Rectal Cancer

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

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Rectal Cancer

Note: Consider Clinical Trials as treatment options for eligible patients. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

PRESENTATION AND EVALUATION

Tumor within rectum

- Pathology review[1]
- 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[2]

Resectable primary, no metastasis

PRIMARY TREATMENT

cT1N0 eligible for TAE **or** TAMIS/TEM resection[3] **or** ESD[4] → TAE **or** TAMIS/TEM[3] **or** ESD[4] → Excision complete and ≤ pT1?

- Yes → Surveillance, see Page 10
- No → Radical surgical resection: LAR, CAA **or** APR, with or without temporary fecal diversion (ileostomy)

cT1 not eligible for TAE **or** TAMIS/TEM resection[3] **or** T2N0 → Radical surgical resection: LAR, CAA **or** APR, with or without temporary fecal diversion (ileostomy)

Stage II and stage III

- mrT3N0-1 with high risk features[5] or > mrT3N1 → Neoadjuvant therapy[6] (consider clinical trial if available) → Patient with cCR[7]?
  - Yes → Deferral of surgery with watch-and-wait may be considered based on multidisciplinary discussion
  - No → Radical surgical resection: LAR, CAA **or** APR, with or without temporary fecal diversion (ileostomy)
- mrT3N0-1 without high risk features → Radical surgical resection: LAR, CAA **or** APR, with or without temporary fecal diversion (ileostomy)

Radical surgical resection: LAR, CAA **or** APR, with or without temporary fecal diversion (ileostomy) → Consider adjuvant chemotherapy[8] if not previously given → Surveillance, see Page 10

Unresectable primary, no metastasis, see Page 3

Unresectable primary, no metastasis, see Page 3

Stage IV with carcinomatosis, see Page 4

APR = abdominoperineal resection
CAA = coloanal anastomosis
cCR = clinical complete response
CEA = carcinoembryonic antigen
CRM = circumferential resection margin
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] Consider MD Anderson approved GI biomarkers
[2] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[3] Criteria for eligibility for transanal excision: cT1 (EUS or MRI), low grade, no lymphovascular or perineural invasion
[4] Criteria for eligibility for ESD: superficial T1 without endoscopic evidence of deeper invasion. See Page 11 for Principles of Endoscopic Therapy.
[5] 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)

[6] See Page 15 for Principles of Neoadjuvant Therapy
[7] Criteria for cCR:
- No palpable mass on digital rectal exam
- Flat scar without residual mass or ulceration on endoscopic exam
- mrTRG0

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

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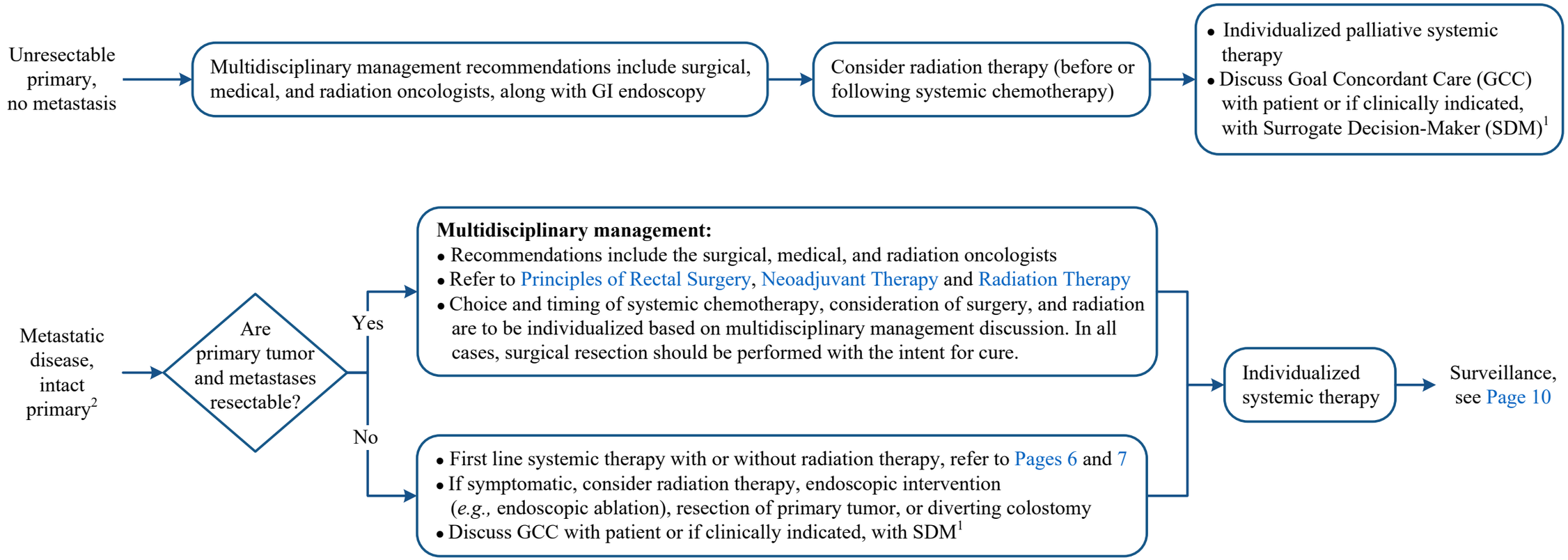
Rectal Cancer

Note: Consider Clinical Trials as treatment options for eligible patients. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

PRESENTATION

PRIMARY TREATMENT



[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 SDM 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 4 for Stage IV with carcinomatosis

Rectal Cancer

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PRESENTATION[1] AND EVALUATION

Stage IV with carcinomatosis

- CEA
- Pathology review[2]
- 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 Surrogate Decision-Maker (SDM)[3]

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

Yes → Continue current chemotherapy regimen until progression of disease followed by second line chemotherapy[4,5] if tolerating therapy and ECOG performance status ≤ 2
- Best supportive care
- Consideration and discussion of clinical trials when available

No → Evaluation of symptomatic primary or metastatic disease (*e.g.*, obstruction). See Page 3.
- 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[4,5] if tolerating therapy and ECOG performance status ≤ 2
- Best supportive care
- Consideration and discussion of clinical trials when available

Yes →
- Consider 3-6 months of systemic therapy[4,5]
- Consider immunotherapy for MSI-High tumors[4,5]

Diagnostic laparoscopy with washings and biopsies as indicated

Disease progression?

Yes → Continue current chemotherapy regimen until progression of disease followed by second line chemotherapy[4,5] if tolerating therapy and ECOG performance status ≤ 2
- Best supportive care
- Consideration and discussion of clinical trials when available

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[4,5] if tolerating therapy and ECOG performance status ≤ 2
- Best supportive care
- Consideration and discussion of clinical trials when available

Complete cytoreduction →
- Surveillance with imaging and tumor markers as indicated
- Consider evaluation for minimal residual disease and further systemic therapy[4,5]

ECOG = Eastern Cooperative Oncology Group
CEA = carcinoembryonic antigen colorectal cancer
MSI = microsatellite instability
HIPEC = heated intraperitoneal chemotherapy

[1] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[2] Confirm biomarker studies include expanded *RAS, BRAF V600E*, *HER2* amplification, MSI status, and *NTRK* gene fusion (if positive for MSI-H). Refer to MD Anderson approved GI biomarkers.
[3] 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 SDM 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).
[4] See Page 14 for Principles of Systemic Therapy
[5] See Page 6 or 7 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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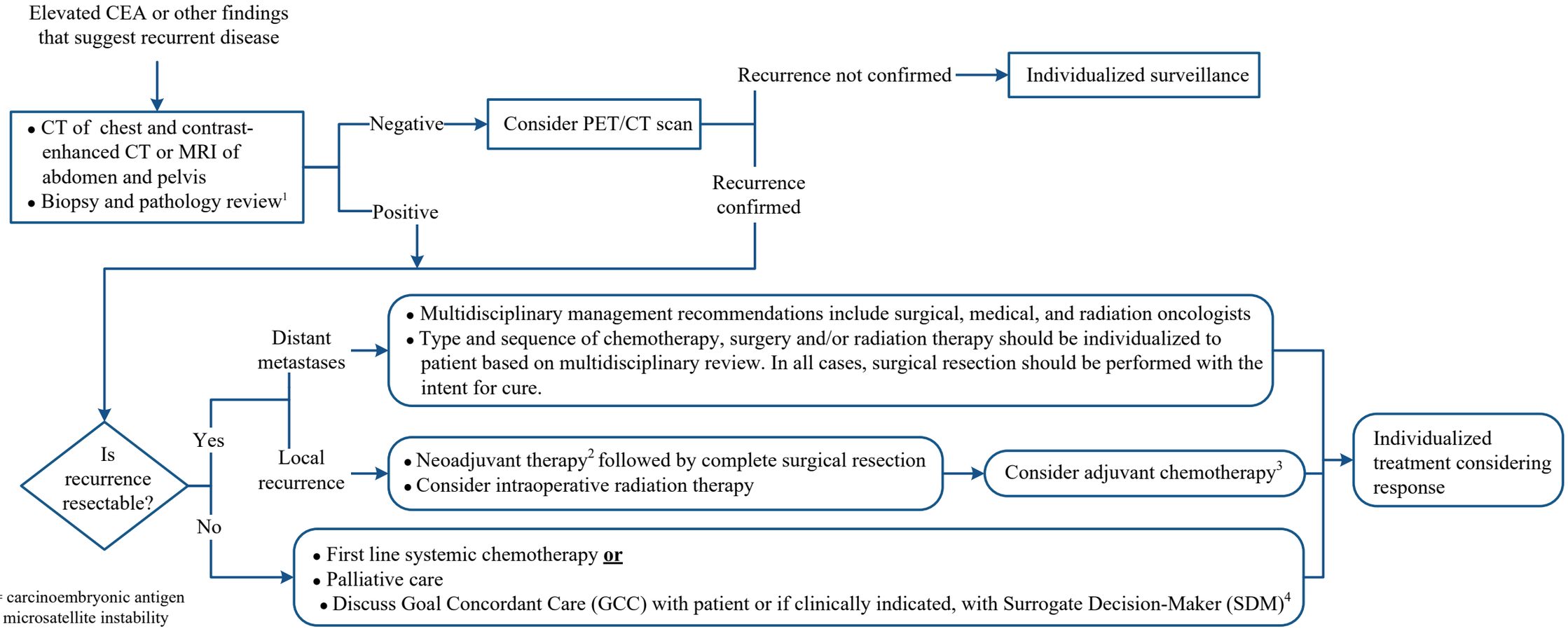
Note: Consider Clinical Trials as treatment options for eligible patients. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

EVALUATION AND MANAGEMENT OF SUSPECTED OR DOCUMENTED RECURRENT RECTAL CANCER



CEA = carcinoembryonic antigen
MSI = microsatellite instability

[1] Confirm biomarker studies include expanded *RAS, BRAF V600E*, MSI status, NTRK gene fusion (if MSI-H), and HER2 amplification upon diagnosis of stage IV. Refer to MD Anderson approved GI biomarkers.
[2] See Page 15 for Principles of Neoadjuvant Therapy
[3] Capecitabine or 5-fluorouracil/leucovorin or 5-fluorouracil/leucovorin/oxaliplatin based on multidisciplinary review
[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 SDM 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).

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Rectal Cancer

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

First-line Therapy

Patient able to tolerate intensive therapy

- FOLFOX with or without bevacizumab[1] **or**
- FOLFOX with or without anti-epidermal growth factor receptor (EGFR) therapy[2,3] **or**
- CapeOx[4,5] with or without bevacizumab[1] **or**
- CapeOx[4,5] with or without panitumumab[2,3]

- FOLFIRI with or without bevacizumab[1] **or**
- FOLFIRI with or without anti-EGFR therapy[2,3]

- FOLFOXIRI[6] with or without bevacizumab[1,7] **or**
- FOLFOXIRI[6] with anti-EGFR therapy[2,3]

- Nivolumab with or without ipilimumab (if dMMR/MSI-H) **or**
- Pembrolizumab (if dMMR/MSI-H)
- Screen for *NTRK* gene fusion, especially if dMMR/MSI-H. If positive, may use larotrectinib or entrectinib.

Second-line Therapy

- Consider the following second-line therapy if received any of the first line therapy options:
  - Encorafenib (if *BRAF V600E*) with anti-EGFR therapy[2,3] **or**
  - Single agent nivolumab or pembrolizumab (if dMMR/MSI-H) and did not receive immunotherapy in first line setting **or**
  - Consider nivolumab with ipilimumab for those who previously received single agent pembrolizumab (if dMMR/MS-H) **or**
  - Fam-trastuzumab deruxtecan-nxki (for *HER2*-amplified) **or**
  - Trastuzumab with either pertuzumab or lapatinib or tucatinib (for *HER2*-amplified and *RAS* and *BRAF* WT) **or**
  - Screen for *NTRK* gene fusion, especially if dMMR/MSI-H. If positive, may use larotrectinib or entrectinib.
  - Clinical trial
- 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[1] **or**
  - FOLFOX with anti-EGFR therapy[2,3], if did not receive anti-EFGR therapy in first-line setting **or**
  - CapeOx[4,5] with or without bevacizumab[1] **or**
  - CapeOx[4,5] with or without panitumumab[2,3], 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[1] **or**
  - FOLFIRI with anti-EGFR therapy[2,3] if did not receive anti-EGFR therapy as first-line setting
- If no suitable second-line therapy options, consider third-line therapy options

Third-line (plus) Therapy

Consider one of the following:

- Clinical trial **or**
- Trifluridine/tipiracil with or without bevacizumab[1] **or**
- Regorafenib
- Anti-EGFR therapy[2] with or without irinotecan, if not previously given or if stable disease from prior anti-EFGR therapy[2] **or**
- Rechallenge with FOLFOX or CapeOx[4,5], if no prior progression on oxaliplatin **or**
- Reconsider second line therapy options as indicated and not previously given

anti-EGFR = cetuximab or panitumumab
dMMR = deficient mismatch repair
CapeOx = capecitabine[4,5] and oxaliplatin
FOLFOX = infusional 5-fluorouracil, leucovorin and oxaliplatin
FOLFIRI = infusional 5-fluorouracil, leucovorin and irinotecan
FOLFOXIRI = infusional 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan
MSI = microsatellite instability

[1] Elderly patients with a prior arterial thrombotic event are at increased risk of stroke, myocardial infarct and other arterial events. The incidence of venous thrombosis is statistically significant in colorectal cancer patients.
[2] A *RAS* mutation indicates resistance to cetuximab and panitumumab
[3] Consider anti-EGFR therapy only if primary tumor is left sided/rectal cancer
[4] 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.
[5] Patients on warfarin or phenytoin should switch to appropriate alternative agents prior to starting capecitabine due to potential drug-drug interactions
[6] Consider regimen only in patients with adequate ECOG. Check blood counts regularly. May be best used for neoadjuvant therapy.
[7] Best suited for surgically resectable patients

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Rectal Cancer

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

First-line Therapy

Patient not able to tolerate intensive therapy

- Capecitabine[1,2] with or without bevacizumab[3] **or**
- Infusional 5-fluorouracil with leucovorin and bevacizumab[3] **or**
- Anti-EGFR therapy[4,5] (for *RAS* WT/*BRAF* WT and left sided tumors only) **or**
- Single agent nivolumab or pembrolizumab (if dMMR/MSI-H) **or**
- Trastuzumab with either pertuzumab or lapatinib or tucatinib (for *HER2*-amplified, *RAS* and *BRAF* WT) **or**
- Encorafenib (if *BRAF V600E*) with anti-EGFR therapy[4,5]

Improvement in functional status?

Second-line Therapy

Yes → Consider first-line therapy for patients able to tolerate intensive therapy on Page 6

No → Best supportive care

anti-EGFR = cetuximab or panitumumab
dMMR = deficient mismatch repair
MSI = microsatellite instability

[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. The incidence of venous thrombosis is statistically significant in colorectal cancer patients.
[4] A *RAS* mutation indicates resistance to cetuximab and panitumumab
[5] Consider anti-EGFR therapy only if primary tumor is left sided/rectal cancer

Note: Consider Clinical Trials as treatment options for eligible patients. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

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 • 5-fluorouracil 400 mg/m^2 IV bolus on Day 1, 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
mFOLFIRI	• Irinotecan 180 mg/m^2 IV over 90 minutes on Day 1 • Leucovorin 400 mg/m^2 IV over 2 hours during irinotecan infusion on Day 1 • 5-fluorouracil 400 mg/m^2 IV bolus, 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] 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 • 5-fluorouracil 400 mg/m^2 IV bolus on Day 1, 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
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

[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] A *RAS* mutation indicates resistance to cetuximab and panitumumab (refer to Principles of Systemic Therapy on Page 14)

Continued on the Next Page

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Rectal Cancer

Note: Consider Clinical Trials as treatment options for eligible patients. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

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 every 2 weeks
Irinotecan	• Irinotecan 180 mg/m^2 IV over 90 minutes on Day 1 • Repeat every 2 weeks **or** • Irinotecan 300-350 mg/m^2 IV over 90 minutes on Day 1 • Repeat every 3 weeks
Anti-EGFR therapy[a] **plus Irinotecan**	• Cetuximab[a] 500 mg/m^2 IV every 2 weeks or panitumumab[a] 6 mg/kg IV on Day 1 • With or without irinotecan 180 mg/m^2 IV on Day 1 • Repeat every 2 weeks
FOLFOXIRI[b]	Consider dosing as FOLFIRINOX for toxicity • Oxaliplatin 85 mg/m^2 IV over 2 hours on Day 1 • Irinotecan 180 mg/m^2 IV over 90 minutes on Day 1 • 5-fluorouracil 2,400 mg/m^2 IV continuous infusion over 46 hours on Day 1 • Repeat every 2 weeks
***BRAF V600E* Mutation**	• Encorafenib 300 mg PO once daily in combination with cetuximab[a] 400 mg/m^2 IV on Day 1, then 250 mg/m^2 IV weekly or panitumumab[a] 6 mg/kg IV every 2 weeks
Microsatellite instability (MSI-H)/ deficient mismatch repair (dMMR)	• 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
***HER2*-amplification (*RAS* and *BRAF V600E* 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-nxki 6.4 mg/kg IV on Day 1 every 21 days
***NTRK* gene fusion positive**	• Larotrectinib 100 mg PO twice daily • Entrectinib 600 mg PO once daily

[a] A *RAS* mutation indicates resistance to cetuximab and panitumumab (refer to Principles of Systemic Therapy on Page 14)

[b] Consider regimen only in patients with adequate Eastern Cooperative Oncology Group (ECOG). Check blood counts regularly. May be best used for neoadjuvant therapy.

Rectal Cancer

Note: Consider Clinical Trials as treatment options for eligible patients. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

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 • CEA: 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 scan of chest 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	• Physical exam: every 6-12 months for 3 years • CEA: every 6-12 months for 3 years • Proctoscopic examination following local excision: every 6-12 months for 3 years • CT scan of chest 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 (low risk)	• Physical exam: every 6 months for 2 years, then every 6-12 months for 3 years • CEA: every 6 months for 2 years, then every 6-12 months for 3 years • CT scan of chest 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 (high risk) and Stage III	• 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 • CT scan of chest 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 - 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 • CT scan of chest 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	• 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)

CEA = carcinoembryonic antigen colorectal cancer NED = no evidence of disease

[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] **Note:** Surveillance imaging with PET/CT alone is not recommended as primary imaging modality when there is no contraindication to conventional contrast-enhanced CT scan

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PRINCIPLES OF ENDOSCOPIC THERAPY

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 and from the Japan Gastroenterology Endoscopy Society guidelines.

- 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
- 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 the following endoscopic features: narrow-band imaging international colorectal endoscopic (NICE) classification type 3, or Kudo pit pattern classification type V. Nonpedunculated lesions with these features should be biopsied (in the area of surface feature disruption), tattooed (unless in or near the cecum), and referred for surgical resection. Pedunculated polyps with these features should undergo endoscopic polypectomy, as overall histological features may still be favorable.
- Superficial submucosal invasion can be suspected based on the following endoscopic features: nongranular lateral spreading tumors (LST-NG) morphology with suspicious surface features, 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, superficial T1N0 lesions eligible for TAE/TAMIS/TEM are potentially eligible for ESD, provided there is no endoscopic or histopathologic evidence for high-risk features such as deep submucosal involvement, lymphovascular invasion, perineural invasion or tumor budding
- Superficial lesions with adenoma, high grade dysplasia, or intramucosal adenocarcinoma should be removed with endoscopic resection

Note: Consider Clinical Trials as treatment options for eligible patients. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

PRINCIPLES OF RECTAL SURGERY

Transanal Excision [including transanal minimally invasive surgery (TAMIS) or transanal endoscopic microsurger (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 below)
- 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. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

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. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

PRINCIPLES OF RECTAL SURGERY - METASTASES

Liver

- 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.

PRINCIPLES OF SYSTEMIC THERAPY

- The presence of the *BRAF* mutation indicates anti-EGFR resistance
- The presence of microsatellite instability (MSI-H) status regardless if due to somatic or germline mutation may benefit from immune checkpoint inhibition
- Any *RAS* mutation indicates resistance to cetuximab and panitumumab (see Colon Cancer algorithm)

Note: Consider Clinical Trials as treatment options for eligible patients. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

PRINCIPLES OF NEOADJUVANT THERAPY

- All patients with locally advanced (stage II and III) rectal cancer should be evaluated for neoadjuvant therapy. Standard neoadjuvant treatment should include combination **chemoradiation therapy or short course radiation therapy** (see Page 16 for Principles of Radiation Therapy), however a number of alternative approaches may be considered in a multidisciplinary setting including neoadjuvant chemotherapy alone, and chemotherapy before or after chemoradiation therapy/short course radiation therapy.
- 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, Monday through Friday on days of radiation therapy
- Radiation therapy plus capecitabine 825 mg/m^2 PO twice daily, Monday through Friday on days of radiation therapy

Postoperative adjuvant chemotherapy for patients receiving preoperative 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. For adenomatous polyp with high-grade dysplasia or adenomatous polyp with invasive adenocarcinoma, recommendations are the same as for colon cancer. Refer to Colon Cancer algorithm.

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 IMRT/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

IMRT = intensity-modulated radiation therapy
VMAT = volumetric-modulated arc therapy

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DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Gastrointestinal Center providers at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

Core Development Team Leads

George Chang, MD (Colon and Rectal Surgery)
Prajnan Das, MD (GI Radiation Oncology)
Benny Johnson, DO (GI Medical Oncology)

Workgroup Members

Tharakeswara Bathala, MD (Abdominal Imaging)
Brian Bednarski, MD (Colon and Rectal Surgery)
Wendy Covert, PharmD (Pharmacy Clinical Programs)
Arvind Dasari, MBBS (GI Medical Oncology)
Keith Fournier, MD (Surgical Oncology)
Wendy Garcia, BS♦
Phillip Ge, MD (Gastroenterology Hepatology & Nutrition)
Harmeet Kaur, MD (Abdominal Imaging)
Bryan Kee, MD (GI Medical Oncology)
Scott Kopetz, MD, PhD (GI Medical Oncology)
Bruce Minsky, MD (GI Radiation Oncology)
Michael Overman, MD (GI Medical Oncology)
Miguel Rodriguez-Bigas, MD (Colon and Rectal Surgery)
Tara Sagebiel, MD (Abdominal Imaging)
John Skibber, MD (Colon and Rectal Surgery)
Melissa Taggart, MD (Anatomical Pathology)
Ching-Wei Tzeng, MD (Surgical Oncology)
Abhineet Uppal, MD (Colon and Rectal Surgery)
Jean Nicolas Vauthey, MD (Surgical Oncology)
Eduardo Vilar-Sanchez, MD, PhD (Cancer Prevention)
Mary Lou Warren, DNP, APRN, CNS-CC♦
Michael White, MD (Colon and Rectal Surgery)
Robert Wolff, MD (GI Medical Oncology)
Y. Nancy You, MD (Colon and Rectal Surgery)

♦ Clinical Effectiveness Development Team