National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Rectal Cancer

Version 4.2013

NCCN.org

IMPORTANT NOTE REGARDING LEUCOVORIN SHORTAGE, PLEASE SEE MS-17

Continue

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NCCN Guidelines Version 4.2013 Panel Members
Rectal Cancer

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

Tanios Bekaii-Saab, MD †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Emily Chan, MD, PhD †
Vanderbilt-Ingram Cancer Center

Yi-Jen Chen, MD, PhD §
City of Hope Comprehensive Cancer Center

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

Harry S. Cooper, MD ≠
Fox Chase Cancer Center

Paul F. Engstrom, MD †
Fox Chase Cancer Center

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

Marwan G. Fakih, MD †
University of Michigan Comprehensive Cancer Center

Moon J. Fenton, MD, PhD †
St. Jude Children's Research Hospital/ University of Tenessee Cancer Institute

Charles S. Fuchs, MD, MPH †
Dana-Farber/Brigham and Women's Cancer Center

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

Steven Hunt, MD ¶
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Ahmed Kamel, MD ф
University of Alabama at Birmingham Comprehensive Cancer Center

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

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

Kilian Salerno May, MD §
Roswell Park Cancer Institute

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

Kate Murphy, BA ¥ (In memoriam)
Fight Colorectal Cancer

Eric Rohren, MD, PhD ф
The University of Texas MD Anderson Cancer Center

David P. Ryan, MD †
Massachusetts General Hospital Cancer Center

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

Sunil Sharma, MD †
Huntsman Cancer Institute at the University of Utah

David Shibata, MD ¶
Moffitt Cancer Center

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

William Small, Jr., MD §
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Constantinos T. Sofocleous, MD, PhD ф
Memorial Sloan-Kettering Cancer Center

* Alan P. Venook, MD † ‡
UCSF Helen Diller Family Comprehensive Cancer Center

Christopher G. Willett, MD §
Duke Cancer Institute

NCCN
Deborah Freedman-Cass, PhD
Lauren Gallagher, RPh, PhD
Kristina M. Gregory, RN, MSN, OCN

Continue

† Medical oncology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
≠ Pathology
‡ Hematology/Hematology oncology
Þ Internal medicine
ф Diagnostic/Interventional radiology
¥ Patient advocate
*Writing Committee Member

NCCN Guidelines Panel Disclosures

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NCCN Guidelines Version 4.2013 Table of Contents
Rectal Cancer

NCCN Rectal Cancer Panel Members
Summary of the Guidelines Updates
Clinical Presentations and Primary Treatment:
- Pedunculated polyp with invasive cancer (REC-1)
- Sessile polyp with invasive cancer (REC-1)
- Rectal cancer appropriate for resection (REC-2)
  - ▸T1-2, N0: Primary and Adjuvant Treatment (REC-3)
  - ▸T3, N0 or T any, N1-2: Primary and Adjuvant Treatment (REC-4)
  - ▸T4 and/or locally unresectable: Primary and Adjuvant Treatment (REC-4)
  - ▸T any, N any, M1: Resectable Metastases Treatment (REC-5)
  - ▸T any, N any, M1: Unresectable Metastases or Medically Inoperable Treatment (REC-6)

Surveillance (REC-7)
Recurrence and Workup (REC-8)
Serial CEA Elevation (REC-8)

Principles of Pathologic Review (REC-A)
Principles of Surgery (REC-B)
Principles of Adjuvant Therapy (REC-C)
Principles of Radiation Therapy (REC-D)
Chemotherapy for Advanced or Metastatic Disease (REC-E)
Principles of Survivorship (REC-F)

Staging (ST-1)

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

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

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

See NCCN Categories of Evidence and Consensus

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN 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® (NCCN®) 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. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2012.

NCCN Guidelines Version 4.2013 Updates Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion

Summary of changes in the 4.2013 version of the Colon Guidelines from the 3.2013 version include:

REC-A 5 of 6
The following added:
MSI Testing - See NCCN Guidelines for Colorectal Cancer Screening
- **The panel recommends that MMR protein testing be performed for all patients younger than 50 years with rectal cancer, based on an increased likelihood of Lynch syndrome in this population.**

REC-E 3 of 9
- **FOLFOX and CapeOx added as treatment options in therapy after second progression for patients treated previously with irinotecan-based chemotherapy.**

Summary of changes in the 3.2013 version of the Rectal Cancer Guidelines from the 2.2013 version include:

REC-10
- **Unresectable metachronous metastases, previous adjuvant FOLFOX within the past 12 months: Primary treatment regimens made consistent with therapy after first progression regimens on page REC-E 1 of 9. The following regimens added: FOLFIRI ± ziv-aflibercept, Irinotecan ± bevacizumab, Irinotecan ± ziv-aflibercept, (Cetuximab or panitumumab) (KRAS WT gene only) + irinotecan.**

REC-E 1 of 9, REC-E 2 of 9, REC-E 3 of 9
- **Regorafenib added as a treatment option in therapy after first, second, or third progression, depending on previous lines of therapy. Best supportive care and clinical trial also listed as alternate options to regorafenib.**

REC-E 8 of 9
- **Regorafenib regimen added: regorafenib 160 mg PO daily days 1-21, repeat every 28 days.**

REC-E 9 of 9
- **Reference for regorafenib added: Grothey A, Sobrero AF, Siena S, et al. Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after standard therapies [abstract]. J Clin Oncol 2012;30 (suppl 4):LBA385.**

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NCCN Guidelines Version 4.2013 Updates
Rectal Cancer

Summary of changes in the 2.2013 version of the Guidelines for Rectal Cancer from the 1.2013 version include:

MS-1
- **The discussion section updated to reflect the changes in the algorithm.**

Summary of changes in the 1.2013 version of the Guidelines for Rectal Cancer from the 3.2012 version include:

REC-2
- **Workup: Chest/abdominal/pelvic CT, footnote "f" added: "CT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast." Also applies to REC-7.**

REC-3
- **Footnote "h" modified: High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or *sm3 invasion*.**

REC-5
- **Adjuvant therapy recommendations following staged or synchronous resection of metastases + rectal lesion: "Adjuvant therapy for stage III disease (REC-4)" changed to "FOLFOX/CapeOx preferred."**
- **Footnote "q" modified: "There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status."**

REC-6
- **Clinical stage changed to "T Any, N Any, M1 Unresectable synchronous metastases or Medically inoperable."**

REC-9
- **No previous chemotherapy, resection: "Adjuvant therapy for stage III disease (REC-4)" changed to "FOLFOX/CapeOx preferred."**
- **No previous chemotherapy, neoadjuvant chemotherapy, recommendation changed from REC-E to REC-4.**
- **No previous chemotherapy, growth on neoadjuvant chemotherapy: "Observation" added.**
- **Previous chemotherapy, resection: "(preferred for previous oxaliplatin-based therapy)" added to "Observation."**
- **No progression change to "No growth on neoadjuvant chemotherapy."**
- **Progression changed to "Growth on neoadjuvant chemotherapy."**

REC-A 1 of 6
- **Transanal excision, bullet 2 modified: Unfavorable histopathologic features: >3 cm in size, T1, with grade III, or lymphovascular invasion, positive margin, *or sm3 depth of tumor invasion*.**

REC-A 3 of 6
- **Pathologic stage, bullet 2 modified: "Irregular discrete tumor deposits in pericolic or perirectal fat *away* from the leading edge of the tumor..." The following sentences were deleted, "In the 7th AJCC staging manual, extranodal deposits are staged as pN1c. In stage II colon cancer, the presence of extranodal tumor deposits significantly worsens the 5 year disease-free survival 80% vs 50-60% ($p<0.01$)."**

REC-A 5 of 6
- **BRAF Mutation Testing, bullet 1 modified: "There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status."**

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NCCN Guidelines Version 4.2013 Updates
Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion

Summary of changes in the 1.2013 version of the Guidelines for Rectal Cancer from the 3.2012 version include:

REC-C 1 of 2
- **Postoperative adjuvant chemotherapy: FLOX deleted.**

REC-E
- **Expanded from a total of 7 pages to a total of 9 pages to accommodate regimen listings.**

REC-E 1 of 9
- **Therapy After First Progression, "± bevacizumab" added to FOLFIRI and to irinotecan.**
- **Therapy After First Progression, "FOLFIRI ± ziv-aflibercept" added as a treatment option.**
- **Therapy After First Progression, "Irinotecan ± ziv-aflibercept" added as a treatment option.**

REC-E 2 of 9
- **Therapy After First Progression, "± bevacizumab" added to FOLFOX and to CapeOx.**

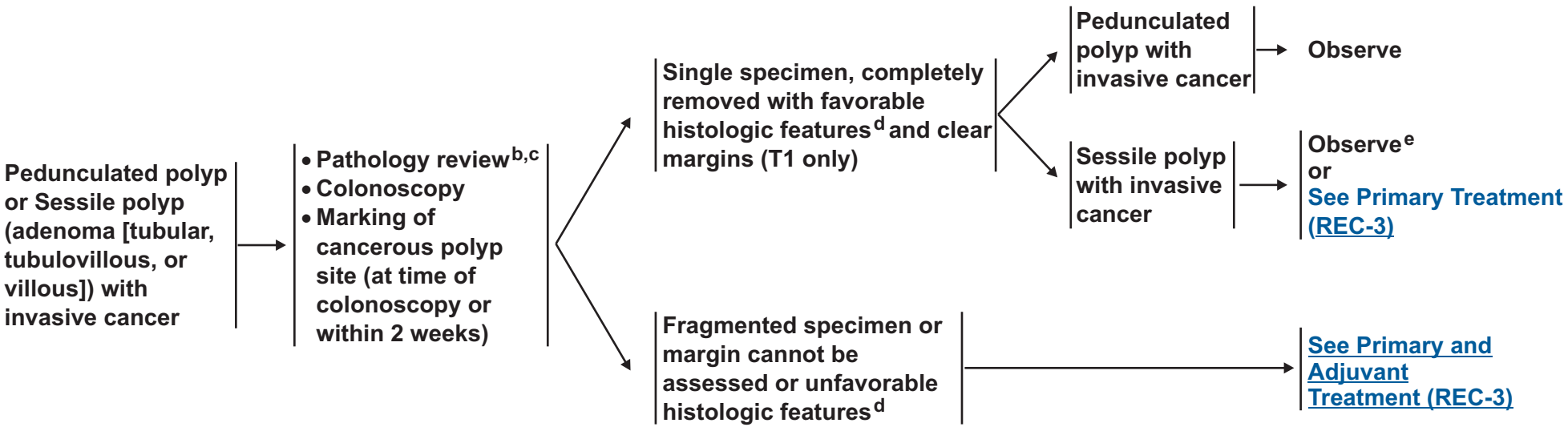
REC-E 3 of 9
- **Therapy After First Progression, "± bevacizumab" added to FOLFOX and to CapeOx.**
- **Therapy After First Progression, "± bevacizumab" added to FOLFIRI, irinotecan and to irinotecan + oxaliplatin.**
- **Therapy After First Progression, "± ziv-aflibercept" added to FOLFIRI.**
- **Therapy After First Progression, "± ziv-aflibercept" added to irinotecan.**

REC-E 5 of 9
- **Footnote "5", the following sentences were deleted: "There are insufficient data to support continuation of bevacizumab with a second-line regimen after progression on a bevacizumab-containing first line regimen, and such continuation of bevacizumab beyond progression is not recommended. If bevacizumab is not used in initial therapy, it may be appropriate to consider, if there is no contraindication to therapy."**
- **Footnote "9" modified: "There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status."**
- **Footnote "11" added: "There are no data to suggest activity of FOLFIRI-ziv-aflibercept in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients."**

REC-E 7 of 9
- **The following regimen was added:**
  FOLFIRI + ziv-aflibercept[12]
  Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1
  Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1
  5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
  Ziv-aflibercept 4 mg/kg IV
  Repeat every 2 weeks

REC-E 9 of 9
- **Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22949147.**

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



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

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

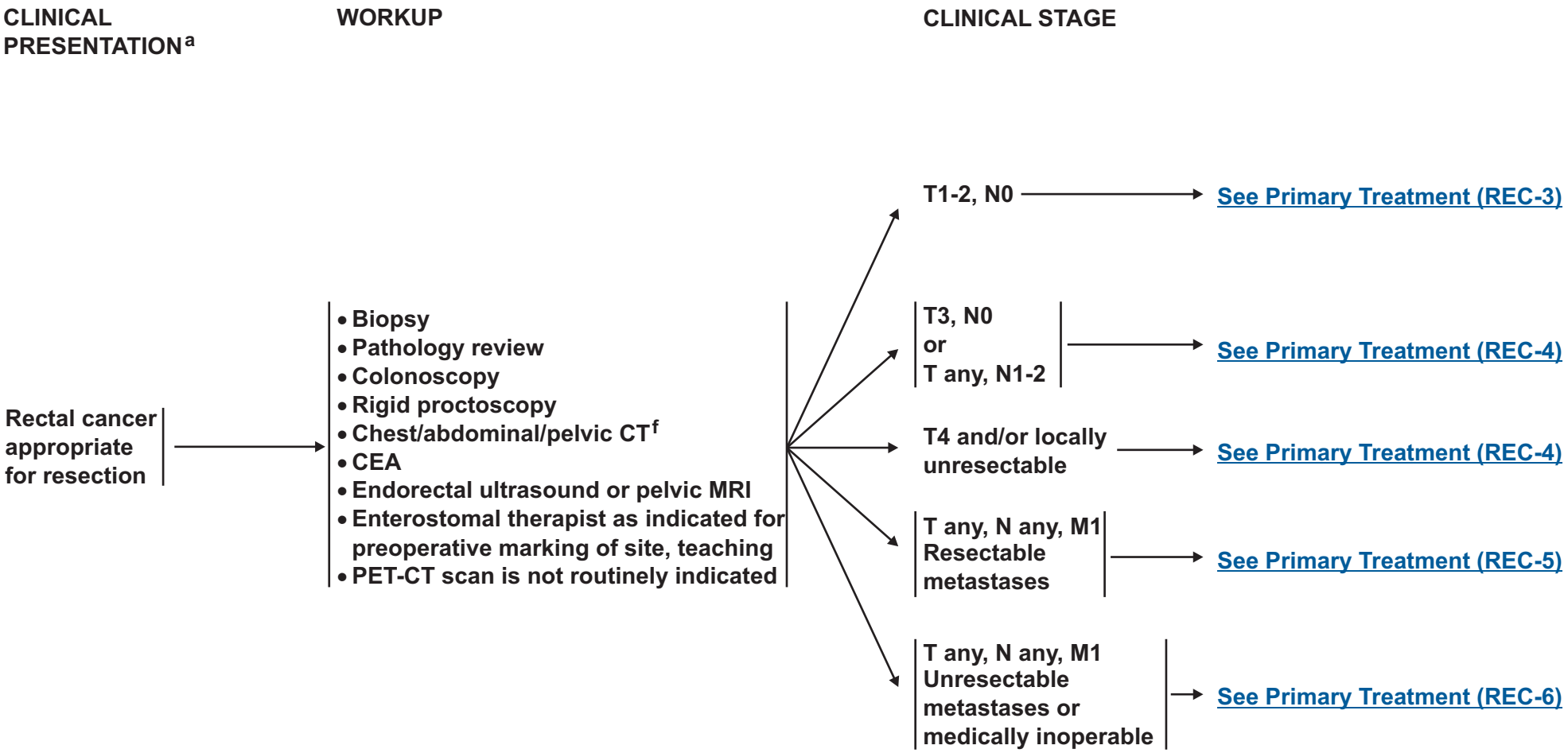
[c] It has not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis. College of American Pathologists Consensus Statement 1999. Prognostic factors in colorectal cancer. Arch Pathol Lab Med 2000;124:979-994.

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

[e] Observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, or hematogenous metastasis, but not lymph node metastasis) than polypoid malignant polyps. See Principles of Pathologic Review (REC-A) - Endoscopically removed malignant polyp.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



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

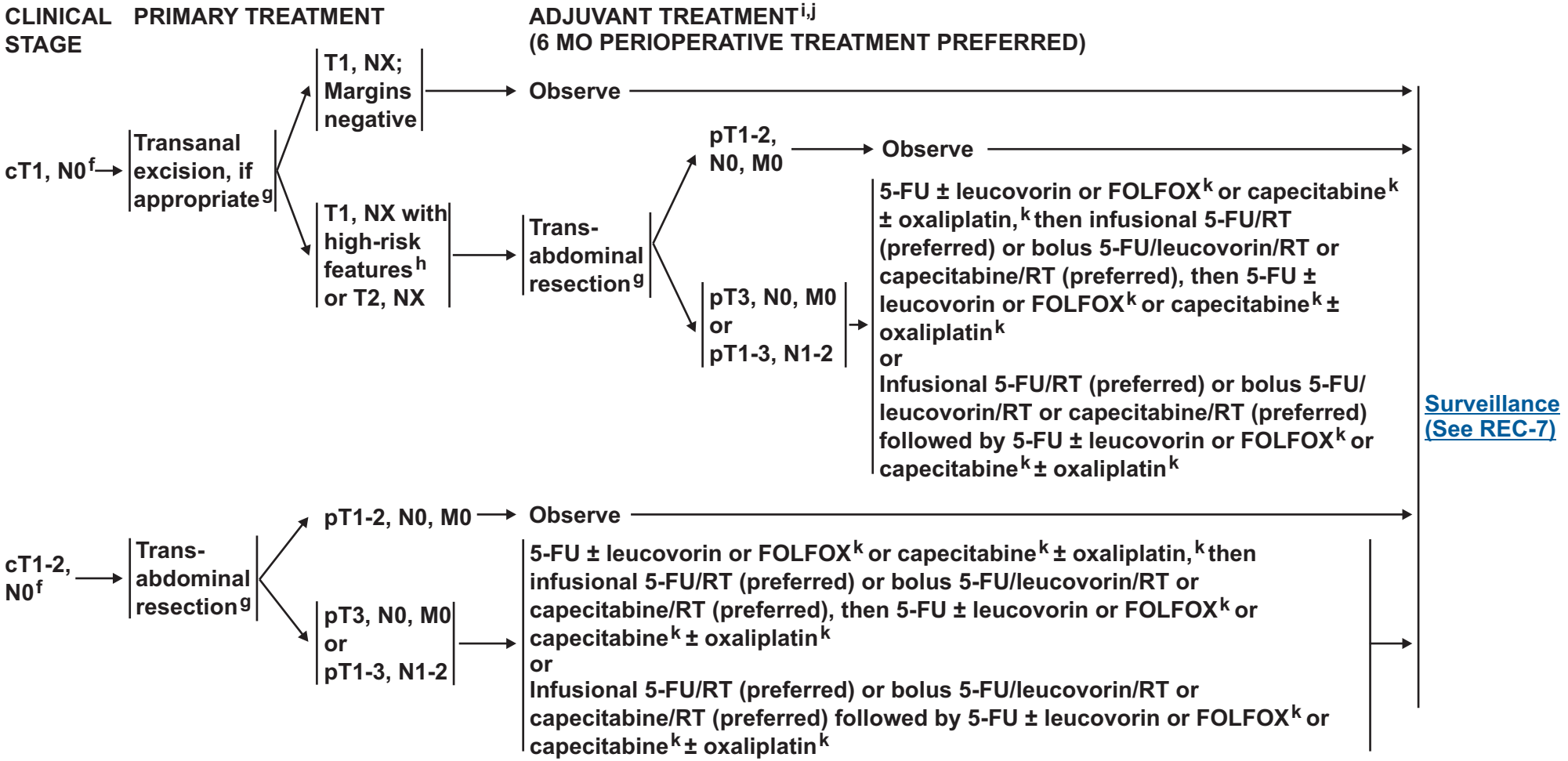
[f] CT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NCCN Guidelines Version 4.2013
Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion



[f] T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.

[g] See Principles of Surgery (REC-B).

[h] High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion.

[i] See Principles of Adjuvant Therapy (REC-C).

[j] See Principles of Radiation Therapy (REC-D).

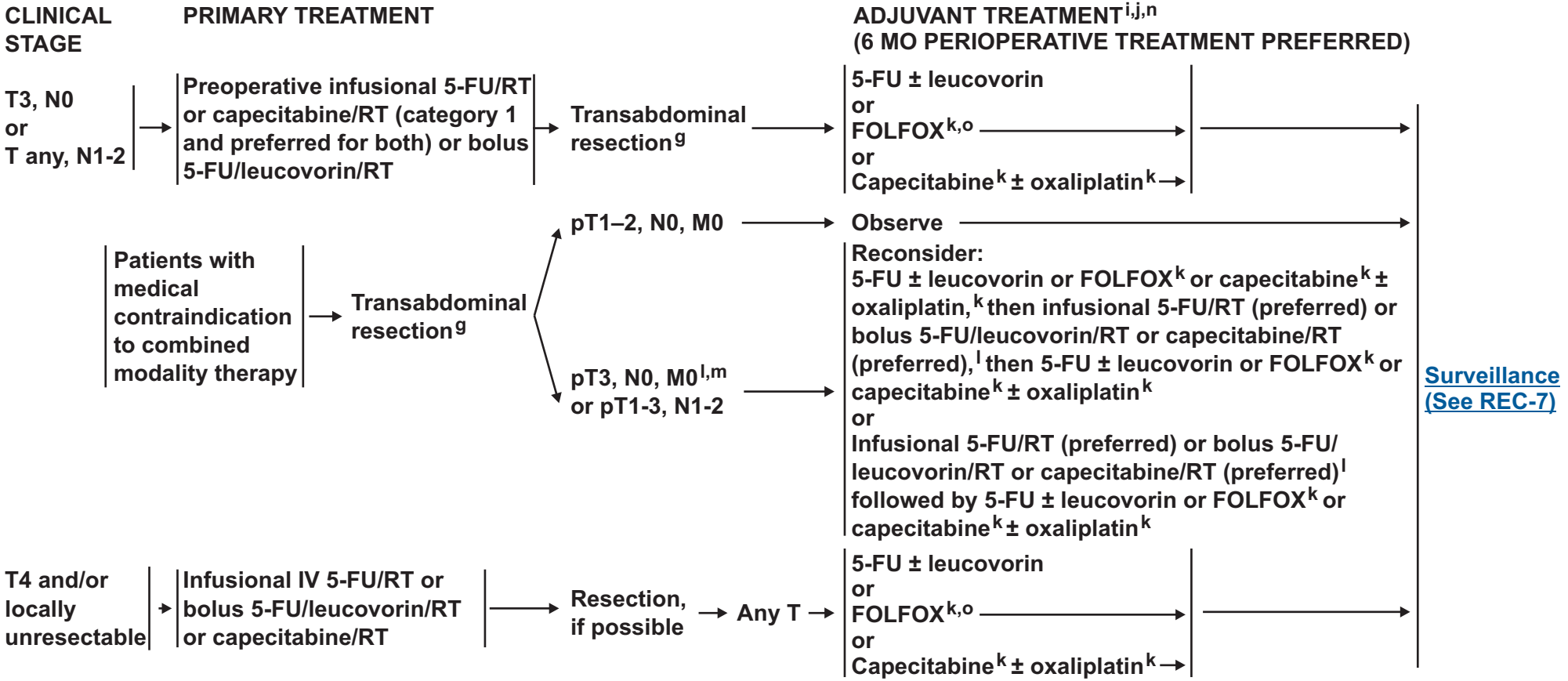
[k] The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NCCN Guidelines Version 4.2013
Rectal Cancer

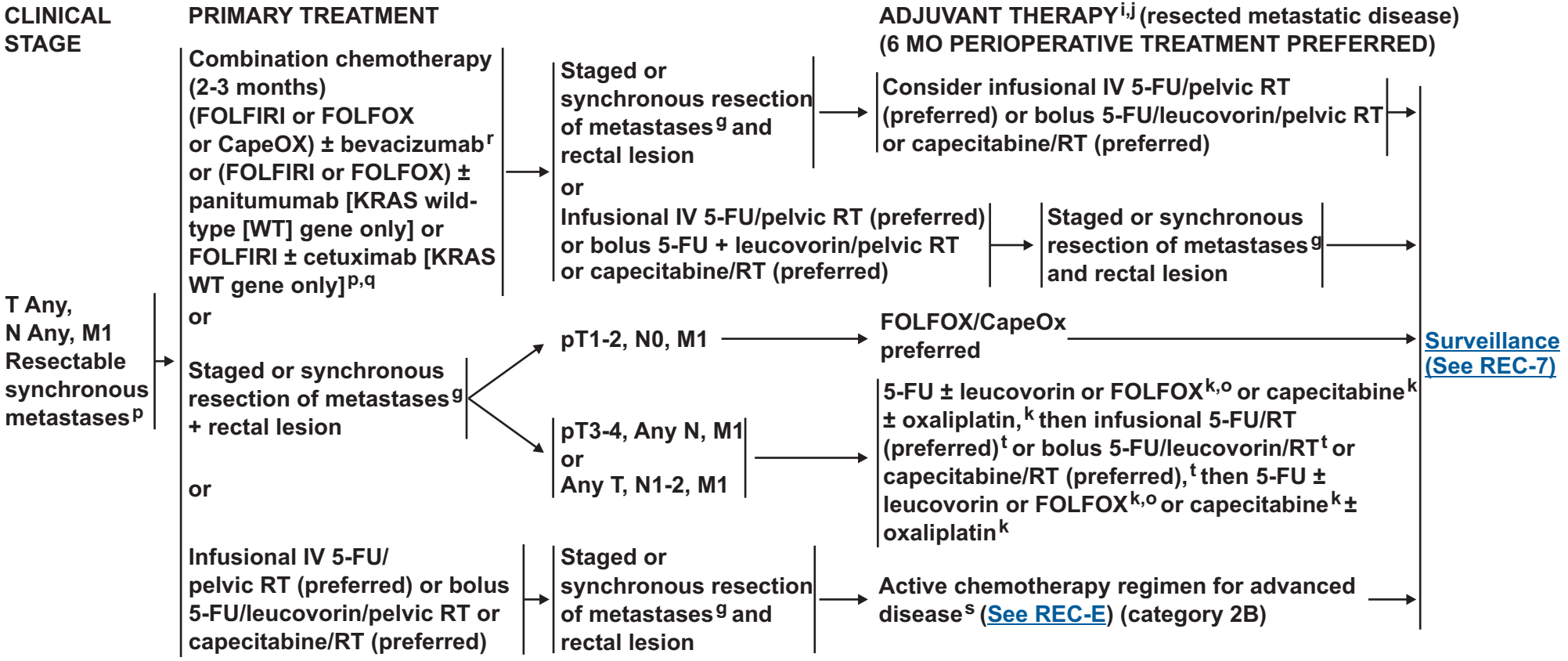
NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion



[g] See Principles of Surgery (REC-B).
[i] See Principles of Adjuvant Therapy (REC-C).
[j] See Principles of Radiation Therapy (REC-D).
[k] The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data in colon cancer.
[l] The use of agents other than fluoropyrimidines (eg, oxaliplatin) are not recommended concurrently with RT.
[m] For patients with proximal T3, N0 disease with clear margins and favorable prognostic features, the incremental benefit of RT is likely to be small. Consider chemotherapy alone.
[n] Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.
[o] An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



[g] See Principles of Surgery (REC-B).
[i] See Principles of Adjuvant Therapy (REC-C).
[j] See Principles of Radiation Therapy (REC-D).
[k] The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.
[o] An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.
[p] Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS and BRAF Mutation Testing.
[q] There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status.
[r] The safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery. There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.
[s] FOLFOXIRI is not recommended in this setting.
[t] RT is only recommended for patients at increased risk for pelvic recurrence.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

CLINICAL STAGE | **PRIMARY TREATMENT**

T Any, N Any, M1 Unresectable synchronous metastases[p] or Medically inoperable

→ **Symptomatic** → **Combination systemic chemotherapy[u] or 5-FU/RT or Capecitabine/RT (category 2B) or Resection of involved rectal segment or Laser recanalization or Diverting colostomy or Stenting** → **See Chemotherapy for Advanced or Metastatic Disease (REC-E)**

→ **Asymptomatic** → **See Chemotherapy for Advanced or Metastatic Disease (REC-E)** → **Reassess response to determine resectability**

[p] Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS and BRAF Mutation Testing.
[u] See Chemotherapy for Advanced or Metastatic Disease (REC-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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

SURVEILLANCE[w]

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA[v] 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[f] annually for up to 5 y for patients at high risk for recurrence[x]
- Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo
  - If advanced adenoma, repeat in 1 y
  - If no advanced adenoma,[y] repeat in 3 y, then every 5 y[z]
- Consider proctoscopy every 6 mo x 5 y for patient status post LAR[aa]
- PET-CT scan is not routinely recommended
- See Principles of Survivorship (REC-F)

→ Serial CEA elevation or documented recurrence → See Workup and Treatment (REC-8)

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

[v] If patient is a potential candidate for resection of isolated metastasis.

[w] 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(33):8512-8519.

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

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

[z] 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.

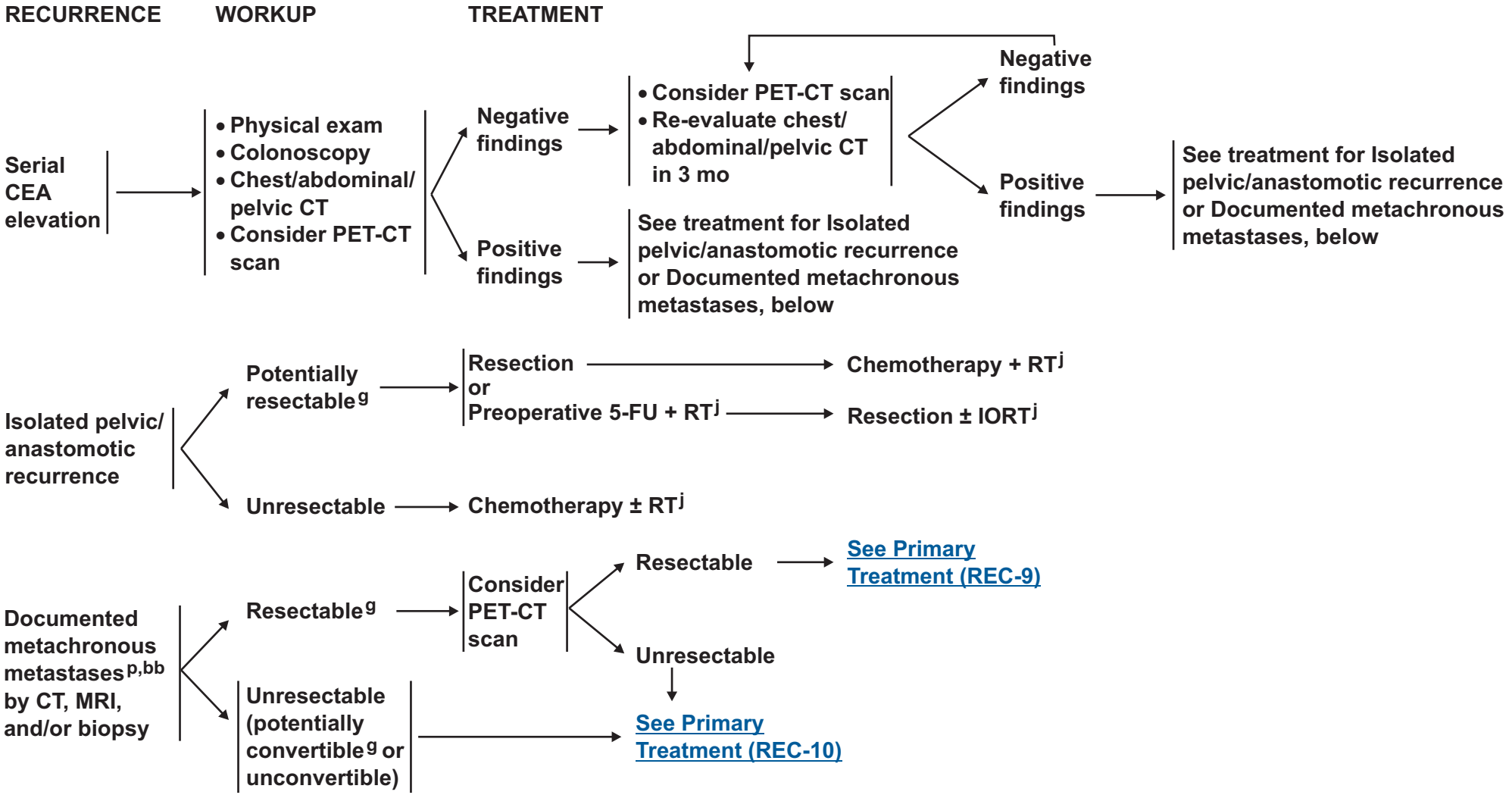
[aa] Patients with rectal cancer should also undergo limited endoscopic evaluation of the rectal anastomosis to identify local recurrence. Optimal timing for surveillance is not known. No specific data clearly support rigid versus flexible proctoscopy. The utility of routine endoscopic ultrasound for early surveillance is not defined.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NCCN Guidelines Version 4.2013
Rectal Cancer

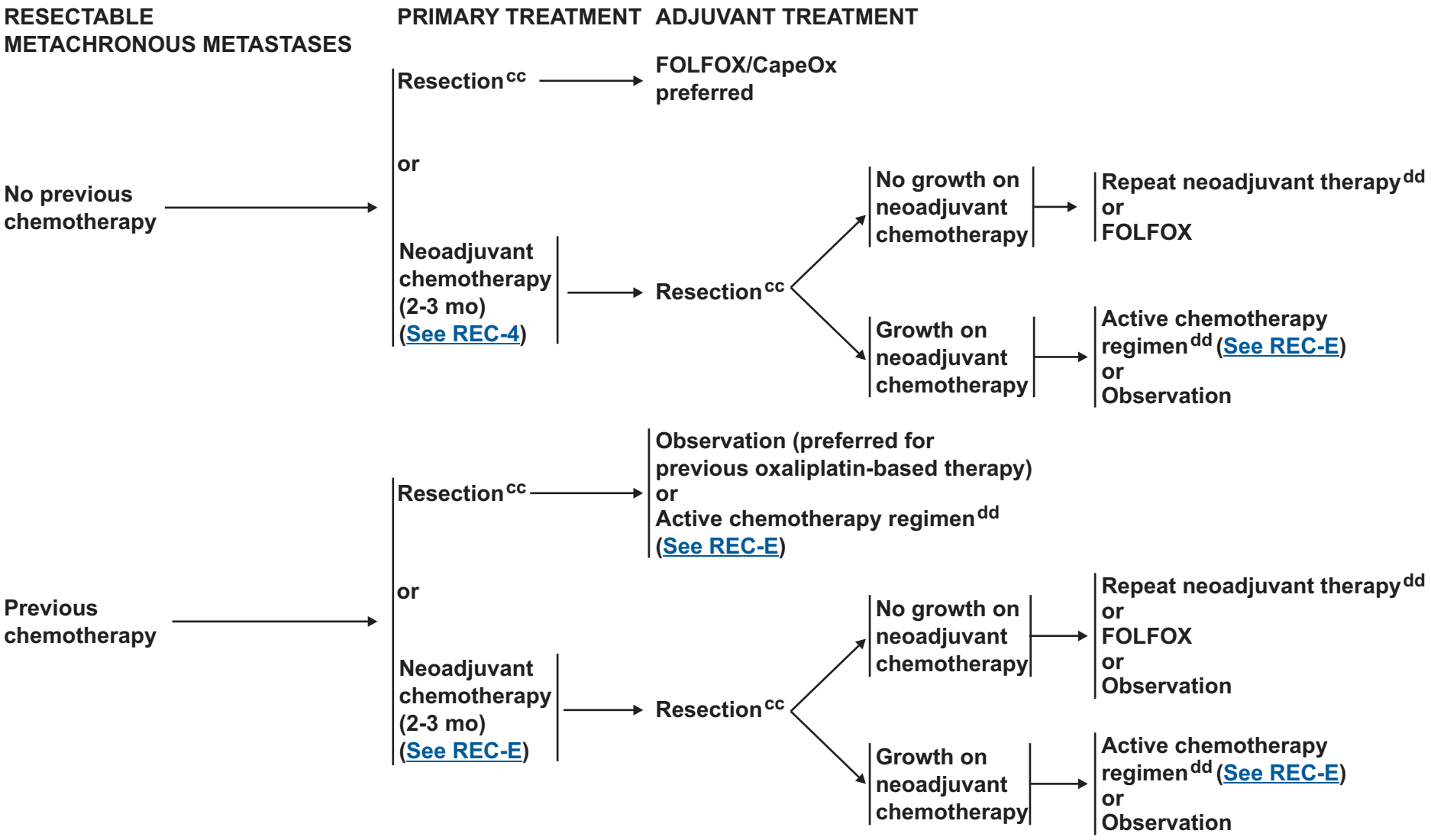
NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion



g See Principles of Surgery (REC-B).
j See Principles of Radiation Therapy (REC-D).
p Determination of tumor KRAS (if KRAS non-mutated,consider BRAF testing). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS and BRAF Mutation Testing.
bb 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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



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

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

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

UNRESECTABLE METACHRONOUS METASTASES

PRIMARY TREATMENT

- **Previous adjuvant FOLFOX within past 12 months** →
  - **FOLFIRI ± bevacizumab**
    or
    FOLFIRI ± ziv-aflibercept
    or
    Irinotecan ± bevacizumab
    or
    Irinotecan ± ziv-aflibercept
    or
    FOLFIRI + (cetuximab or panitumumab) (KRAS WT gene only)[p,ee]
    or
    (Cetuximab or panitumumab) (KRAS WT gene only)[p,ee] + irinotecan
- **Previous adjuvant FOLFOX >12 months**
- **Previous 5-FU/LV or capecitabine**
- **No previous chemotherapy**

→ **Active chemotherapy regimen (See REC-E)**

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

- **Converted to resectable** → **Resection[cc]** → **Active chemotherapy regimen[dd] (See REC-E) or Observation**
- **Remains unresectable** → **Active chemotherapy regimen (See REC-E)**

[g] See Principles of Surgery (REC-B).

[p] Determination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS and BRAF Mutation Testing.

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

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

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

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF PATHOLOGIC REVIEW (1 of 6)

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 to be a "malignant polyp."
- Favorable histologic features grade 1 or 2, no angiolymphatic invasion, and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as: 1) tumor <1 mm from the transected margin, 2) tumor <2 mm from the transected margin, and 3) tumor cells present within the diathermy of the transected margin.[1-4]
- Unfavorable histologic features grade 3 or 4, angiolymphatic invasion, or a "positive margin." See above for definition of a positive margin.
- 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 outcome (residual disease, recurrent disease, mortality, or 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]

Transanal Excision

- Favorable histopathologic features: <3 cm size, T1, grade I or II, no lymphatic or venous invasion, or negative margins.[8,9]
- Unfavorable histopathologic features: >3 cm in size, T1, with grade III, or lymphovascular invasion, positive margin, or sm3 depth of tumor invasion.[8-10]

Rectal Cancer Appropriate for Resection

- Histologic confirmation of primary malignant rectal neoplasm

See Pathologic Stage on REC-A 2 of 6
See Lymph Node Evaluation on REC-A 4 of 6
See KRAS and BRAF Mutation Testing REC-A 5 of 6
See references on REC-A 6 of 6

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF PATHOLOGIC REVIEW (2 of 6)

Pathologic Stage

- **The following parameters should be reported:**
  - **Grade of the cancer**
  - **Depth of penetration (T), the T stage, is based on viable tumor. Acellular mucin pools are not considered to be residual tumor in those cases treated with neoadjuvant therapy.**
  - **Number of lymph nodes evaluated and number positive (N). Acellular mucin pools are not considered to be residual tumor in those cases treated with neoadjuvant therapy.**
  - **Status of proximal, distal, and circumferential (radial) margins.[11-12]**
  - **A positive circumferential resection margin (CRM) has been defined as ≤1 mm[13-14]** **See Staging (ST-1)**
  - **CRM[13-17]**
  - **Neoadjuvant treatment effect[15,16,18,19]**
  - **Lymphovascular invasion[15,16,20]**
  - **Perineural invasion[21-23]**
  - **Extranodal tumor deposits[24-25]**
- **CRM - A positive CRM is defined as tumor ≤1 mm from the margin. This assessment includes both tumor within a lymph node as well as direct tumor extension. However, if CRM positivity is based solely on intranodal tumor, it should be stated in the pathology report. A positive CRM is a more powerful predictor of local recurrence in patients treated with neoadjuvant therapy. A positive CRM secondary to lymph node metastasis in some studies has been associated with lower recurrence rates than by direct extension.[13-17]**
- **Neoadjuvant treatment effect - The most recent College of American Pathologists Guidelines on examination specimens of the rectum and the AJCC Cancer Staging Manual, Seventh Edition require commenting on treatment effect after neoadjuvant therapy. The minimum requirement is:**
  - **Treatment effect present.**
  - **No definitive response identified.**

  The system used to grade tumor response as modified from Ryan R, et al. Histopathology 2005;47:141-146.
  - **0 (complete response) - no viable cancer cells.**
  - **1 (moderate response) - single cells or small groups of cancer cells.**
  - **2 (minimal response) - residual cancer outgrown by fibrosis.**
  - **3 (poor response) - minimal or no tumor kill; extensive residual cancer.**

    According to the College of American Pathologists, it is optional to grade the tumor response to treatment. However, the NCCN Rectal Cancer Guidelines Panel recommends grading tumor response.[15,16,18,19]

See Pathologic Stage continued on REC-A 3 of 6

See Endoscopically Removed Malignant Polyps, Rectal Cancer Appropriate for Resection on REC-A 1 of 6

See Lymph Node Evaluation on REC-A 4 of 6

See KRAS and BRAF Mutation Testing on REC-A 5 of 6

See references on REC-A 6 of 6

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF PATHOLOGIC REVIEW (3 of 6)

Pathologic Stage (continued)

- **Perineural invasion (PNI) - The presence of PNI is associated with a significantly worse prognosis. In multivariate analysis, PNI has been shown to be an independent prognostic factor for cancer-specific and overall disease-free survival. For stage II rectal cancer, those with PNI have a significantly worse 5-year disease-free survival compared to those without PNI (29% vs. 82% [p=.0005]). In stage III rectal cancer, those with PNI have a significantly worse prognosis.[21-23]**

- **Extranodal tumor deposits - Irregular discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered to be extranodal tumor deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular invasion or, more rarely, PNI. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report.**

See Endoscopically Removed Malignant Polyps, Rectal Cancer Appropriate for Resection on REC-A 1 of 6
See Pathologic Stage on REC-A 2 of 6
See Lymph Node Evaluation on REC-A 4 of 6
See KRAS and BRAF Mutation Testing on REC-A 5 of 6
See references on REC-A 6 of 6

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF PATHOLOGIC REVIEW (4 of 6)

Lymph Node Evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately identify early-stage colorectal cancers.[11,12,26] 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.[26-34] Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Two studies confined only to rectal cancer have reported 14 and >10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.[30,33] The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade, and tumor site.[27] For stage II (pN0) colon cancer, if fewer than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs. 19, $p < .05$, 7 vs. 10, $p < .001$).[35,36] If 12 lymph nodes is considered the number needed to accurately stage stage II tumors, then only 20% of cases treated with neoadjuvant therapy had adequate lymph node sampling.[36] To date, the number of lymph nodes needed to accurately stage neoadjuvant-treated cases is unknown. However, it is not known what is the clinical significance of this in the neoadjuvant setting, as postoperative therapy is indicated in all patients who receive preoperative therapy regardless of the surgical pathology results.

Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry

- Examination of the sentinel lymph node allows an intense histologic and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple H & E sections and/or immunohistochemistry (IHC) to detect cytokeratin-positive cells.[37-39] The AJCC Cancer Staging Manual, Seventh Edition[40] considers "tumor clusters" <0.2 mm to be isolated tumor cells (pN0) and not metastatic carcinoma. However, some investigators believe that size should not affect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.[41,42]
- Some studies have shown that the detection of IHC cytokeratin-positive cells in stage II (N0) colon cancer (defined by H & E) has a worse prognosis, while others have failed to show this survival difference. In these studies, isolated tumor cells were considered to be micrometastases.[43-47]
- At the present time the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.[37-39,43-47]

See Endoscopically Removed Malignant Polyps, Rectal Cancer Appropriate for Resection on REC-A 1 of 6
See Pathologic Stage on REC-A 2 of 6
See KRAS and BRAF Mutation Testing on REC-A 5 of 6
See references on REC-A 6 of 6

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF PATHOLOGIC REVIEW (5 of 6)

KRAS Mutation Testing

- Mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to therapy with antibodies targeted to the epidermal growth factor receptor (EGFR).[48,49]
- Testing for mutations in codons 12 and 13 should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).
- The testing can be performed on formalin-fixed paraffin-embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the KRAS mutations are similar in both specimen types.[50]

BRAF Mutation Testing

- Patients with a V600E BRAF mutation appear to have a poorer prognosis. There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after a patient has progressed on first-line therapy.[51,52]
- Testing for the BRAF V600E mutation can be performed on formalin-fixed paraffin-embedded tissues. This is usually performed by PCR amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting BRAF V600E mutation. This testing should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) and qualified to perform high complexity clinical laboratory (molecular pathology) testing.

Evaluation of Mesorectum (TME)

- The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal 2/3).[53-55]

MSI Testing - See NCCN Guidelines for Colorectal Cancer Screening

- The panel recommends that MMR protein testing be performed for all patients younger than 50 years with rectal cancer, based on an increased likelihood of Lynch syndrome in this population.

See Endoscopically Removed Malignant Polyps, Rectal Cancer Appropriate for Resection on REC-A 1 of 6
See Pathologic Stage on REC-A 2 of 6
See Lymph Node Evaluation on REC-A 4 of 6
See references on REC-A 6 of 6

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF PATHOLOGIC REVIEW (6 of 6) - 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] Hager T, Gall FP, and Hermanek P. Local excision of cancer of the rectum. Dis Colon Rect 1983;26:149-151.
[9] Willett, CG, Tepper JE, Donnelly S, et al. Patterns of failure following local excision and local excision and postoperative radiation therapy for invasive rectal adenocarcinoma. J Clin Oncol 1989;7:1003-1008.
[10] Nascimbeni R, Burgart LJ, Nivatvongs S, and Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum 2002;45:2001-2006.
[11] Compton CC and Greene FL. The staging of colorectal cancer: 204 and beyond. Cancer J Clin 2004;54:295-308.
[12] Compton CC, Fielding LP, Burkhardt LJ, et al. Prognostic factors in colorectal cancer. College of American pathologists consensus statement. Arch Pathol Lab Med 2000;124:979-994.
[13] Nagtegaal ID, Merijnenca M, Kranenbarg EK, et al. Circumferential margin involvement is still an important predictive local occurrence in rectal carcinoma. Not one millimeter but two millimeters is the limit. Am J Surg Pathol 2002;26:350-357.
[14] Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surgery 2002;89 327-334.
[15] Washington MK, Berlin J, Branton P, et al. Protocol for examination of specimens from patients with primary carcinoma of the colon and rectum. Arch Pathol Lab Med 2009;133:1539.
[16] Edge SB, Byrd D, Compton C, et al (eds). AJCC Cancer Staging Manual 7th Edition. Springer NY, 2010.
[17] Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26:303-312.
[18] Rodel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23:8688-8696.
[19] Gavioli M, Luppi G, Losi L, et al. Incidence and clinical impact of sterilized disease and minimal residual disease after preoperative radiochemotherapy for rectal cancer. Dis Colon Rectum 2005;48:1851-1857.
[20] Nissan A, Stojadinovic A, Shia J, et al. Predictors of recurrence in patients with T2 and early T3, N0 adenocarcinoma of the rectum treated by surgery alone. J Clin Oncol 2006;24:4078-4084.
[21] Liebig C, Ayala G, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clin Oncol 2009;27:5131-5137.
[22] Fujita S, Shimoda T, Yoshimura K, et al. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. J Surg Oncol 2003;84:127-131.
[23] Quah HM. Identification of patients with high risk stage II colon cancer for adjuvant therapy. Dis Colon Rect 2008;51:53-507.
[24] Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. J Clin Pathol 2007;117:287-294.
[25] Lo DS, Pollett A, Siu LL, et al. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. Cancer 2008;112:50-54.
[26] Sobin HL and Green EFL. TNM classification. Clarification of number of regional lymph nodes for PN0. Cancer 2001;92:452.
[27] 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.
[28] Chaplin S, Scerottini G-P, Bosman FT, et al. 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.
[29] 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.
[30] Pocard M, Panis Y, Malassagane B, et al. Assessing the effectiveness of mesorectal excision in rectal cancer. Dis Colon Rectum 1998;41:839-845.
[31] 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.
[32] 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.
[33] Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 2001;19:157-162.
[34] 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.
[35] Wichmann MW, Mollar C, Meyer G, et al. Effect of pre-operative radiochemotherapy on lymph node retrieval after resection of rectal cancer. Arch Surg 2002;137:206-210.
[36] Baxter NN, Morris AM, Rothenberger DA, and Tepper JE. Impact of pre-operative radiation for rectal cancer on subsequent lymph node evaluation: population based analysis. Int J Radiation Oncology Biol Phys 2005;61:426-431.
[37] 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.
[38] 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 Gastroinest Surg 2002;6:322-330.
[39] 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.
[40] AJCC Cancer Staging Manual, 7th ed. Edge SB, Byrd D, Compton CC, et al. (editors) Springer, New York, 2010.
[41] 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.
[42] Hermanek P, Hutter RVP, Sobin LH, Wittekind CH. Classification of isolated tumor cells and micrometastasis. Cancer 1999;86:2668-73.
[43] 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.
[44] 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.
[45] 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.
[46] 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.
[47] 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.
[48] Lievre A, Bachatte J-B, Blige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with Cetuximab. J Clin Oncol 2008;26:374-379.
[49] Amado IG, Wolf M, Peters M, et al. Wild-type KRAS is required for panitunumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-1634.
[50] Etienne-Gimeldi M-C, Formenta J-L, Francoual M, et al. KRAS mutations in treatment outcome in colorectal cancer in patients receiving exclusive fluoropyrimidine. Clin Cancer Research 2008;14:4830-4835.
[51] Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26:5705-5712.
[52] Bokmeyer C, Cutsem EV, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer 2012;48:1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22753904.
[53] Parfitt JR and Driman KR. Total mesorectal excision specimen for rectal cancer: A review of its pathological assessment. J Clin Pathol 60:849-855, 2007.
[54] Jass JR, 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 in colorectal carcinoma. Human Pathol 38:537-545, 2007.
[55] Nagtegaal ID, Vandevelde CJA, Derworp EV, et al. Macroscopic evaluation of the rectal cancer resection margin: Clinical significance of the pathologist in quality control. J Clin Oncol 20: 1729-1734, 2002.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF SURGERY (1 of 3)

Transanal Excision:[1]

- **Criteria**
  - **<30% circumference of bowel**
  - **<3 cm in size**
  - **Margin clear (>3 mm)**
  - **Mobile, nonfixed**
  - **Within 8 cm of anal verge**
  - **T1 only**
  - **Endoscopically removed polyp with cancer or indeterminate pathology**
  - **No lymphovascular invasion or PNI**
  - **Well to moderately differentiated**
  - **No evidence of lymphadenopathy on pretreatment imaging**
- **When the lesion can be adequately identified in the rectum, transanal endoscopic microsurgery (TEM) may be used. TEM for more proximal lesions may be technically feasible.**

Transabdominal Resection: Abdominoperineal resection or low anterior resection or coloanal anastomosis using total mesorectal excision

- **Management principles**
  - **The treating surgeon should perform a rigid proctoscopy before initiating treatment.**
  - **Remove primary tumor with adequate margins.**
  - **Laparoscopic surgery is preferred in the setting of a clinical trial.**[2]
  - **Treat draining lymphatics by total mesorectal excision.**
  - **Restore organ integrity, if possible.**
  - **Surgery should be 5-10 weeks following full-dose 5.5-week neoadjuvant chemoradiation.**
- **Total mesorectal excision**
  - **Reduces positive radial margin rate.**
  - **Extend 4-5 cm below distal edge of tumors for an adequate mesorectal excision. In distal rectal cancers (ie, <5 cm from anal verge), negative distal bowel wall margin of 1-2 cm may be acceptable; this must be confirmed to be tumor free by frozen section.**
  - **Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision.**
- **Lymph node dissection**[3,4]
  - **Biopsy or remove clinically suspicious nodes beyond the field of resection if possible.**
  - **Extended resection is not indicated in the absence of clinically suspected nodes.**

See Criteria for Resectability of Metastases on REC-B 2 of 3

[1] Nash GM, Weiser MR, Guillem JG, et al. Long-term survival after transanal excision of T1 rectal cancer. Dis Colon Rectum 2009;52:577-82.
[2] Long-term outcomes from laparoscopic surgery have not been reported. Current clinical trials are exploring open versus laparoscopic approach.
[3] Gunderson LL, Sargent DJ, Tepper JB, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol 2004;22(10):1785-1796.
[4] Greene FL, Stewart AK, Norton HJ. New tumor-node-metastasis staging strategy for node-positive (stage III) rectal cancer: an analysis. J Clin Oncol 2004;22(10):1778-1784.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF SURGERY (2 of 3)
CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIONAL THERAPIES WITHIN SURGERY

Liver

- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.[1]
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[2,3]
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.[4-6] Plan for a debulking resection (less than an R0 resection) is not recommended.
- Patients with resectable metastatic disease and primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization or staged liver resections can be considered.
- Ablative techniques may be considered alone or in conjunction with resection.[1] All original sites of disease need to be amenable to ablation or resection.
- Some institutions use arterially directed embolic therapy in select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, with predominant hepatic metastases (category 3).
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable (category 3).
- Re-resection can be considered in selected patients.[7]

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[8-11]
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.[12-15]
- Re-resection can be considered in selected patients.[16]
- Ablative techniques can be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable (category 3)

Evaluation for Conversion to Resectable Disease

- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.[17-20]
- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites need to be amenable to resection.[21] Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[22]

See footnotes on REC-B 3 of 3

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

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF SURGERY (3 of 3) - REFERENCES

[1]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.

[2]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.

[3]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.

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

[5]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.

[6]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.

[7]Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. Ann Surg 1997;225:51-62.

[8]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.

[9]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.

[10]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.

[11]Sakamoto T, Tsubota N, Iwanaga K, Yuki T, Matsuoka H, Yoshimura M. Pulmonary resection for metastases from colorectal cancer. Chest 2001;119:1069-1072.

[12]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.

[13]Irshad K, Ahmad F, Morin JE, Mulder DS. Pulmonary metastases from colorectal cancer: 25 years of experience. Can J Surg 2001;44:217-221.

[14]Ambiru S, Miyazaki M, Ito H, et al. Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 1998;82:274-278.

[15]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.

[16]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.

[17]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.

[18]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.

[19]Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol. 2006 May 1;24(13):2065-72.

[20]Pawlik TM, Olino K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg. 2007 Jul;11(7):860-8.

[21]Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol. 2006 Aug 20;24(24):3939-45.

[22]Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13:1284-92.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF ADJUVANT THERAPY (1 of 2)

Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy. A total of approximately 6 months of perioperative treatment is preferred.

Postoperative Adjuvant Chemotherapy:

- **mFOLFOX 6[1]**
  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 to a total of 6 mo perioperative therapy.
- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)[2]**
  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 to a total of 6 mo perioperative therapy.
- **Capecitabine[3]**
  Capecitabine 1250 mg/m^2 twice daily days 1-14 every 3 weeks to a total of 6 months perioperative therapy.
- **CapeOx[4]**
  Oxaliplatin 130 mg/m^2 over 2 hours, day 1. Capecitabine 1000 mg/m^2 twice daily days 1-14 every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy.
- **5-FU 500 mg/m^2 IV bolus weekly x 6 + leucovorin 500 mg/m^2 IV weekly x 6, each 8-week cycle. Repeat every 8 weeks to a total of 6 months perioperative therapy.[5]**

Dosing Schedules for Concurrent Chemotherapy/RT:

- **XRT + continuous infusion 5-FU[6]**
  5-FU 225 mg/m^2 over 24 hours 5 or 7 days/week during XRT
- **XRT + 5-FU/leucovorin[7]**
  5-FU 400 mg/m^2 IV bolus + leucovorin 20 mg/m^2 IV bolus for 4 days during week 1 and 5 of XRT
- **XRT + Capecitabine[8,9]**
  Capecitabine 825 mg/m^2 twice daily 5 or 7 days/week + XRT x 5 weeks

IMPORTANT NOTE REGARDING LEUCOVORIN SHORTAGE, PLEASE SEE MS-17

See footnotes on REC-C 2 of 2

*Leucovorin 400 mg/m^2 is the equivalent of levoleucovorin 200 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24-h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2 over 48 hours) to minimize medication errors.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

PRINCIPLES OF ADJUVANT THERAPY (2 of 2) - REFERENCES

[1]Cassidy J, Clarke S, Diaz Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008;26:2006-12.

[2]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.

[3]Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352(26):2696-2704.

[4]Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007;25:102-109. Haller DG, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer. J Clin Oncol 2011;29:1465-1471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21383294

[5]Petrelli N, Douglass Jr HO, Herrare L, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. J Clin Oncol 1989;7:1419-1426.

[6]O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994; 331:502-507.

[7]Tepper JE, O'Connell M, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control--final report of Intergroup 0114. J Clin Oncol 2002;20:1744-1750.

[8]Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04 [abstract]. J Clin Oncol 2011;29 (suppl):3503. Available at: http://abstract.asco.org/AbstView_102_76910.html

[9]Hofheinz R, Wenz FK, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: A randomized, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-588.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

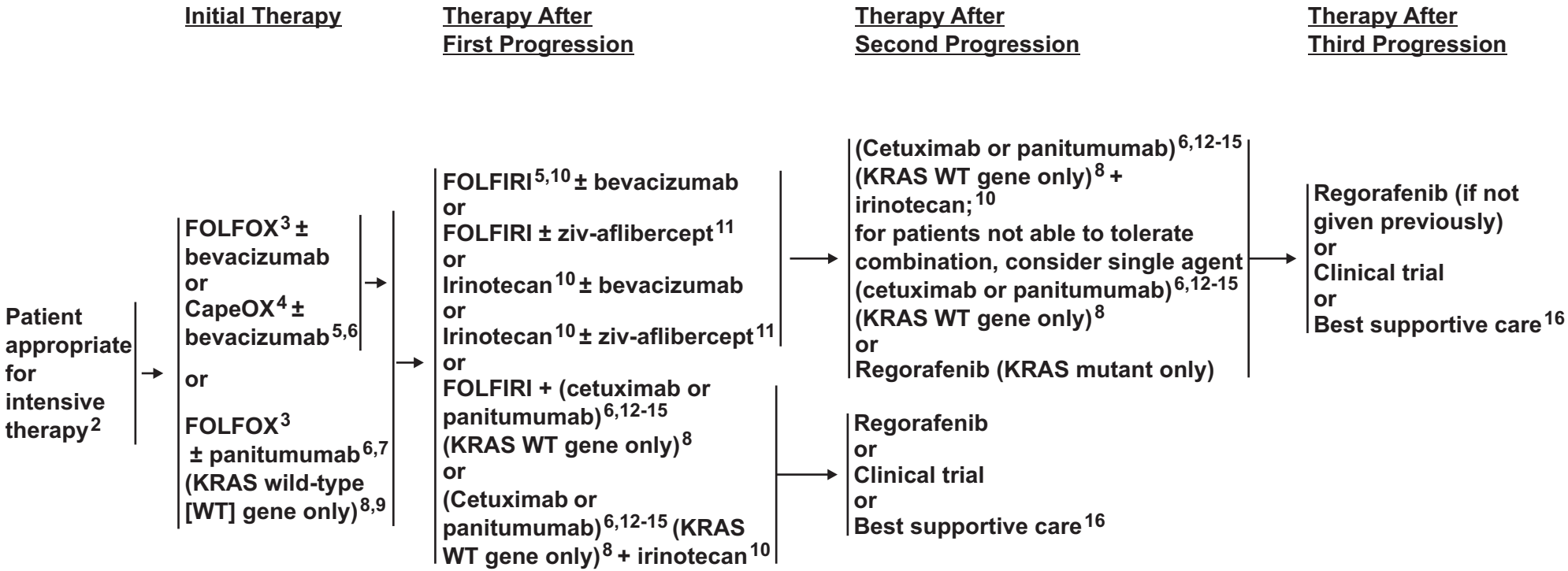
PRINCIPLES OF RADIATION THERAPY

- Radiation therapy fields should include the tumor or tumor bed, with a 2-5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
- Multiple radiation therapy fields should be used (generally a 3- or 4-field technique). Positioning and other techniques to minimize the volume of small bowel in the fields should be encouraged.
- For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.
- Intensity-modulated radiation therapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations including re-irradiation of recurrent disease after previous radiotherapy.
- Radiation doses:
  - 45-50 Gy in 25-28 fractions to the pelvis.
  - For resectable cancers, after 45 Gy a tumor bed boost with a 2 cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4-9.0 Gy in 3-5 fractions for postoperative radiation.
  - Small bowel dose should be limited to 45 Gy.
- Intraoperative radiation therapy (IORT), if available, should be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers. If IORT is not available, 10-20 Gy external beam radiation and/or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.
- For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.
- 5-fluorouracil-based chemotherapy should be delivered concurrently with radiation therapy.
- In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiotherapy, IMRT, or stereotactic body radiation therapy (SBRT). (category 3)
- Side effect management:
  Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.
  Male patients should be counseled on infertility risks and given information regarding sperm banking.
  Female patients should be counseled on infertility risks and given information regarding oocyte, egg or ovarian tissue banking prior to treatment.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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



Additional options on REC-E 2 of 9 through REC-E 3 of 9

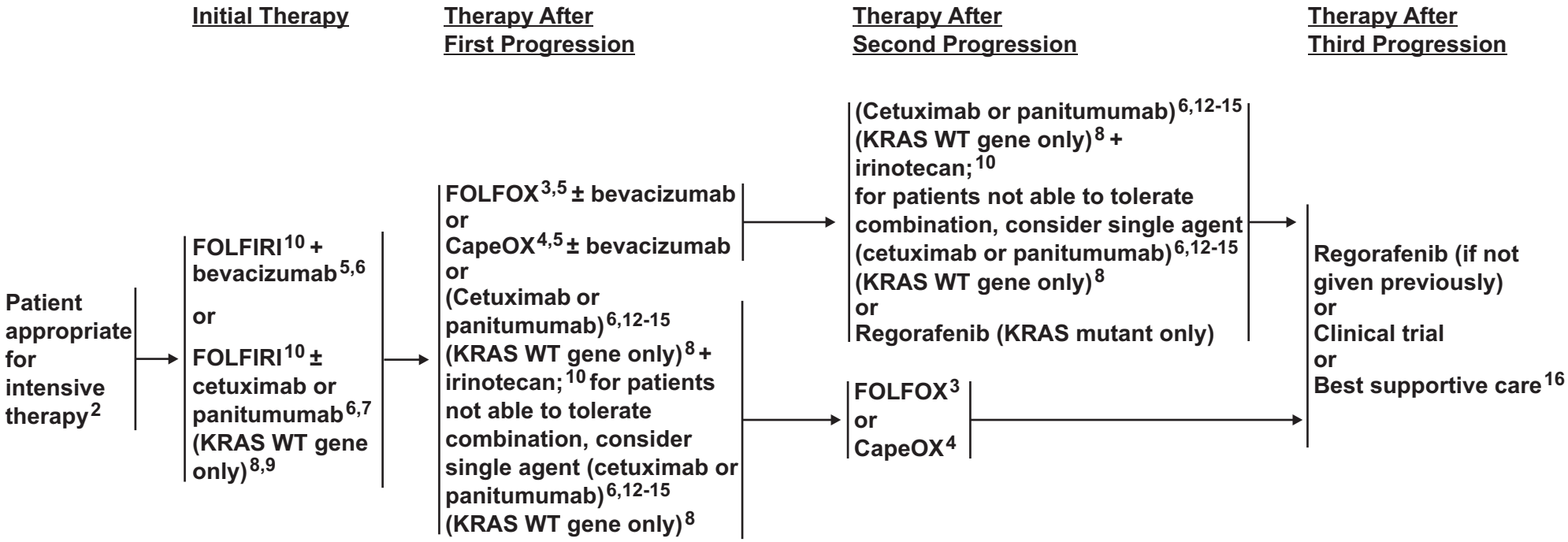
Patients not appropriate for intensive therapy, see REC-E 4 of 9

See footnotes on REC-E 5 of 9

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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



Additional options on REC-E 1 of 9 through REC-E 3 of 9

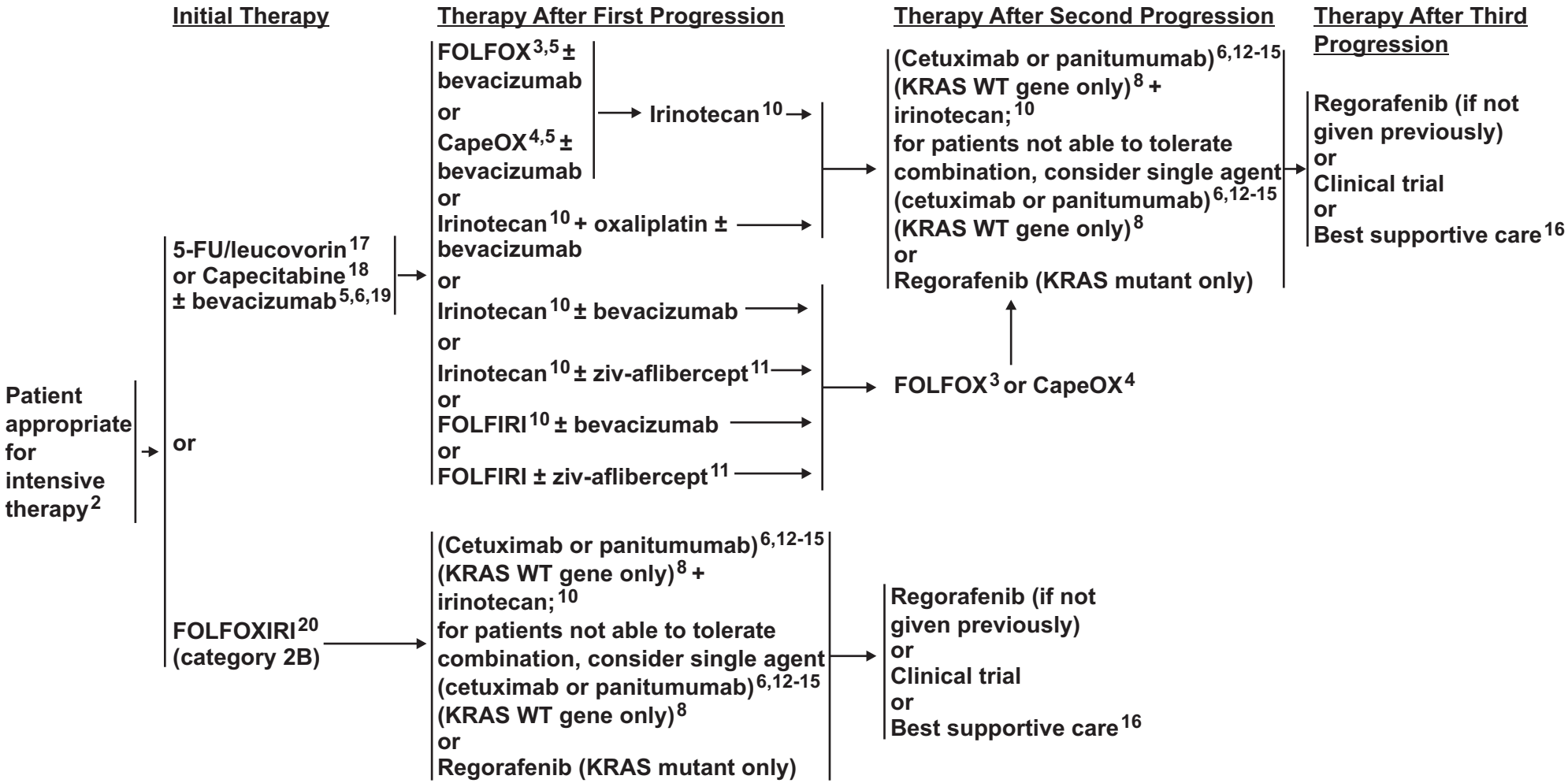
Patients not appropriate for intensive therapy, see REC-E 4 of 9

See footnotes on REC-E 5 of 9

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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



Additional options on REC-E 1 of 9 through REC-E 2 of 9

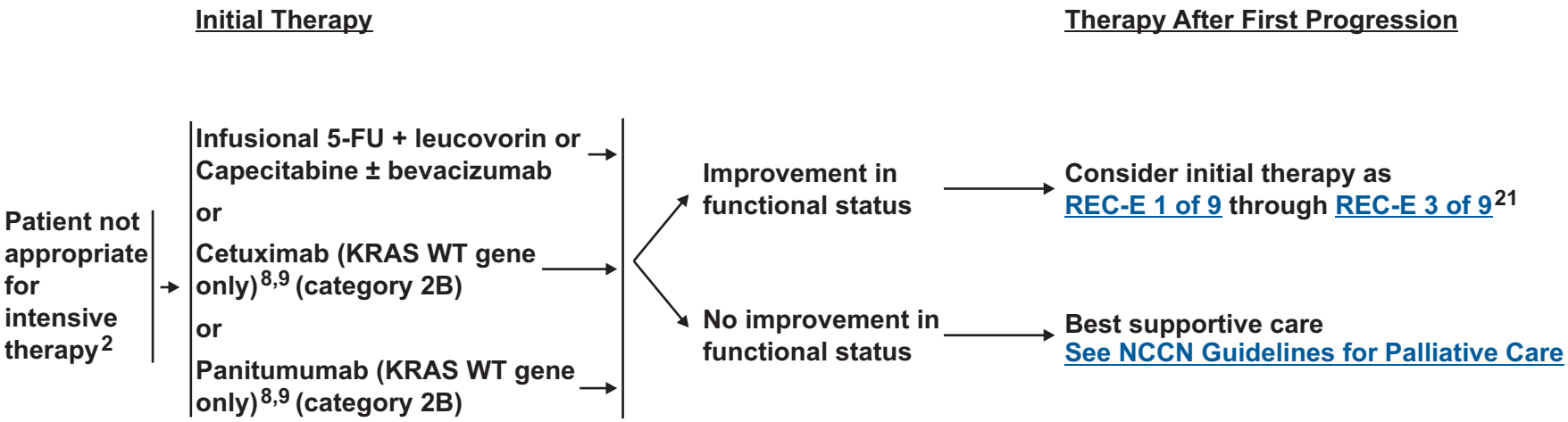
Patients not appropriate for intensive therapy, see REC-E 4 of 9

See footnotes on REC-E 5 of 9

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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



See footnotes on REC-E 5 of 9

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (5 of 9)

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

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

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

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

[5] There is an increased risk of stroke and other arterial events, especially in those aged ≥ 65 years. The use of bevacizumab may interfere with wound healing.

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

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

[8] See Principles of Pathologic Review (REC-A 5 of 6) - KRAS and BRAF Mutation Testing.

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

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

[11] There are no data to suggest activity of FOLFIRI-ziv-aflibercept in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.

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

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

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

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

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

[17] Infusional 5-FU is preferred.

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

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

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

[21] 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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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

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

mFOLFOX6 + Bevacizumab [2,3,¶]
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)† IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

mFOLFOX6 + Panitumumab [2,4]
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)† IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

CapeOX [1,5]
Oxaliplatin 130 mg/m^2 IV over 2 hours, day 1
Capecitabine 850-1000‡ mg/m^2 twice daily PO for 14 days
Repeat every 3 weeks

CapeOX + Bevacizumab [1,5,6,¶]
Oxaliplatin 130 mg/m^2 IV over 2 hours, day 1
Capecitabine 850-1000‡ mg/m^2 PO twice daily for 14 days
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

IMPORTANT NOTE REGARDING LEUCOVORIN SHORTAGE, PLEASE SEE MS-17

See References on REC-E 9 of 9

*Leucovorin 400 mg/m^2 is the equivalent of levoleucovorin 200 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24-h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2 over 48 hours) to minimize medication errors.

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

¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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

FOLFIRI[7]
Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1
Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Repeat every 2 weeks

FOLFIRI[7] + Bevacizumab[8,¶]
Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1
Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFIRI[7] + Cetuximab
Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1
Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† IV continuous infusion
Repeat every 2 weeks
Cetuximab 400 mg/m^2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 60 minutes weekly[9]
or Cetuximab 500 mg/m^2 IV over 2 hours, day 1, every 2 weeks[10]

FOLFIRI[7] + Panitumumab[11]
Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1
Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept[12]
Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1
Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Ziv-aflibercept 4 mg/kg IV
Repeat every 2 weeks

Capecitabine[13]
850-1250 mg/m^2 PO twice daily, days 1-14
Repeat every 3 weeks

Capecitabine[13] + Bevacizumab[6¶]
Capecitabine 850-1250 mg/m^2 PO twice daily, days 1-14
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

IMPORTANT NOTE REGARDING LEUCOVORIN SHORTAGE, PLEASE SEE MS-17

See References on REC-E 9 of 9

*Leucovorin 400 mg/m^2 is the equivalent of levoleucovorin 200 mg/m^2.
†NCCN recommends limiting chemotherapy orders to 24-h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2 over 48 hours) to minimize medication errors.
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[14]
Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)[7]
Leucovorin* 400 mg/m² IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)† continuous infusion
Repeat every 2 weeks

Weekly
Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV bolus injection 1 hour after the start of leucovorin. Repeat weekly.[15]
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week[16]

IROX[17]
Oxaliplatin 85 mg/m² IV over 2 hours, followed by irinotecan 200 mg/m² over 30 or 90 minutes every 3 weeks

FOLFOXIRI[18]
Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² day 1, leucovorin 400* mg/m² day 1, fluorouracil 1600 mg/m²/day x 2 days (total 3200 mg/m² over 48 hours)† continuous infusion starting on day 1. Repeat every 2 weeks

Irinotecan
Irinotecan 125 mg/m² IV over 30-90 minutes, days 1 and 8
Repeat every 3 weeks[19,20]
Irinotecan 300-350 mg/m² IV over 30-90 minutes, day 1
Repeat every 3 weeks

Cetuximab (KRAS WT gene only) ± irinotecan[10,21]
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly
or Cetuximab 500 mg/m² IV every 2 weeks[10]
±
Irinotecan 300-350 mg/m² IV every 3 weeks
or Irinotecan 180 mg/m² IV every 2 weeks
or Irinotecan 125 mg/m² on days 1 and 8 and repeat every 3 weeks

Cetuximab (KRAS WT gene only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[21]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[10]

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

Regorafenib[23]
Regorafenib 160 mg PO daily days 1-21
Repeat every 28 days

IMPORTANT NOTE REGARDING LEUCOVORIN SHORTAGE, PLEASE SEE MS-17

See References on REC-E 9 of 9

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

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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

[1] Cassidy J, Clarke S, Diaz Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008;26:2006-12.

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

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

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

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

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

[7] 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.

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

[9] 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.

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

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

[12] Allegra CJ, Lakomy R, Tabernero J, et al. Effects of prior bevacizumab (B) use on outcomes from the VELOUR study: A phase III study of aflibercept (Afl) and FOLFIRI in patients (pts) with metastatic colorectal cancer (mCRC) after failure of an oxaliplatin regimen [abstract]. J Clin Oncol 2012;30 (suppl.):3505. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/3505

[13] 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.

[14] 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.

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

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

[19] 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.

[20] 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.

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

[22] 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.

[23] Grothey A, Sobrero AF, Siena S, et al. Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after standard therapies [abstract]. J Clin Oncol 2012;30 (suppl 4):LBA385. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=115&abstractID=87795.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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

Colorectal Cancer Surveillance:

- See REC-7
- Long-term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning are not recommended beyond 5 years.

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

- Chronic diarrhea or incontinence
  - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.
- Urogenital dysfunction after resection and/or pelvic radiation[6,7]
  - Screen for sexual dysfunction, erectile dysfunction, dyspareunia, and vaginal dryness
  - Screen for urinary incontinence, frequency, and urgency
  - Consider referral to urologist or gynecologist for persistent symptoms.

Prescription for Survivorship and Transfer of Care to Primary Care Physician:[8] **(If primary physician will be assuming cancer surveillance responsibilities)**

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

Cancer Screening Recommendations:

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

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

Counseling Regarding Healthy Lifestyle and Wellness:[9]

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

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

[1] Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer. Cancer 2007;110: 2075-2082.
[2] Sprangers MAG, Taal BG, Aaronson NK, et al. Quality of life in colorectal cancer: stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-369.
[3] Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther 2003;18:987-994.
[4] DeSnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. Eur J Cancer Care 2006;15:244-251.
[5] McGough C, Baldwin C, Frost C, Andreyev HJN. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. Br J Cancer 2004;90:2278-2287.
[6] Lange MM, Mass CP, Marijnen CAM, et al. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer 2009;45:1578-88.
[7] Lange MM, Mass CP, Marijnen CAM, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. Brit J Cancer 2008;95:1020-28.
[8] Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.:The National Academies Press;2006.
[9] Kushi LH, Byers T, Doyle C, et al and The American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity CA Cancer J Clin 2006;56:254-281.

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.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NCCN Guidelines Version 4.2013 Staging Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion

Table 1. Definitions for T, N, M

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria[a]
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum[b]
T4b	Tumor directly invades or is adherent to other organs or structures[b,c]

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

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

Table 2. Anatomic Stage/Prognostic Groups

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	Any T	Any N	M1b	-	-

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

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

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

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

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

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, Seventh Edition (2010), published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) 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 SBM, on behalf of the AJCC.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview MS-2
Risk Assessment MS-2
TNM Staging MS-3
Pathology MS-3
The Role of Vitamin D in Colorectal Cancer MS-5
Clinical Presentation and Treatment of Nonmetastatic Disease MS-6
- Management of Polypoid Cancer MS-6
- Management of Rectal Cancer MS-6
  - Clinical Evaluation/Staging MS-7
  - Surgical Approaches MS-8
  - Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease MS-10
    - Preoperative versus postoperative radiation MS-11
    - Concurrent chemotherapy with radiation MS-12
    - Induction chemotherapy MS-14
    - Preoperative chemotherapy without chemoradiation MS-14
    - Technical aspects of radiation therapy MS-14
    - Short-course radiation MS-15
    - Response to neoadjuvant treatment MS-16
    - Wait-and-see non-operative approach for clinical complete responders MS-16
    - Adjuvant chemotherapy MS-17
    - Leucovorin shortage MS-17
  - Recommendations for patients with T1 and T2 lesions MS-18
  - Recommendations for patients with T3 lesions and lesions with nodal involvement MS-18
  - Recommendations for patients with T4 lesions and/or locally unresectable disease MS-19

Principles of the Management of Metastatic Disease MS-19
- Liver-Directed Therapies MS-20
  - Hepatic Arterial Infusion MS-20
  - Liver-Directed Radiation MS-21
  - Tumor Ablation MS-21
- Peritoneal Carcinomatosis MS-22
- Determining Resectability MS-23
- Conversion to Resectability MS-23
- Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease MS-25
  - Perioperative Bevacizumab for Resectable Metastatic Disease MS-26
  - Perioperative Cetuximab and Panitumumab for Resectable Metastatic Disease: The Role of KRAS and BRAF Status MS-27
- Chemotherapy for Advanced or Metastatic Disease MS-29
- Recommendations for Treatment of Resectable Synchronous Metastases MS-29
- Recommendations for Treatment of Unresectable Synchronous Metastases MS-30
- Recommendations for Treatment of Metachronous Metastases MS-31

End Points for Advanced Colorectal Cancer Clinical Trials MS-32
Post-Treatment Surveillance MS-32
- Managing an Increasing CEA Level MS-33

Treatment of Locally Recurrent Disease MS-33
Survivorship MS-34
Summary MS-35
References MS-37

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2012, an estimated 40,290 new cases of rectal cancer will occur in the United States (23,500 cases in men; 16,790 cases in women). During the same year, it is estimated that 51,690 people will die from rectal and colon cancer combined.[1] Despite these statistics, the incidence per 100,000 population of colon and rectal cancers has decreased from 60.5 in 1976 to 46.4 in 2005.[2] In addition, mortality from colorectal cancer has decreased by more almost 35% from 1990 to 2007,[3] possibly because of earlier diagnoses through screening and better treatment modalities.

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing rectal cancer. These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, neoadjuvant treatment, surgical management, adjuvant treatment, management of recurrent and metastatic disease, patient surveillance, and survivorship. These guidelines overlap considerably with the NCCN Guidelines for Colon Cancer, especially in the treatment of metastatic disease. The recommendations in these guidelines are classified as category 2A except where noted. The panel unanimously endorses patient participation in a clinical trial over standard or accepted therapy, especially for cases of advanced disease and for patients with locally aggressive colorectal cancer who are receiving combined modality treatment.

Risk Assessment

Approximately 20% of cases of colorectal cancer are associated with familial clustering,[4,5] and first-degree relatives of patients with newly diagnosed colorectal adenomas[6] or invasive colorectal cancer[7] are at increased risk for colorectal cancer. Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC])[8,9] and familial adenomatous polyposis (FAP).[10] Therefore, it is recommended that all patients with colorectal cancer be queried regarding their family history and considered for risk assessment, as detailed in the NCCN Guidelines for Colorectal Cancer Screening (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Lynch syndrome is the most common form of genetically determined colorectal cancer predisposition, accounting for 2% to 4% of all colorectal cancer cases.[8,9,11,12] This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Although identifying a germline mutation in an MMR gene through sequencing is definitive for Lynch syndrome, patients usually undergo selection by considering family history and performing an initial test on tumor tissue before sequencing. One of two different initial tests can be performed on colorectal cancer specimens to identify individuals who might have Lynch syndrome: immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation, or analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units.[13] Testing the *BRAF* gene for mutation is indicated when immunohistochemical analysis shows that MLH1 expression is absent in the tumor. The presence of a *BRAF* mutation indicates that *MLH1* expression is down-regulated through somatic methylation of the promoter region of the gene and not through a germline mutation.[13]

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

The panel recommends that MMR protein testing be performed for all patients younger than 50 years with colorectal cancer, based on an increased likelihood of Lynch syndrome in this population.[14] Some centers, however, now perform immunohistochemistry (and sometimes MSI) testing on all colorectal tumors to determine which patients should have genetic testing for Lynch syndrome. The cost effectiveness of this so-called reflex testing approach has been confirmed for colorectal cancer, and this approach was endorsed by the Evaluation of Genomic Applications in Prevention and Practice (EGAPP) working group at the Centers for Disease Control and Prevention (CDC).[15] A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening (available online at www.NCCN.org).

TNM Staging

The NCCN Guidelines for Rectal Cancer adhere to the current TNM staging system of the 7th edition of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual (Table 1 of the guidelines).[16] Several changes to the staging of colorectal cancer were made in the 7th edition.[17] For instance, based on new data showing differential prognosis,[18] T4 lesions have now been subdivided into T4a (tumor penetrates to the surface of the visceral peritoneum) and T4b (tumor directly invades or is adherent to other organs or structures). Another change of note is the subdivision of N1 into N1a (metastasis in 1 node), N1b (metastasis in 2-3 nodes), and N1c (without regional nodal metastases, but with tumor deposits in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues); and of N2 into N2a (metastasis in 4-6 nodes) and N2b (metastasis in 7 or more nodes). These subsets reflect new data showing that the number of involved nodes influences prognosis[19] and new data on the prognostic value of tumor deposits within the lymph drainage area of the primary tumor.[20-24] Stage I rectal cancer is defined as T1-T2, N0, M0. Stage II disease is subdivided into IIA (if the primary tumor is T3, N0, M0), IIB (for T4a, N0, M0 lesions), and IIC (for T4b, N0, M0). Stage III disease is subdivided into IIIA (T1-2, N1/N1c, M0 or T1, N2a, M0), IIIB (T3-4a, N1/N1c, M0 or T2-T3, N2a, M0 or T1-T2, N2b, M0), and IIIC (T4a, N2a, M0 or T3-4a, N2b, M0 or T4b, N1-2, M0). Stage IVA disease is defined as any T, any N, and the presence of distant metastasis confined to 1 organ or site (M1a). Stage IVB disease is defined as any T, any N, with metastases in more than 1 organ or site or in the peritoneum (M1b).[16] The prefixes "p" and "yp" used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.[16]

Pathology

Pathologic staging information is provided by examination of the surgical specimen. Some of the information that should be detailed in the report of the pathologic evaluation of rectal cancer[25] includes: (1) gross description of the tumor and specimen; (2) grade of the cancer; (3) depth of penetration and extension to adjacent structures (T); (4) number of regional lymph nodes evaluated; (5) number of positive regional lymph nodes (N); (6) the presence of distant metastases to other organs or sites including non-regional lymph nodes (M); (7) the status of proximal, distal, and circumferential (radial) margins[16,25-30]; (8) neoadjuvant treatment effect[16,25,31,32]; (9) lymphovascular invasion[16,25,33]; (10) perineural invasion[34-36]; and (11) the number of tumor deposits.[20-24]

The 7th edition of the AJCC staging manual 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 status of the resection margins.[16] The completeness of the resection is scored as R0 for complete tumor resection with all margins negative; R1 for incomplete tumor resection with microscopic involvement of a margin;

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

and R2 for incomplete tumor resection with gross residual tumor that was not resected.[16]

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer.[37] Whereas the radial margin for resected segments of the colon that are completely encased by a peritonealized (serosal) surface is also referred to as the peritoneal margin, the CRM is very important in segments of the colon or rectum that are either not encased or only partially encased in peritoneum.[37] The CRM is the closest radial margin between the deepest penetration of the tumor and the edge of resected soft tissue around the rectum (ie, the retroperitoneal or subperitoneal aspect of the tumor) or from the edge of a lymph node and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen that often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen.[38] The panel defines a positive CRM as tumor within 1 mm from the transected margin.[28,30,39]

Accurate pathologic assessment of the CRM of resected rectal tumor specimens is very important since the CRM has been shown to be a strong predictor of both local recurrence and overall survival,[37,39-41] including in patients undergoing neoadjuvant therapy,[29] and is an important consideration when post-operative treatment decisions are made. Furthermore, in a retrospective study of over 17,000 patients with rectal cancer, CRM was found to be a better predictor of local recurrence for patients undergoing surgery as initial therapy than for those who had received preoperative therapy.[29] CRM positivity based solely on intranodal tumor should be noted as such; some studies have shown that positive intranodal CRM is associated with lower recurrence rates than a positive CRM by direct tumor extension. Additional components of the pathological evaluation of the surgical specimen following a total mesorectal excision (TME) are described under ‘Surgical Approaches,’ below.

The AJCC and the College of American Pathologists (CAP) recommend evaluation of 10-14 and 12-18 lymph nodes to accurately identify early stage colorectal cancers, respectively.[16,25,37] The number of lymph nodes that can be retrieved varies with age and gender of the patient and on tumor grade or site.[42] The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify early stage rectal cancer.[43] Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Two studies confined only to rectal cancer have reported 14 and >10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.[44,45] Furthermore, the mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs. 19, $P < .05$; 7 vs. 10, $P \leq 0.0001$).[46,47] The panel recommends a minimum of 12 lymph nodes be examined.

Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells and the identification of particular tumor antigens through immunohistochemical analysis have been reported.[48,49] Although results of some of these studies seem promising, there is no uniformity in the definition of “true” clinically relevant metastatic carcinoma. Some studies have considered detection of single cells by immunohistochemistry or by H&E, so-called isolated tumor cells (ITC), to be micrometastasis.[49,50] In addition, results of one study demonstrated that, following neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.[51] Furthermore, in a recent study involving 156 patients with colon cancer and 44 patients with rectal cancer, this “ultra-staging” of lymph nodes

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

only changed the staging for 1% of patients.[52] Others have noted that micrometastasis found in node-negative patients did not predict outcome.[53] Presently, the use of sentinel lymph nodes and detection of cancer cells by immunohistochemistry should be considered investigational, and the results should be used with caution in clinical management decisions.

There is also potential benefit of assessing regional lymph nodes for isolated tumor cells. One study of 312 consecutive pN0 patients found that positive cytokeratin staining was associated with a higher risk of recurrence.[54] Relapse occurred in 14% of patients with positive nodes compared to 4.7% of those with negative nodes (HR, 3.00; 95% CI, 1.23 to 7.32; *P* = .013). A recent systematic review and metaanalysis came to a similar conclusion, finding decreased survival in pN0 patients with immunohistochemical or reverse transcriptase polymerase chain reaction (RT-PCR) evidence of tumor cells in regional nodes.[55] As with sentinel nodes, the molecular detection of cancer cells by in regional nodes should be also considered investigational, and the results should be used with caution in clinical management decisions.

The 7th edition of the AJCC Staging Manual and the most recent College of American Pathologists Guidelines require that the pathology report comment on treatment effects of neoadjuvant therapy.[16,25] The minimum requirement is a yes/no whether a definitive treatment effect is identified. However, it is the opinion of the panel, as well as of the College of American Pathologists, that the tumor response should be graded on a scale of 0 (complete response – no viable cancer cells observed) to 3 (poor response – minimal or no tumor kill; extensive residual cancer).[16,25,31,32]

Several studies have demonstrated that the presence of perineural invasion (PNI) is associated with a significantly worse prognosis.[34-36] For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at 1 institution found a 4-fold greater 5-year survival in patients without perineural invasion versus patient whose tumors invaded nearby neural structures.[35] Multivariate analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year disease-free survival compared to those without PNI (29% vs. 82%; *P* = .0005).[36] Similar results were seen for patients with stage III disease.[34]

Extra-nodal tumor deposits, or satellite nodules, are irregular discrete tumor deposits in the perirectal fat that are away from the leading edge of the tumor and show no evidence of residual lymph node tissue, but that are within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor. Most of these tumor deposits are thought to be due to lymphovascular invasion or occasionally perineural invasion. The number of extra-nodal tumor deposits should be recorded in the pathology report, since they have been shown to be associated with reductions in disease-free and overall survival.[20-24] Multivariate survival analysis in one study showed that patients with pN0 tumors without satellite nodules had a 91.5% 5-year survival rate compared to 37.0% for patients with pN0 tumors and the presence of satellite nodules (*P* < .0001).[24] Extra-nodal tumor deposits are classified as pN1c.[16]

The Role of Vitamin D in Colorectal Cancer

Prospective studies have suggested that vitamin D deficiency may contribute to colorectal cancer incidence and that vitamin D supplementation may decrease colorectal cancer risk.[56-59] Furthermore, 3 prospective studies showed that low vitamin D levels were associated with increased mortality of patients with colorectal cancer, especially in stage III and IV disease.[60,61] Moreover, in a study of 515 patients with

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

stage IV colorectal cancer, 82% of patients were found to be vitamin D-insufficient (levels <30 ng/mL) and 50% found to be vitamin D-deficient (<20 ng/mL).[62] Nonetheless, no study has yet examined whether vitamin D supplementation improves patient outcomes. In a recent report, the Institute of Medicine concluded that data supporting a role for vitamin D were only conclusive in bone health, not in cancer and other diseases.[63] Citing this report and the lack of level 1 evidence, the panel does not currently recommend routine screening for vitamin D deficiency or supplementation of vitamin D in patients with colorectal cancer.

Clinical Presentation and Treatment of Nonmetastatic Disease

Management of Polypoid Cancer

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or villous adenoma, physicians should review pathology[64] and consult with the patient. A malignant rectal polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1).[65] Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore incapable of regional nodal metastasis.[37] The panel recommends marking the cancerous polyp site at the time of colonoscopy or within 2 weeks.

In patients with pedunculated polyps with invasive cancer (tubular, tubulovillous, or villous adenoma), no additional surgery is required if the polyp has been completely resected with favorable histological features.[64] Favorable histological features include lesions of grade 1 or 2 without angiolymphatic invasion and with a negative resection margin.[64] For patients with a completely removed, single-specimen, sessile polyp (pT1) with favorable histological features and clear margins, observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than polyploid malignant polyps. Also see the section on 'Endoscopically removed malignant polyp' in 'Principles of Pathologic Review' (REC-A) in the guidelines. Rectal surgery is also an option for these patients.

Rectal surgery is also recommended for patients with polyps with unfavorable histological features or when the specimen is fragmented or margins cannot be assessed. Unfavorable histological features for adenomas are grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. In such cases, risk of nodal involvement is higher. 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 for an endoscopically removed polyp has been defined as the presence of tumor within 1-2 mm from the transected margin or by the presence of tumor cells within the diathermy of the transected margin.[64,66-68]

For a polyp with fragmented specimen or margins that cannot be assessed, either a transanal excision or a transabdominal resection is recommended. In patients with unfavorable pathologic features, transabdominal resection should be considered in order to include lymphadenectomy. Results from a preoperative endoscopic ultrasound evaluation may provide additional information to guide choice of surgical approach, although the accuracy of this method to detect residual cancer is limited (see section on 'Clinical Evaluation/Staging,' below).[69] All patients who have resected polyps should undergo surveillance as described in the guidelines.[70]

Management of Rectal Cancer

Rectal cancer has been defined as a cancerous lesion located within 12 cm of the anal verge by rigid proctoscopy.[71] Some support for this

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

definition comes from the study of Kapiteijn et al,[72] which included a subgroup analysis of the risk of recurrence of rectal cancer based on tumor location. Univariate analyses indicated that local recurrence rates were low for patients who had tumors with an inferior margin of 10.1 cm or more from the anal verge, and that no significant differences between patients in this group receiving radiotherapy and surgery were observed when they were compared to those undergoing surgery alone.[72] A recent retrospective review of patients with rectal or rectosigmoid cancer demonstrated that treatment options were impacted by whether the location of the rectal lesion was characterized by rigid proctoscopy or colonoscopy.[73]

The determination of an optimal treatment plan for an individual patient with rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (ie, curative or palliative), consideration must also be given to the likely functional results of treatment, including the probability of maintaining or restoring normal bowel function/anal continence and preserving genitourinary functions. For patients with distal rectal cancer, in particular, the simultaneous achievement of the goals of cure and of minimal impact on quality of life can be challenging.[74] Furthermore, the risk of pelvic recurrence is higher in patients with rectal cancer compared to those with colon cancer, and locally recurrent rectal cancer has frequently been associated with a poor prognosis.[75-77] Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy that combines chemoradiation (chemoRT) with operative treatment for selected patients are recommended.

Clinical Evaluation/Staging

The initial clinical workup of patients with rectal cancer provides important preoperative information on the clinical stage of disease. Since the clinical stage of the disease is used to direct decisions regarding choice of primary treatment, including surgical intent (eg, curative or palliative) and approaches, and whether to recommend preoperative chemoRT, the implications of either clinically under-staging or over-staging rectal cancer can be substantial.

Patients who present with rectal cancer appropriate for resection require a complete staging evaluation, including total colonoscopy to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum; and rigid proctoscopy to provide a determination of the location of the cancer (ie, measurement of the distance of the tumor from the anal verge should be performed by the responsible surgeon using rigid proctoscopy). They also require a complete physical examination, including carcinoembryonic antigen (CEA) determination and assessment of performance status to determine operative risk. In addition, the accessibility of rectal cancer to evaluation by certain imaging modalities, such as endorectal ultrasound and magnetic resonance imaging (MRI) makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.[78] The consensus of the panel is that a positron emission tomography (PET) scan is not routinely indicated. Additional information regarding the extent of disease and the occurrence of distant metastases can be determined preoperatively through CT scans. Thus, endorectal ultrasound or pelvic MRI, and CT scans of the chest, abdomen, and pelvis are recommended for the preoperative staging of rectal cancer. CT should be with IV and oral contrast, and if the CT of the abdomen and pelvis is inadequate or if CT with IV contrast is contraindicated, an abdominal/pelvic MRI with contrast plus a non-contrast chest CT should be considered.

Results from a meta-analysis of 90 studies involving the accuracy of endoscopic ultrasound, MRI, and CT in preoperatively staging rectal cancer demonstrated that endoscopic ultrasound and MRI have

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

similarly high sensitivities for evaluating the depth of tumor penetration into the muscularis propria (94%), although endoscopic ultrasound was found to be more specific than MRI in the evaluation of local tumor invasion (86% vs. 69%).[79] Only a very limited number of studies using CT for the purpose of T-staging have been performed, and it is not currently considered to be an optimal method for staging the extent of tumor penetration.[79,80] Accurate assessment of nodal status is one of the greatest challenges in the preoperative staging of rectal cancer. In the meta-analysis of Bipat et al,[79] the sensitivities and specificities of the 3 imaging modalities for accurately evaluating lymph node involvement were comparable: CT (55% and 74%); endoscopic ultrasound (67% and 78%); and MRI (66% and 76%). However, only CT and MRI can evaluate iliac and mesenteric or retroperitoneal nodes.[79] Results from another recent meta-analysis of 84 articles, indicated that none of the 3 imaging modalities were significantly superior to another method with respect to an accurate determination of tumor N-stage.[81] A disadvantage of endoscopic ultrasound is a high degree of operator dependence.[79] An advantage of MRI is its ability to provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia.[79] Hence, MRI evaluation of patients with more advanced rectal cancer has the potential to provide information useful in the prediction of the CRM prior to radical surgery.[80-82]

Clinical staging is also based on histopathologic examination of the specimen obtained via biopsy or local excision (eg, excised polyps). Endoscopic biopsy specimens of the lesion should undergo careful pathology review for evidence of invasion into the muscularis mucosa. If removal of the rectum is contemplated, early consultation with an enterostomal therapist is recommended for preoperative marking of the site and patient teaching purposes.

Surgical Approaches

A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancer lesions.[83,84] These methods include local procedures, such as polypectomy, transanal excision, and transanal endoscopic microsurgery (TEM), and more invasive procedures involving a transabdominal resection (eg, low anterior resection [LAR], proctectomy with total mesorectal excision [TME] and coloanal anastomosis, or abdominoperineal resection [APR]).[83,84]

Transanal excision may be appropriate for selected T1, N0 early-stage cancers. Small (<3 cm), well to moderately differentiated tumors that are within 8 cm of the anal verge and limited to less than 30% of the rectal circumference and for which there is no evidence of nodal involvement can be approached with transanal excision with negative margins. Transanal endoscopic microsurgery (TEM) can facilitate excision of small tumors through the anus when lesions can be adequately identified in the rectum. TEM may be technically feasible for more proximal lesions. Both transanal excision and TEM involve a full thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (>3 mm) deep and mucosal margins are required, and tumor fragmentation should be avoided. The excised specimen should be oriented and pinned before fixation and brought to the pathologist by the surgeon to facilitate an oriented histopathologic evaluation of the specimen. Advantages of a local procedure include minimal morbidity (eg, a sphincter-sparing procedure) and mortality and rapid postoperative recovery.[74,85] If pathologic examination reveals adverse features such as positive margins, lymphovascular invasion (LVI), poor differentiation, or invasion into the lower third of the submucosa (sm3 level),[86,87]a more radical resection is recommended. Data are limited on long-term patient outcomes, including risk of local recurrence, for patients undergoing local excision for T2 tumors.[85]

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Limitations of a transanal excision include the absence of pathologic staging of nodal involvement. Further, there is evidence to indicate that lymph node micrometastases are both common in early rectal lesions and unlikely to be identified by endorectal ultrasound.[88] These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.[85,89] A recent retrospective study of 282 patients undergoing either transanal excision or radical resection for T1 rectal cancer from 1985 to 2004 showed respective local recurrence rates of 13.2% and 2.7% for these 2 groups (P = .001).[89] A similar retrospective study of 2,124 patients showed local recurrence rates of 12.5% and 6.9% for patients undergoing local excision versus standard resection, respectively (P = .003).[85]

Patients with rectal cancer who do not meet requirements for local surgery should be treated with a transabdominal resection. Organ-preserving procedures that maintain sphincter function are preferable, but not possible in all cases. Preoperative chemoRT may result in tumor downsizing and a decrease in tumor bulk (see section on 'Neoadjuvant/Adjuvant Therapy,' below); sphincter preservation may become possible in cases where initial tumor bulk prevented consideration of such surgery and exposure to the tumor is improved by chemoRT.

In transabdominal resections, total mesorectal excision (TME) is recommended. A TME involves an en bloc removal of the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia as a "tumor package" through sharp dissection and is designed to spare the autonomic nerves.[74,84,90] The lymphatic drainage regions of rectal tumors are influenced by their position in the rectum. More distal tumors are more likely to be characterized by both upward and lateral lymphatic drainage whereas the likelihood of only upward mesorectal drainage is much higher for more proximal tumors.[91] The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.[92] The panel does not recommend extension of nodal dissection beyond the field of resection (eg, into the distribution of iliac lymph nodes) unless these nodes are clinically suspicious. In cases where anal function is intact and distal clearance is adequate, the TME may be followed by creation of a coloanal anastomosis.

For lesions in the mid to upper rectum, a low anterior resection (LAR) extended 4-5 cm below the distal edge of the tumor, followed by creation of a colorectal anastomosis, is the treatment of choice. Where creation of an anastomosis is not possible, colostomy is required. Wide TME is recommended in order to facilitate adequate lymphadenectomy and improve the probability of achieving negative circumferential margins.

An abdominoperineal resection (APR) should be performed when the tumor directly involves the anal sphincter or the levator muscles. An APR is also necessary in cases where a margin-negative resection of the tumor would result in loss of anal sphincter function and incontinence. An APR involves en bloc resection of the rectosigmoid, the rectum, and the anus, as well as the surrounding mesentery, mesorectum (TME), and perianal soft tissue, and it necessitates creation of a colostomy.[93]

Pathologists play a key role in evaluating the surgical specimen following TME which includes a macroscopic assessment of both its external appearance/completeness and the CRM.[94,95] Detailed descriptions of how the quality of the mesorectal specimens should be scored were provided in the Dutch Rectal Cancer Trial, and these guidelines are endorsed by the NCCN panel.[28]

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Recent retrospective comparisons of the outcomes of patients undergoing an APR versus a LAR in the treatment of rectal cancer have shown those treated with an APR to have worse local control and overall survival.[96,97] Whether these differences can be attributed to the surgical procedure alone, to patient- and tumor-related characteristics, or some combination of these factors is presently unclear. However, results from a recent retrospective study of 3,633 patients with T3-4 rectal cancer tumors included in 5 large European trials suggest that there is an association between the APR procedure itself and the increased risks of recurrence and death.[96]

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer are limited.[98,99] One large prospective multicentre study, which included 4405 patients with rectal cancer but was not randomized, found no differences in recurrence or survival, although complications and other measures of quality indicated a benefit to the laparoscopic approach.[100] The COREAN trial randomized patients with stage II or III low- to mid-rectal cancer to an open or laparoscopic resection.[101] The primary endpoint, 3-year disease-free survival, has not yet been reported, but short-term benefits to the laparoscopic approach were seen.

To date, the highest level of evidence for the benefits of the laparoscopic approach comes from the CLASICC trial. In the CLASICC trial comparing laparoscopically-assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer.[98] No significant differences in local recurrence, DFS, or overall survival were observed between the 2 groups of patients with colon or rectal cancer based on surgical approach. A 5-year follow-up of the CLASICC trial showed that this lack of difference in local recurrence, DFS, or overall survival was maintained for patients with rectal cancer, despite a trend towards better 5-year overall survival after laparoscopic surgery (52.9% and 60.3% for open and laparoscopic surgery, respectively; $P = .132$).[102] Factors that may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically-assisted surgery for colorectal cancer have been described,[103] and longer-term outcomes from laparoscopic rectal surgery have not been reported.

Reviews and meta-analyses including these and additional small trials have also been published.[104-109] They found the laparoscopic approach to be safe and feasible. Laparoscopic resection appears to have long-term outcomes similar to or better than that of open resection, but additional high-level evidence is required. Additional clinical trials exploring open versus laparoscopic surgery for rectal cancer are ongoing (including clinicaltrials.gov NCT00297791 [COLOR II], NCT00470951 [CTS-179], NCT00726622 [ACOSOG-Z6051], and NCT00147134 [JCOG0404]. At this time, laparoscopic surgery for rectal cancer is preferred in the setting of a clinical trial.

Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease

Neoadjuvant/adjuvant therapy of stage II (T3-4, node-negative disease with tumor penetration through the muscle wall) or stage III (node-positive disease without distant metastasis) rectal cancer often includes locoregional treatment due to the relatively high risk of locoregional recurrence. This risk is associated with the close proximity of the rectum to pelvic structures and organs, the absence of a serosa surrounding the rectum, and technical difficulties associated with obtaining wide surgical margins at resection. In contrast, adjuvant treatment of colon cancer is more focused on preventing distant metastases since this disease is characterized by lower rates of local recurrence.

Although radiation therapy has been associated with decreased rates of local recurrence of rectal cancer, it is also associated with increased

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

toxicity (eg, radiation-induced injury, hematologic toxicities, etc.) relative to surgery alone.[38,110] It has been suggested that some patients with disease at lower risk of local recurrence (eg, proximal rectal cancer staged as T3, N0, M0, characterized by clear margins and favorable prognostic features) may be adequately treated with surgery and adjuvant chemotherapy.[38,111,112] However, 22% of 188 patients clinically staged with T3, N0 rectal cancer by either EUS or MRI who subsequently received preoperative chemoRT had positive lymph nodes following pathologic review of the surgical specimens according to results of a recent retrospective multicenter study,[113] suggesting that many patients are under-staged and would benefit from chemoRT. Therefore, the guidelines recommend preoperative chemoRT for patients with T3, N0 disease.

Combined-modality therapy consisting of surgery, radiation therapy (RT), and chemotherapy is recommended for the majority of patients with stage II or stage III rectal cancer. Use of perioperative pelvic RT in the treatment of patients with stage II/III rectal cancer continues to evolve. In these patients, the current guidelines recommend concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis preoperatively and chemotherapy postoperatively. A total of 6 months perioperative chemotherapy with or without RT is preferred.

Preoperative versus postoperative radiation

Several studies have compared the administration of radiation preoperatively versus postoperatively.[114,115] A large prospective, randomized trial from the German Rectal Cancer Study Group (the CAO/ARO/AIO-94 trial) compared preoperative versus postoperative chemoRT in the treatment of clinical stage II/III rectal cancer.[114] Results of this study indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs 13%; P = .006) and treatment-associated toxicity (27% vs 40%; P = .001), although overall survival was similar in the 2 groups. Long-term followup of this trial was recently published.[116] The improvement in local control persisted, with the 10-year cumulative incidence of local recurrence at 7.1% and 10.1% in the preoperative and postoperative treatment arms, respectively (P = .048). Overall survival at 10 years was again similar between the groups (59.6% and 59.9%, respectively; P = .85), as was disease-free survival and the occurrence of distant metastases.

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue.[114,115,117] First of all, reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Although some studies have indicated that preoperative radiation or chemoRT is associated with increased rates of sphincter preservation in rectal cancer patients,[114,115] this conclusion is not supported by 2 meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.[118,119] Second, irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Third, preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by post-surgical adhesions. Finally, preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected). One disadvantage of using preoperative RT is the possibility of over-treating early-stage tumors that do not require adjuvant radiation.[114,120] Improvements in preoperative staging techniques, such as MRI or CT scans, have allowed for more accurate staging, but the risk of over-staging disease has not been eliminated.[113] Weighing these advantages and disadvantages, the panel recommends preoperative chemoRT for patients with stage II/III rectal cancer.

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Postoperative chemoRT is recommended when stage I rectal cancer is upstaged to stage II or III after pathologic review of the surgical specimen. Postoperative chemoRT regimens commonly employ a "sandwich" approach – whereby chemotherapy (typically 5-FU based) is administered before and after the chemoRT regimen.[112,121,122] The use of FOLFOX or capecitabine chemotherapy before and after postoperative chemoRT is an extrapolation of the available data in colon cancer.[123,124]

Concurrent chemotherapy with radiation

A number of randomized trials have evaluated the effectiveness of the addition of chemotherapy to radiation administered either preoperatively following clinical evaluation/staging (eg, T3-4 by endoscopic ultrasound) or postoperatively following pathologic staging of rectal cancer as pT3 and/or N1-2.[125,126] Putative benefits of the addition of chemotherapy concurrent with either pre- or postoperative RT include local RT sensitization and systemic control of disease (ie, eradication of micrometastases). Preoperative chemoRT also has the potential to increase rates of pathologic complete response and sphincter preservation.

In a study of patients with T3-4 rectal cancer without evidence of distant metastases who were randomly assigned to receive either preoperative RT alone or preoperative concurrent chemoRT with 5-FU/LV, no difference in overall survival or sphincter preservation was observed in the 2 groups, although patients receiving chemoRT were significantly more likely to exhibit a pathologic complete response (11.4% vs 3.6%; $P < .05$) and grade 3/4 toxicity (14.6% vs 2.7%; $P < .05$) and less likely to exhibit local recurrence of disease (8.1% vs 16.5%; $P < .05$).[126] These conclusions have been supported in a 2009 systematic review that included 4 randomized controlled trials.[125]

Preliminary results of a phase III trial that included an evaluation of the addition of chemotherapy to preoperative RT in patients with T3-4 resectable rectal cancer demonstrated that use of 5-FU/LV chemotherapy enhanced the tumoricidal effect of RT when the 2 approaches were used concurrently.[127] Significant reductions in tumor size, pTN stage, and lymphatic, vascular, and perineural invasion rates were observed with use of combined-modality therapy compared with use of RT and surgery without chemotherapy.[127] More mature results from this trial, however, which included 4 treatment groups (preoperative RT; preoperative chemoRT; preoperative RT plus postoperative chemotherapy; and preoperative chemoRT plus postoperative chemotherapy), indicated that no significant differences in overall survival were associated with adding 5-FU-based chemotherapy preoperatively or postoperatively.[128] Although local recurrence rates were significantly higher in the group receiving preoperative RT alone, the addition of chemotherapy after concurrent chemoRT did not significantly impact local recurrence rates. In subsequent exploratory analyses of data from the group of patients in this trial who underwent complete tumor resection without evidence of distant disease before or at surgery, those patients with disease characterized as ypT0-2 showed significant benefit from adjuvant chemotherapy with respect to DFS and overall survival.[129] These findings may indicate that patients are more likely to benefit from adjuvant therapy if their disease can be down-staged by chemoRT. Of note, patients with stage II/III rectal cancer enrolled in this trial were found to be 2.6-times more likely to develop distant metastases than local recurrence of disease after a median follow-up of over 5 years.[128]

With respect to the type of chemotherapy administered concurrently with RT, [112]the equivalence of bolus 5-FU/LV and infusional 5-FU in concurrent chemoRT for rectal cancer is supported by the results of a

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

phase III trial (median follow-up of 5.7 years) in which similar outcomes with respect to overall survival and relapse-free survival were observed when an infusion of 5-FU or bolus 5-FU plus LV was administered concurrently with postoperative RT, although hematologic toxicity was greater in the group of patients receiving bolus 5-FU.[122] On the other hand, results from an earlier trial from the North Central Cancer Treatment Group (NCCTG) showed that postoperative administration of infusional 5-FU during pelvic irradiation was associated with longer overall survival when compared to bolus 5-FU.[121] Most of the patients in this study had node-positive disease.

Recent studies have shown that capecitabine is equivalent to 5-FU in perioperative chemoradiation therapy.[130,131] The randomized NSABP R-04 trial compared the preoperative use of infusional 5-FU with or without oxaliplatin to capecitabine with or without oxaliplatin in 1,608 patients with stage II or III rectal cancer.[131] No differences in complete pathologic response, sphincter-saving surgery, or surgical downstaging were seen between the regimens, while toxicity was increased with the inclusion of oxaliplatin. Similarly, a phase III randomized trial in which 401 patients with stage II or III rectal cancer received capecitabine- or 5-FU-based chemoradiation either pre- or postoperatively showed that capecitabine was non-inferior to 5-FU with regards to 5-year OS (capecitabine 75.7% vs. 5-FU 66.6%; $P = .0004$), with capecitabine showing showed borderline significance for superiority ($P = .053$).[130] Furthermore, in this trial capecitabine demonstrated a significant improvement in 3-year disease-free survival (75.2% vs 66.6%; $P = .034$).[130] Because of these studies, capecitabine given concurrently with radiation therapy is now listed in the guidelines as a category 2A recommendation. The panel feels that capecitabine is an acceptable alternative to infusional 5-FU in those patients who are able to manage the responsibilities inherent in self-administered, oral chemotherapy.

In attempts to improve on the outcomes achieved with neoadjuvant 5-FU/RT or capecitabine/RT, several large randomized phase III trials (ACCORD 12, STAR-01, R-04, and CAO/ARO/AIO-04) addressed the addition of oxaliplatin to the regimens. In a planned interim report of primary tumor response in the STAR-01 trial, grade 3 and 4 adverse events occurred more frequently in patients receiving infusional 5-FU/oxaliplatin/RT than in those receiving infusional 5-FU/RT (24% vs. 8%, $P < .001$), while there was no difference in pathologic response between the arms of the study (16% pathologic complete response in both arms).[132] Recently reported results of the NSABP R-04 trial also showed that the addition of oxaliplatin did not improve clinical outcomes including the end points of ypCR, sphincter-saving surgery, and surgical downstaging, while it increased toxicity.[131] Further follow-up of these trials is necessary to see if there is a difference in local recurrence rates and PFS over time. The primary end points of overall survival for the STAR-01 trial and local tumor control for the R-04 trial will be reported in the future.

Similar results were seen in the ACCORD 12/0405-Prodige 2 trial, in which capecitabine/RT (45 Gy) was compared to CapeOx/RT (50 Gy) and the primary endpoint was pathologic complete response (ypCR).[133] Here, the grade 3 and 4 toxicity rates were 25% and 11% ($P < .001$), and the ypCR rates were 19.2% and 13.9% ($P = .09$) for the oxaliplatin-containing arm and the control arm, respectively. Although patients treated with oxaliplatin and the higher radiation dose in the ACCORD 12 trial had an increased rate of minimal residual disease at the time of surgery (39.4% vs. 28.9%, $P = .008$),[133] this did not translate to improved local recurrence rates, disease-free survival, or overall survival at 3 years.[134] The addition of oxaliplatin to neoadjuvant chemoradiation is thus not recommended at this time.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Initial results of the German CAO/ARO/AIO-04 trial were recently published.[135] This trial also assessed the addition of oxaliplatin to a fluorouracil RT regimen. In contrast to STAR-01, R-04, and ACCORD 12, higher rates of pathologic complete response were seen in the oxaliplatin arm (17% vs. 13%, *P* = .038)[135], but this result could be because of differences in the fluorouracil schedule between the arms.[136] The primary endpoint of this trial, disease-free survival, will be reported in the future. Importantly, oxaliplatin was also added to the adjuvant therapy in the AIO-04 trial but not in the other trials, so cross-trial comparisons will be limited.

The randomized phase II EXPERT-C trial assessed complete response rate with the addition of cetuximab to the radiation treatment in 165 patients.[137] Patients in the control arm received CapeOx followed by Capecitabine/RT, then surgery followed by CapeOx. Patients randomized to the cetuximab arm received the same therapy with weekly cetuximab throughout all phases. A significant improvement in overall survival was seen in patients with *KRAS* wild-type tumors treated with cetuximab (HR, 0.27; 95% CI, 0.07-0.99; *P* = .034). However, the primary endpoint in complete response rate was not met, and further evaluation of this regimen is warranted. Additional phase II trials assessing the effects of adding irinotecan or bevacizumab to neoadjuvant or adjuvant regimens have begun.[138-140] However, at this time the panel does not endorse the use of irinotecan, bevacizumab, cetuximab, panitumumab, or oxaliplatin with concurrent radiotherapy for rectal cancer.

Induction chemotherapy

Several small trials have tested the utility of a course of neoadjuvant chemotherapy preceding chemoradiation and resection. In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CapeOx either before chemoradiation or after surgery.[141] Similar pathologic complete response rates were seen, and induction chemotherapy appeared to be less toxic and better tolerated. Another phase II trial randomized patients to chemoradiation and surgery with or without FOLFOX induction therapy.[142] There were no differences between the clinical outcomes, but the group receiving induction therapy experienced higher toxicity. The phase II AVACROSS study assessed the safety and efficacy of adding bevacizumab to induction therapy with CapeOx prior to capecitabine/bevacizumab-chemoradiation and surgery.[143] The regimen was well tolerated with a pathologic complete response rate of 36%. This approach remains investigational at this time and is not endorsed by the panel for routine care.

Preoperative chemotherapy without chemoradiation

The ongoing N1048/C81001/Z6092 trial by The Alliance for Clinical Trials in Oncology is asking whether chemotherapy alone is effective in treating stage II or III high rectal cancer in patients with at least 20% tumor regression following neoadjuvant treatment (clinicaltrials.gov NCT01515787). This approach would spare patients the morbidities associated with radiation.

Technical aspects of radiation therapy

With respect to administration of RT, multiple RT fields should include the tumor or tumor bed with a 2-5 cm margin, presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures; inclusion of the inguinal nodes for tumors invading into the distal anal canal can also be considered. Recommended doses of radiation are typically 45-50 Gy in 25-28 fractions to the pelvis using 3 or 4 fields. Positioning and other techniques to minimize radiation to the small bowel are encouraged. The Radiation Therapy Oncology Group (RTOG) has established normal pelvic contouring atlases for females and males (available online

at http://www.rtog.org/CoreLab/ContouringAtlases.aspx).[144] Intensity modulated radiotherapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations including re-irradiation of recurrent disease.

Coordination of preoperative therapy, surgery, and adjuvant chemotherapy is important. For patients treated with preoperative chemoRT, the panel recommends an interval of 5 to 10 weeks following completion of full-dose 5-½ week chemoRT prior to surgical resection in order to allow patient recuperation from chemoRT-associated toxicities. Although longer intervals from completion of chemoRT to surgery have been shown to be associated with an increase in pathologic complete response rates,[145-148] it is unclear whether such longer intervals are associated with clinical benefit. Nevertheless, when longer intervals are clinically necessary, they do not appear to increase the blood loss, time associated with surgery, or positive margin rate.[149]

Short-course radiation

Several European studies have looked at the efficacy of a shorter course of preoperative radiation (25 Gy over 5 days), not combined with chemotherapy, for the treatment of rectal cancer. The results of the Swedish Rectal Cancer Trial evaluating the use of short-course RT administered preoperatively for resectable rectal cancer showed a survival advantage and a decreased rate of local recurrence with this approach compared with surgery alone.[150] However, a follow-up study published in 2005 showed that the patients with short-course preoperative RT had increased relative risk for postoperative hospitalization due to bowel obstructions and other gastrointestinal complications.[151] A number of other studies also investigating the effectiveness of preoperative short-course RT in patients with rectal cancer staged as T1-3 have demonstrated that overall survival was not significantly affected despite improvements in local control of disease.[72,152,153] A recent multicenter, randomized study of 1,350 patients with rectal cancer compared (a) short-course preoperative RT and no postoperative treatment with (b) no preoperative RT and a postoperative approach that included chemoRT in selected patients (ie, those with a positive CRM following resection) and no RT in patients without evidence of residual disease following surgery.[154] Results indicated that patients in the preoperative RT arm (a) had significantly lower local recurrence rates and a 6% absolute improvement in 3-year DFS (P=0.03), although no difference in overall survival was observed between the 2 arms of the study.[154,155]

Long-term (12-year) follow-up of one of the short-course radiation trials (the Dutch TME trial[152]) was recently reported.[156] The analysis showed that 10-year survival was significantly improved in stage III patients with a negative circumferential margin in the radiotherapy plus surgery group compared to the group that received surgery alone (50% vs. 40%; P=0.032).[156] However, this long follow-up showed that secondary malignancies and other non-rectal cancer causes of death were more frequent in the radiotherapy group than in the control group (14% vs 9% for secondary malignancies), negating any survival advantage in the node-negative subpopulation.

Few studies have directly compared preoperative short-course radiation and more conventional preoperative long-course chemoradiation. One randomized study of 312 patients in Poland showed no differences in local recurrence or survival.[157] Similarly, a Australian/New Zealand trial that randomized 326 patients to short-course radiation or long-course chemoradiation found no differences in local recurrence and overall survival rates.[158]

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Overall, it appears that short-course RT gives effective local control and the same overall survival as more conventional RT schedules, and therefore may be an appropriate choice in some situations.

Response to neoadjuvant treatment

50-60% of patients are downstaged following neoadjuvant therapy, with about 20% of patients showing a pathologic complete response.[129,159-164] Recent studies have suggested that the response to neoadjuvant treatment correlates with long-term outcomes in patients with rectal cancer. In the MERCURY prospective cohort trial, 111 patients were assessed by MRI and pathologic staging.[165] On multivariate analysis, MRI-assessed tumor regression grade was significantly associated with overall and disease-free survival. Patients with poor tumor regression grade had 5-year survival rates of 27% versus 72% for patients with good tumor regression grade (P = .001), and disease-free survival rates were 31% versus 64% (P = .007). A recent retrospective review of 725 patients with rectal cancer found similar results.[162] In this study, pathologically determined response to neoadjuvant treatment correlated with long-term outcomes. Five-year recurrence-free survival rates were 90.5%, 78.7%, and 58.5% for patients with complete, intermediate, and poor responses, respectively (P < .001). Distant metastases and local recurrences also correlated with the level of response.

In addition to its prognostic value, there is some initial evidence of predictive value to neoadjuvant treatment response. Subgroup analysis of the EORTC 22921 trial showed that patients downstaged to ypT0-2 were more likely to benefit from adjuvant chemotherapy than patients with ypT3-4 staging.[129] Similar results were seen from another retrospective review.[166] Although no prospective data to predict the benefit of adjuvant therapy in patients with tumor downstaging or a pathologic complete response exists, the panel believes that such patients should be strongly considered for adjuvant chemotherapy.

Wait-and-see non-operative approach for clinical complete responders

As preoperative treatment and imaging modalities have improved, some have suggested that patients with a clinical complete response to chemoradiation may be able to be spared the morbidities of surgery. In 2004, Habr-Gama et al[167] retrospectively compared the outcomes of 71 patients who were observed without surgery following complete clinical response (27% of patients) to the outcome of 22 patients (8%) who had incomplete clinical responses but complete pathologic responses post-TME. The overall and disease-free survival rates at 5 years were 100% and 92%, respectively, in the non-operative group compared to 88% and 83%, respectively, in the resected group. However, other studies did not achieve as impressive results, and many clinicians were skeptical of the approach.[168]

A more recent prospective study included a more thorough assessment of treatment response and used very strict criteria to select 21 of 192 patients (11%) with clinical complete responses who were then observed with careful follow-up and compared to 20 patients with a complete pathologic response after resection.[169] Only 1 patient in the non-operative group developed a local recurrence after a mean follow-up of 25 months; that patient underwent successful salvage surgery. No statistical differences in long-term outcomes were seen between the groups. The cumulative probabilities for 2-year disease-free survival and overall survival were 89% (95% CI, 43% to 98%) and 100%, respectively in the wait-and-see group and 93% (95% CI, 59% to 99%) and 91% (95% CI, 59% to 99%), respectively, in the resected group. Short-term functional outcomes, however, were better in the wait-and-see group, with better bowel function scores, less incontinence, and 10 patients avoiding permanent colostomy.

Despite these impressive results, many still believe that longer follow-up, larger sample sizes, and additional careful observational studies are

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

needed before patients with a clinical complete response are routinely managed by a wait-and-see approach.[170]

Adjuvant chemotherapy

Adjuvant chemotherapy is recommended for all patients with stage II/III rectal cancer following neoadjuvant chemoRT/surgery regardless of the surgical pathology results, although few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well defined.[171] The addition of 5-FU-based adjuvant chemotherapy to preoperative chemoRT provided no benefit to the rate of local recurrence in the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group Trial 22921.[128] However, this study did show an improvement in disease-free survival (HR, 0.87; 95% CI, 0.72-1.04; *P* = .13) of patients receiving adjuvant chemotherapy (+/- RT) following preoperative RT (+/- 5-FU-based chemotherapy).[128] A recent systematic review and metaanalysis of 9785 patients with non-metastatic rectal cancer from 21 randomized controlled trials from 1975 until March 2011 concluded that overall survival and disease-free survival are improved with the addition of postoperative 5-FU-based therapy.[172]

Most of the support for use of FOLFOX or capecitabine as adjuvant chemotherapy in rectal cancer is an extrapolation from the data available for colon cancer.[123,124] The phase III ECOG E3201 trial was designed to investigate the effect of adding either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) to 5-FU/LV-based adjuvant chemotherapy administered to stage II/III rectal cancer patients following either preoperative or postoperative chemoRT. This study was replaced with an alternative trial with bevacizumab, but results from an initial 165 patients indicate that adjuvant FOLFOX can be safely used in this patient population.[173] Nevertheless, the optimal duration of treatment with adjuvant FOLFOX in rectal cancer is still unclear.[174,175] In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX.[176] The use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) is justified when preoperative chemoRT is administered.

A recent systematic review and meta-analysis of 10 studies involving more than 15000 patients with colorectal cancer looked at the effect of timing of adjuvant therapy following resection.[177] Results of this analysis showed that each 4-week delay in chemotherapy results in a 14% decrease in overall survival, indicating that adjuvant therapy should be administered as soon as the patient is medically able. These results are consistent with other similar analyses.[178]

Leucovorin shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levo-leucovorin is equivalent to 400 mg/m^2 of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.[179] Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high dose (500 mg/m^2) or low dose (20 mg/m^2) leucovorin.[180] Also, the Mayo Clinic and North Central Cancer Treatment (NCTTG) group determined that there was no therapeutic difference between the use of high (200

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

mg/m^2) or low (20 mg/m^2) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.[181] Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

Recommendations for patients with T1 and T2 lesions

Node-negative T1 lesions are treated with transabdominal resection or transanal excision, as appropriate (see section on 'Surgical Approaches,' above). If pathology review after local excision reveals a poorly differentiated histology, positive margins, invasion into the lower third of the submucosa (sm3 level), or LVI or if the tumor is restaged to T2, then a transabdominal re-resection should be performed.[86,87] For such high-risk patients who cannot undergo additional surgery, systemic chemotherapy with chemoradiation (a "sandwich regimen" as described below) should be considered as an adjuvant treatment in order to avoid the risk of undertreatment, being that the lymph node status is unknown.

Node-negative T2 lesions are treated with transabdominal resection, since local recurrence rates of 11% to 45% have been observed for T2 lesions following local excision alone.[74,182,183] In selected lesions that are staged by endoscopic ultrasound or MRI as T1-2, N0 and without adverse pathologic features (eg, negative margins, no lymphovascular invasion, well to moderately differentiated, and no sm3 invasion), local excision with negative margins may give results comparable to transabdominal resection.[184]

Following transabdominal resection, patients with tumors staged as pT1-2, N0, M0 require no further treatment. If pathology review reveals pT3, N0, M0 or node-positive disease, a "sandwich regimen," consisting of (1) an optional first round of adjuvant chemotherapy with 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin,[185] followed by (2) concurrent 5-FU/RT (infusional (preferred) or bolus infusion along with LV) or capecitabine/RT (preferred), followed by (3) 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin, is recommended.

The panel recommends perioperative therapy for a total duration of approximately 6 months. For patients with pathologic evidence of proximal T3, N0, M0 disease with clear margins and favorable prognostic features following an upfront resection, the incremental benefit of RT is likely to be small and chemotherapy alone can be considered, although most patients are not likely to be part of this subset.

Recommendations for patients with T3 lesions and lesions with nodal involvement

Patients clinically staged as having resectable T3, N0 or T any, N1-2 lesions should initially be treated with preoperative combined-modality therapy unless medically contraindicated. Preoperative infusional 5-FU/RT or capecitabine/RT are the preferred treatment options (category 1 for both). An alternative regimen is bolus 5-FU/LV/RT. Patients who receive preoperative radiotherapy should undergo transabdominal resection 5 to 10 weeks following completion of neoadjuvant therapy. The panel recommends postoperative adjuvant therapy for a duration giving approximately 6 months total of pre- and postoperative chemotherapy (regardless of surgical pathology results) with 5-FU with or without LV; or FOLFOX; or capecitabine with or without oxaliplatin.

Upfront surgery for patients with disease characterized as T3, N0 or T any, N1-2 should be reserved for those patients with medical contraindications to chemoRT. Following initial transabdominal

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

resection, patients with subsequent pathologic staging of disease as pT1-2, N0, M0 can be followed with observation only. For patients with disease pathologically staged as pT3, N0, M0 or pT1-3, N1-2, M0, approximately 6 months of postoperative chemotherapy "sandwich regimen" (see Recommendations for patients with T1 and T2 lesions, above) should be reconsidered. For some patients with pathologic evidence of proximal T3, N0, M0 disease with clear margins and favorable prognostic features following transabdominal resection, the incremental benefit of RT is likely to be small and chemotherapy alone can be considered, although this subset of patients is small.

Recommendations for patients with T4 lesions and/or locally unresectable disease

Patients with T4 and/or locally unresectable disease are treated with preoperative infusional 5-FU/RT or bolus 5-FU with LV/RT or capecitabine/RT. If possible, resection should be considered following preoperative chemoRT. For patients with T4 tumors or recurrent cancers or if margins are very close or positive, intraoperative radiotherapy (IORT),[186-188] which involves direct exposure of tumors to RT during surgery while removing normal structures from the field of treatment, should be considered as an additional boost to facilitate resection. If IORT is not available, 10-20 Gy and/or brachytherapy to a limited volume can be considered soon after surgery, prior to adjuvant chemotherapy. Adjuvant therapy to complete 6 months with either 5-FU with or without LV; or FOLFOX; or capecitabine with or without oxaliplatin is recommended regardless of the surgical pathology results.

For unresectable cancers, doses higher than 54 Gy may be required; the dose of radiation to the small bowel should be limited to 45 Gy.

Principles of the Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with colorectal cancer will develop colorectal metastases,[189-191] and 80% to 90% of these patients have unresectable metastatic liver disease.[190,192-195] Metastatic disease most frequently develops metachronously after treatment for locoregional colorectal cancer, with the liver as the most common site of involvement.[196] However, 20% to 34% of patients with colorectal cancer present with synchronous liver metastases.[195,197] Some evidence indicates that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In a retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement (P = .008) and more bilobar metastases (P = .016) than patients diagnosed with metachronous liver metastases.[198]

It has been estimated that more than half of patients who die of colorectal cancer have liver metastases at autopsy, with metastatic liver disease as the cause of death in most patients.[199] Reviews of autopsy reports of patients who died from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients.[194] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[190,200] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than 3 tumors, and a disease-free interval of fewer than 12 months, have been associated with a poor prognosis in patients with colorectal cancer.[197,201-205]

However, studies of selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

population and should be the goal for a substantial number of these patients.[190,206] Recent reports have shown 5-year disease-free survival rates of approximately 20% in patients who have undergone resection of liver metastases.[202,205] 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[207] (discussed further in Determining Resectability). For patients presenting with unresectable metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver (discussed in more detail below in Recommendations for Treatment of Unresectable Synchronous Metastases).[208]

Evidence supporting resection of extrahepatic metastases in patients with metastatic colorectal cancer is extremely limited. In a recent retrospective analysis of patients undergoing concurrent complete resection of hepatic and extrahepatic disease, the 5-year survival rate was lower than in patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence.[209,210] However, a recent international analysis of 1629 patients with colorectal liver metastases showed that 16% of the 171 patients (10.4%) who underwent concurrent resection of extrahepatic and hepatic disease remained disease-free at a median follow-up of 26 months, suggesting that concurrent resection may be of significant benefit in well-selected patients (ie, those with smaller total number of metastases).[211]

Recent data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken. However, in a retrospective analysis, 5-year survival was shown to decrease with each subsequent curative-intent surgery, and the presence of extrahepatic disease at the time of surgery was independently associated with a poor prognosis.[212] In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year overall and progression-free survival rates were reported to be 73% and 22%, respectively.[213] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[214]

Liver-Directed Therapies

Although the standard of care for patients with resectable metastatic disease is surgical resection, select patients with liver-only or liver-dominant metastatic disease have liver-directed treatment options in addition to or instead of surgical resection.[215] The role of non-extirpative liver-directed therapies in the treatment of colorectal metastases is controversial.

Hepatic Arterial Infusion

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (ie, hepatic arterial infusion [HAI]) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAI and intravenous 5-FU with or without leucovorin (LV) was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.[194,216] The study was not powered for long-term survival, but a trend (not significant) was seen towards better long-term outcome in the group receiving HAI at later follow-up periods.[194,217] Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy has been compared with systemic chemotherapy, although most have not shown a survival benefit of HAI

therapy.[194] However, a recent randomized trial using HAI to deliver irinotecan-loaded drug-eluting beads (DEBIRI) reported an overall survival benefit (22 months vs. 15 months; *P* = .031).[218] Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.[206] Limitations on the use of HAI therapy include the potential for biliary toxicity[194] and the requirement of specific technical expertise. Panel consensus is that HAI therapy should be considered selectively, and only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Liver-Directed Radiation

Liver-directed radiation therapies include arterial radioembolization with yttrium-90 microspheres[219-226] and conformal (stereotactic) external beam radiation therapy.[227]

A recent, prospective, randomized phase III trial of 44 patients showed that radioembolization combined with chemotherapy can lengthen time to progression in patients with liver-limited metastatic colorectal cancer following progression on initial therapy (2.1 vs. 4.5 months; *P* = .03).[228] The effect on the primary end point of time to liver progression was more pronounced (2.1 vs. 5.5 months; *P* = .003). While toxicity with radioembolization is relatively low, the data supporting its efficacy is limited to very small trials and trials with highly selected patients. Therefore, the use of arterial directed therapies, such as radioembolization, in highly selected patients with chemotherapy-resistant/-refractory disease characterized by predominant liver metastases and no obvious systemic disease remains a category 3 recommendation based on the limited amount of evidence[229] and different institutional practice patterns.

External beam radiotherapy to the metastatic site can be considered in highly selected cases in which the patient has a limited number of liver or lung metastases or the patient is symptomatic (category 3 recommendation) or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include three-dimensional conformal radiotherapy, stereotactic body radiosurgery (SBRT),[193] and intensity-modulated radiotherapy (IMRT), which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.[230-233]

Tumor Ablation

Although resection is the standard approach for the local treatment of resectable metastatic disease, some patients who cannot undergo resection because of comorbidity, location of the metastatic lesions, or an estimate of inadequate liver volume after resection may be candidates for tumor ablation therapy.[234] Several retrospective studies have compared radiofrequency ablation (RFA) and liver resection in the treatment of liver metastases.[235-238] Most of these studies have shown RFA to be inferior to resection in terms of rates of local recurrence and 5-year overall survival.[234,239] Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, technological limitations of RFA, or a combination of these factors is currently unclear.[235] A 2010 ASCO clinical evidence review determined that RFA has not been well-studied in the setting of colorectal cancer liver metastases, with no randomized controlled trials having been reported.[238] The ASCO panel concluded that a compelling need exists for more research in this area. A 2012 Cochrane Database systematic review recently came to similar conclusions.[240]

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Recently, a trial was reported in which 119 patients were randomized to receive systemic treatment or systemic treatment plus RFA with or without resection.[241] No difference in overall survival was seen, but progression-free survival was improved at 3 years in the RFA group (27.6% vs. 10.6%; HR, 0.63; 95% CI, 0.42-0.95; *P* = .025).

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

Peritoneal Carcinomatosis

Approximately 17% of patients with metastatic colorectal cancer have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis.[242] The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative, and consists of systemic therapy (see Chemotherapy for Advanced or Metastatic Disease) with palliative surgery or stenting if needed. Patients with peritoneal metastases generally have a shorter progression-free and overall survival than those without peritoneal involvement.[242]

Several surgical series have addressed the role of cytoreductive surgery (ie, peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis without extra-abdominal metastases.[243-247] In the only randomized controlled trial of this approach, Verwaal et al[248] randomized 105 patients to receive standard therapy (5-FU/LV with or without palliative surgery) or undergo aggressive cytoreductive surgery and HIPEC with mitomycin C; postoperative 5-FU/LV was given to 33 of 47 patients. Overall survival was 12.6 months in the standard arm and 22.3 months in the HIPEC arm (*P* = .032). However, treatment-related morbidity was high, and the mortality was 8% in the HIPEC group, mostly related to bowel leakage. In addition, long-term survival does not seem to be improved by this treatment as seen by follow-up results.[249] Importantly, this trial was performed without oxaliplatin, irinotecan, or molecularly targeted agents. Some experts have argued that the overall survival difference seen might have been much smaller if these agents had been used (ie, the control group would have had better outcomes).[250]

Other criticisms of the Verwaal trial have been published.[250] One important point is that the trial included patients with peritoneal carcinomatosis of appendiceal origin, a group which has seen greater benefit with the cytoreductive surgery/HIPEC approach.[243,251,252] A retrospective multicenter cohort study reported overall median survival times of 30 and 77 months for patients with peritoneal carcinomatosis of colorectal origin and appendiceal origin, respectively.[252] The overall median survival time for patients with pseudomyxoma peritonei, which arises from mucinous appendiceal carcinomas, was not reached at the time of publication. A recent retrospective international registry study reported 10- and 15-year survival rates of 63% and 59%, respectively, in patients with pseudomyxoma peritonei from mucinous appendiceal carcinomas treated with cytoreductive surgery and HIPEC, suggesting that the approach is beneficial in this population.[253]

The individual components of this approach have not been well-studied. In fact, studies in rats have suggested that the hyperthermia component of the treatment is irrelevant.[254] Results of a retrospective cohort study also suggest that heat may not affect outcomes from the procedure.[244] In addition, significant morbidity and mortality are associated with this

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

procedure. A 2006 meta-analysis of 2 randomized controlled trials and 12 other studies reported morbidity rates ranging from 23% to 44% and mortality rates ranging from 0% to 12%.[247] While the risks are reportedly decreasing with time (ie, recent studies report 1%-5% mortality rates at centers of excellence[250]), the benefits of the approach have not been definitively shown. Therefore, the panel currently considers the treatment of disseminated carcinomatosis with cytoreductive surgery and HIPEC to be investigational and does not endorse such therapy outside of a clinical trial. The panel recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities.

Determining Resectability

The consensus of the panel is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (ie, with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status. The criteria for determining patient suitability for resection of metastatic disease are the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve.[255-258] It should be noted that size alone is rarely a contraindication to resection of a tumor. Resectability differs fundamentally from end points that focus more on palliative measures. Instead, the resectability end point is focused on the potential of surgery to cure the disease.[259] Resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), because incomplete resection or debulking has not been shown to be beneficial.[191,255]

Conversion to Resectability

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, preoperative chemotherapy is being increasingly considered in highly selected cases in an attempt to downsize colorectal metastases and convert them to a resectable status. Patients presenting with large numbers of metastatic sites within the liver or lung are unlikely to achieve an R0 resection simply on the basis of a favorable response to chemotherapy, as the probability of complete eradication of a metastatic deposit by chemotherapy alone is low. These patients should be regarded as having unresectable disease not amenable to conversion therapy. In some highly selected cases, however, patients with significant response to conversion chemotherapy can be converted from unresectable to resectable status.[234]

Any active metastatic chemotherapeutic regimen can be used in an attempt to convert a patient's unresectable status to a resectable status, because the goal is not specifically to eradicate micrometastatic disease, but rather to obtain the optimal size regression of the visible metastases. An important point to keep in mind is that irinotecan- and oxaliplatin-based chemotherapeutic regimens may cause liver steatohepatitis and sinusoidal liver injury, respectively.[260-264] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable. Some of the trials addressing various conversion therapy regimens are discussed below.

In the study of Pozzo et al, it was reported that chemotherapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%)

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

of the patients with initially unresectable liver metastases to undergo liver resection.[257] 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),[192] 42 patients with unresectable liver metastases were treated with FOLFOX. Twenty-five patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study, 1104 initially unresectable patients with colorectal liver disease were treated with chemotherapy, which included oxaliplatin in the majority of cases, and 138 patients (12.5%) classified as "good responders" underwent secondary hepatic resection.[201] The 5-year disease-free survival rate for these 138 patients was 22%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%; 2 of the 24 had lung metastases) were able to undergo curative resection after treatment.[265] The median overall survival time in this group was 42.4 months.

In addition, first-line FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI (infusional 5-FU, LV, irinotecan) in 2 randomized clinical trials in unresectable patients.[266,267] In both studies, FOLFOXIRI led to an increase in R0 secondary resection rates: 6% versus 15%, *P* = .033 in the Gruppo Oncologico Nord Ovest (GONO) trial[266]; and 4% versus 10%, *P* = .08 in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.[267] In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs. 8%), with a median overall survival of 23.4 vs. 16.7 months (*P* = .026).[268]

More recent favorable results of randomized clinical trials evaluating FOLFIRI or FOLFOX for the purpose of conversion of unresectable disease to resectable disease in combination with anti-epidermal growth factor receptor (EGFR) inhibitors have been reported.[269,270] For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.[269] Retrospective analysis showed that, in both treatment arms combined, resectability increased from 32% to 60% after chemotherapy in patients with wild-type *KRAS* (*P* < .0001) with the addition of cetuximab. A recent meta-analysis of 4 randomized controlled trials concluded that the addition of cetuximab or panitumumab to chemotherapy significantly increased the response rate, the R0 resection rate (from 11%-18%; RR 1.59; *P* = .04), and progression-free survival, but not overall survival in patients with wild-type *KRAS*-containing tumors.[271]

The role of bevacizumab in the unresectable patient, whose disease is felt to be potentially convertible to resectability with a reduction in tumor size, has also been studied. Data seem to suggest that bevacizumab modestly improves the response rate to irinotecan-based regimens.[272] As such, when an irinotecan-based regimen is selected for an attempt to convert unresectable disease to resectability, the use of bevacizumab would seem to be an appropriate consideration. On the other hand, a 1400-patient, randomized, double-blind, placebo-controlled trial of CapeOx or FOLFOX with or without bevacizumab showed no benefit in terms of response rate or tumor regression for the addition of bevacizumab, as measured by both investigators and an independent radiology review committee.[273] Therefore, arguments for use of bevacizumab with oxaliplatin-based therapy in this "convert to resectability" setting are not compelling. However, because it is not

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

When initial chemotherapy is planned for patients with unresectable disease that is felt to be potentially convertible to resectability, the panel recommends that a surgical re-evaluation be planned approximately 2 months after initiation of chemotherapy, and that those patients who continue to receive chemotherapy undergo surgical re-evaluation approximately every 2 months thereafter.[264,274-276] Reported risks associated with chemotherapy include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.[260] To limit the development of hepatotoxicity, it is therefore recommended that surgery should be performed as soon as possible after the patient becomes resectable.

Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

The panel recommends consideration of administration of a course of an active systemic chemotherapy regimen for metastatic disease, for a total perioperative treatment time of approximately 6 months, for most patients undergoing liver or lung resection, to increase the likelihood that residual microscopic disease will be eradicated. A recent metaanalysis identified 3 randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.[277] The pooled analysis showed a benefit of chemotherapy in progression-free survival (pooled HR, 0.75; CI, 0.62-0.91; *P* = .003) and disease-free survival (pooled HR, 0.71; CI, 0.58-0.88; *P* = .001), but not in overall survival (pooled HR, 0.74; CI, 0.53-1.05; *P* = .088).

The choice of chemotherapy regimen in the preoperative setting is dependent on a number of factors, including the chemotherapy history of the patient and the response rates and safety/toxicity issues associated with the regimens. Regimens recommended for adjuvant therapy and neoadjuvant therapy are the same. However, if the tumor grows while the patient is receiving neoadjuvant treatment, an active regimen for advanced disease or observation is recommended.

Although the benefits of perioperative chemotherapy for patients with liver metastases have not yet been fully validated in randomized clinical trials, a recent European Organisation for Research and Treatment of Cancer phase III study (EORTC 40983) evaluating use of perioperative FOLFOX (6 cycles before and 6 cycles after surgery) for patients with initially resectable liver metastases demonstrated absolute improvements in 3-year progression-free survival of 8.1% (*P* = .041) and 9.2% (*P* = .025) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[278] The partial response rate after preoperative FOLFOX was 40%, and operative mortality was <1% in both treatment groups. However, no difference in overall survival was seen between the groups, perhaps because second-line therapy was given to 77% of the patients in the surgery only arm and to 59% of the patients in the chemotherapy arm.[279]

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

Potential advantages of the preoperative chemotherapy approach include earlier treatment of micrometastatic disease; determination of

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

responsiveness to chemotherapy, which can be prognostic and help plan postoperative therapy; and avoidance of local therapy in those who progress early. Potential disadvantages include missing the "window of opportunity" for resection because of the possibility of disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.[194,280,281] Importantly, results from a study of colorectal cancer patients receiving preoperative chemotherapy indicated that viable cancer was still present in most of the original sites of metastases when these sites were examined pathologically despite achievement of a complete response as evaluated on CT scan.[281,282] It is therefore essential that during treatment with preoperative chemotherapy, frequent evaluations are undertaken and close communication is maintained between medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed that optimizes exposure to the preoperative regimen and facilitates an appropriately timed surgical intervention.[260]

Other reported risks associated with the preoperative chemotherapy approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.[260-264] To reduce the development of hepatotoxicity, the neoadjuvant period is usually limited to 2 to 3 months, and patients should be carefully monitored by a multidisciplinary team.

It is important to note that some of the treatment approaches for patients diagnosed with rectal cancer and resectable synchronous lung or liver metastases differ relative to those for patients diagnosed with similarly staged colon cancer. In particular, initial treatment options for synchronous resectable rectal cancer include preoperative chemoRT directed toward treatment of the primary cancer; a preoperative combination chemotherapy regimen plus a biologic agent to target metastatic disease; and a surgical approach (ie, staged or synchronous resection of metastases and rectal lesion). Advantages of an initial chemoRT approach include a possible decreased risk of pelvic failure following surgery, while a disadvantage is that preoperative pelvic RT may decrease tolerance to systemic bevacizumab-containing adjuvant regimens, thereby limiting subsequent treatment of systemic disease. Data to guide decisions regarding optimal treatment approaches in this population of patients are very limited.

Based largely on extrapolation from stage III disease and limited randomized data for stage IV disease, the panel recommends the use of postoperative adjuvant chemotherapy in patients who have undergone liver or lung resection and who have received preoperative chemoRT. Postoperative chemoRT is recommended for patients with synchronous metastases who have not received prior chemoRT and who are at higher risk for pelvic recurrence following staged or synchronous resection of metastases and rectal lesion (ie, patients with disease staged as pT3-4, Any N, M1 or Any T, N1-2, M1).

Perioperative Bevacizumab for Resectable Metastatic Disease

The efficacy of bevacizumab in combination with FOLFOX and FOLFIRI in the treatment of unresectable metastatic disease (see Chemotherapy for Advanced or Metastatic Disease in the NCCN Guidelines for Colon Cancer) has led to its use in combination with these regimens in the preoperative setting. However, the safety of administering bevacizumab pre- or postoperatively in combination with 5-FU-based regimens has not been adequately evaluated. A retrospective evaluation of data from 2 randomized clinical 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

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

compared to the group receiving chemotherapy alone while undergoing major surgery (13% vs. 3.4%, respectively; *P* = .28).[283] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to surgery, the incidence of wound healing complications in either group of patients was low (1.3% vs. 0.5%; *P* = .63). The panel recommends at least a 6-week interval (which corresponds to 2 half-lives of the drug[284]) between the last dose of bevacizumab and elective surgery. Further support for this recommendation comes from results of a single-center, nonrandomized, phase II trial of patients with potentially resectable liver metastases.[285] This study showed no increase in bleeding or wound complications when the bevacizumab component of CapeOX plus bevacizumab therapy was stopped 5 weeks prior to surgery (ie, bevacizumab excluded from the sixth cycle of therapy). In addition, no significant differences in bleeding, wound, or hepatic complications were observed in a retrospective trial evaluating effects of preoperative bevacizumab stopped ≤8 weeks vs. >8 weeks prior to resection of liver colorectal metastases for patients receiving oxaliplatin- or irinotecan-containing regimens.[286]

A recent meta-analysis of randomized controlled trials demonstrated that the addition of bevacizumab to chemotherapy is associated with a higher incidence of treatment-related mortality than chemotherapy alone (RR, 1.33; 95% CI, 1.02-1.73; *P* = .04); hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal perforation (7.1%) were the most common causes of fatality.[287] Venous thromboembolisms, however, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[288]

Perioperative Cetuximab and Panitumumab for Resectable Metastatic Disease: The Role of KRAS and BRAF Status

EGFR has been shown to be overexpressed in 19% of colorectal tumors.[289] EGFR testing of colorectal tumor cells has no proven predictive value in determining likelihood of response to either cetuximab or panitumumab. Data from the BOND-1 study indicated that the intensity of immunohistochemical staining of EGFR in colorectal tumor cells did not correlate with the response rate to cetuximab.[290] A similar conclusion was drawn with respect to panitumumab.[291] Therefore, routine EGFR testing is not recommended, and no patient should be considered for or excluded from cetuximab or panitumumab therapy based on EGFR test results.

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways, but EGFR status as assessed using immunohistochemistry is not predictive of treatment efficacy.[290,292] Furthermore, cetuximab and panitumumab are only effective in approximately 10% to 20% of patients with colorectal cancer.[290,292,293] The RAS/RAF/MAPK pathway is downstream of EGFR; mutations in components of this pathway are being studied in search of predictive markers for efficacy of these therapies.

Approximately 40% of colorectal cancers are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the *KRAS* gene.[294,295] A sizable body of literature has shown that these *KRAS* mutations are predictive of response to cetuximab or panitumumab therapy,[294,296-304] and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of colorectal cancer characterized by these mutations.[305,306] Results are mixed as far as the prognostic value of

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

KRAS mutations, and the test is not recommended for prognostic reasons.

A recent retrospective study from De Roock et al[307] raised the possibility that codon 13 mutations (G13D) may not be absolutely predictive of non-response. Another recent retrospective study showed similar results.[308] However, as the article by De Roock et al[307] states, these findings are hypothesis-generating only, and prospective studies are needed to determine if patients with *KRAS* G13D mutations can, in fact, benefit from anti-EGFR therapy. Currently, use of anti-EGFR agents in patients whose tumors have G13D mutations remains investigational, and is not endorsed by the panel for routine practice.

The panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer *at diagnosis of stage IV disease*. The recommendation for *KRAS* testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *KRAS* status is appropriate to plan for the treatment continuum so that the information may be obtained in a non–time-sensitive manner, and the patient and provider can discuss the implications of a *KRAS* mutation, if present, while other treatment options still exist. Note that because anti-EGFR agents have no role in the management of stage I, II, or III disease, *KRAS* genotyping of colorectal cancers at these earlier stages is not recommended. *KRAS* mutations are early events in colorectal cancer formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.[309,310] For this reason, *KRAS* genotyping can be performed on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of *KRAS* genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable. The panel recommends that *KRAS* gene testing be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.[311] No specific testing methodology is recommended.[312]

Although certain mutations of *KRAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *KRAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *KRAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of colorectal cancers are characterized by a specific mutation in the *BRAF* gene (V600E).[313,314] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.[313,315] Activation of the protein product of the non-mutated *BRAF* gene occurs downstream of the activated KRAS protein in the EGFR pathway; the mutated *BRAF* protein product is believed to be constitutively active,[316-318] thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

The utility of *BRAF* status as a predictive marker is unclear. Limited data from unplanned retrospective subset analyses of patients with metastatic colorectal cancer treated in the first-line setting suggest that although a *BRAF* V600E mutation confers a poor prognosis regardless of treatment, patients with disease characterized by this mutation may receive some benefit from the addition of cetuximab to front-line therapy.[319,320] On the other hand, results from the randomized phase III Medical Research Council (MRC) COIN trial suggest that cetuximab may have no effect or even a detrimental effect in patients with *BRAF*-mutated tumors treated with CapeOx or FOLFOX in the first-line setting.[315] Overall, the panel believes that there are insufficient data to

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on *BRAF* V600E mutation status.

In subsequent lines of therapy, retrospective evidence suggests that mutated *BRAF* is a marker of resistance to anti-EGFR therapy in the non-first-line setting of metastatic disease.[321-323] A retrospective study of 773 primary tumor samples from chemotherapy-refractory patients showed that *BRAF* mutations conferred a significantly lower response rate to cetuximab (2/24; 8.3%) compared with tumors with wild-type *BRAF* (124/326; 38.0%; *P* = .0012).[324] Furthermore, recently reported prospective data from the multicenter, randomized, controlled PICCOLO trial is consistent with this conclusion, with a detrimental effect seen for the addition of panitumumab to irinotecan in the non-first-line setting.[325]

Despite uncertainty over its role as a predictive marker, it is clear that mutations in *BRAF* are a strong prognostic marker.[295,315,320,326-328] A recent prospective analysis of tissues from patients with stage II and III colon cancer enrolled in the PETACC-3 trial showed that the *BRAF* mutation is prognostic for overall survival in patients with low levels of microsatellite instability (MSI-L) or stable microsatellites (MSS) (HR, 2.2; 95% CI, 1.4-3.4; *P* = .0003).[295] Moreover, an updated analysis of the CRYSTAL trial showed that patients with metastatic colorectal tumors carrying a *BRAF* mutation have a worse prognosis than those with the wild-type gene.[320] Additionally, *BRAF* mutation status predicted overall survival in the AGITG MAX trial, with an HR of 0.49 (CI, 0.33-0.73; *P* = .001).[326] The overall survival in patients with *BRAF* mutations in the COIN trial was 8.8 months, while those with *KRAS* mutations and wild-type tumors had overall survival times of 14.4 months and 20.1 months, respectively.[315]

For patients with *KRAS* wild-type tumors, the panel includes the option of *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[329]) at diagnosis of *KRAS* wild-type stage IV disease. Testing for the *BRAF* V600E mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed by PCR amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting this mutation. As with *KRAS* testing, *BRAF* testing should be performed only in CLIA-88 molecular pathology laboratories.

Chemotherapy for Advanced or Metastatic Disease

The continuum of care approach to the management of patients with metastatic rectal cancer is the same as described for patients with metastatic colon cancer. Please refer to Chemotherapy for Advanced or Metastatic Disease in the Guidelines for Colon Cancer.

Recommendations for Treatment of Resectable Synchronous Metastases

As part of the pre-treatment workup, the panel recommends tumor *KRAS* gene status testing for all patients with metastatic colorectal cancer at the time of diagnosis of metastatic disease. If *KRAS* is found to be wild-type, *BRAF* testing can be considered (see The Role of *KRAS* and *BRAF* Status, above).

When patients present with colorectal cancer and synchronous liver metastases, resection of the primary tumor and liver can be done in a simultaneous or staged approach.[330-333] When the remnant liver is insufficient in size based on cross-sectional imaging volumetrics, preoperative portal vein embolization of the involved liver can be done to expand the future liver remnant.[334] In other cases, complete resection can be safely achieved using 2-stage liver resection.[330]

Surgery can be preceded by combination chemotherapy for 2 to 3 months (FOLFOX, CapeOX, or FOLFIRI regimens with or without bevacizumab; or FOLFOX or FOLFIRI with panitumumab [for *KRAS*

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

wild-type tumors only]; or FOLFIRI with cetuximab [for *KRAS* wild-type tumors only]) with or without subsequent chemoRT (infusional 5-FU/pelvic RT [preferred] or bolus 5-FU with LV/pelvic RT or capecitabine/RT [preferred]). ChemoRT (same options) can be considered postoperatively for patients who did not receive it before resection. Alternatively, surgery can be preceded by the same chemoRT options without combination therapy. These patients should have adjuvant therapy with an advanced disease regimen for a total duration of pre- plus postoperative chemotherapy of 6 months. Upfront systemic treatment has the goal of early eradication of micrometastases, while the goal of consolidating chemoRT is local control of disease prior to surgery. For patients receiving neoadjuvant therapy, surgery should be performed 5 to 10 weeks following completion of treatment.

Surgery can also be the initial treatment, with adjuvant therapy based on pathology results. In the population of patients with pT1-2, N0, M0 disease, the competing risk of distant metastases is considered to be higher than that of locoregional recurrence. Therefore, the panel recommends that these patients receive 6 months of adjuvant therapy, FOLFOX or CapeOx preferred, without radiation. The panel recommends that those at higher risk for pelvic failure relative to systemic disease (ie, disease pathologically staged as pT3-4, Any N or Any T, N1-2) undergo postoperative chemoRT using the “sandwich” approach (ie, chemotherapy followed by concurrent chemoRT followed by chemotherapy for 6 months total duration).[121,122] The sandwich approach recommended is (1) 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin, followed by (2) infusional 5-FU/RT (preferred) or bolus 5-FU with LV/RT or capecitabine/RT (preferred), followed by (3) 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin.

Recommendations for Treatment of Unresectable Synchronous Metastases

Patients with unresectable metastases or who are medically inoperable are treated according to whether they are symptomatic or asymptomatic. Symptomatic patients are treated with chemotherapy alone, combined modality therapy with 5-FU/RT or capecitabine/RT (category 2B), resection of the involved rectal segment, laser canalization, diverting colostomy, or stenting. Primary treatment should be followed by an active chemotherapy regimen for advanced or metastatic disease.

For patients with asymptomatic liver or lung disease that is deemed to be unresectable, the panel recommends chemotherapy for advanced or metastatic disease to attempt to render these patients candidates for resection (see Determining Resectability and Conversion to Resectability, above). Chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[335] These patients should be re-evaluated for resection after 2 months of chemotherapy and every 2 months thereafter while undergoing such therapy.

Results from a recent study suggest that there may be some benefit in both overall survival and progression-free survival from resection of the primary in the setting of unresectable colorectal metastases.[336] Other retrospective analyses have also shown a potential benefit.[337,338] However, the prospective, multicenter, phase II NSABP C-10 trial showed that patients with an asymptomatic primary colon tumor and unresectable metastatic disease who received mFOLFOX6 with bevacizumab experienced an acceptable level of morbidity without upfront resection of the primary tumor.[339] The median overall survival was 19.9 months. Notably, symptomatic improvement in the primary is often seen with first-line systemic chemotherapy even within the first 1

to 2 weeks. Furthermore, complications from the primary lesion are uncommon in these circumstances,[208] and its removal delays initiation of systemic chemotherapy. Overall, the panel believes that the risks of surgery outweigh the possible benefits of this approach. Routine palliative resection of a synchronous primary lesion should therefore only be considered if the patient has an unequivocal imminent risk of obstruction or acute significant bleeding.[208]

An intact primary tumor is not a contraindication to bevacizumab use. The risk of gastrointestinal perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, as large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare (see Chemotherapy for Advanced or Metastatic Disease in the Discussion section of the NCCN Guidelines for Colon Cancer, available at www.NCCN.org).

Recommendations for Treatment of Metachronous Metastases

On documentation of metachronous, potentially resectable, metastatic disease with dedicated contrast-enhanced CT or MRI, characterization of the disease extent using PET/CT scan should be considered. PET/CT is used at this juncture to promptly characterize the extent of metastatic disease, and to identify possible sites of extrahepatic disease that could preclude surgery.[340,341] Specifically, Joyce et al[340] reported that the preoperative PET changed or precluded curative-intent liver resection in 25% of patients.

As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) of *KRAS* genotype should be performed to define whether anti-EGFR agents can be considered among the potential options. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS* gene, this testing is currently optional and is not a necessary part of deciding whether to use anti-EGFR agents (see The Role of *KRAS* and *BRAF* Status, above). Close communication between members of the multidisciplinary treatment team is recommended, including upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases.

The management of metachronous metastatic disease is distinguished from that of synchronous disease through also including an evaluation of the chemotherapy history of the patient and through the absence of transabdominal resection. Patients with resectable disease are classified according to whether they have undergone previous chemotherapy. For patients who have resectable metastatic disease, treatment is resection with 6 months of perioperative chemotherapy (pre- or postoperative or a combination of both). There are also cases when perioperative chemotherapy is not recommended in metachronous disease. In particular, patients with a history of previous chemotherapy and an upfront resection can be observed or may be given an active regimen for advanced disease. Observation is preferred if oxaliplatin-based therapy was previously administered. In addition, observation is an appropriate option for patients whose tumors grew through neoadjuvant treatment.

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

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

End Points for Advanced Colorectal Cancer Clinical Trials

In the past few years, there has been much debate over what end points are most appropriate for clinical trials in advanced colorectal cancer.[342] Quality of life is an outcome that is rarely measured but is of unquestioned clinical relevance.[343] While overall survival is also of clear clinical relevance, it is often not used because large numbers of patients and long follow-up periods are required.[343] Progression-free survival is often used as a surrogate, but its correlation with overall survival is inconsistent at best, especially when subsequent lines of therapy are administered.[343,344] GROUP Español Multidisciplinar en Cancer Digestivo (GEMCAD) recently proposed particular aspects of clinical trial design to be incorporated into trials that use progression-free survival as an end point.[345]

A recent study, in which individual patient data from 3 randomized controlled trials were pooled, tested end points that take into account subsequent lines of therapy: duration of disease control, which is the sum of progression-free survival times of each active treatment; and time to failure of strategy, which includes intervals between treatment courses and ends when the planned lines of treatment end (because of death, progression, or administration of a new agent).[344] The authors found a better correlation between these end points and overall survival than between progression-free survival and overall survival. Further evaluation of these and other surrogate end points is warranted.

Post-Treatment Surveillance

Following curative-intent surgery, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and to identify new metachronous neoplasms at a preinvasive stage. The approach to monitoring and surveillance of patients with rectal cancer is similar to that described for colon cancer with the addition of proctoscopy to evaluate the rectal anastomosis for local recurrence for patients who have undergone an LAR. The optimal timing for surveillance of the rectal anastomosis is not known. Furthermore, no specific data clearly support the use of rigid versus flexible proctoscopy, and the utility of endoscopic ultrasound for early surveillance is not defined.

Advantages of more intensive follow-up of stage II and/or stage III patients have been demonstrated prospectively in several studies[346-348] and in 3 meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[349-351] Other 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.[352] The meta-analysis demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor. However, in the final analysis of Intergroup trial 0114 comparing bolus 5-FU to bolus 5-FU/LV in patients with surgically resectable rectal cancer, local recurrence rates continued to rise after 5 years.[112] Further, a population-based report indicated that long-term survival is possible in patients treated for local recurrence of rectal cancer (overall 5-year relative survival rate of 15.6%), thereby providing support for more intensive post-treatment follow-up in these patients.[353] Nevertheless, controversies remain regarding selection of optimal strategies for following patients after potentially curative colorectal cancer surgery.[354,355]

The following panel recommendations for post-treatment surveillance pertain to patients with stage I-stage III disease who have undergone successful treatment (ie, no known residual disease): history and

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

physical examination every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years; and a CEA test at baseline and every 3 to 6 months for 2 years, then every 6 months for a total of 5 years if the patient is a potential candidate for resection of isolated metastases.[349,356,357] Colonoscopy is recommended at approximately 1 year following resection (or at approximately 3 to 6 months post-resection if not performed preoperatively due to an obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia), in which case colonoscopy should be repeated in 1 year.[358] More frequent colonoscopies may be indicated in patients who present with colorectal cancer before age 50.[358] Proctoscopy should be considered every 6 months for 5 years to evaluate for local recurrence at the rectal anastomosis for patients who have undergone an LAR, as discussed above. Chest, abdominal, and pelvic CT scans are recommended annually for up to 5 years in stage II and III patients (ie, patients considered at high risk of recurrence, for example those with lymphatic or venous invasion by the tumor or with poorly differentiated tumors).[349,355] Routine CEA monitoring and CT scanning are not recommended beyond 5 years. Routine use of PET/CT to monitor for disease recurrence is not recommended. The CT that accompanies a PET/CT is usually a noncontrast CT, and therefore not of ideal quality for routine surveillance.

Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps since data show that patients with a history of colorectal cancer have an increased risk of developing second cancers,[359] particularly in the first 2 years following resection; the use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original colorectal cancer.[358] CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver. Hence, CT scan is not routinely recommended in patients who are not candidates for potentially curative resection of liver or lung metastases.

Managing an Increasing CEA Level

Managing patients with an elevated CEA level after resection should include colonoscopy; chest, abdominal, and pelvic CT scans; physical examination; and consideration of a PET/CT scan. If imaging study results are normal in the face of a rising CEA, repeat CT scans are recommended every 3 months until either disease is identified or CEA level stabilizes or declines. Panel opinion was divided on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans (ie, some panel members favored use of PET/CT in this scenario whereas others noted that the likelihood of PET/CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). Use of PET/CT scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called blind or CEA-directed laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,[360] nor do they recommend use of anti-CEA-radiolabeled scintigraphy.

Treatment of Locally Recurrent Disease

Locally recurrent rectal cancer is characterized by isolated pelvic/anastomotic recurrence of disease. In a single-center study, Yu et al reported low rates of 5-year local recurrence (ie, 5-year locoregional control rate of 91%) for patients with rectal cancer treated with surgery and either RT or chemoRT, and 49% of recurrences occurred in the low pelvic and presacral regions with an additional 14% occurring in the mid

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

and high pelvis.[361] Patients with disease recurrence at the anastomotic site are more likely than those with an isolated pelvic recurrence to be cured following re-resection.[362,363]

Potentially resectable isolated pelvic/anastomotic recurrence is optimally managed with resection followed by adjuvant chemoRT or with preoperative RT and concurrent infusional 5-FU. Intraoperative radiotherapy (IORT) or brachytherapy should be considered with resection if it can be safely delivered.[364-366] In a study of 43 consecutive patients with advanced pelvic recurrence of colorectal cancer who had not undergone prior RT, treatment with 5 weeks of 5-FU by infusion concurrent with RT enabled the majority of patients (77%) to undergo re-resection with curative intent.[363] Studies of patients who previously received pelvic radiotherapy show that re-irradiation can be effective, with acceptable rates of toxicity.[367,368] In one such study of 48 patients with recurrent rectal cancer and a history of pelvic radiation, the 3-year rate of grade 3 to 4 late toxicity was 35%, and 36% of treated patients were able to undergo surgery following radiation.[367] IMRT can be used in this setting of re-irradiation.

Patients with unresectable lesions are treated with chemotherapy with or without radiation according to their ability to tolerate therapy. Debulking that results in gross residual cancer is not recommended.

Survivorship

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

Other recommendations include monitoring for late sequelae of rectal cancer or of the treatment of rectal cancer,[369] such as chronic diarrhea or incontinence (eg, patients with stoma).[370-373] Urogenital dysfunction following resection and/or pelvic irradiation is common.[370,374-376] Patients should be screened for sexual dysfunction, erectile dysfunction, dyspareunia, vaginal dryness, and urinary incontinence, frequency, and urgency. Referral to a gynecologist or urologist can be considered for persistent symptoms. Specific management interventions to address side effects of colorectal cancer are described in a recent review,[377] and a survivorship care plan for patients with colorectal cancer has recently been published.[378]

Evidence indicates that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy body mass index (BMI), engaging in regular exercise, and making certain dietary choices are associated with improved outcomes after treatment for colon cancer. For example, a retrospective study of patients with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[379] In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, disease-free survival was found to be directly correlated related to how much exercise these patients received.[380] Furthermore, a diet consisting of more fruits, vegetables, poultry, and fish, and less red meat, and higher in whole grains and lower in refined grains and concentrated sweets, was found to be associated with an improved outcome in terms of cancer recurrence or death.[381] In addition, a recent study of a large cohort of men treated for stage I through III colorectal cancer showed an association between increased physical activity and lower rates of

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

colorectal cancer-specific mortality and overall mortality.[382] A discussion of lifestyle characteristics that may be associated with a decreased risk of colorectal cancer recurrence, such as those recommended by the American Cancer Society,[383] also provides "a teachable moment" for the promotion of overall health, and an opportunity to encourage patients to make choices and changes compatible with a healthy lifestyle.

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written if the primary physician will be assuming cancer surveillance responsibilities.[384] The prescription should include an overall summary of treatments received, including surgeries, radiation treatments, and chemotherapy. The possible clinical course should be described, including the expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment. Surveillance recommendations should be included, as should a delineation of the appropriate timing of transfer of care with specific responsibilities identified for the primary care physician and the oncologist.

Summary

The NCCN Rectal Cancer panel believes that a multidisciplinary approach, including representation from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology is necessary for treating patients with rectal cancer. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes when possible. Patients with very early stage tumors that are node-negative by endorectal ultrasound or endorectal or pelvic MRI and who meet carefully defined criteria can be managed with a transanal excision. A transabdominal resection is appropriate for all other rectal lesions. Preoperative chemoRT is preferred for the majority of patients with suspected or proven T3-4 disease and/or regional node involvement, and adjuvant chemotherapy is recommended. Patients with recurrent localized disease should be considered for resection with or without radiotherapy.

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) can be achieved. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease or when a response to chemotherapy may convert a patient from an unresectable to a resectable state (ie, conversion therapy). Other options for patients with resectable synchronous metastases are initial treatment with chemoRT or chemotherapy with or without bevacizumab or cetuximab/panitumumab (*KRAS* wild type tumor only) followed by consolidating chemoRT. Resection should be followed by adjuvant therapy based on prior therapy received.

The recommended post-treatment surveillance program for rectal cancer patients includes serial CEA determinations, as well as periodic chest, abdominal, and pelvic CT scans, and periodic evaluations by colonoscopy and proctoscopy. Recommendations for patients with disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression and plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy options for advanced or metastatic disease depend on whether or not the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOX, and FOLFOXIRI (category 2B). Addition of a biologic agent (ie, bevacizumab, cetuximab, or panitumumab) is either recommended or listed as an option in combination with some of

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

these regimens, depending on available data. Chemotherapy options for patients with progressive disease are dependent on the choice of initial therapy. The panel endorses the concept that treating patients in a clinical trial has priority over standard treatment regimens.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22237781.

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

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

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

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

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

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

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

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

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

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

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

13. Hendriks YM, de Jong AE, Morreau H, et al. Diagnostic approach and management of Lynch syndrome (hereditary nonpolyposis colorectal carcinoma): a guide for clinicians. CA Cancer J Clin 2006;56:213-225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16870997.

14. Wright DM, Arnold JL, Parry B, et al. Immunohistochemistry to detect hereditary nonpolyposis colorectal cancer in young patients: the 7-year Auckland experience. Dis Colon Rectum 2011;54:552-558. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21471755.

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

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

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

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

18. Altekruse SF, Kosary CL, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2007. National Cancer Institute, Bethesda, MD 2010. Available at: http://seer.cancer.gov/csr/1975_2007/.

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

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

21. Nagtegaal ID, Quirke P. Colorectal tumour deposits in the mesorectum and pericolon; a critical review. Histopathology 2007;51:141-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17532768.

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

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

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

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

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

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

28. Nagtegaal ID, Marijnen CA, Kranenbarg EK, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. Am J Surg Pathol 2002;26:350-357. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11859207.

29. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26:303-312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182672.

30. Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg 2002;89:327-334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11872058.

31. Gavioli M, Luppi G, Losi L, et al. Incidence and clinical impact of sterilized disease and minimal residual disease after preoperative

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

radiochemotherapy for rectal cancer. Dis Colon Rectum 2005;48:1851-1857. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16132481.

32. Rodel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23:8688-8696. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16246976.

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

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

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

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

37. Compton CC. Key issues in reporting common cancer specimens: problems in pathologic staging of colon cancer. Arch Pathol Lab Med 2006;130:318-324. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16519558.

38. Lai LL, Fuller CD, Kachnic LA, Thomas CR, Jr. Can pelvic radiotherapy be omitted in select patients with rectal cancer? Semin Oncol 2006;33:S70-74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17178292.

39. Glynne-Jones R, Mawdsley S, Novell JR. The clinical significance of the circumferential resection margin following preoperative pelvic chemo-radiotherapy in rectal cancer: why we need a common language. Colorectal Dis 2006;8:800-807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17032329.

40. Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 1994;344:707-711. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7915774.

41. Mawdsley S, Glynne-Jones R, Grainger J, et al. Can histopathologic assessment of circumferential margin after preoperative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for 3-year disease-free survival? Int J Radiat Oncol Biol Phys 2005;63:745-752. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16199310.

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

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

44. Pocard M, Panis Y, Malassagne B, et al. Assessing the effectiveness of mesorectal excision in rectal cancer: prognostic value of the number of lymph nodes found in resected specimens. Dis Colon Rectum 1998;41:839-845. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9678368.

45. Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 2001;19:157-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11134208.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

46. Baxter NN, Morris AM, Rothenberger DA, Tepper JE. Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. Int J Radiat Oncol Biol Phys 2005;61:426-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15667963.

47. Wichmann MW, Muller C, Meyer G, et al. Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer. Arch Surg 2002;137:206-210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11822961.

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

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

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

51. Braat AE, Oosterhuis JW, Moll FC, et al. Sentinel node detection after preoperative short-course radiotherapy in rectal carcinoma is not reliable. Br J Surg 2005;92:1533-1538. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16231281.

52. Wiese D, Sirop S, Yestrepsky B, et al. Ultrastaging of sentinel lymph nodes (SLNs) vs. non-SLNs in colorectal cancer--do we need both? Am J Surg 2010;199:354-358; discussion 358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20226909.

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

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

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

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

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

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

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

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

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

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

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

63. Dietary Reference Intakes for Calcium and Vitamin D. Institute of Medicine of the National Academies; 2010. Available at: http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx. Accessed August 2, 2012.

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

65. Hamilton SR, Bosman FT, Boffetta P, et al. Carcinoma of the colon and rectum. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. WHO Classification of Tumours of the Digestive System. Lyon: IARC; 2010.

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

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

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

69. Garcia-Aguilar J, Hernandez de Anda E, Rothenberger DA, et al. Endorectal ultrasound in the management of patients with malignant rectal polyps. Dis Colon Rectum 2005;48:910-916; discussion 916-917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15868240.

70. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin 2006;56:143-159; quiz 184-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16737947.

71. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001;93:583-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11309435.

72. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11547717.

73. Schoellhammer HF, Gregorian AC, Sarkisyan GG, Petrie BA. How important is rigid proctosigmoidoscopy in localizing rectal cancer? Am J Surg 2008;196:904-908; discussion 908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19095107.

74. Baxter NN, Garcia-Aguilar J. Organ preservation for rectal cancer. J Clin Oncol 2007;25:1014-1020. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17350952.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

75. Rajput A, Bullard Dunn K. Surgical management of rectal cancer. Semin Oncol 2007;34:241-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17560986.

76. Weiser MR, Landmann RG, Wong WD, et al. Surgical salvage of recurrent rectal cancer after transanal excision. Dis Colon Rectum 2005;48:1169-1175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15793645.

77. Wiig JN, Larsen SG, Giercksky KE. Operative treatment of locally recurrent rectal cancer. Recent Results Cancer Res 2005;165:136-147. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15865028.

78. Bartram C, Brown G. Endorectal ultrasound and magnetic resonance imaging in rectal cancer staging. Gastroenterol Clin North Am 2002;31:827-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12481733.

79. Bipat S, Glas AS, Slors FJM, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology 2004;232:773-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15273331.

80. Klessen C, Rogalla P, Taupitz M. Local staging of rectal cancer: the current role of MRI. Eur Radiol 2007;17:379-389. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17008990.

81. Lahaye MJ, Engelen SM, Nelemans PJ, et al. Imaging for predicting the risk factors--the circumferential resection margin and nodal disease--of local recurrence in rectal cancer: a meta-analysis. Semin Ultrasound CT MR 2005;26:259-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16152740.

82. Beets-Tan RG, Beets GL. Rectal cancer: review with emphasis on MR imaging. Radiology 2004;232:335-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15286305.

83. Guillem JG, Cohen AM. Current issues in colorectal cancer surgery. Semin Oncol 1999;26:505-513. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10528898.

84. Lindsetmo RO, Joh YG, Delaney CP. Surgical treatment for rectal cancer: an international perspective on what the medical gastroenterologist needs to know. World J Gastroenterol 2008;14:3281-3289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18528924.

85. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. Ann Surg 2007;245:726-733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17457165.

86. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum 2002;45:200-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11852333.

87. Yamamoto S, Watanabe M, Hasegawa H, et al. The risk of lymph node metastasis in T1 colorectal carcinoma. Hepatogastroenterology 2004;51:998-1000. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15239233.

88. Landmann RG, Wong WD, Hoepfl J, et al. Limitations of early rectal cancer nodal staging may explain failure after local excision. Dis Colon Rectum 2007;50:1520-1525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17674104.

89. Nash GM, Weiser MR, Guillem JG, et al. Long-term survival after transanal excision of T1 rectal cancer. Dis Colon Rectum 2009;52:577-582. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19404055.

90. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg 1982;69:613-616. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6751457.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

91. Steup WH, Moriya Y, van de Velde CJH. Patterns of lymphatic spread in rectal cancer. A topographical analysis on lymph node metastases. Eur J Cancer 2002;38:911-918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11978516.

92. Schlag PM. Surgical Sphincter Preservation in Rectal Cancer. Oncologist 1996;1:288-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10388006.

93. Marr R, Birbeck K, Garvican J, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. Ann Surg 2005;242:74-82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15973104.

94. Nagtegaal ID, van de Velde CJ, van der Worp E, et al. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. J Clin Oncol 2002;20:1729-1734. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11919228.

95. Parfitt JR, Driman DK. The total mesorectal excision specimen for rectal cancer: a review of its pathological assessment. J Clin Pathol 2007;60:849-855. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17046842.

96. den Dulk M, Putter H, Collette L, et al. The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer. Eur J Cancer 2009;45:1175-1183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19128956.

97. Pahlman L, Bohe M, Cedermark B, et al. The Swedish rectal cancer registry. Br J Surg 2007;94:1285-1292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17661309.

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

99. Ng SSM, Leung KL, Lee JFY, et al. Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. Ann Surg Oncol 2008;15:2418-2425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18392659.

100. Lujan J, Valero G, Biondo S, et al. Laparoscopic versus open surgery for rectal cancer: results of a prospective multicentre analysis of 4,970 patients. Surg Endosc 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22736289.

101. Kang SB, Park JW, Jeong SY, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. Lancet Oncol 2010;11:637-645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20610322.

102. Jayne DG, Thorpe HC, Copeland J, et al. Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. Br J Surg 2010;97:1638-1645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20629110.

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

104. Araujo SE, da Silva eSousa AH, Jr., de Campos FG, et al. Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial. Rev Hosp Clin Fac Med Sao Paulo 2003;58:133-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12894309.

105. Gopall J, Shen XF, Cheng Y. Current status of laparoscopic total mesorectal excision. Am J Surg 2012;203:230-241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22269656.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

106. Kuhry E, Schwenk WF, Gaupset R, et al. Long-term results of laparoscopic colorectal cancer resection. Cochrane Database Syst Rev 2008:CD003432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18425886.

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

108. Trastulli S, Cirocchi R, Listorti C, et al. Laparoscopic vs open resection for rectal cancer: a meta-analysis of randomized clinical trials. Colorectal Dis 2012;14:e277-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22330061.

109. Xiong B, Ma L, Zhang C. Laparoscopic Versus Open Total Mesorectal Excision for Middle and Low Rectal Cancer: A Meta-analysis of Results of Randomized Controlled Trials. J Laparoendosc Adv Surg Tech A 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22881123.

110. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. J Clin Oncol 2005;23:6199-6206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16135487.

111. Gunderson LL, Sargent DJ, Tepper JE, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol 2004;22:1785-1796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15067027.

112. Tepper JE, O'Connell M, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control--final report of intergroup 0114. J Clin Oncol 2002;20:1744-1750. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11919230.

113. Guillem JG, Diaz-Gonzalez JA, Minsky BD, et al. cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. J Clin Oncol 2008;26:368-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18202411.

114. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15496622.

115. Wagman R, Minsky BD, Cohen AM, et al. Sphincter preservation in rectal cancer with preoperative radiation therapy and coloanal anastomosis: long term follow-up. Int J Radiat Oncol Biol Phys 1998;42:51-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9747819.

116. Sauer R, Liersch T, Merkel S, et al. Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years. J Clin Oncol 2012;30:1926-1933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22529255.

117. Kachnic LA. Should preoperative or postoperative therapy be administered in the management of rectal cancer? Semin Oncol 2006;33:S64-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17178291.

118. Bujko K, Kepka L, Michalski W, Nowacki MP. Does rectal cancer shrinkage induced by preoperative radio(chemo)therapy increase the likelihood of anterior resection? A systematic review of randomised trials. Radiother Oncol 2006;80:4-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16730086.

119. Wong RK, Tandan V, De Silva S, Figueredo A. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. Cochrane Database Syst Rev 2007:CD002102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17443515.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

120. Madoff RD. Chemoradiotherapy for rectal cancer--when, why, and how? N Engl J Med 2004;351:1790-1792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15496630.

121. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994;331:502-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8041415.

122. Smalley SR, Benedetti JK, Williamson SK, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol 2006;24:3542-3547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16877719.

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

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

125. Ceelen WP, Van Nieuwenhove Y, Fierens K. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev 2009:CD006041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19160264.

126. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24:4620-4625. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17008704.

127. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results--EORTC 22921. J Clin Oncol 2005;23:5620-5627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16009958.

128. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-1123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16971718.

129. Collette L, Bosset J-F, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol 2007;25:4379-4386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17906203.

130. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579-588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22503032.

131. Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04 [abstract]. J Clin Oncol 2011;29 (suppl):3503. Available at: http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=76910.

132. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773-2780. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21606427.

133. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

J Clin Oncol 2010;28:1638-1644. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20194850.

134. Gerard J-P, Azria D, Gourgou-Bourgade S, et al. Clinical results at 3 years of the ACCORD 12 randomized trial in rectal cancer [abstract]. ASCO Meeting Abstracts 2012;30:389. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/4_suppl/389.

135. Rodel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22627104.

136. Glynne-Jones R. Rectal cancer-the times they are a-changing. Lancet Oncol 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22627103.

137. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30:1620-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22473163.

138. Chiorean EG, Sanghani S, Schiel MA, et al. Phase II and gene expression analysis trial of neoadjuvant capecitabine plus irinotecan followed by capecitabine-based chemoradiotherapy for locally advanced rectal cancer: Hoosier Oncology Group GI03-53. Cancer Chemother Pharmacol 2012;70:25-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22610353.

139. Kim SY, Hong YS, Kim DY, et al. Preoperative chemoradiation with cetuximab, irinotecan, and capecitabine in patients with locally advanced resectable rectal cancer: a multicenter Phase II study. Int J Radiat Oncol Biol Phys 2011;81:677-683. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20888703.

140. Spigel DR, Bendell JC, McCleod M, et al. Phase II study of bevacizumab and chemoradiation in the preoperative or adjuvant treatment of patients with stage II/III rectal cancer. Clin Colorectal Cancer 2012;11:45-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21840771.

141. Fernandez-Martos C, Aparicio J, Salud A, et al. Multicenter randomized phase II study of chemoradiation (CRT) followed by surgery (S) and chemotherapy (CT) versus induction CT followed by CRT and S in high-risk rectal cancer: GCR-3 final efficacy and safety results. ASCO Meeting Abstracts 2009;27:4103. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/4103.

142. Marechal R, Vos B, Polus M, et al. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: a randomized multicentric phase II study. Ann Oncol 2012;23:1525-1530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22039087.

143. Nogue M, Salud A, Vicente P, et al. Addition of bevacizumab to XELOX induction therapy plus concomitant capecitabine-based chemoradiotherapy in magnetic resonance imaging-defined poor-prognosis locally advanced rectal cancer: the AVACROSS study. Oncologist 2011;16:614-620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21467148.

144. Gay HA, Barthold HJ, O'Meara E, et al. Pelvic normal tissue contouring guidelines for radiation therapy: a radiation therapy oncology group consensus panel atlas. Int J Radiat Oncol Biol Phys 2012;83:e353-362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22483697.

145. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 1999;17:2396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561302.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

146. Habr-Gama A, Perez RO, Proscurshim I, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? Int J Radiat Oncol Biol Phys 2008;71:1181-1188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18234443.

147. Moore HG, Gittleman AE, Minsky BD, et al. Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. Dis Colon Rectum 2004;47:279-286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14991488.

148. Tulchinsky H, Shmueli E, Figer A, et al. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 2008;15:2661-2667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18389322.

149. Tran C-L, Udani S, Holt A, et al. Evaluation of safety of increased time interval between chemoradiation and resection for rectal cancer. Am J Surg 2006;192:873-877. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17161111.

150. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997;336:980-987. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9091798.

151. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. J Clin Oncol 2005;23:8697-8705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16314629.

152. Peeters KCMJ, Marijnen CAM, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007;246:693-701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17968156.

153. Siegel R, Burock S, Wernecke KD, et al. Preoperative short-course radiotherapy versus combined radiochemotherapy in locally advanced rectal cancer: a multi-centre prospectively randomised study of the Berlin Cancer Society. BMC Cancer 2009;9:50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19200365.

154. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811-820. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19269519.

155. Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. J Clin Oncol 2010;28:4233-4239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20585099.

156. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12:575-582. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21596621.

157. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215-1223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16983741.

158. Ngan S, Fisher R, Goldstein D, et al. A randomized trial comparing local recurrence (LR) rates between short-course (SC) and long-course (LC) preoperative radiotherapy (RT) for clinical T3 rectal cancer: An intergroup trial (TROG, AGITG, CSSANZ, RACS) [abstract]. J Clin

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Oncol 2010;28; 15s (suppl):3509. Available at: http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=42290.

159. Das P, Skibber JM, Rodriguez-Bigas MA, et al. Clinical and pathologic predictors of locoregional recurrence, distant metastasis, and overall survival in patients treated with chemoradiation and mesorectal excision for rectal cancer. Am J Clin Oncol 2006;29:219-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16755173.

160. Das P, Skibber JM, Rodriguez-Bigas MA, et al. Predictors of tumor response and downstaging in patients who receive preoperative chemoradiation for rectal cancer. Cancer 2007;109:1750-1755. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17387743.

161. Fietkau R, Barten M, Klautke G, et al. Postoperative chemotherapy may not be necessary for patients with ypN0-category after neoadjuvant chemoradiotherapy of rectal cancer. Dis Colon Rectum 2006;49:1284-1292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16758130.

162. Park IJ, You YN, Agarwal A, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol 2012;30:1770-1776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22493423.

163. Silberfein EJ, Kattepogu KM, Hu CY, et al. Long-term survival and recurrence outcomes following surgery for distal rectal cancer. Ann Surg Oncol 2010;17:2863-2869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20552409.

164. Smith KD, Tan D, Das P, et al. Clinical significance of acellular mucin in rectal adenocarcinoma patients with a pathologic complete response to preoperative chemoradiation. Ann Surg 2010;251:261-264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19864936.

165. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol 2011;29:3753-3760. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21876084.

166. Janjan NA, Crane C, Feig BW, et al. Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. Am J Clin Oncol 2001;24:107-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11319280.

167. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-717; discussion 717-718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15383798.

168. Glynne-Jones R, Wallace M, Livingstone JI, Meyrick-Thomas J. Complete clinical response after preoperative chemoradiation in rectal cancer: is a "wait and see" policy justified? Dis Colon Rectum 2008;51:10-19; discussion 19-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18043968.

169. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633-4640. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22067400.

170. Glynne-Jones R, Hughes R. Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation. Br J Surg 2012;99:897-909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22539154.

171. Wolmark N, Wieand HS, Hyams DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst 2000;92:388-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10699069.

172. Petersen SH, Harling H, Kirkeby LT, et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Syst Rev 2012;3:CD004078. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22419291.

173. Benson AB, Catalan P, Meropol NJ, et al. ECOG E3201: Intergroup randomized phase III study of postoperative irinotecan, 5-fluorouracil (FU), leucovorin (LV) (FOLFIRI) vs oxaliplatin, FU/LV (FOLFOX) vs FU/LV for patients (pts) with stage II/ III rectal cancer receiving either pre or postoperative radiation (RT)/ FU [abstract]. J Clin Oncol 2006;24 (June 20 suppl):3526. Available at: http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/3526.

174. Fakih M. Treating rectal cancer: key issues reconsidered. Oncology (Williston Park) 2008;22:1444-1446. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19322952.

175. Minsky BD, Guillem JG. Multidisciplinary management of resectable rectal cancer. New developments and controversies. Oncology (Williston Park) 2008;22:1430-1437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19086601.

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

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

178. Des Guetz G, Nicolas P, Perret GY, et al. Does delaying adjuvant chemotherapy after curative surgery for colorectal cancer impair survival? A meta-analysis. Eur J Cancer 2010;46:1049-1055. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20138505.

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

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

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

182. Garcia-Aguilar J, Mellgren A, Sirivongs P, et al. Local excision of rectal cancer without adjuvant therapy: a word of caution. Ann Surg 2000;231:345-351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10714627.

183. Sengupta S, Tjandra JJ. Local excision of rectal cancer: what is the evidence? Dis Colon Rectum 2001;44:1345-1361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11584215.

184. Willett CG, Compton CC, Shellito PC, Efird JT. Selection factors for local excision or abdominoperineal resection of early stage rectal cancer. Cancer 1994;73:2716-2720. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8194011.

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

186. Hahnloser D, Haddock MG, Nelson H. Intraoperative radiotherapy in the multimodality approach to colorectal cancer. Surg Oncol Clin N

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Am 2003;12:993-1013, ix. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14989129.

187. Valentini V, Balducci M, Tortoreto F, et al. Intraoperative radiotherapy: current thinking. Eur J Surg Oncol 2002;28:180-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11884054.

188. Willett CG, Czito BG, Tyler DS. Intraoperative radiation therapy. J Clin Oncol 2007;25:971-977. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17350946.

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

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

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

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

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

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

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

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

197. Hayashi M, Inoue Y, Komeda K, et al. Clinicopathological analysis of recurrence patterns and prognostic factors for survival after hepatectomy for colorectal liver metastasis. BMC Surg 2010;10:27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20875094.

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

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

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

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

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

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

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

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

205. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15849507.

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

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

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

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

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

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

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

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

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

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

216. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med 1999;341:2039-2048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10615075.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

217. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. N Engl J Med 2005;352:734-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15716576.

218. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res 2012;32:1387-1395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22493375.

219. Benson A, Mulcahy MF, Siskin G, et al. Safety, response and survival outcomes of Y90 radioembolization for liver metastases: Results from a 151 patient investigational device exemption multi-institutional study [abstract]. Journal of Vascular and Interventional Radiology 2011;22 (suppl):S3. Available at: http://www.jvir.org/article/S1051-0443(11)00003-0/fulltext.

220. Cosimelli M, Golfieri R, Cagol PP, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer 2010;103:324-331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20628388.

221. Gray B, Van Hazel G, Hope M, et al. Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 2001;12:1711-1720. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11843249.

222. Hong K, McBride JD, Georgiades CS, et al. Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization. J Vasc Interv Radiol 2009;20:360-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19167245.

223. Lim L, Gibbs P, Yip D, et al. A prospective evaluation of treatment with Selective Internal Radiation Therapy (SIR-spheres) in patients with unresectable liver metastases from colorectal cancer previously treated with 5-FU based chemotherapy. BMC Cancer 2005;5:132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16225697.

224. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. Cancer 2009;115:1849-1858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19267416.

225. Seidensticker R, Denecke T, Kraus P, et al. Matched-Pair Comparison of Radioembolization Plus Best Supportive Care Versus Best Supportive Care Alone for Chemotherapy Refractory Liver-Dominant Colorectal Metastases. Cardiovasc Intervent Radiol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21800231.

226. van Hazel GA, Pavlakis N, Goldstein D, et al. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. J Clin Oncol 2009;27:4089-4095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652069.

227. Katz AW, Carey-Sampson M, Muhs AG, et al. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. Int J Radiat Oncol Biol Phys 2007;67:793-798. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17197128.

228. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol 2010;28:3687-3694. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20567019.

229. Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. Cochrane Database Syst Rev 2009. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19821394.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

230. ACR–ASTRO Practice Guideline for Intensity-Modulated Radiation Therapy (IMRT). The American College of Radiology; 2011. Available at: http://www.acr.org/~/media/EABB986BC4FF4A78B53B001A059F27B3.pdf. Accessed September 10, 2012.

231. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. Cancer 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21432842.

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

233. Meyer J, Czito B, Yin F-F, Willett C. Advanced radiation therapy technologies in the treatment of rectal and anal cancer: intensity-modulated photon therapy and proton therapy. Clin Colorectal Cancer 2007;6:348-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17311699.

234. Abdalla EK. Commentary: Radiofrequency ablation for colorectal liver metastases: do not blame the biology when it is the technology. Am J Surg 2009;197:737-739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18789420.

235. Gleisner AL, Choti MA, Assumpcao L, et al. Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. Arch Surg 2008;143:1204-1212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19075173.

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

237. Reuter NP, Woodall CE, Scoggins CR, et al. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? J Gastrointest Surg 2009;13:486-491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18972167.

238. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol 2010;28:493-508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19841322.

239. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg 2009;250:440-448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19730175.

240. Cirocchi R, Trastulli S, Boselli C, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. Cochrane Database Syst Rev 2012;6:CD006317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22696357.

241. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22431703.

242. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J Clin Oncol 2012;30:263-267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22162570.

243. Chua TC, Pelz JO, Kerscher A, et al. Critical analysis of 33 patients with peritoneal carcinomatosis secondary to colorectal and appendiceal signet ring cell carcinoma. Ann Surg Oncol 2009;16:2765-2770. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19641972.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

244. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28:63-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19917863.

245. Esquivel J, Sticca R, Sugarbaker P, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. Ann Surg Oncol 2007;14:128-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17072675.

246. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 2004;22:3284-3292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15310771.

247. Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol 2006;24:4011-4019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921055.

248. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737-3743. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14551293.

249. Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15:2426-2432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18521686.

250. Sugarbaker PH, Ryan DP. Cytoreductive surgery plus hyperthermic perioperative chemotherapy to treat peritoneal metastases from colorectal cancer: standard of care or an experimental approach? Lancet Oncol 2012;13:e362-369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22846841.

251. El Halabi H, Gushchin V, Francis J, et al. The role of cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) in patients with high-grade appendiceal carcinoma and extensive peritoneal carcinomatosis. Ann Surg Oncol 2012;19:110-114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21701929.

252. Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer 2010;116:5608-5618. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20737573.

253. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 2012;30:2449-2456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22614976.

254. Klaver YL, Hendriks T, Lomme RM, et al. Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study. Ann Surg 2011;254:125-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21502859.

255. Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. Surg Oncol Clin N Am 2003;12:165-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12735137.

256. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist 2008;13:51-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18245012.

257. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

acid in colorectal cancer patients. Ann Oncol 2004;15:933-939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15151951.

258. Vauthey J-N, Zorzi D, Pawlik TM. Making unresectable hepatic colorectal metastases resectable--does it work? Semin Oncol 2005;32:118-122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16399448.

259. Folprecht G, Grothey A, Alberts S, et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol 2005;16:1311-1319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15870084.

260. Bilchik AJ, Poston G, Curley SA, et al. Neoadjuvant chemotherapy for metastatic colon cancer: a cautionary note. J Clin Oncol 2005;23:9073-9078. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16361615.

261. Choti MA. Chemotherapy-associated hepatotoxicity: do we need to be concerned? Ann Surg Oncol 2009;16:2391-2394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19554374.

262. Kishi Y, Zorzi D, Contreras CM, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol 2010;17:2870-2876. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20567921.

263. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460-466. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14998849.

264. Vauthey J-N, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065-2072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648507.

265. Delaunoit T, Alberts SR, Sargent DJ, et al. Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. Ann Oncol 2005;16:425-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15677624.

266. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 2007;25:1670-1676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470860.

267. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). Br J Cancer 2006;94:798-805. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16508637.

268. Masi G, Vasile E, Loupakis F, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. J Natl Cancer Inst 2011;103:21-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21123833.

269. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010;11:38-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19942479.

270. Tan BR, Zubal B, Hawkins W, et al. Preoperative FOLFOX plus cetuximab or panitumumab therapy for patients with potentially resectable hepatic colorectal metastases [abstract]. Gastrointestinal Cancers Symposium 2009:497. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=63&abstractID=10593.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

271. Petrelli F, Barni S. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. Int J Colorectal Dis 2012;27:997-1004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22358385.

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

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

274. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8:347-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11352309.

275. Pawlik TM, Olino K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 2007;11:860-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17492335.

276. Rivoire M, De Cian F, Meeus P, et al. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. Cancer 2002;95:2283-2292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12436433.

277. Ciliberto D, Prati U, Roveda L, et al. Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: a systematic review and meta-analysis of randomized controlled trials. Oncol Rep 2012;27:1849-1856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22446591.

278. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-1016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18358928.

279. Nordlinger B, Sorbye H, Glimelius B, et al. EORTC liver metastases intergroup randomized phase III study 40983: Long-term survival results [abstract]. ASCO Meeting Abstracts 2012;30:3508. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/3508.

280. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. J Clin Oncol 2005;23:2038-2048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15774795.

281. van Vledder MG, de Jong MC, Pawlik TM, et al. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? J Gastrointest Surg 2010;14:1691-1700. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20839072.

282. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol 2006;24:3939-3945. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921046.

283. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol 2005;91:173-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16118771.

284. Package Insert. AVASTIN® (bevacizumab). Genentech, Inc.; 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125085s02 38lbl.pdf. Accessed June 5, 2012.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

285. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. J Clin Oncol 2008;26:1830-1835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18398148.

286. Reddy SK, Morse MA, Hurwitz HI, et al. Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. J Am Coll Surg 2008;206:96-9106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18155574.

287. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis. JAMA 2011;305:487-494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21285426.

288. Hurwitz HI, Saltz LB, Van Cutsem E, et al. Venous Thromboembolic Events With Chemotherapy Plus Bevacizumab: A Pooled Analysis of Patients in Randomized Phase II and III Studies. J Clin Oncol 2011;29:1757-1764. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21422411.

289. Ooi A, Takehana T, Li X, et al. Protein overexpression and gene amplification of HER-2 and EGFR in colorectal cancers: an immunohistochemical and fluorescent in situ hybridization study. Mod Pathol 2004;17:895-904. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15143334.

290. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15269313.

291. Hecht JR, Mitchell E, Neubauer MA, et al. Lack of correlation between epidermal growth factor receptor status and response to Panitumumab monotherapy in metastatic colorectal cancer. Clin Cancer Res 2010;16:2205-2213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20332321.

292. Saltz LB, Meropol NJ, Loehrer PJ, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004;22:1201-1208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14993230.

293. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-1664. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470858.

294. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-1634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18316791.

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

296. Baselga J, Rosen N. Determinants of RASistance to anti-epidermal growth factor receptor agents. J Clin Oncol 2008;26:1582-1584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18316790.

297. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009;27:663-671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19114683.

298. Dahabreh IJ, Terasawa T, Castaldi PJ, Trikalinos TA. Systematic review: Anti-epidermal growth factor receptor treatment effect modification by KRAS mutations in advanced colorectal cancer. Ann Intern Med 2011;154:37-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21200037.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

299. De Roock W, Piessevaux H, De Schutter J, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 2008;19:508-515. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17998284.

300. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757-1765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18946061.

301. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25:3230-3237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17664471.

302. Lievre A, Bachet J-B, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008;26:374-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18202412.

303. Tejpar S, Peeters M, Humblet Y, et al. Relationship of efficacy with KRAS status (wild type versus mutant) in patients with irinotecan-refractory metastatic colorectal cancer (mCRC), treated with irinotecan (q2w) and escalating doses of cetuximab (q1w): The EVEREST experience (preliminary data) [abstract]. J Clin Oncol 2008;26 (May 20 suppl):4001. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/4001.

304. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-1417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19339720.

305. Package Insert. Cetuximab (Erbitux®). Branchburg, NJ: ImClone Systems Incorporated; 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125084s225lbl.pdf. Accessed August 31, 2012.

306. Package Insert. Vectibix® (Panitumumab). Thousand Oaks, CA: Amgen Inc.; 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125147s0148lbl.pdf. Accessed August 31, 2012.

307. De Roock W, Jonker DJ, Di Nicolantonio F, et al. Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. JAMA 2010;304:1812-1820. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20978259.

308. Tejpar S, Celik I, Schlichting M, et al. Association of KRAS G13D Tumor Mutations With Outcome in Patients With Metastatic Colorectal Cancer Treated With First-Line Chemotherapy With or Without Cetuximab. J Clin Oncol 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22734028.

309. Artale S, Sartore-Bianchi A, Veronese SM, et al. Mutations of KRAS and BRAF in primary and matched metastatic sites of colorectal cancer. J Clin Oncol 2008;26:4217-4219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18757341.

310. Etienne-Grimaldi M-C, Formento J-L, Francoual M, et al. K-Ras mutations and treatment outcome in colorectal cancer patients receiving exclusive fluoropyrimidine therapy. Clin Cancer Res 2008;14:4830-4835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18676755.

311. Wang HL, Lopategui J, Amin MB, Patterson SD. KRAS mutation testing in human cancers: The pathologist's role in the era of personalized medicine. Adv Anat Pathol 2010;17:23-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20032635.

312. Monzon FA, Ogino S, Hammond MEH, et al. The role of KRAS mutation testing in the management of patients with metastatic

 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

colorectal cancer. Arch Pathol Lab Med 2009;133:1600-1606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19792050.

313. Tol J, Nagtegaal ID, Punt CJA. BRAF mutation in metastatic colorectal cancer. N Engl J Med 2009;361:98-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19571295.

314. Van Cutsem E, Lang I, Folprecht G, et al. Cetuximab plus FOLFIRI: Final data from the CRYSTAL study on the association of KRAS and BRAF biomarker status with treatment outcome [abstract]. J Clin Oncol 2010;28 (May 20 suppl):3570. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/3570.

315. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011;377:2103-2114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21641636.

316. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417:949-954. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12068308.

317. Ikenoue T, Hikiba Y, Kanai F, et al. Functional analysis of mutations within the kinase activation segment of B-Raf in human colorectal tumors. Cancer Res 2003;63:8132-8137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14678966.

318. Wan PT, Garnett MJ, Roe SM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 2004;116:855-867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15035987.

319. Bokemeyer C, Cutsem EV, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer 2012;48:1466-1475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22446022.

320. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab Plus Irinotecan, Fluorouracil, and Leucovorin As First-Line Treatment for Metastatic Colorectal Cancer: Updated Analysis of Overall Survival According to Tumor KRAS and BRAF Mutation Status. J Clin Oncol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21502544.

321. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26:5705-5712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19001320.

322. Laurent-Puig P, Cayre A, Manceau G, et al. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. J Clin Oncol 2009;27:5924-5930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19884556.

323. Loupakis F, Ruzzo A, Cremolini C, et al. KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer. Br J Cancer 2009;101:715-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19603018.

324. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol 2010;11:753-762. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20619739.

325. Seymour MT, Brown SR, Richman S, et al. Addition of panitumumab to irinotecan: Results of PICCOLO, a randomized controlled trial in advanced colorectal cancer (aCRC). ASCO Meeting Abstracts 2011;29:3523. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/3523.

326. Price TJ, Hardingham JE, Lee CK, et al. Impact of KRAS and BRAF Gene Mutation Status on Outcomes From the Phase III AGITG MAX Trial of Capecitabine Alone or in Combination With Bevacizumab

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

and Mitomycin in Advanced Colorectal Cancer. J Clin Oncol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21646616.

327. Saridaki Z, Papadatos-Pastos D, Tzardi M, et al. BRAF mutations, microsatellite instability status and cyclin D1 expression predict metastatic colorectal patients' outcome. Br J Cancer 2010;102:1762-1768. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20485284.

328. Samowitz WS, Sweeney C, Herrick J, et al. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. Cancer Res 2005;65:6063-6069. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16024606.

329. Santini D, Spoto C, Loupakis F, et al. High concordance of BRAF status between primary colorectal tumours and related metastatic sites: implications for clinical practice. Ann Oncol 2010;21:1565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20573852.

330. Adam R, Miller R, Pitombo M, et al. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. Surg Oncol Clin N Am 2007;16:525-536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17606192.

331. Boostrom SY, Vassiliki LT, Nagorney DM, et al. Synchronous rectal and hepatic resection of rectal metastatic disease. J Gastrointest Surg 2011;15:1583-1588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21748454.

332. Chen J, Li Q, Wang C, et al. Simultaneous vs. staged resection for synchronous colorectal liver metastases: a metaanalysis. Int J Colorectal Dis 2011;26:191-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20669024.

333. Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol 2007;14:3481-3491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17805933.

334. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 2008;247:451-455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18376189.

335. Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1284-1292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16955384.

336. Faron M, Bourredjem A, Pignon J-P, et al. Impact on survival of primary tumor resection in patients with colorectal cancer and unresectable metastasis: Pooled analysis of individual patients' data from four randomized trials [abstract]. ASCO Meeting Abstracts 2012;30:3507. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/3507.

337. Karoui M, Roudot-Thoraval F, Mesli F, et al. Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study. Dis Colon Rectum 2011;54:930-938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21730780.

338. Venderbosch S, de Wilt JH, Teerenstra S, et al. Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. Ann Surg Oncol 2011;18:3252-3260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21822557.

339. McCahill LE, Yothers G, Sharif S, et al. Primary mFOLFOX6 Plus Bevacizumab Without Resection of the Primary Tumor for Patients Presenting With Surgically Unresectable Metastatic Colon Cancer and an Intact Asymptomatic Colon Cancer: Definitive Analysis of NSABP Trial C-10. J Clin Oncol 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22869888.

340. Joyce DL, Wahl RL, Patel PV, et al. Preoperative positron emission tomography to evaluate potentially resectable hepatic

colorectal metastases. Arch Surg 2006;141:1220-1226; discussion 1227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17178965.

341. Pelosi E, Deandreis D. The role of 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) in the management of patients with colorectal cancer. Eur J Surg Oncol 2007;33:1-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17126522.

342. Gill S, Berry S, Biagi J, et al. Progression-free survival as a primary endpoint in clinical trials of metastatic colorectal cancer. Curr Oncol 2011;18 Suppl 2:S5-S10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21969810.

343. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol 2012;30:1030-1033. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22370321.

344. Chibaudel B, Bonnetain F, Shi Q, et al. Alternative end points to evaluate a therapeutic strategy in advanced colorectal cancer: evaluation of progression-free survival, duration of disease control, and time to failure of strategy--an Aide et Recherche en Cancerologie Digestive Group Study. J Clin Oncol 2011;29:4199-4204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21969501.

345. Carrera G, Garcia-Albeniz X, Ayuso JR, et al. Design and endpoints of clinical and translational trials in advanced colorectal cancer. a proposal from GROUP Espanol Multidisciplinar en Cancer Digestivo (GEMCAD). Rev Recent Clin Trials 2011;6:158-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21241233.

346. Pietra N, Sarli L, Costi R, et al. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. Dis Colon Rectum 1998;41:1127-1133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9749496.

347. Rodriguez-Moranta F, Salo J, Arcusa A, et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. J Clin Oncol 2006;24:386-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16365182.

348. Secco GB, Fardelli R, Gianquinto D, et al. Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. Eur J Surg Oncol 2002;28:418-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12099653.

349. Desch CE, Benson AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23:8512-8519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16260687.

350. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2007. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17253476.

351. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ 2002;324:813-813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11934773.

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

353. Guyot F, Faivre J, Manfredi S, et al. Time trends in the treatment and survival of recurrences from colorectal cancer. Ann Oncol 2005;16:756-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15790673.

354. Li Destri G, Di Cataldo A, Puleo S. Colorectal cancer follow-up: useful or useless? Surg Oncol 2006;15:1-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16891116.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

355. Pfister DG, Benson AB, 3rd, Somerfield MR. Clinical practice. Surveillance strategies after curative treatment of colorectal cancer. N Engl J Med 2004;350:2375-2382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15175439.

356. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 2006;24:5313-5327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17060676.

357. Macdonald JS. Carcinoembryonic antigen screening: pros and cons. Semin Oncol 1999;26:556-560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10528904.

358. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. CA Cancer J Clin 2006;56:160-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16737948.

359. Green RJ, Metlay JP, Propert K, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of Intergroup 0089. Ann Intern Med 2002;136:261-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11848723.

360. Martin EW, Minton JP, Carey LC. CEA-directed second-look surgery in the asymptomatic patient after primary resection of colorectal carcinoma. Ann Surg 1985;202:310-317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4037904.

361. Yu TK, Bhosale PR, Crane CH, et al. Patterns of locoregional recurrence after surgery and radiotherapy or chemoradiation for rectal cancer. Int J Radiat Oncol Biol Phys 2008;71:1175-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18207667.

362. Hoffman JP, Riley L, Carp NZ, Litwin S. Isolated locally recurrent rectal cancer: a review of incidence, presentation, and management. Semin Oncol 1993;20:506-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8211198.

363. Lowy AM, Rich TA, Skibber JM, et al. Preoperative infusional chemoradiation, selective intraoperative radiation, and resection for locally advanced pelvic recurrence of colorectal adenocarcinoma. Ann Surg 1996;223:177-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8597512.

364. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol 2008;15:1937-1947. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18389321.

365. Kuehne J, Kleisli T, Biernacki P, et al. Use of high-dose-rate brachytherapy in the management of locally recurrent rectal cancer. Dis Colon Rectum 2003;46:895-899. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12847362.

366. Wang JJ, Yuan HS, Li JN, et al. CT-guided radioactive seed implantation for recurrent rectal carcinoma after multiple therapy. Med Oncol 2010;27:421-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19415534.

367. Das P, Delclos ME, Skibber JM, et al. Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior pelvic irradiation. Int J Radiat Oncol Biol Phys 2010;77:60-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19695792.

368. Valentini V, Morganti AG, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. Int J Radiat Oncol Biol Phys 2006;64:1129-1139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16414206.

369. Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer : patient-reported symptoms 4 years after diagnosis. Cancer

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

2007;110:2075-2082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17849466.

370. Desnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. Eur J Cancer Care (Engl) 2006;15:244-251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16882120.

371. Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther 2003;18:987-994. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14616164.

372. McGough C, Baldwin C, Frost G, Andreyev HJ. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. Br J Cancer 2004;90:2278-2287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15162154.

373. Sprangers MA, Taal BG, Aaronson NK, te Velde A. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7720441.

374. Baxter NN, Habermann EB, Tepper JE, et al. Risk of pelvic fractures in older women following pelvic irradiation. JAMA 2005;294:2587-2593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16304072.

375. Lange MM, Maas CP, Marijnen CA, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. Br J Surg 2008;95:1020-1028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18563786.

376. Lange MM, Marijnen CA, Maas CP, et al. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer 2009;45:1578-1588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19147343.

377. Denlinger CS, Barsevick AM. The challenges of colorectal cancer survivorship. J Natl Compr Canc Netw 2009;7:883-893. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19755048.

378. Faul LA, Shibata D, Townsend I, Jacobsen PB. Improving survivorship care for patients with colorectal cancer. Cancer Control 2010;17:35-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20010517.

379. Dignam JJ, Polite BN, Yothers G, et al. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. J Natl Cancer Inst 2006;98:1647-1654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17105987.

380. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol 2006;24:3535-3541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16822843.

381. Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA 2007;298:754-764. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17699009.

382. Meyerhardt JA, Giovannucci EL, Ogino S, et al. Physical activity and male colorectal cancer survival. Arch Intern Med 2009;169:2102-2108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20008694.

383. Kushi LH, Byers T, Doyle C, et al. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2006;56:254-281; quiz 313-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17005596.

384. Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. 2006. Available at: http://www.nap.edu/openbook.php?isbn=0309095956.

Version 4.2013, 11/26/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**