National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Rectal Cancer

NCCN Evidence Blocks™

Version 6.2020 — June 25, 2020

NCCN.org

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Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocacy
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
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NCCN Guidelines Panel Disclosures

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Clinical Trials: NCCN believes that the best management for any patient with cancer 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/member_institutions.aspx.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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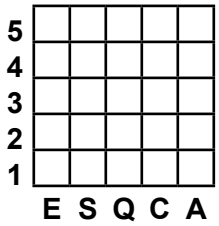
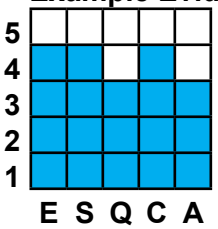
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

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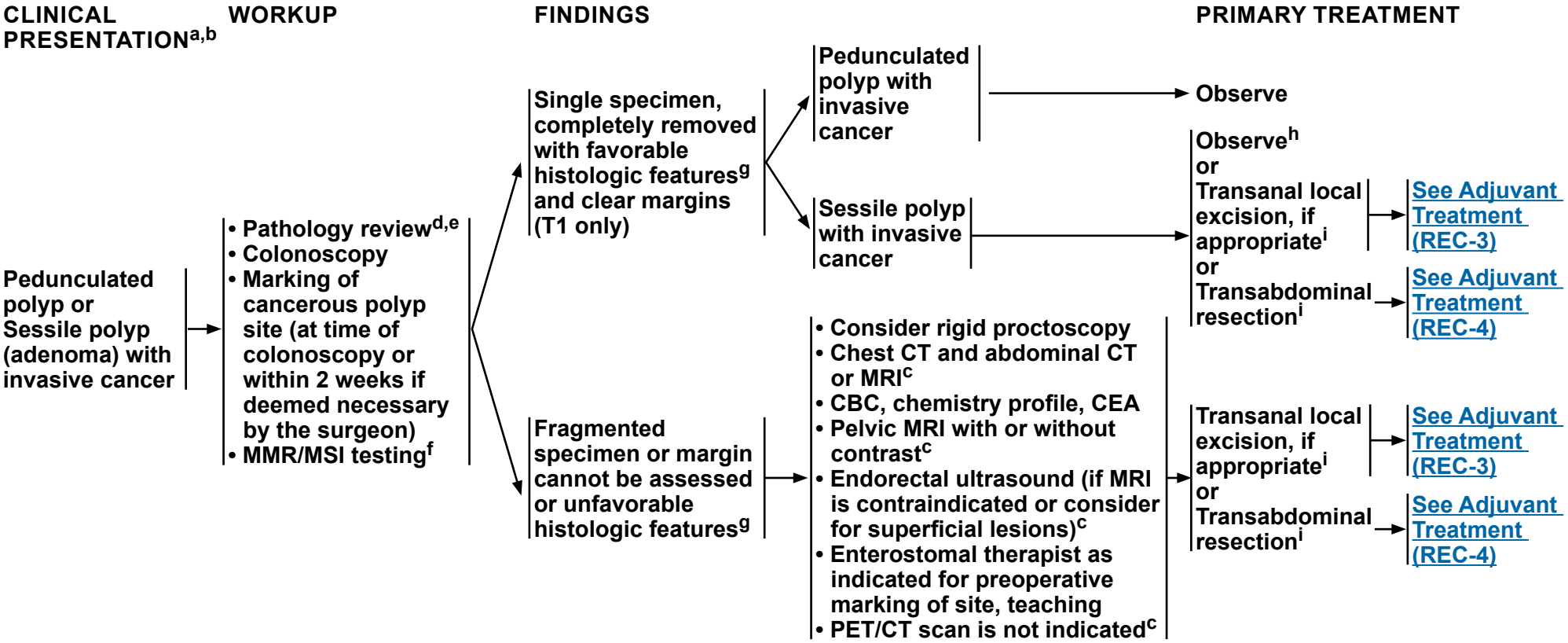

[a] All patients with rectal cancer should be counseled for family history. Patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

[b] For melanoma histology, see the NCCN Guidelines for Cutaneous Melanoma.

[c] See Principles of Imaging (REC-A).

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

[e] 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.

[f] See Principles of Pathologic Review (REC-B, 5 of 9) - MSI or MMR Testing.

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

[h] 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-B) - Endoscopically removed malignant polyp.

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

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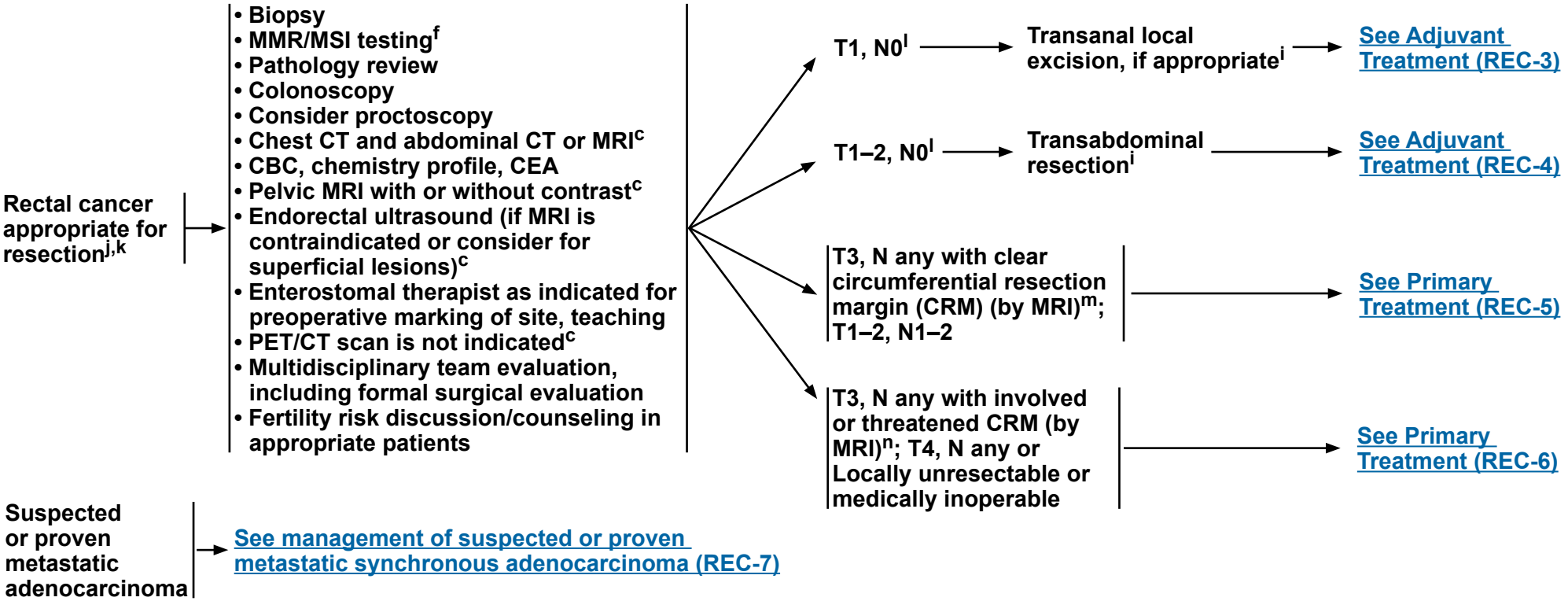

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[b] For melanoma histology, see the NCCN Guidelines for Cutaneous Melanoma.

[c] See Principles of Imaging (REC-A).

[f] See Principles of Pathologic Review (REC-B, 5 of 9) - MSI or MMR Testing.

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

[j] For tools to aid optimal assessment and management of older adults with cancer, see the NCCN Guidelines for Older Adult Oncology.

[k] The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.

[l] T1-2, N0 should be based on assessment of pelvic MRI (preferred) or endorectal ultrasound.

[m] CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane.

[n] CRM measured at the closest distance of the tumor to the mesorectal fascia. Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.

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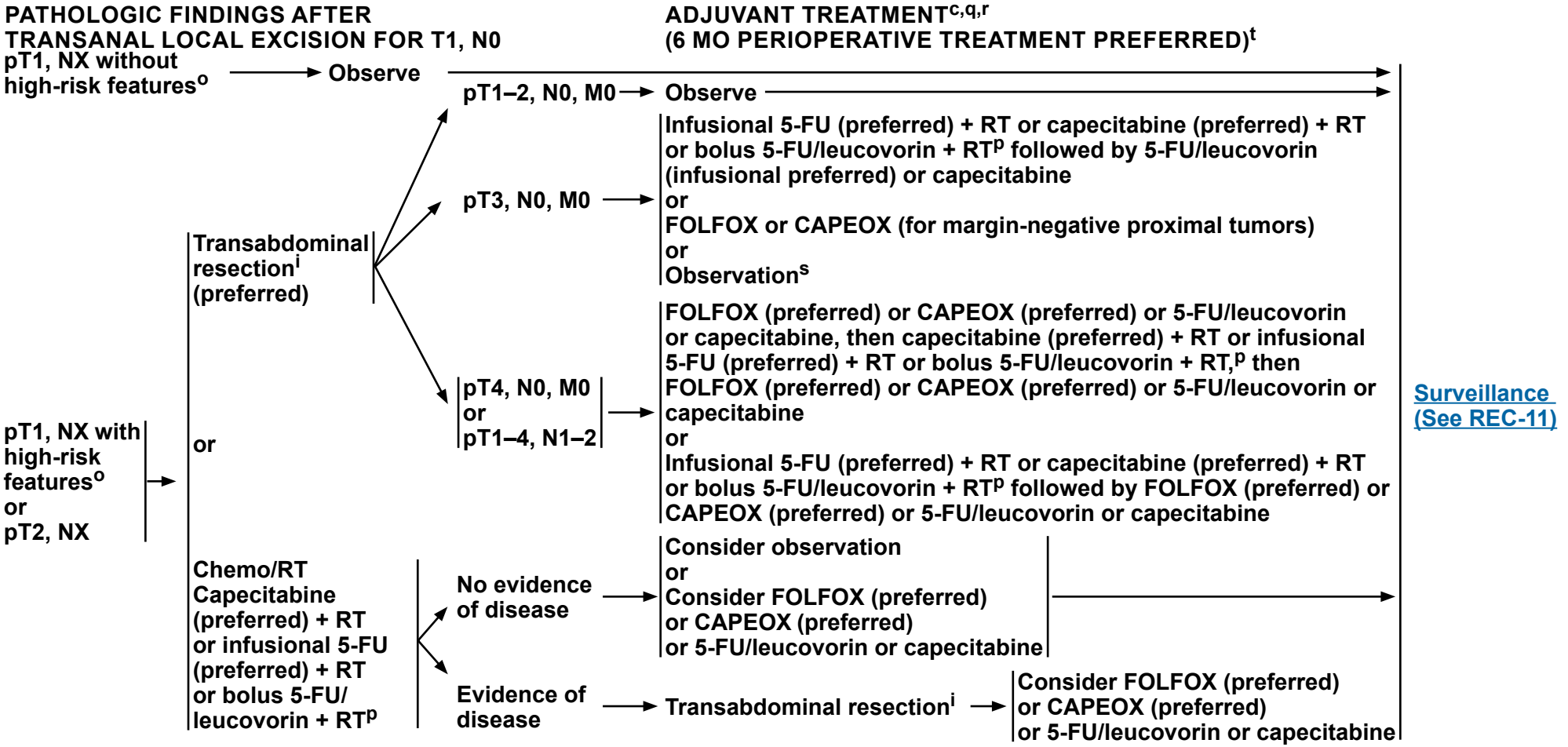

See Evidence Blocks on REC-4A

[c] See Principles of Imaging (REC-A).
[i] See Principles of Surgery (REC-C).
[o] High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion (submucosal invasion to the lower third of the submucosal level).
[p] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[q] See Principles of Adjuvant Therapy (REC-D).
[r] See Principles of Radiation Therapy (REC-E).
[s] Observation following transabdominal resection can be considered in patients with pT3N0 rectal cancer if the tumor was well-differentiated or moderately well-differentiated carcinoma invading less than 2 mm into the mesorectum, without lymphatic or venous vessel involvement and was located in the upper rectum. Willett CG, Badizadegan K, Ancukiewicz M, Shellito PC. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 1999;42:167-173.
[t] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 years or older has not been proven.

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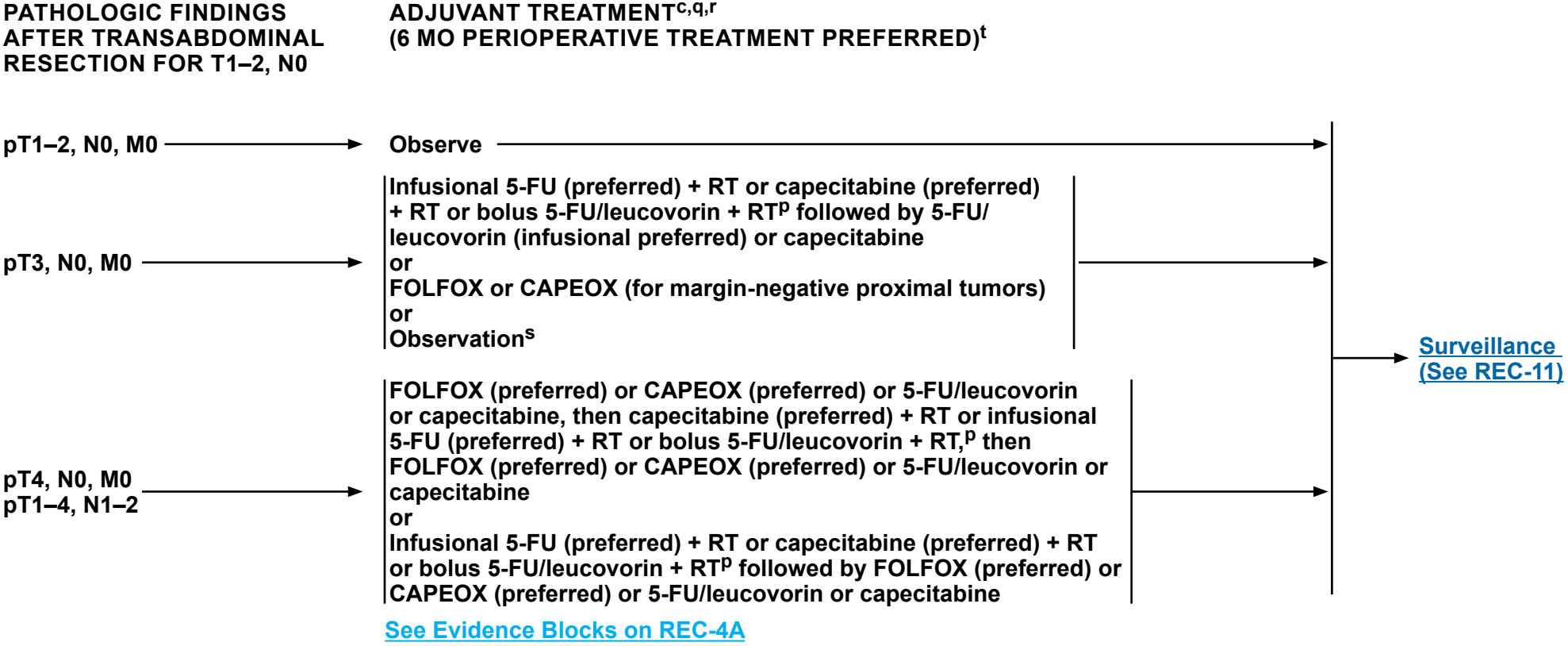

See Evidence Blocks on REC-4A

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[q] See Principles of Adjuvant Therapy (REC-D).
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EVIDENCE BLOCKS FOR NEOADJUVANT/ADJUVANT THERAPY

	Chemoradiation for T1, NX with high-risk features or T2, NX (REC-3)	Chemotherapy after chemoRT, without resection, for T1, NX with high-risk features or T2, NX (REC-3)	Adjuvant chemotherapy for T1, NX with high-risk features or T2, NX (REC-3)	Adjuvant chemotherapy for margin-negative proximal tumors found to be pT3, N0, M0 after transabdominal resection (REC-3 and REC-4)	Adjuvant Treatment for pT3-4, N0, M0 or pT1-4, N1-2 (REC-4)
Capecitabine/RT		—	—	—	
Infusional 5-FU/RT		—	—	—	
Bolus 5-FU/leucovorin/RT		—	—	—	
Bolus 5-FU/leucovorin	—			—	
Capecitabine	—			—	
FOLFOX	—				
CapeOx	—				
Infusional 5-FU/leucovorin	—			—	

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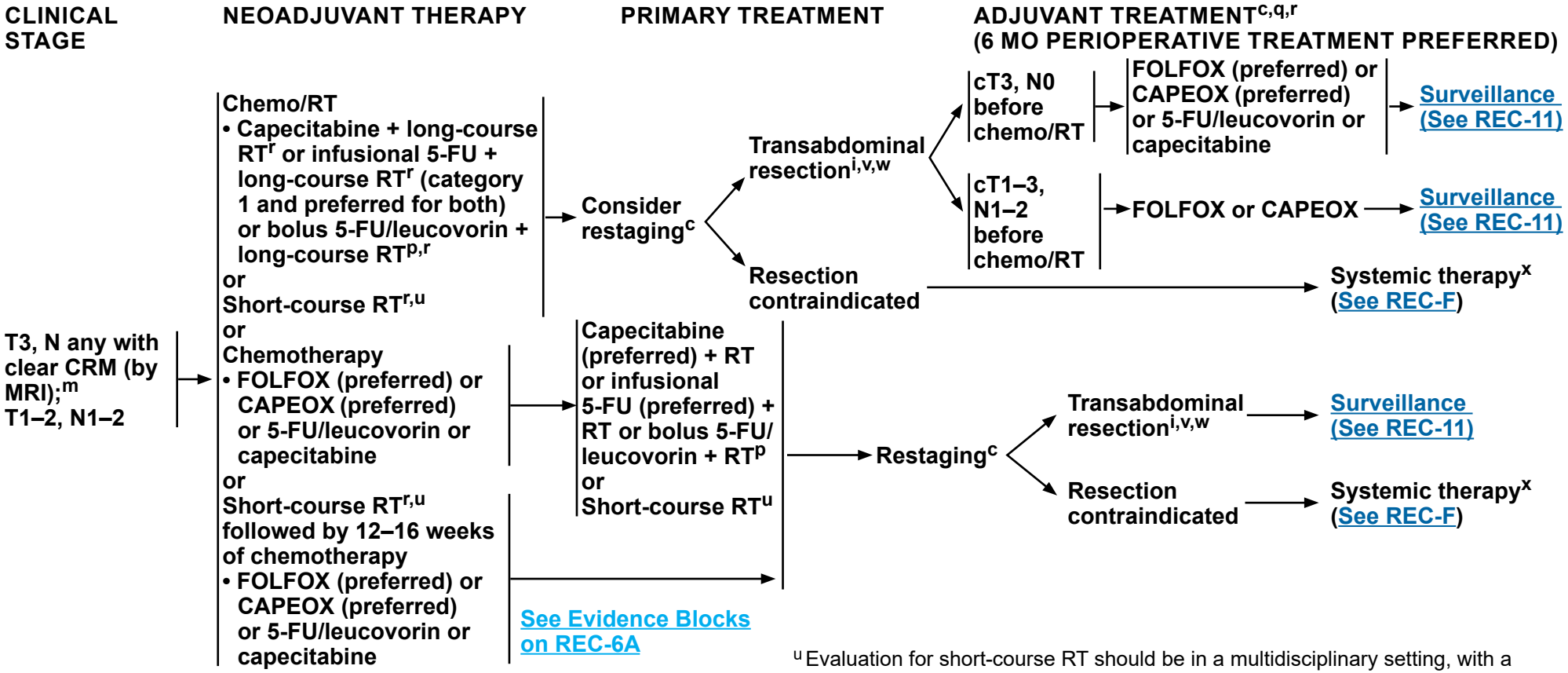

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[m] CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane.
[p] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[q] See Principles of Adjuvant Therapy (REC-D).
[r] See Principles of Radiation Therapy (REC-E).
[u] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.
[v] If patient treated with short-course RT, surgery should be within 1 week or delayed 6–8 weeks.
[w] In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of his/her risk tolerance.
[x] FOLFOXIRI is not recommended in this setting.

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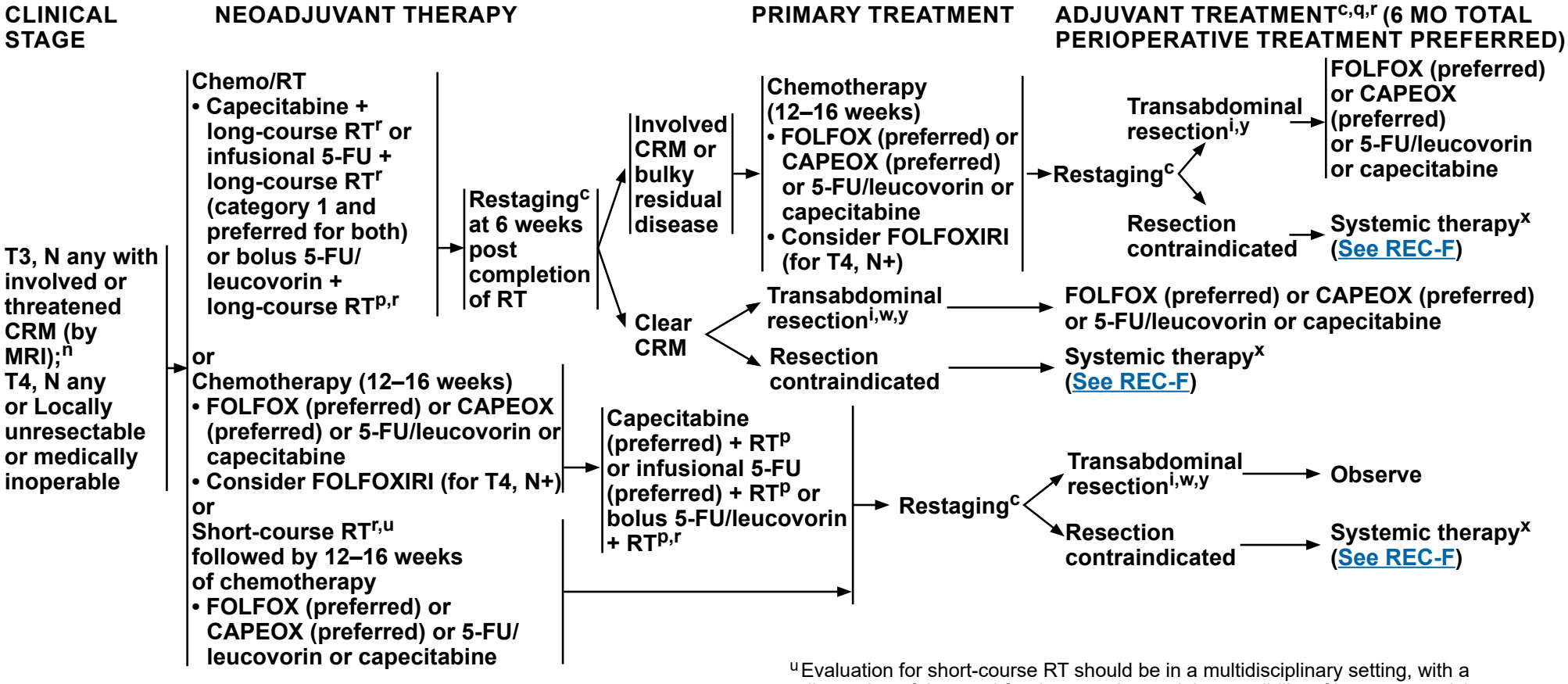

See Evidence Blocks on REC-6A

[c] See Principles of Imaging (REC-A).
[i] See Principles of Surgery (REC-C).
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[q] See Principles of Adjuvant Therapy (REC-D).
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[x] FOLFOXIRI is not recommended in this setting.
[y] For select patients who may be candidates for intraoperative radiation (IORT), see Principles of Radiation Therapy (REC-E).

Surveillance (See REC-11)

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EVIDENCE BLOCKS FOR NEOADJUVANT/ADJUVANT THERAPY FOR CLINICAL STAGE II-III AND/OR LOCALLY UNRESECTABLE OR MEDICALLY INOPERABLE
(REC-5) and (REC-6)

Neoadjuvant Therapy	
Capecitabine/long-course RT	
Infusional 5-FU/ long-course RT	
Bolus 5-FU/leucovorin/ long-course RT	
Short-course RT	
FOLFOX	
CapeOx	
5-FU/leucovorin	
Capecitabine	
FOLFOXIRI	
Short-course RT followed by FOLFOX	
Short-course RT followed by CAPEOX	
Short-course RT followed by 5-FU/leucovorin	
Short-course RT followed by capecitabine	

Neoadjuvant Therapy after Chemotherapy	
Capecitabine/RT	
Infusional 5-FU/RT	
Bolus 5-FU/leucovorin/RT	
Short-course RT	

Adjuvant Treatment	
5-FU/leucovorin	
Capecitabine	
FOLFOX	
CapeOx	

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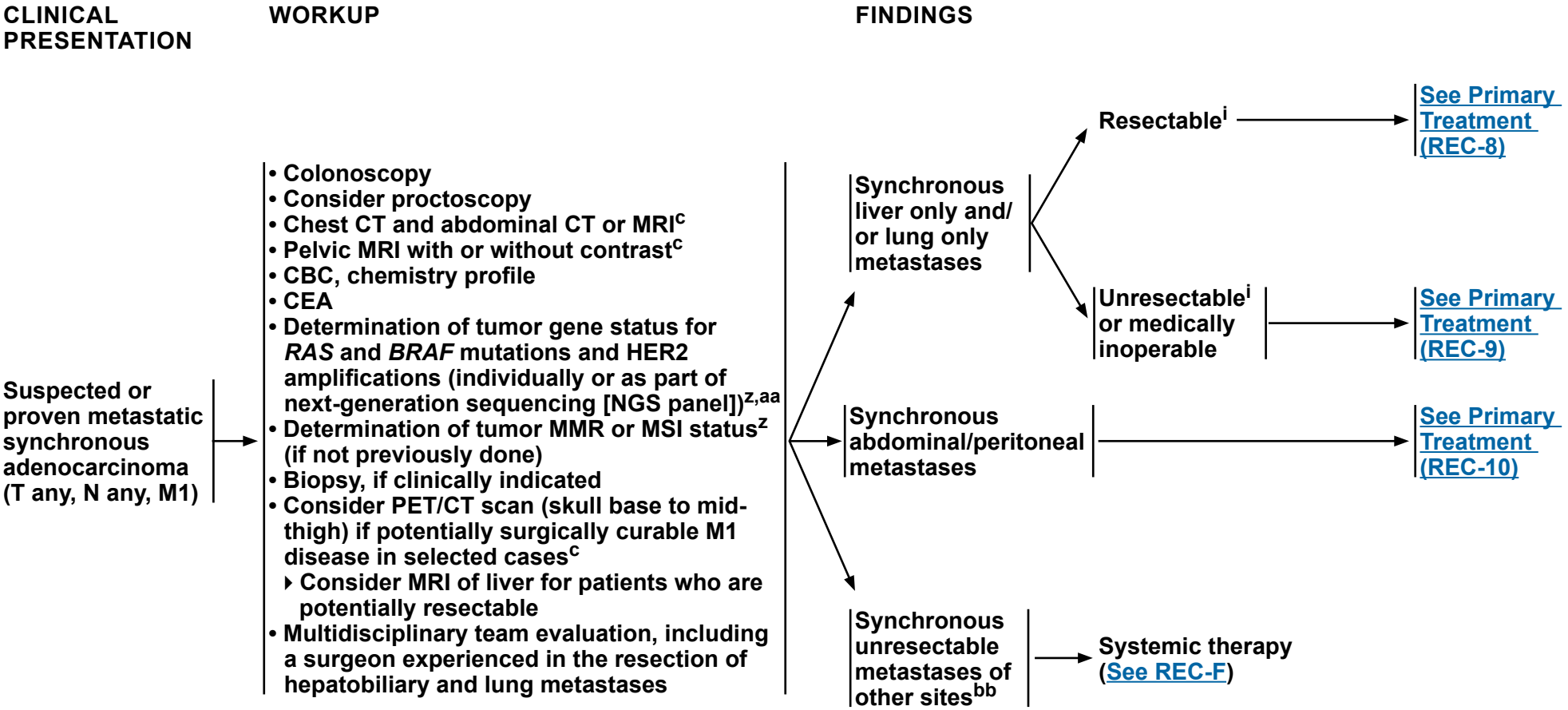

[c] See Principles of Imaging (REC-A).
[i] See Principles of Surgery (REC-C).
[z] See Principles of Pathologic Review (REC-B 5 of 9) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[aa] If known RAS/RAF mutation, HER2 testing is not indicated. NGS panels have the ability to pick up rare and actionable mutations and fusions.
[bb] Consider resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

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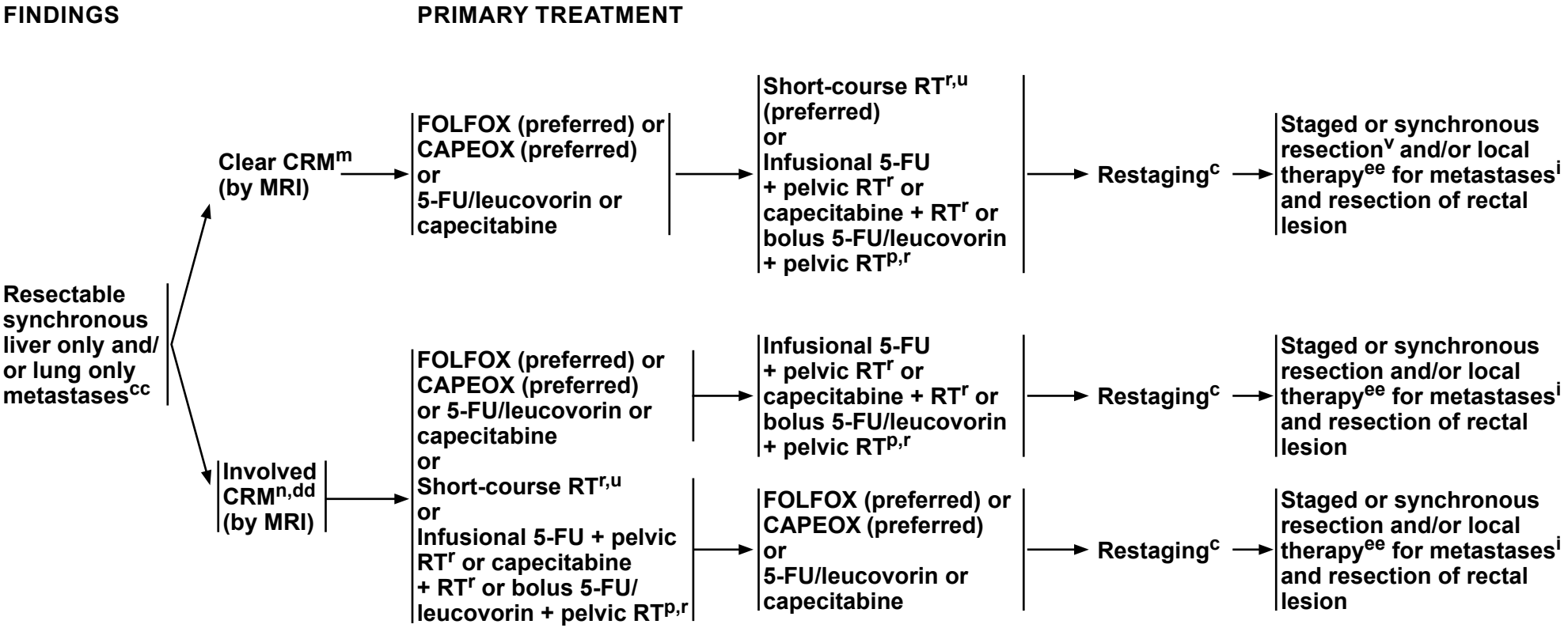

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[p] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[r] See Principles of Radiation Therapy (REC-E).
[u] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.
[v] If patient treated with short-course RT, surgery should be within 1 week or delayed 6–8 weeks.
[cc] If obstructing lesion, consider diversion or resection (see REC-10).
[dd] There are limited data regarding available treatment options.
[ee] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E).

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EVIDENCE BLOCKS FOR NEOADJUVANT THERAPY FOR RESECTABLE SYNCHRONOUS METASTASES (REC-8)

FOLFOX	
CapeOx	
5-FU/leucovorin	
Capecitabine	
Short-course RT	
Infusional 5-FU/RT	
Capecitabine/RT	
Bolus 5-FU/leucovorin/RT	

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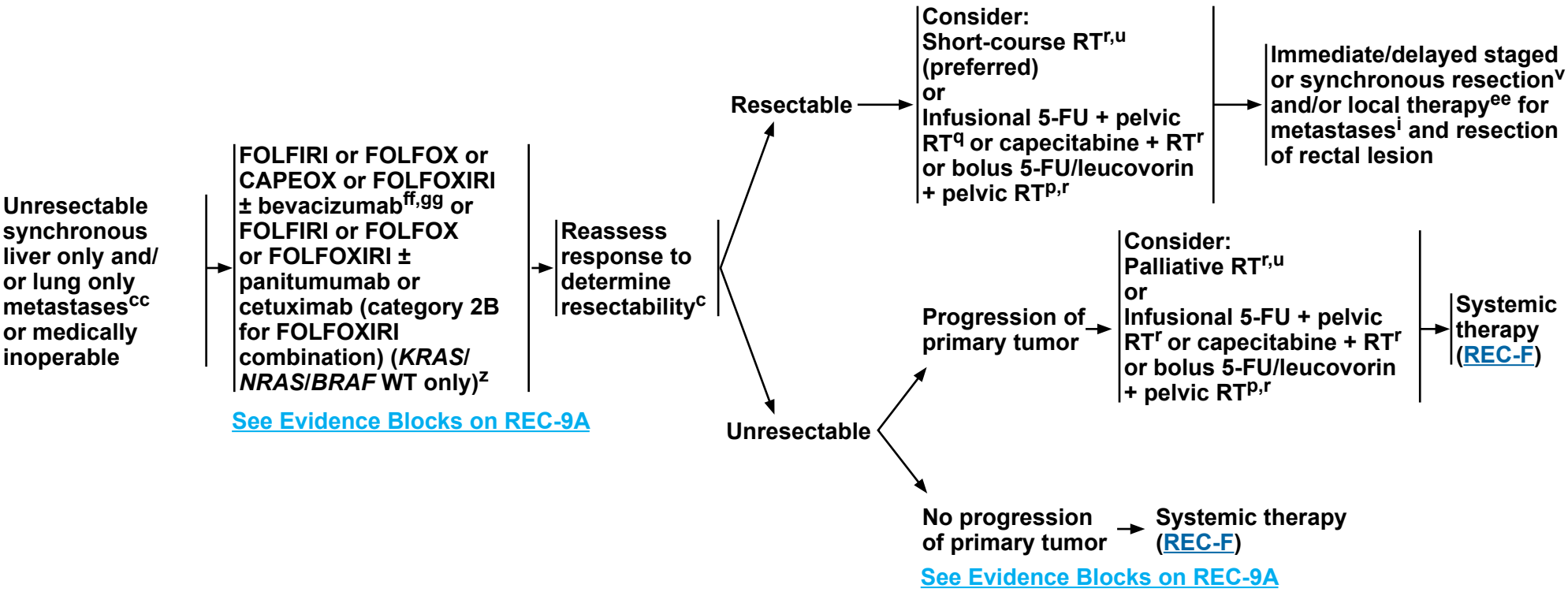

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[r] See Principles of Radiation Therapy (REC-E).
[u] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.
[v] If patient treated with short-course RT, surgery should be within 1 week or delayed 6–8 weeks.
[z] See Principles of Pathologic Review (REC-B 5 of 9) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing.
[cc] If obstructing lesion, consider diversion or resection (see REC-10).
[ee] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E).
[ff] There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery, and re-initiation of bevacizumab should be delayed at least 6–8 weeks postoperatively. There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.
[gg] An FDA-approved biosimilar is an appropriate substitution for bevacizumab.

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EVIDENCE BLOCKS FOR UNRESECTABLE SYNCHRONOUS LIVER AND/OR LUNG METASTASES ONLY OR MEDICALLY INOPERABLE (REC-9)

Primary treatment	
FOLFOX	
FOLFOX/bevacizumab	
FOLFOX/cetuximab	
FOLFOX/panitumumab	
CapeOx	
CapeOx/bevacizumab	
FOLFIRI	
FOLFIRI/bevacizumab	
FOLFIRI/cetuximab	
FOLFIRI/panitumumab	
FOLFOXIRI	
FOLFOXIRI/bevacizumab	
FOLFOXIRI/panitumumab	
FOLFOXIRI/cetuximab	

Preoperative chemoradiation following conversion to resectability	
Short-course RT	
Infusional 5-FU/RT	
Capecitabine/RT	
Bolus 5-FU/leucovorin/RT	

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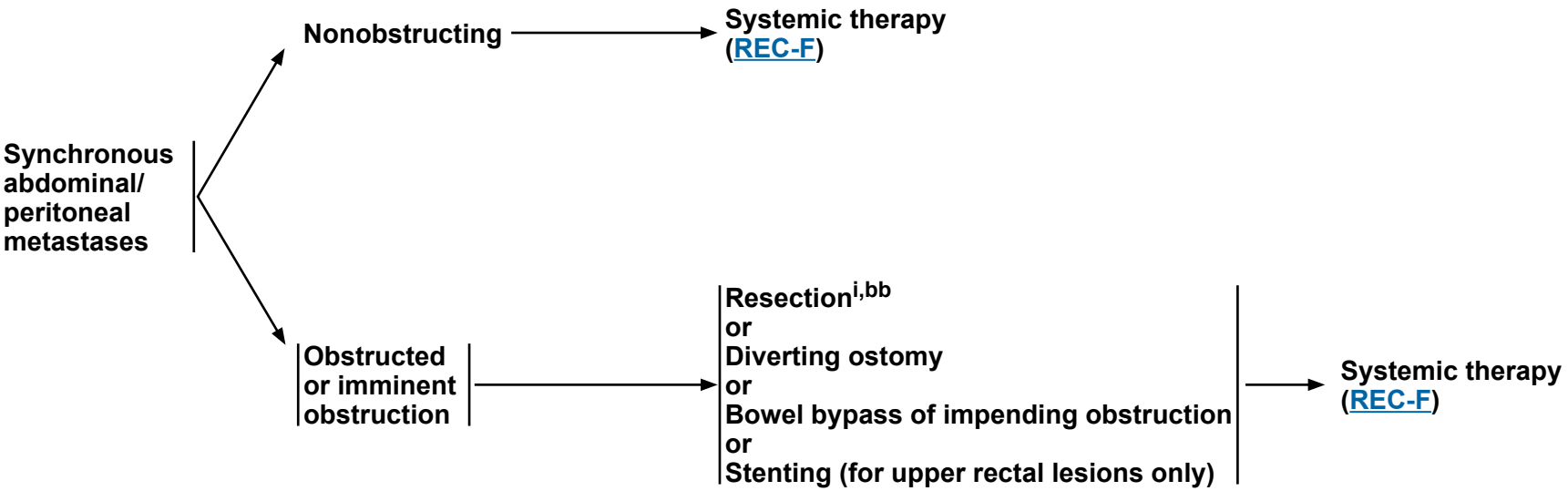
FINDINGS | **PRIMARY TREATMENT**



[i] See Principles of Surgery (REC-C).
[bb] Consider resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

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SURVEILLANCE[c]

Transanal local excision only →
- Proctoscopy (with EUS or MRI with contrast) every 3–6 mo for the first 2 y, then every 6 mo for a total of 5 y
- Colonoscopy[a] at 1 y after surgery
  - If advanced adenoma, repeat in 1 y
  - If no advanced adenoma,[hh] repeat in 3 y, then every 5 y[ii]

Stage I with full surgical staging →
- Colonoscopy[a] at 1 y after surgery
  - If advanced adenoma, repeat in 1 y
  - If no advanced adenoma,[hh] repeat in 3 y, then every 5 y[ii]

Stage II–IV →
- History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA[jj] every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/abdominal/pelvic CT
  - Stage II, III: every 6–12 mo (category 2B for frequency <12 mo) for a total of 5 y
  - Stage IV: every 3–6 mo (category 2B for frequency <6 mo) x 2 y, then every 6–12 mo for a total of 5 y
- Colonoscopy[a] in 1 y after surgery 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,[hh] repeat in 3 y, then every 5 y[ii]
- PET/CT scan is not recommended
- See Principles of Survivorship (REC-G)

→ **Serial CEA elevation or documented recurrence** → See Workup and Treatment (REC-12)

[a] All patients with rectal cancer should be counseled for family history. Patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[c] See Principles of Imaging (REC-A).
[hh] Villous polyp, polyp >1 cm, or high-grade dysplasia.
[ii] Kahi CJ, Boland CR, Dominitz JA, et al. Colonoscopy surveillance after colorectal cancer resection: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2016;150:758-768.
[jj] If patient is a potential candidate for resection of isolated metastasis.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2020
Rectal Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
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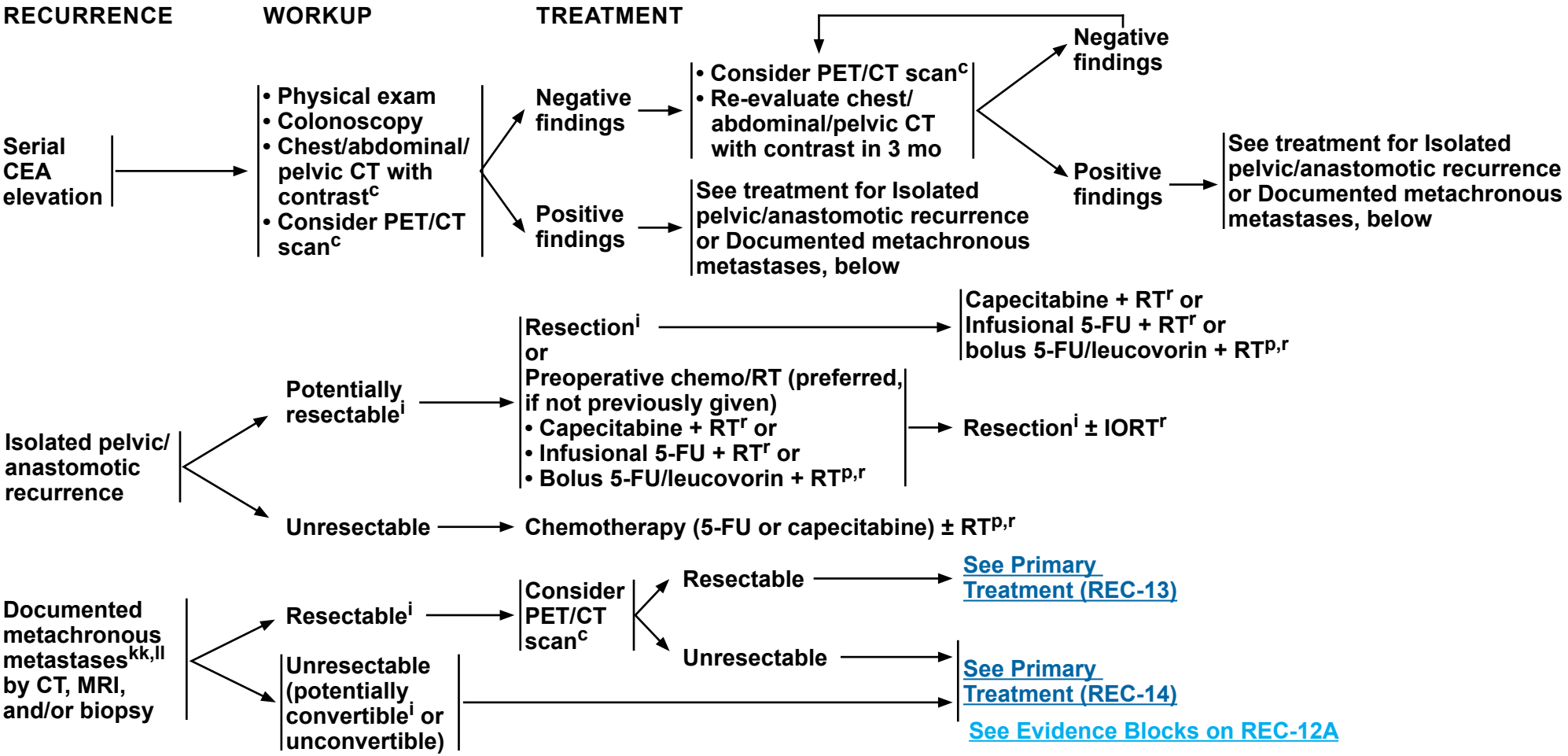
Discussion



[c] See Principles of Imaging (REC-A).
[i] See Principles of Surgery (REC-C).
[p] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[r] See Principles of Radiation Therapy (REC-E).

[kk] Determination of tumor gene status for *RAS* and *BRAF* mutations and HER2 amplifications (individually or as part of NGS panel). If known *RAS/RAF* mutation, HER2 testing is not indicated. See Principles of Pathologic Review (REC-B 5 of 9) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing. NGS panels have the ability to pick up rare and actionable mutations and fusions.
[ll] Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

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EVIDENCE BLOCKS FOR NEOADJUVANT/ADJUVANT THERAPY FOR ISOLATED PELVIC RECURRENCE (REC-12)

	Neoadjuvant	Adjuvant	Unresectable
Capecitabine/RT			
Infusional 5-FU/RT			
Bolus 5-FU/RT			

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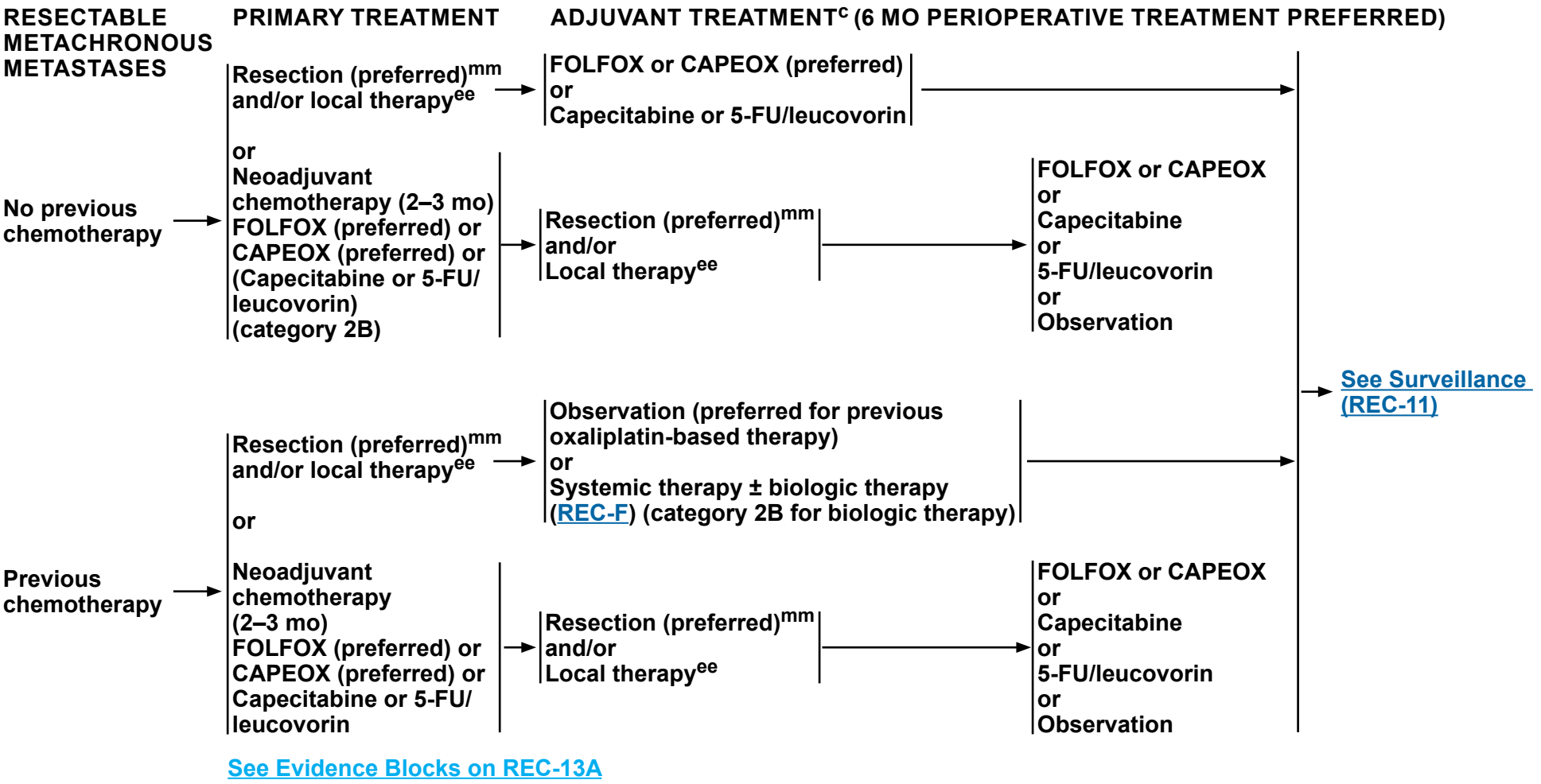

See Evidence Blocks on REC-13A

[c] See Principles of Imaging (REC-A).
[ee] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E).
[mm] 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.

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EVIDENCE BLOCKS FOR NEOADJUVANT/ADJUVANT THERAPY FOR RESECTABLE METACHRONOUS METASTASES (REC-13)

	Neoadjuvant Therapy (with or without previous chemotherapy)	Adjuvant Therapy
FOLFOX		
CapeOx		
Capecitabine		
5-FU/leucovorin		

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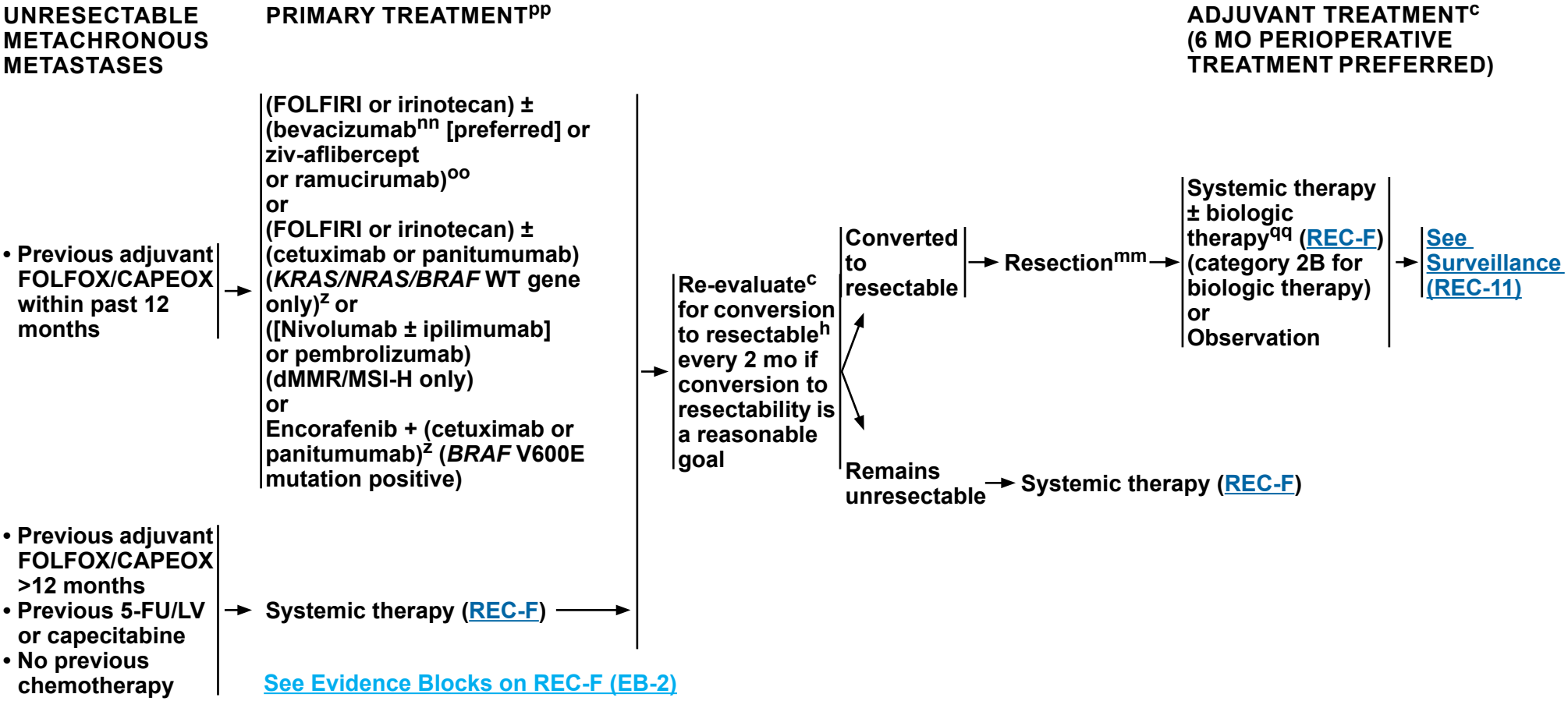

[c] See Principles of Imaging (REC-A).
[h] See Principles of Surgery (REC-C).
[z] See Principles of Pathologic Review (REC-B 5 of 9) - *KRAS, NRAS*, and *BRAF* Mutation Testing.
[mm] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[nn] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[oo] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[pp] For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[qq] Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.

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PRINCIPLES OF IMAGING[1-3]

Initial Workup/Staging

- **Chest CT and abdominal CT or MRI**
  - **Evaluate local extent of tumor or infiltration into surrounding structures.**
  - **Assess for distant metastatic disease to lungs, thoracic and abdominal lymph nodes, liver, peritoneal cavity, and other organs.**
  - **CT performed with intravenous iodinated contrast and oral contrast material unless contraindicated.**
  - **Intravenous contrast is not required for the chest CT (but usually given if performed with abdominal CT scan).**
  - **If IV iodinated contrast material is contraindicated because of significant contrast allergy, then MR examination of the abdomen with IV gadolinium-based contrast agent (GBCA) can be obtained instead. In patients with chronic renal failure (glomerular filtration rate [GFR] <30 mL/min) who are not on dialysis, IV iodinated contrast material is also contraindicated, and IV GBCA can be administered in select cases using gadofosveset trisodium, gadoxetate disodium, gadobenate dimeglumine, or gadoteridol.**
  - **If iodinated and gadolinium contrast are both contraindicated due to significant allergy or chronic renal failure without dialysis, then consider MR without IV contrast or consider PET/CT imaging.**
- **Pelvic MRI with or without contrast or endorectal ultrasound (only if MRI is contraindicated [eg, pacemaker])**
  (See Pelvic MRI Requirements (REC-A 3 of 4) and Reporting (REC-A 4 of 4)
  - **Assess T and N stage of the primary rectal tumor.**
  - **Pelvic MRI or CT can be used for workup of synchronous metastatic disease.**
  - **Pelvic MRI can be performed with or without intravenous gadolinium contrast per institutional preferences.**
  - **Pelvic MRI may not be required for local staging if tumor is known to be definite T1 or if patient is not a candidate for primary tumor resection (eg, widespread metastases, plan for permanent colonic diversion).**
  - **The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.**
- **PET/CT is not routinely indicated.**
  - **PET/CT does not supplant a contrast-enhanced diagnostic CT or MR and should only be used to evaluate an equivocal finding on a contrast-enhanced CT or MR scan or in patients with strong contraindications to IV contrast administration.**
  - **Consider PET/CT (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases.**
- **If liver-directed therapy or surgery is contemplated, a hepatic MRI with intravenous routine extra-cellular or hepatobiliary GBCA is preferred over CT (and PET/CT) to assess exact number and distribution of metastatic foci for local treatment planning.**

Restaging and Follow up/Surveillance (REC-A 2 of 4)

[1] Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology 2010;257:674-84.
[2] van Kessel CS, Buckens CF, van den Bosch MA, et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol 2012;19:2805-2813.
[3] ACR manual on contrast media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.

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PRINCIPLES OF IMAGING[1-3]

Restaging

- **Chest CT and abdominal CT or MRI and pelvic MRI**
  - **Prior to surgery for restaging**
  - **Prior to adjuvant treatment to assess response to primary therapy or resection**
  - **During re-evaluation of conversion to resectable disease**
- **PET/CT is not indicated.**

Follow up/Surveillance

- **Stage I disease:**
  - **Imaging is not routinely indicated and should only be based on symptoms and clinical concern for recurrent/metastatic disease.**
- **Stage II & III disease:**
  - **Chest, abdominal, and pelvic CT every 6–12 months (category 2B for frequency <12 months) for a total of 5 years.**
  - **MRI or EUS of the rectum every 3–6 months for 2 years, then every 6 months for a total of 5 years (for patients with transanal local excision only).**
  - **PET/CT examination is not recommended.**
- **Stage IV disease:**
  - **Chest, abdominal, and pelvic CT every 3–6 months (category 2B for frequency <6 months) x 2 years, then every 6–12 months for a total of 5 years.**
  - **MRI or EUS of the rectum every 3–6 months for 2 years, then every 6 months for a total of 5 years (for patients with trans-anal excision only).**
- **PET/CT is not indicated.**

[1] Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology 2010;257:674-84.
[2] van Kessel CS, Buckens CF, van den Bosch MA, et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol 2012;19:2805-2813.
[3] ACR manual on contrast media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.

Continued

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PRINCIPLES OF IMAGING
Pelvic MRI Requirements[3]

Patient Preparation

Rectal distension with gel	**Not a requirement. There is controversy on the effect of rectal distension on accurately assessing the distance of tumor to mesorectal fascia (MRF)**
Use of spasmolytic agents	**Not a requirement. Can help decrease bowel movement-related artifacts if needed**

MRI Hardware Requirement

Magnet strength	**Minimum requirement 1.5 T** **1.0 T magnets produce limited signal and should be avoided when possible**
Coil	**External surface body coil adequate and preferred to endorectal coils**

MRI Sequences

2D high-resolution T2-weighted	**• Slice thickness 1–3 mm (no more than 4 mm). 3D T2-weighted sequences are not adequate substitute** **• Main sequences for T staging and detection of pathologic lymph nodes** **• Axial, sagittal, and coronal plane to assess extent and relationship to all surrounding structures** **• Axial and coronal slices should be angulated along the short (perpendicular) and long (parallel) axis of tumor for tumors in the middle and upper part of the rectum and along the anal canal for low rectal tumors**
T1-weighted without contrast	**Not a requirement for staging. May be helpful in assessing other pelvic organs and/or pathologies**
Diffusion-weighted imaging (DWI)	**Not a requirement for T staging or detection of pathologic lymph node. Helpful in assessing treatment response after neoadjuvant therapy (assessing the yT-stage)**
T1-weighted with contrast	**Not a requirement for staging[a]**

[a] IV contrast can be administered (after completion of non-contrast scans) if DCE (dynamic contrast-enhanced) MRI and/or perfusion assessment is needed for tumor response evaluation, currently performed primarily in investigational setting.

[3] ACR manual on contrast media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.

Continued

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PRINCIPLES OF IMAGING
Pelvic MRI Reporting[3]

At presentation (before neoadjuvant therapy)	• Distance from the anal verge or anorectal junction to the lower aspect of the tumor • Tumor length • T-stage of primary mass • Tumor deposits within the mesorectum • Involvement of the mesorectal fascia and the smallest distance (mm) between the tumor and the MRF and its location[b] • N-stage • Presence/absence of suspicious extramesorectal lymph nodes • Additional findings that can be provided in synoptic report: ‣ The circumferential location of the tumor ‣ In T3 tumor, the extent (mm) of extramural growth or depth of invasion ‣ Number of suspicious lymph nodes ‣ Presence/absence of extramural vascular invasion (EMVI) ‣ Morphologic pattern of tumor growth (eg, annular, polypoid, mucinous, ulcerated, perforated)
After neoadjuvant therapy	• Distance from the anal verge or anorectal junction to the lower aspect of the remaining tumor • Tumor length • Presence/absence of a residual tumor (high signal on T2-weighted images) • Presence/absence of fibrosis (low signal on T2-weighted images) • yT-stage and any remaining tumor deposits within the mesorectum • yN-stage and number of remaining suspicious lymph nodes • Presence of any remaining suspicious extramesorectal lymph nodes • Persistent involvement/regression from the MRFb • The smallest distance (mm) between the remaining tumor and the mesorectal fascia and its locationa • Additional findings that can be provided in synoptic report: ‣ The circumferential location of the remaining tumor within the wall ‣ In the case of a yT3 tumor, the extent (mm) of extramural growth ‣ The morphologic pattern of tumor growth ‣ Presence/absence of EMVI (no clear consensus on reporting this finding)

[b] CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane. Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.

[3] ACR manual on contrast media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.

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PRINCIPLES OF PATHOLOGIC REVIEW

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 histopathologic 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. In several studies, tumor budding has been shown to be an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.
- 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 Local 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.
- The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.

Pathologic Stage on REC-B (2 of 9)
Lymph Node Evaluation on REC-B (4 of 9)
Sentinel Lymph Node Evaluation on REC-B (4 of 9)
KRAS, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B (5 of 9)
HER2 Testing and *NTRK* Fusions on REC-B (6 of 9)

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PRINCIPLES OF PATHOLOGIC REVIEW

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, circumferential (radial), and mesenteric margins.[11-12]
  - CRM[13-17]
  - Neoadjuvant treatment effect[15,16,18,19]
  - Lymphovascular invasion[15,16,20]
  - Perineural invasion (PNI)[21-23]
  - 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, Eighth 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, 8th 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]

Pathologic Stage (continued) on REC-B (3 of 9)
Lymph Node Evaluation on REC-B (4 of 9)
Endoscopically Removed Malignant Polyps, Transanal Local Excision, Rectal Cancer Appropriate for Resection on REC-B (1 of 9)
KRAS, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B (5 of 9)
HER2 Testing and *NTRK* Fusions on REC-B (6 of 9)

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PRINCIPLES OF PATHOLOGIC REVIEW

Pathologic Stage (continued)

- **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, overall, and 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.[20-25]**
- **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 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.**
- **Tumor budding - In recent years, tumor budding has been identified as a new prognostic factor in colon cancer. Recently, there was an international consensus conference on tumor budding reporting.[26] A tumor bud is defined as a single cell or a cluster of ≤4 cells detected by hematoxylin and eosin (H&E) at the advancing edge of the invasive carcinoma. The total number of buds should be reported from a selected hot spot measuring 0.785 mm (20x ocular in most microscopes/via a conversion factor). Budding is separated into three grades: low grade (0–4 buds), intermediate grade (5–9 buds), and high grade (10 or more buds). Two recent studies[27,28] using this scoring system have shown tumor budding to be an independent prognostic factor for stage II colon cancer. An ASCO guideline for stage II colon cancer designates tumor budding as an adverse (high-risk) factor.[29] Several studies have shown that high-grade tumor budding in pT1 colorectal carcinomas, including malignant polyps, is associated with an increased risk of lymph node metastasis; however, methodologies for assessing tumor budding and grade were not uniform.[30-34]**

Endoscopically Removed Malignant Polyps, Transanal Local Excision, Rectal Cancer Appropriate for Resection on REC-B (1 of 9)
Pathologic Stage on REC-B (2 of 9)
Lymph Node Evaluation on REC-B (4 of 9)
KRAS, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B (5 of 9)
HER2 Testing and *NTRK* Fusions on REC-B (6 of 9)

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PRINCIPLES OF PATHOLOGIC REVIEW

Lymph Node Evaluation

- The AJCC and CAP recommend examination of a minimum of 12 lymph nodes to accurately stage rectal cancer.[11,12,35] 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.[35-43] Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Two studies confined only to rectal cancer have reported 14 and >10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.[39,42] The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade, and tumor site.[36] 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, $P < .001$).[44,45] 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.[45] 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 lymph nodes (sentinel or routine) by intense histologic and/or immunohistochemical investigation helps to detect the presence of metastatic disease. The detection of single cells by immunohistochemistry (IHC) or by multiple H&E levels and/or clumps of tumor cells <0.2 mm are considered isolated tumor cells (pN0).[46] The 8th edition of the AJCC Cancer Staging Manual and Handbook[46] defines clumps of tumor cells ≥0.2 mm in diameter or clusters of 10–20 tumor cells as micrometastasis and recommends that these micrometastases be considered as standard positive lymph nodes (pN+).
- At the present time the use of sentinel lymph nodes and detection of isolated tumor cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.[47-54] 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 some of these studies, what are presently defined as isolated tumor cells were considered to be micrometastases.[50-54]

Evaluation of Mesorectum (TME)

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

Endoscopically Removed Malignant Polyps, Transanal Local Excision, Rectal Cancer Appropriate for Resection on REC-B (1 of 9)
Pathologic Stage on REC-B (2 of 9)
KRAS, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B (5 of 9)
HER2 Testing and *NTRK* Fusions on REC-B (6 of 9)

References

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PRINCIPLES OF PATHOLOGIC REVIEW

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 individually or as part of an NGS panel. Patients with any known _KRAS_ mutation (exon 2, 3, 4) or _NRAS_ mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab.[58-60] _BRAF_ V600E mutation makes response to panitumumab or cetuximab highly unlikely.[61-63]**
- **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.[64]**

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

- **Universal MMR[a] or MSI[a] testing is recommended in all newly diagnosed patients with rectal cancer. 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 (LS) in the vast majority of cases. However, approximately 1% of cancers with _BRAF_ V600E mutations (and loss of MLH-1) are LS. Caution should be exercised in excluding cases with a strong family history from germline screening in the case of _BRAF_ V600E mutations.[65]**
- **Stage II MSI high (MSI-H) patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.[66]**
- **MMR or MSI testing should be performed only in CLIA-approved laboratories.**
- **Testing for MSI may be accomplished by polymerase chain reaction (PCR) or a validated NGS panel, the latter especially in patients with metastatic disease who require genotyping of _RAS_ and _BRAF_.**
- **IHC refers to staining tumor tissue for protein expression of the four MMR genes known to be mutated in LS (MLH1, MSH2, MSH6, and PMS2.) A normal IHC test implies that all four MMR proteins are normally expressed (retained). Loss (absence) of expression of one or more of the four DNA MMR proteins is often reported as abnormal or positive IHC. When IHC is reported as positive, caution should be taken to ensure that positive refers to absence of mismatch expression and not presence of expression. NOTE: Normal is the presence of positive protein staining (retained) and abnormal is negative or loss of staining of protein. Loss of protein expression by IHC in any one of the MMR genes guides further genetic testing (mutation detection to the genes where the protein expression is not observed). Abnormal MLH1 IHC should be followed by tumor testing for _BRAF_ V600E mutation. The presence of _BRAF_ V600E mutation is consistent with sporadic cancer. However, caution should be exercised in excluding cases from germline screening on the basis of _BRAF_ V600E mutations in the setting of a strong family history.[65]**

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Lymph Node Evaluation on REC-B (4 of 9)
HER2 Testing and _NTRK_ Fusions on REC-B (6 of 9)

[a] IHC for MMR and DNA analysis for MSI are different assays and measure different biological effects caused by deficient MMR function.

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PRINCIPLES OF PATHOLOGIC REVIEW

HER2 Testing

- Diagnostic testing is via immunohistochemistry, fluorescence in situ hybridization (FISH), or NGS.
- Positive by immunohistochemistry is defined as: 3+ staining in more than 50% of tumor cells. 3+ staining is defined as an intense membrane staining that can be circumferential, basolateral, or lateral. Those that have a HER2 score of 2+ should be reflexed to FISH testing.[67-69] HER2 amplification by FISH is considered positive when the HER2:CEP17 ratio is ≥2 in more than 50% of the cells.[67-69] NGS is another methodology for testing for HER2 amplification.[70]
- Anti-HER2 therapy is only indicated in HER2-amplified tumors that are also *RAS* and *BRAF* wild-type.

***NTRK* Fusions**

- *NTRK* fusions are extremely rare in colorectal carcinomas.[71] The overall incidence is approximately 0.35% in a cohort of 2314 colorectal carcinomas, with *NTRK* fusions confined to those tumors that are pan–wild-type *KRAS, NRAS*, and *BRAF*. In one study of 8 colorectal cancers harboring *NTRK* fusions, 7 were found in the small subset that were dMMR (MLH-1)/MSI-H.[72] These data support limiting the subpopulation of colorectal cancers that should be tested for *NTRK* fusions to those with wild-type *KRAS, NRAS, BRAF*, and arguably to those that are MMR deficient (dMMR)/MSI-H.[72]
- *NTRK* inhibitors have been shown to have activity ONLY in those cases with *NTRK* fusions, and NOT with *NTRK* mutations.
- Methodologies for detecting *NTRK* fusions are IHC,[73] FISH, DNA-based NGS, and RNA-based NGS.[72,74] In one study, DNA-based sequencing showed an overall sensitivity and specificity of 81.1% and 99.9%, respectively, for detection of *NTRK* fusions when compared to RNA-based sequencing and immunohistochemistry showed an overall sensitivity of 87.9% and specificity of 81.1%. Since approximately 1 in 5 tumors identified as having an *NTRK* fusion by IHC will be a false positive, tumors that test positive by IHC should be confirmed by RNA NGS. That same study commented that RNA-based sequencing appears to be the optimal way to approach *NTRK* fusions, because the splicing out of introns simplifies the technical requirements of adequate coverage and because detection of RNA-level fusions provides direct evidence of functional transcription.[74] However, selection of the appropriate assay for *NTRK* fusion detection depends on tumor type and genes.

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PRINCIPLES OF PATHOLOGIC REVIEW - 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] Lugli A, Kirsch R, Ajioka Y, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol 2017;30:1299-1311.
[27] Lee VWK, Chan KF. Tumor budding and poorly-differentiated cluster in prognostication in Stage II colon cancer. Pathol Res Pract 2018;214:402-407.
[28] Romiti A, Roberto M, Marchetti P, et al. Study of histopathologic parameters to define the prognosis of stage II colon cancer. Int J Colorectal Dis 2019;34:905-913.

Continued

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PRINCIPLES OF PATHOLOGIC REVIEW - REFERENCES

[29] Costas-Chavarri A, Nandakumar G, Temin S, et al. Treatment of patients with early-stage colorectal cancer: ASCO Resource-Stratified Guideline. J Glob Oncol 2019;5:1-19.
[30] Koelzer VH, Zlobec I, Lugli A. Tumor budding in colorectal cancer – ready for diagnostic practice? Hum Pathol 2016;47:4-19.
[31] Bosch SL, Teerenstra S, de Wilt JH, et al. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 2013;45:827-834.
[32] Brown IS, Bettington ML, Bettington A, et al. Adverse histological features in malignant colorectal polyps: a contemporary series of 239 cases. J Clin Pathol 2016;69:292-299.
[33] Backes Y, Elias SG, Groen JN, et al. Histologic factors associated with need for surgery in patients with pedunculated T1 colorectal carcinomas. Gastroenterology 2018;154:1647-1659.
[34] Pai RK, Chen YW, Jakubowski MA, et al. Colorectal carcinomas with submucosal invasion (pT1): analysis of histopathological and molecular factors predicting lymph node metastasis. Mod Pathol 2017;30:113-122.
[35] Sobin HL and Green EFL. TNM classification. Clarification of number of regional lymph nodes for PN0. Cancer 2001;92:452.
[36] Sarli L, Bader G, Lusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. Eur J Cancer 2005;41:272-279.
[37] 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.
[38] 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.
[39] Pocard M, Panis Y, Malassagane B, et al. Assessing the effectiveness of mesorectal excision in rectal cancer. Dis Colon Rectum 1998;41:839-845.
[40] 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.
[41] 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.
[42] 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.
[43] 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.
[44] 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.
[45] 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.
[46] AJCC Cancer Staging Manual, 8th ed. Amin MB, Edge SB, Greene F, et al. (editors) Springer, New York, 2017.
[47] 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.
[48] 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.
[49] 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.
[50] 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.
[51] 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.
[52] 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.
[53] 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.
[54] 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.
[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.

Continued

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PRINCIPLES OF PATHOLOGIC REVIEW - REFERENCES

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 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.

59 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.

60 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.

61 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.

62 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.

63 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.

64 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.

65 Parsms MT, Buchanan DD, Thompson B, et al. Correlation of tumor *BRAF* mutations and MLH-1 methylation with germline mismatch repair (MMR) gene mutation status: a literature review accessions utility of tumor features for MMR variant classification. J Med Genet 2012;49:151-157.

66 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.

67 Valtorta E, Martino C, Sartore-Bianchi A, et al. Assessment of a HER2 scoring system for colorectal cancer: results from a validation study. Mod Pathol 2015;28:1481-1491.

68 Evaluation of Trastuzumab in Combination With Lapatinib or Pertuzumab in Combination With Trastuzumab-Emtansine to Treat Patients With HER2-positive Metastatic Colorectal Cancer (HERACLES). https://clinicaltrials.gov/ct2/show/NCT03225937

69 Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:738-746.

70 Cenaj O, Ligon AH, Hornick JL, et al. Detection of ERBB2 amplification by next-generation sequencing predicts HER2 expression in colorectal carcinoma. Am J Clin Pathol 2019;152:97-108.

71 Solomon JP, Hechtman JF. Detection of NTRK fusions: Merits and limitations of current diagnostic platforms. Cancer Res 2019;79:3163-3168.

72 Cocco E, Benhamida J, Middha S, et al. Colorectal carcinomas containing hypermethylated MLH1 promotor and wild-type *BRAF*/KRAS are enriched for targetable kinase fusions. Cancer Res 2019;79:1047-1053.

73 Hechtman JF, Benayed R, Hyman DM, et al. Pan-Trk Immunohistochemistry is an efficient and reliable screen for the detection of NTRK fusions. Am J Surg Pathol 2017;41:1547-1551.

74 Solomon JP, Linkov I, Rosado A, et al. NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. Mod Pathol 2019 Aug 2 [Epub ahead of print].

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PRINCIPLES OF SURGERY

Transanal Local 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
  - Full-thickness excision must be feasible
- When the lesion can be adequately localized to the rectum, local excision of more proximal lesions may be technically feasible using advanced techniques, such as transanal microscopic surgery or transanal minimally invasive surgery (TAMIS).

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

- Management principles
  - The treating surgeon should be experienced in rectal cancer surgery, and specifically with TME. For patients with predicted positive margins based on preoperative imaging, or lateral pelvic lymph node involvement, the surgeon should be experienced in extended resections beyond the TME plane and have a multidisciplinary team available if necessary.[2]
  - The treating surgeon should assess the distal margin before initiating treatment by digital rectal examination ± rigid or flexible endoscopy, particularly for non-palpable lesions.
  - Anticipated circumferential margins should be assessed by MRI (See Principles of Imaging, REC-A) prior to any required neoadjuvant therapy, and again considered prior to surgery. If margins are involved, assessment for feasibility of resection beyond the TME plane is required. Such an extended resection (± reconstruction) should involve careful pre-operative planning and may require a multidisciplinary team.
  - Remove primary tumor with adequate circumferential and distal margins.
  - Treat draining lymphatics by TME.
  - Sphincter preservation and restoration of organ integrity should be achieved without compromise of oncologic resection and consideration of anticipated patient functional outcome and quality of life.
  - Surgery should be 5–12 weeks following full-dose 5.5-week neoadjuvant chemoradiation. For short-course neoadjuvant radiation therapy, surgery can be considered at 3–7 days or 4–8 weeks.
- TME is a standard component of radical rectal cancer surgery. TME reduces the positive radial margin and local recurrence rates.
  - 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,[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 TME.
    - ◊ 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 generally indicated for acute bowel obstruction or perforation from cancer.
    - ◊ Thorough abdominal exploration is required.
- Lymph node dissection[6,7]
  - Clinically suspicious nodes beyond the field of resection should be biopsied and/or removed, if possible. Extensive resection of M1 lymph nodes is not indicated.
  - Extended lymph node resection is not indicated in the absence of clinically suspected nodes.

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PRINCIPLES OF SURGERY
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.
- Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and 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 may be considered alone or in conjunction with resection for resectable disease. All original sites of disease need to be amenable to ablation or resection.
- Ablative techniques can also 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 or Ablatable Disease

- Re-evaluation for resection and ablation 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]

References

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PRINCIPLES OF SURGERY - 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] Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. Br J Surg 2013;100:1009-1014.
[3] Fleshman J, Branda ME, Sargent DJ, et al. Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: Follow-up results of the ACOSOG Z6051 randomized controlled trial. Ann Surg 2019;269:589-595.
[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, et al. Surgical resection of liver metastases from colo-rectal cancers. Int Surg 1987;72:70-72.
[13] Fong Y, Fortner J, Sun RL, et al. 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, et al. 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, et al. Surgery for pulmonary metastases from colorectal carcinoma. Ann Thorac Surg 2000;70:380-383.
[18] Sakamoto T, Tsubota N, Iwanaga K, et al. 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, et al. 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, 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.
[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):860-868.
[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):3939-3945.
[29] Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1284-1292.

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PRINCIPLES OF ADJUVANT THERAPY

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,[a] leucovorin 400 mg/m² IV day 1,[b] 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 months perioperative therapy.
- **Capecitabine[5]**
  Capecitabine 1000–1250 mg/m² PO twice daily days 1–14 every 3 weeks to a total of 6 months perioperative therapy.
- **CAPEOX[6,7]**
  Oxaliplatin 130 mg/m² IV day 1.[a] Capecitabine 1000 mg/m² PO 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 IV over 24 hours 5 or 7 days/week during XRT
- **XRT + Capecitabine[10,11]**
  Capecitabine 825 mg/m² PO twice daily 5 days/week + XRT x 5 weeks
- **XRT + 5-FU/leucovorin[12,c]**
  5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 days during week 1 and 5 of XRT

[a] 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 R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
[b] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[c] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

References

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PRINCIPLES OF ADJUVANT THERAPY - 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.
[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.
[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.
[9] 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] 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.
[11] 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.
[12] 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.

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PRINCIPLES OF RADIATION THERAPY

General Principles

- **Fluoropyrimidine-based chemotherapy should be delivered concurrently with radiation therapy.**
- **In patients with a limited number of liver or lung metastases, ablative radiotherapy to the metastatic site can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), or stereotactic body radiation therapy (SBRT).**

Treatment Information

- **Image-guided radiation therapy (IGRT) with kilovoltage (kV) imaging and cone-beam CT imaging should be routinely used during the course of treatment with IMRT and SBRT.**
- **IMRT/SBRT 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, or patients with localized oligometastases.**
- **Intraoperative radiation therapy (IORT), if available, may be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers. Arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.**
- **Target Volumes**
  - **Radiation therapy fields should include the tumor or tumor bed, with a 2- to 5-cm margin, the mesorectum, 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 is encouraged.**
  - **For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.**
- **RT Dosing**
  - **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 week of completion of therapy or delayed 6–8 weeks can also be considered for patients with stage T3 rectal cancer.[1]**
    - **For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.**
  - **If IORT is not available, 10–20 Gy external beam radiation therapy (EBRT) and/or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.**

Supportive Care

- **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.

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

INITIAL THERAPY[c]

Patient appropriate for intensive therapy

- **FOLFOX ± bevacizumab[d]**
  or
  CAPEOX ± bevacizumab[d]
  or
  FOLFOX + (cetuximab or panitumumab)[e]
  (*KRAS/NRAS/BRAF* WT only)
  → **Progression** → **See REC-F (2 of 13)**
- **or**
  FOLFIRI[f] ± bevacizumab[d]
  or
  FOLFIRI[f] + (cetuximab or panitumumab)[e]
  (*KRAS/NRAS/BRAF* WT only)
  → **Progression** → **See REC-F (3 of 13)**
- **or**
  FOLFOXIRI[f,g] ± bevacizumab[d]
  → **Progression** → **See REC-F (4 of 13)**
- **or**
  Pembrolizumab* (dMMR/MSI-H only)[e,h,i,j]
  → **Progression** → **See REC-F (5 of 13)**

See Evidence Blocks on REC-F (EB-1)

Patient not appropriate for intensive therapy

- **Infusional 5-FU + leucovorin ± bevacizumab[d]**
  or
  Capecitabine ± bevacizumab[d]
  or
  (Cetuximab or panitumumab)[e] (category 2B)
  (*KRAS/NRAS/BRAF* WT only)
  or
  (Nivolumab or pembrolizumab)
  (dMMR/MSI-H only)[e,h,i,j]
  or
  Nivolumab + ipilimumab
  (dMMR/MSI-H only)[e,h,i,j] (category 2B)
  or
  (Trastuzumab[k] + [pertuzumab or lapatinib])[e,l]
  (HER2-amplified and *RAS* and *BRAF* WT)

→ **Progression**

- **Improvement in functional status** → **Consider initial therapy as above[m]**
  or
  If previous fluoropyrimidine, see REC-F (5 of 13)
- **No improvement in functional status** → **Best supportive care**
  See NCCN Guidelines for Palliative Care

* Patients should be followed closely for 10 weeks to assess for response

See footnotes on REC-F (7 of 13)

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,n]

Previous oxaliplatin-based therapy without irinotecan

SUBSEQUENT THERAPY[c,o,p]

- FOLFIRI[f] or irinotecan[f]
  or
  FOLFIRI[f] + (bevacizumab[d,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r])
  or
  Irinotecan[f] + (bevacizumab[d,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r])
  - Irinotecan[f] + (cetuximab or panitumumab)[e,s,t] (*KRAS/NRAS/BRAF* WT only)
    - Regorafenib[w] or Trifluridine + tipiracil[w]
      - Regorafenib[w,x] or Trifluridine + tipiracil[w,x] or Best supportive care
        See NCCN Guidelines for Palliative Care
    - Regorafenib[w] or Trifluridine + tipiracil[w]
      - Regorafenib[w,x] or Trifluridine + tipiracil[w,x] or Best supportive care
        See NCCN Guidelines for Palliative Care
    - ([Nivolumab ± ipilimumab] or pembrolizumab)[v] (dMMR/MSI-H only)[e,h,i,j]
      or
      (Trastuzumab[k] + [pertuzumab or lapatinib])[e,l] (HER2-amplified and *RAS* and *BRAF* WT)
      - See Subsequent therapy
  - or
  - FOLFIRI[f] + (cetuximab or panitumumab)[e,s,t] (*KRAS/NRAS/BRAF* WT only)
    or
    Irinotecan[f] + (cetuximab or panitumumab)[e,s,t] (*KRAS/NRAS/BRAF* WT only)
    or
    Encorafenib + (cetuximab or panitumumab)[e,u] (*BRAF* V600E mutation positive)
    - Regorafenib[w] or Trifluridine + tipiracil[w]
      - Regorafenib[w,x] or Trifluridine + tipiracil[w,x] or Best supportive care
        See NCCN Guidelines for Palliative Care
    - ([Nivolumab ± ipilimumab] or pembrolizumab)[v] (dMMR/MSI-H only)[e,h,i,j]
      or
      (Trastuzumab[k] + [pertuzumab or lapatinib])[e,l] (HER2-amplified and *RAS* and *BRAF* WT)
      - See Subsequent therapy
  - or
  - ([Nivolumab ± ipilimumab] or pembrolizumab)[v] (dMMR/MSI-H only)[e,h,i,j]
    or
    (Trastuzumab[k] + [pertuzumab or lapatinib])[e,l] (HER2-amplified and *RAS* and *BRAF* WT)
    - See Subsequent therapy

See Evidence Blocks on REC-F (EB-2) and REC-F (EB-3)

See footnotes REC-F (7 of 13)

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,n]

Previous irinotecan-based therapy without oxaliplatin

SUBSEQUENT THERAPY[c,o,p]

- FOLFOX or CAPEOX
- or FOLFOX + bevacizumab[d]
- or CAPEOX + bevacizumab[d]
- or FOLFOX + (cetuximab or panitumumab)[e,s] (*KRAS/NRAS/BRAF* WT only)
- or Irinotecan[f] + (cetuximab or panitumumab)[e,s,t] (*KRAS/NRAS/BRAF* WT only)
- or Encorafenib + (cetuximab or panitumumab)[e,u] (*BRAF* V600E mutation positive)
- or ([Nivolumab ± ipilimumab] or pembrolizumab)[v] (dMMR/MSI-H only)[e,h,i,j]
- or (Trastuzumab[k] + [pertuzumab or lapatinib])[e,l] (HER2-amplified and *RAS* and *BRAF* WT)

→ See Subsequent therapy

- Irinotecan[f] + (cetuximab or panitumumab)[e,s,t] (*KRAS/NRAS/BRAF* WT only)
- or Regorafenib[w]
- or Trifluridine + tipiracil[w]
- or ([Nivolumab ± ipilimumab] or pembrolizumab)[v] (dMMR/MSI-H only)[e,h,i,j]
- or (Trastuzumab[k] + [pertuzumab or lapatinib])[e,l] (HER2-amplified and *RAS* and *BRAF* WT)

→ See Subsequent therapy

- FOLFOX or CAPEOX
- or ([Nivolumab ± ipilimumab] or pembrolizumab)[v] (dMMR/MSI-H only)[e,h,i,j]
- or (Trastuzumab[k] + [pertuzumab or lapatinib])[e,l] (HER2-amplified and *RAS* and *BRAF* WT)

→ See Subsequent therapy

- Regorafenib[w]
- or Trifluridine + tipiracil[w]

- Regorafenib[w]
- or Trifluridine + tipiracil[w]

- Regorafenib[w,x]
- or Trifluridine + tipiracil[w,x]
- or Best supportive care

See NCCN Guidelines for Palliative Care

See Evidence Blocks on REC-F (EB-2) and REC-F (EB-3)

See footnotes REC-F (7 of 13)

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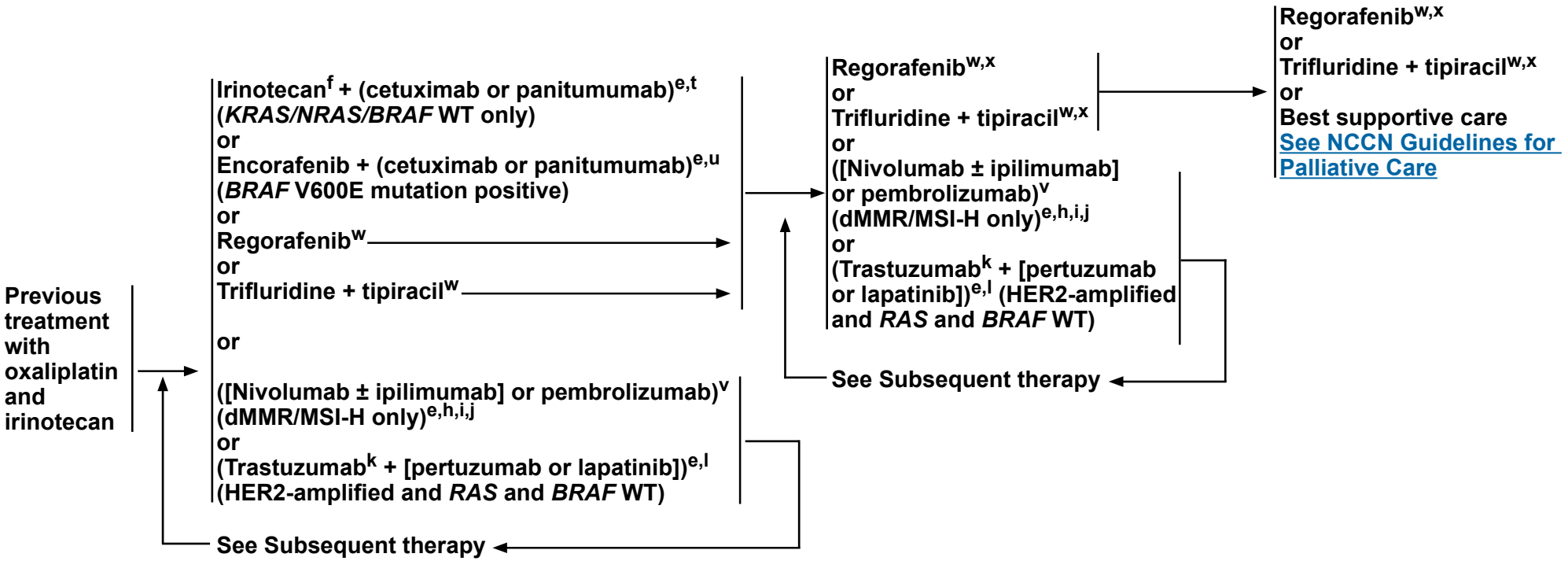
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,n]

SUBSEQUENT THERAPY[c,o,p]



See Evidence Blocks on REC-F (EB-2) and REC-F (EB-3)

See footnotes REC-F (7 of 13)

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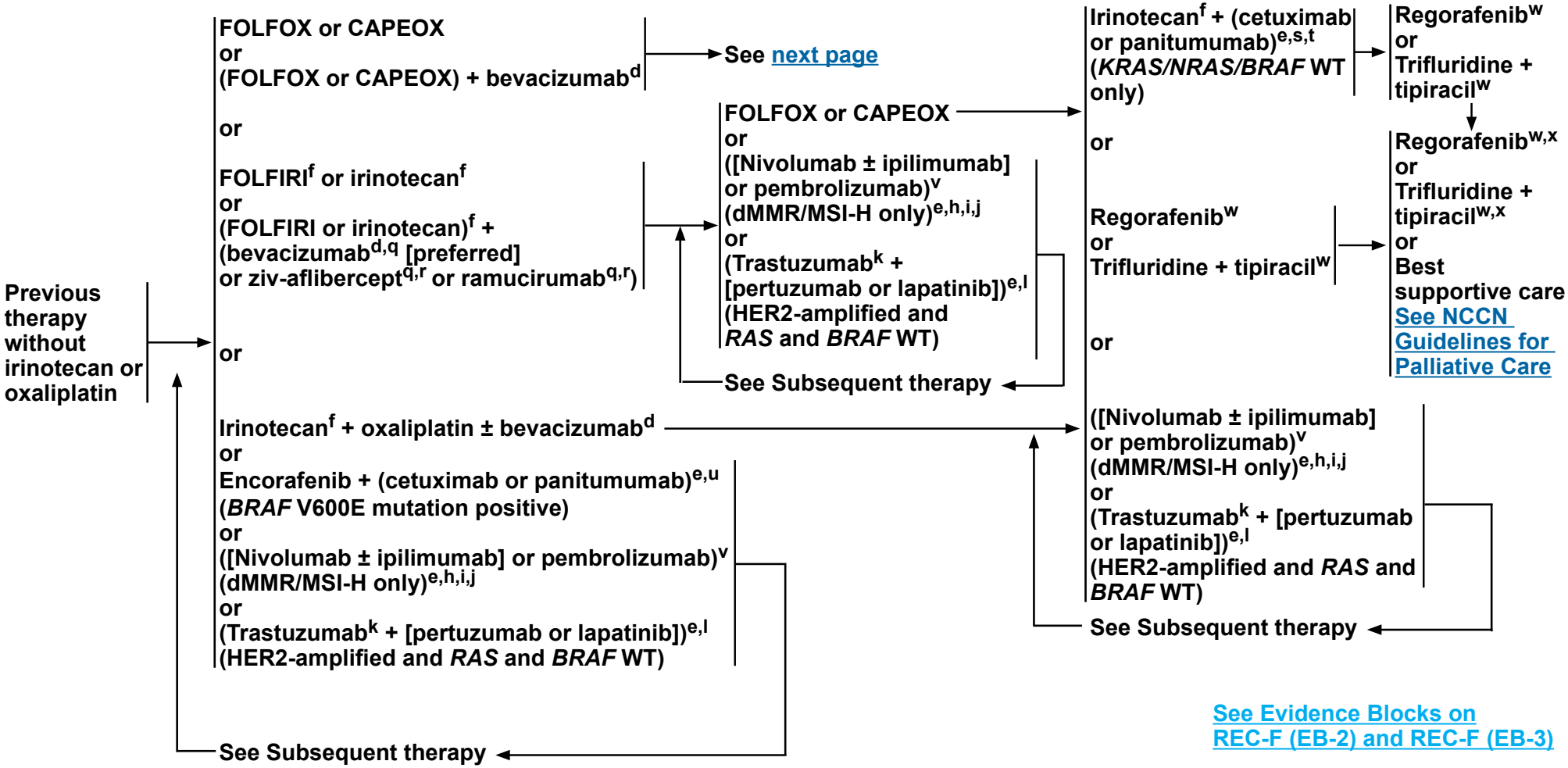
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,n]

SUBSEQUENT THERAPY[c,o,p]



See Evidence Blocks on REC-F (EB-2) and REC-F (EB-3)

See footnotes REC-F (7 of 13)

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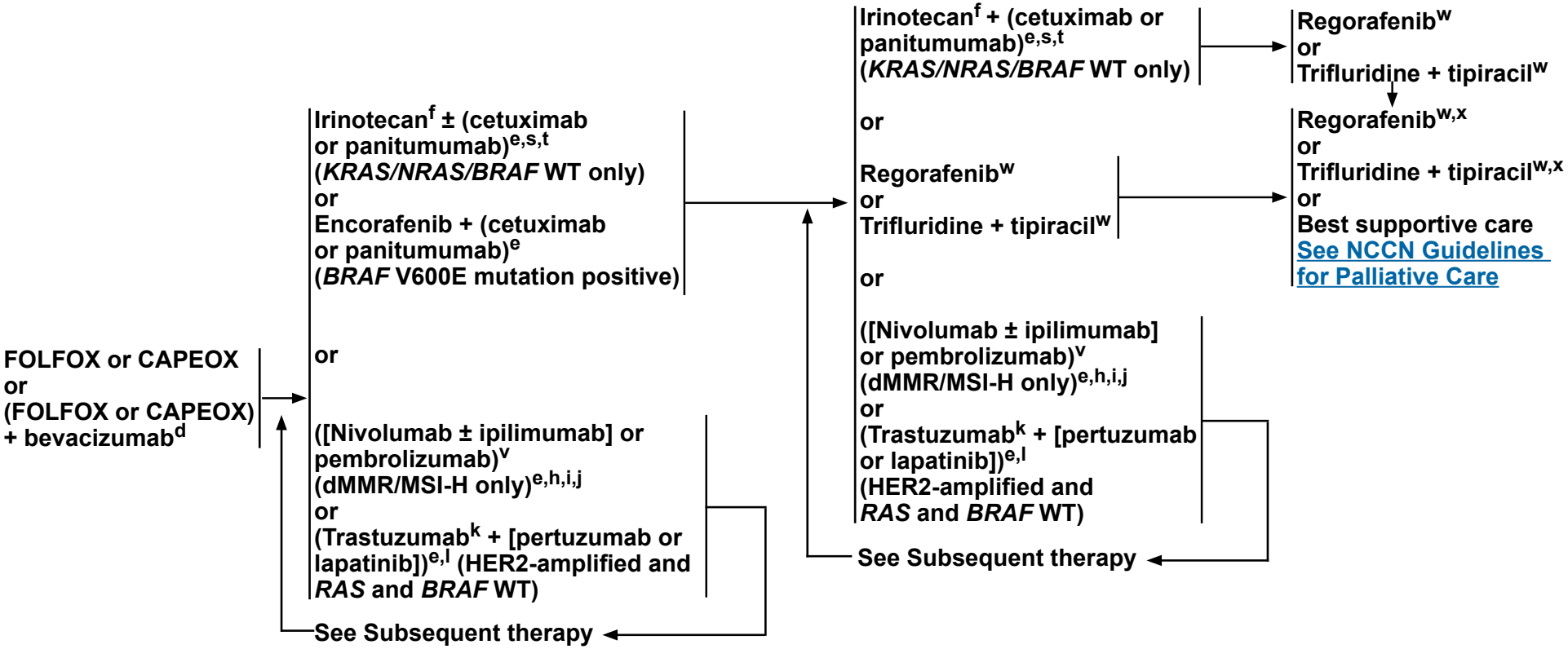
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,n]

SUBSEQUENT THERAPY[c,o,p] following fluoropyrimidine without irinotecan or oxaliplatin



See Evidence Blocks on REC-F (EB-2) and REC-F (EB-3)

See footnotes REC-F (7 of 13)

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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC DISEASE
REC-F (1 OF 13)

Regimen	First-Line Therapy
FOLFOX	
FOLFOX/bevacizumab	
FOLFOX/cetuximab	
FOLFOX/panitumumab	
CapeOx	
CapeOx/bevacizumab	
5-FU/leucovorin	
FOLFIRI	
FOLFIRI/bevacizumab	
FOLFIRI/cetuximab	
FOLFIRI/panitumumab	

Regimen	First-Line Therapy
FOLFOXIRI	
FOLFOXIRI/bevacizumab	
5-FU/leucovorin/bevacizumab	
Capecitabine	
Capecitabine/bevacizumab	
Cetuximab	
Panitumumab	
Nivolumab	
Pembrolizumab	
Nivolumab/ipilimumab	
Trastuzumab/Pertuzumab	
Trastuzumab/Lapatinib	

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National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2020
Rectal Cancer
NCCN Evidence Blocks™

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

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Discussion

EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC DISEASE

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FOLFIRI/bevacizumab (no prior bevacizumab)	
FOLFIRI/ziv-aflibercept (after prior bevacizumab)	
FOLFIRI/ziv-aflibercept (no prior bevacizumab)	
FOLFIRI/ramucirumab (after prior bevacizumab)	
FOLFIRI/ramucirumab (no prior bevacizumab)	
FOLFIRI/cetuximab	
FOLFIRI/panitumumab	
Irinotecan	
Irinotecan/cetuximab	
Irinotecan/panitumumab	

Regimen	Second-Line Therapy
Encorafenib/cetuximab	
Encorafenib/panitumumab	
Larotrectinib	
Entrectinib	
Irinotecan/bevacizumab (after prior bevacizumab)	
Irinotecan/bevacizumab (no prior bevacizumab)	
Irinotecan/ziv-aflibercept (after prior bevacizumab)	
Irinotecan/ziv-aflibercept (no prior bevacizumab)	
Irinotecan/ramucirumab (after prior bevacizumab)	
Irinotecan/ramucirumab (no prior bevacizumab)	
Irinotecan/oxaliplatin	
IROX/bevacizumab (after prior bevacizumab)	
IROX/bevacizumab (no prior bevacizumab)	
Nivolumab	
Pembrolizumab	
Nivolumab/ipilimumab	

Regimen	Second-Line Therapy
Trastuzumab/pertuzumab	
Trastuzumab/lapatinib	
FOLFOX	
FOLFOX/bevacizumab (after prior bevacizumab)	
FOLFOX/bevacizumab (no prior bevacizumab)	
CapeOx/bevacizumab (after prior bevacizumab)	
CapeOx/bevacizumab (no prior bevacizumab)	
Regorafenib	
Trifluridine/tipiracil	
CapeOx	
Panitumumab	
Cetuximab	

Previous oxaliplatin-based therapy on REC-F (2 of 13)
Previous irinotecan-based therapy on REC-F (3 of 13)
Previous FOLFOXIRI on REC-F (4 of 13)
Previous fluoropyrimidine on REC-F (5 of 13)

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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC DISEASE

Regimen	Third-Line Therapy	Subsequent Therapy
CapeOx		
Cetuximab		
FOLFOX		
Irinotecan		—
Irinotecan/cetuximab		
Irinotecan/panitumumab		
Encorafenib/cetuximab		
Encorafenib/panitumumab		
Larotrectinib		
Entrectinib		
Nivolumab		
Pembrolizumab		
Nivolumab/ipilimumab		

Regimen	Third-Line Therapy	Subsequent Therapy
Trastuzumab/pertuzumab		
Trastuzumab/lapatinib		
Panitumumab		
Regorafenib (previous trifluridine/tipiracil)		
Regorafenib (no previous trifluridine/tipiracil)		
Trifluridine/tipiracil (previous regorafenib)		
Trifluridine/tipiracil (no previous regorafenib)		

Previous oxaliplatin-based therapy on REC-F (2 of 13)
Previous irinotecan-based therapy on REC-F (3 of 13)
Previous FOLFOXIRI on REC-F (4 of 13)
Previous fluoropyrimidine on REC-F (5 of 13)

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE
FOOTNOTES

[a] For chemotherapy references, see Chemotherapy Regimens and References (REF-F [8 of 13]).
[b] For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[c] Chest/abdominal/pelvic CT with contrast or chest CT and abdominal/pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used. See Principles of Imaging (REC-A).
[d] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[e] See Principles of Pathologic Review (REC-B 5 of 9).
[f] Irinotecan should be used with caution 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.
[g] FOLFOXIRI should be strongly considered for patients with excellent performance status.
[h] These therapies are FDA approved for colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. However, a number of patients in the clinical trials had not received all three prior systemic therapies. Thirty-seven percent of patients received nivolumab monotherapy and 24% received ipilimumab/nivolumab combination therapy in first- or second-line, and 28% and 31% of patients had not received all three indicated prior therapies before treatment with nivolumab or ipilimumab/nivolumab, respectively.
[i] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[j] If disease response, consider discontinuing checkpoint inhibitor after 2 years of treatment.
[k] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[l] If no previous HER2 inhibitor.
[m] The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.
[n] Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases. See Principles of Surgery (REC-C).
[o] Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.
[p] If patients had therapy stopped for reasons other than progression (eg, cumulative toxicity, elective treatment break, patient preference), rechallenge is an option at time of progression.
[q] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[r] 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.
[s] If neither previously given.
[t] Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.
[u] In the second-line setting for *BRAF* V600E mutation positive tumors, there is phase 3 evidence for better efficacy with targeted therapies over FOLFIRI.
[v] If no previous treatment with a checkpoint inhibitor.
[w] Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.
[x] If not previously given.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

mFOLFOX 6[1,2,3,y]
Oxaliplatin 85 mg/m² IV day 1[z]
Leucovorin 400 mg/m² IV day 1[aa]
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

mFOLFOX7[4]
Oxaliplatin 85 mg/m² IV day 1[z]
Leucovorin 400 mg/m² IV day 1[aa]
5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

FOLFOX + bevacizumab[5,c]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFOX + panitumumab[6] (*KRAS/NRAS/BRAF* WT only)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFOX + cetuximab[7] (*KRAS/NRAS/BRAF* WT only)
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[8]
Oxaliplatin 130 mg/m² IV day 1[z]
Capecitabine 1000[bb] mg/m² twice daily PO for 14 days
Repeat every 3 weeks

CAPEOX + bevacizumab[8,c,y]
Oxaliplatin 130 mg/m² IV day 1[z]
Capecitabine 1000[bb] mg/m² PO twice daily for 14 days
Bevacizumab 7.5 mg/kg IV day 1
Repeat every 3 weeks

FOLFIRI[9,10]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin[aa] 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks

FOLFIRI + bevacizumab[11,c,y]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[y] 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).
[z] 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 R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
[aa] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[bb] 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.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

FOLFIRI + cetuximab (*KRAS/NRAS/BRAF* WT only)
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly[12]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

FOLFIRI + panitumumab[14] (*KRAS/NRAS/BRAF* WT only)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept[15]
Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ramucirumab[16]
Ramucirumab 8 mg/kg over 60 minutes, day 1
Repeat every 2 weeks

FOLFOXIRI[17]
Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² IV day 1,[z]
Leucovorin 400[aa] mg/m² day 1, fluorouracil 1200 mg/m²/day x 2 days (total 2400 mg/m² over 48 hours) continuous infusion starting on day 1.
Repeat every 2 weeks
The dose used in European studies was 3200 mg/m². U.S. patients have been shown to have poorer tolerance for 5-FU. The dose listed above is recommended for U.S. patients.

FOLFOXIRI + bevacizumab[18,c,y]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

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

IROX + bevacizumab[c,y]
Bevacizumab 7.5 mg/kg IV on day 1
Repeat every 3 weeks

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[20]
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)[9]
Leucovorin[aa] 400 mg/m² IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks

Weekly
Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV bolus injection 1 hour after the start of leucovorin. Repeat weekly.[21]
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week[21]

Bolus or infusional 5-FU + bevacizumab[c,y]
Bevacizumab 5 mg/kg IV on day 1
Repeat every 2 weeks

[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[y] 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).
[z] 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 R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
[aa] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

Capecitabine[22,bb]
Capecitabine 850–1250 mg/m² PO twice daily, days 1–14
Repeat every 3 weeks

Capecitabine + bevacizumab[23,c,y]
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Irinotecan
Irinotecan 125 mg/m² IV over 30–90 minutes, days 1 and 8
Repeat every 3 weeks[24,25]
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

Irinotecan + cetuximab (*KRAS/NRAS/BRAF* WT only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[26]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

Irinotecan + panitumumab[14,27] (*KRAS/NRAS/BRAF* WT only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Irinotecan + bevacizumab[28,c,y]
Irinotecan 180 mg/m² IV, day 1
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks
or
Irinotecan 300–350 mg/m² IV, day 1
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Irinotecan + ramucirumab[16]
Ramucirumab 8 mg/kg IV over 60 minutes every 2 weeks

Irinotecan + ziv-aflibercept
Irinotecan 180 mg/m² IV, day 1
Ziv-aflibercept 4 mg/kg IV, day 1
Repeat every 2 weeks

Cetuximab (*KRAS/NRAS/BRAF* WT only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[26]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

Panitumumab[29] (*KRAS/NRAS/BRAF* WT only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib
Regorafenib 160 mg PO daily on days 1–21[30]
or
First cycle: Regorafenib 80 mg PO daily on days 1–7, then 120 mg PO daily on days 8–14, then 160 mg PO daily on days 15–21[31]
Subsequent cycles: Regorafenib 160 mg PO daily on days 1–21
Repeat every 28 days

Trifluridine + tipiracil[32]
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

[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[y] 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).
[bb] 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.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

Pembrolizumab[33] (dMMR/MSI-H only)
Pembrolizumab 2 mg/kg IV every 3 weeks
or Pembrolizumab 200 mg IV every 3 weeks
or Pembrolizumab 400 mg IV every 6 weeks

Nivolumab[34] (dMMR/MSI-H only)
Nivolumab 3 mg/kg every 2 weeks
or Nivolumab 240 mg IV every 2 weeks
or Nivolumab 480 mg IV every 4 weeks

Nivolumab + ipilimumab[35] (dMMR/MSI-H only)
Nivolumab 3 mg/kg (30-minute IV infusion) and ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for four doses, then Nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 4 weeks

Trastuzumab[k] + pertuzumab[36]
(HER2-amplified and *RAS* and *BRAF* WT)
Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, then 6 mg/kg IV every 21 days
Pertuzumab 840 mg IV loading dose on day 1 of cycle 1, then 420 mg IV every 21 days

Trastuzumab[k] + lapatinib[37]
(HER2-amplified and *RAS* and BRAF WT)
Trastuzumab 4 mg/kg IV loading dose on day 1 of cycle 1, then 2 mg/kg IV weekly
Lapatinib 1000 mg PO daily

Encorafenib + cetuximab[38-40]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Cetuximab 400 mg/m^2 followed by 250 mg/m^2 weekly

Encorafenib + panitumumab[38-40]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

Larotrectinib[41]
(*NTRK* gene fusion positive)
100 mg PO twice daily

Entrectinib[42]
(*NTRK* gene fusion positive)
600 mg PO once daily

[k] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

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References

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES

[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.

[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] Hochster HS, Grothey A, Hart L, et al. Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONcePT. Ann Oncol 2014;25:1172-1178.

[5] 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.

[6] 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.

[7] Venook AP, Niedzwiecki D, Lenz H-J, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wildtype advanced or metastatic colorectal cancer: A randomized clinical trial. JAMA 2017;317:2392-2401.

[8] 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.

[9] 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.

[10] 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.

[11] 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;15:1065-1075.

[12] 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.

[13] 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.

[14] 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.

[15] 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.

[16] 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.

[17] 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.

[18] Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015;16:1306-1315.

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

[20] 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.

[21] 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.

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

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES

[23] Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol 2013;14:1077-1085.
[24] 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.
[25] 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.
[26] 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.
[27] Andre T, Blons H, Mabro M, et al. Panitumumab combined with irinotecan for patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study. Ann Oncol 2013;24:412-419.
[28] Yildiz R, Buyukberber S, Uner A, et al. Bevacizumab plus irinotecan-based therapy in metastatic colorectal cancer patients previously treated with oxaliplatin-based regimens. Cancer Invest 2010;28:33-37.
[29] 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.
[30] 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.
[31] Bekaii-Saab, TS, Ou F-S, Anderson DM, et al. Regorafenib dose optimization study (ReDOS): Randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC)—An ACCRU Network study. J Clin Oncol 2018;36(suppl 4S;abstr 611).
[32] 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.
[33] Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-2520.
[34] Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair deficient/microsatellite instability–high colorectal cancer (CheckMate 142): results of an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-1191
[35] Overman MJ, Lonardi S, Wong K et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair–deficient/microsatellite instability–high metastatic colorectal cancer. J Clin Oncol 2018;36:773-779.
[36] Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2019;20:518-530.
[37] Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:738-746.
[38] Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with *BRAF* V600E-mutant metastatic colorectal cancer: Safety lead-in results from the phase III BEACON Colorectal Cancer Study. J Clin Oncol 2019;37:1460-1469.
[39] Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E-Mutated Colorectal Cancer. N Engl J Med. 2019;381:1632-1643.
[40] Kopetz S, Grothey A, Van Cutsem E. et al. Encorafenib plus cetuximab with or without binimetinib for BRAF V600E-mutant metastatic colorectal cancer: Quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC) [abstract]. J Clin Oncol 2020;38,(suppl 4;abstr 8).
[41] Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739.
[42] Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with *NTRK* fusion-positive tumours: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. ESMO 2018 Congress Presentation. October 21, 2018.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer 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-11.
- 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.

Survivorship Care Planning

The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to the patient.[1]

- Develop survivorship care plan that includes:
  - Overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received.
  - Description of possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment.
  - Surveillance recommendations.
  - Delineate appropriate timing of transfer of care with specific responsibilities identified for primary care physician and oncologist.
  - Health behavior recommendations.

Management of Late/Long-Term Sequelae of Disease or Treatment[2-6]

- For issues related to distress, pain, neuropathy, fatigue, or sexual dysfunction, see NCCN Guidelines for Survivorship.
- Bowel function changes: chronic diarrhea, incontinence, stool frequency, stool clustering, urgency, cramping
  - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, pelvic floor rehabilitation, and protective undergarments.
  - Management of an ostomy
    - ◊ Consider participation in an ostomy support group or coordination of care with a health care provider specializing in ostomy care (ie, ostomy nurse).
    - ◊ Screen for distress around body changes (See NCCN Guidelines for Distress Management) and precautions around involvement with physical activity (SPA-A in the NCCN Guidelines for Survivorship).
- For oxaliplatin-induced neuropathy
  - Consider duloxetine for painful neuropathy only, not effective for numbness, tingling, or cold sensitivity.[7]
  - Refer to pain management specialist for refractory cases.
  - Pregabalin or gabapentin are not recommended.
- Urogenital dysfunction after resection and/or pelvic radiation[8,9]
  - 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.
- Potential for pelvic fractures/decreased bone density after pelvic radiation
  - Consider bone density monitoring.

Counseling Regarding Healthy Lifestyle and Wellness[10]

See NCCN Guidelines for Survivorship

- Undergo all age and gender-appropriate cancer and preventive health screenings as per national guidelines.
- 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. Diet recommendations may be modified based on severity of bowel dysfunction.
- Consider daily aspirin 325 mg for secondary prevention.
- Eliminate or limit alcohol consumption, no more than 1 drink/day for women, and 2 drinks/day for men.
- 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.

References

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

[1] Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.:The National Academies Press;2006.
[2] Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer. Cancer 2007;110: 2075-2082.
[3] 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.
[4] Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. Aliment Pharmacol Ther 2003;18:987-994.
[5] 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.
[6] 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.
[7] Lavoie Smith EM, Pang H, Cirrincione C, et al. Effect pf duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy. JAMA 2013;309:1359-1367.
[8] Lange MM, Mass CP, Marijnen CAM, et al. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer 2009;45:1578-88.
[9] 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.
[10] Kushi LH, Byers T, Doyle C, et al and The American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity CA Cancer J Clin 2006;56:254-281.

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American Joint Committee on Cancer (AJCC) TNM Staging Classification for Rectal Cancer 8th ed., 2017

Table 1. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres** to adjacent organs or structures

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

M	**Distant Metastasis**
M0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

* 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).

** 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 classification should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Rectal Cancer 8th ed., 2017

Table 2. **Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 6.2020
Rectal Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Rectal Cancer. Last updated 06/25/20

Table of Contents

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2020, an estimated 43,340 new cases of rectal cancer will occur in the United States (25,960 cases in men; 17,380 cases in women). During the same year, it is estimated that 53,200 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 addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[3] and is currently down by about 50% from peak mortality rates.[1] These improvements in incidence of and mortality from CRC are thought to be a result of cancer prevention and earlier diagnoses through screening and of better treatment modalities.

More recent data show continued rapid declines in incidence among those aged 65 years or older, with a decrease of 3.3% annually between 2011 and 2016.[4] Conversely, incidence has increased among those younger than 65 years, with a 1% annual increase in those aged 50 to 64 years and 2% annual increase in those younger than 50 years. CRC death rates also showed age-dependent trends, declining by 3% annually for those 65 years and older, compared to a 0.6% annual decline for individuals aged 50 to 64 years and a 1.3% annual increase for individuals younger than 50 years.[4] Likewise, a retrospective cohort study of the SEER CRC registry found that the incidence of CRC in patients younger than 50 years has been increasing.[5] 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. One review suggests that CRC that occurs in young adult patients may be clinicopathologically and genetically different from CRC in older adults, although this has not been confirmed broadly. If cancer in this population is different, there would be a need to develop specific treatment strategies for this population.[6]

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer. These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, perioperative treatment, 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 CRC 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 CRC, 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 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 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 CRC are associated with familial clustering, and first-degree relatives of patients with colorectal adenomas or invasive CRC are at increased risk for CRC.[8-12] Genetic susceptibility to CRC includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis CRC [HNPCC]) and familial adenomatous polyposis (FAP).[13-15] Therefore, it is recommended that all patients with CRC be queried regarding their family history and considered for risk assessment, as detailed in the NCCN Guidelines for Colorectal Cancer Screening. Results from a randomized controlled trial (RCT) suggest that most individuals without a personal history of CRC and with one first-degree relative with CRC diagnosed before age 50 years or two first-degree relatives with CRC diagnosed at any age can safely be screened with colonoscopy every 6 years.[16]

CRC is a heterogeneous disease. An international consortium recently reported a molecular classification, defining four different subtypes: CMS1 (MSI Immune), hypermutated, microsatellite unstable (see *Lynch Syndrome* and *Microsatellite Instability*, below), with strong immune activation; CMS2 (Canonical), epithelial, chromosomally unstable, with marked WNT and MYC signaling activation; CMS3 (Metabolic), epithelial, with evident metabolic dysregulation; and CMS4 (Mesenchymal), prominent transforming growth factor β activation, stromal invasion, and angiogenesis.[17] However, this classification is not yet recommended in clinical practice.

Lynch Syndrome

Lynch syndrome is the most common form of genetically determined CRC predisposition, accounting for 2% to 4% of all CRC cases.[13,14,18,19] 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 CRC specimens to identify individuals who might have Lynch syndrome: 1) immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation; or 2) analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units.[20] 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.[20]

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.[21-24] The cost-effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for CRC, and this approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the Centers for Disease Control and Prevention (CDC)[25-27] and by the American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and ASCO in a guideline on molecular

biomarkers for CRC.[28] The U.S. Multi-Society Task Force on Colorectal Cancer also recommends universal genetic testing of tumors of all patients with newly diagnosed CRC, as does the American Gastroenterological Association.[29,30] The Cleveland Clinic recently reported on its experiences implementing such a screening approach.[31]

The NCCN Colon/Rectal Cancer Panel endorses universal MMR or MSI testing of all patients with newly diagnosed colon or rectal cancer to identify individuals with Lynch syndrome. This testing is also relevant for treatment selection in stage IV disease (see *Systemic Therapy for Advanced or Metastatic Disease*, below). An infrastructure needs to be in place to handle the screening results in either case. A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening.

The Role of Vitamin D in CRC

Prospective studies have suggested that vitamin D deficiency may contribute to CRC incidence and/or that vitamin D supplementation may decrease CRC risk.[32-38] Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with CRC.[39-42] In fact, a systematic review and meta-analysis of 5 studies totaling 2330 patients with CRC compared the outcomes of patients in the highest and lowest categories of vitamin D levels and found better overall survival (OS) (hazard ratio [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.[43] Another meta-analysis determined that the relationship between vitamin D levels and mortality is linear.[44]

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.[45] A later analysis of the same study reported that the effect of vitamin D supplementation on recurrence of advanced adenomas varied significantly based on the genotype of the vitamin D receptor, indicating that only individuals with specific vitamin D receptor alleles may benefit from vitamin D supplementation for prevention of advanced adenomas.[46]

Furthermore, no study has yet definitively shown that vitamin D supplementation improves outcomes in patients with CRC. Several studies have reported that supplementation did not improve survival.[47-49] In addition, while the randomized, double-blind, phase II SUNSHINE trial reported a longer progression-free survival (PFS) for previously untreated metastatic CRC (mCRC) patients randomized to standard treatment plus high-dose vitamin D supplementation compared to those randomized to standard treatment plus low-dose vitamin D supplementation (13.0 months vs. 11.0 months), this difference was not significant (HR, 0.64; 95% CI, 0–0.90; P = .02).[50] There was also no significant difference between high- and standard-dose vitamin D supplementation for overall response rate (ORR) or OS. In a 2010 report, the Institute of Medicine (now known as the National Academy of Medicine) concluded that data supporting a role for vitamin D were only conclusive in bone health, and not in cancer and other diseases.[51] 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 CRC.

Other Risk Factors for CRC

It is well-recognized that individuals with inflammatory bowel disease (ie, ulcerative colitis, Crohn's disease) are at an increased risk for CRC.[52-54] Other possible risk factors for the development of CRC 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).[53,55-70] In fact, in the EPIC cohort of almost 350,000 individuals, those who adhered to five healthy lifestyle

factors (healthy weight, physical activity, non-smoking, limited alcohol consumption, and healthy diet) had an HR for the development of CRC of 0.63 (95% CI, 0.54–0.74) compared with those who adhered to ≤1 of the factors.[71] Other large studies support the conclusion that adherence to healthy lifestyle factors can reduce the risk of CRC.[72,73]

Some data suggest that consumption of dairy may lower risk for the development of CRC.[70,74,75] However, a recent systematic review and meta-analysis of 15 cohort studies (>900,000 subjects; >5200 cases of CRC) only found an association between risk for colon cancer in men and the consumption of nonfermented milk.[76] 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 CRC, including the consumption of fish and legumes.[77-79] Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may also decrease the risk for CRC.[80-85] In fact, the USPSTF recommends that adults aged 50 to 59 years with a 10-year cardiovascular disease risk ≥10% and a life expectancy of ≥10 years and without an increased bleeding risk take low-dose aspirin daily for at least 10 years for the primary prevention of both cardiovascular disease and CRC.[86]

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption are associated with a poor prognosis.[61,87-91] Conversely, post-diagnosis fish consumption may be associated with a better prognosis.[92] A family history of CRC increases risk while improving prognosis.[93] Data on the effect of dairy consumption on prognosis after diagnosis of CRC are conflicting.[94,95]

The relationship between diabetes and CRC is complex. Whereas diabetes and insulin use may increase the risk of developing CRC, treatment with metformin appears to decrease risk, at least in women.[96-105] Results of a small randomized study suggest that 1 year of low-dose metformin in non-diabetic patients with previously resected colorectal adenomas or polyps may reduce the likelihood of subsequent adenomas or polyps.[106] In addition, although patients with CRC and diabetes appear to have a worse prognosis than those without diabetes,[107,108] patients with CRC and diabetes treated with metformin seem to have a survival benefit over those not treated with metformin.[102,109,110] The data regarding the effects of metformin on CRC incidence and mortality, however, are not completely consistent, with some studies seeing no effect.[111,112]

TNM Staging

The NCCN Guidelines for Rectal Cancer adhere to the current TNM (tumor, node, metastases) staging system of the AJCC Cancer Staging Manual (Table 1 of the guidelines).[113] The TNM categories reflect very similar survival outcomes for rectal and colon cancer; these diseases therefore share the same staging system.

In the 8th edition of the AJCC Cancer Staging Manual, T1 tumors involve the submucosa; T2 tumors penetrate through the submucosa into the muscularis propria; T3 tumors penetrate through the muscularis propria; T4a tumors directly penetrate to the surface of the visceral peritoneum; and T4b tumors directly invade or are adherent to other organs or structures.[113]

Regional lymph node classification includes N1a (1 positive lymph node); N1b (2–3 positive lymph nodes), N2a (4–6 positive nodes); and N2b (7 or more positive nodes). In addition, tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis (ie, satellite tumor nodules) have been classified as N1c. Within each T stage, survival is inversely correlated with N stage (N0, N1a, N1b, N2a, and N2b).[113]

In rectal cancer, T stage has more prognostic value than N stage: patients with stage IIIA disease (T1–2) have longer rectal cancer-specific survival than patients with stage IIA (T3), IIB (T4a), and IIC (T4b) rectal cancer.[114]

Metastatic disease is classified as M1a when metastases are to only one site/solid organ (including to lymph nodes outside the primary tumor regional drainage area). M1b is used for metastases to multiple distant sites or solid organs, exclusive of peritoneal carcinomatosis. The 8th edition of the AJCC Cancer Staging Manual includes the M1c category for peritoneal carcinomatosis with or without blood-borne metastasis to visceral organs.[113] Patients with peritoneal metastases have a shorter PFS and OS than those without peritoneal involvement.[115]

The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.[113]

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 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, circumferential (radial), and mesenteric margins[116-120]; 8) neoadjuvant treatment effect[121,122]; 9) lymphovascular invasion (LVI)[123]; 10) perineural invasion (PNI)[124-126]; and 11) the number of tumor deposits.[127-131]

Margins

The 8th 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.[113]

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer.[132] 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.[132] 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 (mm). 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.[133] The panel defines an involved or threatened CRM as tumor within 1 mm from the resected margin.[118,120,134,135] This definition differs slightly from the recommendations of the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting in that ESGAR defined the mesorectal fascia as “involved” when the distance between the mesorectal fascia and the tumor is ≤1 mm, while in their template, “threatened/involved” is listed as ≤2 mm.[136]

Accurate pathologic assessment of the CRM of resected rectal tumor specimens is crucial, because the CRM has been shown to be a strong predictor of both local recurrence and OS,[132,134,137,138] including in patients undergoing neoadjuvant therapy,[119,139] and is an important consideration when postoperative treatment decisions are made. Furthermore, in a retrospective study of more than 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.[119] 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 CAP recommend evaluation of 12 lymph nodes to accurately identify early-stage CRCs.[113,132,140] The number of lymph nodes that can be retrieved varies with age and gender of the patient and on tumor grade or site.[141] The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify early-stage rectal cancer.[142] 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.[143,144] 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.[145] 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, $P \leq .0001$).[146-148] In fact, retrieval of fewer lymph nodes may be a marker of a higher tumor response and better prognosis following neoadjuvant treatment.[149,150]

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.[151,152] 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.[152,153] In addition, results of one study demonstrated that, following neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.[154] Furthermore, in a recent study involving 156 patients with colon cancer and 44 patients with rectal cancer, this “ultrastaging” of lymph nodes only changed the staging for 1% of patients.[155] Others have noted that micrometastasis found in node-negative patients did not predict outcome.[156] 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.[157]

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.[158] 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.[159] The 8th edition of the AJCC Cancer Staging Manual notes that micrometastases have been defined as clusters of 10 to 20 tumor cells or clumps of tumor ≥0.2 mm in diameter and recommends that these micrometastases be considered as standard positive nodes.[113]

Response to Treatment

The most recent CAP Guidelines require that the pathology report comment on treatment effects of neoadjuvant therapy.[140] 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).[121,122,140,160]

Perineural Invasion

Several studies have demonstrated that the presence of PNI is associated with a significantly worse prognosis.[124-126,161-163] 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.[125] 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).[126] Similar results were seen for patients with stage III disease.[124] A meta-analysis that included 58 studies and 22,900 patients also found that PNI is associated with a worse 5-year OS (Relative risk [RR], 2.09; 95% CI, 1.68–2.61) and 5-year DFS (RR, 2.35; 95% CI, 1.66–3.31).[162] PNI is therefore included as a high-risk factor for systemic recurrence.

Tumor Deposits

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 tumor deposits should be recorded in the pathology report, since they have been shown to be associated with reductions in DFS and OS.[127-131,163] 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).[131] Another retrospective study found a similar difference in 5-year OS rates (80.3% vs. 34.9%, respectively; P < .001).[164] The association of tumor deposits with decreased survival also holds in patients with rectal cancer who had neoadjuvant chemoradiation (chemoRT).[165-167] Tumor deposits are classified as pN1c.[113]

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 the pathology[168] 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).[169] Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore incapable of regional nodal metastasis.[132] The panel recommends marking the malignant polyp site at the time of colonoscopy or within 2 weeks if deemed necessary by the surgeon. All patients with a malignant polyp should undergo MMR or MSI testing at diagnosis.

In patients with pedunculated or sessile polyps (adenomas), no additional surgery is required if the polyp has been completely resected with favorable histologic features.[168,170] Favorable histologic features include lesions of grade 1 or 2 without angiolymphatic invasion and with a negative resection margin.[168] 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* 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. A complete workup is recommended prior to surgery for patients with polyps showing these characteristics since

extensive disease is more likely in this situation (see section on *Clinical Evaluation/Staging* under *Management of Localized Rectal Cancer*). 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.[168,171-173] In addition, several studies have shown that tumor budding is an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.[174-177]

Rectal surgery consists of either a transanal local excision, if appropriate, or a transabdominal resection. In patients with unfavorable pathologic features, transabdominal resection should be considered in order to include lymphadenectomy. All patients who have malignant polyps removed by transanal local excision or transabdominal resection should undergo total colonoscopy to rule out other synchronous polyps and should undergo surveillance as described in the guidelines.

Management of Localized Rectal Cancer

Rectal cancer is a cancerous lesion in the rectum, which lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI (see Figure 1). The rectum ends at the superior border of the functional anal canal, defined as the palpable upper border of the anal sphincter and puborectalis muscles of the anorectal ring.

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.[178] Furthermore, the risk of pelvic recurrence is higher in patients with rectal cancer compared to those with colon cancer, and locally recurrent rectal cancer is associated with a poor prognosis.[179-181] Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy that combines chemoRT, chemotherapy, and operative treatment for most patients is recommended.[182]

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 whether to recommend preoperative chemoRT, the implications of either clinically understaging or overstaging rectal cancer can be substantial. Based on this, a multidisciplinary team evaluation is recommended, including a formal surgical evaluation. A discussion of infertility risks and counseling on fertility preservation, if appropriate, should be carried out prior to the start of treatment.

Patients who present with rectal cancer appropriate for resection require a complete staging evaluation, which includes total colonoscopy to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum. Proctoscopy can also be considered. Patients with rectal cancer also require a complete physical examination, including carcinoembryonic antigen (CEA) determination and assessment of performance status to determine operative risk.

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. All patients with rectal cancer should undergo MMR or MSI testing at diagnosis.

Imaging also plays a critical role in preoperative evaluation, both for evaluation of the primary tumor and to assess for the presence of distant metastases. Preoperative imaging for rectal cancer includes chest/abdominal CT and pelvic MRI or chest CT and abdominal/pelvic MRI, as described below.

Preoperative Pelvic Imaging in Rectal Cancer

The accessibility of rectal cancer to evaluation by pelvic MRI with contrast makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.[183,184] Pelvic MRI has the 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.[185-190] The CRM by MRI is measured at the closest distance of the tumor to the mesorectal fascia. The panel defines a clear CRM as >1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane. An involved or threatened CRM, in contrast, is within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle.[135] 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.[191] 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; $P < .05$). MRI has also been shown to be accurate for the prediction of T and N stage.[192] ESGAR has developed consensus guidelines for standardized imaging of rectal cancer by MRI.[136]

Only a 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.[185,188,193] In addition, CT has poor sensitivity for the prediction of CRM status.[194] Furthermore, CT has lower sensitivity and specificity for the prediction of lymph node involvement than MRI (CT, 55% and 74%; MRI, 66% and 76%).[193] Therefore, pelvic CT is not recommended for rectal staging.

A 2004 meta-analysis showed that endoscopic ultrasound (EUS) and MRI have similar sensitivities and specificities for evaluation of lymph nodes (EUS, 67% and 78%; MRI, 66% and 76%).[193] However, newer data suggest that EUS is not very accurate for rectal cancer staging.[195] Furthermore, EUS cannot fully image high or bulky rectal tumors nor regions beyond the immediate area of the primary tumor (eg, tumor deposits, vascular invasion).[185]Another disadvantage of EUS is a high degree of operator dependence.[193] At this time, the panel recommends that EUS may be used to evaluate the pelvis if MRI is contraindicated (eg, because of a pacemaker), or it may be considered as an alternative for superficial lesions.

Preoperative Imaging for Distant Metastases

Additional information regarding the occurrence of distant metastases should be determined preoperatively through chest and abdominal imaging. Chest imaging should be by CT scan, whereas imaging of the abdomen can be performed with CT or MRI. Lung metastases occur in approximately 4% to 9% of patients with colon and rectal cancer,[196-198] and

studies have shown that 20% to 34% of patients with CRC present with synchronous liver metastases.[199,200]

The consensus of the panel is that a PET scan is not indicated for preoperative staging of rectal cancer. 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.

Restaging/Assessing Treatment Response

Restaging after neoadjuvant treatment is done to detect distant metastases that would change the treatment strategy, to plan the surgical approach, and, increasingly, to determine if additional therapy or resection can be avoided for select patients (see *Watch-and-Wait Nonoperative Approach for Clinical Complete Responders* and *Preoperative Chemotherapy Without Chemoradiation*, below). MRI, CT, and EUS have been used for restaging after neoadjuvant treatment, but the accuracy of these techniques for determining T stage and lymph node involvement is limited.[201-209] As with initial staging, the panel recommends pelvic MRI for restaging with chest and abdominal imaging to assess for distant disease. Abdominal/pelvic CT has been shown to identify resectable liver metastases in 2.2% (95% CI, 0.8%–5.1%) of patients during restaging, with false-positive findings that could cause unnecessary treatment in 1.3% (95% CI, 0.3%–3.9%) of patients.[210] In this study, the use of restaging abdominal/pelvic CT was at the physician's discretion, and no difference was seen in relapse-free survival (RFS) for those who had an abdominal/pelvic CT before resection compared with those who did not.

Advanced functional MRI techniques (eg, 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.[208,211-213] FDG PET/CT is also being investigated for its ability to accurately determine response to neoadjuvant treatment.[212,214]

At this time, the panel recommends chest CT, abdominal CT or MRI, and pelvic MRI for restaging.

Surgical Approaches

A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancer lesions.[215,216] These methods include local procedures, such as polypectomy, transanal local 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]).[215,216]

Transanal Local Excision

Transanal local 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 local excision with negative margins.[217] In addition, full-thickness excision must be feasible.

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 local excision.[218] A small prospective, single-blind, randomized trial compared laparoscopic surgery with laparoscopy combined with TEM in 60 patients with rectal cancer.[219] The TEM group had shorter operation times and hospital stays, and no local nor distant recurrences were seen in either group after a median follow-up of 28 months.

Both transanal local 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 locally 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. If pathologic examination reveals adverse features such as positive margins, LVI, poor differentiation, or invasion into the lower third of the submucosa (sm3 level),[220,221] 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.[222] 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.[223] A meta-analysis also suggests that this approach of neoadjuvant chemoRT followed by local excision may be a safe and effective alternative for patients with any T and any N stage of rectal cancer who refuse or are unfit for transabdominal resection.[224] Further studies in this area are needed.

Advantages of a local procedure include minimal morbidity (eg, a sphincter-sparing procedure) and mortality and rapid postoperative recovery.[178,222] Limitations of a local excision include the absence of pathologic staging of nodal involvement. Further, evidence indicates that lymph node micrometastases are both common in early rectal lesions and unlikely to be identified by endorectal ultrasound.[225] These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.[222,226,227] A retrospective study of 282 patients undergoing either transanal local 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).[227] 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).[222] More recently, an analysis of >164,000 individuals from the National Cancer Database (NCDB) 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).[228] In the T1, N0 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,[226,229] although not all studies have seen such results.[230]

Thus, careful patient selection for local excision of T1, N0 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 neoadjuvant treatment.

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.[178,216,231] 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.[232] The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.[233] 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.[234] 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.[235] An extralevator APR may have benefits over a conventional APR approach, including lower rates of intraoperative perforation, CRM involvement, and local recurrence, although inconsistencies are seen between studies.[236,237]

Pathologists play a key role in evaluating the surgical specimen, including a macroscopic assessment of both its external appearance/completeness and the CRM.[238,239] The panel defines an involved or threatened CRM as tumor within 1 mm from the resected margin (see *Pathology*, above).[118,120,134,135] 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.[118]

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.[240,241] 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.[240] Importantly, quality of life between patients with or without a permanent colostomy appears to be fairly comparable.[242,243]

Laparoscopic Resection

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer have matured in recent years.[244-247] One large prospective multicenter 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.[248] The phase III COLOR II trial, powered for non-inferiority, 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.[249] No differences were seen in completeness of resection, percentage of patients with a positive CRM, morbidity, or mortality between the arms. The primary endpoint of locoregional recurrence at 3 years was identical in the two groups, at 5.0%, and no statistically significant differences were seen in DFS or OS.[244]

In the CLASICC trial comparing laparoscopically assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer.[250] No significant differences in local recurrence, DFS, or OS were observed between the two 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).[251]

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 with the laparoscopic approach.[252] The primary endpoint, 3-year DFS, did not differ between the two 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.[245] Factors that may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically assisted surgery for CRC have been described,[253] and longer-term outcomes from laparoscopic rectal surgery have not been reported.

Two other trials, ACOSOG Z6051 and ALaCaRT, have reported pathologic outcomes.[246,247] In Z6051, the primary endpoint was a composite of CRM >1 mm, negative distal margin, and TME completeness.[246] No significant differences were observed between the arms in these three 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 these initial results. Follow-up results of Z6051 reported similar 2-year DFS rates between laparoscopic (79.5%) and open resection (83.2%).[254] Locoregional and distant recurrence rates were also found to be similar between laparoscopic and open resection (4.6% vs. 4.5% for locoregional recurrences and 14.6% vs. 16.7% for distant recurrences). In ALaCaRT, the primary endpoint was also a composite of resection quality measures.[247] 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). Follow-up results for ALaCaRT showed similar recurrence, DFS, and OS rates for laparoscopic versus open resection after 2 years.[255] Two-year locoregional recurrence rates were 5.4% and 3.1%, 2-year DFS rates were 80% and 82%, and 2-year OS rates were 94% and 93% for laparoscopic resection and open resection, respectively. As in Z6051, the criteria for non-inferiority of the laparoscopic approach were not met in the initial ALaCaRT report, but the techniques were found to not differ significantly after longer follow-up with oncologic outcomes.

An analysis of results from >18,000 individuals in the NCDB undergoing LAR for rectal cancer found short-term oncologic outcomes to be similar between the open and laparoscopic approaches.[256] In addition, older reviews and meta-analyses consistently found the laparoscopic approach to be safe and feasible,[245,257-270] even though a meta-analysis published in 2017 found that the risk for a non-complete mesorectal excision is

significantly higher in patients receiving a laparoscopic resection compared with those receiving an open resection.[271]

Several studies have also compared outcomes of robotic-assisted resection to conventional laparoscopic resection.[272-276] Comparable results are generally seen between the approaches in conversion to open resection, TME quality, postoperative complications, and quality of life.

In conclusion, some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared to open surgery,[244,245] whereas other studies have shown the laparoscopic approach to be associated with higher rates of CRM positivity and incomplete TME.[246,247] The panel defined principles by which minimally invasive 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.[277]

Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease

Neoadjuvant/adjuvant therapy for 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 usually 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.[133,278,279] 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.[133,280,281] 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,[282] suggesting that many patients are under-staged and would benefit from chemoRT. Therefore, the guidelines recommend preoperative treatment 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. The current guidelines recommend several possible sequences of therapy, depending on predicted CRM status and response to initial therapy. 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 RT preoperatively versus postoperatively for stage II/III rectal cancer.[283,284] 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.[283] 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 two groups. Long-term follow-up of this trial was later published.[285] 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 T3, N0 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).[286] Another SEER database review found that a cancer-specific survival benefit with adjuvant RT differed with the risk stratification of analyzed patients (patients with high-risk disease benefited from adjuvant RT while those with low-risk disease did not).[287]

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue.[283,284,288] 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,[283,284] this conclusion is not supported by two meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.[289,290] 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 overtreating early-stage tumors that do not require adjuvant radiation.[283,291] Improvements in preoperative staging with pelvic MRI have allowed for more accurate staging, but the risk of overstaging disease has not been eliminated.[282] The phase II QuickSilver trial investigated whether certain patients selected as having good prognosis by MRI imaging may avoid chemoRT by having primary surgery.[292] Of the 82 patients who were identified as candidates for primary surgery, only 4.9% were found to have a positive CRM following surgery, demonstrating the feasibility of this approach. However, more data are needed for this approach to be adopted into clinical practice.

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.

Concurrent Chemotherapy with Radiation

A number of randomized trials have evaluated the effectiveness of the addition of concurrent chemotherapy to radiation administered either preoperatively following clinical evaluation/staging (eg, T3–4 by EUS) or postoperatively following pathologic staging of rectal cancer as pT3 and/or N1–2.[293] 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 two 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%; $P < .05$).[293]

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/leucovorin (LV) chemotherapy enhanced the tumoricidal effect of RT when the two approaches were used concurrently.[294] Significant reductions in tumor size, pTN stage, lymphatic invasion, vascular invasion, and PNI rates were observed with use of combined-modality therapy compared with use of RT and surgery without chemotherapy.[294] More mature results from this trial, which included four 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.[295]

The conclusions of these trials have been supported in a 2009 systematic review that included four RCTs.[296] In addition, a recent Cochrane review of six RCTs 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.[297] Similarly, a separate Cochrane review of 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.[298] Another recent meta-analysis of five RCTs comparing neoadjuvant chemoRT with neoadjuvant radiotherapy came to similar conclusions.[279]

With respect to the type of chemotherapy administered concurrently with RT,[281] 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 RFS 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.[299] 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.[300] 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.[301,302] 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.[302,303] No differences in locoregional 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 ($P = .053$).[301] Furthermore, in this trial capecitabine demonstrated a significant improvement in 3-year DFS (75.2% vs. 66.6%; $P = .034$).[301] Because of these studies, capecitabine given concurrently with RT is listed in the

guidelines as 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, CAO/ARO/AIO-04, and FOWARC) 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).[304] 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 locoregional events, DFS, OS, pathologic complete response, sphincter-saving surgery, and surgical downstaging, while it increased toxicity.[302,303] Further follow-up of these trials is necessary to see if there is a difference in local recurrence rates and PFS over time. The primary 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.[305] 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. The results did not change after longer term follow-up.[306]

Results of the German CAO/ARO/AIO-04 trial have been published.[307,308] 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%, $P = .038$)[308], but this result could be because of differences in the fluorouracil schedule between the arms.[309] 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 ($P = .03$).[307] 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.

In line with CAO/ARO/AIO-04, early results from the Chinese FOWARC phase III open-label, multicenter trial, which randomized patients with locally advanced rectal cancer to neoadjuvant treatment consisting of infusional 5-FU/LV-RT, FOLFOX-RT, or FOLFOX, found that FOLFOX-RT resulted in higher rates of pathologic complete response and downstaging than the other regimens.[310] However, final results from FOWARC showed no significant improvement in 3-year DFS, local recurrence rates, or OS for FOLFOX with or without RT compared to 5-FU/LV-RT.[311]

Another randomized, multicenter, phase III trial looked at the addition of oxaliplatin during concurrent capecitabine chemoRT in the adjuvant setting for pathologic stage II/III disease.[312] Interim analysis showed no significant difference in 3-year DFS, OS, local recurrences, or distant metastases, with an increase in grade 3/4 acute toxicity in the CAPEOX-RT group.

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.[313] 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.[314,315] 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.[316] 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.

Another phase II study, RaP Study/STAR-03, also assessed the potential role of panitumumab in neoadjuvant chemoRT in patients with *KRAS* wild-type, cT3, N0 or cT2–3, N1–2, mid to low rectal cancer with a predicted negative CRM.[317] All patients were treated with panitumumab-chemoRT followed by resection and adjuvant FOLFOX. The primary endpoint of pathologic complete response was observed in 10.9% (95% CI, 4.7–17.1) of participants, not meeting the pre-specified level of 16%.

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.[318] The 5-year OS rate was 80%, and the 5-year RFS 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. Other randomized trials have also investigated the use of targeted therapies (eg, bevacizumab, ziv-aflibercept) within neoadjuvant therapy for localized rectal cancer with mixed conclusions.[319-324]

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 and the Total Neoadjuvant Therapy Approach

Several small trials have tested the utility of a course of neoadjuvant chemotherapy preceding chemoRT and resection.[325-330] This approach is referred to as a total neoadjuvant therapy (TNT) approach. In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CAPEOX either before chemoRT or after surgery.[327,331] 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.[329] 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.[330] The regimen was well tolerated with a pathologic complete response rate of 36%. A pooled analysis of two phase II trials, EXPERT and EXPERT-C, assessed the safety and efficacy of neoadjuvant chemotherapy followed by chemoRT and surgery.[332] Of the 269 patients who were included, 91.1% completed chemotherapy, 88.1% completed chemoRT, and 89.2% underwent curative surgery. Five-year PFS and OS rates were 66.4% and 73.3%, respectively.

A single-institution retrospective cohort analysis of patients with T3/4 or node-positive rectal cancer compared the outcomes after either 1) a

traditional approach of neoadjuvant chemoRT then resection with planned adjuvant chemotherapy (n = 320); or 2) a TNT approach of induction chemotherapy then chemoRT before resection (n = 308). Patients in the TNT group received a greater percentage of the planned chemotherapy dose than those in the adjuvant chemotherapy group. The complete response rates were 36% and 21% in the TNT and adjuvant chemotherapy groups, respectively.

A few trials have investigated the use of FOLFOXIRI as neoadjuvant chemotherapy for locally advanced rectal cancer. The prospective, single-arm phase II FORTUNE study investigated the use of FOLFOXIRI as initial therapy for patients with stage II or III rectal cancer.[333] After initial chemotherapy, patients were either treated with surgery or RT/chemoRT followed by surgery, depending on the response to initial FOLFOXIRI. Of 103 patients who completed neoadjuvant therapy, pCR and tumor downstaging rates were 20.4% and 42.7%, respectively. Another phase II trial of patients with node-positive, cT4, or high-risk T3 rectal cancer investigated the use of induction FOLFOXIRI plus bevacizumab followed by capecitabine-based chemoRT with bevacizumab.[320] Surgery was performed 8 weeks after completion of the chemoRT. Of 49 enrolled patients, 44 completed surgery and 2-year DFS was 80%. While the NCCN Panel recommends induction chemotherapy with FOLFOXIRI as an option for T4, node-positive rectal cancer, the addition of targeted agents (such as bevacizumab) is not currently recommended in this setting.

It is not known whether it is better to start with chemotherapy, then follow with chemoRT, or vice versa when following a TNT approach. Preliminary results from the phase II Organ Preservation in Rectal Adenocarcinoma (OPRA) trial (NCT02008656) suggest that initiating treatment with chemoRT may improve colostomy-free survival but due to imbalances in study design, the results are open to interpretation.[334,335] The randomized phase II CAO/ARO/AIO-12 study also looked at this question, comparing TNT approaches using either induction chemotherapy with FOLFOX followed by 5-FU/oxaliplatin chemoRT or chemoRT followed by consolidation chemotherapy.[336] This trial reported that upfront chemoRT led to higher completion rates for chemoRT, but lower completion rates for chemotherapy compared to upfront chemotherapy. Pathologic complete response was observed in 17% of those who received upfront chemotherapy and 25% of those who received upfront chemoRT. Longer follow-up is needed to determine if these differences in response will lead to an improvement in oncologic outcomes.

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

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.[337] All 32 of the participants had an R0 resection, and the 4-year DFS was 84% (95% CI, 67%–94%). Another phase II trial, which included 60 patients with stage II/III rectal cancer (excluding cT4b) from eight institutions, assessed the R0 resection rate after FOLFOX plus either bevacizumab or cetuximab.[338] An R0 resection was achieved in 98.3% of the participants, and the pathologic complete response rate was 16.7%.

The phase III FOWARC trial, discussed above, compared neoadjuvant therapy with and without radiation (without additional therapy for those with stable or progressive disease) and found that neoadjuvant FOLFOX without radiation gave lower rates of pathologic complete response than regimens that included radiation (6.6% vs. 14.0% for 5-FU-RT and 27.5%

for FOLFOX-RT).[310] The rate of downstaging in the FOLFOX group was similar to the 5-FU-RT group but lower than the FOLFOX-RT group (35.5% vs. 37.1% for 5-FU-RT and 56.4% for FOLFOX-RT). However, final results from FOWARC showed no significant improvement in DFS, local recurrence rates, or OS for FOLFOX with or without RT compared to 5-FU/LV-RT.[311] Three-year DFS was 72.9%, 77.2%, and 73.5% (*P* = .709); 3-year local recurrence rate after resection was 8.0%, 7.0%, and 8.3% (*P* = .873); and 3-year OS was 91.3%, 89.1%, and 90.7% (*P* = .971) for 5-FU/LV-RT, FOLFOX-RT, and FOLFOX without RT, respectively.

A 2015 systematic review identified one randomized phase III trial, six single-arm phase II trials, and one retrospective case series study that addressed the effectiveness of neoadjuvant chemotherapy (without chemoRT) and surgery in patients with locally advanced rectal cancer.[339] The ranges of R0 resection and pathologic complete response rates were 90% to 100% and 4% to 33%, respectively.

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, but the panel considers it investigational at this time for most patients with stage II/III rectal cancer. One exception is the panel's recommendation of FOLFOX or CAPEOX alone as an option for pT3, N0, M0, margin-negative tumors, high in the rectum or at the rectosigmoid junction. However, this approach is only appropriate in this small subset of tumors that behave more like colon tumors, and therefore may be treated as such.

Technical Aspects of Radiation Therapy

Multiple RT fields should include the tumor or tumor bed with a 2- to 5-cm margin, the mesorectum, the 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 three or four 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 https://www.rtog.org/CoreLab/ContouringAtlases.aspx).[340] Intensity-modulated RT (IMRT) or stereotactic body RT (SBRT) 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, localized oligometastases, or unique anatomical situations where IMRT/SBRT facilitates the delivery of recommended target volumes while respecting accepted normal tissue dose-volume constraints.[341]

Coordination of preoperative chemoRT and surgery is important. Although longer intervals from completion of chemoRT to surgery have been shown to be associated with an increase in pathologic complete response rates,[342-347] it is unclear whether such longer intervals are associated with clinical benefit. Results of one NCDB analysis suggest that an interval of >8 weeks is associated with increased odds of pathologic complete response,[348] 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.[349,350]

The GRECCAR6 phase III, multicenter, randomized, open-label, parallel-group controlled trial randomized patients with stage II/III rectal cancer

treated with chemoRT to a 7-week or an 11-week interval before surgery.[351] The pathologic complete response rate was not different between the groups (15.0% vs. 17.4%; *P* = .60), but the morbidity (44.5% vs. 32%; *P* = .04), medical complications (32.8% vs. 19.2%; *P* = .01), and rate of complete mesorectal resection (78.7% vs. 90%; *P* = .02) were worse in the 11-week group. The rate of anastomotic leaks and the mean length of hospital stay were similar between the groups.

Based on these data, the panel recommends an interval of 5 to 12 weeks following completion of full-dose 5.5-week chemoRT prior to surgical resection for patients treated with preoperative chemoRT in order to allow patient recuperation from chemoRT-associated toxicities.

Short-Course Radiation

Several European studies have looked at the efficacy of a shorter course of preoperative RT (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.[352] However, a follow-up study published in 2005 showed that the patients with short-course preoperative RT had increased RR for postoperative hospitalization due to bowel obstructions and other gastrointestinal complications.[353] 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.[354-356] A more recent multicenter, randomized study of 1350 patients with rectal cancer compared 1) short-course preoperative RT and no postoperative treatment with 2) 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.[357] Results indicated that patients in the preoperative RT arm 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.[357,358]

Long-term (12-year) follow-up of one of the short-course RT trials (the Dutch TME trial[355]) was reported.[359] The analysis showed that 10-year survival was significantly improved in patients with stage III disease and a negative CRM in the RT plus surgery group compared to the group that received surgery alone (50% vs. 40%; *P* = .032).[359] However, this long follow-up showed that secondary malignancies and other non-rectal cancer causes of death were more frequent in the RT group than in the control group (14% vs. 9% for secondary malignancies), negating any survival advantage in the node-negative subpopulation.

A few studies have compared short-course RT to long-course chemoRT. One randomized study of 312 patients in Poland directly compared preoperative short-course RT and more conventional preoperative long-course chemoRT and found no differences in local recurrence or survival.[360] Similarly, an Australian/New Zealand trial (Trans-Tasman Radiation Oncology Group [TROG] trial 01.04) that randomized 326 patients to short-course RT or long-course chemoRT found no differences in local recurrence and OS rates.[361] In addition, rates of late toxicity, distant recurrence, and RFS were not significantly different between the arms. Patients in the long-course arm were more likely to experience serious adverse events (eg, radiation dermatitis rates, 0% vs. 5.6%; *P* = .003), whereas patients in the short-course arm were more likely to have a permanent stoma (38.0% vs. 29.8%; *P* = .13).[362] However, no overall difference was seen in health-related quality of life between the groups.[363] Finally, a trial compared short-course RT with long-course chemoRT with delayed surgery in both groups.[364] 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. The 3-year DFS was better in the long-course arm than in the short course arm (75% vs. 59%; *P* = .022), with no difference in OS.[365]

The randomized phase III Polish II study randomized patients with cT3/cT4 rectal cancer to either preoperative short-course radiation followed by FOLFOX4 or preoperative long-course chemoRT with bolus 5-FU/LV and oxaliplatin.[366] Of 515 patients eligible for analysis, preoperative acute treatment toxicity was lower with short-course RT (*P* = .006). No differences in local efficacy or 3-year DFS were observed between the groups, although 3-year OS was higher for the short-course group (73% vs. 65%, *P* = .046). However, long-term results of this trial showed no difference in 8-year OS (49% for both groups).[367] The rate of late complications was also similar between the two groups.

The randomized RAPIDO trial assessed the use of preoperative short-course (5 x 5 Gy) RT followed by 6 cycles of CAPEOX or 9 cycles of FOLFOX4 compared to long-course (25–28 x 2.0–1.8 Gy) capecitabine-based chemoRT before resection in patients with clinical stage T3 or T4 rectal cancer. Early results of 901 evaluable patients showed a high percentage of patients who completed at least 75% of their prescribed chemotherapy (84% for the short-course arm compared to 57% in the long-course arm).[368] While considerable toxicity did occur during preoperative therapy, there were no significant differences noted in the surgical procedures performed or postoperative complications between the two arms. A more mature analysis of the RAPIDO trial reported that in 920 randomized patients, pathologic complete response rates were 27.7% for the short-course arm compared to 13.8% for the long-course arm (OR 2.40; *P* < .001).[369] The primary outcome of 3-year disease-related treatment failure was lower in the short-course arm compared to the long-course arm (23.7% vs. 30.4%; HR, 0.76 [0.60–0.96]; *P* = .02). Probability of distant metastasis and locoregional failure were also lower for short-course RT compared to long-course RT. Overall health, quality of life, and LAR syndrome score were comparable between the two treatment arms.

A 2014 systematic review identified 16 studies (RCTs, phase II trials, and retrospective studies) that addressed the interval between short-course RT and resection of rectal cancer.[370] 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 locally advanced rectal cancer. A multidisciplinary evaluation, including a discussion of the need for downstaging 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 downstaged following neoadjuvant therapy, with about 20% of patients showing a pathologic complete response.[371-377] 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.[378] 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%.[379] A recent retrospective review of 725 patients with rectal cancer found similar results.[375] In this study, pathologically determined response to neoadjuvant treatment correlated with long-term outcomes. Five-year RFS 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. Other studies have also shown a prognostic effect of response to neoadjuvant treatment.[380,381]

In addition to its prognostic value, there is some initial evidence of predictive value to neoadjuvant treatment response. Subgroup analysis of the EORTC 22921 trial showed that patients downstaged to ypT0–2 were more likely to benefit from adjuvant chemotherapy than patients with ypT3–4 staging.[371] Similar results were seen from another retrospective review.[382] 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.

Watch-and-Wait 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[383] 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.[384]

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.[385] Only one 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 watch-and-wait 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 watch-and-wait 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 nonoperative approach may warrant further study.[386-389] 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 RFS of 69%, which rose to 94% after resections were performed.[387] A retrospective case series analysis compared patients who agreed to a watch-and-wait strategy after having a clinical complete response on neoadjuvant therapy with those who underwent surgery following neoadjuvant therapy and were found to have a pathologic complete response at resection.[390] This study found that the watch-and-wait strategy resulted in excellent rectal preservation and pelvic tumor control. However, worse survival and a higher incidence of distant

tumor progression were noted in patients in the watch-and-wait group with local regrowth versus those without.

Several systematic reviews have been published on the nonoperative approach.[391-393] They all show that the approach is likely safe with the use of resection in patients with tumor regrowth, but that the data are very limited.

Despite the impressive results of prospective trials, 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 watch-and-wait approach.[394] 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.[201-209,395] In addition, lymph node metastases are still seen in a subset of patients with pathologic complete response.[396] Keeping these caveats in mind, the panel believes that a nonoperative management approach may be considered in centers with experienced multidisciplinary teams after a careful discussion with the patient about his or her risk tolerance.

The use of nonoperative management of rectal cancer has been increasing in the United States, likely representing both some early adoption of the approach described herein as well as disparities in the receipt of appropriate rectal cancer resection.[397] An analysis of the NCDB from 2004 through 2008 looked at all patients with clinical stage II/III rectal cancer who received neoadjuvant chemoRT only (for whom surgery was "not part of the planned first course of treatment") or neoadjuvant chemoRT plus resection.[398] No data were available regarding the clinical response to neoadjuvant therapy. Although the patients in this study represent a very different population than the trials discussed above, it is important to note that those with the nonoperative approach had a worse OS (HR, 1.90; 95% CI, 1.75–2.04). These results underscore the importance of careful patient selection, vigilant surveillance, and resection of recurrences for those choosing a watch-and-wait approach.

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; however, few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well-defined.[399,400] 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.[295] 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).[295] 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).[401] 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.[402,403]

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.[404] The open-label phase II ADORE trial randomized 321 patients with resected

rectal cancer and neoadjuvant therapy to adjuvant 5-FU/LV or FOLFOX.[405] The FOLFOX arm had higher 3-year DFS, at 71.6% versus 62.9% (HR, 0.66; 95% CI, 043–0.99; *P* = .047). A long-term analysis confirmed these results with a 6-year DFS of 68.2% in the FOLFOX arm compared to 56.8% in the 5-FU/LV arm (HR, 0.63; 95% CI, 0.43–0.93; *P* = .018).[406] 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).[307]

A 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.[407] In addition, a meta-analysis of four 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.[408] 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.[409,410] A systematic review published in 2017 identified 8 phase III trials and 1 randomized phase II trial comparing adjuvant chemotherapy with observation in patients with nonmetastatic rectal cancer treated with neoadjuvant chemoRT.[411] The authors report that the data are not robust enough to warrant routine use of adjuvant therapy in this population.

Most database studies have also failed to see much of a benefit to adjuvant chemotherapy in this setting.[412-414] However, two similar analyses that used the NCDB from 2006 to 2013 or from 2006 and 2012 and that looked only at patients achieving a pathologic complete response after neoadjuvant chemoRT (n = 2891; n = 2764) found a significant improvement in OS with the use of adjuvant chemotherapy.[415,416]

An 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.[417] 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.[418] Pathologic stage, age, and postoperative readmissions were associated with a decreased likelihood of receiving adjuvant treatment. Other database analyses show that adjuvant chemotherapy is used in 74% to 92% of patients in this setting.[412,413]

A randomized, phase III study of the ECOG-ACRIN Research Group (E5204) compared FOLFOX alone to FOLFOX in combination with bevacizumab as adjuvant treatment for patients with stage II or III rectal cancer who had already undergone neoadjuvant chemoRT and complete resection.[419] While the trial was terminated due to poor accrual, in the 355 registered patients, no difference was seen in 5-year OS or 5-year DFS between the two arms. However, the bevacizumab-containing arm had higher rates of early therapy discontinuation and patient withdrawal from the trial.

Although conclusive data on the benefits of adjuvant therapy in patients with stage II/III rectal cancer are lacking, the panel recommends its use. Choice of regimen depends on initial clinical staging and predicted CRM status, with FOLFOX or CAPEOX as preferred or only options for higher risk patients and 5-FU/LV or capecitabine as additional options in some cases. For example, these less intensive adjuvant chemotherapy options might be especially appropriate in patients whose cancer 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 colon or rectal cancer looked at the effect of timing of adjuvant therapy following primary tumor resection.[420] 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.[421] The optimal duration of adjuvant treatment in rectal cancer is still unclear.[422,423] In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX.[424] 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 for a full discussion).[425]

Among the multigene assays used in colon cancer is the Oncotype DX colon cancer assay, which quantifies the expression of seven recurrence-risk genes and five reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.[426] 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.[427] 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.[428,429]

A recent prospectively designed validation study assessed this assay for predicting recurrence risk in patients with stage II and III rectal cancer.[430] For patients who underwent surgery without neoadjuvant therapy in the Dutch 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 CRC.

Leucovorin Shortage

A shortage of LV recently existed in the United States. No specific data are available to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levoleucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levoleucovorin is equivalent to 400 mg/m^2 of standard LV. Use of levoleucovorin should only be considered during times of LV shortage since levoleucovorin is substantially more expensive than LV.

Another option is for practices or institutions to use lower doses of LV for all doses in all patients, because the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg of LV was associated with similar survival and 3-year recurrence rates as 25 mg of LV when given with bolus 5-FU as adjuvant therapy to patients after R0 resections for CRC.[431] Another study showed no difference in response rate or survival in patients with mCRC receiving bolus 5-FU with either high-dose (500 mg/m^2) or low-dose (20 mg/m^2) LV.[432] Furthermore, the Mayo Clinic and

NCCTG determined that no therapeutic difference was seen between the use of high-dose (200 mg/m^2) or low-dose (20 mg/m^2) LV with bolus 5-FU in the treatment of advanced CRC, although the 5-FU doses were different in the treatment arms.[433] Finally, if none of the above options is available, treatment without LV would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

NCCN Recommendations for Nonmetastatic Rectal Cancer

Recommendations for Patients with T1 and T2 Lesions

Node-negative T1 lesions are treated with transabdominal resection or transanal local excision, as appropriate (see section on *Surgical Approaches*, above). If pathology review after local excision reveals no high-risk features, then no additional treatment is required. If, however, 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 pT2, additional treatment is required. The options are: 1) transabdominal resection (preferred) followed by adjuvant therapy based on pathologic stage (see *Adjuvant Treatment Recommendations for cT1–2 N0 Rectal Cancer*, below); or 2) chemoRT. For patients treated with transanal local excision and then chemoRT, options for the next phase of treatment depend on whether there is evidence of residual disease. If there is no evidence of disease, observation or chemotherapy without resection may be considered. If there is evidence of disease, transabdominal resection should be performed, with or without adjuvant chemotherapy. Chemotherapy options are listed in the guidelines. Results of a meta-analysis suggest that transanal local excision followed by chemoRT without a transabdominal resection may be associated with higher rates of local recurrence than transanal local excision followed by transabdominal resection.[434] Careful surveillance of patients forgoing transabdominal resection in this setting is advised.

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.[178,435,436] Following transabdominal resection of patients with clinical stage T1–2 N0 rectal cancer, patients should receive adjuvant therapy based on pathologic stage (see *Adjuvant Treatment Recommendations for cT1–2 N0 Rectal Cancer*, below). For all patients with locoregional rectal cancer, the panel recommends perioperative therapy for a total duration of approximately 6 months.

Adjuvant Treatment Recommendations for cT1–2 N0 Rectal Cancer

Patients who had a transabdominal resection for stage cT1–2 rectal cancer are given further treatment based on the pathologic stage as delineated in detail in the guidelines. Patients with tumors staged as pT1–2, N0, M0 require no further treatment. If pathology review reveals pT3, N0, M0, chemoRT followed by chemotherapy is one option. Observation can also be considered in these patients if the tumor was well-differentiated or moderately well-differentiated carcinoma invading less than 2 mm into the mesorectum, without lymphatic or venous vessel involvement and was located in the upper rectum.[437] Finally, chemotherapy with FOLFOX or CAPEOX alone is an option for margin-negative proximal tumors.

For resected patients with positive nodes and/or pT4 disease, chemotherapy and chemo RT can be given as a “sandwich regimen,” consisting of chemotherapy followed by concurrent chemoRT followed by additional chemotherapy.[281,299,300] Alternatively, chemoRT can be the initial therapy followed by chemotherapy.

The panel recommends perioperative therapy for a total duration of approximately 6 months.

Recommendations for Patients with T3, N any Lesions with Clear CRM by MRI or with T1–2, N1–2 Lesions

Patients clinically staged as T3, N any with prediction of clear margins by MRI have the same treatment options as those clinically staged as T1–2, N1–2. Prediction of CRM status by MRI is discussed above (see *Preoperative Pelvic Imaging in Rectal Cancer*).

The first option for these patients is chemoRT or short-course RT followed by transabdominal resection and adjuvant chemotherapy based on initial clinical stage; specific options are listed in the guidelines. If long-course chemoRT is used, then restaging can be considered before resection. If short-course RT is used, surgery should be within 1 week or delayed 6 to 8 weeks.

In those patients who achieve a complete clinical response to initial chemoRT or short-course RT with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a watch-and-wait nonoperative management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of his/her risk tolerance. The data supporting this approach are discussed in *Watch-and-Wait Nonoperative Approach for Clinical Complete Responders*, above.

Another option for the sequence of treatment in this population is to use a TNT approach, starting with chemotherapy followed by either chemoRT or short-course RT, then restaging and transabdominal resection. Alternatively, a TNT approach may start with short-course RT, followed by 12 to 16 weeks of chemotherapy, then restaging and transabdominal resection.

A poor clinical response does not necessarily imply unresectability, and surgical exploration is usually appropriate when resection is being considered. 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 or short-course RT, 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 *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer). FOLFOXIRI is not recommended in this setting.

Recommendations for Patients with T3, N any Lesions with Involved or Threatened CRM by MRI, with T4, N any Lesions, with Locally Unresectable Disease, or Who Are Medically Inoperable

Patients in this group can start with chemoRT with restaging at 6 weeks after completion of treatment. If pelvic MRI reveals an involved CRM or bulky residual disease, then 12 to 16 weeks of chemotherapy, restaging, transabdominal resection, and additional chemotherapy are recommended. This approach has been assessed in a small study of 45 patients.[438] Twenty-two percent of the patients eventually underwent an R0 resection, with 3-year PFS and 5-year OS in the entire population at 30% (95% CI, 15.0–46.0) and 44.0% (95% CI, 26.0–61.0), respectively.

If a clear CRM is predicted by MRI after initial chemoRT, then transabdominal resection and adjuvant chemotherapy are recommended. Alternatively, a watch-and-wait, nonoperative approach may be considered as described above for patients with clinical stage T3, N any with clear CRM by MRI or T1–2, N1–2 lesions.

Alternatively, a TNT approach can be used in these patients. In this approach, 12 to 16 weeks of chemotherapy are followed by chemoRT, restaging, and transabdominal resection. Alternatively, a TNT approach

may start with short-course RT, followed by 12 to 16 weeks of chemotherapy, then restaging and transabdominal resection. When a TNT approach is used, resection should be performed unless there is a clear contraindication. 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 *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer).

For unresectable cancers, doses higher than 54 Gy may be required; the dose of RT 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),[439-443] which involves direct exposure of tumors to RT during surgery while removing normal structures from the field of treatment, may 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.

Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with CRC will develop colorectal metastases,[444-446] and 80% to 90% of these patients have unresectable metastatic liver disease.[200,445,447-449] Metastatic disease most frequently develops metachronously after treatment for locoregional CRC, with the liver as the most common site of involvement.[450] However, 20% to 34% of patients with CRC present with synchronous liver metastases.[199,200] 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.[451]

It has been estimated that more than half of patients who die of CRC have liver metastases at autopsy, with metastatic liver disease as the cause of death in most patients.[452] Reviews of autopsy reports of patients who died from CRC showed that the liver was the only site of metastatic disease in one-third of patients.[449] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[445,453] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than three tumors, and a disease-free interval of fewer than 12 months, have been associated with a poor prognosis in patients with CRC.[199,454-458]

Other groups, including ESMO, have established guidelines for the treatment of mCRC.[459] 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.[445,460] Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,[455,458] and a recent meta-analysis reported a median 5-year survival of 38%.[461] 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.[462-464] 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[465] (discussed further in *Determining Resectability*).

Colorectal metastatic disease sometimes occurs in the lung.[444] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.[466-468] A series of 378 patients found that resection of pulmonary metastases resulted in a 3-year RFS rate of 28% and a 3-year OS rate of 78%.[468] Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases[467,469-473] and an analysis of patients who underwent hepatic resection followed by subsequent pulmonary resection showed positive outcomes.[474]

Evidence supporting resection of extrahepatic metastases in patients with mCRC 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.[475,476] 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).[473] A recent systematic review concluded similarly that carefully selected patients might benefit from this approach.[477]

Recent data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken.[478] 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.[479-482] In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year OS and PFS rates were reported to be 73% and 22%, respectively.[479] 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.[483] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[467,484,485]

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*).[486]

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. Image-guided ablation has historically been used for non-surgical patients[487-489] but is also indicated for small metastases that can be treated with margins, in combination with surgery or alone, as long as all visible disease is treated.[490] SBRT (also called stereotactic ablative radiotherapy [SABR]) is a reasonable option for patients who cannot be resected or ablated, as discussed in subsequent paragraphs.[448,491,492] Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins[488] or safely treated by SBRT. In select patients with liver-only or liver-dominant metastatic disease that

cannot be resected or ablated, other local, arterially directed treatment options may be offered.[493-495]

A meta-analysis of 90 studies concluded that hepatic arterial infusion chemotherapy (HAIC), yttrium-90 microsphere radioembolization, and transcatheter arterial chemoembolization (TACE) have similar efficacy in patients with unresectable colorectal hepatic metastases.[496] Local therapies are described in more detail below. The exact role of non-extirpative local therapies in the treatment of colorectal metastases remains 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, HAIC) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAIC and intravenous 5-FU with or without LV was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.[449,497] 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 HAIC at later follow-up periods.[449,498] Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAIC was compared with systemic chemotherapy, although most have not shown a survival benefit of HAIC.[449] Results of some studies also suggest that HAIC may be useful in the conversion of patients from an unresectable to a resectable status.[499-501]

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAIC.[460] Limitations on the use of HAIC include the potential for biliary toxicity[449] and the requirement of specific technical expertise. Panel consensus is that HAIC 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

Transhepatic Arterial Chemoembolization

TACE involves hepatic artery catheterization to locally deliver chemotherapy followed by arterial occlusion.[494] A randomized trial compared the arterial delivery of irinotecan-loaded drug-eluting beads (DEBIRI) and reported an OS benefit (22 months vs. 15 months; $P = .031$) of DEBIRI when compared to systemic FOLFIRI.[502] A 2013 meta-analysis identified five observational studies and one randomized trial and concluded that, although DEBIRI appears to be safe and effective for patients with unresectable colorectal liver metastases, additional trials are needed.[503] A more recent trial randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to FOLFOX/bevacizumab/DEBIRI.[504] 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.[505-510] A 2013 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.[511]

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 mCRC following progression on initial therapy (2.1 vs. 4.5 months; $P = .03$).[512] 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.[513] In the refractory setting, a CEA level ≥90 and LVI at the time of primary resection were negative prognostic factors for OS.[514] Additional risk factors include tumor volume and liver replacement by disease as well as albumin and bilirubin levels, performance status, and the presence of extrahepatic disease for both glass[515] and resin[516] microspheres. 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.[515,517,518]

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX +/- bevacizumab vs. FOLFOX +/- bevacizumab) were reported.[519] 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/yttrium-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/yttrium-90 arm vs. 12.6 months for the chemotherapy only arm; HR, 0.69; 95% CI, 0.55–0.90; *P* = .002).

The FOXFIRE and FOXFIREGlobal studies were performed in the same manner as the SIRFLOX trial with the intention to compile all data and allow assessment of oncologic outcomes in a larger cohort.[520] Pooled data from 1103 patients in these three prospective trials showed similar findings as in the SIRFLOX trial with prolongation of the liver PFS in the group treated by radioembolization but no difference in OS and PFS. Of interest was the unexpected finding of survival benefit with radioembolization plus chemotherapy compared to chemotherapy alone in the subgroup of patients with right-sided primary origin (HR, 0.67; 95% CI, 0.48–0.92). Based on these data, further investigation is needed to identify the role of radioembolization at earlier stages of disease in patients with right-sided primary origin.

Whereas very little data show any impact on patient survival and the data supporting its efficacy are limited, toxicity with radioembolization is relatively low.[519,521-523] Consensus amongst panel members is that arterially directed catheter therapy and, in particular, yttrium-90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

Tumor Ablation

Resection is the standard approach for the local treatment of resectable metastatic disease. However, patients with liver or lung oligometastases can also be considered for tumor ablation therapy, particularly in cases that may not be optimal for resection.[524,525] Ablative techniques include radiofrequency ablation (RFA),[488,526] microwave (MW) ablation, cryoablation, and electro-coagulation (irreversible electroporation).[527] There is extensive evidence on the use of RFA as a reasonable treatment option for non-surgical candidates and for recurrent disease after hepatectomy with small liver metastases that can be treated with clear margins.[488,526,528-530]

A small number of older retrospective studies have compared RFA and resection in the treatment of liver or lung metastases.[463,531-534] Most of these studies have shown RFA to be relatively inferior to resection in terms of rates of local recurrence and 5-year OS.[524,531] Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, lack of treatment assessment based on the ability to achieve margins,

technological limitations of RFA, or a combination of these factors remains unclear.[533]

A 2012 phase II trial randomized 119 patients to receive systemic treatment alone (FOLFOX with or without bevacizumab) or systemic treatment plus RFA.[535] No difference in OS was initially 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). A subsequent analysis following prolonged follow-up of the same population in this phase II randomized, controlled trial showed that OS was improved in the combined modality arm (HR, 0.58; 95% CI, 0.38–0.88, *P* = .01), with a 3-, 5-, and 8-year OS of 56.9%, 43.1%, and 35.9% for the combined modality arm compared to 55.2%, 30.3%, and 8.9% for the chemotherapy alone arm.[490] This study documented a long-term survival benefit for patients receiving RFA in addition to chemotherapy compared to those treated by chemotherapy only.

Data on ablative techniques other than RFA are growing.[525,536-543] However, in a comparison of RFA with MW ablation, outcomes were similar with no local tumor progression for metastases ablated with margins greater than 10 mm (A0) and a relatively better control of perivascular tumors with the use of MW (*P* = .021).[543] Similarly, two recent studies and a position paper by a panel of experts indicated that ablation may provide acceptable oncologic outcomes for selected patients with small liver metastases that can be ablated with sufficient margins.[487-489] In the same way, a 2018 systematic review confirmed that MW provides oncologic outcomes similar to resection.[544] Recent publications indicated that the significance of margin creation is particularly important for *RAS*-mutant metastases.[545-547]

Resection or ablation (either alone or in combination with resection) should be reserved for patients with metastatic disease that is entirely amenable to local therapy with adequate margins. Use of surgery, ablation, or the combination of both modalities, with the goal of less-than-complete eradication of all known sites of disease, is not recommended other than in the scope of a clinical trial.

Liver- or Lung-Directed Radiation

Local radiation therapies include arterial radioembolization with microspheres[514,515,548-556] and conformal (stereotactic) external beam RT (EBRT).[557]

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 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 RT (CRT), SBRT,[448,491,492,558] and IMRT, which uses computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to healthy tissue.[559-563]

Peritoneal Carcinomatosis

Approximately 17% of patients with mCRC have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis. Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.[115,564] The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative, and primarily consists of systemic therapy (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer) with palliative surgery or stenting (upper rectal lesions only) if needed for obstruction or impending obstruction.[565-567] 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.[568,569]

Determining Resectability

The consensus of the panel is that patients diagnosed with potentially resectable mCRC 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.[570-573] 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.[574] 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.[575] 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.[446,570]

The role of PET/CT in determining resectability of patients with mCRC 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.[524]

Any active metastatic systemic 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.[576-580] Studies have reported that chemotherapy-associated liver injury (including severe sinusoidal dilatation and steatohepatitis) is associated with morbidity and complications following hepatectomy for colorectal liver metastases.[576,577,580,581] 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 a study by 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.[572] 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,[447] 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.[454] The 5-year DFS rate for these 138 patients was 22%. In addition, results from a retrospective analysis of 795 previously untreated patients with mCRC 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.[582] 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 two randomized clinical trials in patients with unresectable disease.[583,584] 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[583]; and 4% versus 10%, *P* = .08 in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.[584] 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).[585]

More recent favorable results of randomized clinical trials evaluating FOLFIRI, FOLFOX, or FOLFOXIRI in combination with anti-epidermal growth factor receptor (EGFR) inhibitors for the purpose of conversion of unresectable disease to resectable disease have been reported. For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.[586] Retrospective analysis showed that in both treatment arms combined resectability increased from 32% to 60% after chemotherapy in patients with wild-type *KRAS* exon 2 with the addition of cetuximab (*P* < .0001). Final analysis of this trial showed that the median OS of the entire cohort was 35.7 months (95% CI, 27.2–44.2 months), with no difference between the arms.[587] Another recent RCT compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable CRC metastatic to the liver.[588] 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).

The randomized, phase II VOLFI trial compared the efficacy and safety of mFOLFOXIRI in combination with panitumumab to FOLFOXIRI alone in patients with *RAS* wild-type, primarily non-resectable mCRC.[589] Of the cohort with unresectable, potentially convertible metastases, 75% were ultimately converted to resectable with FOLFOXIRI + panitumumab compared to 36.4% with FOLFOXIRI alone. ORR was also improved in the combination compared to FOLFOXIRI alone while PFS was similar between the two treatments and OS showed a trend in favor of the combination. A recent meta-analysis of four RCTs 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.[590] The randomized, phase III TRIPLETE study will compare mFOLFOXIRI plus panitumumab to mFOLFOX6 plus panitumumab as initial therapy for patients with unresectable *RAS* and *BRAF* wild-type mCRC.[591]

The role of bevacizumab in the patient with unresectable mCRC, 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.[592] 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.[593] Therefore, arguments for use of bevacizumab with oxaliplatin-based therapy in this "convert to resectability" setting are not compelling. However, because it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

When chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation be planned 2 months after initiation of chemotherapy, and that those patients who continue to receive chemotherapy undergo surgical re-evaluation every 2 months thereafter.[580,594-596] Reported risks associated with chemotherapy include the potential for development of liver sinusoidal dilatation, steatosis, or steatohepatitis.[576,581,597] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable.

Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

Perioperative administration of chemotherapy is recommended for most patients undergoing liver or lung resection with the goal of increasing the likelihood that residual microscopic disease will be eradicated. In 2018, the panel revised its recommendations for treatment of synchronous liver and/or lung metastases, favoring a TNT approach to treating these patients. Neoadjuvant and/or adjuvant therapy may still be considered for patients with resectable metachronous metastases. A meta-analysis identified three randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.[598] 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.[599] Additional recent meta-analyses have also failed to observe a statistically significant OS benefit with the addition of adjuvant chemotherapy in resectable mCRC.[600-602]

The choice of chemotherapy regimen in the perioperative setting depends on several factors, including the chemotherapy history of the patient, whether disease is synchronous or metachronous, and the response rates and safety/toxicity issues associated with the regimens, as outlined in the guidelines. Biologics are not recommended in the perioperative metastatic setting, with the exception of initial therapy in unresectable patients who may be converted to a resectable state.

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 (six cycles before and six 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.[603] 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.[604] Furthermore, a multi-institutional phase II study investigating the feasibility and efficacy of preoperative mFOLFOX6 for patients with resectable liver metastases demonstrated the feasibility of this approach.[605] Three-year OS and PFS rates were 81.9% and 47.4%, respectively.

The optimal sequencing of systemic therapy and resection remains unclear. Patients with resectable disease may undergo resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) systemic therapy can be used.[600,606]

Potential advantages of preoperative therapy include: earlier treatment of micrometastatic disease, determination of responsiveness to therapy (which can be prognostic and help in planning postoperative therapy), and avoidance of local therapy for those patients with early disease progression. Potential disadvantages include missing the “window of opportunity” for resection because of the possibility of disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.[449,607,608] In fact, results from recent studies of patients with CRC receiving preoperative therapy 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.[608-610] Therefore, during treatment with preoperative systemic therapy, frequent evaluations must be undertaken and close communication must be maintained among medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed that optimizes exposure to the preoperative regimen and facilitates an appropriately timed surgical intervention.[576]

Other reported risks associated with the preoperative therapy approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.[576-580] 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 chemotherapy regimen 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.

Perioperative Bevacizumab for Resectable Metastatic Disease

The efficacy of bevacizumab in combination with FOLFOX and FOLFIRI in the treatment of unresectable metastatic disease (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer) has led to a study of 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 two randomized clinical trials of 1132 patients receiving chemotherapy with or without bevacizumab as initial therapy for mCRC 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).[611] 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 randomized phase III HEPATICA trial, which closed prematurely due to poor accrual, found that global quality-of-life scores were higher in patients receiving CAPEOX plus bevacizumab than those receiving CAPEOX alone after resection of liver metastases, but no conclusions could be drawn regarding the primary endpoint of DFS.[612]

A meta-analysis of RCTs published in 2011 demonstrated that the addition of bevacizumab to chemotherapy was 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.[613] Venous thromboembolisms, however, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[614] Another meta-analysis showed that bevacizumab was associated with a significantly higher risk of hypertension, gastrointestinal hemorrhage, and perforation, although the overall risk for hemorrhage and perforation is quite low.[615] The risk of stroke and other arterial events is increased in patients receiving bevacizumab, especially in those aged 65 years or older. Gastrointestinal perforation is a rare but important side effect of bevacizumab therapy in patients with CRC.[611,616]

Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to gastrointestinal perforation. The FDA recently approved a safety label warning of the risk for necrotizing fasciitis, sometimes fatal and usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation after bevacizumab use.[617]

The panel recommends against the use of bevacizumab as neoadjuvant treatment of patients with resectable metastatic rectal cancer. For patients who receive bevacizumab for unresectable disease and are converted to a resectable state, the panel recommends at least a 6-week interval (which corresponds to two half-lives of the drug[617]) between the last dose of bevacizumab and surgery. Re-initiation of bevacizumab should be delayed at least 6 to 8 weeks postoperatively.

Perioperative Cetuximab and Panitumumab for Resectable Metastatic Disease

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).[618] 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 recommends against panitumumab and cetuximab in the neoadjuvant setting. The panel also points out cetuximab and panitumumab should be used with caution in patients with unresectable disease that could potentially be converted to a resectable status.

Systemic Therapy for Advanced or Metastatic Disease

The current management of disseminated mCRC involves various active drugs, either in combination or as single agents. 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 toxicity

profiles of the constituent drugs. Although the specific regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[619] 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: 1) preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive; and 2) 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, in part, 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 a 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 *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer for a detailed discussion of the various options for systemic treatment. The roles of biomarkers for treatment selection in the advanced and metastatic disease setting are discussed below.

Biomarkers for Systemic Therapy

As the role of targeted therapy for treatment of advanced CRC or mCRC has become increasingly prominent, the NCCN Panel has expanded its recommendations regarding biomarker testing. Currently, determination of tumor gene status for *KRAS/NRAS* and *BRAF* mutations, as well as HER2 amplifications and MSI/MMR status (if not previously done), are recommended for patients with mCRC. Testing may be carried out for individual genes or as part of a next-generation sequencing (NGS) panel, although no specific methodology is recommended. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as neurotrophic tyrosine receptor kinase (*NTRK*) fusions. Specific information about each of these biomarkers may be found in the sections below.

KRAS and NRAS Mutations

EGFR has been reported to be overexpressed in 49% to 82% of colorectal tumors.[620-623] EGFR testing of colorectal tumor cells has no proven predictive value in determining likelihood of response to either cetuximab or panitumumab. Data from the BOND study indicated that the intensity of immunohistochemical staining of EGFR in colorectal tumor cells did not correlate with the response rate to cetuximab.[624] A similar conclusion was drawn with respect to panitumumab.[625] 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.

A sizable body of literature has shown that tumors with a mutation in codon 12 or 13 of exon 2 of the *KRAS* gene are essentially insensitive to cetuximab or panitumumab therapy.[626-635] More recent evidence shows mutations in *KRAS* outside of exon 2 and mutations in *NRAS* are also predictive for a lack of benefit to cetuximab and panitumumab.[636,637]

The panel therefore strongly recommends *RAS* (*KRAS/NRAS)* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with mCRC. 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. ASCO released a Provisional Clinical Opinion Update on extended *RAS* testing in patients with mCRC that is consistent with the NCCN Panel's recommendations.[638] A guideline on molecular biomarkers for CRC developed by the ASCP, CAP, AMP, and ASCO also recommends *RAS* testing consistent with the NCCN recommendations.[28]

The recommendation for *RAS* testing, at this point, is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *RAS* 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 *RAS* 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, *RAS* genotyping of CRCs at these earlier stages is not recommended.

KRAS mutations are early events in CRC formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.[639,640] For this reason, *RAS* 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 *RAS* 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.[641] No specific testing methodology is recommended.[642] The three genes can be tested individually or as part of an NGS panel.

Approximately 40% of CRCs are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the *KRAS* gene.[626,643] A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy,[626-635] and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of CRC characterized by these mutations.[644,645] 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.[646] At this time, however, the test is not recommended for prognostic reasons.

A retrospective study from De Roock et al[647] raised the possibility that codon 13 mutations (G13D) in *KRAS* may not be absolutely predictive of non-response. Another retrospective study showed similar results.[648] However, a more recent retrospective analysis of three randomized controlled phase III trials concluded that patients with *KRAS* G13D mutations were unlikely to respond to panitumumab.[649] Results from a prospective phase II single-arm trial assessed the benefit of cetuximab monotherapy in 12 patients with refractory mCRC whose tumors contained *KRAS* G13D mutations.[650] 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.[651] However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. A meta-analysis of eight RCTs came to the same conclusion: that tumors with *KRAS* G13D mutations are no more likely to respond to EGFR inhibitors than tumors with other *KRAS* mutations.[652] The panel believes that patients with any known *KRAS* mutation, including G13D, should not be treated with cetuximab or panitumumab.

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.[653] 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.[636] 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 published.[654] 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 *RAS* 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 *RAS* 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.[644] The NCCN Colon/Rectal Cancer Panel believes that *RAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known *RAS* mutation should not be treated with either cetuximab or panitumumab.

BRAF V600E *Mutations*

Although mutations in *RAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *RAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *RAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of CRCs are characterized by a specific mutation in the *BRAF* gene (V600E).[655,656] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.[655-657] 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,[658-660] thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

Limited data from unplanned retrospective subset analyses of patients with mCRC 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.[656,661] A planned subset analysis of the PRIME trial also found that mutations in *BRAF* indicated a poor prognosis but were not predictive of benefit to panitumumab added to FOLFOX in first-line treatment of mCRC.[636] 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.[657]

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.[662-664] 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).[665] 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.[666]

A meta-analysis published in 2015 identified nine phase III trials and one 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).[667] 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 ORR (RR, 1.31; 95% CI, 0.83–2.08, *P* = .25) compared with control arms. Similarly, another meta-analysis identified seven RCTs 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.[668]

It is clear that mutations in *BRAF* are a strong prognostic marker.[643,656,657,669-672] A 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).[643] 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.[656] Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (CI, 0.33–0.73; *P* = .001).[670] 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.[657] In addition, a secondary analysis of the N0147 and C-08 trials found that *BRAF* mutations were significantly associated with worse survival after recurrence of resected stage III colon cancer, with a stronger association for primary tumors located in the distal colon.[673] 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.[674] 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, unless given as part of a BRAF-inhibitor regimen (eg, encorafenib plus cetuximab or panitumumab).[675-677] The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[678]) 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, or *BRAF* status can be determined by NGS.

HER2 Amplification/Overexpression

HER2 is a member of the same family of signaling kinase receptors as EGFR and has been successfully targeted in breast cancer in both the advanced and adjuvant settings. HER2 is rarely amplified/overexpressed in CRC (approximately 3% overall), but the prevalence is higher in *RAS/BRAF*–wild type tumors (reported at 5%–14%).[679-681] Specific molecular diagnostic methods have been proposed for HER2 testing in CRC,[682] and HER2-targeted therapies are now recommended as subsequent therapy options in patients with tumors that have HER2 overexpression.[680,683] Based on this, the NCCN Guidelines recommend testing for HER2 amplifications for patients with mCRC. If the tumor is already known to have a *KRAS*/*NRAS* or *BRAF* mutation, HER2 testing is

not required. As HER2-targeted therapies are still under investigation, enrollment in a clinical trial is encouraged.

Evidence does not support a prognostic role of HER2 overexpression.[684] In addition to its role as a predictive marker for HER2-targeted therapy, initial results indicate HER2 amplification/overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.[679,685] For example, in a cohort of 97 patients with *RAS/BRAF*–wild-type mCRC, median PFS on first-line therapy without an EGFR inhibitor was similar regardless of HER2 status.[679] However, in second-line therapy with an EGFR inhibitor, the PFS was significantly shorter in those with HER2 amplification compared with those without HER2 amplification (2.9 months vs. 8.1 months; HR, 5.0; $P < .0001$).

dMMR/MSI-H Status

The percentage of stage IV colorectal tumors characterized as MSI-high (MSI-H) (MMR-deficient [dMMR]) ranges from 3.5% to 5.0% in clinical trials and was 6.5% in the Nurses' Health Study and Health Professionals Follow-up Study.[686-688] dMMR tumors contain thousands of mutations, which can encode mutant proteins with the potential to be recognized and targeted by the immune system. However, programmed death ligands PD-L1 and PD-L2 on tumor cells can suppress the immune response by binding to programmed death receptor-1 (PD-1) on T-effector cells. This system evolved to protect the host from an unchecked immune response. Many tumors upregulate PD-L1 and thus evade the immune system.[689] It has therefore been hypothesized that dMMR tumors may be sensitive to PD-1 inhibitors. Subsequently, this hypothesis was confirmed in clinical trials, leading to the addition of recommendations for checkpoint inhibitors for dMMR/MSI-H disease.[690-692] The NCCN Guidelines recommend universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer. In addition to its role as a predictive marker for immunotherapy use in the advanced CRC setting, MMR/MSI status can also help to identify individuals with Lynch syndrome (see *Lynch Syndrome*, above).

NTRK Fusions

Three *NTRK* genes encode the tropomyosin receptor kinase (TRK) proteins. TRK expression is primarily in the nervous system where these kinases help to regulate pain, perception of movement/position, appetite, and memory. *NTRK* gene fusions lead to overexpression of the TRK fusion protein, resulting in constitutively active downstream signaling.[693] Recent studies have estimated that about 0.2% to 1% of CRCs carry *NTRK* gene fusions.[694,695] A study of 2314 CRC specimens, of which 0.35% had *NTRK* fusions, found that *NTRK* fusions were limited to cancers that were wild-type for *KRAS*, *NRAS*, and *BRAF*. Furthermore, a majority of the CRCs harboring *NTRK* fusions were also dMMR.[696] These results may support limiting testing for *NTRK* fusions to those with wild-type *KRAS*, *NRAS*, and *BRAF.* TRK inhibitors are treatment options for patients with mCRC that is *NTRK* gene fusion-positive.[693,697,698]

Recommendations for Treatment of Resectable Synchronous Metastases

When patients present with CRC and synchronous liver-only or lung-only metastases, the panel now recommends a TNT approach, with choice of preoperative therapy based on the predicted status of the CRM by MRI. Upfront systemic treatment has the goal of early eradication of micrometastases, whereas the goal of short-course RT or long-course chemoRT is local control of disease prior to surgery/local therapy. Those with a predicted clear CRM should receive chemotherapy as described in the guidelines followed by short-course RT or long-course chemoRT. Those with a CRM predicted to be involved can receive 1) chemotherapy followed by long-course chemoRT; or 2) short-course RT or long-course chemoRT followed by chemotherapy. As in other settings, the total

perioperative therapy should not exceed 6 months. Restaging should be performed before resection.

There is NCCN Member Institutional variation in the choice of neoadjuvant therapy approach for resectable synchronous metastases. Standard practice at some institutions is to start with chemotherapy and then to stratify further treatment based on the degree of metastatic disease and the response to initial therapy. If the risk of distant failure is deemed to be the greater concern, resection would be the next course of treatment. If local failure appears more likely, then RT would be given before surgery.

Resection of the primary tumor and liver can be done in a simultaneous or staged approach following neoadjuvant treatment.[699-706] 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.[707-709] In addition, neoadjuvant short-course radiation of T1–T3 primary rectal tumors is an option in this setting.[710] Locally ablative procedures can be considered instead of or in addition to resection in cases of liver or lung oligometastases (see *Local Therapies for Metastases*, above), but resection is preferred.

If a patient is treated with short-course RT, surgery should be within 1 week or delayed 6 to 8 weeks. For the remaining patients, surgery/local therapy should be performed 5 to 12 weeks following completion of treatment. 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 synchronous liver-only or lung-only metastases or who are medically inoperable are treated with intensive systemic therapy 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.[711] These patients should be re-evaluated for resection after 2 months of chemotherapy and every 2 months thereafter while undergoing such therapy. Patients who become resectable should receive short-course RT (preferred) or long-course chemoRT followed by immediate or delayed staged or synchronous resection and/or local therapy for metastases and resection of the rectal lesion. Patients who remain unresectable after initial systemic therapy should proceed to second-line systemic therapy for advanced or metastatic disease. Palliative RT or chemoRT can be given prior to second-line therapy if progression of the primary tumor occurred during first-line treatment.

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.[712] Other retrospective analyses have also shown a potential benefit.[713,714] 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.[715] 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,[486] and its removal delays initiation of systemic chemotherapy. In fact, a recent systematic review concluded that

resection of the primary tumor does not reduce complications and does not improve OS.[716] However, a different systematic review concluded that, while data are not strong, resection of the primary tumor may provide a survival benefit.[717] Another systematic review and meta-analysis identified five studies that compared open to laparoscopic palliative colectomies in this setting.[718] The laparoscopic approach resulted in shorter lengths of hospital stays ($P < .001$), fewer postoperative complications ($P = .01$), 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 is therefore not recommended. Diversion or resection can be considered for obstructing lesions.

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 *Systemic Therapy for Advanced or Metastatic Disease* in the Discussion section of the NCCN Guidelines for Colon Cancer).

Recommendations for Treatment of Metachronous Metastases

In a single-institution, retrospective analysis of 735 patients with stage II/III rectal cancer treated with preoperative chemoRT followed by TME, the 5-year rates of liver and lung recurrences were 6.3% and 10.2%, respectively.[719] Resection of liver-only and lung-only recurrences resulted in comparable survival (5.3 years and 5.1 years, respectively; $P = .39$).

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 in select cases if a surgical cure of M1 disease is feasible. 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.[720,721] 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.[722] 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, and 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. A meta-analysis of 18 studies including 1059 patients with hepatic colorectal metastases found that PET or PET/CT results changed management in 24% of patients.[723]

As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) of *RAS* and *BRAF* genotype should be performed (see *Perioperative Cetuximab and Panitumumab for Resectable Metastatic Disease: 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 or lung oligometastases (see *Local Therapies for Metastases*, above), but resection is preferred. For patients without a history of chemotherapy use, FOLFOX or CAPEOX are preferred, with capecitabine and 5-FU/LV as additional category 2B options. There are also cases when perioperative chemotherapy is not recommended in resectable 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 (category 2B for the use of biologic agents in these settings). Observation is preferred if oxaliplatin-based therapy was previously administered.

Patients determined to have unresectable disease through cross-sectional imaging scan (including those considered potentially convertible) should receive an active systemic therapy regimen based on prior chemotherapy history (see *Second-line or Subsequent Systemic Therapy* in the Discussion section of the NCCN Guidelines for Colon Cancer). In the case of liver metastases only, HAIC 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 CRC Clinical Trials

In the past few years, there has been much debate over what endpoints are most appropriate for clinical trials in advanced CRC.[724] Quality of life is an outcome that is rarely measured but is of unquestioned clinical relevance.[725] 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.[725] PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.[725-727] GRUPO Español Multidisciplinar en Cáncer Digestivo (GEMCAD) recently proposed particular aspects of clinical trial design to be incorporated into trials that use PFS as an endpoint.[728]

A recent study, in which individual patient data from three RCTs 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).[726] 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.[729,730] 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 CRC 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,[731] and a recent study found that 95% of recurrences occurred in the first 5 years.[732]

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[733-735] and in multiple meta-analyses of RCTs designed to compare low-intensity and high-intensity programs of surveillance.[736-740] In the final analysis of the 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.[281] 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.[741]

Results from a recent RCT 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).[742] 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.[742] The randomized COLOFOL trial of 2509 patients with stage II or III CRC looked at follow-up testing with CT of the thorax and abdomen and CEA screening, comparing a high-frequency surveillance approach (CT and CEA at 6, 12, 18, 24, and 36 months post-surgery) to a low-frequency approach (CT and CEA at 12 and 36 months post-surgery).[743] This trial reported no significant difference in 5-year overall mortality or CRC-specific mortality between the two screening approaches.

The CEAwatch trial compared usual follow-up care to CEA measurements every 2 months, with imaging performed if CEA increases were seen twice, in 3223 patients treated for non-mCRC at 11 hospitals in the Netherlands.[744] 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. However, no OS or disease-specific survival benefit was seen.[745] Another randomized trial of 1228 patients found that more intensive surveillance led to earlier detection of recurrences than a less intensive program (less frequent colonoscopy and liver ultrasound and the absence of an annual chest x-ray) but also did not affect OS.[746]

The randomized phase III PRODIGE 13 trial will compare 5-year OS after intensive radiologic monitoring (abdominal ultrasound, chest/abdomen/pelvis CT, and CEA) with a lower intensity program (abdominal ultrasound and chest x-ray) in patients with resected stage II or III colon or rectal tumors.[747] Meta-analyses support the conclusion that more intensive surveillance of patients with resected CRC results in earlier detection of recurrences, without any effect on survival.[737,738]

Patients who had resection of mCRC can undergo subsequent curative-intent resection of recurrent disease (see *Surgical Management of Colorectal Metastases*, above), and therefore should undergo post-treatment surveillance. 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.[748]

Controversies remain regarding selection of optimal strategies for following patients after potentially curative CRC 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 panel recommendations for post-treatment surveillance pertain to patients who have undergone successful treatment (ie, no known residual disease) and are separated into three groups: 1) those who received

transanal local excision only; 2) patients with stage I disease and full surgical staging; and 3) patients with stage II through IV disease.

For all three groups, 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.[749] More frequent colonoscopies may be indicated in patients who present with CRC before age 50.[749] Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps since data show that patients with a history of CRC have an increased risk of developing second cancers,[750] 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 CRC.[749]

Proctoscopy with EUS or MRI is recommended to evaluate the rectal anastomosis for local recurrence in patients treated with transanal local excision only. 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.[751] In these 112 patients, 20 anoscopies, 44 proctoscopies, and 495 flexible sigmoidoscopies were performed.

For the stage II–IV group, history and physical examination is recommended every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years; and a CEA test (also see *Managing an Increasing CEA Level*, below) is recommended at baseline and every 3 to 6 months for 2 years,[752] then every 6 months for a total of 5 years for patients with stage III disease and those with stage II disease if the clinician determines that the patient is a potential candidate for aggressive curative surgery.[736,752,753] 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.[736,754] 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.[755] Those scanned once per year survived a median of 54 months versus 43 months for those scanned three to four 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, use of PET/CT to monitor for disease recurrence is not recommended.[754,756] 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 endorsed the Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer, from Cancer Care Ontario (CCO).[757,758] 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 semi-annual to annual scans for 5 years (category 2B for more frequent than annual scanning). The panel bases its recommendation on the fact that approximately 10% of disease recurrences occur after 3 years.[732,759] The American Society of Colon and Rectal Surgeons also released surveillance guidelines, which are also

very similar to NCCN surveillance recommendations.[760] One exception is the inclusion of intensive surveillance for patients with resected stage I colon or rectal cancer if the provider deems the patient to be at increased risk for recurrence.

All patients with rectal cancer should be counseled for family history. For patients with suspected Lynch syndrome, FAP, or attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

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 CRC were false positives, with most being single high readings or repeat readings in the range of 5 to 15 ng/mL.[761] In this study, false-positive results >15 ng/mL were rare, and all results >35 ng/mL represented true positives. Following a systematic review and meta-analysis, the pooled sensitivity and specificity of CEA at a cutoff of 10 ng/mL were calculated at 68% (95% CI, 53%–79%) and 97% (95% CI, 90%–99%), respectively.[762,763] In the first 2 years post-resection, a CEA cutoff of 10 ng/mL is estimated to detect 20 recurrences, miss 10 recurrences, and result in 29 false positives.

A PET/CT scan may be considered in the scenario of an elevated CEA with negative, good-quality CT scans. A systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT in this setting.[764] 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. An analysis of outcomes of 88 patients treated for CRC under surveillance who had normal or equivocal conventional imaging results with an elevated CEA found that PET/CT had a sensitivity of 88% and a specificity of 88% for the detection of recurrences.[765]

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,[766] 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.[767] In a more recent, single-institution, retrospective analysis of 735 patients with stage II/III rectal cancer treated with preoperative chemoRT followed by TME, locoregional recurrence rate at 5 years was 4.6%, occurring at a median of 24.7 months.[719]

The panel recommends that patients with unresectable lesions be treated with chemotherapy with or without radiation according to their ability to tolerate therapy. Debulking that results in gross residual cancer is not recommended. Potentially resectable isolated pelvic/anastomotic recurrence should be managed with preoperative chemoRT followed by resection (preferred if chemoRT was not previously given) or by resection followed by adjuvant chemoRT. IORT or brachytherapy should be considered with resection if it can be safely delivered.[441,768-770]

A retrospective study found that re-resection was not associated with improved survival in patients with isolated locoregional recurrence (3.6 years with surgery vs. 3.2 years without surgery; *P* = .353).[719] Older studies have shown that patients with disease recurrence at the anastomotic site are more likely to be cured following re-resection than those with an isolated pelvic recurrence.[771,772] In a study of 43 consecutive patients with advanced pelvic recurrence of CRC 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.[772] Studies of patients who previously received pelvic radiation show that re-irradiation can be effective, with acceptable rates of toxicity.[773-775] 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.[773] IMRT can be used in this setting of re-irradiation.

Survivorship

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.[776] The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to the patient. The care plan should include an overall summary of treatments received, including surgeries, radiation treatments, and chemotherapy. The possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment should be described. Finally, surveillance and health behavior recommendations should be part of the care plan.

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 are recommended (see the NCCN Guidelines for Survivorship). 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.[777]

Other recommendations include monitoring for late sequelae of rectal cancer or of the treatment of rectal cancer, such as bowel function changes (eg, patients with stoma).[778-783] Urogenital dysfunction following resection and/or pelvic irradiation is common.[778,784-786] 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 CRC survivors include oxaliplatin-induced peripheral neuropathy, fatigue, insomnia, cognitive dysfunction, and emotional or social distress.[787-792] Specific management interventions to address side effects of CRC have been described,[793] and a survivorship care plan for patients with CRC has been published.[794]

The NCCN Guidelines for Survivorship provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in specialty cancer survivor clinics and primary care practices. These guidelines include many topics with potential relevance to survivors of CRC, including anxiety, depression, and distress; cognitive dysfunction; fatigue; pain; sexual dysfunction; healthy lifestyles; and immunizations. Concerns related to employment, insurance, and disability are also discussed. The American Cancer Society (ACS) has also established guidelines for the care of survivors of CRC, 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.[777]

Healthy Lifestyles for Survivors of CRC

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 CRC. 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.[795] In addition, a recent study of a large cohort of men treated for stage I through III CRC showed an association between increased physical activity and lower rates of CRC-specific mortality and overall mortality.[796] More recent data support the conclusion that physical activity improves outcomes. In a cohort of greater than 2000 survivors of non-mCRC, those who spent more time in recreational activity had a lower mortality than those who spent more leisure time sitting.[797] In addition, recent evidence suggests that both pre- and post-diagnosis physical activity decrease CRC mortality. Women enrolled in the Women's Health Initiative study who subsequently developed CRC had lower CRC-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.[798] Similar results were seen in other studies and in recent meta-analyses of prospective studies.[799-802]

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.[803] Recent analyses confirm the increased risk for recurrence and death in obese patients.[88] Data from the ACCENT database also found that pre-diagnosis BMI has a prognostic impact on outcomes in patients with stage II/III CRC undergoing adjuvant therapy.[804] However, a recent analysis of participants in the Cancer Prevention Study II Nutrition Cohort who subsequently developed non-mCRC found that pre-diagnosis obesity but not post-diagnosis obesity was associated with higher all-cause and CRC-specific mortality.[805] A meta-analysis of prospective cohort studies found that pre-diagnosis obesity was associated with increased CRC-specific and all-cause mortality.[806] Other analyses confirm the increased risk for recurrence and death in obese patients.[88,807-810]

In contrast, pooled data from first-line clinical trials in the ARCAD database indicate that a low BMI may be associated with an increased risk of progression and death in the metastatic setting, whereas a high BMI may not be.[811] In addition, results of one retrospective observational study of a cohort of 3408 patients with resected stage I to III CRC suggest that the relationship between mortality and BMI might be U shaped, with the lowest mortality for those with a BMI 28 kg/m^2.[812] However, several possible explanations for this so-called “obesity paradox” have been suggested.[813] Overall the panel believes that survivors of CRC should be encouraged to achieve and maintain a healthy body weight (see the NCCN Guidelines for Survivorship).

A diet consisting of more fruits, vegetables, poultry, and fish, less red meat, more whole grains, and fewer refined grains and concentrated sweets was found to be associated with an improved outcome in terms of cancer recurrence or death.[814] 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 CRC.[94] 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.[815] 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.[816] The link between red and processed meats and mortality in survivors of non-mCRC 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 CRC-specific mortality than those with low intake (RR, 1.79; 95% CI, 1.11–2.89).[90]

A discussion of lifestyle characteristics that may be associated with a decreased risk of CRC recurrence, such as those recommended by the ACS,[817] 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 CRC, suggesting that survivors may be open to health behavior change.[818]

Therefore, survivors of CRC should be encouraged to 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); consume a healthy diet with emphasis on plant sources; eliminate or limit alcohol consumption to no more than 1 drink/day for women and 2 drinks/day for men; and quit smoking.[819] Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy), and diet recommendations may be modified based on the severity of bowel dysfunction.[820]

Secondary Chemoprevention for CRC Survivors

Limited data suggest a link between post-colorectal-cancer-diagnosis statin use and increased survival.[111,821,822] A meta-analysis that included four studies found that post-diagnosis statin use increased OS (HR, 0.76; 95% CI, 0.68–0.85; $P < .001$) and cancer-specific survival (HR, 0.70; 95% CI, 0.60–0.81; $P < .001$).[821]

Abundant data show that low-dose aspirin therapy after a diagnosis of CRC decreases the risk of recurrence and death.[823-829] For example, a population-based, observational, retrospective cohort study of 23,162 patients with CRC in Norway found that post-diagnosis aspirin use was associated with improved CRC-specific survival (HR, 0.85; 95% CI, 0.79–0.92) and OS (HR, 0.95; 95% CI, 0.90–1.01).[823] Some evidence suggests that tumor mutations in *PIK3CA* may be predictive of response to aspirin, although the data are somewhat inconsistent and other predictive markers have also been suggested.[825,830-835] In addition, a meta-analysis of 15 RCTs showed that while non-aspirin NSAIDs were better for preventing recurrence, low-dose aspirin was safer and thereby had a more favorable risk-to-benefit profile.[836]

Based on these data, the panel believes that survivors of CRC can consider taking 325 mg aspirin daily to reduce their risk of recurrence and death. Importantly, aspirin may increase the risk of gastrointestinal bleeding and hemorrhagic stroke, and these risks should be discussed with CRC survivors.[837]

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. 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 local excision. A transabdominal resection is appropriate for 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.

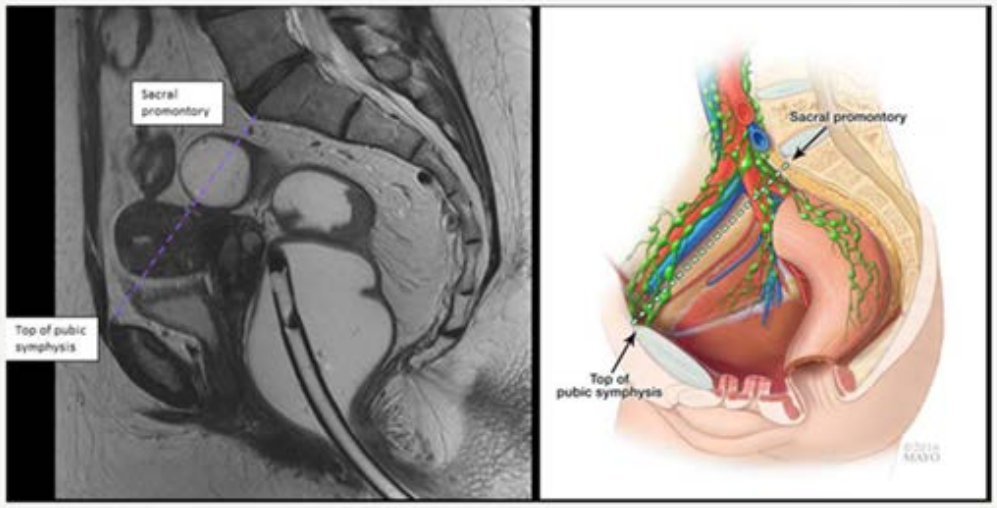
The recommended post-treatment surveillance program for patients following treatment for rectal cancer includes serial CEA determinations, as well as periodic chest, abdominal, and pelvic CT scans, and periodic evaluation by colonoscopy. Patients with recurrent localized disease

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 systemic therapy options for advanced or metastatic disease depend on whether or not the patient is appropriate for intensive therapy; the biomarker status of the tumor; and for patients with progressive disease, the choice of initial therapy.

Figure 1. Definition of Rectum



"Rectum" is defined as the portion of bowel located below the pelvic inlet (an imaginary line drawn from the sacral promontory to the top of the pubic symphysis) as determined by a dedicated MRI of the pelvis

- Upper rectum: above the anterior peritoneal reflection
- Mid-rectum: at the anterior peritoneal reflection
- Lower-rectum: below the anterior peritoneal reflection

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31912902.

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 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.

4. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32133645.

5. 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.

6. Weinberg BA, Marshall JL, Salem ME. The Growing Challenge of Young Adults With Colorectal Cancer. Oncology (Williston Park) 2017;31:381-389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28516436.

7. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed June 23, 2020.

8. 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.

9. 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.

10. 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.

11. 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.

12. Quintero E, Carrillo M, Leoz ML, et al. Risk of advanced neoplasia in first-degree relatives with colorectal cancer: a large multicenter cross-sectional study. PLoS Med 2016;13:e1002008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27138769.

13. 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.

14. 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.

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

16. 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;33:4188-4193. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26527788.

17. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350-1356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26457759.

18. 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.

19. 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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.

28. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. J Mol Diagn 2017;19:187-225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28185757.

29. 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.

30. 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.

31. 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.

32. McCullough ML, Zoltick ES, Weinstein SJ, et al. Circulating Vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts. JNCI: Journal of the National Cancer Institute 2018:djy087-djy087. Available at: http://dx.doi.org/10.1093/jnci/djy087.

33. 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.

34. 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.

35. 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.

36. Ekmekcioglu C, Haluza D, Kundi M. 25-Hydroxyvitamin D Status and Risk for Colorectal Cancer and Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Epidemiological Studies. Int J Environ Res Public Health 2017;14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28134804.

37. 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.

38. 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.

39. 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.

40. 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.

41. 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.

42. Yuan C, Sato K, Hollis BW, et al. Plasma 25-Hydroxyvitamin D Levels and Survival in Patients with Advanced or Metastatic Colorectal Cancer: Findings from CALGB/SWOG 80405 (Alliance). Clin Cancer Res 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31548349.

43. 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.

44. Ou B, Zhao J, Guan S, Lu A. Plasma 25-hydroxyvitamin D levels and survival of colorectal cancer patients: a meta-analysis. Eur J Cancer 2015;51:786-788. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25746389.

45. 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.

46. Barry EL, Peacock JL, Rees JR, et al. Vitamin D Receptor Genotype, Vitamin D3 Supplementation, and Risk of Colorectal Adenomas: A Randomized Clinical Trial. JAMA Oncol 2017;3:628-635. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27978548.

47. Urashima M, Ohdaira H, Akutsu T, et al. Effect of Vitamin D Supplementation on Relapse-Free Survival Among Patients With Digestive Tract Cancers: The AMATERASU Randomized Clinical Trial. Jama 2019;321:1361-1369. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30964526.

48. Lewis C, Xun P, He K. Vitamin D supplementation and quality of life following diagnosis in stage II colorectal cancer patients: a 24-month prospective study. Support Care Cancer 2016;24:1655-1661. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26408324.

49. Jeffreys M, Redaniel MT, Martin RM. The effect of pre-diagnostic vitamin D supplementation on cancer survival in women: a cohort study within the UK Clinical Practice Research Datalink. BMC Cancer 2015;15:670. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26458897.

50. Ng K, Nimeiri HS, McCleary NJ, et al. Effect of High-Dose vs Standard-Dose Vitamin D3 Supplementation on Progression-Free Survival Among Patients With Advanced or Metastatic Colorectal Cancer: The SUNSHINE Randomized Clinical Trial. Jama 2019;321:1370-1379. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30964527.

51. Ross AC, Taylor CL, Yaktine AL, Valle HBD, eds. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press (US); 2011.

52. 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.

53. 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.

54. 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.

55. 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.

56. 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.

57. 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.

58. 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.

59. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer--viewpoint of the IARC Working Group. N Engl J Med 2016;375:794-798. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27557308.

60. 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.

61. 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.

62. 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.

63. 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;24:6-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24722538.

64. 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.

65. 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.

66. Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ 2016;354:i3857. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27510511.

67. 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.

68. Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med 2016;176:816-825. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27183032.

69. 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.

70. Vieira AR, Abar L, Chan DSM, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol 2017;28:1788-1802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28407090.

71. Aleksandrova K, Pischon T, Jenab M, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. BMC Med 2014;12:168. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25319089.

72. Song M, Giovannucci E. Preventable incidence and mortality of carcinoma associated with lifestyle factors among white adults in the United States. JAMA Oncol 2016;2:1154-1161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27196525.

73. Kohler LN, Garcia DO, Harris RB, et al. Adherence to diet and physical activity cancer prevention guidelines and cancer outcomes: a systematic review. Cancer Epidemiol Biomarkers Prev 2016;25:1018-1028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27340121.

74. 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.

75. 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.

76. 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.

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

82. 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.

83. 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.

84. 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.

85. Cao Y, Nishihara R, Wu K, et al. Population-wide impact of long-term use of aspirin and the risk for cancer. JAMA Oncol 2016;2:762-769. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26940135.

86. Bibbins-Domingo K, Force USPST. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2016;164:836-845. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27064677.

87. 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.

88. 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.

89. 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.

90. 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.

91. 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.

92. Song M, Zhang X, Meyerhardt JA, et al. Marine omega-3 polyunsaturated fatty acid intake and survival after colorectal cancer

diagnosis. Gut 2016;66:1790-1796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27436272.

93. 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.

94. 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.

95. 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.

96. 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.

97. 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.

98. 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.

99. Rokkas T, Portincasa P. Colon neoplasia in patients with type 2 diabetes on metformin: A meta-analysis. Eur J Intern Med 2016;33:60-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27318643.

100. Nie Z, Zhu H, Gu M. Reduced colorectal cancer incidence in type 2 diabetic patients treated with metformin: a meta-analysis. Pharm Biol 2016;54:2636-2642. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27159666.

101. 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.

102. He XK, Su TT, Si JM, Sun LM. Metformin is associated with slightly reduced risk of colorectal cancer and moderate survival benefits in diabetes mellitus: A meta-analysis. Medicine (Baltimore) 2016;95:e2749. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26886616.

103. Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. World J Gastroenterol 2015;21:6026-6031. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26019469.

104. 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;3:1458-1466. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25091592.

105. 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.

106. Higurashi T, Hosono K, Takahashi H, et al. Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial. Lancet Oncol 2016;17:475-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26947328.

107. Zhu B, Wu X, Wu B, et al. The relationship between diabetes and colorectal cancer prognosis: A meta-analysis based on the cohort studies.

PLoS One 2017;12:e0176068. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28423026.

108. 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.

109. Meng F, Song L, Wang W. Metformin improves overall survival of colorectal cancer patients with diabetes: A meta-analysis. J Diabetes Res 2017;2017:5063239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28271076.

110. 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.

111. Zanders MM, van Herk-Sukel MP, Vissers PA, et al. Are metformin, statin and aspirin use still associated with overall mortality among colorectal cancer patients with diabetes if adjusted for one another? Br J Cancer 2015;113:403-410. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26180924.

112. Kowall B, Stang A, Rathmann W, Kostev K. No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. Pharmacoepidemiol Drug Saf 2015;24:865-874. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26132313.

113. Amin MB, Greene FL, Edge S, et al., eds. AJCC Cancer Staging Manual (ed 8th Edition). New York: Springer; 2017.

114. Huang B, Mo S, Zhu L, et al. The survival and clinicopathological differences between patients with stage IIIA and stage II rectal cancer: An analysis of 12,036 patients in the SEER database. Oncotarget 2016;7:79787-79796. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27806332.

115. 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.

116. 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.

117. 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.

118. 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.

119. 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.

120. 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.

121. 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.

122. 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.

123. 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.

124. 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.

125. 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.

126. 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.

127. 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.

128. 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.

129. 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.

130. 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.

131. 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.

132. 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.

133. 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.

134. 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.

135. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. Bmj 2006;333:779. Available at: https://pubmed.ncbi.nlm.nih.gov/16984925/.

136. Beets-Tan RGH, Lambregts DMJ, Maas M, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol 2018;28:1465-1475. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29043428.

137. 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.

138. 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.

139. 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.

140. Tang L, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. College of American Pathologists 2016. Available at: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cp-colon-16protocol-3400.pdf.

141. 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.

142. 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.

143. 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.

144. 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.

145. 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.

146. 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.

147. Han J, Noh GT, Yeo SA, et al. The number of retrieved lymph nodes needed for accurate staging differs based on the presence of preoperative chemoradiation for rectal cancer. Medicine (Baltimore) 2016;95:e4891. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27661032.

148. 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.

149. 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.

150. 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.

151. 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.

152. 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.

153. 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.

154. 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.

155. 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.

156. 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.

157. 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.

158. 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.

159. 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.

160. 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:

161. Al-Sukhni E, Attwood K, Gabriel EM, et al. Lymphovascular and perineural invasion are associated with poor prognostic features and outcomes in colorectal cancer: A retrospective cohort study. Int J Surg 2016;37:42-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27600906.

162. Knijn N, Mogk SC, Teerenstra S, et al. Perineural invasion is a strong prognostic factor in colorectal cancer: a systematic review. Am J Surg Pathol 2016;40:103-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26426380.

163. Mayo E, Llanos AA, Yi X, et al. Prognostic value of tumour deposit and perineural invasion status in colorectal cancer patients: a SEER-based population study. Histopathology 2016;69:230-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26802566.

164. Yagi R, Shimada Y, Kameyama H, et al. Clinical significance of extramural tumor deposits in the lateral pelvic lymph node area in low rectal cancer: a retrospective study at two institutions. Ann Surg Oncol 2016;23:552-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27393567.

165. 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.

166. 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;7:6335-6344. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26695441.

167. Lord AC, Graham Martínez C, D'Souza N, et al. The significance of tumour deposits in rectal cancer after neoadjuvant therapy: a systematic review and meta-analysis. Eur J Cancer 2019;122:1-8. Available at: https://pubmed.ncbi.nlm.nih.gov/31593786/.

168. 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.

169. 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.

170. 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.

171. 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.

172. 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.

173. 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.

174. Choi DH, Sohn DK, Chang HJ, et al. Indications for subsequent surgery after endoscopic resection of submucosally invasive colorectal carcinomas: a prospective cohort study. Dis Colon Rectum 2009;52:438-445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19333043.

175. Choi JY, Jung SA, Shim KN, et al. Meta-analysis of predictive clinicopathologic factors for lymph node metastasis in patients with early colorectal carcinoma. J Korean Med Sci 2015;30:398-406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25829807.

176. Park KJ, Choi HJ, Roh MS, et al. Intensity of tumor budding and its prognostic implications in invasive colon carcinoma. Dis Colon Rectum 2005;48:1597-1602. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15937624.

177. Rogers AC, Winter DC, Heeney A, et al. Systematic review and meta-analysis of the impact of tumour budding in colorectal cancer. Br J Cancer 2016;115:831-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27599041.

178. 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.

179. 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.

180. 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.

181. 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.

182. Morino M, Risio M, Bach S, et al. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus

conference. Surg Endosc 2015;29:755-773. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25609317.

183. 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.

184. Zhang G, Cai YZ, Xu GH. Diagnostic accuracy of MRI for assessment of T category and circumferential resection margin involvement in patients with rectal cancer: A meta-analysis. Dis Colon Rectum 2016;59:789-799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27384098.

185. Balyasnikova S, Brown G. Optimal imaging strategies for rectal cancer staging and ongoing management. Curr Treat Options Oncol 2016;17:32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27255100.

186. Battersby NJ, How P, Moran B, et al. Prospective validation of a low rectal cancer magnetic resonance imaging staging system and development of a local recurrence risk stratification model: The MERCURY II Study. Ann Surg 2016;263:751-760. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25822672.

187. 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.

188. 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.

189. 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.

190. 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.

191. 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.

192. Faletti R, Gatti M, Arezzo A, et al. Preoperative staging of rectal cancer using magnetic resonance imaging: comparison with pathological staging. Minerva Chir 2018;73:13-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28497665.

193. 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.

194. Wolberink SV, Beets-Tan RG, de Haas-Kock DF, et al. Conventional CT for the prediction of an involved circumferential resection margin in primary rectal cancer. Dig Dis 2007;25:80-85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17384512.

195. Ashraf S, Hompes R, Slater A, et al. A critical appraisal of endorectal ultrasound and transanal endoscopic microsurgery and decision-making in early rectal cancer. Colorectal Dis 2012;14:821-826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21920011.

196. Choi DJ, Kwak JM, Kim J, et al. Preoperative chest computerized tomography in patients with locally advanced mid or lower rectal cancer: its role in staging and impact on treatment strategy. J Surg Oncol 2010;102:588-592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20607759.

197. Grossmann I, Avenarius JK, Mastboom WJ, Klaase JM. Preoperative staging with chest CT in patients with colorectal carcinoma: not as a

routine procedure. Ann Surg Oncol 2010;17:2045-2050. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20151212.

198. Qiu M, Hu J, Yang D, et al. Pattern of distant metastases in colorectal cancer: a SEER based study. Oncotarget 2015;6:38658-38666. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26484417.

199. 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.

200. 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.

201. 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.

202. 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.

203. 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.

204. 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.

205. 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.

206. 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.

207. 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.

208. 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.

209. 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.

210. Park HJ, Jang JK, Park SH, et al. Restaging abdominopelvic computed tomography before surgery after preoperative chemoradiotherapy in patients with locally advanced rectal cancer. JAMA Oncol 2018;4:259-262. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29181529.

211. 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.

212. Joye I, Deroose CM, Vandecaveye V, Haustermans K. The role of diffusion-weighted MRI and (18)F-FDG PET/CT in the prediction of pathologic complete response after radiochemotherapy for rectal cancer: a systematic review. Radiother Oncol 2014;113:158-165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25483833.

213. Lambregts DM, Rao SX, Sassen S, et al. MRI and diffusion-weighted MRI molumetry for identification of complete tumor responders after preoperative chemoradiotherapy in patients with rectal cancer: a bi-institutional validation study. Ann Surg 2015;262:1034-1039. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25211270.

214. Memon S, Lynch AC, Akhurst T, et al. Systematic review of FDG-PET prediction of complete pathological response and survival in rectal cancer. Ann Surg Oncol 2014;21:3598-3607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24802909.

215. 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.

216. 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.

217. 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.

218. 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.

219. Chen Y, Guo R, Xie J, et al. Laparoscopy combined with transanal endoscopic microsurgery for rectal cancer: A prospective, single-blinded, randomized clinical trial. Surg Laparosc Endosc Percutan Tech 2015;25:399-402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26429049.

220. 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.

221. 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.

222. 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.

223. 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.

224. Shaikh I, Askari A, Ouru S, et al. Oncological outcomes of local excision compared with radical surgery after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis 2015;30:19-29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25367179.

225. 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.

226. 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.

227. 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.

228. 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.

229. 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.

230. 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.

231. 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.

232. 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.

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

234. 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.

235. 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.

236. 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.

237. Negoi I, Hostiuc S, Paun S, et al. Extralevator vs conventional abdominoperineal resection for rectal cancer-A systematic review and meta-analysis. Am J Surg 2016;212:511-526. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27317475.

238. 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.

239. 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.

240. 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.

241. 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.

242. 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.

243. 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.

244. 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.

245. 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.

246. 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.

247. 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.

248. 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.

249. 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.

250. 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.

251. 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.

252. 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.

253. 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.

254. Fleshman J, Branda ME, Sargent DJ, et al. Disease-free Survival and Local Recurrence for Laparoscopic Resection Compared With Open Resection of Stage II to III Rectal Cancer: Follow-up Results of the ACOSOG Z6051 Randomized Controlled Trial. Ann Surg 2019;269:589-595. Available at: https://pubmed.ncbi.nlm.nih.gov/30080730/.

255. Stevenson ARL, Solomon MJ, Brown CSB, et al. Disease-free Survival and Local Recurrence After Laparoscopic-assisted Resection or Open Resection for Rectal Cancer: The Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial. Ann Surg 2019;269:596-602. Available at: https://pubmed.ncbi.nlm.nih.gov/30247332/.

256. 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;19:124-131; discussion 131-122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25091847.

257. 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.

258. 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.

259. 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.

260. 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.

261. 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.

262. 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.

263. 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.

264. 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.

265. 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.

266. 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.

267. 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.

268. 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.

269. 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.

270. 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;31:805-811. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26847617.

271. Martinez-Perez A, Carra MC, Brunetti F, de'Angelis N. Pathologic outcomes of laparoscopic vs open mesorectal excision for rectal cancer: A systematic review and meta-analysis. JAMA Surg 2017;152:e165665. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28196217.

272. Huang YM, Huang YJ, Wei PL. Outcomes of robotic versus laparoscopic surgery for mid and low rectal cancer after neoadjuvant chemoradiation therapy and the effect of learning curve. Medicine (Baltimore) 2017;96:e8171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28984767.

273. Jayne D, Pigazzi A, Marshall H, et al. effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer: The ROLARR randomized clinical trial. JAMA 2017;318:1569-1580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29067426.

274. Kim MJ, Park SC, Park JW, et al. Robot-assisted versus laparoscopic surgery for rectal cancer: A phase II open label prospective randomized controlled trial. Ann Surg 2018;267:243-251. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28549014.

275. Li X, Wang T, Yao L, et al. The safety and effectiveness of robot-assisted versus laparoscopic TME in patients with rectal cancer: A meta-analysis and systematic review. Medicine (Baltimore) 2017;96:e7585. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28723798.

276. Prete FP, Pezzolla A, Prete F, et al. Robotic versus laparoscopic minimally invasive surgery for rectal cancer: A systematic review and meta-analysis of randomized controlled trials. Ann Surg 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28984644.

277. 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.

278. 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.

279. 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.

280. 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.

281. 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.

282. 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.

283. 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.

284. 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.

285. 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.

286. 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.

287. Huang YX, Lin YZ, Li JL, et al. Role of postoperative radiotherapy in pT3N0 rectal cancer: A risk-stratification system based on population analyses. Cancer Med 2019;8:1024-1033. Available at: https://pubmed.ncbi.nlm.nih.gov/30714683/.

288. 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.

289. 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.

290. 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.

291. 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.

292. Kennedy ED, Simunovic M, Jhaveri K, et al. Safety and Feasibility of Using Magnetic Resonance Imaging Criteria to Identify Patients With "Good Prognosis" Rectal Cancer Eligible for Primary Surgery: The Phase 2 Nonrandomized QuickSilver Clinical Trial. JAMA Oncol 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30973610.

293. 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.

294. 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.

295. 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.

296. 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.

297. 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.

298. 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.

299. 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.

300. 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.

301. 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.

302. 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.

303. 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.

304. 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.

305. 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.

306. Azria D, Doyen J, Jarlier M, et al. Late toxicities and clinical outcome at 5 years of the ACCORD 12/0405-PRODIGE 02 trial comparing two neoadjuvant chemoradiotherapy regimens for intermediate-risk rectal cancer. Ann Oncol 2017;28:2436-2442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28961836.

307. 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.

308. 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.

309. 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.

310. Deng Y, Chi P, Lan P, et al. Modified FOLFOX6 with or without radiation versus fluorouracil and leucovorin with radiation in neoadjuvant treatment of locally advanced rectal cancer: initial results of the Chinese FOWARC multicenter, open-label, randomized three-arm phase III trial. J Clin Oncol 2016;34:3300-3307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27480145.

311. Deng Y, Chi P, Lan P, et al. Neoadjuvant Modified FOLFOX6 With or Without Radiation Versus Fluorouracil Plus Radiation for Locally Advanced Rectal Cancer: Final Results of the Chinese FOWARC Trial. J Clin Oncol 2019;37:3223-3233. Available at: https://pubmed.ncbi.nlm.nih.gov/31557064/.

312. Feng YR, Zhu Y, Liu LY, et al. Interim analysis of postoperative chemoradiotherapy with capecitabine and oxaliplatin versus capecitabine alone for pathological stage II and III rectal cancer: a randomized multicenter phase III trial. Oncotarget 2016;7:25576-25584. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27014909.

313. 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.

314. 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.

315. 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.

316. 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.

317. Pinto C, Di Bisceglie M, Di Fabio F, et al. Phase II study of preoperative treatment with external radiotherapy plus panitumumab in low-risk, locally advanced rectal cancer (RaP Study/STAR-03). Oncologist 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29523646.

318. 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.

319. Borg C, Mantion G, Boudghène F, et al. Efficacy and Safety of Two Neoadjuvant Strategies With Bevacizumab in MRI-Defined Locally Advanced T3 Resectable Rectal Cancer: Final Results of a Randomized, Noncomparative Phase 2 INOVA Study. Clin Colorectal Cancer 2019;18:200-208.e201. Available at: https://pubmed.ncbi.nlm.nih.gov/31311761/.

320. Masi G, Vivaldi C, Fornaro L, et al. Total neoadjuvant approach with FOLFOXIRI plus bevacizumab followed by chemoradiotherapy plus bevacizumab in locally advanced rectal cancer: the TRUST trial. Eur J Cancer 2019;110:32-41. Available at: https://pubmed.ncbi.nlm.nih.gov/30739838/.

321. Maeda K, Shibutani M, Otani H, et al. Neoadjuvant Radiotherapy with Capecitabine Plus Bevacizumab for Locally Advanced Lower Rectal Cancer: Results of a Single-institute Phase II Study. Anticancer Res 2018;38:4193-4197. Available at: https://pubmed.ncbi.nlm.nih.gov/29970549/.

322. 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.

323. Fernández-Martos C, Pericay C, Losa F, et al. Effect of Aflibercept Plus Modified FOLFOX6 Induction Chemotherapy Before Standard Chemoradiotherapy and Surgery in Patients With High-Risk Rectal Adenocarcinoma: The GEMCAD 1402 Randomized Clinical Trial. JAMA Oncol 2019;5:1566-1573. Available at: https://pubmed.ncbi.nlm.nih.gov/31465088/.

324. Bendell JC, Thompson D, Hemphill BM, et al. A Phase 2 Study of 5-Fluorouracil (5-FU), Ziv-Aflibercept, and Radiation for the Preoperative and Adjuvant Treatment of Patients with Stage II/III Rectal Cancer. Cancer Invest 2017;35:535-540. Available at: https://pubmed.ncbi.nlm.nih.gov/28792245/.

325. 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.

326. 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.

327. 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.

328. 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;40:283-287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25374145.

329. 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.

330. 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.

331. 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.

332. Sclafani F, Brown G, Cunningham D, et al. PAN-EX: a pooled analysis of two trials of neoadjuvant chemotherapy followed by chemoradiotherapy in MRI-defined, locally advanced rectal cancer. Ann Oncol 2016;27:1557-1565. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27217542.

333. Zhang J, Huang M, Cai Y, et al. Neoadjuvant Chemotherapy With mFOLFOXIRI Without Routine Use of Radiotherapy for Locally Advanced Rectal Cancer. Clin Colorectal Cancer 2019;18:238-244. Available at: https://pubmed.ncbi.nlm.nih.gov/31378655/.

334. Smith JJ, Chow OS, Gollub MJ, et al. Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. BMC Cancer 2015;15:767. Available at: https://pubmed.ncbi.nlm.nih.gov/26497495/.

335. Garcia-Aguilar J, Patil S, Kim JK, et al. Preliminary results of the organ preservation of rectal adenocarcinoma (OPRA) trial [abstract]. Journal of Clinical Oncology 2020;38:4008-4008. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.4008.

336. Fokas E, Allgauer M, Polat B, et al. Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12. J Clin Oncol 2019:Jco1900308. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31150315.

337. 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.

338. Hasegawa S, Goto S, Matsumoto T, et al. A multicenter phase 2 study on the feasibility and efficacy of neoadjuvant chemotherapy without radiotherapy for locally advanced rectal cancer. Ann Surg Oncol 2017;24:3587-3595. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28685354.

339. Jalil O, Claydon L, Arulampalam T. Review of neoadjuvant chemotherapy alone in locally advanced rectal cancer. J Gastrointest Cancer 2015;46:219-236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26133151.

340. 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.

341. Bae BK, Kang MK, Kim JC, et al. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. Radiat Oncol J 2017;35:208-216. Available at: https://pubmed.ncbi.nlm.nih.gov/29037023/.

342. 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.

343. 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.

344. 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.

345. Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. Ann Surg 2016;263:458-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24263329.

346. 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.

347. 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.

348. 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.

349. 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.

350. 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;222:367-374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26897480.

351. Lefevre JH, Mineur L, Kotti S, et al. Effect of interval (7 or 11 weeks) between neoadjuvant radiochemotherapy and surgery on complete pathologic response in rectal cancer: a multicenter, randomized, controlled trial (GRECCAR-6). J Clin Oncol 2016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27432930.

352. 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.

353. 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.

354. 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.

355. 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.

356. 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.

357. 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.

358. 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.

359. 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.

360. 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.

361. 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.

362. Ansari N, Solomon MJ, Fisher RJ, et al. Acute Adverse Events and Postoperative Complications in a Randomized Trial of Preoperative Short-course Radiotherapy Versus Long-course Chemoradiotherapy for T3 Adenocarcinoma of the Rectum: Trans-Tasman Radiation Oncology Group Trial (TROG 01.04). Ann Surg 2017;265:882-888. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27631775.

363. McLachlan SA, Fisher RJ, Zalcberg J, et al. The impact on health-related quality of life in the first 12 months: A randomised comparison of preoperative short-course radiation versus long-course chemoradiation for T3 rectal cancer (Trans-Tasman Radiation Oncology Group Trial 01.04). Eur J Cancer 2016;55:15-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26771873.

364. 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.

365. Latkauskas T, Pauzas H, Kairevice L, et al. Preoperative conventional chemoradiotherapy versus short-course radiotherapy with delayed surgery for rectal cancer: results of a randomized controlled trial. BMC Cancer 2016;16:927. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27903247.

366. Bujko K, Wyrwicz L, Rutkowski A, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized

phase III study. Ann Oncol 2016;27:834-842. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26884592.

367. Cisel B, Pietrzak L, Michalski W, et al. Long-course preoperative chemoradiation vs. 5 x 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: Long-term results of the randomized Polish II study. Ann Oncol 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31192355.

368. van der Valk MJM, Marijnen CAM, van Etten B, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. Radiother Oncol 2020;147:75-83. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32240909.

369. Hospers G, Bahadoer RR, Dijkstra EA, et al. Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: The randomized RAPIDO trial [abstract]. J Clin Oncol 2020;38. Available at: https://meetinglibrary.asco.org/record/185464/abstract.

370. 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.

371. 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.

372. 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.

373. 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.

374. 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.

375. 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.

376. 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.

377. 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.

378. 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.

379. 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.

380. Fokas E, Strobel P, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy as a prognostic factor and individual-level

surrogate for disease-free survival in rectal cancer. J Natl Cancer Inst 2017;109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29206996.

381. Karagkounis G, Thai L, Mace AG, et al. prognostic implications of pathological response to neoadjuvant chemoradiation in pathologic stage III rectal cancer. Ann Surg 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29465458.

382. 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.

383. 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.

384. 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.

385. 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.

386. 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.

387. 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.

388. 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.

389. 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.

390. Smith JJ, Strombom P, Chow OS, et al. Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy. JAMA Oncol 2019:e185896. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30629084.

391. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2017;2:501-513. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28479372.

392. Sammour T, Price BA, Krause KJ, Chang GJ. Nonoperative management or 'watch and wait' for rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy: A critical appraisal. Ann Surg Oncol 2017;24:1904-1915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28324284.

393. Kong JC, Guerra GR, Warrier SK, et al. Outcome and salvage surgery following "watch and wait" for rectal cancer after neoadjuvant therapy: A systematic review. Dis Colon Rectum 2017;60:335-345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28177997.

394. 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.

395. Nahas SC, Rizkallah Nahas CS, Sparapan Marques CF, et al. Pathologic complete response in rectal cancer: can we detect it? Lessons learned from a proposed randomized trial of watch-and-wait treatment of rectal cancer. Dis Colon Rectum 2016;59:255-263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26953983.

396. 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.

397. Ellis CT, Samuel CA, Stitzenberg KB. National trends in nonoperative management of rectal adenocarcinoma. J Clin Oncol 2016;34:1644-1651. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27022115.

398. Ellis CT, Dusetzina SB, Sanoff H, Stitzenberg KB. Long-term survival after chemoradiotherapy without surgery for rectal adenocarcinoma: A word of caution. JAMA Oncol 2017;3:123-125. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27768159.

399. Bujko K, Glimelius B, Valentini V, et al. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: A meta-analysis of randomized trials comparing surgery +/- a fluoropyrimidine and surgery + a fluoropyrimidine +/- oxaliplatin. Eur J Surg Oncol 2015;41:713-723. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25911110.

400. 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.

401. 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.

402. 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.

403. 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.

404. 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://ascopubs.org/doi/abs/10.1200/jco.2006.24.18_suppl.3526.

405. 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.

406. Hong YS, Kim SY, Lee JS, et al. Oxaliplatin-Based Adjuvant Chemotherapy for Rectal Cancer After Preoperative Chemoradiotherapy (ADORE): Long-Term Results of a Randomized Controlled Trial. J Clin Oncol 2019;37:3111-3123. Available at: https://pubmed.ncbi.nlm.nih.gov/31593484/.

407. 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.

408. 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.

409. 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.

410. 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.

411. Carvalho C, Glynne-Jones R. Challenges behind proving efficacy of adjuvant chemotherapy after preoperative chemoradiation for rectal cancer. Lancet Oncol 2017;18:e354-e363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28593861.

412. Loree JM, Kennecke HF, Lee-Ying RM, et al. Impact of postoperative adjuvant chemotherapy following long-course chemoradiotherapy in stage II rectal cancer. Am J Clin Oncol 2016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27819876.

413. Hu X, Li YQ, Li QG, et al. Adjuvant chemotherapy seemed not to have survival benefit in rectal cancer patients with ypTis-2N0 after preoperative radiotherapy and surgery from a population-based propensity score analysis. Oncologist 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29674444.

414. Garlipp B, Ptok H, Benedix F, et al. Adjuvant treatment for resected rectal cancer: impact of standard and intensified postoperative chemotherapy on disease-free survival in patients undergoing preoperative chemoradiation-a propensity score-matched analysis of an observational database. Langenbecks Arch Surg 2016;401:1179-1190. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27830368.

415. Polanco PM, Mokdad AA, Zhu H. Association of adjuvant chemotherapy with overall survival in patients with rectal cancer and pathologic complete response following neoadjuvant chemotherapy and resection. JAMA Oncol 2018:Published online April 19, 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29710272.

416. Shahab D, Gabriel E, Attwood K, et al. Adjuvant chemotherapy is associated with improved overall survival in locally advanced rectal cancer after achievement of a pathologic complete response to chemoradiation. Clin Colorectal Cancer 2017;16:300-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28420585.

417. 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.

418. 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.

419. Chakravarthy AB, Zhao F, Meropol NJ, et al. Intergroup Randomized Phase III Study of Postoperative Oxaliplatin, 5-Fluorouracil, and Leucovorin Versus Oxaliplatin, 5-Fluorouracil, Leucovorin, and Bevacizumab for Patients with Stage II or III Rectal Cancer Receiving Preoperative Chemoradiation: A Trial of the ECOG-ACRIN Research Group (E5204). Oncologist 2020;25:e798-e807. Available at: https://pubmed.ncbi.nlm.nih.gov/31852811/.

420. 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.

421. 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.

422. 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.

423. 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.

424. 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.

425. 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.

426. 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.

427. 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.

428. 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.

429. 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.

430. 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.

431. 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.

432. 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.

433. 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.

434. Borstlap WA, Coeymans TJ, Tanis PJ, et al. Meta-analysis of oncological outcomes after local excision of pT1-2 rectal cancer requiring adjuvant (chemo)radiotherapy or completion surgery. Br J Surg

2016;103:1105-1116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27302385.

435. 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.

436. 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.

437. Willett CG, Badizadegan K, Ancukiewicz M, Shellito PC. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 1999;42:167-173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10211491.

438. Sclafani F, Brown G, Cunningham D, et al. Systemic chemotherapy as salvage treatment for locally advanced rectal cancer patients who fail to respond to standard neoadjuvant chemoradiotherapy. Oncologist 2017;22:728-736. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28476941.

439. 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.

440. 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.

441. 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.

442. 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.

443. 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.

444. 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.

445. 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.

446. 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.

447. 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.

448. 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.

449. 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.

450. 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.

451. 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.

452. 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.

453. 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.

454. 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.

455. 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.

456. 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.

457. 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.

458. 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.

459. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-1422. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27380959.

460. 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.

461. 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.

462. 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.

463. 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.

464. 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.

465. 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.

466. 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.

467. Gonzalez M, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: systematic review and meta-analysis. Future Oncol 2015;11:31-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25662325.

468. 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.

469. 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.

470. Hadden WJ, de Reuver PR, Brown K, et al. Resection of colorectal liver metastases and extra-hepatic disease: a systematic review and proportional meta-analysis of survival outcomes. HPB (Oxford) 2016;18:209-220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27017160.

471. 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.

472. 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.

473. 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.

474. Wiegering A, Riegel J, Wagner J, et al. The impact of pulmonary metastasectomy in patients with previously resected colorectal cancer liver metastases. PLoS One 2017;12:e0173933. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28328956.

475. 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.

476. 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.

477. 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.

478. Wurster EF, Tenckhoff S, Probst P, et al. A systematic review and meta-analysis of the utility of repeated versus single hepatic resection for colorectal cancer liver metastases. HPB (Oxford) 2017;19:491-497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28347640.

479. 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.

480. 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.

481. 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.

482. 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.

483. 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.

484. 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.

485. 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.

486. 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.

487. 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;25:3438-3454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25994193.

488. 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.

489. 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.

490. Ruers T, Van Coevorden F, Punt CJ, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst 2017;109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28376151.

491. 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.

492. 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.

493. 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.

494. 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.

495. 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.

496. Zacharias AJ, Jayakrishnan TT, Rajeev R, et al. Comparative effectiveness of hepatic artery based therapies for unresectable colorectal

liver metastases: a meta-analysis. PLoS One 2015;10:e0139940. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26448327.

497. 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.

498. 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.

499. Chan DL, Alzahrani NA, Morris DL, Chua TC. Systematic review and meta-analysis of hepatic arterial infusion chemotherapy as bridging therapy for colorectal liver metastases. Surg Oncol 2015;24:162-171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26133575.

500. Levi FA, Boige V, Hebbar M, et al. Conversion to resection of liver metastases from colorectal cancer with hepatic artery infusion of combined chemotherapy and systemic cetuximab in multicenter trial OPTILIV. Ann Oncol 2016;27:267-274. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26578731.

501. Pak LM, Kemeny NE, Capanu M, et al. Prospective phase II trial of combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases: Long term results and curative potential. J Surg Oncol 2018;117:634-643. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29165816.

502. 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.

503. 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.

504. 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;121:3649-3658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26149602.

505. 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.

506. 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.

507. 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.

508. 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.

509. 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.

510. 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.

511. 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.

512. 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.

513. 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.

514. 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;14:296-305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26277696.

515. Hickey R, Lewandowski RJ, Prudhomme T, et al. 90Y radioembolization of colorectal hepatic metastases using glass microspheres: safety and survival outcomes from a 531-patient multicenter study. J Nucl Med 2016;57:665-671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26635340.

516. Kurilova I, Beets-Tan RGH, Flynn J, et al. Factors Affecting Oncologic Outcomes of 90Y Radioembolization of Heavily Pre-Treated Patients With Colon Cancer Liver Metastases. Clin Colorectal Cancer 2019;18:8-18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30297264.

517. 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.

518. 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.

519. van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol 2016;34:1723-1731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26903575.

520. Wasan HS, Gibbs P, Sharma NK, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol 2017;18:1159-1171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28781171.

521. 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.

522. 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.

523. 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.

524. 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.

525. Correa-Gallego C, Gonen M, Fischer M, et al. Perioperative complications influence recurrence and survival after resection of hepatic colorectal metastases. Ann Surg Oncol 2013;20:2477-2484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23608971.

526. 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.

527. Scheffer HJ, Vroomen LG, Nielsen K, et al. Colorectal liver metastatic disease: efficacy of irreversible electroporation--a single-arm phase II clinical trial (COLDFIRE-2 trial). BMC Cancer 2015;15:772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26497813.

528. 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.

529. 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.

530. Sucandy I, Cheek S, Golas BJ, et al. Longterm survival outcomes of patients undergoing treatment with radiofrequency ablation for hepatocellular carcinoma and metastatic colorectal cancer liver tumors. HPB (Oxford) 2016;18:756-763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27593593.

531. 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.

532. 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.

533. 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.

534. 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.

535. 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.

536. 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.

537. 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.

538. 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.

539. 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.

540. 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.

541. 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.

542. 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.

543. Shady W, Petre EN, Do KG, et al. Percutaneous Microwave versus Radiofrequency Ablation of Colorectal Liver Metastases: Ablation with Clear Margins (A0) Provides the Best Local Tumor Control. J Vasc Interv Radiol 2018;29:268-275.e261. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29203394.

544. Meijerink MR, Puijk RS, van Tilborg A, et al. Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis. Cardiovasc Intervent Radiol 2018;41:1189-1204. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29666906.

545. Odisio BC, Yamashita S, Huang SY, et al. Local tumour progression after percutaneous ablation of colorectal liver metastases according to RAS mutation status. Br J Surg 2017;104:760-768. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28240361.

546. Calandri M, Yamashita S, Gazzera C, et al. Ablation of colorectal liver metastasis: Interaction of ablation margins and RAS mutation profiling on local tumour progression-free survival. Eur Radiol 2018;28:2727-2734. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29417253.

547. Shady W, Petre EN, Vakiani E, et al. Kras mutation is a marker of worse oncologic outcomes after percutaneous radiofrequency ablation of colorectal liver metastases. Oncotarget 2017;8:66117-66127. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29029497.

548. 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.

549. 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.

550. 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.

551. 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.

552. 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.

553. 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.

554. 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.

555. 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.

556. 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.

557. 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.

558. Agolli L, Bracci S, Nicosia L, et al. Lung metastases treated with stereotactic ablative radiation therapy in oligometastatic colorectal cancer patients: outcomes and prognostic factors after long-term follow-up. Clin Colorectal Cancer 2016;16:58-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27522627.

559. 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.

560. ACR practice parameter for intensity modulated radiation therapy (IMRT). The American College of Radiology; 2016. Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/imrt-ro.pdf?la=en. Accessed June 23, 2020.

561. 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.

562. 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.

563. 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.

564. Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol 2016;17:1709-1719. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27743922.

565. 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.

566. Takahashi H, Okabayashi K, Tsuruta M, et al. Self-expanding metallic stents versus surgical intervention as palliative therapy for obstructive colorectal cancer: a meta-analysis. World J Surg 2015;39:2037-2044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25894403.

567. van Hooft JE, van Halsema EE, Vanbiervliet G, et al. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline.

Gastrointest Endosc 2014;80:747-761 e741-775. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25436393.

568. 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.

569. 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.

570. 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.

571. 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.

572. 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.

573. 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.

574. 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.

575. 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.

576. 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.

577. 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.

578. 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.

579. 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.

580. 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.

581. Zhao J, van Mierlo KMC, Gomez-Ramirez J, et al. Systematic review of the influence of chemotherapy-associated liver injury on outcome after partial hepatectomy for colorectal liver metastases. Br J Surg 2017;104:990-1002. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28542731.

582. 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.

583. 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.

584. 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.

585. 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.

586. 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.

587. Folprecht G, Gruenberger T, Bechstein W, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). Ann Oncol 2014;25:1018-1025. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24585720.

588. 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.

589. Modest DP, Martens UM, Riera-Knorrenschild J, et al. FOLFOXIRI Plus Panitumumab As First-Line Treatment of RAS Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFI Study (AIO KRK0109). J Clin Oncol 2019;37:3401-3411. Available at: https://pubmed.ncbi.nlm.nih.gov/31609637/.

590. 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.

591. Borelli B, Moretto R, Lonardi S, et al. TRIPLETE: a randomised phase III study of modified FOLFOXIRI plus panitumumab versus mFOLFOX6 plus panitumumab as initial therapy for patients with unresectable RAS and BRAF wild-type metastatic colorectal cancer. ESMO Open 2018;3:e000403. Available at: https://pubmed.ncbi.nlm.nih.gov/30018814/.

592. 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.

593. 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.

594. 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.

595. 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.

596. 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.

597. van Mierlo KM, Zhao J, Kleijnen J, et al. The influence of chemotherapy-associated sinusoidal dilatation on short-term outcome after partial hepatectomy for colorectal liver metastases: A systematic review with meta-analysis. Surg Oncol 2016;25:298-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27566036.

598. 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.

599. 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.

600. 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.

601. Khoo E, O'Neill S, Brown E, et al. Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. HPB (Oxford) 2016;18:485-493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27317952.

602. Brandi G, De Lorenzo S, Nannini M, et al. Adjuvant chemotherapy for resected colorectal cancer metastases: Literature review and meta-analysis. World J Gastroenterol 2016;22:519-533. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26811604.

603. 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.

604. 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.

605. Nagayama S, Hasegawa S, Hida K, et al. Multi-institutional phase II study on the feasibility of liver resection following preoperative mFOLFOX6 therapy for resectable liver metastases from colorectal cancers. Int J Clin Oncol 2017;22:316-323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27752787.

606. 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.

607. 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.

608. 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.

609. 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.

610. Bischof DA, Clary BM, Maithel SK, Pawlik TM. Surgical management of disappearing colorectal liver metastases. Br J Surg 2013;100:1414-1420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24037559.

611. 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.

612. Snoeren N, van Hillegersberg R, Schouten SB, et al. Randomized phase iii study to assess efficacy and safety of adjuvant CAPOX with or without bevacizumab in patients after resection of colorectal liver metastases: HEPATICA study. Neoplasia 2017;19:93-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28088688.

613. 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.

614. 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.

615. Dai F, Shu L, Bian Y, et al. Safety of bevacizumab in treating metastatic colorectal cancer: a systematic review and meta-analysis of all randomized clinical trials. Clin Drug Investig 2013;33:779-788. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23979925.

616. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 2008;26:3523-3529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18640933.

617. Package Insert. AVASTIN® (bevacizumab). Genentech, Inc.; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125085s332lbl.pdf. Accessed June 23, 2020.

618. 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.

619. Goldberg RM, Rothenberg ML, Van Cutsem E, et al. The continuum of care: a paradigm for the management of metastatic colorectal cancer. Oncologist 2007;12:38-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17227899.

620. 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.

621. 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.

622. 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.

623. 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.

624. 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.

625. 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.

626. 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.

627. 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.

628. 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.

629. 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.

630. 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.

631. 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.

632. 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.

633. 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.

634. 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.

635. 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.

636. 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.

637. 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;26:13-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25115304.

638. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: American Society of Clinical Oncology provisional clinical opinion update 2015. J Clin Oncol 2016;34:179-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26438111.

639. 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.

640. 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.

641. 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.

642. 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.

643. 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.

644. Package Insert. Vectibix® (Panitumumab). Thousand Oaks, CA: Amgen Inc.; 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf. Accessed June 23, 2020.

645. Package Insert. Cetuximab (Erbitux®). Branchburg, NJ: ImClone Systems Incorporated; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125084s273lbl.pdf. Accessed June 23, 2020.

646. 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.

647. 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.

648. 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.

649. 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.

650. 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;26:2503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26371285.

651. Segelov E, Thavaneswaran S, Waring PM, et al. Response to cetuximab with or without irinotecan in patients with refractory metastatic colorectal cancer harboring the KRAS G13D mutation: Australasian Gastro-Intestinal Trials Group ICECREAM study. J Clin Oncol 2016;34:2258-2264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27114605.

652. Rowland A, Dias MM, Wiese MD, et al. Meta-analysis comparing the efficacy of anti-EGFR monoclonal antibody therapy between KRAS G13D and other KRAS mutant metastatic colorectal cancer tumours. Eur J Cancer 2016;55:122-130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26812186.

653. 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.

654. 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.

655. 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.

656. 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.

657. 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.

658. 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.

659. 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.

660. 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.

661. 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.

662. 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.

663. 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.

664. 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.

665. 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.

666. 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.

667. 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.

668. 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.

669. 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.

670. 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.

671. 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.

672. 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.

673. Sinicrope FA, Shi Q, Allegra CJ, et al. Association of DNA mismatch repair and mutations in BRAF and KRAS with survival after recurrence in stage III colon cancers : A secondary analysis of 2 randomized clinical trials. JAMA Oncol 2017;3:472-480. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28006055.

674. 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.

675. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. N Engl J Med 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31566309.

676. Kopetz S, Grothey A, Cutsem EV, et al. Encorafenib plus cetuximab with or without binimetinib for BRAF V600E-mutant metastatic colorectal cancer: Quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC) [abstract]. J Clin Oncol 2020;38; suppl 4:8. Available at: https://meetinglibrary.asco.org/record/181898/abstract.

677. Kopetz S, Grothey A, Cutsem EV, et al. BEACON CRC: a randomized, 3-Arm, phase 3 study of encorafenib and cetuximab with or without binimetinib vs. choice of either irinotecan or FOLFIRI plus cetuximab in BRAF V600E–mutant metastatic colorectal cancer [abstract]. Annals of Oncology 2019;30:iv137-iv151. Available at: https://doi.org/10.1093/annonc/mdz183.004.

678. 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.

679. Raghav KPS, Overman MJ, Yu R, et al. HER2 amplification as a negative predictive biomarker for anti-epidermal growth factor receptor antibody therapy in metastatic colorectal cancer [abstract]. ASCO Meeting Abstracts 2016;34:3517. Available at: http://meetinglibrary.asco.org/content/168395-176.

680. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:738-746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27108243.

681. Sartore-Bianchi A, Amatu A, Porcu L, et al. HER2 Positivity Predicts Unresponsiveness to EGFR-Targeted Treatment in Metastatic Colorectal Cancer. Oncologist 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30952821.

682. Valtorta E, Martino C, Sartore-Bianchi A, et al. Assessment of a HER2 scoring system for colorectal cancer: results from a validation study.

Mod Pathol 2015;28:1481-1491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26449765.

683. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol 2019;20:518-530. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30857956.

684. Wu SW, Ma CC, Li WH. Does overexpression of HER-2 correlate with clinicopathological characteristics and prognosis in colorectal cancer? Evidence from a meta-analysis. Diagn Pathol 2015;10:144. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26276145.

685. Martin V, Landi L, Molinari F, et al. HER2 gene copy number status may influence clinical efficacy to anti-EGFR monoclonal antibodies in metastatic colorectal cancer patients. Br J Cancer 2013;108:668-675. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23348520.

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

687. Lochhead P, Kuchiba A, Imamura Y, et al. Microsatellite instability and BRAF mutation testing in colorectal cancer prognostication. J Natl Cancer Inst 2013;105:1151-1156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23878352.

688. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res 2014;20:5322-5330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25139339.

689. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-2454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22658127.

690. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-2520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26028255.

691. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-1191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28734759.

692. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 2018;36:773-779. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29355075.

693. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med 2018;378:731-739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29466156.

694. Okamura R, Boichard A, Kato S, et al. Analysis of NTRK Alterations in Pan-Cancer Adult and Pediatric Malignancies: Implications for NTRK-Targeted Therapeutics. JCO Precis Oncol 2018;2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30637364.

695. Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with NTRK gene fusions. Mod Pathol 2019;32:147-153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30171197.

696. Cocco E, Benhamida J, Middha S, et al. Colorectal Carcinomas Containing Hypermethylated MLH1 Promoter and Wild-Type BRAF/KRAS Are Enriched for Targetable Kinase Fusions. Cancer Res 2019;79:1047-1053. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30643016.

697. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020;21:531-540. Available at: https://pubmed.ncbi.nlm.nih.gov/32105622/.

698. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31838007.

699. 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.

700. 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.

701. 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.

702. 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.

703. 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.

704. 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.

705. 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.

706. 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.

707. 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.

708. 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.

709. 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.

710. Yoon HI, Koom WS, Kim TH, et al. Upfront systemic chemotherapy and short-course radiotherapy with delayed surgery for locally advanced rectal cancer with distant metastases: outcomes, compliance, and favorable prognostic factors. PLoS One 2016;11:e0161475. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27536871.

711. 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.

712. 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.

713. 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.

714. 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.

715. 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.

716. 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.

717. 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.

718. 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.

719. Ikoma N, You YN, Bednarski BK, et al. Impact of recurrence and salvage surgery on survival after multidisciplinary treatment of rectal cancer. J Clin Oncol 2017;35:2631-2638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28657814.

720. 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.

721. 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.

722. 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.

723. Maffione AM, Lopci E, Bluemel C, et al. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. Eur J Nucl Med Mol Imaging 2015;42:152-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25319712.

724. 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.

725. 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.

726. 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.

727. 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.

728. 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.

729. 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.

730. 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.

731. 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.

732. 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.

733. 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.

734. 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.

735. 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.

736. 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.

737. Jeffery M, Hickey BE, Hider PN, See AM. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2016;11:CD002200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27884041.

738. Mokhles S, Macbeth F, Farewell V, et al. Meta-analysis of colorectal cancer follow-up after potentially curative resection. Br J Surg 2016;103:1259-1268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27488593.

739. 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.

740. 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.

741. 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.

742. 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.

743. Wille-Jorgensen P, Syk I, Smedh K, et al. Effect of More vs Less Frequent Follow-up Testing on Overall and Colorectal Cancer-Specific Mortality in Patients With Stage II or III Colorectal Cancer: The COLOFOL Randomized Clinical Trial. Jama 2018;319:2095-2103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29800179.

744. 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.

745. Verberne CJ, Zhan Z, van den Heuvel ER, et al. Survival analysis of the CEAwatch multicentre clustered randomized trial. Br J Surg 2017;104:1069-1077. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28376235.

746. Rosati G, Ambrosini G, Barni S, et al. A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. Ann Oncol 2016;27:274-280. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26578734.

747. Lepage C, Phelip JM, Cany L, et al. Effect of 5 years of imaging and CEA follow-up to detect recurrence of colorectal cancer: The FFCD PRODIGE 13 randomised phase III trial. Dig Liver Dis 2015;47:529-531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25933809.

748. 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.

749. Kahi CJ, Boland CR, Dominitz JA, et al. Colonoscopy surveillance after colorectal cancer resection: recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2016;150:758-768 e711. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26892199.

750. 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.

751. 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.

752. 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.

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

754. 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.

755. 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.

756. 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.

757. 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.

758. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer. Cancer Care Ontario; 2016. Available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/256. Accessed June 23, 2020.

759. 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.

760. Steele SR, Chang GJ, Hendren S, et al. Practice guideline for the surveillance of patients after curative treatment of colon and rectal cancer. Dis Colon Rectum 2015;58:713-725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26163950.

761. 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.

762. Nicholson BD, Shinkins B, Mant D. Blood measurement of carcinoembryonic antigen level for detecting recurrence of colorectal cancer. JAMA 2016;316:1310-1311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27673308.

763. Nicholson BD, Shinkins B, Pathiraja I, et al. Blood CEA levels for detecting recurrent colorectal cancer. Cochrane Database Syst Rev 2015:CD011134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26661580.

764. 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.

765. Khan K, Athauda A, Aitken K, et al. Survival outcomes in asymptomatic patients with normal conventional imaging but raised carcinoembryonic antigen levels in colorectal cancer following positron emission tomography-computed tomography imaging. Oncologist 2016;21:1502-1508. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27742904.

766. 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.

767. 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.

768. 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.

769. 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.

770. 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.

771. 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.

772. 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.

773. 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.

774. 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.

775. 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.

776. 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.

777. El-Shami K, Oeffinger KC, Erb NL, et al. American Cancer Society Colorectal Cancer Survivorship Care Guidelines. CA Cancer J Clin 2015;65:428-455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26348643.

778. 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.

779. 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.

780. 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.

781. 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.

782. 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.

783. 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.

784. 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.

785. 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.

786. 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.

787. 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.

788. Lynch BM, Steginga SK, Hawkes AL, et al. Describing and predicting psychological distress after colorectal cancer. Cancer 2008;112:1363-1370. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18318044.

789. 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.

790. Thong MS, Mols F, Wang XS, et al. Quantifying fatigue in (long-term) colorectal cancer survivors: a study from the population-based patient reported outcomes following initial treatment and long term evaluation of survivorship registry. Eur J Cancer 2013;49:1957-1966. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23453750.

791. Vardy JL, Dhillon HM, Pond GR, et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. J Clin Oncol 2015;33:4085-4092. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26527785.

792. 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;33:3423-3430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26282636.

793. 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.

794. 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.

795. 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.

796. 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.

797. 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.

798. 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.

799. 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.

800. 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.

801. 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.

802. Wu W, Guo F, Ye J, et al. Pre- and post-diagnosis physical activity is associated with survival benefits of colorectal cancer patients: a systematic review and meta-analysis. Oncotarget 2016;7:52095-52103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27437765.

803. 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.

804. 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.

805. 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.

806. Lee J, Meyerhardt JA, Giovannucci E, Jeon JY. Association between body mass index and prognosis of colorectal cancer: a meta-analysis of prospective cohort studies. PLoS One 2015;10:e0120706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25811460.

807. Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, et al. Metabolic dysfunction, obesity, and survival among patients with early-stage colorectal cancer. J Clin Oncol 2016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27601537.

808. Daniel CR, Shu X, Ye Y, et al. Severe obesity prior to diagnosis limits survival in colorectal cancer patients evaluated at a large cancer centre. Br J Cancer 2016;114:103-109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26679375.

809. Doleman B, Mills KT, Lim S, et al. Body mass index and colorectal cancer prognosis: a systematic review and meta-analysis. Tech Coloproctol 2016;20:517-535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27343117.

810. Laake I, Larsen IK, Selmer R, et al. Pre-diagnostic body mass index and weight change in relation to colorectal cancer survival among incident cases from a population-based cohort study. BMC Cancer 2016;16:402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27387027.

811. Renfro LA, Loupakis F, Adams RA, et al. Body mass index is prognostic in metastatic colorectal cancer: pooled analysis of patients from first-line clinical trials in the ARCAD database. J Clin Oncol 2016;34:144-150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26503203.

812. Kroenke CH, Neugebauer R, Meyerhardt J, et al. Analysis of body mass index and mortality in patients with colorectal cancer using causal diagrams. JAMA Oncol 2016;2:1137-1145. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27196302.

813. Renehan AG, Sperrin M. The obesity paradox and mortality after colorectal cancer: a causal conundrum. JAMA Oncol 2016;2:1127-1129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27195485.

814. 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.

815. 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.

816. 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.

817. 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.

818. 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.

819. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242-274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22539238.

820. Sun V, Grant M, Wendel CS, et al. Dietary and behavioral adjustments to manage bowel dysfunction after surgery in long-term colorectal cancer survivors. Ann Surg Oncol 2015;22:4317-4324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26159443.

821. Cai H, Zhang G, Wang Z, et al. Relationship between the use of statins and patient survival in colorectal cancer: a systematic review and meta-analysis. PLoS One 2015;10:e0126944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26030771.

822. Cardwell CR, Hicks BM, Hughes C, Murray LJ. Statin use after colorectal cancer diagnosis and survival: a population-based cohort study. J Clin Oncol 2014;32:3177-3183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25092779.

823. Bains SJ, Mahic M, Myklebust TA, et al. Aspirin as secondary prevention in patients with colorectal cancer: an unselected population-based study. J Clin Oncol 2016;34:2501-2508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27247217.

824. Bastiaannet E, Sampieri K, Dekkers OM, et al. Use of aspirin postdiagnosis improves survival for colon cancer patients. Br J Cancer 2012;106:1564-1570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22454078.

825. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA 2009;302:649-658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19671906.

826. Goh CH, Leong WQ, Chew MH, et al. Post-operative aspirin use and colorectal cancer-specific survival in patients with stage I-III colorectal cancer. Anticancer Res 2014;34:7407-7414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25503181.

827. Li P, Wu H, Zhang H, et al. Aspirin use after diagnosis but not prediagnosis improves established colorectal cancer survival: a meta-analysis. Gut 2015;64:1419-1425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25239119.

828. McCowan C, Munro AJ, Donnan PT, Steele RJ. Use of aspirin post-diagnosis in a cohort of patients with colorectal cancer and its association with all-cause and colorectal cancer specific mortality. Eur J Cancer 2013;49:1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23182687.

829. Ng K, Meyerhardt JA, Chan AT, et al. Aspirin and COX-2 inhibitor use in patients with stage III colon cancer. J Natl Cancer Inst 2015;107:345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25432409.

830. Domingo E, Church DN, Sieber O, et al. Evaluation of PIK3CA mutation as a predictor of benefit from nonsteroidal anti-inflammatory drug therapy in colorectal cancer. J Clin Oncol 2013;31:4297-4305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24062397.

831. Elwood PC, Morgan G, Pickering JE, et al. Aspirin in the treatment of cancer: reductions in metastatic spread and in mortality: a systematic review and meta-analyses of published studies. PLoS One 2016;11:e0152402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27096951.

832. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. N Engl J Med 2012;367:1596-1606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23094721.

833. Nan H, Hutter CM, Lin Y, et al. Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants. JAMA 2015;313:1133-1142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25781442.

834. Paleari L, Puntoni M, Clavarezza M, et al. PIK3CA mutation, aspirin use after diagnosis and survival of colorectal cancer. a systematic review and meta-analysis of epidemiological studies. Clin Oncol (R Coll Radiol) 2016;28:317-326. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26712086.

835. Reimers MS, Bastiaannet E, Langley RE, et al. Expression of HLA class I antigen, aspirin use, and survival after a diagnosis of colon cancer. JAMA Intern Med 2014;174:732-739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24687028.

836. Dulai PS, Singh S, Marquez E, et al. Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis. Bmj 2016;355:i6188. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27919915.

837. Whitlock EP, Burda BU, Williams SB, et al. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2016;164:826-835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27064261.