National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Rectal Cancer

Version 2.2016

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Panel Members
Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion

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

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

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

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

Moon J. Fenton, MD, PhD †
St. Jude Children's Research Hospital/ University of Tenessee Health Science Center

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

Jean L. Grem, MD †
Fred & Pamela Buffett Cancer Center

Axel Grothey, MD †
Mayo Clinic Cancer Center

Howard S. Hochster, MD
Yale Cancer Center/Smilow Cancer Hospital

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

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

Natalie Kirilcuk, MD ¶
Stanford Cancer Institute

Smitha Krishnamurthi, MD † Þ
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

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

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

Wells A. Messersmith, MD †
University of Colorado Cancer Center

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

James D. Murphy, MD, MS §
UC San Diego Moores Cancer Center

Steven Nurkin, MD, MS ¶
Roswell Park Cancer Institute

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

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

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

Elena M. Stoffel, MD, MPH ¤
University of Michigan Comprehensive Cancer Center

Eden Stotsky-Himelfarb, BSN, RN ¥
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Christopher G. Willett, MD §
Duke Cancer Institute

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

Continue

† Medical oncology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
≠ Pathology
‡ Hematology/Hematology oncology
Þ Internal medicine
ϕ Diagnostic/Interventional radiology
¤ Gastroenterology
¥ Patient advocate
*Discussion Section Writing Committee

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Table of Contents
Rectal Cancer

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Updates Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion

Updates in Version 2.2016 of the NCCN Guidelines for Rectal Cancer from Version 1.2016 include:

MS-1

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

Updates in Version 1.2016 of the Guidelines for Rectal Cancer from Version 3.2015 include:

REC-1

- **Footnote "b" added: "For melanoma histology, see the NCCN Guidelines for Melanoma." (also applies to REC-2)**

REC-2

- **Workup, bullet 4: "rigid" removed from proctoscopy.**

REC-3

- **T1,NX with high-risk features or T2,NX: the treatment option of Chemo/RT added after transabdominal resection. Chemo/RT options: Capecitabine/RT or infusional 5-FU/RT (preferred for both) or Bolus 5-FU/leucovorin/RT.**
- **Footnote "n" added: "Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU." (also applies to REC-4, REC-5, REC-6, REC-7, and REC-9)**

REC-4

- **Neoadjuvant Therapy: Radiation therapy used in Chemo/RT clarified as "long-course" RT.**
- **Neoadjuvant Therapy: The option of Short-course RT added with the qualifier that it is not recommended for T4 tumors.**
- **Footnote "o" added: "Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity."**

REC-6

- **The treatment option of "Staged or synchronous resection of metastases and rectal lesion" modified to "Staged or synchronous resection *(preferred) and/or local therapy for* metastases and *resection of* rectal lesion"**
- **Footnote "v" modified: "Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. *Determination of tumor MMR or MSI status (if not previously done).* See Principles of Pathologic Review (REC-A 5 of 6) - KRAS, NRAS and BRAF Mutation Testing *and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing."* (also applies to REC-7 and REC-9)**
- **Footnote "z" added to the page: "Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver oligometastases (REC-B and REC-D)." (also applies to REC-10)**

REC-8

- **Surveillance, bullet 3 modified: "Chest/abdominal/pelvic CT ~~annually for up to~~ e*very 3–6 mo x 2 y, then every 6–12 mo or up to a total of* 5 y~~for patients at high risk for recurrence~~"**
- **Surveillance recommendations added for patients after transanal excision only.**
  - **"Proctoscopy (with EUS or MRI) every 3–6 mo for the first 2 y, then every 6 mo for a total of 5 y (for patients treated with transanal excision only)."**

REC-10

- **The treatment option of "Resection" modified to "Resection *(preferred) and/or Local therapy*."**

REC-11

- **Footnote "jj" modified: "Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/*or* cost."**

UPDATES

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Updates
Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion

Updates in Version 1.2016 of the Guidelines for Rectal Cancer from Version 3.2015 include:

REC-A 2 of 6

- **Pathologic Stage: The system used to grade tumor response *as recommended by the AJCC Cancer Staging Manual, 7th Edition, and the CAP guidelines is that* as modified from Ryan R, et al. Histopathology 2005;47:141-146.**
- **Sentence added to last sub-bullet: "Other grading systems that are used are referenced."**

REC-A 5 of 6

- ***KRAS, NRAS*, and *BRAF* Mutation Testing, bullet 1 modified: "All patients with metastatic colorectal cancer should have tumor tissue genotyped for *RAS* ~~mutations~~ (*KRAS* and *NRAS*) *and BRAF mutations*. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab. *Evidence increasingly suggests that BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely, as a single agent, or in combination with cytotoxic chemotherapy."***
- ***KRAS, NRAS*, and *BRAF* Mutation Testing, bullet 2 removed: "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."**
- **Microsatellite Instability (MSI) section modified: "...*or Mismatch Repair (MMR)* Testing"**
  - **Bullet 1 modified: "Lynch syndrome tumors screening (ie, IHC *for MMR* or *PCR for* MSI) should be ~~considered~~ *performed* for *all* patients with colorectal cancer diagnosed at age ≤70 y and also those >70 y who meet the Bethesda guidelines. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal"**
  - **Bullet 2 added: *"The presence of a BRAF V600E mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch syndrome"***
  - **Bullet 3 added: *"*MMR or MSI testing should also be performed for all patients with stage II disease, because stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy."**
  - **Bullet 4 added: MMR or MSI testing should also be performed for all patients with metastatic disease.**
  - **Footnote "*"added: "IHC for MMR and PCR for MSI are different assays measuring the same biological effect."**

REC-A 6 of 6

- **Reference 59 added.**

REC-B 1 of 3

- **The following bullet removed: "Laparoscopic surgery is preferred in the setting of a clinical trial."**
- **The following text added: "Some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared to open surgery, whereas other studies have shown that laparoscopy is associated with higher rates of circumferential margin positivity and incomplete TME. Therefore, minimally invasive resection may be considered based on the following principles:**
  - **◊ The surgeon should have experience performing minimally invasive proctectomy with total mesorectal excision.**
  - **◊ It is not indicated for locally advanced disease with a threatened or high-risk circumferential margin based on staging. For these high-risk tumors, open surgery is preferred.**
  - **◊ It is not indicated for acute bowel obstruction or perforation from cancer.**
  - **◊ Thorough abdominal exploration is required."**

REC-B 3 of 3

- **References 2–5 added.**

UPDATES

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Updates Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion

Updates in Version 1.2016 of the Guidelines for Rectal Cancer from Version 3.2015 include:

REC-C 1 of 2

- **Footnote "*" added: "Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m^2/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger RD, et al. Oxaliplatin can be safely infused at a rate of 1 mg/m^2/min. J Clin Oncol 33, 2015 (suppl; abstr e14665)." (also applies to REC-E 6 of 9)**
- **Footnote "‡" added: "Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU."**

REC-D

- **Bullet 4 modified: "Intensity-modulated radiation therapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations ~~including~~ *such as* reirradiation of previously treated patients with recurrent disease *or unique anatomical situations*."**
- **Bullet 6 added: "Short-course radiation therapy (25 Gy in 5 fractions) with surgery within 1 to 2 weeks of completion of therapy can also be considered for patients with ultrasound or pelvic MRI stage T3 rectal cancer."**
- **Reference added: "Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833."**

REC-E 1 of 9

- **The regimen of trifluridine + tipiracil was added as a subsequent therapy option for patients with disease progression after oxaliplatin- and irinotecan-based chemotherapy. (also applies for REC-E 2 of 9 and REC-E 3 of 9)**

REC-E 5 of 9

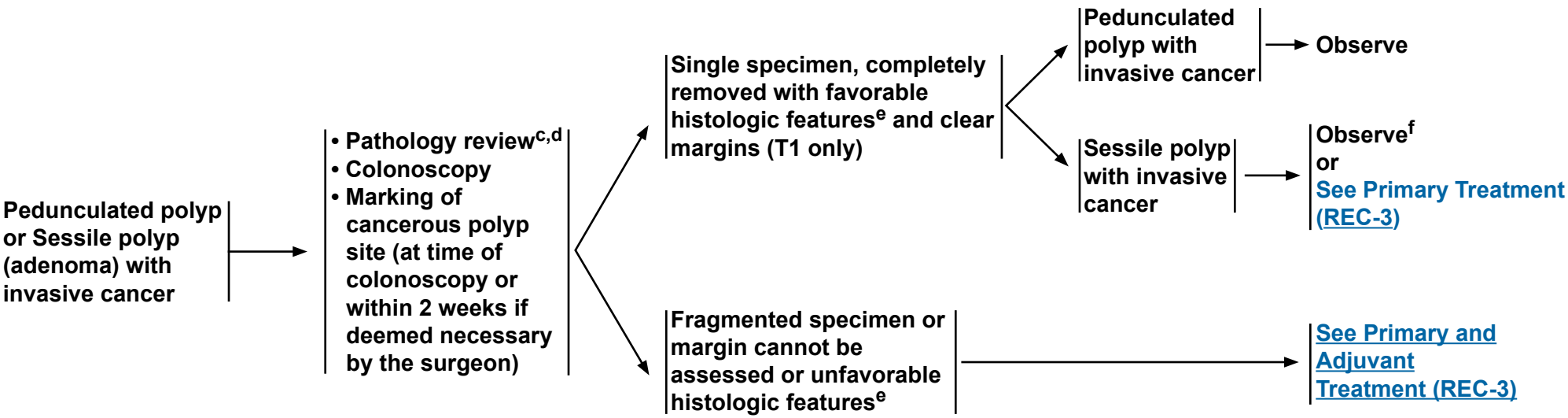
- **Footnote 11 modified: "There are no data to suggest activity of FOLFIRI-ziv-aflibercept *or FOLFIRI-ramucirumab* in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept *and ramucirumab* have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients."**
- **Footnote 12 modified: "Bevacizumab is the preferred anti-angiogenic agent based on toxicity and*/or* cost."**

REC-E 8 of 9

- **The following regimen added: "Trifluridine + tipiracil 35 mg/m^2 (up to a maximum dose of 80 mg per dose (based on the trifuluridine component) PO twice daily days 1–5 and 8–12. Repeat every 28 days"**
- **Footnote "§" added: "It is common practice to start at a lower dose of regorafenib (80 or 120 mg) and escalate, as tolerated."**

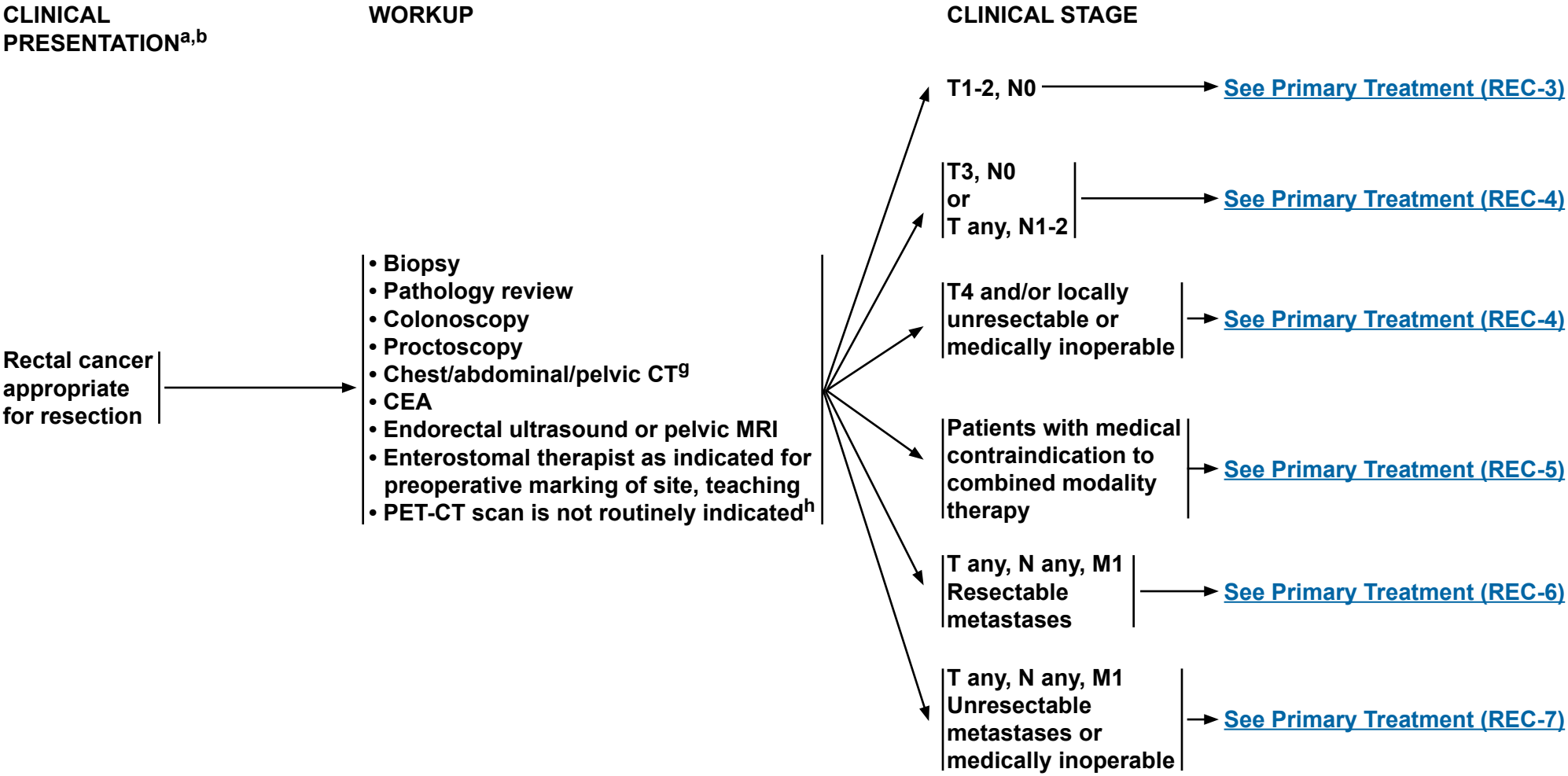
REC-E 9 of 9

- **Reference added: "Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer (RECOURSE). N Engl J Med 2015; 372:1909-19."**



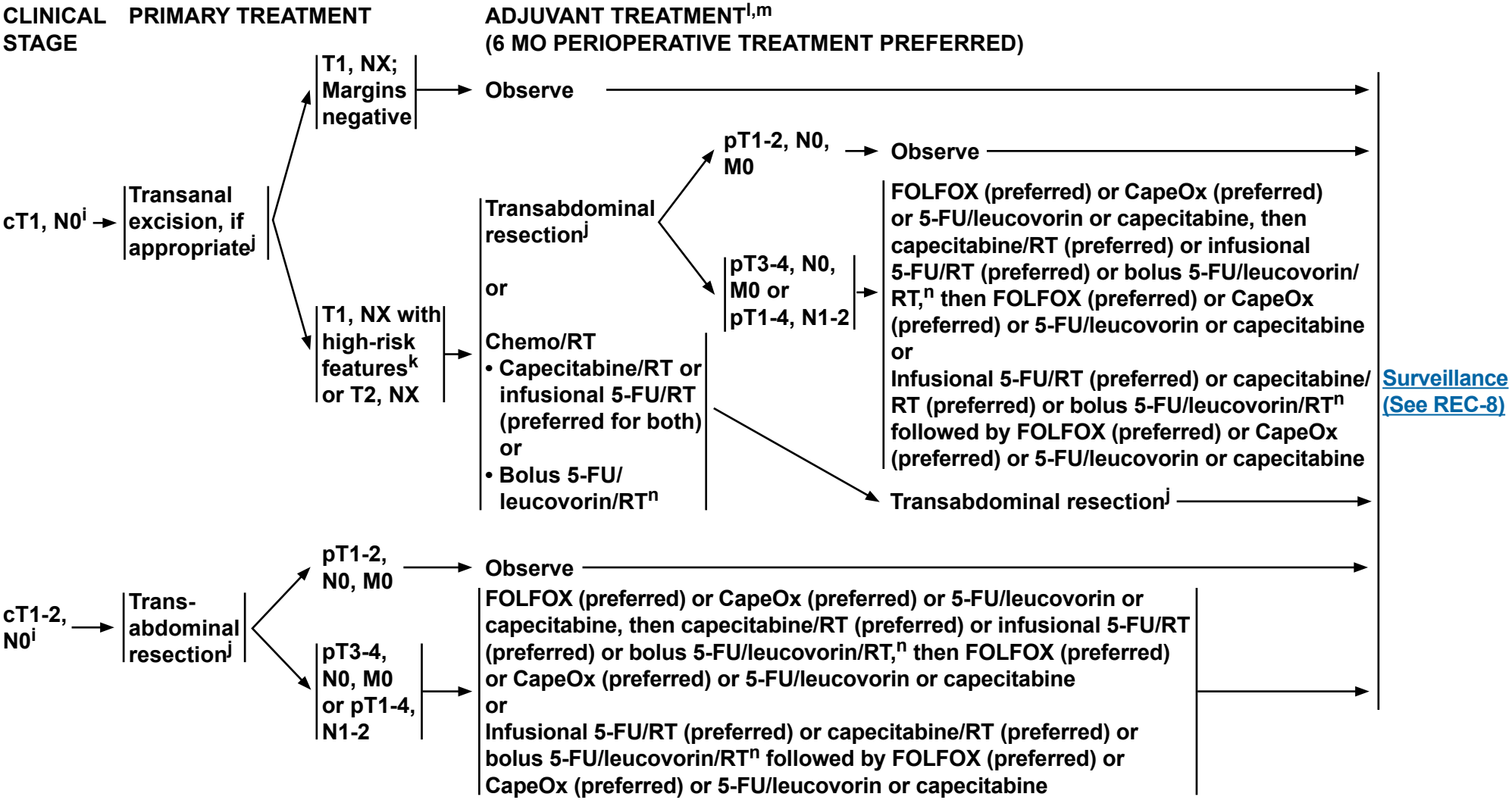
[a]All patients with rectal cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[b]For melanoma histology, see the NCCN Guidelines for Melanoma.
[c]Confirm the presence of invasive cancer (pT1). pTis has no biological potential to metastasize.
[d]It has not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis. College of American Pathologists Consensus Statement 1999. Prognostic factors in colorectal cancer. Arch Pathol Lab Med 2000;124:979-994.
[e]See Principles of Pathologic Review (REC-A) - Endoscopically removed malignant polyp.
[f]Observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, 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.



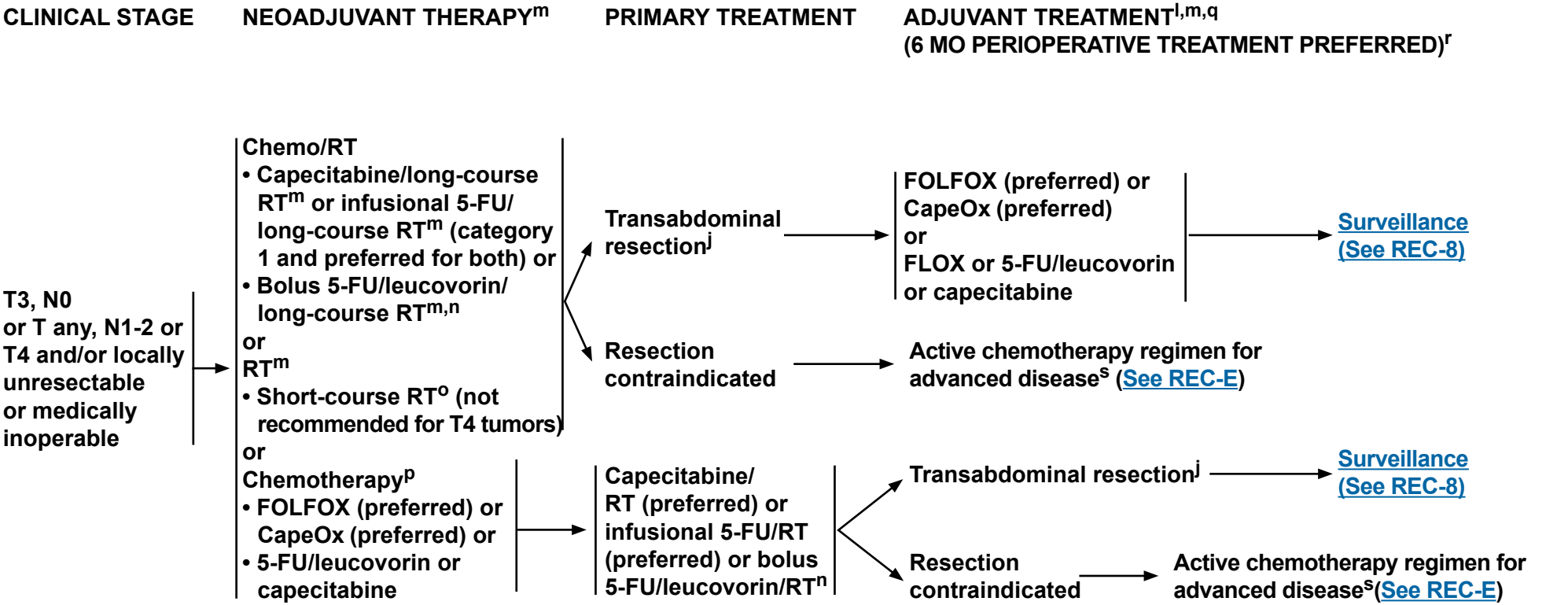
[a]All patients with rectal cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[b]For melanoma histology, see the NCCN Guidelines for Melanoma.
[g]CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.
[h]PET-CT does not supplant a contrast-enhanced diagnostic CT scan. PET-CT should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or in patients with strong contraindications to IV contrast.

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.



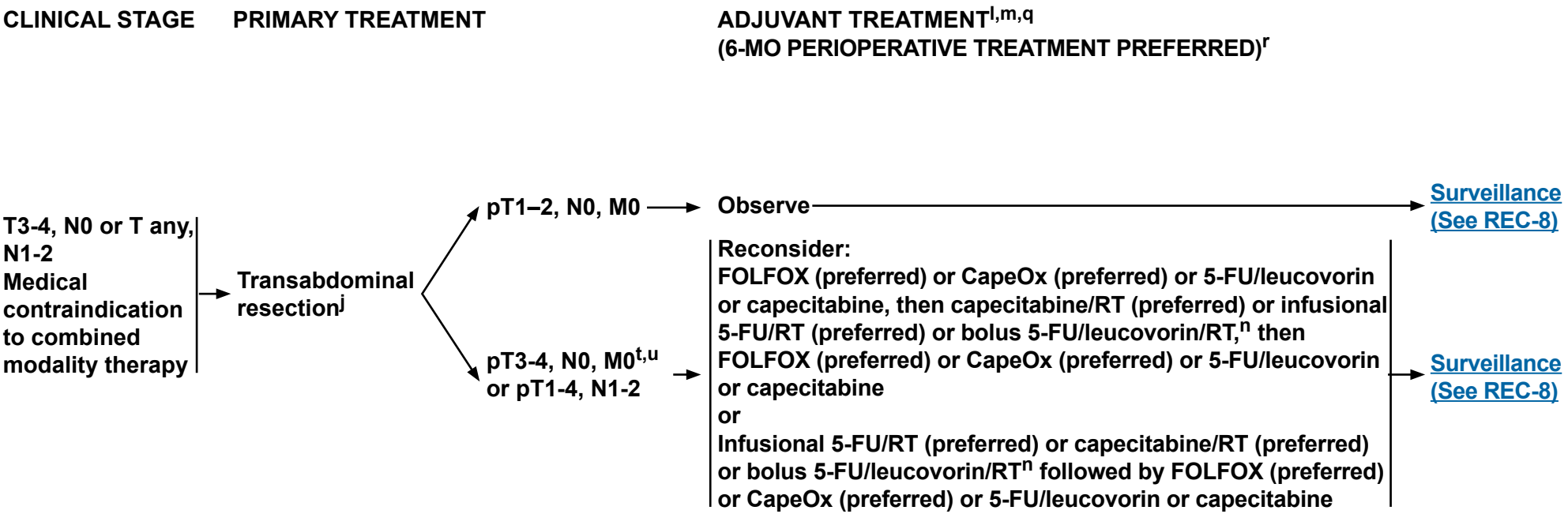
[i]T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.
[j]See Principles of Surgery (REC-B).
[k]High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion.
[l]See Principles of Adjuvant Therapy (REC-C).
[m]See Principles of Radiation Therapy (REC-D).
[n]Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

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.



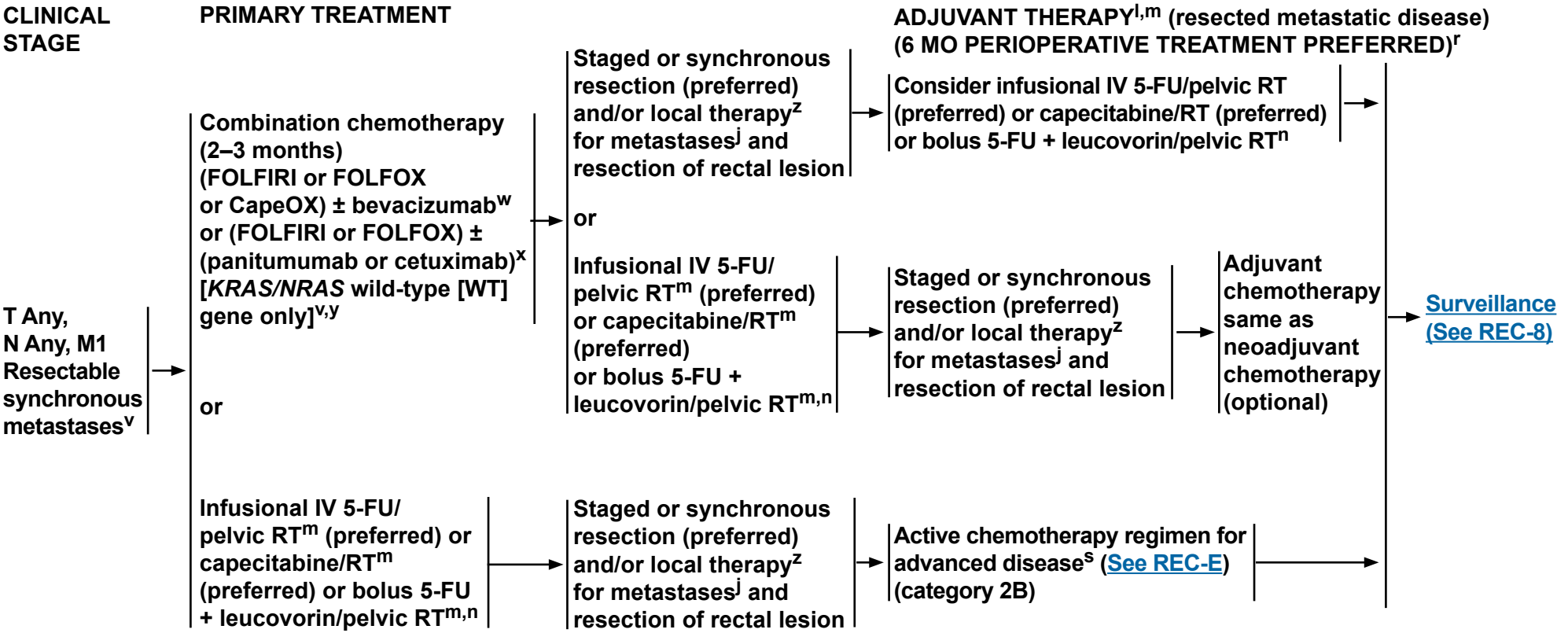
[j] See Principles of Surgery (REC-B).
[l] See Principles of Adjuvant Therapy (REC-C).
[m] See Principles of Radiation Therapy (REC-D).
[n] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[o] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.
[p] Fernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.
Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.
[q] Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.
[r] Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.
[s] FOLFOXIRI is not recommended in this setting.

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.



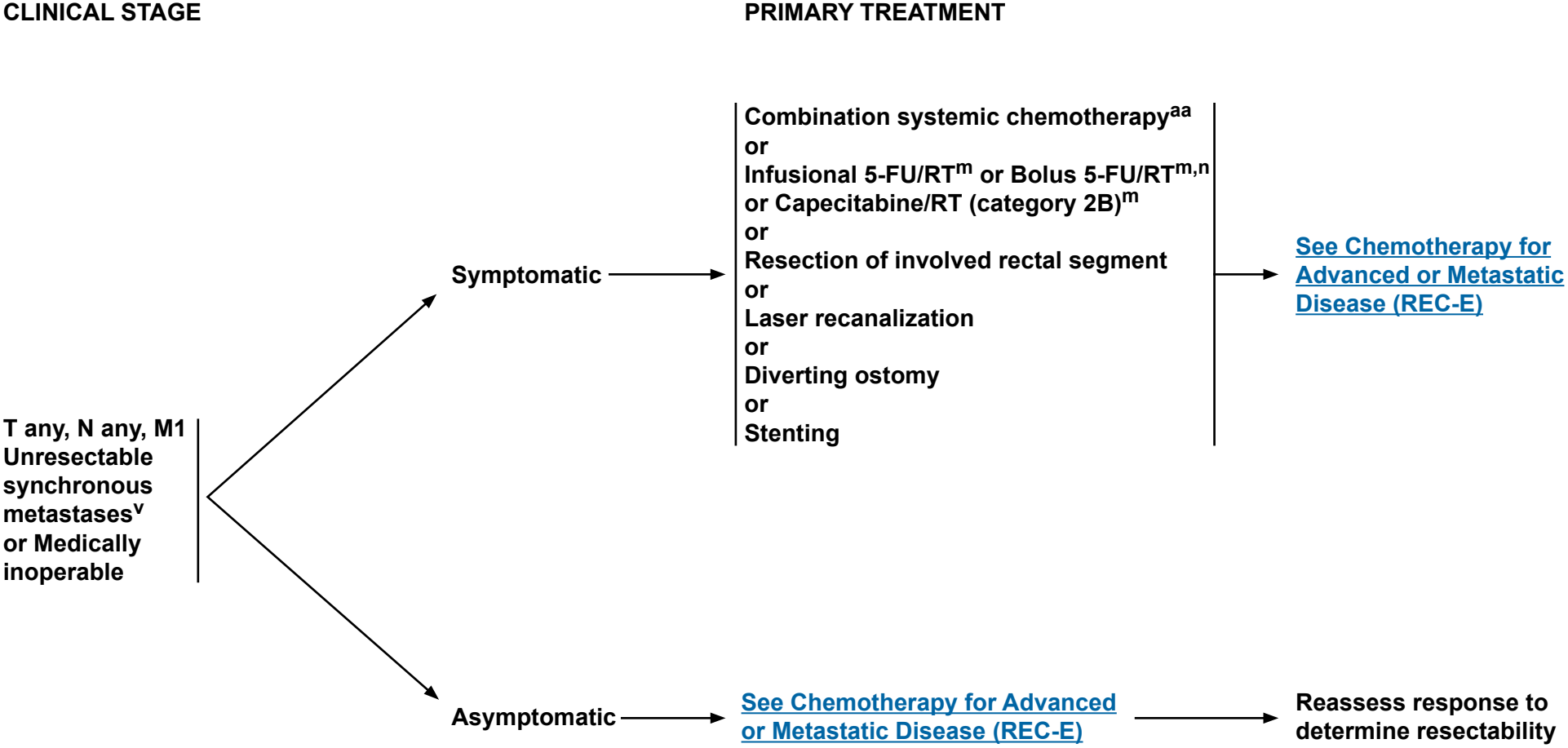
[j] See Principles of Surgery (REC-B).
[l] See Principles of Adjuvant Therapy (REC-C).
[m] See Principles of Radiation Therapy (REC-D).
[n] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[q] Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.
[r] Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.
[t] The use of agents other than fluoropyrimidines (eg, oxaliplatin) are not recommended concurrently with RT.
[u] 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.

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.



[j] See Principles of Surgery (REC-B).
[l] See Principles of Adjuvant Therapy (REC-C).
[m] See Principles of Radiation Therapy (REC-D).
[n] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[r] Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.
[s] FOLFOXIRI is not recommended in this setting.
[v] Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[w] The safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU–based regimens, has not been adequately evaluated. There should be at least a 6-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.
[x] There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.
[y] Evidence increasingly suggests that BRAF V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely.
[z] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver oligometastases (REC-B and REC-D).

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.



[m] See Principles of Radiation Therapy (REC-D).
[n] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[v] Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[aa] 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.

SURVEILLANCE[bb]

- **History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y**
- **CEA[cc] 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[g] every 3–6 mo x 2 y, then every 6–12 mo for up to a total of 5 y[dd]**
- **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,[ee] repeat in 3 y, then every 5 y[ff]**
- **Proctoscopy (with EUS or MRI) every 3–6 mo for the first 2 y, then every 6 mo for a total of 5 y (for patients treated with transanal excision only)**
- **PET-CT scan is not routinely recommended**
- **See Principles of Survivorship (REC-F)**

→ **Serial CEA elevation or documented recurrence** → **See Workup and Treatment (REC-9)**

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

[bb]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.

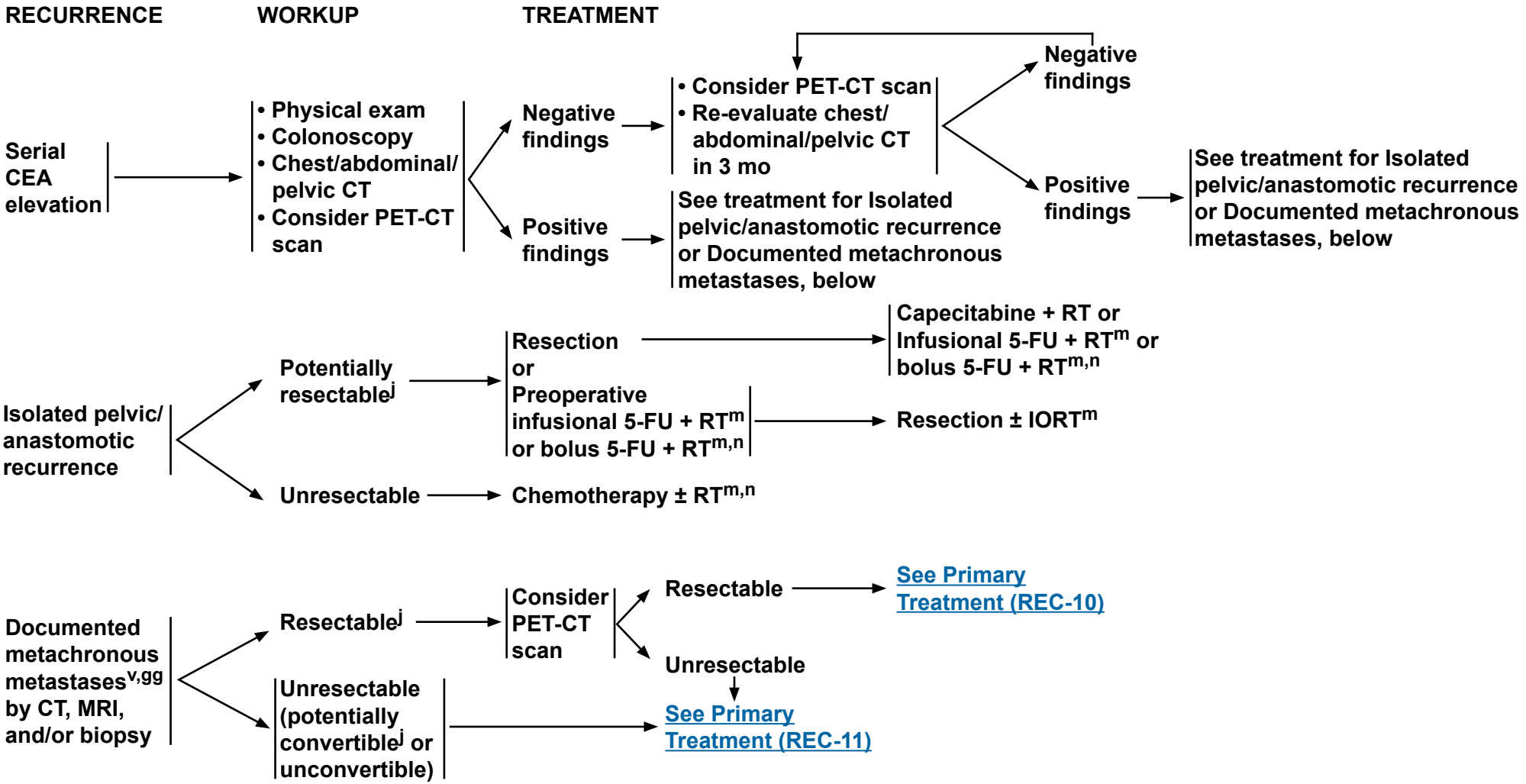
[cc]If patient is a potential candidate for resection of isolated metastasis.

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

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

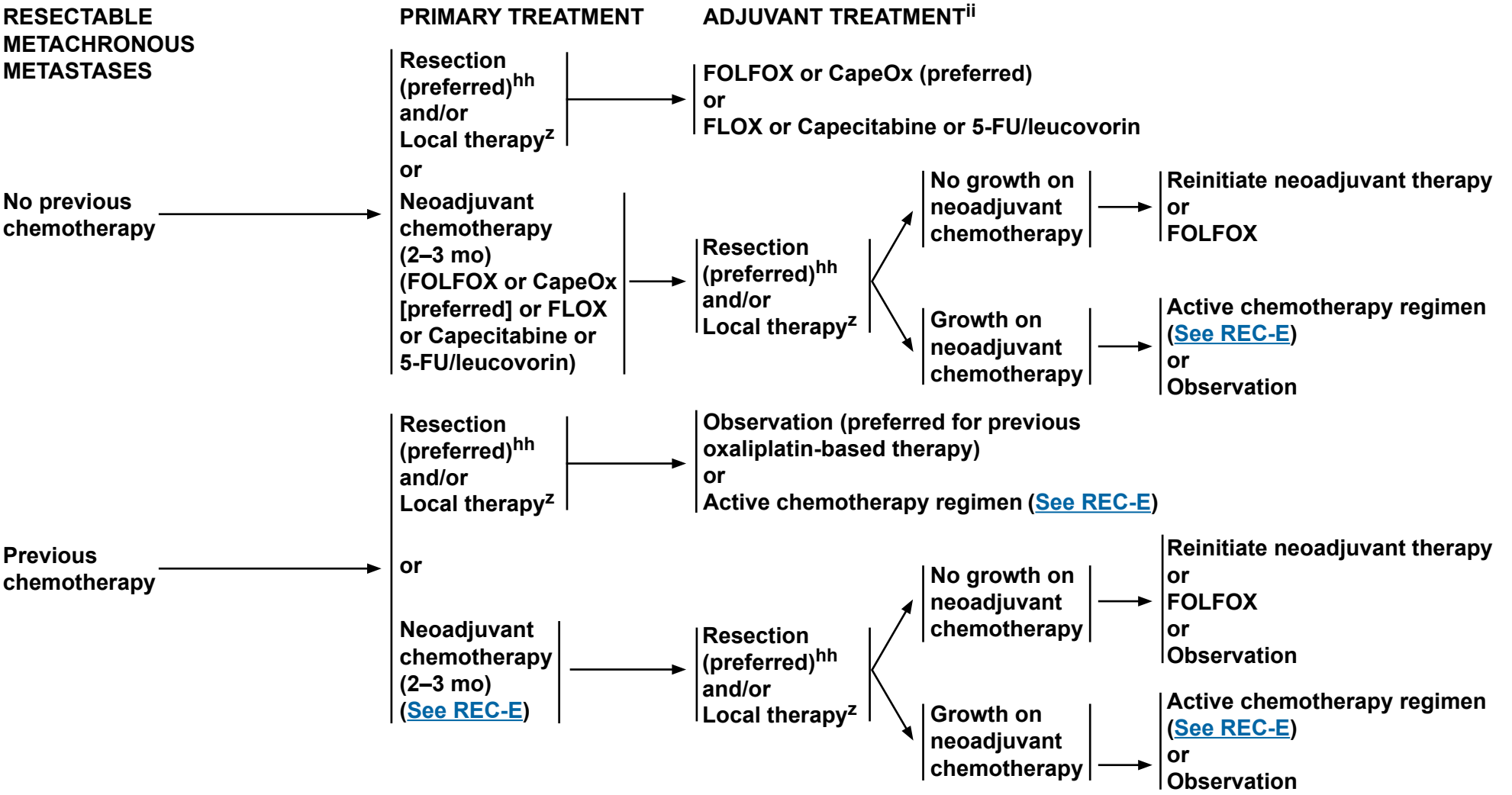
[ff]Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130(6):1865-71.

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.



[j] See Principles of Surgery (REC-B).
[m] See Principles of Radiation Therapy (REC-D).
[n] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[v] Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[gg] 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.

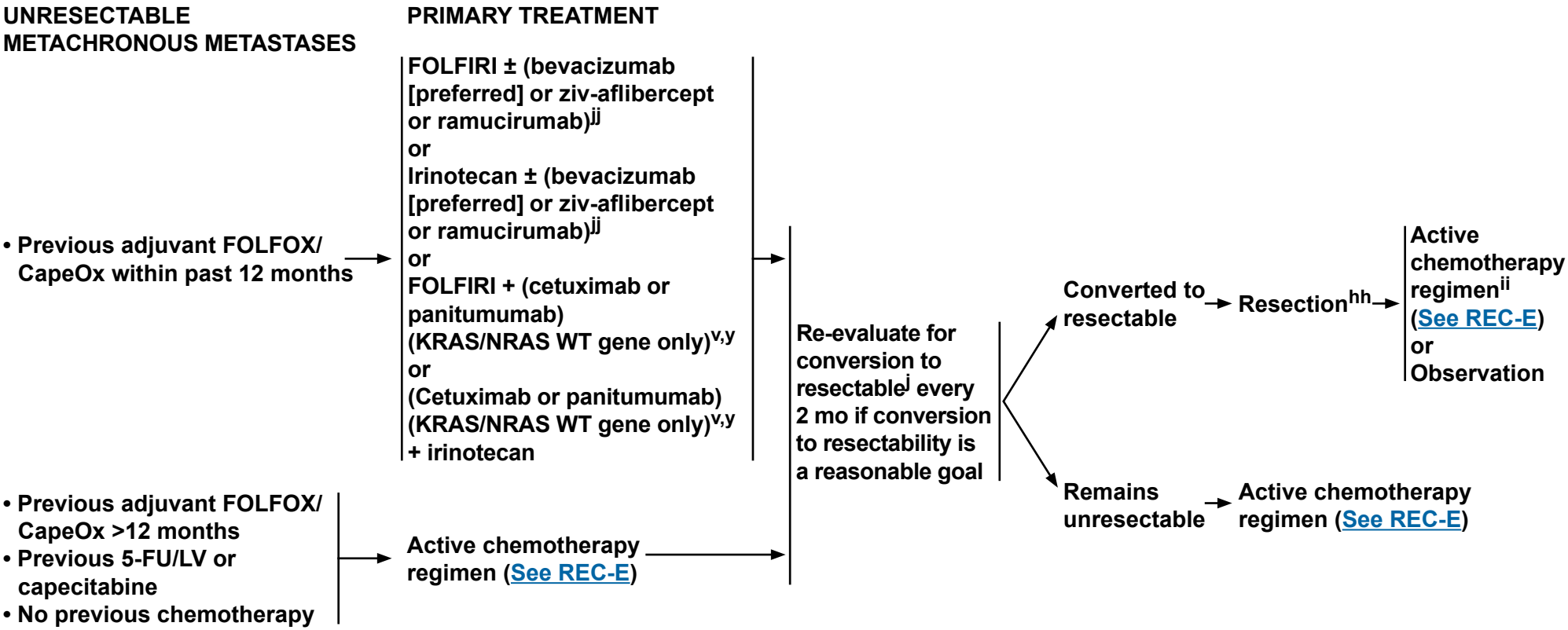


[z]Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver oligometastases (REC-B and REC-D).

[hh]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.

[ii]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.



[j] See Principles of Surgery (REC-B).
[v] Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[y] Evidence increasingly suggests that BRAF V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely.
[hh] 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.
[ii] Perioperative therapy should be considered for up to a total of 6 months.
[jj] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

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

PRINCIPLES OF PATHOLOGIC REVIEW (1 of 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, NRAS, 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.

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 (PNI)[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 (CAP) 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 recommended by the AJCC Cancer Staging Manual, 7th Edition and the CAP Guidelines is that as modified from Ryan R, et al. Histopathology 2005;47:141-146.

- 0 - Complete response: No remaining viable cancer cells.
- 1 - Moderate response: Only small clusters or single cancer cells remaining.
- 2 - Minimal response: Residual cancer remaining, but with predominant fibrosis.
- 3 - Poor response: Minimal or no tumor kill; extensive residual cancer.

  According to CAP, it is optional to grade the tumor response to treatment. However, the NCCN Rectal Cancer Guidelines Panel recommends grading tumor response. Other grading systems that are used are referenced.[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, NRAS, 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.

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, NRAS, 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.

PRINCIPLES OF PATHOLOGIC REVIEW (4 of 6)

Lymph Node Evaluation

- The AJCC and CAP recommend examination of a minimum of 12 lymph nodes to accurately identify early-stage colorectal cancers.[11,12,26] Sampling of 12 lymph nodes may not be achievable in patients who received preoperative chemotherapy. The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, and >30.[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, NRAS, 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.

PRINCIPLES OF PATHOLOGIC REVIEW (5 of 6)

KRAS, NRAS, and *BRAF* Mutation Testing

- **All patients with metastatic colorectal cancer should have tumor tissue genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab.[48-50] Evidence increasingly suggests that *BRAF V600E* mutation makes response to panitumumab or cetuximab highly unlikely, as a single agent, or in combination with cytotoxic chemotherapy.[51-53]**
- **Testing for KRAS, NRAS, and BRAF mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform *high complexity* clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).**
- **The testing can be performed on formalin-fixed paraffin-embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the KRAS, NRAS, and BRAF mutations are similar in both specimen types.[54]**

Evaluation of Mesorectum (TME)

- **The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal 2/3).[55-57]**

Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing

- **Lynch syndrome tumors screening (ie, IHC for MMR or PCR for MSI)* should be performed for all patients with colorectal cancer diagnosed at age ≤70 y and also those >70 y who meet the Bethesda guidelines.[58] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal**
- **The presence of a BRAF V600E mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch syndrome.**
- **MMR or MSI testing should also be performed for all patients with stage II disease, because stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. [59]**
- **MMR or MSI testing should also be performed for all patients with metastatic disease.**

*IHC for MMR and PCR for MSI are different assays measuring the same biological effect.

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.

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.
27Sarli 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]Douillard JY, Oliner KS, Siena S, et al. Panitumumab--FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-1034.
[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/22446022.
[53]Pietrantonio F, Petrelli F, Coinu A, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. Eur J Cancer 2015
[54]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.
[55]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.
[56]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.
[57]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.
[58]Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308:1555-1565.
[59]Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-3226. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20498393.

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

PRINCIPLES OF SURGERY (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.
  - Treat draining lymphatics by total mesorectal excision.
  - Restore organ integrity, if possible.
  - Surgery should be 5–12 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.
- Some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared to open surgery,[2,3] whereas other studies have shown that laparoscopy is associated with higher rates of circumferential margin positivity and incomplete TME.[4,5] Therefore, minimally invasive resection may be considered based on the following principles:
  - The surgeon should have experience performing minimally invasive proctectomy with total mesorectal excision.
  - It is not indicated for locally advanced disease with a threatened or high-risk circumferential margin based on staging. For these high-risk tumors, open surgery is preferred.
  - It is not indicated for acute bowel obstruction or perforation from cancer.
  - Thorough abdominal exploration is required.
- Lymph node dissection[6,7]
  - 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

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

PRINCIPLES OF SURGERY (2 of 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.[8]
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[9,10]
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.[11-13] Plan for a debulking resection (R1/R2 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.[8] All original sites of disease need to be amenable to ablation or resection.
- Some institutions use arterially directed embolic therapy (category 3) in select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, with predominant hepatic metastases.
- Conformal external beam radiation therapy (category 3) may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.
- Re-resection can be considered in selected patients.[14]

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[15-18]
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.[19-22]
- Re-resection can be considered in selected patients.[23]
- 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.[24-27]
- 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.[28] Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[29]

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.

PRINCIPLES OF SURGERY (3 of 3) - REFERENCES

[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]Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Eng L Med 2015;372:1324-1332.
[3]Jeong S-Y, Park JW, Nam BH, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. Lancet Oncol 2014;15:767-774.
[4]Fleshman J, Branda M, Sargent DJ, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes. The ACOSOG Z6051 randomized clinical trial. JAMA 2015;314:1346-1355.
[5]Stevenson ARL, Solomon MJ, Lumley JW, et al. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer. The ALacaRT randomized clinical trial. JAMA 2015;314:1356-1363.
[6]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.
[7]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.·
[8]Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818-825; discussion 825-7.
[9]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.
[10]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.
[11]Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. J Clin Oncol 1997;15:938-946.
[12]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.
[13]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.
[14]Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. Ann Surg 1997;225:51-62.
[15]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.
[16]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.
[17]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.
[18]Sakamoto T, Tsubota N, Iwanaga K, Yuki T, Matsuoka H, Yoshimura M. Pulmonary resection for metastases from colorectal cancer. Chest 2001;119:1069-1072.
[19]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.
[20]Irshad K, Ahmad F, Morin JE, Mulder DS. Pulmonary metastases from colorectal cancer: 25 years of experience. Can J Surg 2001;44:217-221.
[21]Ambiru S, Miyazaki M, Ito H, et al. Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 1998;82:274-278.
[22]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.
[23]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.
[24]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.
[25]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.
[26]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.
[27]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.
[28]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.
[29]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.

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[1,2,3]**
  Oxaliplatin 85 mg/m² IV, day 1,* leucovorin 400 mg/m² IV day 1, 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.**
- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)[4]**
  Leucovorin 400 mg/m² IV day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.
- **Capecitabine[5]**
  Capecitabine 1250 mg/m² twice daily days 1–14 every 3 weeks to a total of 6 months perioperative therapy.
- **CapeOx[6,7]**
  Oxaliplatin 130 mg/m² over 2 hours, day 1. Capecitabine 1000 mg/m² twice daily days 1–14 every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy.
- **5-FU 500 mg/m² IV bolus weekly x 6 + leucovorin 500 mg/m² IV weekly x 6, each 8-week cycle. Repeat every 8 weeks to a total of 6 months perioperative therapy.[8]**

Dosing Schedules for Concurrent Chemotherapy/RT:

- **XRT + continuous infusion 5-FU[9]**
  5-FU 225 mg/m² over 24 hours 5 or 7 days/week during XRT
- **XRT + Capecitabine[11,12]**
  Capecitabine 825 mg/m² twice daily 5 days/week + XRT x 5 weeks
- **XRT + 5-FU/leucovorin[10‡]**
  5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 days during week 1 and 5 of XRT

See footnotes on REC-C 2 of 2

*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger RD, et al. Oxaliplatin can be safely infused at a rate of 1mg/m²/min. J Clin Oncol 33, 2015 (suppl; abstr e14665).

**Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

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

‡Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

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

PRINCIPLES OF ADJUVANT THERAPY (2 of 2) - REFERENCES

[1]Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351.

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

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

[4]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.

[5]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.

[6]Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007;25:102-109.

[7]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.

[8]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.

[8]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.

[10]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.

[11]O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol 2014;32:1927-1934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24799484

[12]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.

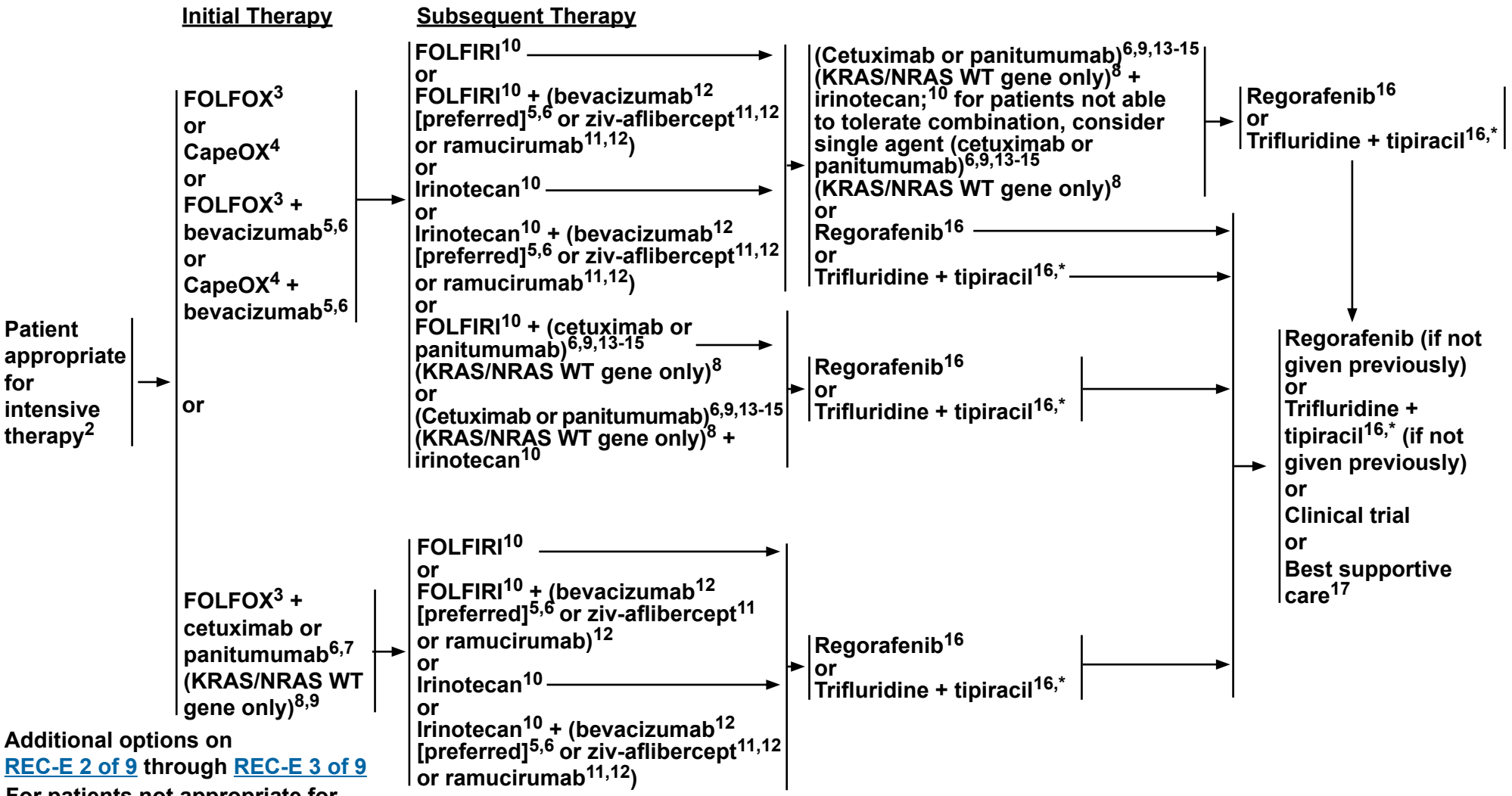
PRINCIPLES OF RADIATION THERAPY

- **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 such as reirradiation of previously treated patients with recurrent disease or unique anatomical situations.**
- **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.**
- **Short-course radiation therapy (25 Gy in 5 fractions) with surgery within 1 to 2 weeks of completion of therapy can also be considered for patients with ultrasound or pelvic MRI stage T3 rectal cancer.[1]**
- **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.

[1]Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833.

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

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



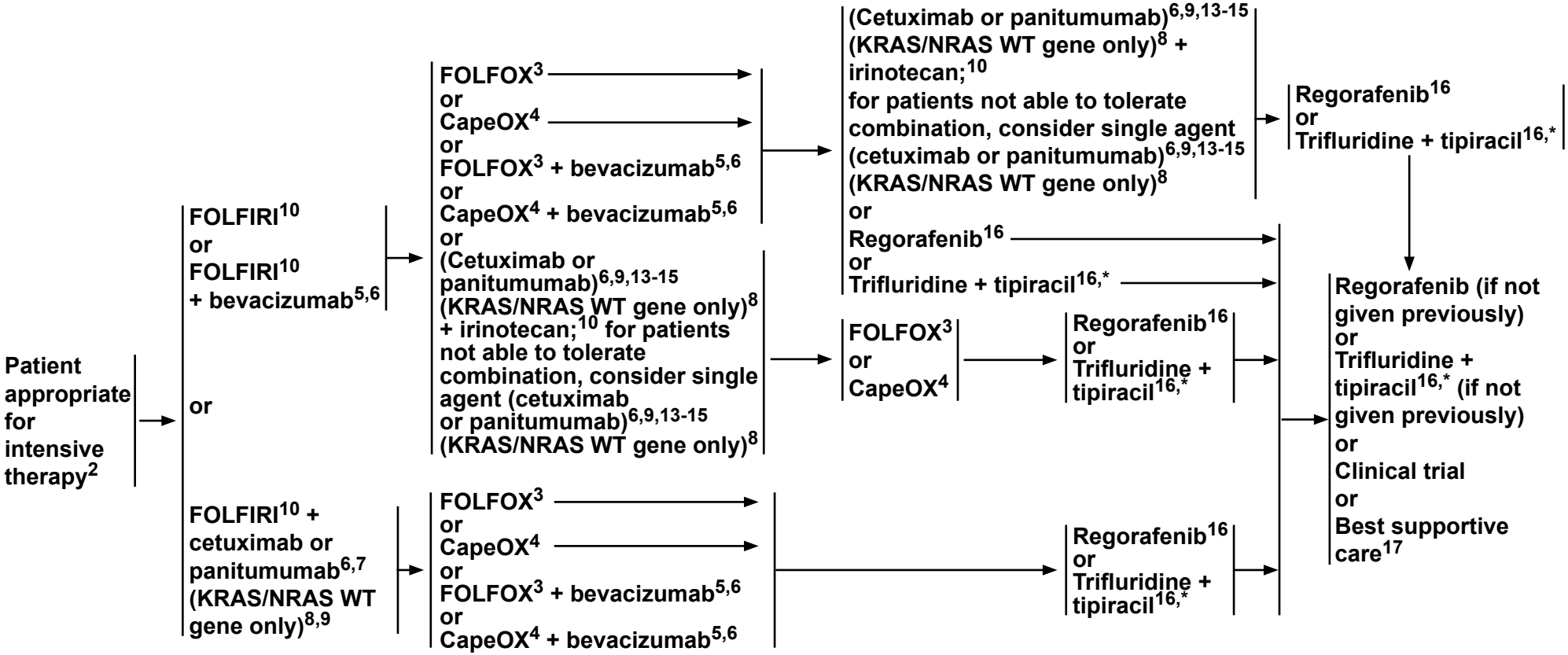
Additional options on REC-E 2 of 9 through REC-E 3 of 9
For patients not appropriate for intensive therapy, see REC-E 4 of 9

*TAS-102

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.

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



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

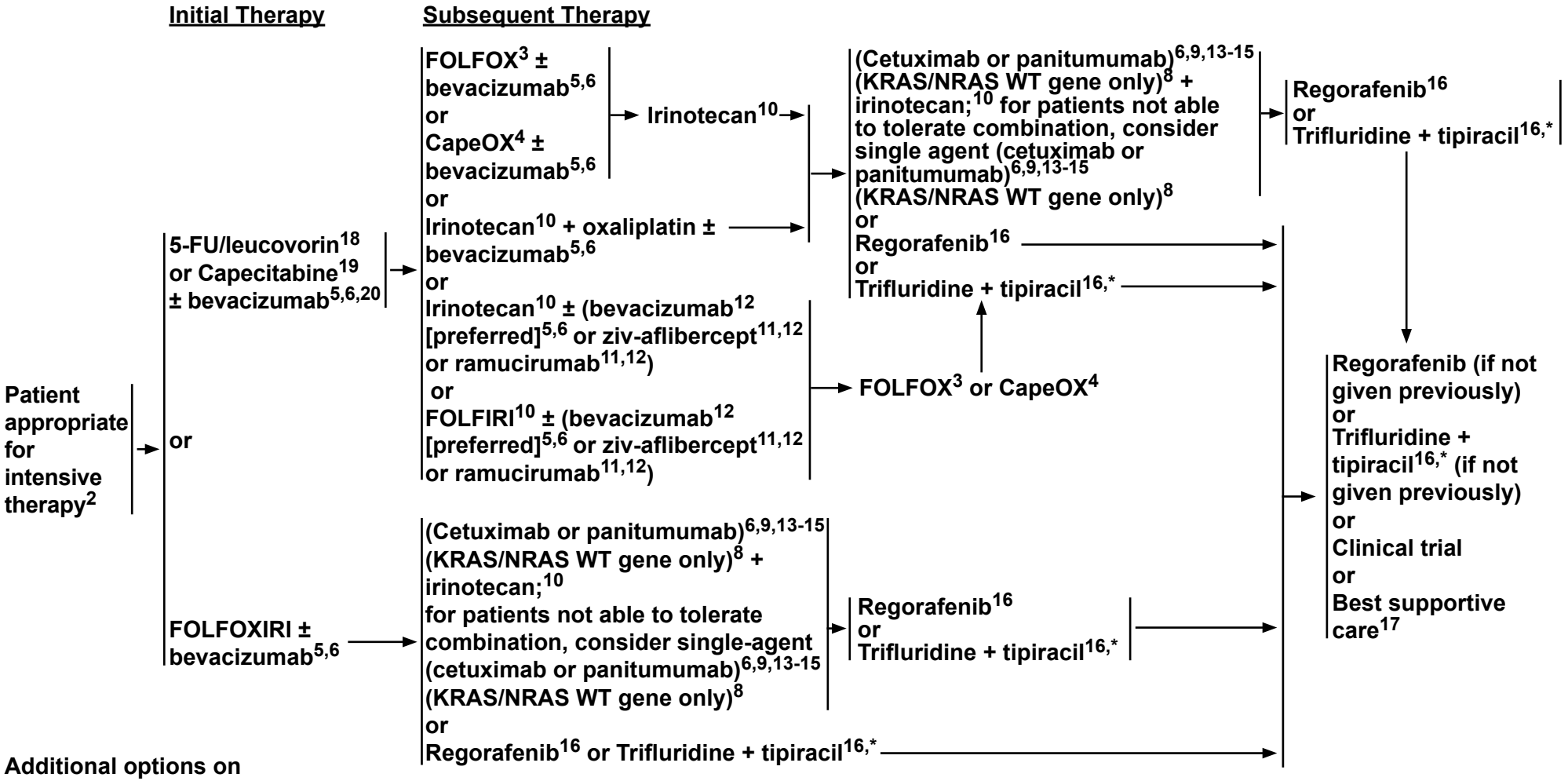
For patients not appropriate for intensive therapy, see REC-E 4 of 9

***TAS-102**

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.

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



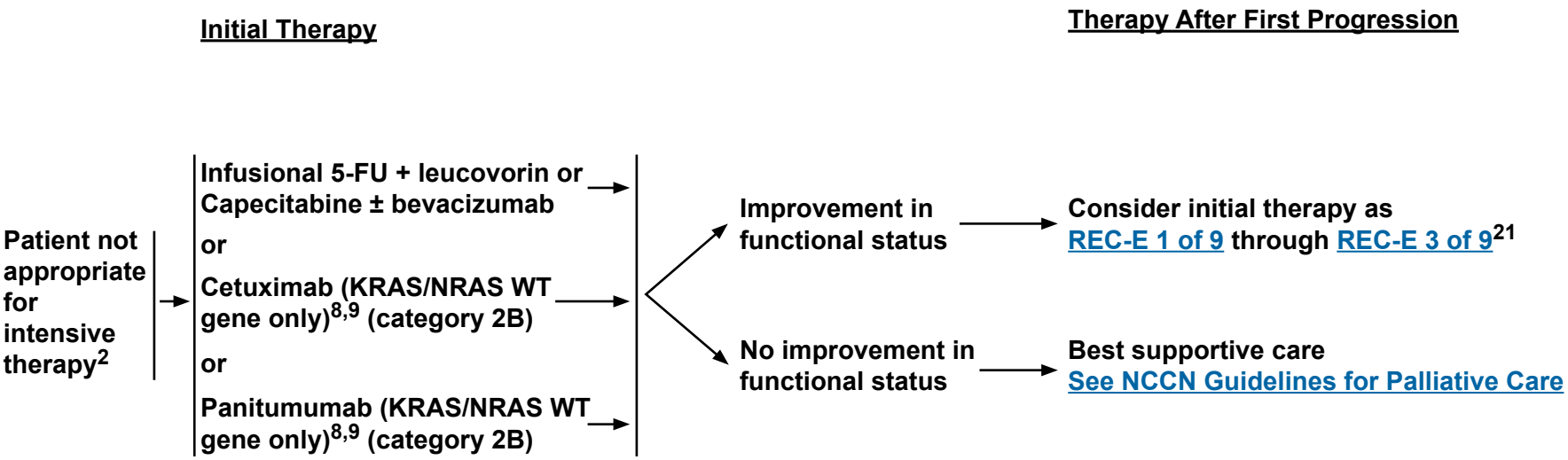
Additional options on REC-E 1 of 9 through REC-E 2 of 9
For patients not appropriate for intensive therapy, see REC-E 4 of 9

*TAS-102

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.

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.

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

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

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

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

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

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

[9]Evidence increasingly suggests that BRAF V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely.

[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 or FOLFIRI-ramucirumab in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.

[12]Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

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

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

[15]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.

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

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

[18]Infusional 5-FU is preferred.

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

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

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

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

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

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

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

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

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

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

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

See References on REC-E 9 of 9

*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger RD, et al. Oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Clin Oncol 33, 2015 (suppl; abstr e14665).
**Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
†NCCN recommends limiting chemotherapy orders to 24-h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 hours) to minimize medication errors.
‡The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large-scale randomized trials.
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (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.

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

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

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

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

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

FOLFIRI + ziv-aflibercept[14]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1**
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion
Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ramucirumab[15]
Irinotecan 180 mg/m² IV over 90 minutes, day 1
Leucovorin 400 mg/m² IV to match duration of irinotecan infusion, day 1**
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Ramucirumab 8 mg/kg over 60 minutes, day 1
Repeat every 2 weeks

Capecitabine[16]
850–1250 mg/m² PO twice daily, days 1–14
Repeat every 3 weeks

Capecitabine[16] + Bevacizumab[7¶]
Capecitabine 850–1250 mg/m² PO twice daily, days 1–14
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

See References on REC-E 9 of 9

**Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
†NCCN recommends limiting chemotherapy orders to 24-hour units (ie, 1200 mg/m²/d NOT 2400 mg/m² over 48 hours) to minimize medication errors.
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (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.

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

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[17]
Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)[8]
Leucovorin 400 mg/m² IV over 2 hours on day 1,**
followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/d 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.[18]
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week[19]

IROX[20]
Oxaliplatin 85 mg/m² IV over 2 hours, followed by irinotecan 200 mg/m² over 30–90 minutes every 3 weeks

FOLFOXIRI[21]
Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² day 1, leucovorin 400 mg/m² day 1, fluorouracil 1600 mg/m²/d x 2 days (total 3200 mg/m² over 48 hours)† continuous infusion starting on day 1.**
Repeat every 2 weeks
± Bevacizumab[22] 5 mg/kg IV, day 1

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

Irinotecan
Irinotecan 125 mg/m² IV over 30–90 minutes, days 1 and 8
Repeat every 3 weeks[23,24]
or Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 300–350 mg/m² IV over 30–90 minutes, day 1
Repeat every 3 weeks

Cetuximab (*KRAS/NRAS* WT gene only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly [25]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[12]

Cetuximab (*KRAS/NRAS* WT gene only) + irinotecan
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[25]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[12]
Irinotecan 300–350 mg/m² IV over 30–90 minutes, day 1
Repeat every 3 weeks
or Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 125 mg/m² IV over 30–90 minutes, days 1 and 8
Repeat every 3 weeks

Panitumumab[26] (*KRAS/NRAS* WT gene only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib[27]
Regorafenib 160 mg§ PO daily days 1–21
Repeat every 28 days

Trifluridine + tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily days 1–5 and 8–12
Repeat every 28 days[28]

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-hour units (ie, 1200 mg/m²/d NOT 2400 mg/m² over 48 hours) to minimize medication errors.
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).
§It is common practice to start at a lower dose of regorafenib (80 or 120 mg) and escalate, as tolerated.

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

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

[1]deGramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced rectal cancer. J Clin Oncol 2000;18:2938-2947.
[2]Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12177775.
[3]Maindrault-Goebel F, deGramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. Ann Oncol 2000;11:1477-1483.
[4]Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. BMC Cancer 2007;7:91.
[5]Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697-4705.
[6]Venook AP, Niedzwiecki D, Lenz H-J, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab or cetuximab for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum [abstract]. ASCO Meeting Abstracts 2014;32:LBA3. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/LBA3.
[7]Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-2019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18421054.
[8]Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. Eur J Cancer 1999;35(9):1343-7.
[9]Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007;25:4779-4786. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17947725.
[10]Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open-label, phase 3 trial. Lancet Oncol 2014. Available: http://www.ncbi.nlm.nih.gov/pubmed/25088940.
[11]Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.
[12]Martín-Martorell P, Roselló S, Rodríguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008;99:455-458.
[13]Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:4706-4713. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20921462.
[14]Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen. J Clin Oncol 2012;30:3499-3506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22949147.
[15]Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomized, double-blind, multicentre, phase 3 study. Lancet Oncol 2015;16:499-508.
[16]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.
[17]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.
[18]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.
[19]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.
[20]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.
[21]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.
[22]Loupakis F, Cremolini C, Masi G, et al. FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first-line treatment of metastatic colorectal cancer (MCRC): results of the phase III randomized TRIBE trial. J Clin Oncol 2013;31(Suppl 4): Abstract 336.
[23]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.
[24]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.
[25]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.
[26]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.
[27]Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23177514.
[28]Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer (RECOURSE). N Engl J Med 2015; 372:1909-19.

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

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

Colorectal Cancer Surveillance:
- See REC-8
- 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
- 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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 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 through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (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.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2016, an estimated 39,220 new cases of rectal cancer will occur in the United States (23,110 cases in men; 16,110 cases in women). During the same year, it is estimated that 49,190 people will die from rectal and colon cancer combined.[1] Despite these statistics, the incidence per 100,000 population of colon and rectal cancers decreased from 60.5 in 1976 to 46.4 in 2005.[2] In fact, the incidence of colorectal cancer decreased at a rate of 4% per year or greater between 2008 and 2011.[3] The incidence rate for colorectal cancer reported by the CDC for 2011 is 40.0 per 100,000 persons.[4] In addition, mortality from colorectal cancer decreased by almost 35% from 1990 to 2007,[5] and in 2011 was down by 47% from peak mortality rates.[3] These improvements in incidence of and mortality from colorectal cancer are thought to be a result of cancer prevention and earlier diagnoses through screening and of better treatment modalities.

Despite the observed improvements in the overall colorectal cancer incidence rate, a retrospective cohort study of the SEER CRC registry found that the incidence of colorectal cancer in patients younger than 50 years has been increasing.[6] The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients 20 to 34 years by 2030. The cause of this trend is currently unknown.

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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Rectal Cancer, an electronic search of the PubMed database was performed to obtain key literature in the field of colorectal cancer published between July 23, 2014 and June 12, 2015, using the following search terms: (colon cancer) OR (colorectal cancer) OR (rectal cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[7]

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

The PubMed search resulted in 782 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting

abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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

Risk Assessment

Approximately 20% of cases of colorectal cancer are associated with familial clustering,[8,9] and first-degree relatives of patients with newly diagnosed colorectal adenomas[10] or invasive colorectal cancer[11] are at increased risk for colorectal cancer. Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC])[12,13] and familial adenomatous polyposis (FAP).[14] 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 website at www.NCCN.org). Results from a recent randomized controlled trial suggest that most individuals without a personal history of colorectal cancer and with one first-degree relative with colorectal cancer diagnosed before age 50 years or two first-degree relatives with colorectal cancer diagnosed at any age can safely be screened with colonoscopy every 6 years.[15]

Lynch Syndrome

Lynch syndrome is the most common form of genetically determined colorectal cancer predisposition, accounting for 2% to 4% of all colorectal cancer cases.[12,13,16,17] 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.[18] 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.[18]

Many NCCN Member Institutions and other comprehensive cancer centers now perform immunohistochemistry and sometimes MSI testing on all newly diagnosed colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome.[19-22] The cost effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for colorectal cancer, and this approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the CDC.[23-25] The US Multi-Society Task Force on Colorectal Cancer also recommends universal genetic testing of tumors of all patients with newly diagnosed colorectal cancer, as does the American Gastroenterological Association.[26,27] The Cleveland Clinic recently reported on its experiences implementing such a screening approach.[28]

An alternative approach is to test all patients with colorectal cancer diagnosed prior to age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines.[29,30] This approach gave a sensitivity of 95.1% (95% CI, 89.8%–99.0%) and a specificity of 95.5% (95% CI, 94.7%–96.1%). This level of sensitivity was better than that of both the revised Bethesda and Jerusalem recommendations (testing all patients diagnosed with colorectal cancer at age <70 years[31]). While this new selective strategy failed to identify 4.9% of Lynch syndrome cases, it resulted in approximately 35% fewer tumors undergoing MMR testing than a universal approach.[29]

The NCCN Colon/Rectal Cancer Panel endorses this selective approach (testing all patients with colorectal cancer diagnosed ≤70 years plus patients diagnosed at older ages who meet the Bethesda guidelines). An infrastructure needs to be in place to handle the screening results in either case. A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening (available online at www.NCCN.org).

Other Risk Factors for Colorectal Cancer

It is well recognized that individuals with inflammatory bowel disease (ie, ulcerative colitis, Crohn's disease) are at an increased risk for colorectal cancer.[32-34] Other possible risk factors for the development of colorectal cancer include smoking, the consumption of red and processed meats, alcohol consumption, diabetes mellitus, low levels of physical activity, metabolic syndrome, and obesity/high body mass index (BMI).[33,35-52] In fact, in the EPIC cohort of almost 350,000 individuals, those who adhered to 5 healthy lifestyle factors (healthy weight, physical activity, non-smoking, limited alcohol consumption, healthy diet) had a hazard ratio (HR) for the development of colorectal cancer of 0.63 (95% CI, 0.54–0.74) compared with those who adhered to ≤1 of the factors.

Some data suggest that consumption of dairy may lower risk for the development of colorectal cancer.[53,54] However, a recent systematic review and meta-analysis of 15 cohort studies (>900,000 subjects; >5200 cases of colorectal cancer) only found an association between risk for colon cancer in men and the consumption of nonfermented milk.[55] No association was seen for rectal cancer in men or for colon or rectal cancer in women, and no association was seen for either cancer in either gender with consumption of solid cheese or fermented milk. Large cohort studies and meta-analyses suggest that other dietary factors may also lower the risk for colorectal cancer, including the consumption of fish and legumes.[56-58] Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs may also decrease the risk for colorectal cancer.[59-63]

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption is associated with a poor prognosis.[38,64-67] Conversely, a family history of colorectal cancer increases risk while improving prognosis.[68] Data on the effect of dairy consumption on prognosis after diagnosis of colorectal cancer are conflicting.[69,70]

The relationship between diabetes and colorectal cancer is complex. Whereas diabetes and insulin use may increase the risk of developing colorectal cancer, treatment with metformin appears to decrease risk, at least in women.[71-76] In addition, although patients with colorectal cancer and diabetes appear to have a worse prognosis than those without diabetes,[77] patients with colorectal cancer treated with metformin seem to have a survival benefit.[78]

TNM Staging

The NCCN Guidelines for Rectal Cancer adhere to the current TNM staging system of the 7th edition of the AJCC Cancer Staging Manual (Table 1 of the guidelines).[79] Several changes to the staging of colorectal cancer were made in the 7th edition.[80] For instance, based on new data showing differential prognosis,[81] 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[82] and new data on the prognostic value of tumor deposits within the lymph drainage area of the primary tumor.[83-87] 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 one organ or site (M1a). Stage IVB disease is defined as any T, any N, with metastases in more than one organ or site or in the peritoneum (M1b).[79] The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.[79]

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[88] 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[79,88-93]; 8) neoadjuvant treatment effect[79,88,94,95]; 9) lymphovascular invasion (LVI)[79,88,96]; 10) perineural invasion (PNI) [97-99]; and 11) the number of tumor deposits.[83-87]

Margins

The 7th edition of the AJCC Cancer 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.[79] 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; and R2 for incomplete tumor resection with gross residual tumor that was not resected.[79]

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer.[100] 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.[100] 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.[101] The panel defines a positive CRM as tumor within 1 mm from the transected margin.[91,93,102]

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 (OS),[100,102-104] including in patients undergoing neoadjuvant therapy,[92,105] and is an important consideration when postoperative 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.[92] 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 pathologic evaluation of the surgical specimen following a total mesorectal excision (TME) are described under *Surgical Approaches*, below.

Lymph Nodes

The AJCC and the College of American Pathologists (CAP) recommend evaluation of 10 to 14 and 12 to 18 lymph nodes to accurately identify early-stage colorectal cancers, respectively.[79,88,100] The number of lymph nodes that can be retrieved varies with age and gender of the patient and on tumor grade or site.[106] The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify early-stage rectal cancer.[107] Most of these studies have combined rectal and colon cancers 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.[108,109] A more recent analysis of patients with stage I or II rectal cancer in the SEER database found that OS improved with greater numbers of lymph nodes retrieved.[110] 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, $P \leq .0001$).[111,112] In fact, retrieval of fewer lymph nodes may be a marker of a higher tumor response and better prognosis following neoadjuvant treatment.[113,114]

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.[115,116] 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 (ITCs), to be micrometastasis.[116,117] In addition, results of one study demonstrated that, following neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.[118] Furthermore, in a recent study involving 156 patients with colon cancer and 44 patients with rectal cancer, this “ultra-staging” of lymph nodes only changed the staging for 1% of patients.[119] Others have noted that micrometastasis found in node-negative patients did not predict outcome.[120] In contrast, a recent meta-analysis found that the presence of micrometastases increases the likelihood of disease

recurrence, whereas the presence of ITCs does not.[121] 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 ITCs. One study of 312 consecutive patients with pN0 disease found that positive cytokeratin staining was associated with a higher risk of recurrence.[122] Relapse occurred in 14% of patients with positive nodes compared to 4.7% of those with negative nodes (HR, 3.00; 95% CI, 1.23–7.32; *P* = .013). A recent systematic review and meta-analysis came to a similar conclusion, finding decreased survival in patients with pN0 disease with immunohistochemical or reverse transcriptase polymerase chain reaction (RT-PCR) evidence of tumor cells in regional nodes.[123] As with sentinel nodes, the molecular detection of cancer cells in regional nodes should be also considered investigational, and the results should be used with caution in clinical management decisions.

Response to Treatment

The 7th edition of the AJCC Cancer Staging Manual and the most recent CAP Guidelines require that the pathology report comment on treatment effects of neoadjuvant therapy.[79,88] 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 CAP and the AJCC, 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).[79,88,94,95,124]

Perineural Invasion

Several studies have demonstrated that the presence of PNI is associated with a significantly worse prognosis.[97-99] For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at one institution found a 4-fold greater 5-year survival in patients without PNI versus patients whose tumors invaded nearby neural structures.[98] Multivariate analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year disease-free survival (DFS) compared to those without PNI (29% vs. 82%; *P* = .0005).[99] Similar results were seen for patients with stage III disease.[97] A meta-analysis that included 38 studies and 12,661 patients also found that PNI is associated with a worse OS and DFS.[125] PNI is therefore included as a high-risk factor for systemic recurrence.

Extranodal Tumor Deposits

Extranodal 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 LVI or occasionally PNI. The number of extranodal tumor deposits should be recorded in the pathology report, since they have been shown to be associated with reductions in DFS and OS.[83-87] 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).[87] The association of tumor deposits with decreased survival also holds in patients with rectal cancer who had neoadjuvant chemoradiation (chemoRT).[126,127] Extranodal tumor deposits are classified as pN1c.[79]

The Role of Vitamin D in Colorectal Cancer

Prospective studies have suggested that vitamin D deficiency may contribute to colorectal cancer incidence and/or that vitamin D supplementation may decrease colorectal cancer risk.[128-132]

Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with colorectal cancer.[133-136] In fact, a systematic review and meta-analysis of 5 studies totaling 2330 patients with colorectal cancer compared the outcomes of patients in the highest and lowest categories of vitamin D levels and found better OS (HR, 0.71; 95% CI, 0.55–0.91) and disease-specific mortality (HR, 0.65; 95% CI, 0.49–0.86) in those with higher vitamin D levels.[137] Moreover, in a study of 515 patients with stage IV colorectal cancer, 82% of patients were found to be vitamin D-insufficient (levels <30 ng/mL) and 50% were found to be vitamin D-deficient (<20 ng/mL).[138]

Results of a recent randomized, double-blind, placebo-controlled trial, however, showed that supplementation with vitamin D and/or calcium had no effect on the recurrence of colorectal adenomas within 3 to 5 years after removal of adenomas in 2259 participants.[139] Furthermore, no study has yet examined whether vitamin D supplementation improves outcomes in patients with colorectal cancer. In a 2010 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.[140] 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[141] 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).[142] Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore incapable of regional nodal metastasis.[100] The panel recommends marking the cancerous polyp site at the time of colonoscopy or within 2 weeks if deemed necessary by the surgeon.

In patients with pedunculated or sessile polyps (adenomas), no additional surgery is required if the polyp has been completely resected with favorable histologic features.[141,143] Favorable histologic features include lesions of grade 1 or 2 without angiolymphatic invasion and with a negative resection margin.[141] For patients with a completely removed, single-specimen, sessile polyp (pT1) with favorable histologic 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 with polyploid malignant polyps. Also see the section on *Endoscopically Removed Malignant Polyps* in *Principles of Pathologic Review* (REC-A) in the algorithm. Rectal surgery is also an option for these patients.

Rectal surgery is also recommended for patients with polyps with unfavorable histologic features or when the specimen is fragmented or margins cannot be assessed. Unfavorable histologic 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 no consensus currently exists 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 to 2 mm from the transected margin or by the presence of tumor cells within the diathermy of the transected margin.[141,144-146]

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).[147] All patients who have resected polyps should undergo surveillance as described in the guidelines.[148]

Management of Localized Rectal Cancer

Rectal cancer has been defined as a cancerous lesion located within 12 cm of the anal verge by proctoscopy.[149] Some support for this definition comes from the study by Kapiteijn et al,[150] 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.[150] 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 proctoscopy or colonoscopy.[151]

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.[152] 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.[153-155] Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy that combines chemoRT with operative treatment for selected patients is 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 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 proctoscopy to determine 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 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 MRI, makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.[156]

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. The consensus of the panel is that a PET scan is not routinely indicated. PET/CT, if done, does not supplant a contrast-enhanced diagnostic CT scan. PET/CT should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or in patients with a strong contraindication to IV contrast.

Results from a meta-analysis of 90 studies involving the accuracy of endoscopic ultrasound, MRI, and CT for preoperative staging of rectal cancer demonstrated that endoscopic ultrasound and MRI have 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%).[157] 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.[157,158] 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,[157] 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.[157] 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.[159] A disadvantage of endoscopic ultrasound is a high degree of operator dependence.[157] An advantage of MRI is its ability to provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia so as to provide information useful in the prediction of the CRM prior to radical surgery.[158-161] Recently published 5-year follow-up results of the MERCURY trial show that high-resolution MRI can accurately assess the CRM preoperatively, differentiating patients with low-risk and high-risk disease.[162] Patients with MRI-clear CRM had a 5-year OS of 62.2% compared with 42.2% in patients with MRI-involved CRM (HR, 1.97; 95% CI, 1.27–3.04; $P < .01$). The preoperative MRI imaging also predicted DFS (HR, 1.65; 95% CI, 1.01–2.69; $P < .05$) and local recurrence (HR, 3.50; 95% CI, 1.53–8.00; $P < .05$). A group of experts developed consensus guidelines for standardized imaging of rectal cancer by MRI.[163]

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.

Restaging / Assessing Treatment Response

Restaging after neoadjuvant treatment is done to plan the surgical approach and, increasingly, to determine if additional therapy or resection can be avoided for select patients. Future and ongoing trials will help to answer these questions (see *Wait-and-See Nonoperative Approach for Clinical Complete Responders* and *Preoperative Chemotherapy Without Chemoradiation*, below). MRI, CT, and EUS are

the most commonly used modalities for restaging after neoadjuvant treatment, but the accuracy of these techniques for determining T stage and lymph node involvement is limited.[164-172] Advanced functional MRI techniques (ex, dynamic contrast-enhanced MRI, diffusion-weighted MRI) allow for the measurement of microcirculation, vascular permeability, and tissue cellularity and thus may be useful for determining response to neoadjuvant treatment and restaging patients with rectal cancer.[171,173]

Surgical Approaches

A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancer lesions.[174,175] 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 TME and coloanal anastomosis, abdominoperineal resection [APR]).[174,175]

Transanal Excision

Transanal excision is only 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.[176] 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. Although data are limited, a 2015 meta-analysis found that TEM may achieve superior oncologic outcomes compared with transanal excision.[177] 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.[152,178] If pathologic examination reveals adverse features such as positive margins, LVI, poor differentiation, or invasion into the lower third of the submucosa (sm3 level),[179,180] 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.[178] Results of a multi-institutional, single-arm, open-label, non-randomized, phase II trial suggest that chemoradiotherapy with CapeOx followed by local excision may be a safe alternative to transabdominal resection in patients with T2N0 distal rectal cancer.[181] Further studies in this area are needed.

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.[182] These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.[178,183,184] A 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).[184] A similar retrospective study of 2124 patients showed local recurrence rates of 12.5% and 6.9% for patients undergoing local excision versus standard resection, respectively (P = .003).[178] More recently, an analysis of >164,000 individuals from the National Cancer Data Base with resected, invasive, nonmetastatic rectal cancer diagnosed from 1998 to 2010 found that

positive margins were more likely after local excision compared to transabdominal excision in both the T1 and T2 populations (95% vs. 76% in T1/T2 combined; $P < .001$).[185] In the T1N0 population, a small but significant decrease in OS was also noted in the local excision group. Interestingly, limited data suggest that TEM might have superior oncologic outcomes in patients with stage I rectal cancer compared with radical resection,[183,186] although not all studies have seen such results.[187]

Thus, careful patient selection for local excision of T1N0 rectal cancer is important, as is the careful examination of the resection specimen with subsequent transabdominal resection in patients found to have T2 disease or high-risk features, as described above.

Transabdominal Resection

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 and Adjuvant Therapy for Resectable Nonmetastatic Disease*, 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, 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.[152,175,188] 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.[189] The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.[190] 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, an LAR extended 4 to 5 cm below the distal edge of the tumor using TME, 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 APR with TME 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.[191] In the NSABP R-04 trial, patients who had an APR reported worse body image, worse micturition symptoms, and less sexual enjoyment at 1-year post surgery than those who had sphincter-sparing surgery.[192] An extralevator APR may have benefits over a conventional APR approach, including lower rates of CRM involvement and local recurrence.[193]

Pathologists play a key role following TME in evaluating the surgical specimen, including a macroscopic assessment of both its external appearance/completeness and the CRM.[194,195] The panel defines a positive CRM as tumor within 1 mm from the transected margin (see *Pathology*, above).[91,93,102] 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.[91]

Recent retrospective comparisons of the outcomes of patients undergoing an APR versus an LAR in the treatment of rectal cancer have shown that those treated with an APR have worse local control and OS.[196,197] 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 3633 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.[196] Importantly, quality of life between patients with or without a permanent colostomy appears to be fairly comparable.[198,199]

Laparoscopic Resection

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer have been maturing in recent years.[200-203]

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.[204] The phase III COLOR II trial, powered for non-inferiority, also randomized patients with localized rectal cancer to laparoscopic or open surgery. Short-term secondary endpoints were met, with patients in the laparoscopic arm losing less blood, having shorter hospital stays, and having a quicker return of bowel function, but with longer operation times.[205] No differences were seen in completeness of resection, percentage of patients with positive CRM, morbidity, or mortality between the arms. The primary endpoint of locoregional recurrence at 3 years was identical in the 2 groups, at 5.0%, and no statistically significant differences were seen in DFS or OS.[200]

In the CLASICC trial comparing laparoscopically assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer.[206] No significant differences in local recurrence, DFS, or OS 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 OS was maintained for patients with rectal cancer, despite a trend towards better 5-year OS after laparoscopic surgery (52.9% and 60.3% for open and laparoscopic surgery, respectively; $P = .132$).[207]

The COREAN trial randomized patients with stage II or III low- to mid-rectal cancer to an open or laparoscopic resection, with short-term benefits seen to the laparoscopic approach.[208] The primary endpoint, 3-year DFS, did not differ between the 2 groups at 72.5% (95% CI, 65.0–78.6) for open surgery and 79.2% (95% CI, 72.3–84.6) for the laparoscopic group.[201] Factors that may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically assisted surgery for colorectal cancer have been described,[209] and longer-term outcomes from laparoscopic rectal surgery have not been reported.

Two other trials, ACOSOG Z6051 and ALaCaRT, have reported pathologic outcomes.[202,203] In Z6051, the primary endpoint was a composite of CRM >1 mm, negative distal margin, and TME completeness.[202] No significant differences were observed between the arms in these 3 measures or in the composite of successful resection. For example, complete or nearly complete TME was achieved in 92.1% (95% CI, 88.7–95.5) in the laparoscopic resection arm and 95.1% (95% CI, 92.2–97.9) in the open resection arm, for a difference of −3.0 (95% CI, −7.4–1.5; *P* = .20). However, the criteria for non-inferiority of the laparoscopic approach were not met. In ALaCaRT, the primary endpoint was also a composite of resection quality measures.[203] Successful resections were achieved in 82% of the laparoscopic resection arm and 89% of the open resection arm, for a difference of -7.0% (95% CI, -12.4% to infinity). A negative CRM was achieved in 93% and 97%, respectively (risk difference, -3.7%; 95% CI, -7.6%–0.1%; *P* = .06). As in Z6051, the criteria for non-inferiority of the laparoscopic approach were not met in ALaCaRT. Longer follow-up with oncologic outcomes of these trials are needed.

Reviews and meta-analyses including these and additional small trials have also been published.[201,210-223] They consistently find the laparoscopic approach to be safe and feasible. In addition, an analysis of results from >18,000 individuals in the National Cancer Data Base undergoing LAR for rectal cancer found short-term oncologic outcomes to be similar between the open and laparoscopic approaches.[224]

In conclusion, some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared to open surgery,[200,201] whereas other studies have shown the laparoscopic approach to be associated with higher rates of CRM positivity and incomplete TME.[202,203] Therefore, the panel defined principles by which laparoscopic resection of rectal cancer can be considered: the procedure can be considered by an experienced surgeon, should include thorough abdominal exploration, and should be limited to lower-risk tumors, as outlined in the guidelines. An international group of experts has defined standards for the technical details of laparoscopic TME.[225]

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 (RT) has been associated with decreased rates of local recurrence of rectal cancer, it is also associated with increased toxicity (eg, radiation-induced injury, hematologic toxicities) relative to surgery alone.[101,226,227] 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.[101,228,229] 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 retrospective multicenter study,[230] 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, concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis (chemoRT), 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 2 possible sequences of therapy: 1) chemoRT preoperatively and chemotherapy postoperatively; or 2) chemotherapy followed by chemoRT followed by resection. The total duration of perioperative therapy, including chemoRT and chemotherapy, should not exceed 6 months.

Preoperative Versus Postoperative Radiation

Several studies have compared the administration of radiation preoperatively versus postoperatively.[231,232] 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.[231] 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 OS was similar in the 2 groups. Long-term follow-up of this trial was later published.[233] 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 ($P = .048$). OS at 10 years was again similar between the groups (59.6% and 59.9%, respectively; $P = .85$), as was DFS and the occurrence of distant metastases. Interestingly, a recent SEER database analysis of 4724 patients with T3N0 rectal cancer found that radiation given after resection was associated with a significant decrease in risk for cancer death compared to surgery without any radiation (HR, 0.69; 95% CI, 0.58–0.82; $P < .001$), while radiation given before resection was not (HR, 0.86; 95% CI, 0.72–1.04; $P = .13$).[234]

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue.[231,232,235] 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 patients with rectal cancer,[231,232] this conclusion is not supported by 2 meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.[236,237] 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.[231,238] 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.[230] Weighing these advantages and disadvantages, the panel recommends preoperative chemoRT for patients with stage II/III rectal cancer. 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.[229,239,240]

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.[241] 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 OS 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%; $P < .05$).[241]

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.[242] Significant reductions in tumor size, pTN stage, and lymphatic, vascular, and PNI rates were observed with use of combined-modality therapy compared with use of RT and surgery without chemotherapy.[242] More mature results from this trial, which included 4 treatment groups (preoperative RT; preoperative chemoRT; preoperative RT plus postoperative chemotherapy; and preoperative chemoRT plus postoperative chemotherapy), however, indicated that no significant differences in OS were associated with adding 5-FU-based chemotherapy preoperatively or postoperatively.[243]

The conclusions of these trials have been supported in a 2009 systematic review that included 4 randomized controlled trials.[244] In addition, a recent Cochrane review of 6 randomized controlled trials found that chemotherapy added to preoperative radiation in patients with stage III, locally advanced rectal cancer reduced the risk of local recurrence, but had no effect on OS, 30-day mortality, sphincter preservation, and late toxicity.[245] Similarly, a separate Cochrane review in stage II and III resectable disease found that the addition of chemotherapy to preoperative radiation enhances pathologic response and improves local control, but has no effect on DFS or OS.[246] Another recent meta-analysis of 5 randomized controlled trials comparing neoadjuvant chemoRT with neoadjuvant radiotherapy came to similar conclusions.[227]

With respect to the type of chemotherapy administered concurrently with RT,[229] the equivalence of bolus 5-FU/LV and infusional 5-FU in concurrent chemoRT for rectal cancer is supported by the results of a phase III trial (median follow-up of 5.7 years) in which similar outcomes with respect to OS 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.[240] 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 OS when compared

to bolus 5-FU.[239] Most of the patients in this study had node-positive disease. The panel considers bolus 5-FU/LV/RT as an option for patients not able to tolerate capecitabine or infusional 5-FU (both preferred in the chemoRT setting).

Recent studies have shown that capecitabine is equivalent to 5-FU in perioperative chemoRT therapy.[247,248] 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 1608 patients with stage II or III rectal cancer.[248,249] No differences in local-regional events, DFS, OS, 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 chemoRT either pre- or postoperatively showed that capecitabine was non-inferior to 5-FU with regard to 5-year OS (capecitabine 75.7% vs. 5-FU 66.6%; $P = .0004$), with capecitabine showing borderline significance for superiority ($P = .053$).[247] Furthermore, in this trial capecitabine demonstrated a significant improvement in 3-year DFS (75.2% vs. 66.6%; $P = .034$).[247] Because of these studies, capecitabine given concurrently with RT 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.

Addition of oxaliplatin: 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).[250] Recently reported results of the NSABP R-04 trial also showed that the addition of oxaliplatin did not improve clinical outcomes including the endpoints of local-regional events, DFS, OS, pathologic complete response, sphincter-saving surgery, and surgical downstaging, while it increased toxicity.[248,249] Further follow-up of these trials is necessary to see if there is a difference in local recurrence rates and progression-free survival (PFS) over time. The primary endpoints of OS for the STAR-01 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.[251] The pathologic complete response rates were similar at 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%, $P = .008$), this did not translate to improved local recurrence rates, DFS, or OS at 3 years.

Results of the German CAO/ARO/AIO-04 trial have been published.[252,253] 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%, $P = .038$)[253], but this result could be because of differences in the fluorouracil schedule between the arms.[254] The primary endpoint of this trial, the 3-year DFS rate, was 75.9% (95%

CI, 72.4%–79.5%) in the oxaliplatin arm versus 71.2% (95% CI, 67.6%–74.9%) in the control group (P = .03).[252] Importantly, oxaliplatin was also added to the adjuvant therapy in the AIO-04 trial but not in the other trials, so cross-trial comparisons are limited.

Based on the results available to date, the addition of oxaliplatin to neoadjuvant chemoRT is not recommended at this time.

Addition of targeted agents: The randomized phase II EXPERT-C trial assessed complete response rate with the addition of cetuximab to radiation treatment in 165 patients.[255] 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 OS was seen in patients with *KRAS* exon 2/3 wild-type tumors treated with cetuximab (HR, 0.27; 95% CI, 0.07–0.99; P = .034). However, the primary endpoint of complete response rate was not met, and other phase II trials have not shown a clear benefit to the addition of cetuximab in this setting.[256,257] Further evaluation of this regimen is warranted.

The randomized, multicenter, phase II SAKK 41/07 trial evaluated the addition of panitumumab to preoperative capecitabine-based chemoRT in patients with locally advanced, *KRAS* wild-type rectal cancer.[258] The primary endpoint was pathologic near-complete plus complete tumor response, which occurred in 53% (95% CI, 36%–69%) of patients in the panitumumab arm versus 32% (95% CI, 16%–52%) in the control arm. Patients receiving panitumumab experienced increased rates of grade 3 or greater toxicity.

A phase II study of 57 patients with resectable T3/T4 rectal cancer evaluated preoperative treatment with capecitabine, oxaliplatin, bevacizumab, and RT, followed by surgery 8 weeks later and adjuvant FOLFOX/bevacizumab.[259] The 5-year OS rate was 80%, and the 5-year relapse-free survival rate was 81%. However, the primary endpoint of pathologic complete response was not met, significant toxicities were observed, and compliance with adjuvant therapy was low.

Additional phase II trials assessing the effects of adding irinotecan or bevacizumab to neoadjuvant or adjuvant regimens have begun.[260-262] However, at this time the panel does not endorse the use of bevacizumab, cetuximab, panitumumab, irinotecan, or oxaliplatin with concurrent radiotherapy for rectal cancer.

Induction Chemotherapy

Several small trials have tested the utility of a course of neoadjuvant chemotherapy preceding chemoRT and resection.[263-268] In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CapeOx either before chemoRT or after surgery.[265,269] 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 chemoRT and surgery with or without FOLFOX induction therapy.[267] 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-chemoRT and surgery.[268] The regimen was well tolerated with a pathologic complete response rate of 36%.

Possible benefits of using chemotherapy first include the early prevention or eradication of micrometastases, higher rates of pathologic complete response, minimizing the time patients need an ileostomy, facilitating resection, and improving the tolerance and completion rates

of chemotherapy. This approach was added to the 2015 version of these guidelines as an acceptable option.

Preoperative Chemotherapy Without Chemoradiation

A small single-center phase II pilot trial treated patients with stage II or III rectal cancer with induction FOLFOX/bevacizumab chemotherapy followed by chemoRT only in those with stable or progressive disease and resection in all patients.[270] All 32 of the participants had an R0 resection, and the 4-year DFS was 84% (95% CI, 67%–94%). The ongoing N1048/C81001/Z6092 PROSPECT trial by The Alliance for Clinical Trials in Oncology is also 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 could 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- to 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 to 50 Gy in 25 to 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).[271] Intensity-modulated RT (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations such as re-irradiation of previously treated recurrent disease or unique anatomical situations.

Coordination of preoperative therapy, surgery, and adjuvant chemotherapy is important. For patients treated with preoperative chemoRT, the panel recommends an interval of 5 to 12 weeks following completion of full-dose 5½-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,[272-276] it is unclear whether such longer intervals are associated with clinical benefit. Results of one National Cancer Data Base analysis suggest that an interval of >8 weeks was associated with increased odds of pathologic complete response,[277] whereas other similar analyses concluded that an interval >56 or 60 days (8–8.5 weeks) is associated with higher rates of positive margins, lower rates of sphincter preservation, and/or shorter survival.[278,279] Nevertheless, when longer intervals are clinically necessary, they do not appear to increase the blood loss, time associated with surgery, or positive margin rate.[280]

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.[281] 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.[282] 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 OS was not significantly affected despite improvements in local control of disease.[150,283,284] A recent multicenter, randomized study of 1350 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.[285] 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* =.03), although no difference in OS was observed between the arms of the study.[285,286]

Long-term (12-year) follow-up of one of the short-course radiation trials (the Dutch TME trial[283]) was reported.[287] The analysis showed that 10-year survival was significantly improved in patients with stage III disease with a negative circumferential margin in the radiotherapy plus surgery group compared to the group that received surgery alone (50% vs. 40%; *P* = .032).[287] 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.

One randomized study of 312 patients in Poland directly compared preoperative short-course radiation and more conventional preoperative long-course chemoRT and found no differences in local recurrence or survival.[288] Similarly, an Australian/New Zealand trial (Trans-Tasman Radiation Oncology Group [TROG] trial 01.04) that randomized 326 patients to short-course radiation or long-course chemoRT found no differences in local recurrence and OS rates.[289] In addition, rates of late toxicity, distant recurrence, and relapse-free survival were not significantly different between the arms. Finally, a recent trial compared short-course RT with long-course chemoRT with delayed surgery in both groups.[290] Although the long-course arm experienced greater tumor downsizing and downstaging compared with short-course treatment, no differences were seen in the R0 resection rates or postoperative morbidity.

A 2014 systematic review identified 16 studies (randomized controlled trials, phase II trials, and retrospective studies) that addressed the interval between short-course radiation and resection of rectal cancer.[291] Lower rates of severe acute post-radiation toxicity but higher rates of minor postoperative complications were seen in the immediate-surgery group (1- to 2-week interval) compared with the delayed surgery group (5- to 13-week interval). The pCR rates were significantly higher in the delayed-surgery group, with no differences in sphincter preservation and R0 resection rates.

Overall, it appears that short-course RT gives effective local control and the same OS as more conventional RT schedules, and therefore is considered as an appropriate option for patients with T3N0 or T1-3N1-2 rectal cancer. Short-course RT is not recommended for T4 disease. A multidisciplinary evaluation, including a discussion of the need for down-staging and the possibility of long-term toxicity, is recommended when considering short-course RT.

Response to Neoadjuvant Treatment

Fifty percent to 60% of patients are down-staged following neoadjuvant therapy, with about 20% of patients showing a pathologic complete response.[292-298] 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.[299] On multivariate analysis, MRI-assessed tumor regression grade was

significantly associated with OS and DFS. 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 DFS rates were 31% versus 64% (*P* = .007). Similarly, in the CAO/ARO/AIO-94 trial, patients with pathologic complete regression had 10-year cumulative incidence of distant metastasis and DFS of 10.5% and 89.5%, respectively, while those with poor regression had corresponding incidences of 39.6% and 63%.[300] A recent retrospective review of 725 patients with rectal cancer found similar results.[296] 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 down-staged to ypT0-2 were more likely to benefit from adjuvant chemotherapy than patients with ypT3-4 staging.[292] Similar results were seen from another retrospective review.[301] Although no prospective data to predict the benefit of adjuvant therapy in patients with tumor downstaging or a pathologic complete response exist, the panel believes that such patients should be strongly considered for adjuvant chemotherapy.

Wait-and-See Nonoperative Approach for Clinical Complete Responders

As preoperative treatment and imaging modalities have improved, some have suggested that patients with a clinical complete response to chemoRT may be able to be spared the morbidities of surgery. In 2004, Habr-Gama et al[302] 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 OS and DFS rates at 5 years were 100% and 92%, respectively, in the nonoperative 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.[303]

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.[304] Only 1 patient in the nonoperative group developed a local recurrence after a mean follow-up of 25 months; that patient underwent successful surgery. No statistical differences in long-term outcomes were seen between the groups. The cumulative probabilities for 2-year DFS and OS were 89% (95% CI, 43%–98%) and 100%, respectively, in the wait-and-see group and 93% (95% CI, 59%–99%) and 91% (95% CI, 59%–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.

Other non-randomized, prospective studies have added to the growing evidence that the non-operative approach may warrant further study.[305-308] For example, one study showed that 49% of patients experienced a complete clinical response after 5-FU-based chemoRT, and found that strict surveillance in these patients, with resection of recurrences when possible, resulted in a 5-year recurrence-free survival of 69%, which rose to 94% after resections were performed.[306]

Despite these impressive results, many still believe that longer follow-up, larger sample sizes, and additional careful observational studies are needed before patients with a clinical complete response are routinely managed by a wait-and-see approach.[309] Furthermore, recent studies have found that neither FDG-PET, nor MRI, nor CT can accurately determine a pathologic complete response, complicating the selection of appropriate patients for a nonoperative approach.[164-172] In addition, lymph node metastases are still seen in a subset of patients with pathologic complete response.[310] Overall, the panel does not support this approach in the routine management of localized rectal cancer.

Adjuvant Chemotherapy

Adjuvant chemotherapy is recommended for all patients with stage II/III rectal cancer following neoadjuvant chemoRT and surgery if they did not receive neoadjuvant chemotherapy 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.[311] The addition of 5-FU adjuvant chemotherapy to preoperative chemoRT provided no benefit to the rate of local recurrence in the EORTC Radiotherapy Group Trial 22921.[243] However, this study did show an improvement in DFS (HR, 0.87; 95% CI, 0.72–1.04; *P* = .13) of patients receiving adjuvant chemotherapy (+/- RT) following preoperative RT (+/- 5-FU–based chemotherapy).[243] Long-term results of the 22921 trial confirmed that adjuvant 5-FU chemotherapy did not improve OS, and the difference in DFS was less pronounced than following the previous analysis (HR, 0.91; 95% CI, 0.77–1.08; *P* = .29).[312] Limitations of this trial include the fact that only 43% of participants received the full course of adjuvant chemotherapy. Other trials have failed to show an improvement in OS or DFS with adjuvant therapy with a fluoropyrimidine alone in this setting.[313,314]

Other trials have investigated the use of more modern agents in the adjuvant setting. 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 patients with stage II/III rectal cancer after 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.[315] The open-label phase II ADORE trial randomized 321 patients with resected rectal cancer and neoadjuvant therapy to adjuvant 5-FU/LV or FOLFOX.[316] The FOLFOX arm had higher 3-year DFS, at 71.6% versus 62.9% (HR, 0.66; 95% CI, 043–0.99; *P* = .047). The CAO/ARO/AIO-04 trial found an improvement in 3-year DFS when oxaliplatin was added to 5-FU in both neoadjuvant and adjuvant treatment (75.9% vs. 71.2%; *P* = .03).[252]

A recent study in which patients who received neoadjuvant chemoRT and experienced a pathologic complete response were observed without additional adjuvant chemotherapy found 5-year DFS and OS rates of 96% and 100%, respectively.[317] In addition, a meta-analysis of 4 randomized trials (1196 patients) concluded that adjuvant fluorouracil-based chemotherapy (5-FU/LV, capecitabine, or CapeOx) after preoperative therapy and surgery did not improve OS, DFS, or the rate of distant recurrences in patients with stage II or III rectal cancer.[318] However, more recent trials that found a DFS benefit to the addition of adjuvant oxaliplatin-based adjuvant therapy were not included in this study, and other meta-analyses have come to the opposite conclusion.[319,320] The panel continues to support the use of adjuvant therapy in this setting.

A recent analysis of the NCCN Colorectal Cancer Database found that, of 2073 patients with stage II/III rectal cancer who received neoadjuvant

chemoRT treatment, 203 patients (9.8%) did not receive any adjuvant chemotherapy as recommended by these guidelines.[321] Multivariate analysis found that complete pathologic response, infection, no closure of ileostomy/colostomy, age, poor performance status, and being on Medicaid or indigent were associated with not receiving adjuvant chemotherapy. Results from the SEER database indicated that even fewer patients in the general population are receiving adjuvant therapy (61.5%) in this setting.[322] Pathologic stage, age, and postoperative readmissions were associated with a decreased likelihood of receiving adjuvant treatment.

Although conclusive data on the use of adjuvant therapy in patients with stage II/III rectal cancer are lacking, the panel recommends use of FOLFOX or CapeOx as preferred options. FLOX, 5-FU/leucovorin, or capecitabine can also be used in this setting. 5-FU and capecitabine might be especially appropriate in patients who responded to neoadjuvant treatment with 5-FU or capecitabine.

Timing and Duration of Adjuvant Therapy: A 2011 systematic review and meta-analysis of 10 studies involving more than 15,000 patients with colorectal cancer looked at the effect of timing of adjuvant therapy following resection.[323] Results of this analysis showed that each 4-week delay in chemotherapy results in a 14% decrease in OS, indicating that adjuvant therapy should be administered as soon as the patient is medically able. These results are consistent with other similar analyses.[324]

The optimal duration of adjuvant treatment in rectal cancer is still unclear.[325,326] In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX.[327] The use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) is justified when preoperative chemoRT is administered.

Multigene Assays

Several multigene assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer (see the NCCN Guidelines for Colon Cancer, available at www.NCCN.org, for a full discussion).[328]

Among the multigene assays used in colon cancer is the Oncotype DX colon cancer assay, which quantifies the expression of 7 recurrence-risk genes and 5 reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.[329] Clinical validation in patients with stage II and III colon cancer from QUASAR and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trials showed that recurrence scores are prognostic for recurrence, DFS, and OS in stage II and III colon cancer, but are not predictive of benefit to adjuvant therapy.[330] For the low, intermediate, and high recurrence risk groups, recurrence at 3 years was 12%, 18%, and 22%, respectively. Similar results were found in other prospectively designed studies.[331,332]

A recent prospectively designed validation study assessed this assay for predicting recurrence risk in patients with stage II and III rectal cancer.[333] For patients who underwent surgery without neoadjuvant therapy in the Dutch Total Mesorectal Excision (TME) trial, recurrence score was predictive of recurrence, distant recurrence, and rectal-cancer-specific survival. In patients with stage II rectal cancer, recurrence at 5 years was 11%, 27%, and 43% for the low, intermediate, and high recurrence risk groups, respectively.

The panel believes the information from this test can further inform the risk of recurrence over other risk factors, but they question the value added. Furthermore, there is no evidence of predictive value in terms of the potential benefit of chemotherapy in patients with colon or rectal

cancer with any of the available multigene assays. The panel believes that there are insufficient data to recommend the use of multigene assays to determine adjuvant therapy for patients with colorectal cancer.

Leucovorin Shortage

A leucovorin shortage recently existed in the United States. No specific data 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.[334] 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.[335] Also, the Mayo Clinic and NCCTG determined that there was no therapeutic difference between the use of high- (200 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.[336] Finally, if none of the above options is 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,[179,180] with or without neoadjuvant chemoRT. After transabdominal resection, chemotherapy with chemoRT (a “sandwich regimen” as described below) should be given to those with positive nodes or pT3-4 disease if neoadjuvant therapy was not given. For patients with high-risk disease after transanal excision who cannot undergo additional surgery, systemic chemotherapy with chemoRT 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.[152,337,338]

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;[339] 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 T3-4 Lesions, Nodal Involvement, Locally Unresectable Disease, or Who Are Medically Inoperable

Patients clinically staged as having resectable T3-4, N0 T any, N1-2 lesions, and/or who have locally unresectable disease or are medically inoperable have 3 options for the sequence of treatment: 1) chemotherapy with long-course RT, then resection if possible, followed by chemotherapy; 2) short-course RT (not recommended for T4 disease), then resection if possible, followed by chemotherapy; or 3) chemotherapy, then chemoRT, then resection if possible. Infusional 5-FU/RT and capecitabine/RT are the preferred chemoRT options (category 1 for both) regardless of the sequence. An alternative chemoRT regimen is bolus 5-FU/LV/RT. The preferred chemotherapy regimens, also regardless of whether given before or after surgery, are FOLFOX or CapeOx, with 5-FU/leucovorin and capecitabine as additional options. Furthermore, in the postoperative setting FLOX can be considered.

Resection should be considered following preoperative therapy unless there is a clear contraindication. The panel advises that a poor clinical response does not necessarily imply unresectability, and surgical exploration is usually appropriate. Transabdominal resection should be performed 5 to 12 weeks following completion of neoadjuvant therapy. The panel recommends that the duration of perioperative chemotherapy, including chemotherapy and chemoRT, be approximately 6 months. When resection is contraindicated following primary treatment, patients should be treated with a systemic regimen for advanced disease (see discussion of *Chemotherapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer, available at www.NCCN.org). FOLFOXIRI is not recommended in this setting.

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 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.

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. For patients with T4 tumors or recurrent cancers or if margins are very close or positive, intraoperative RT (IORT),[340-344] 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 to 20 Gy and/or brachytherapy to a limited volume can be considered.

Principles of the Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with colorectal cancer will develop colorectal metastases,[345-347] and 80% to 90% of these patients have unresectable metastatic liver disease.[346,348-351] Metastatic

disease most frequently develops metachronously after treatment for locoregional colorectal cancer, with the liver as the most common site of involvement.[352] However, 20% to 34% of patients with colorectal cancer present with synchronous liver metastases.[351,353] 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.[354]

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.[355] 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.[350] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[346,356] 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.[353,357-361]

Other groups, including ESMO, have established guidelines for the treatment of metastatic colorectal cancer.[362] The NCCN recommendations are discussed below.

Surgical Management of Colorectal Metastases

Studies of selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this population and should be the goal for a substantial number of these patients.[346,363] Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,[358,361] and a recent meta-analysis reported a median 5-year survival of 38%.[364] In addition, retrospective analyses and meta-analyses have shown that patients with solitary liver metastases have a 5-year OS rate as high as 71% following resection.[365-367] 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[368] (discussed further in *Determining Resectability*).

Colorectal metastatic disease sometimes occurs in the lung.[345] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.[369,370] Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases.[371-374]

Evidence supporting resection of extrahepatic metastases in patients with metastatic colorectal cancer is limited. In a recent retrospective analysis of patients undergoing concurrent complete resection of hepatic and extrahepatic disease, the 5-year survival rate was lower than in patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence.[375,376] However, a recent international analysis of 1629 patients with colorectal liver metastases showed that 16% of the 171 patients (10.4%) who underwent concurrent resection of extrahepatic and hepatic disease remained disease-free at a median follow-up of 26 months, suggesting that concurrent resection may be of significant benefit in well-selected patients (ie, those with a smaller total number of metastases).[374] A recent systematic review concluded

similarly that carefully selected patients might benefit from this approach.[377]

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.[378-381] In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year overall and PFS rates were reported to be 73% and 22%, respectively.[378] A recent meta-analysis of 27 studies including >7200 patients found that those with longer disease-free intervals; those whose recurrences were solitary, smaller, or unilobular; and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.[382] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[383,384]

Patients with a resectable primary rectal tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection, as discussed below in *Recommendations for Treatment of Resectable Synchronous Metastases*. For patients presenting with unresectable metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver (discussed in more detail below in *Recommendations for Treatment of Unresectable Synchronous Metastases*).[385]

Liver-Directed Therapies

The standard of care for patients with resectable metastatic disease is surgical resection. If resection is not feasible, image-guided ablation[386-388] or stereotactic body radiation therapy (SBRT; also called stereotactic ablative radiotherapy [SABR])[349,389,390] are reasonable options, as discussed in subsequent paragraphs. Many patients, however, are not surgical candidates or have disease that cannot be ablated with clear margins[387] or safely treated by SBRT. In select patients with liver-only or liver-dominant metastatic disease that cannot be resected or ablated arterially, liver-directed treatment options may be offered.[391-393] 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 was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.[350,394] The study was not powered for long-term survival, but a trend (not significant) was seen toward better long-term outcome in the group receiving HAI at later follow-up periods.[350,395] 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.[350] Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.[363] Limitations on the use of HAI therapy include the potential for biliary toxicity[350] and the requirement of specific technical expertise. Panel consensus is that HAI therapy should be considered selectively, and only at institutions with

extensive experience in both the surgical and medical oncologic aspects of the procedure.

Arterially Directed Embolic Therapy

Transarterial chemoembolization (TACE) involves hepatic artery catheterization to cause vessel occlusion with locally delivered chemotherapy.[392] A recent randomized trial using HAI to deliver irinotecan-loaded drug-eluting beads (DEBIRI) reported an OS benefit (22 months vs. 15 months; $P = .031$).[396] A 2013 meta-analysis identified 5 observational studies and 1 randomized trial and concluded that, although DEBIRI appears to be safe and effective for patients with unresectable colorectal liver metastases, additional trials are needed.[397] A more recent trial randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to FOLFOX/bevacizumab/DEBIRI.[398] DEBIRI resulted in an improvement in the primary outcome measure of response rate (78% vs. 54% at 2 months; $P = .02$).

Doxorubicin-eluting beads have also been studied; the strongest data supporting their effectiveness come from several phase II trials in hepatocellular carcinoma.[399-404] A recent systematic review concluded that data are not strong enough to recommend TACE for the treatment of colorectal liver metastases except as part of a clinical trial.[405] The panel lacks consensus for the use of arterially directed embolic therapy for colorectal cancer liver metastases. This treatment is therefore listed as a category 3 recommendation for colorectal liver metastases.

Liver-Directed Radiation

Liver-directed radiation therapies include arterial radioembolization with microspheres[406-416] and conformal (stereotactic) external beam RT (EBRT).[417]

EBRT 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, SBRT,[349,389,390,418] and IMRT, which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.[419-422]

Radioembolization

A 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; $P = .03$).[423] The effect on the primary endpoint of time to liver progression was more pronounced (2.1 vs. 5.5 months; $P = .003$). Treatment of liver metastases with yttrium-90 glass radioembolization in a prospective, multicenter, phase II study resulted in a median PFS of 2.9 months for patients with colorectal primaries who were refractory to standard treatment.[424] In the refractory setting, a CEA level ≥90 and lymphovascular invasion at the time of primary resection were negative prognostic factors for OS.[415] Several large case series have been reported for yttrium-90 radioembolization in patients with refractory unresectable colorectal liver metastases, and the technique appears to be safe with some clinical benefit.[425,426]

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX+/- bevacizumab vs. FOLFOX+/- bevacizumab) were reported at the 2015 ASCO Annual Meeting.[427] The trial assessed the safety and efficacy of yttrium-90 radioembolization as first-line therapy in 530 patients with colorectal liver metastases.

Although the primary endpoint was not met, with PFS in the FOLFOX +/- bevacizumab arm at 10.2 months versus 10.7 months in the FOLFOX/Y-90 arm (HR, 0.93; 95% CI, 0.77–1.12; *P* = .43), a prolonged liver PFS was demonstrated for the study arm (20.5 months for the FOLFOX/Y90 arm vs. 12.6 months for the chemotherapy only arm; *P* = .002).

Whereas toxicity with radioembolization is relatively low, the data supporting its efficacy are limited, with very little data showing any impact on patient survival.[428-430] Consensus amongst panel members on the use of radioembolization for colorectal cancer liver metastases is lacking. Therefore, the use of radioembolization remains a category 3 recommendation.

Tumor Ablation

Although resection is the standard approach for the local treatment of resectable metastatic disease, patients with liver oligometastases can be considered for tumor ablation therapy.[431] Ablative techniques include radiofrequency ablation (RFA),[387,432] microwave ablation, cryoablation, percutaneous ethanol injection, and electro-coagulation. Evidence on the use of RFA as a reasonable treatment option for non-surgical candidates and those with recurrent disease after hepatectomy with small liver metastases that can be treated with clear margins is growing.[387,432-434] Data on ablative techniques other than RFA are extremely limited.[435-441]

A small number of retrospective studies have compared RFA and resection in the treatment of liver or lung metastases.[366,441-444] Most of these studies have shown RFA to be inferior to resection in terms of rates of local recurrence and 5-year OS.[431,445] 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.[443] 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.[441] The ASCO panel concluded that a compelling need exists for more research in this area. A 2012 Cochrane Database systematic review came to similar conclusions, as have separate meta-analyses.[437,440,446]

Recently, a trial was reported in which 119 patients were randomized to receive systemic treatment or systemic treatment plus RFA with or without resection.[447] No difference in OS was seen, but PFS was improved at 3 years in the RFA group (27.6% vs. 10.6%; HR, 0.63; 95% CI, 0.42–0.95; *P* = .025). Similarly 2 recent studies and a position paper by a panel of experts on ablation indicated that ablation may provide acceptable oncologic outcomes for selected patients with small liver metastases that can be ablated with sufficient margins.[386-388]

Resection or ablation (either alone or in combination with resection) should be reserved for patients with disease that is completely amenable to local therapy with adequate margins. Use of surgery, ablation, or the combination, with the goal of less-than-complete resection/ablation of all known sites of disease, is not recommended.

Peritoneal Carcinomatosis

Approximately 17% of patients with metastatic colorectal cancer have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis.[448] Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.[448] The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative, and primarily consists of systemic therapy (see *Chemotherapy for Advanced or Metastatic Disease*) with palliative

surgery or stenting if needed for obstruction or impending obstruction.[449] If an R0 resection can be achieved, however, surgical resection of isolated peritoneal disease may be considered at experienced centers. The panel cautions that the use of bevacizumab in patients with colon or rectal stents is associated with a possible increased risk of bowel perforation.[450,451]

Cytoreductive Debulking with Heated Intraperitoneal Chemotherapy

Several surgical series and retrospective analyses have addressed the role of cytoreductive surgery (ie, peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis without extra-abdominal metastases.[452-459] In the only randomized controlled trial of this approach, Verwaal et al[460] 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. OS was 12.6 months in the standard arm and 22.3 months in the HIPEC arm (P = .032). However, treatment-related morbidity was high, and the mortality was 8% in the HIPEC group, mostly related to bowel leakage. In addition, long-term survival does not seem to be improved by this treatment as seen by follow-up results.[461] Importantly, this trial was performed without oxaliplatin, irinotecan, or molecularly targeted agents. Some experts have argued that the OS difference seen might have been much smaller if these agents had been used (ie, the control group would have had better outcomes).[462]

Other criticisms of the Verwaal trial have been published.[462] One important point is that the trial included patients with peritoneal carcinomatosis of appendiceal origin, a group that has seen greater benefit with the cytoreductive surgery/HIPEC approach.[452,463-465] 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, treated with HIPEC or with cytoreductive surgery and early postoperative intraperitoneal chemotherapy.[464] The median OS time for patients with pseudomyxoma peritonei, which arises from mucinous appendiceal carcinomas, was not reached at the time of publication. A recent retrospective international registry study reported 10- and 15-year survival rates of 63% and 59%, respectively, in patients with pseudomyxoma peritonei from mucinous appendiceal carcinomas treated with cytoreductive surgery and HIPEC.[466] HIPEC was not shown to be associated with improvements in OS in this study, whereas completeness of cytoreduction was. Thus, for patients with pseudomyxoma peritonei, optimal treatment is still unclear.[467]

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.[468] Results of a retrospective cohort study also suggest that heat may not affect outcomes from the procedure.[453] In addition, significant morbidity and mortality are associated with this procedure. A 2006 meta-analysis of 2 randomized controlled trials and 12 other studies reported morbidity rates ranging from 23% to 44% and mortality rates ranging from 0% to 12%.[459] Furthermore, recurrences after the procedure are very common.[469] Whereas the risks are reportedly decreasing with time (ie, recent studies report 1%–5% mortality rates at centers of excellence[456,462]), the benefits of the approach have not been definitively shown, and HIPEC remains very controversial.[470-473]

The panel currently considers the treatment of disseminated carcinomatosis with cytoreductive surgery and HIPEC to be investigational and does not endorse this therapy outside of a clinical trial. 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.[474-477] 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.[478] It should be noted that size alone is rarely a contraindication to resection of a tumor. Resectability differs fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease.[479] Resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), because incomplete resection or debulking (R1/R2 resection) has not been shown to be beneficial.[347,474]

The role of PET/CT in determining resectability of patients with metastatic colorectal cancer is discussed in *Recommendations for Treatment of Metachronous Metastases*, below.

Conversion to Resectability

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, 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.[431]

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.[480-484] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable. Some of the trials addressing various conversion therapy regimens are discussed below.

In the study of Pozzo et al, it was reported that chemotherapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection.[476] The median time to progression was 14.3 months, with all of these patients alive at a median follow-up of 19 months. In a phase II study conducted by the NCCTG,[348] 42 patients with unresectable liver metastases were treated with FOLFOX. Twenty-five patients (60%) had tumor reduction and 17 patients (40%; 68% of the

responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study, 1104 patients with initially unresectable colorectal liver 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.[357] The 5-year DFS rate for these 138 patients was 22%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%; 2 of the 24 had lung metastases) were able to undergo curative resection after treatment.[485] The median OS 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 patients with unresectable disease.[486,487] 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[486]; and 4% versus 10%, $P = .08$ in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.[487] In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs. 8%), with a median OS of 23.4 vs. 16.7 months ($P = .026$).[488]

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.[489,490] For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.[489] Retrospective analysis showed that, in both treatment arms combined, resectability increased from 32% to 60% after chemotherapy in patients with wild-type *KRAS* exon 2 ($P < .0001$) with the addition of cetuximab. Another recent randomized controlled trial compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable colorectal cancer metastatic to the liver.[491] The primary endpoint was the rate of conversion to resectability based on evaluation by a multidisciplinary team. After evaluation, 20 of 70 patients (29%) in the cetuximab arm and 9 of 68 patients (13%) in the control arm were determined to be eligible for curative-intent hepatic resection. R0 resection rates were 25.7% in the cetuximab arm and 7.4% in the control arm ($P < .01$). In addition, surgery improved the median survival time compared to unresected participants in both arms, with longer survival in patients receiving cetuximab (46.4 vs. 25.7 months; $P = .007$ for the cetuximab arm and 36.0 vs. 19.6 months; $P = .016$ for the control arm). A recent meta-analysis of 4 randomized controlled trials concluded that the addition of cetuximab or panitumumab to chemotherapy significantly increased the response rate, the R0 resection rate (from 11%–18%; RR 1.59; $P = .04$), and PFS, but not OS in patients with wild-type *KRAS* exon 2-containing tumors.[492]

The role of bevacizumab in the patient with unresectable, metastatic colorectal cancer, 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.[493] 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.[494] Therefore, arguments for use of bevacizumab with oxaliplatin-based therapy in this "convert to resectability" setting are not compelling. However, because it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

When 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.[484,495-497] Reported risks associated with chemotherapy include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.[480] 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 meta-analysis identified 3 randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.[498] The pooled analysis showed a benefit of chemotherapy in PFS (pooled HR, 0.75; CI, 0.62–0.91; *P* = .003) and DFS (pooled HR, 0.71; CI, 0.58–0.88; *P* = .001), but not in OS (pooled HR, 0.74; CI, 0.53–1.05; *P* = .088). Another meta-analysis published in 2015 combined data on 1896 patients from 10 studies and also found that perioperative chemotherapy improved DFS (HR, 0.81; 95% CI, 0.72–0.91; *P* = .0007) but not OS (HR, 0.88; 95% CI, 0.77–1.01; *P* = .07) in patients with resectable colorectal liver metastases.[499]

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 EORTC 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 PFS of 8.1% (*P* = .041) and 9.2% (*P* = .025) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[500] The partial response rate after preoperative FOLFOX was 40%, and operative mortality was <1% in both treatment groups. However, no difference in OS was seen between the groups, perhaps because second-line therapy was given to 77% of the patients in the surgery only arm and to 59% of the patients in the chemotherapy arm.[501]

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.[502,503]

Potential advantages of the preoperative chemotherapy approach include earlier treatment of micrometastatic disease; determination of 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.[350,504,505] Importantly, results from a study of patients with colorectal cancer receiving preoperative chemotherapy indicated that viable cancer was still present in most of the original sites of metastases when these sites were examined pathologically despite achievement of a complete response as evaluated on CT scan.[505,506] 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.[480]

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.[480-484] 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 compared to the group receiving chemotherapy alone while undergoing major surgery (13% vs. 3.4%, respectively; *P* = .28).[507] 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[508]) 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.[509] 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.[510]

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.[511] Venous thromboembolisms, however, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[512]

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

EGFR has been shown to be overexpressed in 49% to 82% of colorectal tumors.[513-516] 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.[517] A similar conclusion was drawn with respect to panitumumab.[518] 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.[517,519] Furthermore, cetuximab and panitumumab are only effective in approximately 10% to 20% of patients with colorectal cancer.[517,519,520] The RAS/RAF/MAPK pathway is downstream of EGFR; mutations in components of this pathway are being studied in search of predictive markers for efficacy of these therapies.

A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of response to cetuximab or panitumumab therapy.[521-530] More recent evidence shows that mutations in *KRAS* outside of exon 2 and mutations in *NRAS* are also predictive for a lack of benefit to cetuximab and panitumumab (see *NRAS and Other KRAS*

Mutations, below).[531,532] The panel therefore strongly recommends *KRAS/NRAS* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer. Patients with known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is implied throughout the guidelines that NCCN recommendations involving cetuximab or panitumumab relate only to patients with disease characterized by *KRAS/NRAS* wild-type genes. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS/NRAS*, this testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see *BRAF V600E Mutations*, below).

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

KRAS mutations are early events in colorectal cancer formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.[533,534] For this reason, *KRAS/NRAS* genotyping can be performed on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of *KRAS/NRAS* genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable.

The panel recommends that *KRAS, NRAS, and BRAF* gene testing be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.[535] No specific testing methodology is recommended.[536]

***KRAS* Exon 2 Mutations:** Approximately 40% of colorectal cancers are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the *KRAS* gene.[521,537] A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy,[521-530] and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of colorectal cancer characterized by these mutations.[538,539] Results are mixed as far as the prognostic value of *KRAS* mutations. In the Alliance N0147 trial, patients with *KRAS* exon 2 mutations experienced a shorter DFS than patients without such mutations.[540] At this time, however, the test is not recommended for prognostic reasons.

A retrospective study from De Roock et al[541] raised the possibility that codon 13 mutations (G13D) in *KRAS* may not be absolutely predictive of non-response to EGFR inhibition. Another retrospective study showed similar results.[542] Furthermore, a more recent retrospective analysis of 3 randomized controlled phase III trials concluded that patients with *KRAS* G13D mutations were unlikely to respond to panitumumab.[543] Results from a prospective phase II single-arm trial assessed the benefit of cetuximab monotherapy in 12 patients with

refractory metastatic colorectal cancer whose tumors contained *KRAS* G13D mutations.[544] The primary endpoint of 4-month progression-free rate was not met (25%), and no responses were seen. Preliminary results of the AGITG phase II ICECREAM trial also failed to see a benefit of cetuximab monotherapy in patients with *KRAS* G13D mutations.[545] However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. Currently, use of anti-EGFR agents in patients whose tumors have G13D mutations remains investigational, and is not endorsed by the panel for routine practice.

***NRAS* and Other *KRAS* Mutations:** In the AGITG MAX study, 10% of patients with wild-type *KRAS* exon 2 had mutations in *KRAS* exons 3 or 4 or in *NRAS* exons 2, 3, and 4.[546] In the PRIME trial, 17% of 641 patients without *KRAS* exon 2 mutations were found to have mutations in exons 3 and 4 of *KRAS* or mutations in exons 2, 3, and 4 of *NRAS*. A predefined retrospective subset analysis of data from PRIME revealed that PFS (HR, 1.31; 95% CI, 1.07–1.60; P = .008) and OS (HR, 1.21; 95% CI, 1.01–1.45; P = .04) were decreased in patients with any *KRAS* or *NRAS* mutation who received panitumumab plus FOLFOX compared to those who received FOLFOX alone.[531] These results show that panitumumab does not benefit patients with *KRAS* or *NRAS* mutations and may even have a detrimental effect in these patients.

Updated analysis of the FIRE-3 trial was recently published.[547] When all *RAS* (*KRAS/NRAS*) mutations were considered, PFS was significantly worse in patients with *RAS*-mutant tumors receiving FOLFIRI plus cetuximab than patients with *RAS*-mutant tumors receiving FOLFIRI plus bevacizumab (6.1 months vs. 12.2 months; P = .004). On the other hand, patients with *KRAS/NRAS* wild-type tumors showed no difference in PFS between the regimens (10.4 months vs. 10.2 months; P = .54). This result indicates that cetuximab likely has a detrimental effect in patients with *KRAS* or *NRAS* mutations.

The FDA indication for panitumumab was updated to state that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* mutation-positive disease in combination with oxaliplatin-based chemotherapy.[538] The NCCN Colon/Rectal Cancer Panel believes that non-exon 2 *KRAS* mutation status and *NRAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab.

***BRAF* V600E Mutations:** Although mutations of *KRAS/NRAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *KRAS/NRAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *KRAS/NRAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of colorectal cancers are characterized by a specific mutation in the *BRAF* gene (V600E).[548,549] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.[548,550] 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,[551-553] 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.[554,555] 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.[550]

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.[556-558] A retrospective study of 773 primary tumor samples from patients with chemotherapy-refractory disease showed that *BRAF* mutations conferred a significantly lower response rate to cetuximab (2/24; 8.3%) compared with tumors with wild-type *BRAF* (124/326; 38.0%; *P* = .0012).[559] Furthermore, data from the multicenter randomized controlled PICCOLO trial are consistent with this conclusion, with a suggestion of harm seen for the addition of panitumumab to irinotecan in the non–first-line setting in the small subset of patients with *BRAF* mutations.[560]

A meta-analysis published in 2015 identified 9 phase III trials and 1 phase II trial that compared cetuximab or panitumumab with standard therapy or best supportive care including 463 patients with metastatic colorectal tumors with *BRAF* mutations (first-line, second-line, or refractory settings).[561] The addition of an EGFR inhibitor did not improve PFS (HR, 0.88; 95% CI, 0.67–1.14; *P* = .33), OS (HR, 0.91; 95% CI, 0.62–1.34; *P* = .63), or overall response rate (ORR) (RR, 1.31; 95% CI, 0.83–2.08, *P* = .25) compared with control arms. Similarly, another meta-analysis identified 7 randomized controlled trials and found that cetuximab and panitumumab did not improve PFS (HR, 0.86; 95% CI, 0.61–1.21) or OS (HR, 0.97; 95% CI, 0.67–1.41) in patients with *BRAF* mutations.[562]

Despite uncertainty over its role as a predictive marker, it is clear that mutations in *BRAF* are a strong prognostic marker.[537,550,555,563-566] A recent prospective analysis of tissues from patients with stage II and III colon cancer enrolled in the PETACC-3 trial showed that the *BRAF* mutation is prognostic for OS in patients with low levels of MSI (MSI-L) or stable microsatellites (MSS) (HR, 2.2; 95% CI, 1.4–3.4; *P* = .0003).[537] 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.[555] Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (CI, 0.33–0.73; *P* = .001).[564] The OS in patients with *BRAF* mutations in the COIN trial was 8.8 months, while those with *KRAS* exon 2 mutations and wild-type *KRAS* exon 2 tumors had OS times of 14.4 months and 20.1 months, respectively.[550] Results from a recent systematic review and meta-analysis of 21 studies, including 9885 patients, suggest that *BRAF* mutation may accompany specific high-risk clinicopathologic characteristics.[567] In particular, an association was observed between *BRAF* mutation and proximal tumor location (OR, 5.22; 95% CI, 3.80–7.17; *P* < .001), T4 tumors (OR, 1.76; 95% CI, 1.16–2.66; *P* = .007), and poor differentiation (OR, 3.82, 95% CI, 2.71–5.36; *P* < .001).

Overall, the panel believes that evidence increasingly suggests that BRAF V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely. The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[568]) at diagnosis of stage IV disease. Testing for the *BRAF* V600E mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed by PCR amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting this mutation.

Recommendations for Perioperative Cetuximab and Panitumumab:
Cetuximab and panitumumab are used in the neoadjuvant setting in patients with resectable synchronous metastatic colorectal cancer and wild-type *RAS* in combination with FOLFIRI or FOLFOX. However, the New EPOC trial, which was stopped early because it met protocol-defined futility criteria, found a lack of benefit to cetuximab with chemotherapy in the perioperative metastatic setting (>85% received FOLFOX or CapeOx; patients with prior oxaliplatin received FOLFIRI).[569] In fact, with less than half of expected events observed, PFS was significantly reduced in the cetuximab arm (14.8 vs. 24.2 months; HR 1.50; 95% CI, 1.00–2.25; $P < .048$). The panel thus cautions that, while the data are not strong enough to prohibit its use, cetuximab in the perioperative setting may harm patients. The panel therefore points out that FOLFOX plus cetuximab should be used with caution in patients with resectable disease and in those with unresectable disease that could potentially be converted to a resectable status.

Chemotherapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colorectal cancer involves various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, ramucirumab, regorafenib, and trifluridine-tipiracil. The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, the mutational profile of the tumor, and the differing efficacy and toxicity profiles of the constituent drugs. Although the specific chemotherapy regimens listed in the guidelines are designated according to whether they pertain to initial therapy or therapy after first, second, or third progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete. For example, if oxaliplatin is administered as a part of an initial treatment regimen but is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the remainder of the treatment regimen would still be considered initial therapy.
Principles to consider at the start of therapy include preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive, and plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices after first progression of disease should be based partly on the prior therapies received (ie, exposing the patient to a range of cytotoxic agents). Furthermore, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, and the potential for surgical cure and the performance status of the patient.

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 NCCN Guidelines for Colon Cancer for a detailed discussion of the various options for systemic treatment (available at www.NCCN.org).

Recommendations for Treatment of Resectable Synchronous Metastases

As part of the pre-treatment workup, the panel recommends tumor *KRAS/NRAS* gene status testing for all patients with metastatic colorectal cancer at the time of diagnosis of metastatic disease. If *KRAS/NRAS* are found to be wild-type, *BRAF* testing can be considered (see *Perioperative Cetuximab and Panitumumab for Resectable*

Metastatic Disease: The Role of KRAS, NRAS, 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 following neoadjuvant treatment (options discussed below).[570-577] Historically, in the staged approach, the primary tumor was usually resected first. However, the approach of liver resection before resection of the primary tumor is now well-accepted. In addition, emerging data suggest that chemotherapy, followed by resection of liver metastases before resection of the primary tumor, might be an effective approach in some patients, although more studies are needed.[578-580] Locally ablative procedures can be considered instead of or in addition to resection in cases of liver oligometastases (see *Liver-Directed Therapies*, above), but resection is preferred.

There are several acceptable sequences of therapy in the setting of resectable synchronous disease. As described in more detail below, options are: 1) combination chemotherapy, resection/local therapy, and optional chemoRT; 2) combination chemotherapy, chemoRT, resection/local therapy, and optional adjuvant combination chemotherapy; and 3) chemoRT, resection/local therapy, then (category 2B) active chemotherapy as for advanced disease. As in other settings, the total perioperative chemotherapy and chemoRT therapy should not exceed 6 months.

Surgery/local therapy 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 or cetuximab [for *KRAS/NRAS* 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/local therapy. For those who did, adjuvant chemotherapy as was given preoperatively can be considered.

Alternatively, surgery/local therapy 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 for 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/local therapy. For patients receiving neoadjuvant therapy, surgery/local therapy should be performed 5 to 12 weeks following completion of treatment.

In the 2014 version of these guidelines, the panel removed the option of surgery as the initial treatment because it believes that the majority of patients should receive preoperative therapy. The panel acknowledges that some patients may not be candidates for chemotherapy or radiation; clinical judgment should be used in such cases.

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.[581] 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 OS and PFS from resection of the primary in the setting of unresectable colorectal metastases.[582] Other retrospective analyses have also shown a potential benefit.[583,584] 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.[585] The median OS 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,[385] and its removal delays initiation of systemic chemotherapy. In fact, a recent systematic review concluded that resection of the primary does not reduce complications and does not improve OS.[586] However, a different systematic review concluded that, while data are not strong, resection of the primary tumor may provide a survival benefit.[587] Another systematic review and meta-analysis identified 5 studies that compared open to laparoscopic palliative colectomies in this setting.[588] The laparoscopic approach resulted in shorter lengths of hospital stays ($P < .001$), fewer postoperative complications ($P = 0.01$), and lower estimated blood loss ($P < .01$).

Overall, the panel believes that the risks of surgery outweigh the possible benefits of 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.[385]

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.[589,590] A recent randomized clinical trial of patients with resectable metachronous metastases also assessed the role of PET/CT in the workup of potential curable disease.[591] While there was no impact of PET/CT on survival, surgical management was changed in 8% of patients after PET/CT. For example, resection was not undertaken for 2.7% of patients because additional metastatic disease was identified (bone, peritoneum/omentum, abdominal nodes). In addition, 1.5% of patients had more extensive hepatic resections and 3.4% had additional organ surgery. An additional 8.4% of patients in the

PET/CT arm had false-positive results, many of which were investigated with biopsies or additional imaging.

As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) of *KRAS/NRAS* genotype should be performed to define whether anti-EGFR agents can be considered among the potential options. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS/NRAS* genes, this testing is currently optional and is not a necessary part of deciding whether to use anti-EGFR agents (see *Perioperative Cetuximab and Panitumumab for Resectable Metastatic Disease: The Role of KRAS, NRAS, 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), with choice of regimens based on previous therapy. Locally ablative procedures can be considered instead of or in addition to resection in cases of liver oligometastases (see *Liver-Directed Therapies*, above), but resection is preferred. For patients without a history of chemotherapy use, FOLFOX or CapeOx are preferred, with FLOX, capecitabine, and 5-FU/LV as additional choices. There are also cases when perioperative chemotherapy is not recommended in metachronous disease. In particular, patients with a history of previous chemotherapy and 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.

Endpoints for Advanced Colorectal Cancer Clinical Trials

In the past few years, there has been much debate over what endpoints are most appropriate for clinical trials in advanced colorectal cancer.[592] Quality of life is an outcome that is rarely measured but is of unquestioned clinical relevance.[593] While OS is also of clear clinical relevance, it is often not used because large numbers of patients and long follow-up periods are required.[593] PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.[593-595] GROUP Español Multidisciplinar en Cancer Digestivo (GEMCAD) recently proposed particular aspects of clinical trial design to be incorporated into trials that use PFS as an endpoint.[596]

A recent study, in which individual patient data from 3 randomized controlled trials were pooled, tested endpoints that take into account

subsequent lines of therapy: duration of disease control, which is the sum of PFS times of each active treatment; and time to failure of strategy, which includes intervals between treatment courses and ends when the planned lines of treatment end (because of death, progression, or administration of a new agent).[594] The authors found a better correlation between these endpoints and OS than between PFS and OS. Another alternative endpoint, time to tumor growth, has also been suggested to predict OS.[597,598] Further evaluation of these and other surrogate endpoints is warranted.

Post-Treatment Surveillance

After curative-intent surgery and adjuvant chemotherapy, if administered, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and identify new metachronous neoplasms at a preinvasive stage. An analysis of data from 20,898 patients enrolled in 18 large, adjuvant colon cancer, randomized trials showed that 80% of recurrences occurred in the first 3 years after surgical resection of the primary tumor,[599] and a recent study found that 95% of recurrences occurred in the first 5 years.[600]

The approach to monitoring and surveillance of patients with rectal cancer is similar to that described for colon cancer.

Surveillance for Locoregional Disease

Advantages of more intensive follow-up of patients after treatment of stage II and/or stage III disease have been demonstrated prospectively in several older studies[601-603] and in multiple meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[604-607] 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.[229] 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.[608]

Results from a recent randomized controlled trial of 1202 patients with resected stage I to III disease showed that intensive surveillance imaging or CEA screening resulted in an increased rate of curative-intent surgical treatment compared with a minimum follow-up group that only received testing if symptoms occurred, but no advantage was seen in the CEA and CT combination arm (2.3% in the minimum follow-up group, 6.7% in the CEA group, 8% in the CT group, and 6.6% in the CEA plus CT group).[609] In this study, no mortality benefit to regular monitoring with CEA, CT, or both was observed compared with minimum follow-up (death rate, 18.2% vs. 15.9%; difference, 2.3%; 95% CI, −2.6%–7.1%). The authors concluded that any strategy of surveillance is unlikely to provide a large survival advantage over a symptom-based approach.[609]

The CEAwatch trial compared usual follow-up care to CEA measurements every two months, with imaging performed if CEA increases were seen twice, in 3223 patients at 11 hospitals treated for non-metastatic colorectal cancer in the Netherlands.[610] The intensive CEA surveillance protocol resulted in the detection of more total recurrences and recurrences that could be treated with curative intent than usual follow-up, and the time to detection of recurrent disease was shorter.

Clearly, controversies remain regarding selection of optimal strategies for following patients after potentially curative colorectal cancer surgery,

and the panel's recommendations are based mainly on consensus. The panel endorses surveillance as a means to identify patients who are potentially curable of metastatic disease with surgical resection.

The following panel recommendations for post-treatment surveillance pertain to patients with stage I through stage III disease who have undergone successful treatment (ie, no known residual disease): history and 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 for T2 or greater lesions.[604,611,612]

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.[613] More frequent colonoscopies may be indicated in patients who present with colorectal cancer before age 50.[613] 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,[614] 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.[613]

Proctoscopy with EUS or MRI is recommended to evaluate the rectal anastomosis for local recurrence only in patients treated with transanal excision. Proctoscopy is not recommended for other patients, because isolated local recurrences are rarely found in these patients and are rarely curable. In fact, in a single-center study of 112 patients who had TME for rectal cancer, only one local recurrence occurred, and it was not identified by rectal surveillance but by CEA and symptoms.[615] In these 112 patients, 20 anoscopies, 44 proctoscopies, and 495 flexible sigmoidoscopies were performed.

Chest, abdominal, and pelvic CT scans are recommended every 3 to 6 months for 2 years and then every 6 to 12 months for up to 5 years.[604,616] 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. A recent analysis of patients with resected or ablated colorectal liver metastases found that the frequency of surveillance imaging did not correlate with time to second procedure or median survival duration.[617] Those scanned once per year survived a median of 54 months versus 43 months for those scanned 3 to 4 times per year (P = .08), suggesting that annual scans may be sufficient in this population.

Routine CEA monitoring and CT scanning are not recommended beyond 5 years. In addition, routine use of PET/CT to monitor for disease recurrence is not recommended.[616,618] The CT that accompanies a PET/CT is usually a noncontrast CT, and therefore is not of ideal quality for routine surveillance.

The ASCO Clinical Practice Guidelines Committee recently endorsed the Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer, from Cancer Care Ontario (CCO).[619,620] These guidelines differ only slightly from the surveillance recommendations in these NCCN Guidelines for Rectal Cancer. While ASCO/CCO recommend abdominal and chest CT annually for 3 years,

the NCCN Panel recommends annual scans for 5 years. The panel bases its recommendation on the fact that approximately 10% of disease recurrences occur after 3 years.[600,621]

Surveillance for Metastatic Disease

Patients who had resection of metastatic colorectal cancer can undergo subsequent curative-intent resection of recurrent disease (*see Surgical Management of Colorectal Metastases*, above). A retrospective analysis of 952 patients who underwent resection at Memorial Sloan Kettering Cancer Center showed that 27% of patients with recurrent disease underwent curative-intent resection and that 25% of those patients (6% of recurrences; 4% of the initial population) were free of disease for ≥36 months.[622]

Panel recommendations for surveillance of patients with stage IV rectal cancer with NED after curative-intent surgery and perioperative treatment are the same as those listed for patients treated for locoregional rectal cancer.

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.

In a recent retrospective chart review at Memorial Sloan Kettering Cancer Center, approximately half of elevations in CEA levels after R0 resection of locoregional colorectal cancer were false positives, with most being single high readings or repeat readings in the range of 5 to 15 ng/mL.[623] In this study, false-positive results >15 ng/mL were rare, and all results >35 ng/mL represented true-positives.

Panel opinion was divided on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans (ie, some panel members favored use of PET/CT in this scenario whereas others noted that the likelihood of PET/CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). A recent systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT in this setting.[624] The pooled estimates of sensitivity and specificity for the detection of tumor recurrence were 94.1% (95% CI, 89.4–97.1%) and 77.2% (95% CI, 66.4–85.9), respectively. Use of PET/CT scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called blind or CEA-directed laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,[625] 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 and high pelvis.[626] Patients with disease recurrence at the anastomotic site are more likely to be cured following re-resection than those with an isolated pelvic recurrence.[627,628]

Potentially resectable isolated pelvic/anastomotic recurrence is optimally managed with resection followed by adjuvant chemoRT or with preoperative RT and concurrent infusional 5-FU. IORT or

brachytherapy should be considered with resection if it can be safely delivered.[342,629-631] 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.[628] Studies of patients who previously received pelvic radiotherapy show that re-irradiation can be effective, with acceptable rates of toxicity.[632-634] 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.[632] 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 prostate cancers); and routine good medical care and monitoring (see the NCCN Guidelines for Survivorship, available at www.NCCN.org). Additional health monitoring should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.

Other recommendations include monitoring for late sequelae of rectal cancer or of the treatment of rectal cancer, such as chronic diarrhea or incontinence (eg, patients with stoma).[635-640] Urogenital dysfunction following resection and/or pelvic irradiation is common.[635,641-643] 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. Other long-term problems common to colorectal cancer survivors include peripheral neuropathy, fatigue, insomnia, cognitive dysfunction, and emotional or social distress.[644-646] Specific management interventions to address side effects of colorectal cancer have been described,[647] and a survivorship care plan for patients with colorectal cancer has recently been published.[648]

Evidence indicates that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy BMI, engaging in regular exercise, and making certain dietary choices are associated with improved outcomes and quality of life after treatment for colorectal cancer. In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, DFS was found to be directly related to how much exercise these patients received.[649] 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 colorectal cancer-specific mortality and overall mortality.[650] More recent data support the conclusion that physical activity improves outcomes. In a cohort of over 2000 survivors of non-metastatic colorectal cancer, those who spent more time in recreational activity had a lower mortality than those who spent more leisure time sitting.[651] In addition, recent evidence suggests that both pre- and post-diagnosis physical activity decreases colorectal cancer mortality. Women enrolled in the Women's Health Initiative study who subsequently developed colorectal cancer had lower colorectal cancer-specific mortality (HR, 0.68; 95% CI, 0.41–1.13) and all-cause mortality (HR, 0.63; 95% CI, 0.42–0.96) if they reported high levels of physical

activity.[652] Similar results were seen in other studies and in recent meta-analyses of prospective studies.[653-655]

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.[656] Recent analyses confirm the increased risk for recurrence and death in obese patients.[657] Data from the ACCENT database also found that pre-diagnosis BMI has a prognostic impact on outcomes in patients with stage II/III colorectal cancer undergoing adjuvant therapy.[658] However, a recent analysis of participants in the Cancer Prevention Study-II Nutrition Cohort who subsequently developed colorectal cancer found that pre-diagnosis obesity but not post-diagnosis obesity was associated with higher all-cause and colorectal cancer-specific mortality.[659]

A diet consisting of more fruits, vegetables, poultry, and fish, less red meat, 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.[660] There is also some evidence that higher postdiagnosis intake of total milk and calcium may be associated with a lower risk of death in patients with stage I, II, or III colorectal cancer.[70] Recent analysis of the CALGB 89803 trial found that higher dietary glycemic load was also associated with an increased risk of recurrence and mortality in patients with stage III disease.[661] Another analysis of the data from CALGB 89803 found an association between high intake of sugar-sweetened beverages and an increased risk of recurrence and death in patients with stage III colon cancer.[662] The link between red and processed meats and mortality in survivors of non-metastatic colorectal cancer has been further supported by recent data from the Cancer Prevention Study II Nutrition Cohort, in which survivors with consistently high intake had a higher risk of colorectal cancer-specific mortality than those with low intake (RR, 1.79; 95% CI, 1.11–2.89).[64]

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 (ACS),[663] also provides “a teachable moment” for the promotion of overall health, and an opportunity to encourage patients to make choices and changes compatible with a healthy lifestyle. In addition, a recent trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of colorectal cancer, suggesting that survivors may be open to health behavior change.[664]

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.[665] 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.

The ACS has also established guidelines for the care of survivors of colorectal cancer, including surveillance for recurrence, screening for subsequent primary malignancies, the management of physical and psychosocial effects of cancer and its treatment, and promotion of healthy lifestyles.[666]

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. Perioperative chemoRT and chemotherapy are preferred for the majority of patients with suspected or proven T3-4 disease and/or regional node involvement.

The recommended post-treatment surveillance program for patients following treatment for rectal cancer includes serial CEA determinations, as well as periodic chest, abdominal, and pelvic CT scans, and periodic evaluation by colonoscopy. Patients with recurrent localized disease should be considered for resection with chemotherapy and radiation. If resection is not possible, then chemotherapy is given with or without radiation.

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. Perioperative chemotherapy and chemoRT are used in the synchronous setting, and perioperative chemotherapy is used in the metachronous setting.

Recommendations for patients with disseminated, unresectable 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. Addition of a biologic agent (ie, bevacizumab, cetuximab, panitumumab) is listed as an option in combination with some of these regimens, depending on available data. Systemic therapy 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.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26742998.

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;34:573-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21217399.

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25559415.

4. Henley SJ, Singh SD, King J, et al. Invasive cancer incidence and survival--United States, 2011. MMWR Morb Mortal Wkly Rep 2015;64:237-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25763875.

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

6. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg 2014:1-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25372703.

7. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed March 1, 2016.

8. 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.

9. 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.

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

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

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

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

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

15. Hennink SD, van der Meulen-de Jong AE, Wolterbeek R, et al. Randomized comparison of surveillance intervals in familial colorectal cancer. J Clin Oncol 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26527788.

16. 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.

17. 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.

18. 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.

19. Beamer LC, Grant ML, Espenschied CR, et al. Reflex immunohistochemistry and microsatellite instability testing of colorectal tumors for Lynch syndrome among US cancer programs and follow-up of abnormal results. J Clin Oncol 2012;30:1058-1063. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22355048.

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

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

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

23. 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.

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

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

26. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2014;109:1159-1179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25070057.

27. Rubenstein JH, Enns R, Heidelbaugh J, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch syndrome. Gastroenterology 2015;149:777-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26226577.

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

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

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

31. Boland CR, Shike M. Report from the Jerusalem workshop on Lynch syndrome-hereditary nonpolyposis colorectal cancer.

Gastroenterology 2010;138:2197 e2191-2197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20416305.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

46. Magalhaes B, Peleteiro B, Lunet N. Dietary patterns and colorectal cancer: systematic review and meta-analysis. Eur J Cancer Prev

2012;21:15-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21946864.

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

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

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

50. Keum N, Greenwood DC, Lee DH, et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. J Natl Cancer Inst 2015;107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25618901.

51. Klatsky AL, Li Y, Nicole Tran H, et al. Alcohol intake, beverage choice, and cancer: a cohort study in a large kaiser permanente population. Perm J 2015;19:28-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25785639.

52. Shen D, Mao W, Liu T, et al. Sedentary behavior and incident cancer: a meta-analysis of prospective studies. PLoS One 2014;9:e105709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25153314.

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

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

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

56. Orlich MJ, Singh PN, Sabate J, et al. Vegetarian dietary patterns and the risk of colorectal cancers. JAMA Intern Med 2015;175:767-776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25751512.

57. Yu XF, Zou J, Dong J. Fish consumption and risk of gastrointestinal cancers: a meta-analysis of cohort studies. World J Gastroenterol 2014;20:15398-15412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25386090.

58. Zhu B, Sun Y, Qi L, et al. Dietary legume consumption reduces risk of colorectal cancer: evidence from a meta-analysis of cohort studies. Sci Rep 2015;5:8797. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25739376.

59. Chan AT, Giovannucci EL, Meyerhardt JA, et al. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA 2005;294:914-923. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16118381.

60. Flossmann E, Rothwell PM, British Doctors Aspirin T, the UKTIAAT. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007;369:1603-1613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17499602.

61. Friis S, Poulsen AH, Sorensen HT, et al. Aspirin and other non-steroidal anti-inflammatory drugs and risk of colorectal cancer: a Danish

cohort study. Cancer Causes Control 2009;20:731-740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19122977.

62. Friis S, Riis AH, Erichsen R, et al. Low-dose aspirin or nonsteroidal anti-inflammatory drug use and colorectal cancer risk: a population-based, case-control study. Ann Intern Med 2015;163:347-355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26302241.

63. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 2010;376:1741-1750. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20970847.

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

65. Phipps AI, Shi Q, Newcomb PA, et al. Associations between cigarette smoking status and colon cancer prognosis among participants in North Central Cancer Treatment Group phase III trial N0147. J Clin Oncol 2013;31:2016-2023. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23547084.

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

67. Yang B, Jacobs EJ, Gapstur SM, et al. Active smoking and mortality among colorectal cancer survivors: the Cancer Prevention Study II nutrition cohort. J Clin Oncol 2015;33:885-893. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25646196.

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

69. Dik VK, Murphy N, Siersema PD, et al. Prediagnostic intake of dairy products and dietary calcium and colorectal cancer survival-results from the EPIC Cohort Study. Cancer Epidemiol Biomarkers Prev 2014;23:1813-1823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24917183.

70. Yang B, McCullough ML, Gapstur SM, et al. Calcium, vitamin D, dairy products, and mortality among colorectal cancer survivors: the Cancer Prevention Study-II nutrition cohort. J Clin Oncol 2014;32:2335-2343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24958826.

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

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

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

74. Sehdev A, Shih YC, Vekhter B, et al. Metformin for primary colorectal cancer prevention in patients with diabetes: a case-control study in a US population. Cancer 2015;121:1071-1078. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25424411.

75. Singh S, Singh H, Singh PP, et al. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2013;22:2258-2268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24042261.

76. Zhang ZJ, Li S. The prognostic value of metformin for cancer patients with concurrent diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2014;16:707-710. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24460896.

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

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

79. Edge S, Byrd D, Compton C, et al., eds. AJCC Cancer Staging Manual (ed 7th Edition). New York: Springer; 2010.

80. 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.

81. 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/.

82. 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.

83. 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.

84. 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.

85. 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.

86. 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.

87. 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.

88. 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.

89. 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.

90. 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.

91. 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.

92. 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.

93. 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.

94. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16132481.

95. 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.

96. 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.

97. 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.

98. 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.

99. 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.

100. 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.

101. 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.

102. 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.

103. 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.

104. 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.

105. Hwang MR, Park JW, Park S, et al. Prognostic impact of circumferential resection margin in rectal cancer treated with preoperative chemoradiotherapy. Ann Surg Oncol 2014;21:1345-1351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24468928.

106. 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.

107. 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.

108. 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.

109. 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.

110. Kidner TB, Ozao-Choy JJ, Yoon J, Bilchik AJ. Should quality measures for lymph node dissection in colon cancer be extrapolated to rectal cancer? Am J Surg 2012;204:843-847; discussion 847-848. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22981183.

111. 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.

112. 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.

113. de Campos-Lobato LF, Stocchi L, de Sousa JB, et al. Less than 12 nodes in the surgical specimen after total mesorectal excision following neoadjuvant chemoradiation: it means more than you think! Ann Surg Oncol 2013;20:3398-3406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23812804.

114. Kim HJ, Jo JS, Lee SY, et al. Low lymph node retrieval after preoperative chemoradiation for rectal cancer is associated with improved prognosis in patients with a good tumor response. Ann Surg Oncol 2015;22:2075-2081. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25395150.

115. 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.

116. 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.

117. 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.

118. 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.

119. 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.

120. 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.

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

122. 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.

123. 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.

124. Ryan R, Gibbons D, Hyland JM, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 2005;47:141-146. Available at:

125. Yang Y, Huang X, Sun J, et al. Prognostic value of perineural invasion in colorectal cancer: a meta-analysis. J Gastrointest Surg 2015;19:1113-1122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25663635.

126. Gopal P, Lu P, Ayers GD, et al. Tumor deposits in rectal adenocarcinoma after neoadjuvant chemoradiation are associated with poor prognosis. Mod Pathol 2014;27:1281-1287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24434897.

127. Zhang LN, Xiao WW, Xi SY, et al. Tumor deposits: markers of poor prognosis in patients with locally advanced rectal cancer following neoadjuvant chemoradiotherapy. Oncotarget 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26695441.

128. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014;2:76-89. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24622671.

129. 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.

130. 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.

131. 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.

132. 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.

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

134. 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.

135. Ng K, Venook AP, Sato K, et al. Vitamin D status and survival of metastatic colorectal cancer patients: results from CALGB/SWOG 80405 (Alliance) [abstract]. ASCO Meeting Abstracts 2015;33:3503. Available at: http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/3503.

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

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

138. 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.

139. Baron JA, Barry EL, Mott LA, et al. A trial of calcium and vitamin D for the prevention of colorectal adenomas. N Engl J Med 2015;373:1519-1530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26465985.

140. 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 March 1, 2016.

141. 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.

142. 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.

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

144. 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.

145. 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.

146. 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.

147. 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.

148. 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.

149. 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.

150. 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.

151. 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.

152. 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.

153. 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.

154. 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.

155. 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.

156. 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.

157. 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.

158. 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.

159. 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.

160. 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.

161. Xie H, Zhou X, Zhuo Z, et al. Effectiveness of MRI for the assessment of mesorectal fascia involvement in patients with rectal cancer: a systematic review and meta-analysis. Dig Surg 2014;31:123-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24942675.

162. Taylor FG, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol 2014;32:34-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24276776.

163. Beets-Tan RG, Lambregts DM, Maas M, et al. Magnetic resonance imaging for the clinical management of rectal cancer patients: recommendations from the 2012 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol 2013;23:2522-2531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23743687.

164. de Jong EA, Ten Berge JC, Dwarkasing RS, et al. The accuracy of MRI, endorectal ultrasonography, and computed tomography in predicting the response of locally advanced rectal cancer after

preoperative therapy: a metaanalysis. Surgery 2016;159:688-699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26619929.

165. Dickman R, Kundel Y, Levy-Drummer R, et al. Restaging locally advanced rectal cancer by different imaging modalities after preoperative chemoradiation: a comparative study. Radiat Oncol 2013;8:278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24286200.

166. Guillem JG, Ruby JA, Leibold T, et al. Neither FDG-PET Nor CT can distinguish between a pathological complete response and an incomplete response after neoadjuvant chemoradiation in locally advanced rectal cancer: a prospective study. Ann Surg 2013;258:289-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23187748.

167. Hanly AM, Ryan EM, Rogers AC, et al. Multicenter Evaluation of Rectal cancer ReImaging pOst Neoadjuvant (MERRION) therapy. Ann Surg 2014;259:723-727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23744576.

168. Kuo LJ, Chiou JF, Tai CJ, et al. Can we predict pathologic complete response before surgery for locally advanced rectal cancer treated with preoperative chemoradiation therapy? Int J Colorectal Dis 2012;27:613-621. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22080392.

169. Memon S, Lynch AC, Bressel M, et al. Systematic review and meta-analysis of the accuracy of MRI and endorectal ultrasound in the restaging and response assessment of rectal cancer following neoadjuvant therapy. Colorectal Dis 2015;17:748-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25891148.

170. Ryan JE, Warrier SK, Lynch AC, Heriot AG. Assessing pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review. Colorectal Dis 2015;17:849-861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26260213.

171. van der Paardt MP, Zagers MB, Beets-Tan RG, et al. Patients who undergo preoperative chemoradiotherapy for locally advanced rectal cancer restaged by using diagnostic MR imaging: a systematic review and meta-analysis. Radiology 2013;269:101-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23801777.

172. Zhao RS, Wang H, Zhou ZY, et al. Restaging of locally advanced rectal cancer with magnetic resonance imaging and endoluminal ultrasound after preoperative chemoradiotherapy: a systemic review and meta-analysis. Dis Colon Rectum 2014;57:388-395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24509465.

173. Hotker AM, Garcia-Aguilar J, Gollub MJ. Multiparametric MRI of rectal cancer in the assessment of response to therapy: a systematic review. Dis Colon Rectum 2014;57:790-799. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24807605.

174. 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.

175. 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.

176. 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.

177. Clancy C, Burke JP, Albert MR, et al. Transanal endoscopic microsurgery versus standard transanal excision for the removal of rectal neoplasms: a systematic review and meta-analysis. Dis Colon Rectum 2015;58:254-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25585086.

178. 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.

179. 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.

180. 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.

181. Garcia-Aguilar J, Renfro LA, Chow OS, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol 2015;16:1537-1546. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26474521.

182. 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.

183. Kidane B, Chadi SA, Kanters S, et al. Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: a systematic review and meta-analysis. Dis Colon Rectum 2015;58:122-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25489704.

184. 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.

185. Stitzenberg KB, Sanoff HK, Penn DC, et al. Practice patterns and long-term survival for early-stage rectal cancer. J Clin Oncol 2013;31:4276-4282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24166526.

186. Sajid MS, Farag S, Leung P, et al. Systematic review and meta-analysis of published trials comparing the effectiveness of transanal endoscopic microsurgery and radical resection in the management of early rectal cancer. Colorectal Dis 2014;16:2-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24330432.

187. Lu JY, Lin GL, Qiu HZ, et al. Comparison of transanal endoscopic microsurgery and total mesorectal excision in the treatment of T1 rectal cancer: a meta-analysis. PLoS One 2015;10:e0141427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26505895.

188. 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.

189. 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.

190. Schlag PM. Surgical sphincter preservation in rectal cancer. Oncologist 1996;1:288-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10388006.

191. 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.

192. Russell MM, Ganz PA, Lopa S, et al. Comparative effectiveness of sphincter-sparing surgery versus abdominoperineal resection in rectal cancer: patient-reported outcomes in National Surgical Adjuvant Breast

and Bowel Project randomized trial R-04. Ann Surg 2015;261:144-148. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24670844.

193. Huang A, Zhao H, Ling T, et al. Oncological superiority of extralevator abdominoperineal resection over conventional abdominoperineal resection: a meta-analysis. Int J Colorectal Dis 2014;29:321-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24385025.

194. 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.

195. 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.

196. 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.

197. 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.

198. Digennaro R, Tondo M, Cuccia F, et al. Coloanal anastomosis or abdominoperineal resection for very low rectal cancer: what will benefit, the surgeon's pride or the patient's quality of life? Int J Colorectal Dis 2013;28:949-957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23274737.

199. Pachler J, Wille-Jorgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. Cochrane Database Syst Rev 2012;12:CD004323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23235607.

200. Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 2015;372:1324-1332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25830422.

201. Jeong SY, Park JW, Nam BH, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. Lancet Oncol 2014;15:767-774. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24837215.

202. Fleshman J, Branda M, Sargent DJ, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. JAMA 2015;314:1346-1355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26441179.

203. Stevenson AR, Solomon MJ, Lumley JW, et al. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. JAMA 2015;314:1356-1363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26441180.

204. 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 2013;27:295-302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22736289.

205. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210-218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23395398.

206. 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.

207. 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.

208. 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.

209. 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.

210. Ahmad NZ, Racheva G, Elmusharaf H. A systematic review and meta-analysis of randomized and non-randomized studies comparing laparoscopic and open abdominoperineal resection for rectal cancer. Colorectal Dis 2013;15:269-277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22958456.

211. 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.

212. Arezzo A, Passera R, Scozzari G, et al. Laparoscopy for rectal cancer reduces short-term mortality and morbidity: results of a systematic review and meta-analysis. Surg Endosc 2013;27:1485-1502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23183871.

213. 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.

214. 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.

215. 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.

216. Jiang JB, Jiang K, Dai Y, et al. Laparoscopic versus open surgery for mid-low rectal cancer: a systematic review and meta-analysis on short- and long-term outcomes. J Gastrointest Surg 2015;19:1497-1512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26040854.

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

218. Ng SS, Lee JF, Yiu RY, et al. Long-term oncologic outcomes of laparoscopic versus open surgery for rectal cancer: a pooled analysis of 3 randomized controlled trials. Ann Surg 2014;259:139-147. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23598381.

219. 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.

220. Vennix S, Pelzers L, Bouvy N, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst

Rev 2014;4:CD005200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24737031.

221. 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;22:674-684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22881123.

222. Zhang FW, Zhou ZY, Wang HL, et al. Laparoscopic versus open surgery for rectal cancer: a systematic review and meta-analysis of randomized controlled trials. Asian Pac J Cancer Prev 2014;15:9985-9996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25520140.

223. Zhao D, Li Y, Wang S, Huang Z. Laparoscopic versus open surgery for rectal cancer: a meta-analysis of 3-year follow-up outcomes. Int J Colorectal Dis 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26847617.

224. Nussbaum DP, Speicher PJ, Ganapathi AM, et al. Laparoscopic versus open low anterior resection for rectal cancer: results from the National Cancer Data Base. J Gastrointest Surg 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25091847.

225. Miskovic D, Foster J, Agha A, et al. Standardization of laparoscopic total mesorectal excision for rectal cancer: a structured international expert consensus. Ann Surg 2015;261:716-722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25072446.

226. 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.

227. Rahbari NN, Elbers H, Askoxylakis V, et al. Neoadjuvant radiotherapy for rectal cancer: meta-analysis of randomized controlled trials. Ann Surg Oncol 2013;20:4169-4182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24002536.

228. 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.

229. 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.

230. 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.

231. 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.

232. 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.

233. 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.

234. Peng LC, Milsom J, Garrett K, et al. Surveillance, epidemiology, and end results-based analysis of the impact of preoperative or postoperative radiotherapy on survival outcomes for T3N0 rectal

cancer. Cancer Epidemiol 2014;38:73-78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24491755.

235. 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.

236. 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.

237. 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.

238. 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.

239. 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.

240. 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.

241. 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.

242. 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.

243. 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.

244. 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.

245. McCarthy K, Pearson K, Fulton R, Hewitt J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. Cochrane Database Syst Rev 2012;12:CD008368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23235660.

246. De Caluwe L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev 2013;2:CD006041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23450565.

247. 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.

248. O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel

Project trial R-04. J Clin Oncol 2014;32:1927-1934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24799484.

249. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: a phase III randomized clinical trial. J Natl Cancer Inst 2015;107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26374429.

250. 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.

251. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30:4558-4565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23109696.

252. Rodel C, Graeven U, Fietkau R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2015;16:979-989. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26189067.

253. 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;13:679-687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22627104.

254. Glynne-Jones R. Rectal cancer--the times they are a-changing. Lancet Oncol 2012;13:651-653. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22627103.

255. 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.

256. Eisterer W, De Vries A, Ofner D, et al. Preoperative treatment with capecitabine, cetuximab and radiotherapy for primary locally advanced rectal cancer--a phase II clinical trial. Anticancer Res 2014;34:6767-6773. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25368289.

257. Kripp M, Horisberger K, Mai S, et al. Does the addition of cetuximab to radiochemotherapy improve outcome of patients with locally advanced rectal cancer? Long-term results from phase II trials. Gastroenterol Res Pract 2015;2015:273489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25861256.

258. Helbling D, Bodoky G, Gautschi O, et al. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicenter, phase II trial SAKK 41/07. Ann Oncol 2013;24:718-725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23139259.

259. Landry JC, Feng Y, Prabhu RS, et al. Phase II trial of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: 5-year clinical outcomes ECOG-ACRIN Cancer Research Group E3204. Oncologist 2015;20:615-616. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25926352.

260. 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.

261. 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.

262. 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.

263. Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24717570.

264. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol 2006;24:668-674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16446339.

265. Fernandez-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20065174.

266. Perez K, Safran H, Sikov W, et al. Complete neoadjuvant treatment for rectal cancer: The Brown University Oncology Group CONTRE study. Am J Clin Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25374145.

267. 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.

268. 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.

269. Fernandez-Martos C, Garcia-Albeniz X, Pericay C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trialdagger. Ann Oncol 2015;26:1722-1728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25957330.

270. Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 2014;32:513-518. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24419115.

271. 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.

272. 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.

273. 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.

274. 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.

275. Sloothaak DA, Geijsen DE, van Leersum NJ, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 2013;100:933-939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23536485.

276. 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.

277. Probst CP, Becerra AZ, Aquina CT, et al. Extended intervals after neoadjuvant therapy in locally advanced rectal cancer: the key to improved tumor response and potential organ preservation. J Am Coll Surg 2015;221:430-440. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26206642.

278. Huntington CR, Boselli D, Symanowski J, et al. Optimal timing of surgical resection after radiation in locally advanced rectal adenocarcinoma: an analysis of the National Cancer Database. Ann Surg Oncol 2016;23:877-887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26514119.

279. Sun Z, Adam MA, Kim J, et al. Optimal timing to surgery after neoadjuvant chemoradiotherapy for locally advanced rectal cancer. J Am Coll Surg 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26897480.

280. 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.

281. 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.

282. 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.

283. 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.

284. 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.

285. 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.

286. 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.

287. 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.

288. 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.

289. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23008301.

290. Latkauskas T, Pauzas H, Gineikiene I, et al. Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or long-term chemoradiotherapy, both with delayed surgery. Colorectal Dis 2012;14:294-298. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21899712.

291. Bujko K, Partycki M, Pietrzak L. Neoadjuvant radiotherapy (5 x 5 Gy): immediate versus delayed surgery. Recent Results Cancer Res 2014;203:171-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25103005.

292. 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.

293. 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.

294. 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.

295. 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.

296. 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.

297. 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.

298. 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.

299. 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.

300. Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol 2014;32:1554-1562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24752056.

301. 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.

302. 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.

303. 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.

304. 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.

305. Appelt AL, Ploen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 2015;16:919-927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26156652.

306. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 2014;88:822-828. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24495589.

307. Li J, Liu H, Yin J, et al. Wait-and-see or radical surgery for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy: a cohort study. Oncotarget 2015;6:42354-42361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26472284.

308. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 2016;17:174-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26705854.

309. 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.

310. Tranchart H, Lefevre JH, Svrcek M, et al. What is the incidence of metastatic lymph node involvement after significant pathologic response of primary tumor following neoadjuvant treatment for locally advanced rectal cancer? Ann Surg Oncol 2013;20:1551-1559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23188545.

311. 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.

312. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol

2014;15:184-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24440473.

313. Sainato A, Cernusco Luna Nunzia V, Valentini V, et al. No benefit of adjuvant fluorouracil leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): long term results of a randomized trial (I-CNR-RT). Radiother Oncol 2014;113:223-229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25454175.

314. Breugom AJ, van Gijn W, Muller EW, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol 2015;26:696-701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25480874.

315. 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.

316. Hong YS, Nam BH, Kim KP, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol 2014;15:1245-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25201358.

317. Garcia-Albeniz X, Gallego R, Hofheinz RD, et al. Adjuvant therapy sparing in rectal cancer achieving complete response after chemoradiation. World J Gastroenterol 2014;20:15820-15829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25400468.

318. Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16:200-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25589192.

319. Petersen SH, Harling H, Kirkeby LT, et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev 2012;3:CD004078. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22419291.

320. Petrelli F, Coinu A, Lonati V, Barni S. A systematic review and meta-analysis of adjuvant chemotherapy after neoadjuvant treatment and surgery for rectal cancer. Int J Colorectal Dis 2015;30:447-457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25433820.

321. Khrizman P, Niland JC, ter Veer A, et al. Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with neoadjuvant therapy: a national comprehensive cancer network analysis. J Clin Oncol 2013;31:30-38. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23169502.

322. Haynes AB, You YN, Hu CY, et al. Postoperative chemotherapy use after neoadjuvant chemoradiotherapy for rectal cancer: Analysis of Surveillance, Epidemiology, and End Results-Medicare data, 1998-2007. Cancer 2014;120:1162-1170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24474245.

323. 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.

324. 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.

325. 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.

326. 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.

327. 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.

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

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

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

331. Venook AP, Niedzwiecki D, Lopatin M, et al. Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581. J Clin Oncol 2013;31:1775-1781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23530100.

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

333. Reimers MS, Kuppen PJ, Lee M, et al. Validation of the 12-gene colon cancer recurrence score as a predictor of recurrence risk in stage II and III rectal cancer patients. J Natl Cancer Inst 2014;106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25261968.

334. 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.

335. 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.

336. 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.

337. 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.

338. 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.

339. 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.

340. Alberda WJ, Verhoef C, Nuyttens JJ, et al. Intraoperative radiation therapy reduces local recurrence rates in patients with microscopically involved circumferential resection margins after resection of locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2014;88:1032-1040. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24661656.

341. Hahnloser D, Haddock MG, Nelson H. Intraoperative radiotherapy in the multimodality approach to colorectal cancer. Surg Oncol Clin N Am 2003;12:993-1013, ix. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14989129.

342. Hyngstrom JR, Tzeng CW, Beddar S, et al. Intraoperative radiation therapy for locally advanced primary and recurrent colorectal cancer: ten-year institutional experience. J Surg Oncol 2014;109:652-658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24510523.

343. 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.

344. 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.

345. 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.

346. 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.

347. 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.

348. 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.

349. 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.

350. 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.

351. 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.

352. 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.

353. 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.

354. 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.

355. 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.

356. 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.

357. 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.

358. 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.

359. 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.

360. 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.

361. 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.

362. Van Cutsem E, Cervantes A, Nordlinger B, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii1-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25190710.

363. 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.

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

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

366. 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.

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

368. 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.

369. Gonzalez M, Poncet A, Combescure C, et al. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol 2013;20:572-579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23104709.

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

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

372. Headrick JR, Miller DL, Nagorney DM, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. Ann Thorac Surg 2001;71:975-979; discussion 979-980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11269484.

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

374. 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.

375. 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.

376. 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.

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

378. 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.

379. 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.

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

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

382. Luo LX, Yu ZY, Huang JW, Wu H. Selecting patients for a second hepatectomy for colorectal metastases: An systemic review and meta-analysis. Eur J Surg Oncol 2014;40:1036-1048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24915859.

383. 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.

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

385. 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.

386. Gillams A, Goldberg N, Ahmed M, et al. Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, the interventional oncology sans frontieres meeting 2013. Eur Radiol 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25994193.

387. Shady W, Petre EN, Gonen M, et al. Percutaneous radiofrequency ablation of colorectal cancer liver metastases: factors affecting outcomes-a 10-year experience at a single center. Radiology 2015:142489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26267832.

388. Solbiati L, Ahmed M, Cova L, et al. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. Radiology 2012;265:958-968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23091175.

389. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol 2009;27:1585-1591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255313.

390. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27:1572-1578. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255321.

391. 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.

392. Johnston FM, Mavros MN, Herman JM, Pawlik TM. Local therapies for hepatic metastases. J Natl Compr Canc Netw 2013;11:153-160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23411382.

393. Park J, Chen YJ, Lu WP, Fong Y. The evolution of liver-directed treatments for hepatic colorectal metastases. Oncology (Williston Park) 2014;28:991-1003. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25403632.

394. 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.

395. 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.

396. 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.

397. Richardson AJ, Laurence JM, Lam VW. Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review. J Vasc Interv Radiol 2013;24:1209-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23885916.

398. Martin RC, 2nd, Scoggins CR, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26149602.

399. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33:41-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19908093.

400. Martin RC, Howard J, Tomalty D, et al. Toxicity of irinotecan-eluting beads in the treatment of hepatic malignancies: results of a multi-institutional registry. Cardiovasc Intervent Radiol 2010;33:960-966. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20661569.

401. Pawlik TM, Reyes DK, Cosgrove D, et al. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. J Clin Oncol 2011;29:3960-3967. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21911714.

402. Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. Cancer J 2009;15:526-532. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20010173.

403. van Malenstein H, Maleux G, Vandecaveye V, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie 2011;34:368-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21734423.

404. Vogl TJ, Lammer J, Lencioni R, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. AJR Am J Roentgenol 2011;197:W562-570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21940527.

405. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Transarterial (chemo)embolisation versus no intervention or placebo intervention for liver metastases. Cochrane Database Syst Rev 2013;4:CD009498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23633373.

406. 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.

407. 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.

408. 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.

409. 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.

410. Lewandowski RJ, Memon K, Mulcahy MF, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. Eur J Nucl Med Mol Imaging 2014;41:1861-1869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24906565.

411. 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.

412. 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.

413. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol 2012;35:1066-1073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21800231.

414. Sofocleous CT, Garcia AR, Pandit-Taskar N, et al. Phase I trial of selective internal radiation therapy for chemorefractory colorectal cancer liver metastases progressing after hepatic arterial pump and systemic chemotherapy. Clin Colorectal Cancer 2014;13:27-36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24370352.

415. Sofocleous CT, Violari EG, Sotirchos VS, et al. Radioembolization as a salvage therapy for heavily pretreated patients with colorectal cancer liver metastases: factors that affect outcomes. Clin Colorectal Cancer 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26277696.

416. 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.

417. 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.

418. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer 2011;117:4060-4069. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21432842.

419. ACR –ASTRO Practice Parameter for Intensity Modulated Radiation Therapy (IMRT). The American College of Radiology; 2014. Available at: http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/IMRT.pdf . Accessed March 1, 2016.

420. 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.

421. 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.

422. Topkan E, Onal HC, Yavuz MN. Managing liver metastases with conformal radiation therapy. J Support Oncol 2008;6:9-13, 15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18257395.

423. 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.

424. Benson AB, 3rd, Geschwind JF, Mulcahy MF, et al. Radioembolisation for liver metastases: results from a prospective 151

patient multi-institutional phase II study. Eur J Cancer 2013;49:3122-3130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23777743.

425. Kennedy AS, Ball D, Cohen SJ, et al. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for (90)Y resin microspheres. J Gastrointest Oncol 2015;6:134-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25830033.

426. Saxena A, Meteling B, Kapoor J, et al. Is yttrium-90 radioembolization a viable treatment option for unresectable, chemorefractory colorectal cancer liver metastases? A large single-center experience of 302 patients. Ann Surg Oncol 2015;22:794-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25323474.

427. Gibbs P, Heinemann V, Sharma NK, et al. SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 {+/-} bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) {+/-} bev in patients (pts) with metastatic colorectal cancer (mCRC) [abstract]. ASCO Meeting Abstracts 2015;33:3502. Available at: http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/3502.

428. Rosenbaum CE, Verkooijen HM, Lam MG, et al. Radioembolization for treatment of salvage patients with colorectal cancer liver metastases: a systematic review. J Nucl Med 2013;54:1890-1895. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24071510.

429. Saxena A, Bester L, Shan L, et al. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. J Cancer Res Clin Oncol 2014;140:537-547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24318568.

430. Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. Cochrane Database Syst Rev 2009:CD007045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19821394.

431. 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.

432. Wang X, Sofocleous CT, Erinjeri JP, et al. Margin size is an independent predictor of local tumor progression after ablation of colon cancer liver metastases. Cardiovasc Intervent Radiol 2013;36:166-175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22535243.

433. Elias D, De Baere T, Smayra T, et al. Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy. Br J Surg 2002;89:752-756. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12027986.

434. Sofocleous CT, Petre EN, Gonen M, et al. CT-guided radiofrequency ablation as a salvage treatment of colorectal cancer hepatic metastases developing after hepatectomy. J Vasc Interv Radiol 2011;22:755-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21514841.

435. Bala MM, Riemsma RP, Wolff R, Kleijnen J. Microwave coagulation for liver metastases. Cochrane Database Syst Rev 2013;10:CD010163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24122576.

436. Bala MM, Riemsma RP, Wolff R, Kleijnen J. Cryotherapy for liver metastases. Cochrane Database Syst Rev 2013;6:CD009058. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23740609.

437. 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.

438. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Percutaneous ethanol injection for liver metastases. Cochrane Database Syst Rev

2013;5:CD008717. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23728679.

439. Riemsma RP, Bala MM, Wolff R, Kleijnen J. Electro-coagulation for liver metastases. Cochrane Database Syst Rev 2013;5:CD009497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23728692.

440. Weng M, Zhang Y, Zhou D, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. PLoS One 2012;7:e45493. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23029051.

441. 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.

442. Gillams A, Khan Z, Osborn P, Lees W. Survival after radiofrequency ablation in 122 patients with inoperable colorectal lung metastases. Cardiovasc Intervent Radiol 2013;36:724-730. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23070108.

443. 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.

444. 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.

445. 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.

446. Bai H, Huangz X, Jing L, et al. The effect of radiofrequency ablation vs. liver resection on survival outcome of colorectal liver metastases (CRLM): a meta-analysis. Hepatogastroenterology 2015;62:373-377. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25916066.

447. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 2012;23:2619-2626. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22431703.

448. 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.

449. Klaver YL, Leenders BJ, Creemers GJ, et al. Addition of biological therapies to palliative chemotherapy prolongs survival in patients with peritoneal carcinomatosis of colorectal origin. Am J Clin Oncol 2013;36:157-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22314003.

450. Cennamo V, Fuccio L, Mutri V, et al. Does stent placement for advanced colon cancer increase the risk of perforation during bevacizumab-based therapy? Clin Gastroenterol Hepatol 2009;7:1174-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19631290.

451. Small AJ, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. Gastrointest Endosc 2010;71:560-572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20189515.

452. 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.

453. 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.

454. 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.

455. Goere D, Malka D, Tzanis D, et al. Is there a possibility of a cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? Ann Surg 2013;257:1065-1071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23299520.

456. Haslinger M, Francescutti V, Attwood K, et al. A contemporary analysis of morbidity and outcomes in cytoreduction/hyperthermic intraperitoneal chemoperfusion. Cancer Med 2013;2:334-342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23930210.

457. 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.

458. Tabrizian P, Shrager B, Jibara G, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: outcomes from a single tertiary institution. J Gastrointest Surg 2014;18:1024-1031. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24577736.

459. 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.

460. 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.

461. 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.

462. 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.

463. 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.

464. 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.

465. Shaib WL, Martin LK, Choi M, et al. Hyperthermic intraperitoneal chemotherapy following cytoreductive surgery improves outcome in

patients with primary appendiceal mucinous adenocarcinoma: a pooled analysis from three tertiary care centers. Oncologist 2015;20:907-914. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26070916.

466. 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.

467. Faris JE, Ryan DP. Controversy and consensus on the management of patients with pseudomyxoma peritonei. Curr Treat Options Oncol 2013;14:365-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23934509.

468. 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.

469. van Oudheusden TR, Nienhuijs SW, Luyer MD, et al. Incidence and treatment of recurrent disease after cytoreductive surgery and intraperitoneal chemotherapy for peritoneally metastasized colorectal cancer: A systematic review. Eur J Surg Oncol 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26175345.

470. Esquivel J. Colorectal cancer with peritoneal metastases: a plea for cooperation between medical and surgical oncologists. Oncology (Williston Park) 2015;29:521-522. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26178340.

471. Loggie BW, Thomas P. Gastrointestinal cancers with peritoneal carcinomatosis: surgery and hyperthermic intraperitoneal chemotherapy. Oncology (Williston Park) 2015;29:515-521. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26178339.

472. McRee AJ, O'Neil BH. The role of HIPEC in gastrointestinal malignancies: controversies and conclusions. Oncology (Williston Park) 2015;29:523-524, C523. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26178341.

473. O'Dwyer S, Verwaal VJ, Sugarbaker PH. Evolution of treatments for peritoneal metastases from colorectal cancer. J Clin Oncol 2015;33:2122-2123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25897165.

474. 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.

475. 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.

476. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol 2004;15:933-939. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15151951.

477. 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.

478. 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.

479. 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.

480. 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.

481. 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.

482. 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.

483. 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.

484. 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.

485. 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.

486. 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.

487. 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.

488. 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.

489. 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.

490. Tan BR, Zubal B, Hawkins W, et al. Preoperative FOLFOX plus cetuximab or panitumumab therapy for patients with potentially resectable hepatic colorectal metastases [abstract]. Gastrointestinal Cancers Symposium 2009:497. Available at: http://meetinglibrary.asco.org/content/10593-63.

491. Ye LC, Liu TS, Ren L, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J Clin Oncol 2013;31:1931-1938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23569301.

492. 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.

493. 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.

494. 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.

495. 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.

496. 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.

497. 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.

498. 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.

499. Wang ZM, Chen YY, Chen FF, et al. Peri-operative chemotherapy for patients with resectable colorectal hepatic metastasis: A meta-analysis. Eur J Surg Oncol 2015;41:1197-1203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26094113.

500. 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.

501. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-1215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24120480.

502. Araujo R, Gonen M, Allen P, et al. Comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic colorectal cancer. Ann Surg Oncol 2013;20:4312-4321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23897009.

503. Bilchik AJ, Poston G, Adam R, Choti MA. Prognostic variables for resection of colorectal cancer hepatic metastases: an evolving paradigm. J Clin Oncol 2008;26:5320-5321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18936470.

504. 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.

505. 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.

506. 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.

507. 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.

508. Package Insert. AVASTIN® (bevacizumab). Genentech, Inc.; 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125085s312lbl.pdf. Accessed March 1, 2016.

509. 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.

510. 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.

511. 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.

512. 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.

513. Antonacopoulou AG, Tsamandas AC, Petsas T, et al. EGFR, HER-2 and COX-2 levels in colorectal cancer. Histopathology 2008;53:698-706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19102009.

514. McKay JA, Murray LJ, Curran S, et al. Evaluation of the epidermal growth factor receptor (EGFR) in colorectal tumours and lymph node metastases. Eur J Cancer 2002;38:2258-2264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12441262.

515. Spano JP, Lagorce C, Atlan D, et al. Impact of EGFR expression on colorectal cancer patient prognosis and survival. Ann Oncol 2005;16:102-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15598946.

516. Yen LC, Uen YH, Wu DC, et al. Activating KRAS mutations and overexpression of epidermal growth factor receptor as independent predictors in metastatic colorectal cancer patients treated with cetuximab. Ann Surg 2010;251:254-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20010090.

517. 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.

518. 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.

519. 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.

520. 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.

521. 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.

522. 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.

523. 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.

524. 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.

525. 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.

526. 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.

527. 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.

528. 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.

529. 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.

530. 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.

531. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-1034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24024839.

532. Sorich MJ, Wiese MD, Rowland A, et al. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25115304.

533. 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.

534. 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.

535. 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.

536. Monzon FA, Ogino S, Hammond MEH, et al. The role of KRAS mutation testing in the management of patients with metastatic colorectal cancer. Arch Pathol Lab Med 2009;133:1600-1606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19792050.

537. 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.

538. Package Insert. Vectibix® (Panitumumab). Thousand Oaks, CA: Amgen Inc.; 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125147s200lbl.pdf. Accessed October 17, 2015.

539. Package Insert. Cetuximab (Erbitux®). Branchburg, NJ: ImClone Systems Incorporated; 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125084s262lbl.pdf. Accessed October 7, 2015.

540. Yoon HH, Tougeron D, Shi Q, et al. KRAS codon 12 and 13 mutations in relation to disease-free survival in BRAF-wild-type stage III colon cancers from an adjuvant chemotherapy trial (N0147 alliance). Clin Cancer Res 2014;20:3033-3043. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24687927.

541. 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.

542. Tejpar S, Celik I, Schlichting M, et al. Association of KRAS G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetuximab. J Clin Oncol 2012;30:3570-3577. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22734028.

543. Peeters M, Douillard JY, Van Cutsem E, et al. Mutant KRAS codon 12 and 13 alleles in patients with metastatic colorectal cancer: assessment as prognostic and predictive biomarkers of response to panitumumab. J Clin Oncol 2013;31:759-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23182985.

544. Schirripa M, Loupakis F, Lonardi S, et al. Phase II study of single-agent cetuximab in KRAS G13D mutant metastatic colorectal cancer. Ann Oncol 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26371285.

545. Segelov E. The AGITG ICECREAM Study: The Irinotecan Cetuximab Evaluation and Cetuximab Response Evaluation Amongst Patients with a G13D Mutation- analysis of outcomes in patients with refractory metastatic colorectal cancer harbouring the KRAS G13D mutation [abstract]. ESMO European Cancer Congress 2015:32LBA. Available at: http://www.eccocongress.org/Vienna2015/Scientific-Programme/Abstract-search?abstractid=22955.

546. Price TJ, Bruhn MA, Lee CK, et al. Correlation of extended RAS and PIK3CA gene mutation status with outcomes from the phase III AGITG MAX STUDY involving capecitabine alone or in combination with bevacizumab plus or minus mitomycin C in advanced colorectal cancer. Br J Cancer 2015;112:963-970. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25742472.

547. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1065-1075. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25088940.

548. 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.

549. 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.

550. 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.

551. 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.

552. 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.

553. 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.

554. 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.

555. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29:2011-2019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21502544.

556. 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.

557. 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.

558. 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.

559. 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.

560. Seymour MT, Brown SR, Middleton G, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol 2013;14:749-759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23725851.

561. Pietrantonio F, Petrelli F, Coinu A, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. Eur J Cancer 2015;51:587-594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25673558.

562. Rowland A, Dias MM, Wiese MD, et al. Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. Br J Cancer 2015;112:1888-1894. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25989278.

563. Chen D, Huang JF, Liu K, et al. BRAFV600E mutation and its association with clinicopathological features of colorectal cancer: a systematic review and meta-analysis. PLoS One 2014;9:e90607. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24594804.

564. Price TJ, Hardingham JE, Lee CK, et al. Impact of KRAS and BRAF gene mutation status on outcomes from the phase III AGITG MAX trial of capecitabine alone or in combination with bevacizumab and mitomycin in advanced colorectal cancer. J Clin Oncol 2011;29:2675-2682. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21646616.

565. 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.

566. 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.

567. Clancy C, Burke JP, Kalady MF, Coffey JC. BRAF mutation is associated with distinct clinicopathological characteristics in colorectal cancer: a systematic review and meta-analysis. Colorectal Dis 2013;15:e711-718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24112392.

568. 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.

569. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol 2014;15:601-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24717919.

570. 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.

571. 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.

572. 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.

573. Lykoudis PM, O'Reilly D, Nastos K, Fusai G. Systematic review of surgical management of synchronous colorectal liver metastases. Br J Surg 2014;101:605-612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24652674.

574. Mayo SC, Pulitano C, Marques H, et al. Surgical management of patients with synchronous colorectal liver metastasis: a multicenter international analysis. J Am Coll Surg 2013;216:707-716; discussion 716-708. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23433970.

575. Slesser AA, Simillis C, Goldin R, et al. A meta-analysis comparing simultaneous versus delayed resections in patients with synchronous colorectal liver metastases. Surg Oncol 2013;22:36-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23253399.

576. Worni M, Mantyh CR, Akushevich I, et al. Is there a role for simultaneous hepatic and colorectal resections? A contemporary view

from NSQIP. J Gastrointest Surg 2012;16:2074-2085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22972010.

577. 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.

578. De Rosa A, Gomez D, Brooks A, Cameron IC. "Liver-first" approach for synchronous colorectal liver metastases: is this a justifiable approach? J Hepatobiliary Pancreat Sci 2013;20:263-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23325126.

579. Jegatheeswaran S, Mason JM, Hancock HC, Siriwardena AK. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. JAMA Surg 2013;148:385-391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23715907.

580. Lam VW, Laurence JM, Pang T, et al. A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. HPB (Oxford) 2014;16:101-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23509899.

581. 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.

582. Faron M, Pignon JP, Malka D, et al. Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials. Eur J Cancer 2015;51:166-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25465185.

583. 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.

584. 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.

585. McCahill LE, Yothers G, Sharif S, et al. Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10. J Clin Oncol 2012;30:3223-3228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22869888.

586. Cirocchi R, Trastulli S, Abraha I, et al. Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable Stage IV colorectal cancer. Cochrane Database Syst Rev 2012;8:CD008997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22895981.

587. Anwar S, Peter MB, Dent J, Scott NA. Palliative excisional surgery for primary colorectal cancer in patients with incurable metastatic disease. Is there a survival benefit? A systematic review. Colorectal Dis 2012;14:920-930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21899714.

588. Yang TX, Billah B, Morris DL, Chua TC. Palliative resection of the primary tumour in patients with Stage IV colorectal cancer: systematic review and meta-analysis of the early outcome after laparoscopic and open colectomy. Colorectal Dis 2013;15:e407-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23895669.

589. 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.

590. 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.

591. Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA 2014;311:1863-1869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24825641.

592. 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.

593. 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.

594. 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.

595. Shi Q, de Gramont A, Grothey A, et al. Individual patient data analysis of progression-free survival versus overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: findings from the analysis and research in cancers of the digestive system database. J Clin Oncol 2015;33:22-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25385741.

596. 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.

597. Claret L, Gupta M, Han K, et al. Evaluation of tumor-size response metrics to predict overall survival in Western and Chinese patients with first-line metastatic colorectal cancer. J Clin Oncol 2013;31:2110-2114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23650411.

598. Sharma MR, Gray E, Goldberg RM, et al. Resampling the N9741 trial to compare tumor dynamic versus conventional end points in randomized phase II trials. J Clin Oncol 2015;33:36-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25349295.

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

600. Seo SI, Lim SB, Yoon YS, et al. Comparison of recurrence patterns between ≤5 years and >5 years after curative operations in colorectal cancer patients. J Surg Oncol 2013;108:9-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23754582.

601. 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.

602. 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.

603. 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.

604. 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.

605. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2007:CD002200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17253476.

606. 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.

607. Pita-Fernandez S, Alhayek-Ai M, Gonzalez-Martin C, et al. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. Ann Oncol 2015;26:644-656. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25411419.

608. 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.

609. Primrose JN, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled cea and ct follow-up to detect recurrence of colorectal cancer: The facs randomized clinical trial. JAMA 2014;311:263-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24430319.

610. Verberne CJ, Zhan Z, van den Heuvel E, et al. Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: results of the randomized "CEAwatch" trial. Eur J Surg Oncol 2015;41:1188-1196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26184850.

611. 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.

612. Macdonald JS. Carcinoembryonic antigen screening: pros and cons. Semin Oncol 1999;26:556-560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10528904.

613. 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.

614. 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.

615. Martin LA, Gross ME, Mone MC, et al. Routine endoscopic surveillance for local recurrence of rectal cancer is futile. Am J Surg 2015;210:996-1002. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26453291.

616. 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.

617. Hyder O, Dodson RM, Mayo SC, et al. Post-treatment surveillance of patients with colorectal cancer with surgically treated liver metastases. Surgery 2013;154:256-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23889953.

618. Patel K, Hadar N, Lee J, et al. The lack of evidence for PET or PET/CT surveillance of patients with treated lymphoma, colorectal cancer, and head and neck cancer: a systematic review. J Nucl Med

2013;54:1518-1527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23776200.

619. Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer. Cancer Care Ontario; 2012. Available at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=124839. Accessed March 1, 2016.

620. Meyerhardt JA, Mangu PB, Flynn PJ, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: american society of clinical oncology clinical practice guideline endorsement. J Clin Oncol 2013;31:4465-4470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24220554.

621. 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.

622. Butte JM, Gonen M, Allen PJ, et al. Recurrence after partial hepatectomy for metastatic colorectal cancer: potentially curative role of salvage repeat resection. Ann Surg Oncol 2015;22:2761-2771. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25572686.

623. Litvka A, Cercek A, Segal N, et al. False-positive elevations of carcinoembryonic antigen in patients with a history of resected colorectal cancer. J Natl Compr Canc Netw 2014;12:907-913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24925201.

624. Lu YY, Chen JH, Chien CR, et al. Use of FDG-PET or PET/CT to detect recurrent colorectal cancer in patients with elevated CEA: a systematic review and meta-analysis. Int J Colorectal Dis 2013;28:1039-1047. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23407908.

625. 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.

626. 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.

627. 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.

628. 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.

629. 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.

630. 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.

631. 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.

632. 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.

633. Guren MG, Undseth C, Rekstad BL, et al. Reirradiation of locally recurrent rectal cancer: a systematic review. Radiother Oncol 2014;113:151-157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25613395.

634. 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.

635. 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.

636. Downing A, Morris EJ, Richards M, et al. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. J Clin Oncol 2015;33:616-624. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25559806.

637. 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.

638. 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.

639. Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer : patient-reported symptoms 4 years after diagnosis. Cancer 2007;110:2075-2082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17849466.

640. 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.

641. 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.

642. 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.

643. 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.

644. Jansen L, Herrmann A, Stegmaier C, et al. Health-related quality of life during the 10 years after diagnosis of colorectal cancer: a population-based study. J Clin Oncol 2011;29:3263-3269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768465.

645. Mols F, Beijers T, Lemmens V, et al. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. J Clin Oncol 2013;31:2699-2707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23775951.

646. Wright P, Downing A, Morris EJ, et al. Identifying social distress: a cross-sectional survey of social outcomes 12 to 36 months after

colorectal cancer diagnosis. J Clin Oncol 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26282636.

647. 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.

648. 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.

649. 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.

650. 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.

651. Campbell PT, Patel AV, Newton CC, et al. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. J Clin Oncol 2013;31:876-885. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23341510.

652. Kuiper JG, Phipps AI, Neuhouser ML, et al. Recreational physical activity, body mass index, and survival in women with colorectal cancer. Cancer Causes Control 2012;23:1939-1948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23053793.

653. Arem H, Pfeiffer RM, Engels EA, et al. Pre- and postdiagnosis physical activity, television viewing, and mortality among patients with colorectal cancer in the National Institutes of Health-AARP Diet and Health Study. J Clin Oncol 2015;33:180-188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25488967.

654. Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: A meta-analysis of prospective cohort studies. Int J Cancer 2013;133:1905-1913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23580314.

655. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. Ann Oncol 2014;25:1293-1311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24644304.

656. 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.

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

658. Sinicrope FA, Foster NR, Yothers G, et al. Body mass index at diagnosis and survival among colon cancer patients enrolled in clinical trials of adjuvant chemotherapy. Cancer 2013;119:1528-1536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23310947.

659. Campbell PT, Newton CC, Dehal AN, et al. Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 2012;30:42-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22124093.

660. 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.

661. Meyerhardt JA, Sato K, Niedzwiecki D, et al. Dietary glycemic load and cancer recurrence and survival in patients with stage III colon

cancer: findings from CALGB 89803. J Natl Cancer Inst 2012;104:1702-1711. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23136358.

662. Fuchs MA, Sato K, Niedzwiecki D, et al. Sugar-sweetened beverage intake and cancer recurrence and survival in CALGB 89803 (Alliance). PLoS One 2014;9:e99816. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24937507.

663. 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.

664. Hawkes AL, Chambers SK, Pakenham KI, et al. Effects of a telephone-delivered multiple health behavior change intervention (CanChange) on health and behavioral outcomes in survivors of colorectal cancer: a randomized controlled trial. J Clin Oncol 2013;31:2313-2321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23690410.

665. 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.

666. El-Shami K, Oeffinger KC, Erb NL, et al. American Cancer Society Colorectal Cancer Survivorship Care Guidelines. CA Cancer J Clin 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26348643.