fluorouracil/leucovorin (IFL) versus fluorouracil/leucovorin alone (FL in stage III colon cancer (intergroup trial CALGB C89803). J Clin Oncol 2004;23:Abstract 3500.
[6] Van Custem E, Labianca R, Hossfield D, et al. Randomized phase III trial comparing infused irinotecan/5-fluorouracil (5-FU)/folinic acid (IF) versus 5-FU/FA in stage III colon cancer patients (PETACC3). J Clin Oncol 2005;23:No 16S(june 1 suppl). Abstract 8.
[7] Ychou M, Raoul J, Douillard J, et al. A phase III randomized trial of LV5FU2 + CPT-11 versus LV5FU2 alone in high risk colon cancer (FNCLCC Accord02/FFCD9802). J Clin Oncol 2005;23:No 16S(June 1 suppl). Abstract 3502

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 RADIATION THERAPY

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

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

Staging

Table 1

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

Primary Tumor (T)

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

Regional Lymph Nodes (N)§

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

Distant Metastasis (M)

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

Stage Grouping

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

Histologic Grade (G)

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

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

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

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

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

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

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

Manuscript

This manuscript is being updated to correspond with the newly updated algorithm. Last update 04/19/07

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

Colorectal cancer is the third most frequently diagnosed cancer in men and women in the United States. In 2007, an estimated 112,340 new cases of colon cancer will occur. During the same year, it is estimated that 52,180 people will die from colon and rectal cancer.[1] Despite these statistics, mortality from colon cancer has decreased over the past 30 years, possibly because of earlier diagnosis through screening and better treatment modalities.

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

Risk Assessment

Nearly one-third of cases of colon cancer in the US are associated with familial clustering,[3] and first-degree relatives of patients with newly diagnosed colorectal adenomas[4] or invasive colorectal cancer[5] are at increased risk for colorectal cancer. Therefore, it is recommended that colon cancer patients, especially those 50 years or younger and those with suspected hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), or attenuated FAP be counseled regarding their family history, as detailed in the NCCN Colorectal Cancer Screening Clinical Practice Guidelines.

Staging

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

Stage II is subdivided into IIA (if the primary tumor is T3) and IIB (for T4 lesions). Stage III is subdivided into IIIA (T1 to T2, N1, M0), IIIB (T3 to T4, N1, M0), and IIIC (any T, N2, M0). The difference between N1 and

N2 disease is in the number of nodes involved: N1 lesions have 1 to 3 positive regional lymph nodes, whereas N2 tumors have four or more positive regional nodes.

An analysis of Surveillance, Epidemiology, and End Results (SEER) data of 119,363 patients with colon cancer from 1991-2000 allowed determination of the following 5-year survival rates by stage: 93.2% (Stage I); 84.7% (Stage IIA); 72.2% (Stage IIB); 83.4% (Stage IIIA); 64.1% (Stage IIIB); 44.3% (Stage IIIC); and 8.1% (Stage IV).[7] It has been proposed that the lack of correlation between stage and prognosis in this study (ie, increased survival rates for patients with Stage IIIA disease relative to those with disease classified as Stage IIB) may be associated with a number of factors including more common use of adjuvant therapy in the former population of patients.[8]

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

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

Pathology

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

The AJCC and CAP recommend evaluation of a minimum of 12 lymph nodes to accurately identify Stage II colorectal cancers.[6, 11,12] The number of lymph nodes retrieved can vary with age of the patient, gender, and tumor grade or site.[13,14] The extent of surgical resection can also have an impact on the node harvest. The apical lymph node is the most proximal node within 1 cm of vessel ligation at the apex of vascular pedicle. Apical lymph node involvement is significantly associated with adverse outcome.[15,16]

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).[17] Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells, or identification of particular tumor antigens through immunohistochemical (IHC) analysis have been reported.[17-21] While results of some of these studies seem promising, there is no uniformity in the definition of “true” clinically relevant metastatic carcinoma. Some studies have considered detection of single cells by IHC as well as isolated tumor cells (ITC) to be micrometastasis. Presently, the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and the results should be used with caution in clinical management decisions.

Clinical Presentation and Treatment

Workup and Management of the Malignant Polyp

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or villous adenoma, physicians should review pathology and consult with the patient.[22] A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore not considered to be capable of regional nodal metastasis.[6] The panel recommends marking the polyp site at the time of colonoscopy if cancer is suspected or within 2 weeks of the polypectomy when the pathology is known. In patients with invasive cancer and adenoma (tubular, tubulovillous or villous), no additional surgery is required for pedunculated or sessile polyps, if the polyp has been completely resected with favorable histological features.[23] Favorable histological features include lesions of grade 1 or 2, no angiolymphatic invasion and a negative resection margin. However, in addition to the option of observation, the panel includes the option of colectomy in patients with a completely-removed, single-specimen, sessile polyp with favorable histological features and clear margins because it has been reported that patients with sessile polyps have a 10% risk of lymph node metastases.[24] For pedunculated and sessile polyps, unfavorable histopathological features are: grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. It should be noted that there is currently no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as the presence of tumor within 1-2 mm from the transected margin and the presence of tumor cells within the diathermy of the transected margin.[22, 25-27] For a pedunculated or sessile polyp with fragmented specimen or margins that cannot be assessed, or with unfavorable pathology, colectomy with en bloc removal of lymph nodes is recommended.[22, 28, 29] Laparoscopic surgery is an option (see section on Workup and Management of Invasive Nonmetastatic Colon Cancer). All patients who have resected polyps should undergo total colonoscopy to rule out other synchronous polyps, as well as appropriate follow-up surveillance endoscopy.[30] Adjuvant chemotherapy is not recommended for patients with Stage I lesions.

Workup and Management of Invasive Nonmetastatic Colon Cancer

Patients who present with invasive colon cancer require a complete staging workup, including pathologic tissue review, total colonoscopy, a complete blood count, platelets, chemistry profile, carcinoembryonic antigen (CEA) determination, and baseline computed tomographic (CT) scans of the chest, abdomen and pelvis.[31] The consensus of the panel is that a positron emission tomography (PET) scan is not routinely indicated at baseline in the absence of evidence of synchronous metastatic disease. For resectable colon cancer, the surgical procedure of choice is colectomy with en bloc removal of the regional lymph nodes.[32] The extent of colectomy should be based on the tumor location, resecting the portion of the bowel and arterial arcade containing the regional lymph nodes. Examination of a minimum of 12 lymph nodes is necessary to establish Stage II colon cancer.[6] Other nodes, such as those at the origin of the vessel feeding the tumor (ie, apical lymph node) as well as suspicious lymph nodes outside the field of resection, should also be biopsied or removed.

Secondary analyses from the Intergroup INT-0089 trial of patients with high-risk Stage II/III colon cancer receiving adjuvant chemotherapy demonstrated that the accuracy of staging colorectal cancer was associated the number of nodes removed.[33] Furthermore, these analyses also showed that an increase in the number of lymph nodes examined was associated with increased survival for patients with both node-negative and node-positive disease,[13] and that the ratio of metastatic to examined lymph nodes was a significant prognostic factor

for both disease recurrence and overall survival.[34] Resection needs to be complete to be considered curative, and positive lymph nodes left behind indicate an incomplete (R2) resection. Patients considered to have N0 disease but for whom <12 nodes have been examined are suboptimally staged and should be considered at higher risk.

Laparoscopic colectomy has been advanced as an approach to the surgical management of colon cancer. A European trial has shown some survival advantage to the laparoscopic approach, but the number of patients enrolled was small.[35] Recently, initial results from a US trial comparing laparoscopically assisted and open surgery for curable colon cancer were reported.[36] A total of 872 patients with adenocarcinoma of colon (no advanced disease) were randomly assigned to undergo open or laparoscopically assisted colectomy. After a median of 4.4 years follow-up, similar cancer recurrence rates were observed in the two groups. However, results from a subanalysis of results from this trial evaluating short-term outcomes (eg, conversion rate to open colectomy, number of lymph nodes collected, number of complications) based on hospital case volume indicated that these outcomes were significantly more favorable when laparoscopic surgery was performed at hospitals with high case volumes.[37, 38]

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

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

Adjuvant Chemotherapy for Resectable Colon Cancer

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

Other adjuvant regimens studied for the treatment of early-stage colon cancer include 5-FU-based therapies incorporating irinotecan, 5-FU regimens other than FOLFOX which include oxaliplatin, and single agent capecitabine. The US Intergroup trial CALGB C89803 evaluated irinotecan plus bolus 5-FU/LV (IFL regimen) versus 5-FU/LV alone in Stage III colon cancer.[48] The preliminary results presented in 2004 indicated no improvement in terms of either overall survival (P=0.88) or failure free survival (P=0.84) for IFL, as compared to 5-FU/LV. However, IFL has been associated with a greater degree of neutropenia, neutropenic fever, and death.[49] In addition, FOLFIRI (infusional 5-fluorouracil, leucovorin, irinotecan), has not been shown to

be superior to 5-FU/LV in the adjuvant setting,[50, 51] although a trend toward improvement was seen with addition of irinotecan.[50] A randomized phase III trial (NSABP Protocol C-07) compared the efficacy of FLOX (bolus 5-FU/LV/oxaliplatin) with that of FULV (bolus 5-FU/LV) in prolonging 3-year DFS in 2407 patients with Stage II or Stage III colon cancer.[52] Median follow-up was 34 months. Three-year DFS was 76.5% vs. 71.6% for FLOX and FULV respectively, indicating that the addition of oxaliplatin to weekly FULV significantly improved 3-year DFS in patients with Stage II or Stage III colon cancer (P=0.004). Grade 3 NCI-Sanofi neurosensory toxicity, diarrhea or dehydration associated with bowel wall thickening was higher with FLOX than with FULV, and, when cross-study comparisons are made, the incidence of grade 3/4 diarrhea was considerably higher with FLOX than FOLFOX. For example, rates of grade 3/4 diarrhea were 10.8% and 6.7% for patients receiving FOLFOX and infusional 5-FU/LV, respectively, in the MOSAIC trial,[45] whereas 38% and 32.3% of patients were reported to have grade 3/4 diarrhea in the NSABP C-07 trial when receiving FLOX and bolus 5-FU/LV, respectively.[52] Single agent oral capecitabine as adjuvant therapy for patients with Stage III colon cancer was shown to be at least equivalent to bolus IV 5-FU/LV (Mayo clinic regimen) with respect to DFS and overall survival with respective hazard ratios of 0.87 (95% CI, 0.75-1.00) and 0.84 (95% CI, 0.69-1.01) when the capecitabine arm was compared to the 5-FU/LV arm.[53]

The impact of adjuvant chemotherapy for patients with Stage II colon cancer has been addressed in several clinical trials and practice-based studies. Results from a meta-analysis of 5 trials in which patients with Stage II and III colon cancer were randomly assigned to receive surgery alone or surgery followed by adjuvant 5-FU/LV demonstrated that most of the benefit of adjuvant therapy was seen in the patients with Stage III disease.[54] Similarly, an analysis of pooled data from 7 randomized trials indicated that overall survival of patients with resected early-stage colon cancer treated with 5-FU based adjuvant therapy was significantly increased in the subset of patients with positive regional lymph nodes but not in patients with N0 disease when compared to patients not receiving chemotherapy, suggesting that the benefit of adjuvant therapy is greater in patients at higher risk due to nodal status.[55] These clinical trial results are supported by data from the community setting. Using the SEER databases, an analysis of outcomes of patients with Stage II disease based on whether patients had or had not received adjuvant chemotherapy showed that there was no significant difference between these 2 groups with respect to 5-year overall survival (eg, 78% vs. 75% respectively), with a hazard ratio for survival of 0.91 (95% CI, 0.77-1.09) when patients receiving adjuvant treatment were compared with untreated patients.[56]

Following primary surgical treatment, the panel recommends 6 months of adjuvant chemotherapy for patients with Stage III (T1-4, N1-2, M0) resected colon cancer. The treatment options are: 5-fluorouracil/leucovorin/oxaliplatin as the standard of care (category 1),[45, 46, 52] single agent capecitabine (category 2A),[53] or 5-FU/LV (category 2A)[54, 57, 58] The panel concluded that weekly bolus IFL should not be used as adjuvant therapy in colon cancer. All 3 of the postoperative adjuvant therapy regimens listed above are designated as category 2B recommendations for patients with stage II (T3, N0, M0) disease with no high risk features. These patients should be entered in a clinical trial, if possible, or may also be observed. High-risk stage II (T3-T4, N0, M0) patients, defined as those with poor prognostic features including T4 tumors (stage IIB), poor histologic grade (grade 3 or 4 lesions), peritumoral lymphovascular involvement, bowel obstruction at presentation, T3 lesions with localized perforation or close, indeterminate, or positive margins, and inadequately sampled nodes (less than 12 lymph nodes), should be considered for adjuvant chemotherapy[10, 59] with 5-FU/LV, single agent capecitabine, or 5-FU/LV/oxaliplatin (category 2A for all three regimens). It should be noted, however, that there is currently no evidence to indicate that

patients with high-risk stage II disease are more likely to respond to chemotherapy than patients with stage II disease without these high-risk features (ie, factors associated with a poorer prognosis are not necessarily predictive of response to treatment). Furthermore, the benefit of chemotherapy in this population has not been shown to improve overall survival by more than 5%.[54, 55] Decision-making regarding the use of adjuvant therapy for patients with stage II disease should incorporate patient/physician discussions individualized for the patient, and include explanations of the specific characteristics of the disease and the evidence related to the efficacy and possible toxicities associated with treatment, centering on patient choice.[59] Radiation therapy delivered concurrently with 5-FU-based chemotherapy should be considered for patients with disease characterized as T4 tumors penetrating to a fixed structure, and recurrent disease. Radiation therapy fields should be defined by preoperative radiological imaging and/or surgical clips. Intensity-modulated radiotherapy (IMRT) which uses computer-imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,[60] can be considered when the risk of such toxicity is high.

Principles of the Management of Metastatic Disease

Approximately 50%-60% of patients diagnosed with colorectal cancer will develop colorectal metastases.[61, 62] Patients with stage IV (any T, any N, M1) colon cancer or recurrent disease can present with synchronous liver or lung metastases or abdominal peritoneal metastases. Approximately 15%-25% of patients with colorectal cancer present with synchronous liver metastases, although 80%-90% of these patients are initially evaluated to have unresectable metastatic liver disease.[61, 63-65] Metastatic disease more frequently develops metachronously following treatment for colorectal cancer, with the liver as a common site of involvement.[66] There is some evidence to indicate that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In one retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement (P=0.008) and more bilobar metastases (P=0.016) when compared with patients diagnosed with metachronous liver metastases.[67]

It has been estimated that over one-half of patients who die of colorectal cancer have liver metastases at autopsy, and that metastatic liver disease is the cause of death in the majority of these patients.[68] Results from reviews of autopsy reports of patients dying from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients.[63] Furthermore, rates of 5-year survival for patients with metastatic liver disease not undergoing surgery have been shown to approach 0% in a number of studies.[61, 69] However, studies of selected patients undergoing surgery to remove colorectal liver metastases have demonstrated that cure is possible in this population and should be the goal for many patients with colorectal metastatic liver disease.[61, 70] Recent reports have shown 5-year survival rates following resection of hepatic colorectal metastases exceeding 50%.[71, 72] Therefore, decisions relating to patient suitability, or potential suitability, and subsequent selection for metastatic colorectal surgery are critical junctures in the management of metastatic colorectal liver disease.[73]

The criteria for determining patient suitability for resection, or surgical cure, of metastatic disease are evolving, with the emphasis being increasingly placed on the likelihood of achieving negative surgical margins while maintaining adequate liver reserve, as opposed to other criteria, such as the number of liver metastases present.[74, 75] Resectability differs fundamentally from endpoints which focus more on palliative measures of treatment, such as response and DFS. Instead, the resectability endpoint is focused on the potential of surgery to cure

the disease,[76] since partial liver resection or debulking has not been shown to be beneficial.[62] Approaches used in the surgical treatment of liver metastases include preoperative portal vein embolization for the purpose of increasing the volume and function of the portion of the liver which will remain postsurgically, hepatic resection performed in 2 stages for bilobular disease, and the use of ablative methods in combination with resection.[74] The panel does not recommend the use of ablative techniques without resection or in patients for whom negative margins can be achieved with resection alone.[77] Resection of liver metastases should not be performed in the presence of unresectable sites of extrahepatic disease, and hepatic intra-arterial embolization should not routinely be used outside of a clinical trial.

Since the majority of patients diagnosed with metastatic colorectal disease are initially classified as unresectable, neoadjuvant chemotherapy is being increasingly employed to downsize colorectal metastases. Potential advantages of this approach include: earlier treatment of micrometastatic disease, determination of responsiveness to chemotherapy (which can be prognostic and help in the planning of postoperative therapy), and avoidance of local therapy for those patients with early disease progression. Potential disadvantages include: chemotherapy-induced liver injury; and missing the "window of opportunity" for resection through the possibility of either disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.[63, 78] Furthermore, results from a recent study of colorectal cancer patients receiving neoadjuvant chemotherapy indicated that cancer cells were still present in most of the original sites of metastases when these sites were examined pathologically despite achievement of a complete response as evaluated on CT scan.[79] It is therefore essential that during treatment with neoadjuvant chemotherapy, frequent evaluations are undertaken and close communication is maintained between medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed which optimizes exposure to the neoadjuvant regimen and facilitates an appropriately-timed surgical intervention.[80]

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

The most important benefit of the preoperative approach is the potential to convert patients with initially unresectable metastatic disease to a resectable state. In the study of Pozzo et al, it was reported that neoadjuvant therapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection.[75] The median time to progression was 14.3 months, with all of these patients alive at a median follow-up of 19 months. In a phase II study conducted by the North Central Cancer Treatment Group (NCCTG),[65] 44 patients with unresectable liver metastases were treated with FOLFOX4. Twenty five patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6

months of chemotherapy. In another study of 1104 initially unresectable patients with colorectal liver disease, 335 patients (23%) were able to undergo primary hepatic resection and 138 patients (12.5%) classified as "good responders" underwent secondary hepatic resection following neoadjuvant treatment which included oxaliplatin in the majority of cases.[84] The 5-year survival rate for these 138 patients overall was 33%. More recently, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%) were able to undergo curative liver resection following treatment.[85] The median overall survival time in this group was 42.4 months.

Recently, the efficacy of bevacizumab in combination with FOLFOX and FOLFIRI in the treatment of unresectable metastatic disease (see section on Chemotherapy for Advanced or Metastatic Disease) has led to its use in combination with these regimens in the neoadjuvant setting, although the safety of administering bevacizumab pre- or postoperatively, in combination with 5-fluorouracil-based regimens has not been adequately evaluated. A retrospective evaluation of data from 2 randomized trials of 1132 patients receiving chemotherapy with or without bevacizumab as initial therapy for metastatic colorectal cancer indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen when this population was compared to the group receiving chemotherapy alone while undergoing major surgery (13% vs 3.4%, respectively; P=0.28).[86] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to surgery, the incidence of wound healing complications in either group of patients was low (1.3% vs 0.5%; P=0.63). The panel recommends at least a 6 week interval (which corresponds to 2 half-lives of the drug[87]) between the last dose of bevacizumab and elective surgery.

Other reported risks associated with the neoadjuvant approach include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.[80] To limit the development of hepatotoxicity, it is therefore recommended that surgery should be performed as soon as possible after the patient becomes resectable and usually not more than 3-4 months following initiation of preoperative treatment.

Colorectal metastatic disease can also occur in the lung.[88] Most of the treatment recommendations discussed for metastatic colorectal liver disease, with the exception of hepatic arterial infusion (HAI), also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in selected cases.[89] The goal of treatment of most abdominal/peritoneal metastases is palliative, rather than curative. The panel does not recommend cytoreductive resection of disseminated carcinomatosis with hyperthermia and intraperitoneal chemotherapy outside of a clinical trial.

Although only limited data exist regarding the efficacy of adjuvant chemotherapy following resection for metastatic colorectal liver or lung disease, administration of a course of an active systemic chemotherapy regimen for metastatic disease is recommended by the panel for most patients following liver or lung resection to increase the likelihood that residual microscopic disease will be eradicated. Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent administration of chemotherapy directed to the liver metastases through the hepatic artery (i.e. HAI) is listed in the guidelines as an option (category 2B). After hepatic resection, administration of fluorodeoxyuridine (FUDR) by HAI in addition to systemic chemotherapy was shown to be superior to systemic

chemotherapy alone with respect to survival and time to hepatic progression but not time to extrahepatic progression.[63, 90] An investigation of the current role of HAI with FUDR in conjunction with oxaliplatin and capecitabine in the treatment of metastatic colorectal liver disease is underway in the NSABP C-09 trial. Some of the uncertainties regarding patient selection for neoadjuvant chemotherapy are also relevant to the application of HAI.[70] Limitations on the use of HAI therapy include the potential for biliary toxicity[63] and the requirement for specific technical expertise.

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from large bowel (e.g. colorectal liver metastases) is suspected should include total colonoscopy, a complete blood count, platelets, chemistry profile, carcinoembryonic antigen (CEA) determination, a CT scan of the chest, abdomen and pelvis, and a needle biopsy, if clinically indicated.[31] The panel recommends a preoperative PET scan at baseline only if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease. The criterion of potential surgical cure includes patients with metastatic disease that is not initially resectable or ablatable but for whom a surgical cure may become possible following neoadjuvant chemotherapy. A PET scan which utilizes a radioactive derivative of glucose (ie, (18) F-fluorodeoxyglucose PET imaging) to detect tissues associated with increased metabolic activity can become transiently negative following chemotherapy (eg, in the presence of necrotic lesions)[91] and the panel recommends against using PET scan to evaluate response to chemotherapy. False positive PET scan results can occur in the presence of tissue inflammation following surgery or infection.[91] An MRI with IV contrast can be considered as part of the preoperative evaluation of patients with potentially surgically resectable M1 liver disease. For example, an MRI with contrast may be of use in situations where the PET and CT scan results are inconsistent with respect to the extent of disease in the liver. Close communication between members of the multidisciplinary treatment team is recommended.

Resectable synchronous liver or lung metastases

If a patient is a candidate for surgery and the liver or lung metastases are deemed resectable, the panel recommends the following options: colectomy and synchronous or subsequent liver (or lung) resection,[66, 83] neoadjuvant chemotherapy (eg, bevacizumab plus choice of FOLFIRI, FOLFOX,[64] or CapeOX [capecitabine, oxaliplatin]) followed by synchronous or staged colectomy with liver or lung resection, or colectomy followed by neoadjuvant chemotherapy (see above) and a staged resection of metastatic disease. Patients with a solitary lesion in their lungs who can undergo resection should be considered for colectomy followed by staged thoracotomy and pulmonary nodule resection. Biologic waiting period of up to 2 months can distinguish patients who would be more likely to benefit from metastasectomy because of indolent disease. Resection of primary colon cancer prior to initiation of chemotherapy is necessary in patients with moderate or severe symptoms (eg, intestinal obstruction) related to the primary cancer. However, advantages to a neoadjuvant chemotherapy approach include the possibility of downsizing both the primary tumor and metastatic lesions prior to surgery, and a very low rate of complications related to the unresected primary cancer.[64] Patients who have completely resected liver or lung metastases should be offered adjuvant chemotherapy. The panel recommends 6 months as the preferred duration of adjuvant therapy. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B), and, in the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or continuous IV 5-FU infusion. Observation or a shortened course of chemotherapy can be considered for patients who have completed neoadjuvant chemotherapy. Post-treatment follow-up

for patients classified as stage IV and no evidence of disease (NED) is described in the section on Post-Treatment Surveillance.

Unresectable synchronous liver or lung metastases

For patients in which the liver or lung disease is deemed to be unresectable but potentially convertible to a resectable state, the panel recommends preoperative chemotherapy corresponding to initial therapy for metastatic disease (eg, bevacizumab plus choice of FOLFIRI, FOLFOX, or CapeOX.) to attempt to render these patients candidates for resection. Patients with lesions converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer followed by adjuvant therapy for a preferred total duration of 6 months. Recommended options for adjuvant therapy include active chemotherapy regimens for advanced or metastatic disease (category 2B), and, in the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or continuous IV 5-FU infusion. Observation or shortened course of chemotherapy can be considered for patients who have completed neoadjuvant chemotherapy. Primary treatment of unresectable synchronous liver or lung metastases by palliative colon resection should be considered if the patient has an imminent risk of obstruction or significant bleeding. Ablative therapy[92] of liver metastases using radiofrequency ablation or cryosurgery at the time of colon resection can also be considered when all measurable metastatic disease can be treated (category 2B). Patients with unresectable liver metastases not responding to systemic therapy should receive salvage therapy for advanced or metastatic disease. Post-treatment follow-up for patients classified as stage IV and no evidence of disease (NED) is described in the section on Post-Treatment Surveillance.

Synchronous abdominal/peritoneal metastases

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

Workup and Management of Metachronous Metastatic Disease

Upon documentation of metachronous metastases in which disease is or may become potentially resectable, characterization of the extent of disease by PET scan is recommended. PET is used at this juncture to promptly characterize the extent of metastatic disease, and to identify possible sites of extrahepatic disease which could preclude surgery.[93] Two other factors further distinguish the management of metachronous metastatic disease from that of synchronous disease: an evaluation of the chemotherapy history of the patient; and the absence of colectomy. Resectable patients are classified according to whether they have received no previous chemotherapy or prior chemotherapy within or before the previous 12 months. For patients who have not received prior chemotherapy and who have resectable metastatic disease, primary treatment options include neoadjuvant chemotherapy followed by resection and additional postoperative chemotherapy, or initial resection followed by chemotherapy. The optimal sequence of therapeutic interventions is less clear for patients who have received prior adjuvant chemotherapy. In particular, the role of neoadjuvant chemotherapy is less clear for patients who exhibit disease recurrence or progression during or within 12 months of receiving prior chemotherapy. Following surgery, adjuvant therapy with an alternative active metastatic chemotherapy regimen is recommended.

Patients determined by cross-sectional imaging or PET scan to be unresectable should receive an active metastatic chemotherapy regimen based on prior chemotherapy history. Specifically, patients exhibiting disease progression on FOLFOX administered within the

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

Chemotherapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colon cancer uses various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine; irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab.[94-108] 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.[109-113] The choice of therapy is based on consideration of the type and timing of the prior therapy that has been administered and the differing toxicity profiles of the constituent drugs. Although the specific chemotherapy regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[96] For example, if oxaliplatin, administered as a part of an initial treatment regimen, is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the rest of the treatment regimen would still be considered initial therapy. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, as well as plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices following first progression of disease should be based, in part, on the prior therapies received by the patient (ie, exposing patient to a range of cytotoxic agents). Further, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, as well as the potential for surgical cure and the performance status of the patient.

As initial therapy for metastatic disease in a patient with good tolerance to intensive therapy, the panel recommends a choice of 4 chemotherapy regimens: FOLFOX (eg, FOLFOX4 and mFOLFOX6),[97, 105, 114-120] CapeOX,[120-122] FOLFIRI,[98,115,119,123] or 5-FU/LV.[100, 104, 123-125] The panel further recommends that each of these regimens be administered in combination with bevacizumab when used for initial therapy. With respect to the treatment of metastatic disease, the consensus of the panel was that FOLFOX plus bevacizumab and CapeOX plus bevacizumab can be used interchangeably,[120] and that both of these combination regimens, as well as FOLFIRI plus bevacizumab, represent standards of care for the initial treatment of metastatic colorectal cancer. The infusional 5-FU/LV plus bevacizumab regimen is recommended as initial therapy for patients not able to tolerate oxaliplatin or irinotecan since it has been shown to be associated with lower toxicity but also lower overall survival than the combination chemotherapy regimens.[126-129]

Results from several phase II studies have demonstrated that addition of bevacizumab to first-line 5-FU/LV regimens improved overall survival

in patients with metastatic colorectal cancer when compared to survival results for patients receiving these regimens without bevacizumab.[127, 130] A combined analysis of the results of several of these trials showed that addition of bevacizumab to 5-FU/LV-containing regimens was associated with a median survival of 17.9 months versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab.[130] A study of previously untreated patients receiving bevacizumab and irinotecan-5-FU chemotherapy (IFL) also provided support for the inclusion of bevacizumab in initial therapy.[129] In that pivotal trial a markedly longer survival time was observed with the use of bevacizumab: 20.3 months versus 15.6 months (hazard ratio for death = 0.66; P<0.001). Addition of bevacizumab to initial therapy with FOLFOX, bolus 5-FU/LV, or CapeOX significantly improved response rate and time to tumor progression in the TREE 1 & 2 studies which evaluated the safety and efficacy of oxaliplatin/fluoropyrimidine regimens (FOLFOX; CapeOX; and bolus 5-FU/LV plus oxaliplatin) with and without bevacizumab.[128, 131] Although the final analysis of the TREE studies was a historical comparison of 2 sequential cohorts in a single protocol without randomization of patients to plus/minus bevacizumab treatment arms, addition of bevacizumab was shown to increase response rate by approximately 10% and time to tumor progression by 2 months when results for all patients, regardless of 5-FU backbone regimen, were evaluated. In a pooled analysis of patients enrolled in all 3 treatment arms, median survival time associated with administration of a 5-FU backbone regimen without bevacizumab was 18.2 months (95% CI, 14.5-21.6) and 24.4 months (95% CI, 21.4-26.8) when bevacizumab was added to these regimens. No significant differences in activity between the 3 different 5-FU-based regimens were observed in the TREE study although this analysis was limited by small sample sizes. Nevertheless, the bolus 5-FU/LV regimen may be the least efficacious since overall survival for patients in the 3 arms (without and with bevacizumab) were reported to be 19.2 months and 26.0 months for FOLFOX, 17.2 months and 27.0 months for CapeOX, and 17.9 months and 20.7 months for bolus 5-FU/LV. Although addition of bevacizumab to these regimens was associated with an increase in grade 3-4 hypertension, impaired wound healing, and bowel perforation in each arm, the overall tolerability of these regimens in combination with bevacizumab was considered to be acceptable and an increase in the toxicity of chemotherapy-related events was not observed.[128] Of note, the grade 3-4 toxicity associated with bevacizumab plus oxaliplatin-based chemotherapy in the TREE study was significantly less than that reported in the pivotal study involving IFL plus bevacizumab.[129] Very recently, results from a head-to-head phase III study comparing CapeOX (capecitabine dose 1000 mg/m2 twice daily for 14 days) with FOLFOX have been reported. With a median follow-up period of 18.6 months, results from this study support the conclusion that neither regimen is inferior with respect to the other in terms of toxicity or efficacy endpoints when used in the initial treatment of metastatic colorectal cancer.[120] Although a combined analysis of results observed with CapeOX plus bevacizumab and FOLFOX plus bevacizumab showed that the addition of bevacizumab was associated with an increase in progression-free survival (PFS) compared to these regimens without bevacizumab, the significant incremental benefit observed with addition of bevacizumab was more modest than seen in some earlier trials. Results of subset analyses evaluating the benefit of adding bevacizumab to either FOLFOX or CapeOX indicated that bevacizumab was associated with improvements in PFS when added to CapeOX but not FOLFOX, although the PFS curves observed for patients receiving either CapeOX plus bevacizumab or FOLFOX plus bevacizumab were nearly identical. The results of the phase III BICC-C study evaluating the effectiveness of 3 irinotecan-containing regimens with and without bevacizumab demonstrated that, for first-line treatment of advanced colorectal cancer, FOLFIRI is superior to a modified IFL regimen or CapIRI (capecitabine plus irinotecan) in terms of efficacy and safety.[132] In that study, a significant increase in PFS was observed for patients receiving first-line FOLFIRI (7.6 months) when compared to

PFS results for patients receiving either a modified IFL regimen (5.8 months; P=0.007) or CapIRI (5.7 months; P=0.03). Furthermore, when FOLFIRI was combined with bevacizumab, PFS was shown to increase to 9.0 months. Evidence for the comparable efficacy for FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI as initial therapy and were then switched to the other regimen at the time of disease progression.[115] Similar response rates and PFS times were obtained when these 2 regimens were used as first-line therapy. Further support for this conclusion has come from results of a phase III trial comparing the efficacy and toxicity of FOLFOX4 and FOLFIRI regimens in previously untreated patients with metastatic colorectal cancer.[119] No differences were observed in response rate, PFS times, and overall survival in the 2 treatment arms. The results of an ongoing phase III study evaluating the effectiveness of FOLFIRI in combination with bevacizumab in the initial treatment of patients with metastatic disease have not yet been reported.[133]

Convincing, albeit indirect, support for inclusion of bevacizumab in combination with chemotherapeutic agents in the initial treatment of advanced or metastatic colon cancer comes from results of the randomized phase III study E3200, conducted by Eastern Cooperative Oncology Group (ECOG), which demonstrated that bevacizumab in combination with FOLFOX4 improved survival in bevacizumab-naïve patients with previously-treated advanced colorectal cancer. Median overall survival was 12.5 months for patients receiving FOLFOX4 plus bevacizumab compared to 10.7 months for patients receiving FOLFOX4 alone.[134] Use of single agent bevacizumab is not recommended since it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX plus bevacizumab treatment arms.[134] Although this study involved patients with previously-treated disease, the results cannot be used to support use of bevacizumab in patients after first or second progression if they have progressed on a bevacizumab-containing regimen.

The risk of stroke and other arterial events is increased in elderly patients receiving bevacizumab.[87] In addition, use of bevacizumab may interfere with wound healing[86, 87, 128, 131] (see Principles of Management of Metastatic Disease), and gastrointestinal perforation is a relatively rare, but important, side effect of bevacizumab therapy in patients with colorectal cancer.[86, 128, 131]

With respect to the toxicities associated with capecitabine use, the panel noted that patients with diminished creatinine clearance may accumulate levels of the drug,[131, 135] that the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV[128, 131, 135] and that North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.[136] Such toxicities may necessitate modifications in the dosing of capecitabine,[128, 131, 135, 137] and patients on capecitabine should be monitored closely so that dose adjustments can be made at the earliest signs of certain side effects such as hand-foot syndrome. For example, the capecitabine dose was reduced from 1000 mg/m2 twice daily to 850 mg/m2 twice daily on days 1-14 in the TREE studies.[80, 128, 131] It is currently not known whether the efficacy of CapeOX plus bevacizumab and FOLFOX plus bevacizumab remain comparable when capecitabine doses are lower than the 1000 mg/m2 twice daily dose used in the study of Cassidy et al.[120]

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[138, 139] Irinotecan is metabolized by the enzyme uridine diphosphate-glucuronyl transferase 1A1 (UGT1A1) which is also involved in converting substrates, such as bilirubin, into more soluble forms through conjugation with certain glycosyl groups. Deficiencies in UGT1A1 can be caused by certain genetic polymorphisms, and can result in conditions associated with accumulation of unconjugated hyperbilirubinemias, such as types I and

II of Crigler-Najjar syndrome and Gilbert syndrome. Thus, irinotecan should be used with caution and at decreased dose in patients with Gilbert's disease or elevated serum bilirubin.[140] Similarly, certain genetic polymorphisms in the gene encoding for UGT1A1 can result in a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in an accumulation of the drug,[139, 141] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[141] A commercial test is available to detect the UGT1A1*28 allele which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression,[140] and a new warning has been added to the label for Camptosar which indicates that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28,[138] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[141] although guidelines for the use of this test in clinical practice have not been established.

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[142] Results of the OPTIMOX1 study demonstrated that a "stop-and-go" approach employing oxaliplatin-free intervals resulted in decreased neurotoxicity but did not affect overall survival in patients receiving FOLFOX as initial therapy for metastatic disease. Therefore, the panel recommends adjustments in the schedule/timing of the administration of this drug as a means of limiting this adverse effect.[143] Discontinuation of oxaliplatin from FOLFOX or CapeOX should be strongly considered after 3 months of therapy or sooner for unacceptable neurotoxicity (eg, > grade 3) with other drugs in the regimen maintained until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy but oxaliplatin can subsequently be reintroduced if stopped to prevent development of neurotoxicity.

The consensus of the panel is that infusional 5-FU regimens appear to be less toxic than bolus regimens and that any bolus regimen of 5-FU is inappropriate when administered with either irinotecan or oxaliplatin. Therefore, the panel no longer recommends using the IFL (irinotecan, bolus 5-FU/LV) regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial[132] and FOLFOX in the Intergroup trial[97]) at any point in the therapy continuum and it has been removed from the guidelines. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,[104, 123] or the oral route (i.e. capecitabine).[101]

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

Results from a randomized study to evaluate the efficacy of FOLFIRI and FOLFOX6 regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen following first progression showed neither sequence to be significantly superior with respect to PFS or median overall survival.[115] A combined analysis of

data from 7 recent phase III clinical trials in advanced colorectal cancer provided support for a correlation between an increase in median survival and administration of all of the 3 cytotoxic agents (ie, 5-FU/LV, oxaliplatin, and irinotecan) at some point in the continuum of care.[144] Furthermore, overall survival was not found to be associated with the order in which these drugs were received. Single agent irinotecan administered after first progression has been shown to significantly improve overall survival relative to best supportive care[145] or infusional 5-FU/LV.[146] In the study of Rougier et al.,[146] median overall survival was 4.2 months for irinotecan versus 2.9 months for 5-FU (P=0.030) whereas Cunningham et al.[145] reported a surivival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive-care group (P-0.001). Furthermore, no significant differences in overall survival were observed in the Intergroup N9841 trial when FOLFOX was compared to irinotecan monotherapy following first progression of metastatic colorectal cancer.[147]

Cetuximab has been studied trial as both a single agent[107, 148] and in combination with irinotecan[107] in the treatment of metastatic colorectal cancer. A partial response rate of 9% was observed when single agent cetuximab was administered in an open-label phase II trial to 57 patients with colorectal cancer refractory to prior irinotecan-containing therapy.[148] Results from a direct comparison of cetuximab monotherapy and the combination regimen of cetuximab and irinotecan in patients who had progressed following initial therapy with an irinotecan-based regimen indicated that response rates were doubled in the group receiving the combination of cetuximab plus irinotecan when compared with patients receiving cetuximab monotherapy (22.9% versus 10.8% [P-0.007]).[107] Therefore, combination therapy with cetuximab and irinotecan is preferable to cetuximab alone as therapy after first progression for patients who can tolerate this combination regimen. Panitumumab, however, has only been studied as a single agent in the setting of metastatic colorectal cancer for patients with disease progression on initial chemotherapy[106]; respective response rates of 8% versus 0% for panitumumab plus best supportive care versus best supportive care alone were observed, as well as a significant increase in PFS with panitumumab (hazard ratio=0.54; 95% CI, 0.44-0.66). Thus, recommendations for the use of panitumumab in the guidelines are currently restricted to single agent use only. The panel allows that panitumumab can be substituted for cetuximab when either drug is used as a single agent following first or second progression. Although no head-to-head studies comparing cetuximab and panitumumab have been undertaken, this recommendation is supported by the similar response rates observed when each agent was studied as monotherapy. One difference between these 2 agents is that panitumumab is a fully human monoclonal antibody whereas cetuximab is a chimeric monoclonal antibody.[149, 150] There are no data to support use of either cetuximab or panitumumab after failure of the other drug and the panel recommends against this practice. Cetuximab in combination with irinotecan is also indicated following progression for patients refractory to irinotecan-based chemotherapy since it has shown activity in this setting.[107] Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[149, 150]

EGFR testing of colorectal tumor cells has no demonstrated predictive value in determining likelihood of response to either cetuximab or panitumumab. Data from the BOND study indicated that the intensity of immunohistochemical staining of colorectal tumor cells did not correlate with the response rate to cetuximab.[107] A similar conclusion was drawn with respect to panitumumab.[151] Therefore, routine EGFR testing is not recommended, and no patient should be either considered for or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.

With respect to the treatment continuum for metastatic colorectal cancer, there are no data to support the addition of bevacizumab to a regimen following clinical failure of a previous bevacizumab-containing regimen.[134] Therefore, routine use of cetuximab plus bevacizumab in patients who have experienced clinical failure on a bevacizumab-containing regimen is not recommended.

For patients with impaired tolerance to aggressive initial therapy, the guideline recommends single-agent capecitabine,[101, 102] or bolus or infusional 5-FU/leucovorin,[103, 104] with or without bevacizumab (category 2B for combination with bevacizumab). Although a comparison of capecitabine plus bevacizumab versus capecitabine alone as initial therapy for metastatic cancer has not been done, CapeOX plus bevacizumab has been shown to be superior to CapeOX alone in this setting.[128, 131] Metastatic cancer patients with no improvement in functional status should receive best supportive care. Patients showing improvement in functional status should be treated with one of the options specified for therapy after first progression as described above.

The panel recommends that progression of disease following treatment with an EGFR inhibitor alone or a regimen including cetuximab and irinotecan should be followed by either best supportive care or enrollment in a clinical trial. The panel recommends against the use of capecitabine, mitomycin, or gemcitabine, either as single agents or in combination, as salvage therapy in patients exhibiting disease progression following treatment with a fluoropyrimidine-containing regimen. These agents have not been shown to be effective in this setting, and no objective responses were observed when single agent capecitabine was administered in a phase II study of patients with colorectal cancer resistant to 5-FU.[152]

Post-Treatment Surveillance

Following curative-intent surgery, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, identify new metachronous neoplasms at a preinvasive stage, and reassure the patient. Advantages of more intensive follow-up of Stage II and/or Stage III patients have been demonstrated prospectively in several studies[153, 154, 155] and in three recent meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[156-159] Other recent studies impacting on the issue of post-treatment surveillance of colorectal cancer include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials which demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor,[47] and a population-based report indicating increased rates of resectability and survival in patients treated for local recurrence and distant metastases of colorectal cancer, thereby providing support for more intensive post-treatment follow-up in these patients.[160] Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.[161]

The following panel recommendations for post-treatment surveillance pertain to patients with Stage I-Stage III disease who have undergone successful treatment (i.e. no known residual disease): history and physical examination every 3-6 months for 2 years, and then every 6 months for a total of 5 years; a carcinoembryonic antigen (CEA) test at baseline and every 3-6 months for 2 years,[162] then every 6 months for the next 5 years if the clinician determines that the patient is a potential candidate for aggressive curative surgery[159,162,163]; colonoscopy within 1 year of resection (or 3 to 6 months if not performed preoperatively due to obstructing lesion), repeated in 3 years if the colon is free of polyps followed by colonoscopic surveillance every 5 years, or, if first follow-up

colonoscopy is abnormal, repeat colonoscopy after 1 year and, if negative for polyps, repeat colonoscopic surveillance in 3 years and then every 5 years[164]; chest, abdominal and pelvic CT scan are recommended annually every 3 years in Stage III patients at high risk or recurrence (ie, those with perineural or venous invasion of tumor or poorly differentiated tumors) and may be considered annually for 3 years for patients for patients with Stage II disease at high risk for recurrence[159, 165]; PET scan is not routinely recommended.

Initial follow-up office visits at 3 months intervals for history and physical examination may be more useful for patients diagnosed with Stage III disease, whereas patients with a diagnosis of Stage I disease may not need to be seen as frequently (i.e. can be seen once every 6 months). This principle also applies to CEA testing, which is used primarily to monitor for recurrence of the original disease (see section on Managing an Increasing CEA Level), although post-treatment CEA testing is recommended only if the patient is a potential candidate for further intervention.[162] Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps[164] since data show that patients with a history of colorectal cancer have an increased risk of developing second cancers,[166] particularly in the first 2 years following resection.[164] Furthermore, use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original colorectal cancer.[164] The recommended frequency of post-treatment surveillance colonoscopies is higher (ie, annually) for patients with HNPCC.[164] CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver.[159] Hence, CT scan is not routinely recommended in patients who are not candidates for potentially curative resection of liver or lung metastases.[159] Post-treatment PET scan is not routinely recommended for surveillance of patients with resected early-stage colorectal cancer to detect recurrence of the original cancer. Furthermore, PET scan is not routinely recommended to detect metastatic disease in the absence of other evidence of such disease.

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

Managing an Increasing Carcinoembryonic Antigen Level

Managing patients with an elevated CEA level after resection should include colonoscopy, chest, abdominal, and pelvic CT scans, and physical examination. If imaging study results are normal in the face of a rising CEA, repeat scans are indicated every 3 months if symptoms occur. In addition, PET scan may be used to determine if isolated metastases can be demonstrated if CT scan results are negative.[167] The panel does not recommend a so-called "blind" or “CEA-directed” laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative.[168] The panel does not recommend the use of anti-CEA-radiolabeled scintigraphy.[169] PET scan should be considered before surgical resection for patients with a suspected recurrence or those with documented metastases by CT, MRI and/or biopsy. In the case of local recurrence or resectable organ-confined lesion, curative surgery may be possible. Likewise, isolated lesions in the liver or lung may be resected for cure.

Summary

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

The recommended surgical procedure for resectable colon cancer is an en bloc resection and adequate lymphadenectomy. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes when possible. Adjuvant therapy with FOLFOX (category 1), 5-FU/LV (category 2A), or capecitabine (category 2A) is recommended by the panel for patients with Stage III disease, and as an option for patients with high-risk Stage II disease (category 2A for all three treatment options). A patient with metastatic disease in the liver or lung should be considered for surgical resection if he or she is a candidate for surgery and if complete resection (R0) or ablation can be achieved. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease (neoadjuvant) or when a response to chemotherapy can convert a patient from an unresectable to a resectable state. Adjuvant chemotherapy should be considered following resection of liver or lung metastases. The recommended post-treatment surveillance program for colon cancer patients includes serial CEA determinations, as well as periodic chest, abdominal and pelvic CT scans, and colonoscopic evaluations. Recommendations for patients with previously untreated disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, as well as plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy for advanced or metastatic disease includes bevacizumab plus FOLFOX, FOLFIRI, CapeOX or 5-FU/LV.

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

Disclosures for the NCCN Colon Cancer Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Abraxis, Amgen, AstraZeneca, Bristol-Myers Squibb, Genentech, ImClone, MedImmune, NCI, Novartis, Pfizer, Quality Oncology, Roche, Sanofi-Aventis, Schering-Plough, Taiho, TissueLink Medical, U.S. Surgical and Valleylab/Tyco. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

References

1.Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin. 2007;57:43-66.

2. Greene F, Page D, Fleming I, Fritz A. AJCC Cancer Staging Manual. New York: Springer-Verlag; 2002.

3. 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.

4. 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.

5. 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.

6. Compton CC, Greene FL. The staging of colorectal cancer: 2004 and beyond. CA Cancer J Clin. 2004;54:295-308.

7. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst. 2004;96:1420-1425.

8. Burke HB. Outcome prediction and the future of the TNM staging system. J Natl Cancer Inst. 2004;96:1408-1409.

9. 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.

10. 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.

11. Greene FL, Stewart AK, Norton HJ. A new TNM staging strategy for node-positive (stage III) colon cancer: an analysis of 50,042 patients. Ann Surg. 2002;236:416-421; discussion 421.

12. Sobin LH, Greene FL. TNM classification. Clarification of number of regional lymph nodes for pN0. Cancer. 2001;92:452.

13. 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.

14. Le Voyer T, Sigurdson E, Hamlin A, 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.

15. Newland RC, Dent OF, Lyttle MN, et al. Pathologic determinants of survival associated with colorectal cancer with lymph node metastases. A multivariate analysis of 579 patients. Cancer. 1994;73:2076-2082.

16. Chapuis PH, Dent OF, Bokey EL, et al. Adverse histopathological findings as a guide to patient management after curative resection of node-positive colonic cancer. Br J Surg. 2004;91:349-354.

17. 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.

18. Saha S, Van A, Beutler T, et al. Sentinel lymph mapping techniques in colorectal cancer. Sem Oncol. 2004;31:374-381.

19. 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.

20. 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; discussion 628-630.

21. 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.

22. Cooper HS, Deppisch LM, Gourley WK, et al. Endoscopically removed malignant colorectal polyps: clinicopathologic correlations. Gastroenterology. 1995;108:1657-1665.

23. Markowitz AJ, Winawer SJ. Management of colorectal polyps. CA Cancer J Clin. 1997;47:93-112.

24. Nivatvongs S, Rojanasakul A, Reiman HM, et al. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. Dis Colon Rectum. 1991;34:323-328.

25. 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.

26. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology. 2004;127:385-394.

27. 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; discussion 1796-1787.

28. 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.

29. Crawley J, Petras R, Carey W, et al. When is endoscopic polypectomy adequate therapy for colonic polyps containing invasive cancer? Gastroenterology. 1986;91:419-427.

30. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology. 1997;112:594-642.

31. 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.

32. Cohen AM. Surgical considerations in patients with cancer of the colon and rectum. Semin Oncol. 1991;18:381-387.

33. Joseph NE, Sigurdson ER, Hanlon AL, et al. Accuracy of determining nodal negativity in colorectal cancer on the basis of the number of nodes retrieved on resection. Ann Surg Oncol. 2003;10:213-218.

34. 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.

35. 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.

36. 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.

37. 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.

38. Kienle P, Weitz J, Koch M, Buchler MW. Laparoscopic surgery for colorectal cancer. Colorectal Dis. 2006;8 Suppl 3:33-36.

39. Wishner JD, Baker JW, Jr., Hoffman GC, et al. Laparoscopic-assisted colectomy. The learning curve. Surg Endosc. 1995;9:1179-1183.

40. 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;19:51-56.

41. Ota D, Nelson H, Weeks J, et al. Controversies regarding laparoscopic colectomy for malignant diseases. Curr Opin Gen Surg. 1994:208-213.

42. Sun W, Haller DG. Adjuvant therapy of colon cancer. Semin Oncol. 2005;32:95-102.

43. Baddi L, Benson A, 3rd. Adjuvant therapy in stage II colon cancer: current approaches. Oncologist. 2005;10:325-331.

44. Benson III AB. New approaches to the adjuvant therapy of colon cancer. Oncologist. 2006;11:973-980.

45. 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.

46. 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. J Clin Oncol. 2005;23:16S (June 1 suppl). Abstract 3501.

47. 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.

48. Saltz L, Niedzwiecki D, Hollis D, et al. Irinotecan plus fluorouracil/leucovorin (IFL) versus fluorouracil/leucovorin alone (IFL) in stage III colon cancer (Intergroup trial CALGB C89803). J Clin Oncol. 2004;22:No. 14S (July 15 suppl). Abstract 3500.

49. 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.

50. Van Cutsem E, Labianca R, Hossfeld D, et al. Randomized phase III trial comparing infused irinotecan/5-fluorouracil (5-FU)/folinic acid (IF) versus 5-FU/FA in stage III colon cancer patients (pts). (PETACC3). J Clin Oncol. 2005;23: No. 16S (June 1 suppl). Abstract 8.

51. Ychou M, Raoul J, Douillard J, et al. A phase III randomized trial of LV5FU2 + CPT-11 vs. LV5FU2 alone in adjuvant high risk colon cancer (FNCLCC Accord02/FFCD9802). J Clin Oncol. 2005;23: No. 16S (June 1 suppl). Abstract 3502.

52. Wolmark N, Wieand H, Kuebler J, 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. J Clin Oncol. 2005;23: No. 16S (June 1 suppl). Abstract 3500.

53. 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.

54. 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.

55. 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.

56. 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.

57. 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.

58. 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.

59. 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.

60. Hong TS, Ritter MA, Tome WA, Harari PM. Intensity-modulated radiation therapy: emerging cancer treatment technology. Br J Cancer. 2005;92:1819-1824.

61. 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.

62. 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.

63. Kemeny N. Management of liver metastases from colorectal cancer. Oncology (Williston Park). 2006;20:1161-1176, 1179; discussion 1179-1180, 1185-1166.

64. 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.

65. 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.

66. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. J Clin Oncol. 1997;15:938-946.

67. Tsai M, Su Y, Ho M, et al. Clinicopathological features and prognosis in resectable synchronous and metachronous colorectal liver metastases. Ann Surg Oncol. 2007;14:786-794.

68. Foster JH. Treatment of metastatic disease of the liver: a skeptic's view. Semin Liver Dis. 1984;4:170-179.

69. Stangl R, Altendorf-Hofmann A, et al. Factors influencing the natural history of colorectal liver metastases. Lancet. 1994;343:1405-1410.

70. Venook AP. The Kemeny article reviewed. Oncology. 2006;20:477-484.

71. 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.

72. 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, discussion 722-714.

73. 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.

74. Vauthey JN, Zorzi D, Pawlik TM. Making unresectable hepatic colorectal metastases resectable--does it work? Semin Oncol. 2005;32(Suppl 9):S118-122.

75. 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.

76. 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.

77. 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 825-817.

78. 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.

79. 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.

80. Bilchik AJ, Poston G, Curley SA, et al. Neoadjuvant chemotherapy for metastatic colon cancer: a cautionary note. J Clin Oncol. 2005;23:9073-9078.

81. Pawlik TM, Poon RT, Abdalla EK, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. Arch Surg. 2005;140:450-457; discussion 457-458.

82. 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.

83. Fong Y, Salo J. Surgical therapy of hepatic colorectal metastasis. Semin Oncol. 1999;26:514-523.

84. 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.

85. 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.

86. 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.

87. Package Insert. Bevacizumab (Avastin®). South San Francisco, CA, Genentech, Inc. October 2006.

88. Lee WS, Yun SH, Chun HK, et al. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. Int J Colorectal Dis. Nov 16 2006.

89. 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; discussion 979-980.

90. 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.

91. Delbeke D, Martin WH. PET and PET-CT for evaluation of colorectal carcinoma. Semin Nucl Med. 2004;34:209-223.

92. Fraker DL, Soulen M. Regional therapy of hepatic metastases. Hematol Oncol Clin North Am. 2002;16:947-967.

93. 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.

94. Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. J Clin Oncol. 2005;23:4553-4560.

95. Goldberg RM. Therapy for metastatic colorectal cancer. Oncologist. 2006;11:981-987.

96. 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.

97. 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.

98. 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.

99. 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.

100 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.

101. 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.

102. 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.

103. 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.

104. 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.

105. 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.

106. Peeters M, Van Cutsem E, Sienna S, et al. A phase 3 multicenter randomized controlled trial (RCT) of panitumumab plus best supportive care (BSC) vs BSC alone in patients with metastatic colorectal cancer. American Association for Cancer Research 2006 Annual Meeting: Abstract CP-1.

107. 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.

108. 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.

109. Van Cutsem E. Challenges in the use of epidermal growth factor receptor inhibitors in colorectal cancer. Oncologist. 2006;11:1010-1017.

110. Raymond E, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. Semin Oncol. 1998;25(Suppl 5):4-12.

111. O'Dwyer PJ. The present and future of angiogenesis-directed treatments of colorectal cancer. Oncologist. 2006;11:992-998.

112. 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.

113. Rothenberg ML, Blanke CD. Topoisomerase I inhibitors in the treatment of colorectal cancer. Semin Oncol. 1999;26:632-639.

114. 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.

115. 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.

116. 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.

117. 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.

118. 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.

119. 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.

120. Cassidy J, Clarke S, Rubio D, et al. First efficacy and safety results from XELOX-1/NO16966, a randomized 2x2 factorial phase III trial of XELOX vs. FOLFOX6 + bevacizumab or placebo in first-line metastatic colorectal cancer (MCRC). Ann Oncol. 2006;17:(suppl 9). LBA 3.

121. 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.

122. Arkenau H, Schmoll H, Kubicka S, et al. Infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus capecitabine plus oxaliplatin (CAPOX) as first line treatment of metastatic colorectal cancer (MCRC): Results of the safety and efficacy analysis. J Clin Oncol. 2005; 23: 16S (June 1 suppl). Abstract 3507.

123. 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.

124. 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.

125. 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.

126. 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.

127. 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.

128. Hochster H, Hart LL, Ramanathan R, et al. Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): Final analysis of the TREE study. J Clin Oncol. 2006;24: N0. 18S (June 20 suppl). Abstract 3510.

129. 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.

130. 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.

131. Hochster H, Welles L, Hart L, et al. Safety and efficacy of bevicizumab (Bev) when added to oxaliplatin/fluoropyrimidine (O/F) regimens as first-line treatment of metastatic colorectal cancer (mCRC): TREE 1 & 2 studies. J Clin Oncol. 2005;23: 16S (June 1 suppl). Abstract 3515.

132. Fuchs CS, Marshall J, Mitchell EP, et al. Updated results of BICC-C study comparing first-line irinotecan /fluoropyrimidine combinations +/- celecoxib in mCRC: Clinical data cut-off September 1, 2006. Paper presented at: Gastrointestinal Cancers Symposium, 2007; Abstract 276.

133. Sobero A, Ackland S, Carrion R, et al. Efficacy and safety of bevacizumab in combination with irinotecan and infusional 5-FU as first-line treatment for patients with metastatic colorectal cancer. J Clin Oncol. 2006;24:No. 18S (June 20 suppl). Abstract 3544.

134. Giantonio B, Catalano P, Meropol N, et al. High dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E 3200. Gastrointestinal Cancers Symposium. 2005;Abstract 169a.

135. Package insert. Capecitabine (Xeloda®), Nutley, NJ, Roche Laboratories Inc., June 2005.

136. Haller D, Cassidy J, Clarke S, et al. Tolerability of fluoropyrimidines appears to differ by region. J Clin Oncol. 2006;24:16S (June 20 suppl). Abstract 3514.

137. Schmoll HJ, Arnold D. Update on capecitabine in colorectal cancer. Oncologist. 2006;11:1003-1009.

138. Package Insert. Irinotecan hydrochloride injection (Camptosar®), New York, NY, Pfizer, June 2006.

139. 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.

140. LabCorp Capsule. UGT1A1 irinotecan toxicity. Managing medication dosing and predicting response to treatment of cancer with irinotecan (Camptosar, CPT-11). 2006:Available at www.lapcorp.com.

141. 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.

142. Package insert. Oxaliplatin (Eloxatin®), Bedford, OH. Ben Venue Laboratories, November 2004.

143. 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.

144. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. 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.

145. 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.

146. 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.

147. Pitot H, Rowland K, DJ S, et al. N9841: A randomized phase III equivalence trial of irinotecan (CPT-11) versus oxaliplatin/5-fluorouracil (5FU)/leucovorin (FOLFOX4) in patients (pts) with advanced colorectal cancer (CRC) previously treated with 5FU. J Clin Oncol. 2005;23:No. 16S (June 1 suppl). Abstract 3506.

148. Saltz LB, Meropol NJ, Loehrer PJ, Sr., 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.

149. Package Insert. Cetuximab (Erbitux®), Branchburg, NJ, Imclone Systems, Inc. 2004.

150. Package Insert. Panitumumab (Vectibix™), Thousand Oaks, CA, Amgen, September 2006.

151. Hecht J, Mitchell E, Baranda J, et al. Panitumumab antitumor activity in patients (pts) with metastatic colorectal cancer (mCRC) expressing low (1-9%) or negative (<1%) levels of epidermal growth receptor (EGFr). J Clin Oncol. 2006;24: No. 18S (June 1 suppl). Abstract 3506.

152. 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.

153. 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.

154. 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.

155. 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.

156. 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;22:3395-3407.

157. 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.

158. Jeffery M, Hickey B, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev. 2007:CD002200.

159. Desch CE, Benson AB, 3rd, 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.

160. 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.

161. Li Destri G, Di Cataldo A, Puleo S. Colorectal cancer follow-up: useful or useless? Surg Oncol. 2006;15:1-12.

162. 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.

163. Macdonald JS. Carcinoembryonic antigen screening: pros and cons. Semin Oncol. 1999;26:556-560.

164. 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; quiz 185-166.

165. 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.

166. 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.

167. Libutti SK, Alexander HR, Jr., Choyke P, et al. A prospective study of 2-[18F] fluoro-2-deoxy-D-glucose/positron emission tomography scan, 99mTc-labeled arcitumomab (CEA-scan), and blind second-look laparotomy for detecting colon cancer recurrence in patients with increasing carcinoembryonic antigen levels. Ann Surg Oncol. 2001;8:779-786.

168. Martin EW, Jr., 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.

169. Moffat FL, Jr., Pinsky CM, Hammershaimb L, et al. Clinical utility of external immunoscintigraphy with the IMMU-4 technetium-99m Fab' antibody fragment in patients undergoing surgery for carcinoma of the colon and rectum: results of a pivotal, phase III trial. The Immunomedics Study Group. J Clin Oncol. 1996;14:2295-2305.