Rectal Cancer

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Department of Clinical Effectiveness V13
Approved by the Executive Committee of the Medical Staff on 06/17/2025

Rectal Cancer

Note: Consider Clinical Trials as treatment options for eligible patients

PRESENTATION AND EVALUATION[1]

Tumor within rectum

- Pathology review[2]
- CEA
- IHC for MMR protein expression or MSI analysis
- Proctosigmoidoscopic evaluation by surgeon to assess tumor location and characteristics
- High-resolution MRI with rectal protocol (with or without contrast)
- Endorectal ultrasound may be performed in order to facilitate classification of cT1 vs T2 disease
- CT chest with or without contrast
- Contrast-enhanced CT or MRI of abdomen/pelvis
- Colonoscopy (with biopsy if no pathology or pathology non-diagnostic)
- Lifestyle risk assessment[3]

Resectable primary, no metastasis

PRIMARY TREATMENT

cT1N0 eligible for TAE **or** TAMIS/TEM resection[4] **or** ESD[5] → TAE **or** TAMIS/TEM[4] **or** ESD[5] → Excision complete and ≤ pT1?

- Yes → See Page 13 for surveillance; See Page 6 for recurrence
- No → Radical surgical resection: LAR, CAA, **or** APR, with or without temporary fecal diversion (ileostomy) **and/or**; Chemoradiation for patients interested in organ preservation

cT1 not eligible for TAE **or** TAMIS/TEM resection[4] **or** ESD[5] **or** T2N0 → Radical surgical resection: LAR, CAA, **or** APR, with or without temporary fecal diversion (ileostomy) **and/or**; Chemoradiation for patients interested in organ preservation

Stage II and stage III → See Page 3

Unresectable primary, no metastasis, see Page 4

Metastatic disease, intact primary, see Page 4

Stage IV with carcinomatosis, see Page 5

FOLLOW-UP/ SURVEILLANCE

- See Page 13 for surveillance
- See Page 6 for recurrence

APR = abdominoperineal resection
CAA = coloanal anastomosis
CEA = carcinoembryonic antigen
ESD = endoscopic submucosal dissection
IHC = immunohistochemistry
LAR = low anterior resection
MMR = mismatch repair
MSI = microsatellite instability
TAE = transanal excision
TAMIS = transanal minimally invasive surgery
TEM = transanal endoscopic microsurgery

[1] Initial evaluation should include assessment of tumor DNA mismatch repair status and of family history for hereditary cancer syndromes. Universal germline testing is recommended for all patients under age 50 years, and should be discussed with all patients regardless of age.
[2] Refer to Principles of Biomarker Testing
[3] See Physical Activity, Nutrition, Obesity Screening and Management, and Tobacco Cessation Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[4] Criteria for eligibility for transanal excision: cT1 (EUS or MRI), low grade, no lymphovascular or perineural invasion
[5] Criteria for eligibility for ESD: cT1 without endoscopic evidence for deeper invasion, low grade, no lymphovascular or perineural invasion. Refer to Principles of Endoscopic Therapy.

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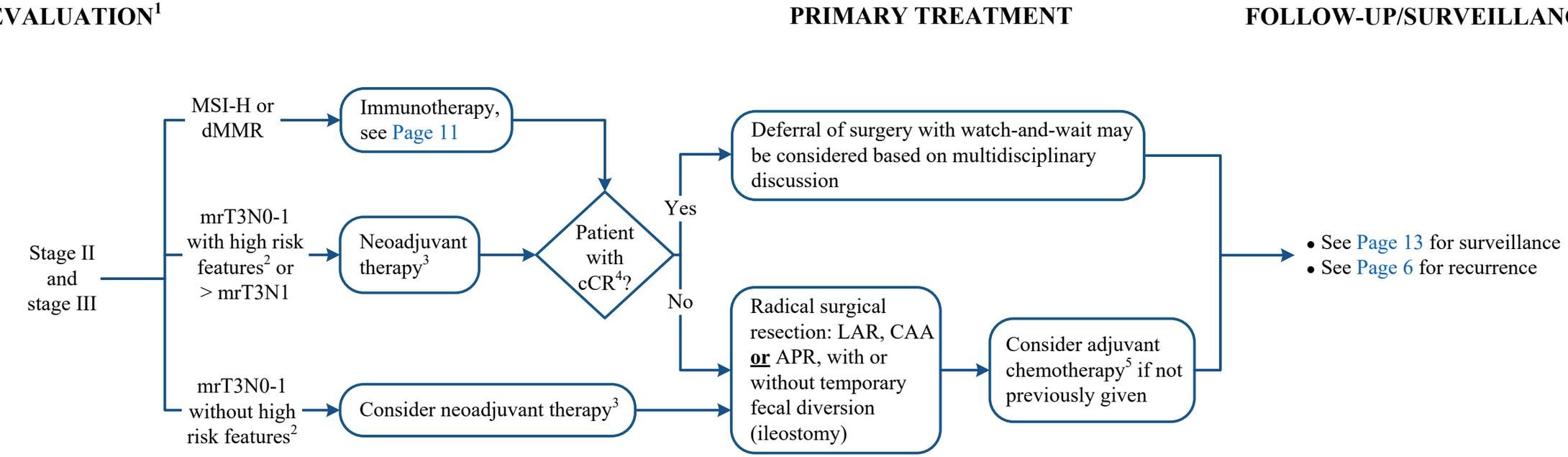

APR = abdominoperineal resection
CAA = coloanal anastomosis
cCR = clinical complete response
CRM = circumferential resection margin
dMMR = deficient mismatch repair
LAR = low anterior resection
MSI-H = microsatellite instability high

[1] Initial evaluation should include assessment of tumor DNA mismatch repair status and of family history for hereditary cancer syndromes. Universal germline testing is recommended for all patients under age 50 years, and should be discussed with all patients regardless of age.

[2] High risk features:
- Tumor in anterior, mid- or low-rectum
- mrN2 classification
- MRI predicted CRM < 2 mm
- Lateral pelvic lymph node metastasis
- MRI extramural vascular invasion
- mrT3c or greater (> 5 mm depth of penetration in mesorectum)

[3] Refer to Principles of Neoadjuvant Therapy

[4] Criteria for cCR:
- No palpable mass on digital rectal exam
- Flat scar without residual mass or ulceration on endoscopic exam
- mrTRG0

[5] Capecitabine or 5-flourouracil/leucovorin or 5-flourouracil/leucovorin/oxaliplatin or capecitabine/oxaliplatin

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PRESENTATION

PRIMARY TREATMENT

FOLLOW-UP/SURVEILLANCE

Unresectable primary, no metastasis → Multidisciplinary management recommendations include surgical, medical, and radiation oncologists, along with GI endoscopy → Consider radiation therapy (before or following systemic chemotherapy) → • Individualized palliative systemic therapy • Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Patient Representative[1]

Metastatic disease, intact primary[2] → Are primary tumor and metastases resectable?

Yes → **Multidisciplinary management:**
- Recommendations include the surgical, medical, and radiation oncologists
- Refer to Principles of Rectal Surgery, Neoadjuvant Therapy and Radiation Therapy
- Choice and timing of systemic chemotherapy, consideration of surgery, and radiation are to be individualized based on multidisciplinary management discussion. In all cases, surgical resection should be performed with the intent for cure.

No →
- Systemic therapy with or without radiation therapy, see Pages 7-9
- If symptomatic, consider radiation therapy, endoscopic intervention[3] (endoscopic ablation or stent placement, if appropriate), resection of primary tumor, or diverting colostomy
- Discuss GCC with patient or if clinically indicated, with Patient Representative[1]

→ Individualized systemic therapy, see Pages 7-9 → • See Page 13 for surveillance • See Page 6 for recurrence

[1] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

[2] See Page 5 for Stage IV with carcinomatosis

[3] Endoscopic stent decompression may be considered in selected circumstances without adjacent angulation. Stents should not be deployed in the distal rectum. Refer to Principles of Endoscopic Therapy.

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Note: Consider Clinical Trials as treatment options for eligible patients

PRESENTATION[1] AND EVALUATION[2]

Stage IV with carcinomatosis

- CEA
- Pathology review[3]
- CT of chest with or without contrast
- Contrast-enhanced CT or MRI of abdomen/pelvis
- Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Patient Representative[4]

Widespread/ unresectable metastasis **or** poor surgical candidate?

Yes → Continue current chemotherapy regimen until progression of disease followed by second line chemotherapy[5] if tolerating therapy and ECOG performance status ≤ 2 (refer to Principles of Systemic Therapy)
- Best supportive care

No →

- Evaluation of symptomatic primary or metastatic disease (*e.g.*, obstruction). See Page 4.
- Consider diagnostic laparoscopy with washings and biopsies as indicated
- Calculate Peritoneal Cancer Index (PCI)[6]

TREATMENT AND EVALUATION

Is peritoneal metastasis site resectable[7]?

No → Continue current chemotherapy regimen until progression of disease followed by second line chemotherapy[5] if tolerating therapy and ECOG performance status ≤ 2 (refer to Principles of Systemic Therapy)
- Best supportive care

Yes →

- Consider 3-6 months of systemic therapy[5] (refer to Principles of Systemic Therapy)
- Consider immunotherapy for MSI-H tumors[5] (refer to Principles of Systemic Therapy)

Diagnostic laparoscopy with washings and biopsies as indicated

Disease progression?

Yes → Continue current chemotherapy regimen until progression of disease followed by second line chemotherapy[5] if tolerating therapy and ECOG performance status ≤ 2 (refer to Principles of Systemic Therapy)
- Best supportive care

No →

Cytopreductive surgery with or without HIPEC on clinical trial[8]

Incomplete cytoreduction → Continue current chemotherapy regimen until progression of disease followed by second line chemotherapy[5] if tolerating therapy and ECOG performance status ≤ 2 (refer to Principles of Systemic Therapy)
- Best supportive care

Complete cytoreduction →

FOLLOW-UP/SURVEILLANCE

- Surveillance with imaging and tumor markers as indicated, see Page 13
- Consider evaluation for minimal residual disease by ctDNA testing and further systemic therapy[5] (refer to Principles of Systemic Therapy)

CEA = carcinoembryonic antigen colorectal cancer
ctDNA = circulating tumor DNA
ECOG = Eastern Cooperative Oncology Group
HIPEC = heated intraperitoneal chemotherapy
MSI-H = microsatellite instability high

[1] See Physical Activity, Nutrition, Obesity Screening and Management, and Tobacco Cessation Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[2] Initial evaluation should include assessment of tumor DNA mismatch repair status and of family history for hereditary cancer syndromes. Universal germline testing is recommended for all patients under age 50 years, and should be discussed with all patients regardless of age.
[3] Refer to Principles of Biomarker Testing
[4] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).
[5] See Pages 7-9 for Systemic Therapy for Advanced or Metastatic Disease as indicated
[6] Harmon, R. L., & Sugarbaker, P. H. (2005). Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer. *International Seminars in Surgical Oncology, 2*, Article 3. https://doi.org/10.1186/1477-7800-2-3
[7] PCI < 20 without prohibitive solid organ involvement (*e.g.*, major hepatectomy required, head of pancreas involved, retroperitoneal lymphadenopathy, prohibitive small bowel or abdominal wall resection)
[8] HIPEC decision and agent to be determined by contemporary available trials

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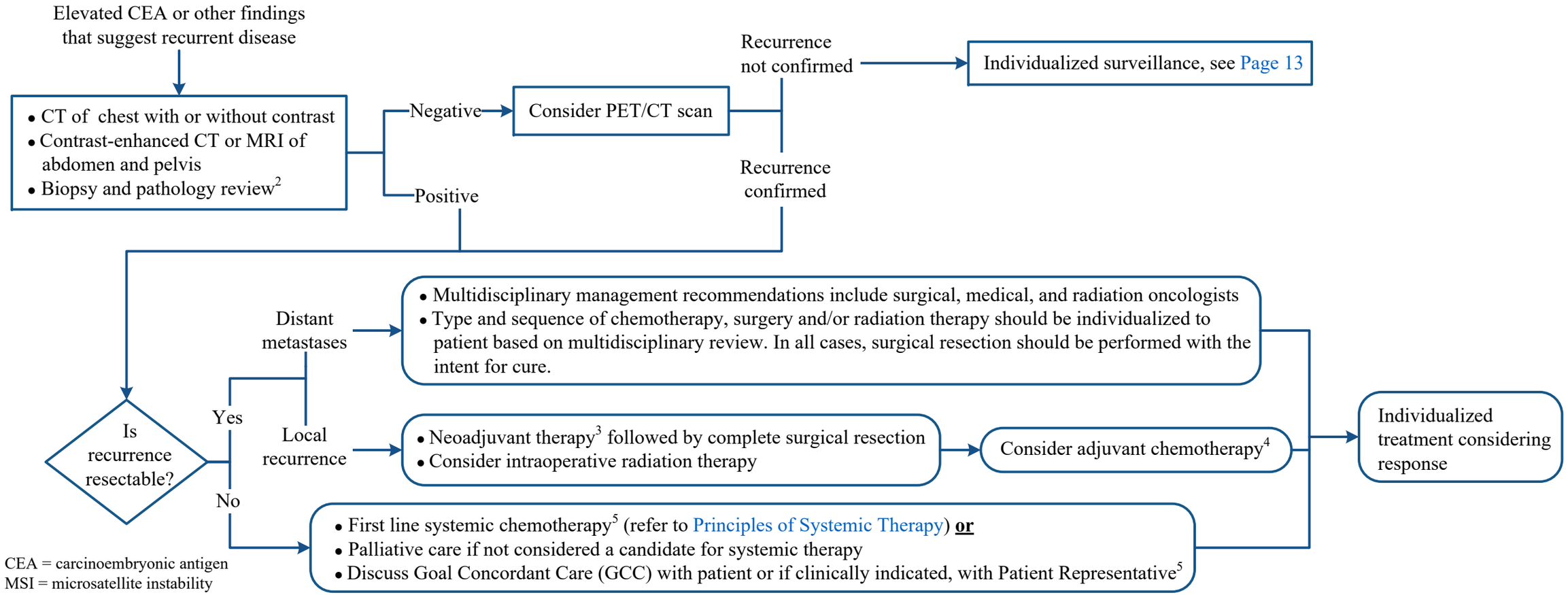
Note: Consider Clinical Trials as treatment options for eligible patients

EVALUATION[1] AND MANAGEMENT OF SUSPECTED OR DOCUMENTED RECURRENT RECTAL CANCER



CEA = carcinoembryonic antigen
MSI = microsatellite instability

[1] Initial evaluation should include assessment of tumor DNA mismatch repair status and of family history for hereditary cancer syndromes. Universal germline testing is recommended for all patients under age 50 years, and should be discussed with all patients regardless of age.
[2] Refer to Principles of Biomarker Testing
[3] Refer to Principles of Neoadjuvant Therapy
[4] Capecitabine or 5-fluorouracil/leucovorin or 5-fluorouracil/leucovorin/oxaliplatin based on multidisciplinary review
[5] See Pages 7-9 for Systemic Therapy for Advanced or Metastatic Disease as indicated
[6] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

Rectal Cancer

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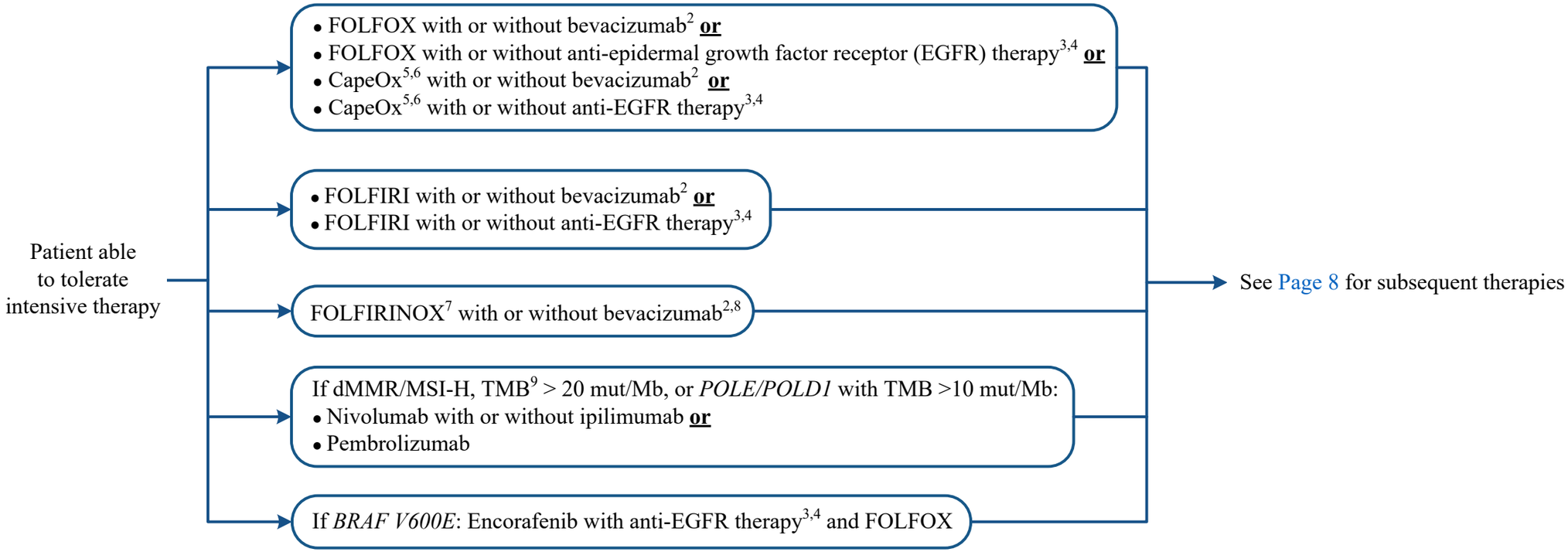
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – First-Line Therapy[1]



anti-EGFR = cetuximab or panitumumab
CapeOx = capecitabine[4,5] and oxaliplatin
dMMR = deficient mismatch repair
ECOG = Eastern Cooperative Oncology Group
FOLFIRI = infusional 5-fluorouracil, leucovorin and irinotecan
FOLFIRINOX = infusional 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan
FOLFOX = infusional 5-fluorouracil, leucovorin and oxaliplatin
MSI-H = microsatellite instability high
TMB = tumor mutational burden

[1] Refer to Systemic Therapy Regimens for Advanced or Metastatic Disease
[2] Elderly patients with a prior arterial thrombotic event are at increased risk of stroke, myocardial infarct and other arterial events
[3] Anti-EGFR therapy is only indicated in *RAS* wild type tumors
[4] Consider anti-EGFR therapy only if primary tumor is left sided/rectal cancer
[5] Patients with diminished creatinine clearance (CrCl) 30-50 mL/minute will require dose reduction. Patients with CrCl < 30 mL/minute will not be eligible to receive capecitabine.
[6] Patients on warfarin or phenytoin should switch to appropriate alternative agents prior to starting capecitabine due to potential drug-drug interactions
[7] Consider regimen only in patients with adequate ECOG. Check blood counts regularly. May be best used for neoadjuvant therapy.
[8] Best suited for surgically resectable patients. If bevacizumab is given, recommend to hold bevacizumab before and after surgery to prevent complications related to wound healing.
[9] TMB > 20 mut/Mb may benefit from first line therapy with immune checkpoint inhibition. Consider a TMB > 10 mut/Mb for subsequent therapy with immune checkpoint inhibitors.

Rectal Cancer

Note: Consider Clinical Trials as treatment options for eligible patients

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – Subsequent Therapies[1]

Patient able to tolerate intensive therapy →

Second-line Therapy

- Consider the following second-line therapy based on molecular profile results:
  - Encorafenib with anti-EGFR therapy[2] (for *BRAF V600E*) if not given previously **or**
  - Single agent nivolumab or pembrolizumab and did not receive immunotherapy in first line setting (for dMMR/MSI-H, TMB > 10 mut/Mb, or *POLE/POLD1* with TMB > 10 mut/Mb) **or**
  - Consider nivolumab with ipilimumab for those who previously received single agent pembrolizumab (for dMMR/MSI-H, TMB > 10 mut/Mb, or *POLE/POLD1* with TMB > 10 mut/Mb) **or**
  - Fam-trastuzumab deruxtecan (for *HER2*-amplified) **or**
  - Trastuzumab with either pertuzumab or lapatinib or tucatinib (for *HER2*-amplified and *RAS* and *BRAF* WT) **or**
  - Adagrasib[3] or sotorasib[3] with anti-EGFR therapy (for *KRAS G12C* mutated tumors) **or**
  - Tropomyosin receptor kinase (TRK) inhibitors (for *NTRK* fusion positive) **or**
  - *RET* receptor kinase inhibitors (for *RET* fusion positive)
- Consider the following additional second-line therapy options if received nivolumab, pembrolizumab, or FOLFIRI as the first line therapy option:
  - FOLFOX with or without bevacizumab[4] **or**
  - FOLFOX with anti-EGFR therapy[2], if did not receive anti-EFGR therapy in first-line setting **or**
  - CapeOx[5,6] with or without bevacizumab[4] **or**
  - CapeOx[5,6] with or without panitumumab[2], if did not receive anti-EFGR therapy in first-line setting
- Consider the following additional second-line therapy options if received nivolumab, pembrolizumab, FOLFOX, or CapeOx as the first line therapy option:
  - FOLFIRI with or without bevacizumab[4] **or**
  - Irinotecan with or without bevacizumab[4]
  - FOLFIRI with anti-EGFR therapy[2] if did not receive anti-EGFR therapy as first-line setting
- Consider third-line therapy options if no suitable second-line therapy options

Third-line (plus) Therapy

Consider one of the following:

- Clinical trial **or**
- Trifluridine/tipiracil with or without bevacizumab[4] **or**
- Regorafenib **or**
- Fruquintinib[3] **or**
- Anti-EGFR therapy[2] with or without irinotecan, if not previously given **or**
- Rechallenge with anti-EGFR therapy[2] if no evidence of *RAS/BRAF* mutations by repeat ctDNA **or**
- Rechallenge with FOLFOX or CapeOx[5,6], if no prior progression on oxaliplatin **or**
- Reconsider second line therapy options as indicated and not previously given **or**
- Repotrectinib[3] (for *NTRK* fusion positive)

anti-EGFR = cetuximab or panitumumab
CapeOx = capecitabine[4,5] and oxaliplatin
ctDNA = circulating tumor DNA
dMMR = deficient mismatch repair
FOLFIRI = infusional 5-fluorouracil, leucovorin and irinotecan
FOLFOX = infusional 5-fluorouracil, leucovorin and oxaliplatin
MSI-H = microsatellite instability high
TMB = tumor mutational burden

[1] Refer to Systemic Therapy Regimens for Advanced or Metastatic Disease
[2] Anti-EGFR therapy is only indicated in *RAS* wild type tumors
[3] Not on MD Anderson formulary
[4] Elderly patients with a prior arterial thrombotic event are at increased risk of stroke, myocardial infarct and other arterial events
[5] Patients with diminished creatinine clearance (CrCl) 30-50 mL/minute will require dose reduction. Patients with CrCl < 30 mL/minute will not be eligible to receive capecitabine.
[6] Patients on warfarin or phenytoin should switch to appropriate alternative agents prior to starting capecitabine due to potential drug-drug interactions

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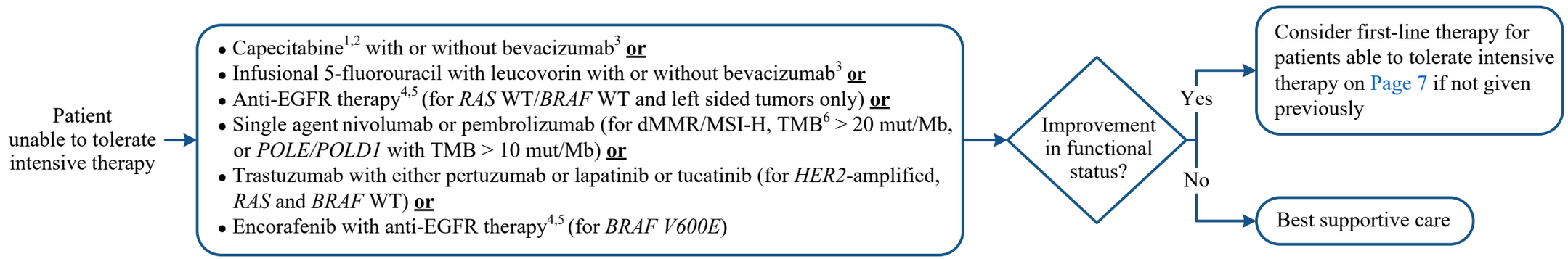
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE



anti-EGFR = cetuximab or panitumumab
EGFR = epidermal growth factor receptor
dMMR = deficient mismatch repair
MSI-H = microsatellite instability high
TMB = tumor mutational burden

[1] Patients with diminished creatinine clearance (CrCl) 30-50 mL/minute will require dose reduction. Patients with CrCl < 30 mL/minute will not be eligible to receive capecitabine.
[2] Patients on warfarin or phenytoin should switch to appropriate alternative agents prior to starting capecitabine due to potential drug-drug interactions
[3] Elderly patients with a prior arterial thrombotic event are at increased risk of stroke, myocardial infarct and other arterial events
[4] Anti-EGFR therapy is only indicated in *RAS* wild type tumors
[5] Consider anti-EGFR therapy only if primary tumor is left sided/rectal cancer
[6] TMB > 20 mut/Mb may benefit from first line therapy with immune checkpoint inhibition. Consider a TMB > 10 mut/Mb for subsequent therapy with immune checkpoint inhibitors.

Note: Consider Clinical Trials as treatment options for eligible patients

SYSTEMIC THERAPY REGIMENS FOR ADVANCED OR METASTATIC DISEASE

CapeOx (XELOX)	• Oxaliplatin 100-130 mg/m^2 IV on Day 1 • Capecitabine[a,b] 850-1,000 mg/m^2 PO twice daily on Days 1-14 • With or without bevacizumab 7.5 mg/kg IV on Day 1 **or** with panitumumab[c] 9 mg/kg IV on Day 1 • Repeat every 3 weeks
mFOLFOX 6	• Oxaliplatin 85 mg/m^2 IV over 2 hours on Day 1 • Leucovorin 400 mg/m^2 IV over 2 hours on Day 1[d] • 5-fluorouracil 400 mg/m^2 IV bolus on Day 1[d], then 5-fluorouracil 2,400 mg/m^2 continuous infusion over 46 hours IV on Day 1 • With or without bevacizumab 5 mg/kg IV on Day 1 **or** with cetuximab[c] 500 mg/m^2 IV or panitumumab[c] 6 mg/kg IV on Day 1 • Repeat every 2 weeks
mFOLFIRI	• Irinotecan 180 mg/m^2 IV on Day 1 • Leucovorin 400 mg/m^2 IV over 2 hours during irinotecan infusion on Day 1[d] • 5-fluorouracil 400 mg/m^2 IV bolus[d], then 5-fluorouracil 2,400 mg/m^2 over 46 hours IV continuous infusion • With or without bevacizumab 5 mg/kg IV on Day 1 **or** with cetuximab[c] 500 mg/m^2 IV or panitumumab[c] 6 mg/kg IV on Day 1 • Repeat every 2 weeks
5-Fluorouracil, leucovorin or capecitabine	• Capecitabine[a,b] 850-1,000 mg/m^2 PO twice daily on Days 1-14 • With or without bevacizumab 7.5 mg/kg IV on Day 1 • Repeat every 3 weeks **or** • Leucovorin 400 mg/m^2 IV over 2 hours on Day 1[d] • 5-fluorouracil 400 mg/m^2 IV bolus on Day 1[d], then 5-fluorouracil 2,400 mg/m^2 over 46 hours IV continuous infusion • With or without bevacizumab 5 mg/kg IV on Day 1 • Repeat every 2 weeks

EGFR = epidermal growth factor receptor

Continued on next page

[a] Patients with diminished creatinine clearance (CrCl) 30-50 mL/minute will require dose reduction. Patients with CrCl < 30 mL/minute will not be eligible to receive capecitabine.
[b] Patients on warfarin or phenytoin should switch to appropriate alternative agents prior to starting capecitabine due to potential drug-drug interactions
[c] Anti-EGFR therapy is only indicated in *RAS* wild type tumors (refer to Principles of Systemic Therapy)
[d] Consider omitting the bolus of fluorouracil and leucovorin for tolerability

Note: Consider Clinical Trials as treatment options for eligible patients

SYSTEMIC THERAPY REGIMENS FOR ADVANCED OR METASTATIC DISEASE - continued

Anti-EGFR therapy[a]	• Panitumumab[a] 6 mg/kg IV on Day 1 every 2 weeks **or** • Panitumumab[a] 9 mg/kg IV on Day 1 every 3 weeks **or** • Cetuximab[a] 500 mg/m^2 IV on Day 1 every 2 weeks
Irinotecan	Irinotecan 180 mg/m^2 IV on Day 1 every 2 weeks
Anti-EGFR therapy[a] plus Irinotecan	• Cetuximab[a] 500 mg/m^2 IV **or** panitumumab[a] 6 mg/kg IV on Day 1 every 2 weeks • With or without irinotecan 180 mg/m^2 IV on Day 1
FOLFIRINOX[b,c]	• Oxaliplatin 85 mg/m^2 IV on Day 1 • Irinotecan 150-180 mg/m^2 IV on Day 1 • 5-fluorouracil 2,400 mg/m^2 IV continuous infusion over 46 hours on Day 1 • With or without bevacizumab 5 mg/kg IV on Day 1 • Repeat every 2 weeks
BRAF V600E	• Encorafenib 300 mg PO once daily with cetuximab[a] 500 mg/m^2 IV on Day 1 and mFOLFOX6 every 2 weeks **or** • Encorafenib 300 mg PO once daily with cetuximab[a] 400 mg/m^2 IV on Day 1, then 250 mg/m^2 IV weekly **or** • Encorafenib 300 mg PO once daily with panitumumab[a] 6 mg/kg IV every 2 weeks
MSI-H/dMMR, *POLE/POLD1* with TMB > 10 mut/Mb, or TMB high[d]	• Nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Ipilimumab 1 mg/kg IV with nivolumab 3 mg/kg IV every 3 weeks for 4 doses, then nivolumab monotherapy at 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks

dMMR = deficient mismatch repair
EGFR = epidermal growth factor receptor
mFOLFOX6 = fluorouracil, leucovorin, oxaliplatin
MSI-H = microsatellite instability high
TMB = tumor mutational burden

Continued on next page

[a] Anti-EGFR therapy is only indicated in *RAS* wild type tumors
[b] Consider regimen only in patients with adequate Eastern Cooperative Oncology Group (ECOG). Check blood counts regularly. May be best used for neoadjuvant therapy.
[c] Consider omitting the bolus of fluorouracil and leucovorin for tolerability
[d] TMB > 20 mut/Mb may benefit from first line therapy with immune checkpoint inhibition. Consider a TMB > 10 mut/Mb for subsequent therapy with immune checkpoint inhibitors.

Note: Consider Clinical Trials as treatment options for eligible patients

SYSTEMIC THERAPY REGIMENS FOR ADVANCED OR METASTATIC DISEASE - continued

***KRAS G12C* Mutation**[a]	• Adagrasib[b] 600 mg PO twice daily • With cetuximab 500 mg/m^2 IV **or** panitumumab 6 mg/kg IV on Day 1 every 2 weeks **or** • Sotorasib[b] 960 mg PO once daily • With cetuximab 500 mg/m^2 IV **or** panitumumab 6 mg/kg IV on Day 1 every 2 weeks
***HER2*-amplification (*RAS* and *BRAF* WT)**	• Trastuzumab 8 mg/kg (loading dose) IV on Day 1, then 6 mg/kg IV every 21 days with pertuzumab 840 mg (loading dose) IV on Day 1, then 420 mg IV every 21 days • Trastuzumab 4 mg/kg (loading dose) IV on Day 1, then 2 mg/kg IV weekly with lapatinib 1,000 mg PO daily • Trastuzumab 8 mg/kg (loading dose) IV on Day 1, then 6 mg/kg IV every 21 days with tucatinib 300 mg twice daily • Fam-trastuzumab deruxtecan 5.4 mg/kg IV on Day 1 every 21 days
Regorafenib	Regorafenib 160 mg PO daily for 21 days then 1 week off; one cycle is every 28 days (recommend to start at 80-120 mg PO daily for 21 days then 1 week off for the first 1-2 months, then dose escalate as appropriate)
Trifluridine-tipiracil	• Trifluridine-tipiracil 35 mg/m^2 of trifluridine component (maximum 80 mg) PO twice per day on Days 1-5 and 8-12 of a 28 day cycle • With or without bevacizumab 5 mg/kg IV on Day 1 and 15
Fruquintinib	Fruquintinib[b] 5 mg once daily on Days 1 to 21 of each 28-day cycle
***NTRK* fusion positive**	• Larotrectinib 100 mg PO twice daily • Entrectinib 600 mg PO once daily • Repotrectinib[b] 160 mg PO daily for the first 14 days, then increase dose to 160 mg twice daily
***RET* fusion positive**	• Selpercatinib 120 mg PO twice daily for patients < 50 kg • Selpercatinib 160 mg PO twice daily for patients ≥ 50 kg

EGFR = epidermal growth factor receptor

[a] Patient experiencing intolerable and unmanageable EGFR toxicities may continue treatment with single-agent adagrasib or sotorasib, although this approach may result in reduced response rates
[b] Not on MD Anderson formulary

Rectal Cancer

Note: Consider Clinical Trials as treatment options for eligible patients

OBSERVATION/SURVEILLANCE[1,2]

Watch-and-Wait	• Physical exam including proctoscopic examination: every 3 months for 3 years, then every 6 months through year 5, then consider annually • Carcinoembryonic antigen (CEA) and circulating tumor DNA (ctDNA)[3]: every 3 months for 3 years, then every 6 months through year 5 • Rectal protocol MRI of the pelvis: every 3-6 months for 2 to 3 years • CT of chest with or without contrast and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for 5 years • Colonoscopy: at one year, then (if normal) after 3 years, and then once every 5 years or sooner if indicated based on findings of prior colonoscopy
Stage I[4]	• Physical exam: every 6-12 months for 3 years • CEA and ctDNA[3]: every 6-12 months for 3 years • Proctoscopic examination following local excision: every 6-12 months for 3 years • CT of chest with or without contrast and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for 3 years • Colonoscopy: at one year, then (if normal) after 3 years, and then once every 5 years or sooner if indicated based on findings of prior colonoscopy
Stage II[4] (low risk)	• Physical exam: every 6 months for 2 years, then every 6-12 months for 3 years • CEA and ctDNA[3]: every 6 months for 2 years, then every 6-12 months for 3 years • CT of chest with or without contrast and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for 3-5 years • Colonoscopy: at one year, then (if normal) after 3 years, and then once every 5 years or sooner if indicated based on findings of prior colonoscopy
Stage II[4] (high risk) and Stage III[1]	• Physical exam: every 3-6 months for 3 years, then every 6-12 months through year 5 • CEA: every 3-6 months for 2 years, then every 6-12 months through year 5 • Consider ctDNA[3] testing every 3-6 months for 3-5 years • CT of chest with or without contrast and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for at least 5 years • Colonoscopy: at one year, then (if normal) after 3 years, and then once every 5 years or sooner if indicated based on findings of prior colonoscopy • Patients with rectal cancer treated with neoadjuvant chemoradiation (particularly those with significant residual tumor burden) may experience late failures (beyond 5 years). The follow-up of these patients should be individualized but may include continue annual follow-up beyond 5 years.
Stage IV[4] – No evidence of disease (NED)	• Physical exam: every 3-4 months for 2 years, then every 6 months for 3 years • CEA: every 3-4 months for 2 years, then every 6 months for 3 years • Consider ctDNA[3] testing every 3-6 months for 3-5 years • CT of chest with or without contrast and CT (with and without contrast) or MRI of abdomen/pelvis: every 4-6 months, then annually after for 5 years • Colonoscopy: at one year from rectal resection, then (if normal) after 3 years, and then once every 5 years or sooner if indicated based on findings of prior colonoscopy
Stage IV[4]	• Individualized if on therapy • Consider referral to GI Endoscopy to evaluate patency of lumen every 3-6 months if primary tumor is intact (or sooner if clinically indicated)

[1] Surveillance should be individualized based on the patient's underlying risk for recurrence and preferences. It should include evaluation on lifestyle risks, treatment-associated toxicity, and psychosocial needs with each visit.
[2] Surveillance imaging with PET/CT alone is not recommended as primary imaging modality when there is no contraindication to conventional contrast-enhanced CT scan
[3] Patients with ctDNA positive result should undergo radiographic evaluation for detection of recurrent disease, and consideration for clinical trial enrollment
[4] Refer to the Survivorship - Rectal Cancer algorithm for recommendations beyond 5 years for post-treatment and NED

Note: Consider Clinical Trials as treatment options for eligible patients

PRINCIPLES OF ENDOSCOPIC THERAPY

High-definition white light endoscopy has become an important tool in the diagnosis and treatment of patients with colorectal polyps and early colorectal cancer. The following principles of endoscopic therapy are adapted from the United States Multi-Society Task Force on Colorectal Cancer recommendations on the endoscopic management of malignant polyps.

- A malignant polyp is defined as the presence of submucosally invasive adenocarcinoma, (*e.g.*, T1) within a polyp
- Where local expertise exists, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) are suitable and complementary techniques in the endoscopic management of colorectal adenomas, superficial/early colorectal carcinomas, and neuroendocrine tumors
- Endoscopic full thickness resection (EFTR) is reserved for carefully selected situations with dense submucosal fibrosis (such as can be seen with prior incomplete polypectomy attempts), deeper lesions such as neuroendocrine tumors, or in situations where a deeper staging resection is clinically warranted (such as with incompletely resected malignant polyps)
- En bloc endoscopic resection is desirable where there is suspicion for early colorectal carcinoma (*e.g.*, submucosal invasion)
- Deep submucosal invasion can be suspected based on surface features that can be optically diagnosed using either high-definition white light endoscopy and/or image-enhanced endoscopy (Olympus narrow band imaging [NBI] or Fujifilm blue light imaging [BLI]/linked color imaging [LCI]). Nonpedunculated lesions with these features should be biopsied (in the area of surface feature disruption), tattooed distally, and referred for surgical resection. Pedunculated polyps with these features should undergo endoscopic polypectomy, as overall histological features may still be favorable depending on Haggitt Classification.
- Superficial submucosal invasion in nonpedunculated lesions can be suspected based on the following endoscopic features: nongranular lateral spreading tumors (LST-NG) with pseudo-depressed morphology, or granular lateral spreading tumors (LST-G) morphology with a dominant nodule. When technically feasible, nonpedunculated lesions with these features should be considered for en bloc endoscopic resection. In the case of LST-G morphology with a dominant nodule, at least the nodular area should be considered for en bloc resection.
- All other nonpedunculated polyps without features suspicious for submucosal invasion can be resected with either EMR or ESD, based on technical feasibility and local expertise
- All pedunculated polyps should be resected en bloc with the stalk, when technically feasible
- Unfavorable pathology characteristics for nonpedunculated polyps include the following features: poor tumor differentiation, lymphovascular invasion, submucosal invasion depth > 1 mm, tumor involvement of the cautery margin, or tumor budding
- Unfavorable pathology characteristics for pedunculated polyps include the following features: poor tumor differentiation, lymphovascular invasion, and tumor within 1 mm of the resection margin
- College of American Pathologists (CAP) synoptic reporting should be performed for all malignant polyps. Pathology reports should include the following information: (1) histologic type, (2) grade of differentiation, (3) tumor extension/invasion, (4) stalk and mucosal margin status, and (5) presence or absence of lymphovascular invasion. Other aspects such as specimen integrity, polyp size, polyp morphology, tumor budding, and depth of submucosal invasion should also be included, as these are all factors which may contribute to the risk of lymph node metastasis and whether additional surgery is recommended.
- Where local expertise exists, T1N0 lesions eligible for transanal excision (TAE) or transanal minimally invasive surgery (TAMIS) or transanal endoscopic microsurgery (TEM) are potentially eligible for ESD, provided there is no endoscopic or histopathologic evidence for high-risk features such as lymphovascular invasion, perineural invasion or tumor budding
- Superficial lesions with adenoma, high grade dysplasia, or intramucosal adenocarcinoma should be removed with endoscopic resection
- Endoscopic Palliation
  - Colon stent placement is indicated for palliation in selected cases involving malignant large bowel obstruction that is not a candidate for diverting colostomy
  - Currently available colonic stents are permanent uncovered metal stents and are therefore neither adjustable nor removable once placed. Due to their uncovered design, colonic stents are subject to tissue ingrowth resulting in recurrent obstruction, and therefore should only be used in palliative situations.
  - Colon stents should be avoided in areas with adjacent angulation, and should not be deployed in the distal rectum

Note: Consider Clinical Trials as treatment options for eligible patients

PRINCIPLES OF BIOMARKER TESTING

Testing Modality and Timing

- Molecular testing may be performed on tissue (formalin-fixed paraffin embedded) or blood-based utilizing CLIA (Clinical Laboratory Improvement Amendments of 1988) approved assays. If being performed with a blood-based assay, consider repeating tissue testing if no alterations are detected to avoid false negative results. Tissue testing may be performed utilizing specimens from the primary or metastatic site.
- Repeat testing may be considered to guide treatment decisions after prior therapies, especially those containing targeted therapy. This can be done through repeat biopsy for tissue profiling or ctDNA (circulating tumor DNA) testing. This includes situations such as anti-epidermal growth factor receptor therapy re-challenge where retesting is recommended. In the setting of treatment refractory tumors where repeat testing is being done, consider utilizing broad panels with DNA with or without RNA profiling to support clinical trial screening.

Microsatellite or Mismatch Repair Evaluation

- All patients with colorectal cancer must be tested irrespective of age, stage or family history at the time of diagnosis
- Testing may be done by Next Generation Sequencing (NGS) panels that include microsatellite instability (MSI), polymerase chain reaction (PCR) for MSI and/or by immunohistochemistry (IHC) for protein expression of mismatched repair (MMR) genes. Loss of protein expression by IHC in any one of the MMR genes helps guide further evaluation of affected genes for Lynch Syndrome. Loss of expression *MLH1* IHC should be followed up by evaluation for sporadic status through *MLH1* promoter methylation and/or *BRAF V600E* mutation.

Mutation Profile Evaluation

- All patients with advanced colorectal cancer should be evaluated by NGS to include *KRAS*, *NRAS*, *BRAF*, *POLE*, *POLD*
  - *KRAS* and *NRAS*: Mutations in codons 12, 13, 59, 61, 117, 146 should be considered activating. For less common mutations, discretion is required based on literature.
  - *BRAF*: Mutations in codon 600 should be considered activating. For other mutations, discretion is required based on classification.
  - *POLE*/*POLD*1: Pathogenic germline or somatic mutations within the exonuclease domain of these genes result in extremely high tumor burden, generally defined as > 10 mut/Mb while ultramutator phenotype typically associated with *POLE/POLD1* mutations has > 50 mut/Mb
- Tumor mutation burden (TMB) by NGS should be assessed in mutations per megabase
- Consider expanded panel testing to include *APC*, *TP53*, *SMAD4*, and *FBXW7* to support prognostication, including for patients under consideration for resection of metastatic disease and, in highly selected cases, transplantation
- Repeat testing for acquired alterations in mitogen-activated protein kinase (MAPK) pathway and other resistance mechanisms, preferably with ctDNA, may be considered to guide treatment decisions
- Repeat ctDNA testing to assess treatment response can be utilized in settings where the information would be used to guide future treatment decisions

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Note: Consider Clinical Trials as treatment options for eligible patients

PRINCIPLES OF BIOMARKER TESTING - continued

HER2 Evaluation

- All patients with advanced colorectal cancer should be evaluated
- Testing may be done via immunohistochemistry (IHC), fluorescence in situ hybridization (FISH) or Next Generation Sequencing (NGS)
- *HER2* amplification is defined as: A) IHC: 3+ staining in more than 50% of tumor cells, or B) FISH: *HER2*/CEP17 ratio ≥ 2 in more than 50% of the cells, or C) IHC 2+ and positive on FISH testing, or D) amplification by NGS

Evaluations of Fusions

- Fusion testing, including *NTRK* and *RET*, should be considered in patients with advanced colorectal cancer, although prevalence is rare. Patients with microsatellite instability (MSI) high are more likely to contain fusions, and these patients should be prioritized for testing.
- RNA-based and fusion-partner agnostic assays for evaluating gene fusions are preferred

Biomarker Testing in Surveillance

- ctDNA (circulating tumor DNA) testing should be offered to surgically resected patients rendered free of disease to guide prognostication and risk stratifying surveillance
  - Tumor-informed assays are preferred over tumor-agnostic assays if tissue is available
  - The first test should be drawn no earlier than 2 weeks after surgical resection due to concerns about sensitivity. Testing should be continued every three months until recurrence or three years. Testing beyond three years may be considered based on patient risk factors.
- Mutation profile should guide timing of surveillance for resected liver metastases

Germline Testing

- Universal germline testing for hereditary syndromes should be recommended for all under age 50 years and discussed with all patients

Note: Consider Clinical Trials as treatment options for eligible patients

PRINCIPLES OF RECTAL SURGERY

Transanal Excision [including transanal minimally invasive surgery (TAMIS) or transanal endoscopic microsurgery (TEM)]

Criteria (must meet all)

- T1N0 staging on ultrasound or high resolution MRI and cross-sectional imaging
- Able to completely remove tumor with 1 cm margin (full-thickness)
- No lymphovascular invasion
- No perineural invasion
- < 30% circumference
- Well- to moderately-differentiated histology
- < 3 cm in greatest dimension

Transabdominal Resection (low anterior resection or coloanal anastomosis using total or tumor-specific mesorectal excision)

General Management Principles

- The treating surgeon should perform an endoscopic evaluation (*e.g.,* proctosigmoidoscopy) before initiating treatment in order to assess the full extent of primary tumor involvement
- Primary tumor resection should include adequate margins of resection and be en bloc with the mesorectum and involved adjacent viscera. Tumor transection or resection that leaves gross residual tumor in the operative field (R2) should be avoided.
- Treatment of draining lymphatics is accomplished by en bloc resection of both the proximally ascending and distally descending nodal basins
- Function restorative reconstruction (*e.g.,* sphincter preservation) performed when possible and deemed appropriate based on an assessment of the underlying functional status of the anal sphincter

Distal and Circumferential Resection Margins

- The distal resection margin should not be involved by tumor and ideally be > 1 cm below the distal extent of the tumor when a total mesorectal excision has been performed. Intramural tumor spread may be present up to 1-2 cm distal to the tumor.
- Determination of the level of distal transection should be based on the level of tumor involvement prior to neoadjuvant therapy
- In cases of proximal rectal location, the distal margin of resection should be at least 4-5 cm below the distal extent of the tumor en bloc with the mesorectum (see Lymphadenectomy Principles on Page 18)
- Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision
- A negative circumferential resection margin (> 1 mm on microscopic evaluation) should be obtained (R0). Resection margins ≤ 1 mm should be considered microscopically positive (R1) and will be at higher risk for recurrence.

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Note: Consider Clinical Trials as treatment options for eligible patients

PRINCIPLES OF RECTAL SURGERY - continued

Transabdominal Resection (low anterior resection or coloanal anastomosis using total or tumor-specific mesorectal excision) - continued

Lymphadenectomy and Mesorectal Excision

- Routine radical lymphadenectomy should be achieved with proximal lymphovascular resection to the origin of the superior hemorrhoidal vessels (include IMA level lymph nodes when clinically suspected to be involved) and distal complete mesorectal excision to include the entire mesorectum or the tumor-specific mesorectum at least 5 cm below the distal extent of the tumor (so called "tumor specific mesorectal excision")
- The mesorectal dissection should be performed sharply within the mesorectal fascial plane to ensure a complete mesorectal excision
- Clinically suspicious nodes beyond the field of resection should be biopsied or removed if possible
- Lateral pelvic lymph node metastases are considered regional lymph nodes and when present, lateral pelvic lymph node dissection (internal iliac and obturator lymph node basins) should be performed

Abdominoperineal Resection

- Tumors located in the distal rectum requiring an abdominoperineal resection are at an increased risk for circumferential resection margin positivity
- In addition to the TME principles as outlined above, the division of the pelvic floor (levator muscles) should be wide around the level of tumor to avoid narrowing or coning of the resection. For anterior or posterior tumors, this could require en bloc resection of the adjacent structure such as the vagina or coccyx in order to ensure a clear margin.
- The approach to the pelvic floor may be trans-abdominal (from above) or trans-perineal (from below) in either a lithotomy or prone position as long as a complete resection with clear margins can be achieved

Minimally Invasive Resection

- A minimally invasive approach (*e.g.,* robotic) should adhere to the same principles of cancer surgery as for open resection

Note: Consider Clinical Trials as treatment options for eligible patients

PRINCIPLES OF SURGERY FOR METASTATIC DISEASE

Liver

- Evaluation by a liver surgeon is highly recommended for resectability of liver metastases
- Complete resection or ablative therapy must be feasible based on anatomic grounds and extent of disease. Maintenance of normal hepatic function is required.
- Resectable extrahepatic sites of metastases do not preclude curative hepatic resection
- Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant therapy. All original sites of disease must be resectable.
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer
- Ablative techniques may be considered in conjunction with resection in otherwise unresectable patients
- Primary tumor should be resected with curative intent (R0). Consider completion with radical lymphadenectomy at time of liver resection if synchronous metastasis at presentation and a non-oncologic resection of the primary was performed.
- Prior resection does not preclude re-resection in selected patients

Lung

- Complete resection must be feasible based on anatomic grounds and the extent of disease. Maintenance of adequate residual pulmonary function is required.
- Resectable extrapulmonary metastases do not preclude resection
- Primary tumor should be resected with curative intent (R0)
- Prior resection does not preclude a subsequent resection in selected patients

Other Sites (other than liver or lung)

- Resection of isolated metastasis outside of the liver or lung may be considered if complete resection can be performed, but treatment should be individualized and based on a multidisciplinary treatment plan
- Peritoneal carcinomatosis
  - Cytoreductive surgery may be considered in selected patients with limited volume disease and where cytoreductive clearance can be achieved. The role of intraperitoneal chemotherapy has not been established.

Note: Consider Clinical Trials as treatment options for eligible patients

PRINCIPLES OF NEOADJUVANT THERAPY

- All patients with locally advanced (stage II and III) rectal cancer should be evaluated for neoadjuvant therapy. For most patients, total neoadjuvant therapy (TNT) is preferred, consisting of long course chemoradiation before or after chemotherapy, or short course radiotherapy followed by chemotherapy. For patients interested in organ preservation or non-operative management, the preferred approach is long course chemoradiation followed by chemotherapy. For patients at high risk of systemic disease, the preferred approach is chemotherapy followed by long course chemoradiation. Neoadjuvant chemotherapy alone can be considered for selected patients based on multidisciplinary discussion.
- The decision for which approach should take into consideration the tumor characteristics, extent of lymph node involvement, and predicted status of the circumferential resection margin. In an effort to optimize the chance for sphincter preservation, neoadjuvant chemoradiation therapy may also be considered for selected patients with earlier stage (*e.g.,* T2N0) tumors that are very low-lying within the rectum.
- In instances of low risk tumors (*e.g.,* proximal rectal cancers with wide radial margins, no extramural vascular invasion on MRI), radiation therapy may be omitted altogether

Dosing Schedule for Concurrent Chemotherapy and Radiation Therapy:

- Radiation therapy plus infusional 5-fluorouracil 250-300 mg/m^2/day IV continuous infusion only on days of radiation therapy
- Radiation therapy plus capecitabine 825 mg/m^2 PO twice daily only on days of radiation therapy

Adjuvant chemotherapy for patients receiving neoadjuvant chemotherapy/radiation therapy:

mFOLFOX 6	• Oxaliplatin 85 mg/m^2 IV over 2 hours on Day 1 • Leucovorin 400 mg/m^2 IV over 2 hours on Day 1 • 5-fluorouracil 400 mg/m^2 IV bolus on Day 1, then 2,400 mg/m^2 IV over 46 hours continuous infusion • Repeat every 2 weeks
CapeOx (XELOX)	• Oxaliplatin 100-130 mg/m^2 IV on Day 1 • Capecitabine 850-1,000 mg/m^2 PO twice daily on Days 1-14, followed by 7 days rest • Repeat every 3 weeks
Capecitabine	• 1,000 mg/m^2 PO twice daily on Days 1-14, followed by 7 days rest • Repeat every 3 weeks
mFOLFIRINOX	• Oxaliplatin 85 mg/m^2 IV over 2 hours on Day 1 • Irinotecan 180 mg/m^2 IV over 90 minutes on Day 1 • Leucovorin 400 mg/m^2 IV over 2 hours during irinotecan on Day 1 • 5-fluorouracil 400 mg/m^2 IV bolus on Day 1, then 2,400 mg/m^2 IV over 46 hours continuous infusion • Repeat every 2 weeks
Infusional 5-fluorouracil/ leucovorin	• Leucovorin 400 mg/m^2 IV over 2 hours on Day 1 • 5-fluorouracil 400 mg/m^2 IV bolus on Day 1, then 2,400 mg/m^2 IV over 46 hours continuous infusion • Repeat every 2 weeks

Note: Consider Clinical Trials as treatment options for eligible patients

PRINCIPLES OF RADIATION THERAPY

- Radiation therapy volumes should include the tumor, the presacral nodes, the mesorectal region and the internal iliac nodes
- Either a 3D technique or intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) should be used
- Radiation therapy can be given with either long course chemoradiation or short course radiation therapy
- Long course chemoradiation: A dose of 50-54 Gy in 1.8-2 Gy fractions should be used
- Long course chemoradiation: Concurrent infusional 5-fluorouracil or capecitabine should be administered
- Short course radiation therapy: A dose of 25 Gy in 5 fractions should be used
- Prone position is preferred (unless the inguinal nodes are being included)
- A full bladder technique is preferred
- Intraoperative radiation therapy (IORT), if available, should be considered for very close or positive margins after resection as an additional boost, especially for patients with T4 or recurrent cancers

Note: Consider Clinical Trials as treatment options for eligible patients

PRINCIPLES OF SYSTEMIC THERAPY

- The presence of microsatellite instability high (MSI-H) status regardless if due to somatic or germline mutation may benefit from immune checkpoint inhibition
- The presence of *POLE/POLD1* with tumor mutational burden (TMB) > 10 mut/Mb or TMB > 20 mut/Mb may benefit from first line therapy with immune checkpoint inhibition. Consider a TMB > 10 mut/Mb for subsequent therapy with immune checkpoint inhibitors.
- Capecitabine was shown to be at least equivalent to adjuvant 5-fluorouracil/leucovorin
- Beware of the unique treatment related toxicities with these agents and engage in active management and prevention of these treatment related toxicities
  - Recommend dihydropyrimidine dehydrogenase (DPD) screening for those with severe adverse drug reactions (ADRs) (*e.g.*, diarrhea, neutropenia, mucositis) after initial exposure to 5-fluorouracil-based regimens
  - Recommend UGT1A*28 screening for severe ADRs after initial exposure to irinotecan
- Metastatic colorectal cancer should be evaluated and managed by multidisciplinary team to define the goal of the therapy: Curative or palliative
- Metastatic frontline treatment standard consists of combination chemotherapy with infusional 5-fluorouracil/leucovorin (or capecitabine) with either irinotecan and/or oxaliplatin based chemotherapy with or without bevacizumab. Alternatively, cetuximab or panitumumab may be considered rather than bevacizumab if inappropriate candidate for bevacizumab and/or *RAS* wild-type.
- Any *RAS* mutation indicates resistance to cetuximab and panitumumab
- The presence of the *BRAF V600E* mutation indicates anti-EGFR resistance. If non-*V600E BRAF* mutation, may still consider anti-EGFR therapy
- Maximize the duration of the effective therapy and timely switching to non-cross resistant chemotherapy agents at the time of tumor progression to allow the maximal exposure of all the active agents for survival
- Early recognition and prevention of treatment related toxicities and timely discontinuation of ineffective or toxic agents to improve the patient's quality of life
- If *RET* or *NTRK* fusion positive, consider biomarker driven therapy

SUGGESTED READINGS

Adam, R., Avisar, E., Ariche, A., Giachetti, S., Azoulay, D., Castaing, D., . . . Bismuth, F. (2001). Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal [liver] metastases. *Annals of Surgical Oncology, 8*(4), 347-353. https://doi.org/10.1007/s10434-001-0347-3

Adam, R., Piedvache, C., Chiche, L., Adam, J. P., Salam, E., Bucur, P., . . . Gelli, M. (2024). Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): Results from a multicentre, open-label, prospective, randomised controlled trial. *The Lancet, 404*(10458), 1107-1118. https://doi.org/10.1016/S0140-6736(24)01595-2

Alberts, S., Horvath, W., Sternfeld, W., Goldberg, R., Mahoney, M., Dakhil, S., . . . Donohue, J. (2005). Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: A North Central Cancer Treatment Group phase II study. *Journal of Clinical Oncology, 23*(36), 9243-9249. https://doi.org/10.1200/JCO.2005.07.740

Aloia, T., Vauthey, J. N., Loyer, E., Ribero, D., Pawlik, T., Wei, S., . . . Abdalla, E. (2006). Solitary colorectal liver metastasis: Resection determines outcome. *Archives of Surgery, 141*(5), 460-467. https://doi.org/10.1001/archsurg.141.5.460

Ambiru, S., Miyazaki, M., Ito, H., Nakagawa, K., Shimizu, H., Kato, A., . . . Nakajima, N. (1998). Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. *Cancer, 82*(2), 274-278. https://doi.org/10.1002/(SICI)1097-0142(19980115)82:23.0.CO;2-R

Andre, T., Elez, E., Lenz, H.-J., Jensen, L. H., Touchefeu, Y., Van Cutsem, E., . . . Lonardi, S. (2025). First results of nivolumab (NIVO) plus ipilimumab (IPI) vs NIVO monotherapy for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) from CheckMate 8HW. *Journal of Clinical Oncology, 43*(Suppl 4), LBA143. https://doi.org/10.1200/JCO.2025.43.4_suppl.LBA143

André, T., Shiu, K., Kim, T. W., Jensen, B. W., Jensen, L. H., Punt, C., . . . Diaz., L. A. (2020). Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: The phase 3 KEYNOTE-177 Study. *Journal of Clinical Oncology, 38*(18). Abstract LBA4. Retrieved from https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.18_suppl.LBA4?af=R

Aschele, C., Cionini, L., Lonardi, S., Pinto, C., Cordio, S., Rosati, G., . . . Boni, L. (2011). 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. *Journal of Clinical Oncology, 29*(20), 2773-2780. https://doi.org/10.1200/JCO.2010.34.4911

Berton, D., Banerjee, S. N., Curigliano, G., Cresta, S., Arkenau, H.-T., Abdeddaim, C., . . . Andre, T. (2021). Antitumor activity of dostarlimab in patients with mismatch repair-deficient/microsatellite instability-high tumors: A combined analysis of two cohorts in the GARNET study. *Journal of Clinical Oncology, 39*(Suppl 15), 2564. https://doi.org/10.1200/JCO.2021.39.15_suppl.2564

Blazer III, D., Kishi, Y., Maru, D., Kopetz, S., Chun, Y., Overman, M., . . . Vauthey, J. N. (2008). Pathologic response to preoperative chemotherapy: A new outcome end point after resection of hepatic colorectal metastases. *Journal of Clinical Oncology, 25*(33), 5344-5351. https://doi.org/10.1200/JCO.2008.17.5299

Bonjer, H., Deijen, C., Abis, G., Cuesta, M., van der Pas, M., de Lange-de Klerk, E., . . . Haglind, E. (2015). A randomized trial of laparoscopic versus open surgery for rectal cancer. *The New England Journal of Medicine, 372*(14), 1324-1332. https://doi.org/10.1056/NEJMoa1414882

Breugom, A., Van Gijn, W., Muller, E., Berglund, Å., van den Broek, C., Fokstuen, T., . . . van de Velde, C. (2014). 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. *Annals of Oncology, 26*(4), 696-701. https://doi.org/10.1093/annonc/mdu560

Brouquet, A., Abdalla, E., Kopetz, S., Garrett, C., Overman, M., Eng, C., . . . Vauthey, J. N. (2011). High survival rate after two-stage resection of advanced colorectal liver metastases: Response-based selection and complete resection define outcome. *Journal of Clinical Oncology, 29*(8), 1083-1090. https://doi.org/10.1200/JCO.2010.32.6132

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SUGGESTED READINGS - continued

Chang, G., Rodriguez-Bigas, M., Eng, C., & Skibber, J. (2009). Lymph node status after neoadjuvant radiotherapy for rectal cancer is a biologic predictor of outcome. *Cancer, 115*(23), 5432-5440. https://doi.org/10.1002/cncr.24622

Chang, G., You, Y., Park, I., Kaur, H., Hu, C. Y., Rodriguez-Bigas, M., . . . Ernst, R. (2012). Pre-treatment high-resolution rectal MRI and treatment response to neoadjuvant chemoradiation. *Diseases of the Colon and Rectum, 55*(4), 371-377. https://doi.org/10.1097/DCR.0b013e31824678e3

Chun, Y., Vauthey, J. N., Boonsirikamchai, P., Maru, D., Kopetz, S., Palavecino, M., . . . Loyer, E. (2009). Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *Journal of The American Medical Association, 302*(21), 2338-2344. https://doi.org/10.1001/jama.2009.1755

Conroy, T., Lamfichekh, N., Etienne, P. L., Rio, E., Francois, E., Mesgouez-Nebout, N., . . . Borg, C. (2019). Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: Final results of PRODIGE 23 phase III trial, a UNICANCER GI trial. *Journal of Clinical Oncology, 38*(15), 4007. https://doi.org/10.1200/JCO.2020.38.15_suppl.4007

Cremolini, C., Loupakis, F., & Falcone, A. (2015). FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *The New England Journal of Medicine, 372*(3), 290-292. https://doi.org/10.1056/NEJMc1413996

Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A., . . . Van Cutsem, E. (2004). Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *The New England Journal of Medicine, 351*(4), 337-345. https://doi.org/10.1056/NEJMoa033025

Das, P., Delclos, M., Skibber, J., Rodriguez-Bigas, M., Feig, B., Chang, G., . . . Crane, C. (2010). Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior pelvic irradiation. *International Journal of Radiation Oncology, Biology, Physics, 77*(1), 60-65. https://doi.org/10.1016/j.ijrobp.2009.04.056

Das, P., Lin, E., Bhatia, S., Skibber, J., Rodriguez-Bigas, M., Feig, B., . . . Crane, C. (2006). Preoperative chemoradiotherapy with capecitabine versus protracted infusion 5-fluorouracil for rectal cancer: A matched-pair analysis. *International Journal of Radiation Oncology, Biology, Physics, 66*(5), 1378-1383. https://doi.org/10.1016/j.ijrobp.2006.07.1374

Dasari, A., Lonardi, S., Garcia-Carbonero, R., Elez, E., Yoshino, T., Sobrero, A., . . . Eng, C. (2023). Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): An international, multicentre, randomised, double-blind, phase 3 study. *The Lancet, 402*(10395), 41-53. https://doi.org/10.1016/S0140-6736(23)00772-9

Douillard, J., Cunningham, D., Roth, A., Navarro, M., James, R., Karasek, P., . . . Rougier, P. (2000). Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *The Lancet, 355*(9209), 1041-1047. https://doi.org/10.1016/S0140-6736(00)02034-1

Douillard, J., Oliner, K., Siena, S., Tabernero, J., Burkes, R., Barugel, M., . . . Patterson, S. (2013). Panitumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *The New England Journal of Medicine, 369*(11), 1023-1034. https://doi.org/10.1056/NEJMoa1305275

Drilon, A., Laetsch, T. M., Kummar, S., Dubios, S. G., Lassen, U. N., Demetri, G. D., . . . Hyman, D. (2018). Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *The New England Journal Of Medicine, 378*(8), 731-739. https://doi.org/10.1056/NEJMoa1714448

Fakih, M. G., Salvatore, L., Esaki, T., Modest, D. P., Lopez-Bravo, D. P., Taieb, J., . . . Pietrantonio, F. (2023). Sotorasib plus panitumumab in refractory colorectal cancer with mutated KRAS G12C. *The New England Journal of Medicine, 389*(23), 2125-2139. https://doi.org/10.1056/NEJMoa2308795

Fleshman, J., Branda, M., Sargent, D., Boller, A., George, V., Abbas, M., . . . Nelson, H. (2015). 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, 314*(13), 1346-1355. https://doi.org/10.1001/jama.2015.10529

Ge, P. S., & Aihara, H. (2022). Advanced endoscopic resection techniques: Endoscopic submucosal dissection and endoscopic full-thickness resection. *Digestive Diseases and Sciences, 67*(5), 1521-1538. https://doi.org/10.1007/s10620-022-07392-0

Continued on next page

SUGGESTED READINGS - continued

Goldberg, R., Sargent, D., Morton, R., Fuchs, C., Ramanathan, R., Williamson, S., . . . Alberts, S. (2004). A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *Journal of Clinical Oncology, 22*(1), 23-30. https://doi.org/10.1200/JCO.2004.09.046

Gourd, K. (2022). ESMO World Congress on gastrointestinal cancer 2022. *The Lancet Oncology, 23*(8), 988. https://doi.org/10.1016/S1470-2045(22)00443-0

Haller, D., Tabernero, J., Maroun, J., de Braud, F., Price, T., Van Cutsem, E., . . . Schmoll, H. J. (2011). Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *Journal of Clinical Oncology*, *29*(11),1465-1471. https://doi.org/10.1200/JCO.2010.33.629

Harmon, R. L., & Sugarbaker, P. H. (2005). Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer. *International Seminars in Surgical Oncology, 2*, Article 3. https://doi.org/10.1186/1477-7800-2-3

Heald, R., & Ryall, R. (1986). Recurrence and survival after total mesorectal excision for rectal cancer. *The Lancet, 327*(8496), 1479-1482. https://doi.org/10.1016/S0140-6736(86)91510-2

Heinemann, V., Von Weikersthal, L., Decker, T., Kiani, A., Vehling-Kaiser, U., Al-Batran, S., . . . Stintzing, S. (2014). 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. *The Lancet Oncology, 15*(10), 1065-1075. https://doi.org/10.1016/S1470-2045(14)70330-4

Hofheinz, R., Wenz, F., Post, S., Matzdorff, A., Laechelt, S., Hartmann, J., . . . Hochhaus, A. (2011). Capecitabine (Cape) versus 5-fluorouracil (5-FU)-based (neo) adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): Long-term results of a randomized, phase III trial. *Journal Of Clinical Oncology, 29*(Suppl 15), 3504. https://doi.org/10.1200/jco.2011.29.15_suppl.3504

Hong, Y., Nam, B. H., Kim, K. P., Kim, J., Park, S., Park, Y., . . . Kim, T. (2014). 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. *The Lancet Oncology, 15*(11), 1245-1253. https://doi.org/10.1016/S1470-2045(14)70377-8

Hospers, G., Bahadoer, R. R., Dijkstra, E. A., Etten, B. V., Marjinen, C., Putter, H., . . . Velde, V. D. (2020). Short-course radiotherapy followed by chemotherapy followed before TME in locally advanced rectal cancer: The randomized RAPIDO trial. *Journal of Clinical Oncology, 38*(15), 4006. https://doi.org/10.1200/JCO.2020.38.15_suppl.4006

Ikoma, N., You, Y., Bednarski, B., Rodriguez-Bigas, M., Eng, C., Das, P., . . . Chang, G. (2017). Impact of recurrence and salvage surgery on survival after multidisciplinary treatment of rectal cancer. *Journal of Clinical Oncology, 35*(23), 2631-2638. https://doi.org/10.1200/JCO.2016.72.1464

Inoue, M., Kotake, Y., Nakagawa, K., Fujiwara, K., Fukuhara, K., & Yasumitsu, T. (2000). Surgery for pulmonary metastases from colorectal carcinoma. *The Annals of Thoracic Surgery, 70*(2), 380-383. https://doi.org/10.1016/S0003-4975(00)01417-X

Jayne, D., Guillou, P., Thorpe, H., Quirke, P., Copeland, J., Smith, A., . . . Brown, J. (2007). Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *Journal of Clinical Oncology, 25*(21), 3061-3068. https://doi.org/10.1200/JCO.2006.09.7758

Kang, S. B., Park, J., Jeong, S. Y., Nam, B., Choi, H., Kim, D., . . . Oh, J. (2010). 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. *The Lancet Oncology, 11*(7), 637-645. https://doi.org/10.1016/S1470-2045(10)70131-5

Kapiteijn, E., Marijnen, C., Nagtegaal, I., Putter, H., Steup, W., Wiggers, T., . . . van de Velde, C. (2001). Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *The New England Journal of Medicine, 345*(9), 638-646. https://doi.org/10.1056/NEJMoa010580

Kawaguchi, Y., Kopetz, S., Kwong, L., Xiao, L., Morris, J. S., Tran Cao, H. S., . . . Vauthey, J.-N. (2021). Genomic sequencing and insight into clinical heterogeneity and prognostic pathway genes in patients with metastatic colorectal cancer. *Journal of the American College of Surgeons, 233*(2), 272-284. https://doi.org/10.1016/j.jamcollsurg.2021.05.027

Continued on next page

SUGGESTED READINGS - continued

Kawaguchi, Y., Kopetz, S., Lillemoe, H. A., Hwang, H., Wang, X., Tzeng, C.-W. D., . . . Vauthey, J.-N. (2020). A new surveillance algorithm after resection of colorectal liver metastases based on changes in recurrence risk and *RAS* mutation status. *Journal of the National Comprehensive Cancer Network, 18*(11), 1500-1508. https://doi.org/10.6004/jnccn.2020.7596

Kawaguchi, Y., Kopetz, S., Tran Cao, H. S., Panettieri, E., De Bellis, M., Nishioka, Y., . . . Vauthey, J.-N. (2021). Contour prognostic model for predicting survival after resection of colorectal liver metastases: Development and multicentre validation study using largest diameter and number of metastases with *RAS* mutation status. *British Journal of Surgery, 108*(8), 968-975. https://doi.org/10.1093/bjs/znab086

Kopetz, S., Chang, G. J., Overman, M. J., Eng, C., Sargent, D. J., Larson, D. W., . . . McWilliams, R. R. (2009). Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *Journal of Clinical Oncology, 27*(22), 3677-3683. https://doi.org/10.1200/JCO.2008.20.5278

Kopetz, S., Grothey, A., Yaeger, R., Cutsem, E. V., Desai, J., Yoshino, T., . . . Guren, T. K. (2019) Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. *New England Journal of Medicine, 381*, 1632-1643. https://doi.org/10.1056/NEJMoal1908075

Kopetz, S., McDonough S., Morris, V., Lenz, H. J., Magliocco, A., Atreya, C., . . . Hochester, H. (2017). Randomized trial of irinotecan and cetuximab with or without vemurafenib in *BRAF*-mutant metastatic colorectal cancer (SWOG 1406). *Journal of Clinical Oncology*, *35*(Suppl 4), 520. https://doi.org/10.1200/JCO.2017.35.4_suppl.520

Kopetz, S., Yoshino, T., Van Cutsem, E., Eng, C., Kim, T. W., Wasan, H. S., . . . Tabernero, J. (2025). BREAKWATER: Analysis of first-line encorafenib + cetuximab + chemotherapy in BRAF V600E-mutant metastatic colorectal cancer. *Journal of Clinical Oncology, 43*(Suppl 4), 16. https://doi.org/10.1200/JCO.2025.43.4_suppl.16

Le, D., Uram, J., Wang, H., Bartlett, B., Kemberling, H., Eyring, A., . . . Diaz Jr., L. (2015). PD-1 blockade in tumors with mismatch-repair deficiency. *The New England Journal of Medicine, 372*(26), 2509-2520. https://doi.org/10.1056/NEJMoa1500596

Locker, G., Hamilton, S., Harris, J., Jessup, J., Kemeny, N., Macdonald, J., . . . Bast Jr, R. (2006). ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *Journal of Clinical Oncology, 24*(33), 5313-5327. https://doi.org/10.1200/JCO.2006.08.2644

Loree, J. M., Wang, Y., Syed, M. A., Sorokin, A. V., Coker, O., Xiu, J., . . . Kopetz, S. (2021). Clinical and functional characterization of atypical *KRAS/NRAS* mutations in metastatic colorectal cancer. *Clinical Cancer Research, 27*(16), 4587-4598. https://doi.org/10.1158/1078-0432.CCR-21-0180

Maddalena, G., Zeineddine, F. A., Rivero-Hinojosa, S., Aushev, V. N., Chowdhury, S., Zeineddine, M. A., . . . Shen, J. P. (2024). Defining the subset of mutations in polymerase epsilon (*POLE*) associated with loss-of-proofreading (LOP) functionality. *Annals of Oncology, 35*(7), 678-680. https://doi.org/10.1016/j.annonc.2024.04.009

Malakorn, S., Yang, Y., Bednarski, B. K., Kaur, H., You, Y. N., Holliday, E. B., . . . Chang, G. J. (2019). Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? *Diseases of the Colon & Rectum, 62*(10), 1158-1166. https://doi.org/10.1097/DCR.0000000000001465

Marijnen, C., Nagtegaal, I., Kapiteijn, E., Kranenbarg, E., Noordijk, E., Van Krieken, J., . . . Leer, J. (2003). Radiotherapy does not compensate for positive resection margins in rectal cancer patients: Report of a multicenter randomized trial. *International Journal of Radiation Oncology, Biology, Physics, 55*(5), 1311-1320. https://doi.org/10.1016/S0360-3016(02)04291-8

Mayer, R., Van Cutsem, E., Falcone, A., Yoshino, T., Garcia-Carbonero, R., Mizunuma, N., . . . Ohtsu, A. (2015). Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *The New England Journal of Medicine, 372*(20), 1909-1919. https://doi.org/10.1056/NEJMoa1414325

MD Anderson Institutional Policy #CLN1202 - Advance Care Planning Policy
Advance Care Planning (ACP) Conversation Workflow (ATT1925)

MERCURY Study Group. (2006). Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: Prospective observational study. *The British Medical Journal, 333*(7572), 779. https://doi.org/10.1136/bmj.38937.646400.5

Continued on next page

SUGGESTED READINGS - continued

Meric-Bernstam, F., Hurwitz, H., Raghav, K. P. S., McWilliams, R. R., Fakih, M., VanderWalde, A., . . . Cuchelkar, V. (2019). Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): An updated report from a multicentre, open label, phase 2a, multi basket study. *The Lancet Oncology*, *20*(4), 518-530. https://doi.org/10.1016/S1470-2045(18)30904-5

Modest, D. P., Martens, U. M., Riera-Knorrenschild, J., Greeve, J., Florschutz, A., Wessendorf, S., . . . Geissler, M. (2019). Folfoxiri plus panitumumab as first-line treatment of *RAS* wild-type metastatic colorectal cancer: The randomized, open-label, Phase II VOLFI Study (AIO KRK0109). *Journal of Clinical Oncology, 35*(37), 3401-3411. https://doi.org/10.1200/JCO.19.01340

National Comprehensive Cancer Network. (2025). *Rectal Cancer* (NCCN Guideline Version 1.2025). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

Ngan, S., Burmeister, B., Fisher, R., Solomon, M., Goldstein, D., Joseph, D., . . . Mackay, J. (2012). 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. *Journal of Clinical Oncology, 30*(31), 3827-3833. https://doi.org/10.1200/JCO.2012.42.9597

Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G., Schlag, P., Rougier, P., . . . Gruenberger, T. (2008). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial. *The Lancet, 371*(9617), 1007-1016. https://doi.org/10.1016/S0140-6736(08)60455-9

Ogura, A., Konishi, T., Cunningham, C., Garcia-Aguilar, J., Iversen, H., Toda, S., . . . Kusters, M. (2019). Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: Results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. *Journal of Clinical Oncology, 37*(1), 33-43. https://doi.org/10.1200/JCO.18.00032

Overman, M., McDermott, R., Leach, J., Lonardi, S., Lenz, H. J., Morse, M., . . . Andre, T. (2017). Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): An open-label, multicentre, phase 2 study. *The Lancet Oncology, 18*(9), 1182-1191. https://doi.org/10.1016/S1470-2045(17)30422-9

Overman, M. J., Lonardi, S., Wong., K. Y. M., Lenz, H., Gelsomino, F., Aglietta, M., . . . Andre, T. (2018). Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *Journal of Clinical Oncology, 36*(8), 773-779. https://doi.org/10.1200/JCO.2017.76.9901

Park, I., You, Y., Agarwal, A., Skibber, J., Rodriguez-Bigas, M., Eng, C., . . . Change, G. (2012). Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. *Journal of Clinical Oncology, 30*(15), 1770-1776. https://doi.org/10.1200/JCO.2011.39.7901

Peeters, K., Marijnen, C., Nagtegaal, I., Kranenbarg, E., Putter, H., Wiggers, T., . . . van de Velde, C. (2007). 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. *Annals of Surgery, 246*(5), 693-701. https://doi.org/10.1097/01.sla.0000257358.56863.ce

Peeters, M., Cervantes-Ruiperez, A., Strickland, A., Ciuleanu, T., Mainwaring, P., Tzekova, V., . . . Gansert, J. (2010). Randomized phase III study of panitumumab (pmab) with FOLFIRI versus FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis by tumor epidermal growth factor receptor (EGFR) staining. *Journal of Clinical Oncology, 28*(Suppl 15), 3565. https://doi.org/10.1200/jco.2010.28.15_suppl.3565

Quirke, P., Steele, R., Monson, J., Grieve, R., Khanna, S., Couture, J., . . . Sebag-Montefiore, D. (2009). Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: A prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *The Lancet, 373*(9666), 821-828. https://doi.org/10.1016/S0140-6736(09)60485-2

Continued on next page

SUGGESTED READINGS - continued

Raghav, K., Siena, S., Takashima, A., Kato, T., Van den Eynde, M., Pietrantonio, F., . . . Yoshino, T. (2024). Trastuzumab deruxtecan in patients with HER2-positive advanced colorectal cancer (DESTINY-CRC02): Primary results from a multicentre, randomised, phase 2 trial. *The Lancet Oncology, 25*(9), 1147-1162. https://doi.org/10.1016/S1470-2045(24)00380-2

Rödel, C., Graeven, U., Fietkau, R., Hohenberger, W., Hothorn, T., Arnold, D., . . . Liersch, T. (2015). 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. *The Lancet Oncology, 16*(8), 979-989. https://doi.org/10.1016/S1470-2045(15)00159-X

Roh, M., Colangelo, L., O'Connell, M., Yothers, G., Deutsch, M., Allegra, C., . . . Wolmark, N. (2009). Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *Journal of Clinical Oncology, 27*(31), 5124-5130. https://doi.org/10.1200/JCO.2009.22.0467

Roh, M., Yothers, G., O'Connell, M., Beart, R., Pitot, H., Shields, A., . . . Wolmark, N. (2011). The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. *Journal of Clinical Oncology, 29*(Suppl 15), 3503. https://doi.org/10.1200/jco.2011.29.15_suppl.3503

Sammour, T., Malakorn, S., Bednarski, B. K., Kaur, H., Shin, U. S., Messick, C., . . . Chang, G. J. (2018). Oncological outcomes after robotic proctectomy for rectal cancer: Analysis of a prospective database. *Annals of Surgery, 267*(3), 521-526. https://doi.org/10.1097/SLA.0000000000002112

Sammour, T., Price, B. A., Krause, K. J., & Chang, G. J. (2017). Nonoperative management or "watch and wait" for rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy: A critical appraisal. *Annals of Surgical Oncology, 24*(7), 1904-1915. https://doi.org/10.1245/s10434-017-5841-3

Sartore-Bianchi, A., Trusolino, L., Martino, C., Bencardino, K., Lonardi, S., Bergamo, F., . . . Siena, S. (2016). 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. *The Lancet Oncology, 17*(6), 738-746. https://doi.org/10.1016/S1470-2045(16)00150-9

Sauer, R., Becker, H., Hohenberger, W., Rödel, C., Wittekind, C., Fietkau, R., . . . Raab, R. (2004). Preoperative versus postoperative chemoradiotherapy for rectal cancer. *The New England Journal of Medicine, 351*(17), 1731-1740. https://doi.org/10.1056/NEJMoa040694

Sauer, R., Liersch, T., Merkel, S., Fietkau, R., Hohenberger, W., Hess, C., . . . Rodel, C. (2012). 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. *Journal of Clinical Oncology, 30*(16), 1926-1933. https://doi.org/10.1200/JCO.2011.40.1836

Schirripa, M., Biason, P., Lonardi, S., Pella, N., Pino, M. S., Urbano, F., . . . Fassan, M. (2019). Class 1, 2, and 3 *BRAF*-mutated metastatic colorectal cancer: A detailed clinical, pathologic, and molecular characterization. *Clinical Cancer Research, 25*(13), 3954-3961. https://doi.org/10.1158/1078-0432.CCR-19-0311

Sebag-Montefiore, D., Stephens, R., Steele, R., Monson, J., Grieve, R., Khanna, S., . . . Parmar, M. (2009). Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): A multicentre, randomised trial. *The Lancet, 373*(9666), 811-820. https://doi.org/10.1016/S0140-6736(09)60484-0

Siena, S., Tabernero, J., Cunningham, D., Koralewski, P., Ruff, P., Rother, M., . . . Douillard, J. (2010). Randomized phase III study of panitumumab (pmab) with FOLFOX4 compared to FOLFOX4 alone as first-line treatment (tx) for metastatic colorectal cancer (mCRC): PRIME trial analysis by epidermal growth factor receptor (EGFR) tumor staining. *Journal of Clinical Oncology, 28*(Suppl 15), 3566. https://doi.org/10.1200/jco.2010.28.15_suppl.3566

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SUGGESTED READINGS - continued

Silberfein, E., Kattepogu, K., Hu, C. Y., Skibber, J., Rodriguez-Bigas, M., Feig, B., . . . Chang, G. (2010). Long-term survival and recurrence outcomes following surgery for distal rectal cancer. *Annals of Surgical Oncology, 17*(11), 2863-2869. https://doi.org/10.1245/s10434-010-1119-8

Snyder, R. A., Hu, C.-Y., Cuddy, A., Francescatti, A. B., Schumacher, J. R., Van Loon, K., . . . Chang, G. J. (2018). Association between intensity of posttreatment surveillance testing and detection of recurrence in patients with colorectal cancer. *JAMA, 319*(20), 2104-2115. https://doi.org/10.1001/jama.2018.5816

Solomon, B. J., Drilon, A., Lin, J. J., Bazhenova, L., Goto, K., De Langen, J., . . . Besse, B. (2023). 1372P repotrectinib in patients (pts) with *NTRK* fusion-positive (*NTRK*+) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial. *Annals of Oncology, 34*(Suppl 2), S787-S788. https://doi.org/10.1016/j.annonc.2023.09.2405

Strickler, J. H., Ng, K., Cercek, A., Fountzilas, C., Sanchez, F. A., Hubbard, J. M., . . . Bekaii-Saab, T. S. (2021). MOUNTAINEER: Open-label, phase II study of tucatinib combined with trastuzumab for HER2-positive metastatic colorectal cancer (SGNTUC-017, trial in progress). J*ournal of Clinical Oncology, 39*(Suppl 3), TPS153-TPS153. https://doi.org/10.1200/JCO.2021.39.3_suppl.TPS153

Subbiah, V., Wolf, J., Konda, B., Kang, H., Spira, A., Weiss, J., . . . Drilon, A. (2022). Tumour-agnostic efficacy and safety of selpercatinib in patients with *RET* fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): A phase 1/2, open-label, basket trial. *The Lancet Oncology, 23*(10), 1261-1273. https://doi.org/10.1016/S1470-2045(22)00541-1

Taylor, F., Quirke, P., Heald, R., Moran, B., Blomqvist, L., Swift, I., . . . Brown, G. (2011). One millimetre is the safe cut-off for magnetic resonance imaging prediction of surgical margin status in rectal cancer. *British Journal of Surgery, 98*(6), 872-879. https://doi.org/10.1002/bjs.7458

Twelves, C. J. (2006). Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) trial: Overview of efficacy, safety, and cost-effectiveness. *Clinical Colorectal Cancer*, *6*(4), 278-87. https://doi.org/10.3816/CCC.2006.n.046

Van Cutsem, E., Köhne, C. H., Hitre, E., Zaluski, J., Chang Chien, C. R., Makhson, A., . . . Rougier, P. (2009). Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *The New England Journal of Medicine, 360*(14), 1408-1417. https://doi.org/10.1056/NEJMoa0805019

Van Cutsem, E., Siena, S., Humblet, Y., Canon, J. L., Maurel, J., Bajetta, E., . . . Peeters, M. (2007). An open-label, single-arm study assessing safety and efficacy of panitumumab in patients with metastatic colorectal cancer refractory to standard chemotherapy. *Annals of Oncology, 19*(1), 92-98. https://doi.org/10.1093/annonc/mdm399

Vauthey, J. N., Pawlik, T., Ribero, D., Wu, T. T., Zorzi, D., Hoff, P., . . . Abdalla, E. (2006). Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *Journal of Clinical Oncology, 24*(13), 2065-2072. https://doi.org/10.1200/JCO.2005.05.3074

Venook, A., Niedzwiecki, D., Lenz, H. J., Innocenti, F., Fruth, B., Meyerhardt, J., . . . Blanke, C. (2017). Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: A randomized clinical trial. *JAMA, 317*(23), 2392-2401. https://doi.org/10.1001/jama.2017.7105

Wang, R., Lian, J., Wang, X., Pang, X., Xu, B., Tang, S., . . . Lu, H. (2023). Intrinsic resistance and efficacy of immunotherapy in microsatellite instability-high colorectal cancer: A systematic review and meta-analysis. *Biomolecules & Biomedicine, 23*(2), 198-208. https://doi.org/10.17305/bjbms.2022.8286

Wibe, A., Eriksen, M., Syse, A., Tretli, S., Myrvold, H., & Soreide, O. (2005). Effect of hospital caseload on long-term outcome after standardization of rectal cancer surgery at a national level. *British Journal of Surgery, 92*(2), 217-224. https://doi.org/10.1002/bjs.4821

Yaeger, R., Weiss, J., Pelster, M. S., Spira, A. I., Barve, M., Sai-Hong, I. O., . . . Klempner, S. J. (2023). Adagrasib with or without cetuximab in colorectal cancer with mutated KRAS G12C. *The New England Journal of Medicine, 388*(1), 44-54. https://doi.org/10.1056/NEJMoa2212419

You, Y. N., Skibber, J. M., Hu, C.-Y., Crane, C. H., Das, P., Kopetz, E. S., . . . Chang, G. J. (2016). Impact of multimodal therapy in locally recurrent rectal cancer. *British Journal of Surgery, 103*(6), 753-762. https://doi.org/10.1002/bjs.10079

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