Colon Cancer

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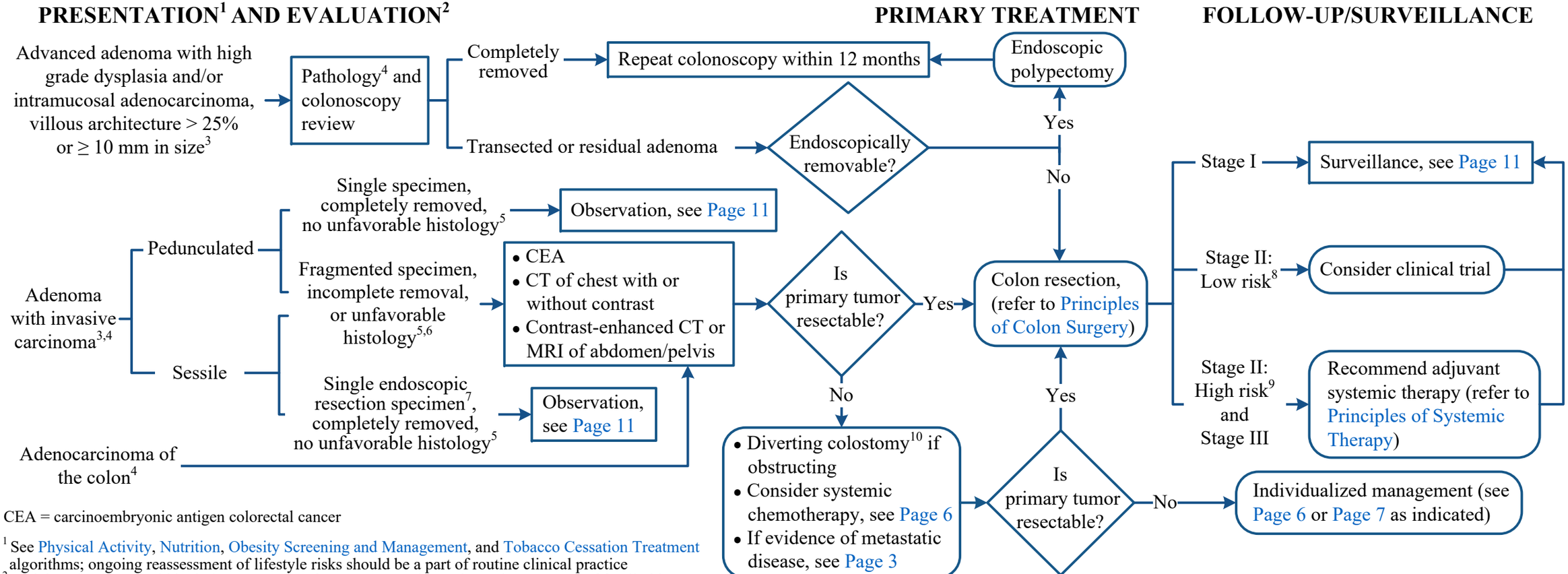
Department of Clinical Effectiveness V13
Approved by the Executive Committee of the Medical Staff on 01/21/2025

Colon Cancer

Note: Consider Clinical Trials as treatment options for eligible patients.



CEA = carcinoembryonic antigen colorectal cancer

[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 patient regardless of age.

[3] Refer to Principles of Endoscopic Therapy

[4] Refer to Principles of Biomarker Testing

[5] Unfavorable histology: • Poor differentiation • Lymphatic, vascular or perineural invasion • Tumor budding • Transection of carcinoma • Resection margin ≤ 1 mm • Mucinous adenocarcinoma

[6] In the absence of unfavorable histology, CT of chest with or without contrast and contrast enhanced CT or MRI of abdomen and pelvis is optional

[7] There is controversy regarding endoscopic management of malignant polyps. The depth of penetration into the submucosa has been shown to be associated with the risk of metastasis or recurrence. Those with minimal penetration into the submucosa and no adverse histologic features may be a candidate for endoscopic resection followed by observation. Careful histopathologic review is prerequisite for this approach. Refer to Principles of Endoscopic Therapy.

[8] Low-risk defined by absence of high-risk features (see footnote 9) or deficient mismatch repair

[9] High-risk features for Stage II colon cancer: • Poor differentiation • Inadequate nodal sampling (< 12 nodes) • Lymphatic, vascular or perineural invasion • T4 disease (invasion of serosa or other organ) • Obstruction • Margin positive or indeterminate • Perforation

[10] Endoscopic stent decompression may be considered in selected circumstances without adjacent angulation. Stents should not be deployed in the distal rectum.

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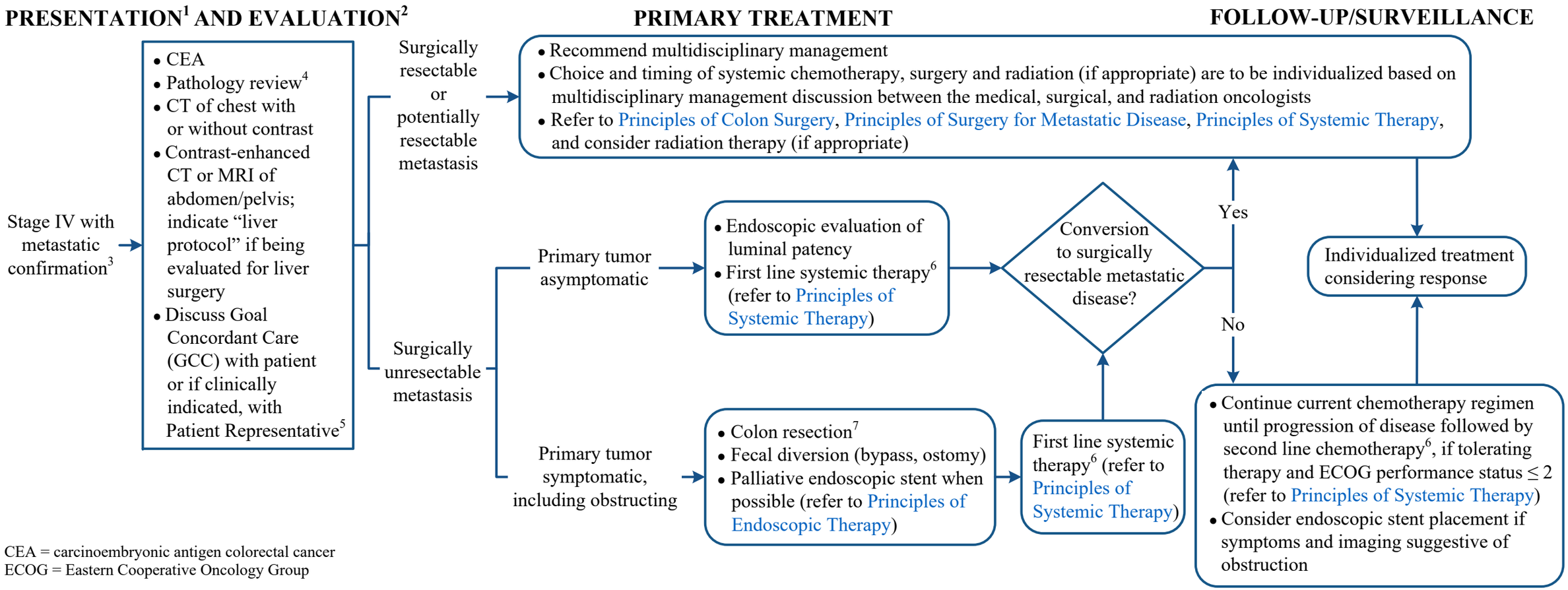

CEA = carcinoembryonic antigen colorectal cancer
ECOG = Eastern Cooperative Oncology Group

[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 patient regardless of age.
[3] See Page 4 for Stage IV with carcinomatosis
[4] Refer to Principles of Biomarker Testing
[5] 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).
[6] See Page 6 or Page 7 for Systemic Therapy for Advanced or Metastatic Disease as indicated
[7] If the potential for resectability of metastases remains, extent of resection should be curative, rather than palliative

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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 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[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 11
- 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

[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 patient 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 Page 6 or Page 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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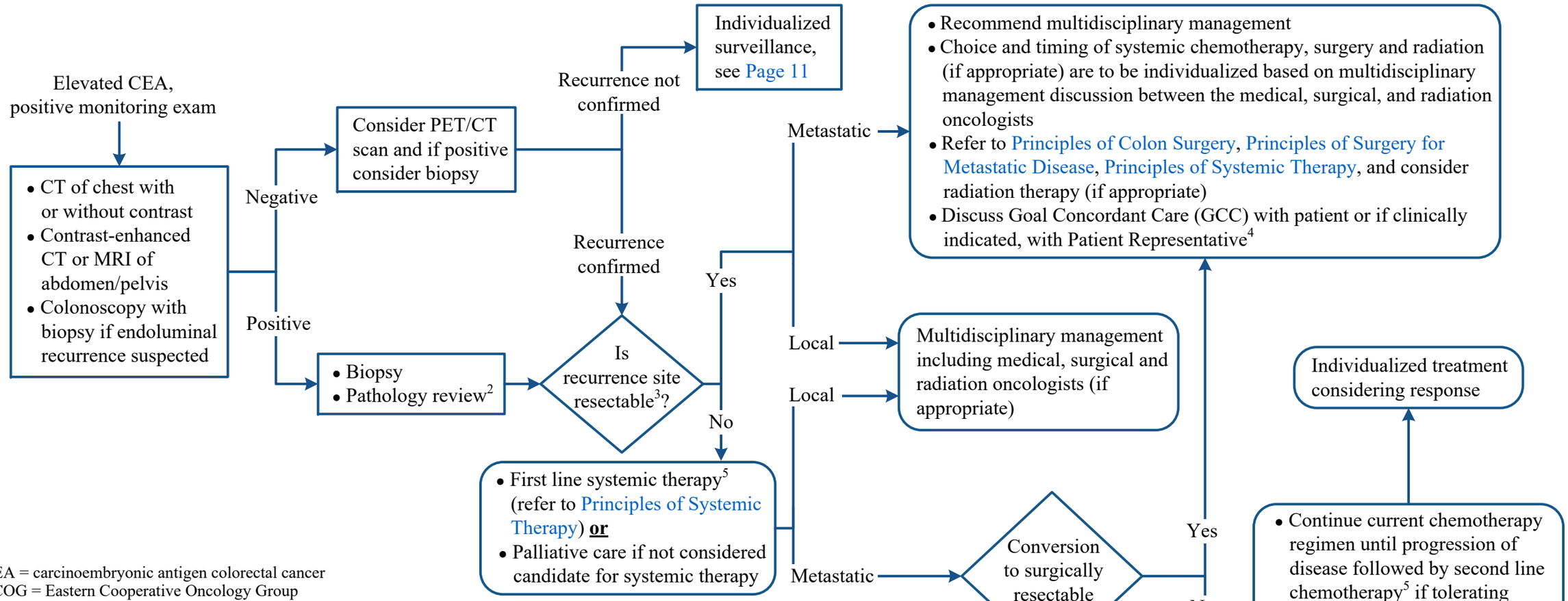
EVALUATION[1] AND MANAGEMENT OF SUSPECTED OR DOCUMENTED RECURRENT COLON CANCER



CEA = carcinoembryonic antigen colorectal cancer
ECOG = Eastern Cooperative Oncology Group

[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 patient regardless of age.
[2] Refer to Principles of Biomarker Testing
[3] Multidisciplinary evaluation to determine resectability, treatment options, and plans
[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 Page 6 or Page 7 for Systemic Therapy for Advanced or Metastatic Disease as indicated

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[1]

Patient able to tolerate intensive therapy

First-line Therapy

- FOLFOX with or without bevacizumab[2] **or**
- FOLFOX with or without anti-epidermal growth factor receptor (EGFR) therapy[3,4] **or**
- CapeOx[5,6] with or without bevacizumab[2] **or**
- CapeOx[5,6] with or without anti-EGFR therapy[3,4]

- FOLFIRI with or without bevacizumab[2]
- FOLFIRI with or without anti-EGFR therapy[3,4]

- FOLFIRINOX[7] with or without bevacizumab[2,8]

If dMMR/MSI-H, *POLE/POLD1*, or TMB[9] > 20 mut/Mb:
- Nivolumab with or without ipilimumab **or**
- Pembrolizumab

Second-line Therapy

- Consider the following second-line therapy based on molecular profile results:
  - Encorafenib with anti-EGFR therapy[3] (for *BRAF V600E*) **or**
  - Single agent nivolumab or pembrolizumab and did not receive immunotherapy in first line setting (for dMMR/MSI-H, *POLE/POLD1*, or TMB > 10 mut/Mb) **or**
  - Consider nivolumab with ipilimumab for those who previously received single agent pembrolizumab (for dMMR/MSI-H, *POLE/POLD1*, or TMB > 10 mut/Mb) **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**
  - Adagrasib[10] or sotorasib[10] 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[2] **or**
  - FOLFOX with anti-EGFR therapy[3], if did not receive anti-EFGR therapy in first-line setting **or**
  - CapeOx[5,6] with or without bevacizumab[2] **or**
  - CapeOx[5,6] with or without panitumumab[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[2] **or**
  - FOLFIRI with anti-EGFR therapy[3] 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[2] **or**
- Regorafenib **or**
- Fruquintinib[10] **or**
- Anti-EGFR therapy[3] with or without irinotecan, if not previously given **or**
- Rechallenge with anti-EGFR therapy if no evidence of *RAS/BRAF* mutations by repeat ctDNA **or**
- Re-challenge with FOLFOX or CapeOx[5,6], if no prior progression on oxaliplatin **or**
- Reconsider second line therapy options as indicated and not previously given

anti-EGFR = cetuximab or panitumumab
CapeOx = capecitabine[5,6] and oxaliplatin
ctDNA = circulating tumor DNA
dMMR = deficient mismatch repair
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 Eastern Cooperative Oncology Group (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.
[10] Not on MD Anderson formulary

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

First-line Therapy

Patient unable to tolerate intensive therapy

- Capecitabine[1,2] with or without bevacizumab[3] **or**
- Infusional 5-fluorouracil 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 (for dMMR/MSI-H, *POLE/POLD1*, or TMB[6] > 20 mut/Mb) **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 if not given previously

No → Consider best supportive care

anti-EGFR = cetuximab or panitumumab
dMMR = deficient mismatch repair
EGFR = epidermal growth factor receptor
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.

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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 on Day 1 • Leucovorin 400 mg/m^2 IV on Day 1[d] • 5-fluorouracil 400 mg/m^2 IV bolus on Day 1[d], then 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 **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 during irinotecan infusion on Day 1[d] • 5-fluorouracil 400 mg/m^2 IV bolus[d], then 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 **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 on Day 1[d] • 5-fluorouracil 400 mg/m^2 IV bolus on Day 1[d], then 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

EGFR = epidermal growth factor receptor

[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
[d] Consider omitting the bolus of fluorouracil and leucovorin for tolerability

Continued on next page

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 every 2 weeks
Irinotecan	Irinotecan 180 mg/m^2 IV on Day 1 every 2 weeks
Anti-EGFR therapy[a] with Irinotecan	• Cetuximab[a] 500 mg/m^2 IV every 2 weeks **or** panitumumab[a] 6 mg/kg IV on Day 1 every 2 weeks • With 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] 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*, 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
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**	• Adagrasib[a] 600 mg PO twice daily • With cetuximab 500 mg/m^2 IV every 2 weeks **or** panitumumab 6 mg/kg IV on Day 1 every 2 weeks **or** • Sotorasib[a] 960 mg PO once daily • With cetuximab 500 mg/m^2 IV every 2 weeks **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-nxki 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 Days 1 and 15
Fruquintinib	Fruquintinib[a] 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[a] 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] Not on MD Anderson formulary

Colon Cancer

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OBSERVATION/SURVEILLANCE[1,2]

Stage I (low risk), managed with endoscopic resection alone	Colonoscopy: at 6-12 months, then (if normal) after 3 years, and then once every five years or sooner if indicated based on findings of prior colonoscopy
Stage I[2,3,4]	• Physical exam: every 6-12 months for 3 years • CEA and ctDNA[5]: every 6-12 months for 3 years • CT scan of chest and contrast-enhanced CT of abdomen/pelvis or MRI: every 12 months for 3 years[2] • 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[6])	• Physical exam: every 6 months for up to 5 years • CEA and ctDNA[5]: every 6 months for up to 5 years • CT scan of chest and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for 3 to 5 years[2] • 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[6]) and Stage III[4]	• Physical exam: every 3-6 months for 2-3 years, then every 6 months through year 5 • CEA: every 3-6 months for 2-3 years, then every 6 months up through year 5 • Consider ctDNA[5] testing every 3-6 months for 3-5 years • CT of chest and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for 5 years[2] • Colonoscopy: at one year, then after 3 years (if normal), and then once every 5 years or sooner if indicated based on findings of prior colonoscopy
Stage IV- NED[4]	• Individualized if on therapy • Physical exam: every 3-4 months for 2 years, then every 6 months for 3 years • Refer to GI endoscopy to evaluate patency of lumen every 4-6 months if primary tumor is intact (or sooner if clinically indicated) • CEA: every 3-4 months for 2 years, then every 6 months for 3 years, then annually • Consider ctDNA[5] testing every 3-6 months for 3-5 years • CT of chest and contrast-enhanced CT or MRI of abdomen/pelvis: every 3-4 months[2] Upon becoming NED, 3-4 months for 2 years, then every 6 months for 3 years, then annually as clinically appropriate and as dictated by primary site, response and site of metastasis.

CEA = carcinoembryonic antigen colorectal cancer ctDNA = circulating tumor DNA 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] Surveillance imaging with PET/CT alone is not recommended as primary imaging modality, unless patient has a contrast allergy or renal dysfunction precluding intravenous contrast
[3] Evidence regarding the role of routine surveillance for patients with stage I colon cancer is controversial. Surveillance should be considered for patients with stage I colon cancer who have an increased risk for recurrence (*e.g.*, poor differentiation, presence of lymphatic, vascular, or perineural invasion, T2 disease).
[4] Refer to the Survivorship Colon Cancer algorithm for recommendations beyond 3 years for stage I and beyond 5 years for stages II to IV-NED
[5] Patients with ctDNA positive result should undergo radiographic evaluation for detection of recurrent disease, and consideration for clinical trial enrollment
[6] Surveillance for patients with low risk stage II colon cancer should be a minimum of 3 years, and up to the clinicians' discretion for years 4 and 5. For high risk stage II colon cancer, 5 years of surveillance is recommended [*e.g.*, poor differentiation, inadequate nodal sampling (< 12 nodes), lymphatic/vascular/perineural invasion, or T4 disease (invasion of serosa or other organ)].

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 (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 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) 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.

Endoscopic Palliation

- Colon stent placement is indicated for palliation in 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 COLON SURGERY

Extent of Bowel Resection

- A minimum of 5-10 cm of normal bowel should be resected on either side of the primary colon tumor. However, the length of bowel to be removed will be dictated by the blood supply of the colon which parallels the lymphatic drainage.
- Synchronous tumors may be resected as separate resections if workup for hereditary cancer is negative or may undergo subtotal colectomy

Mesocolic Excision and Lymphadenectomy

- A complete lymphadenectomy is essential for the treatment and prognosis of colon cancer. Lymphadenectomy should be complete, radical and en bloc.
- Lymph nodes are contained within the mesocolon which should be resected completely and en bloc
- Lymph nodes at the origin of feeding vessels, if suspected to be involved with cancer, should be resected and marked for pathologic examination
- Lymph nodes outside the field of resection considered suspicious should be biopsied or removed
- A minimum of 12 lymph nodes need to be examined to clearly establish stage II (T3 - T4, N0) colon cancer

Minimally Invasive Colectomy

- Oncologic principles for surgical resection including exploration are the same for minimally invasive colectomy as for open colectomy
- Tumors should be preoperatively localized by cross-sectional imaging or endoscopic localization with tattoo or endo-clip marking and abdominal x-ray

Management of Patients with Hereditary Colorectal Cancer Syndromes

- Lynch Syndrome associated carcinoma
  - Individualized treatment may include tumor directed segmental resection or subtotal colectomy with ileo-rectal anastomosis. In rare cases, restorative proctocolectomy with ileal J-pouch anal anastomosis may be performed.
- Familial Adenomatous Polyposis Syndrome (FAP) associated carcinoma
  - Restorative total proctocolectomy with ileal J-pouch anal anastomosis or subtotal colectomy with ileo-rectal anastomosis (if rectal sparing or if patient is a candidate for endoscopic management of rectal polyp burden)

Resection Needs to be Complete to be Considered Curative – Not Palliative

- The completeness of resection should be assessed. The resected mesentery should be en bloc and intact, without defects.
- Involved adjacent organs should be resected en bloc
- The closest distance from the tumor to the non-peritonealized margin should be assessed during pathological evaluation [circumferential resection margin (CRM)]. To be considered margin negative, the CRM should be > 1 mm.
- The completeness of resection should be evaluated and noted in a synoptic operative report

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 must be feasible based on anatomic grounds and the extent of disease; maintenance of normal hepatic function is required
- Resectable extrahepatic 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 unresectable patients
- Primary tumor should be resected with curative intent (R0). Consider completion colectomy with radical lymphadenectomy if synchronous metastasis at presentation and only a palliative 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 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 re-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 without intra-peritoneal chemotherapy may improve survival for patients with limited volume disease and where complete 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 SYSTEMIC THERAPY

- Identify the primary site of tumor when treatment naïve
- Anti-epidermal growth factor receptor (EGFR) therapy is contraindicated in the setting of right sided primary tumors in treatment naïve patients
- 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* or tumor mutational burden (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* mutations, 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

PRINCIPLES OF ADJUVANT SYSTEMIC THERAPY

- Few data are available for the benefit of adjuvant therapy in deficient mismatch repair (dMMR) stage II patients with high-risk features and a thorough discussion is required, especially in those with T4b tumors
- Patients with dMMR undergoing adjuvant therapy should receive a fluoropyrimidine in combination with oxaliplatin if clinically able to tolerate
- In patients with standard risk proficient mismatch repair (pMMR) stage II colon cancer, a thorough discussion is recommended and patients are advised that any 5-year survival benefit is likely to be less than 5%. After such a discussion, if wishing to proceed with adjuvant therapy, they are offered single agent fluoropyrimidine for 3-6 months.
- Patients with pMMR and high-risk stage II colon cancer may be offered adjuvant chemotherapy for 3-6 months and the inclusion of oxaliplatin will need to be individualized based on the observed risk factors, patient preferences and comorbidities
- Stage III patients are offered combination chemotherapy with fluoropyrimidine and oxaliplatin irrespective of (mismatch repair) MMR status
  - Patients with low risk disease (T1-3 and N1) are offered 3 months of CapeOx or 3-6 months of FOLFOX. Patients with high-risk disease are offered 3-6 months of CapeOx or 6 months of FOLFOX.
- Adjuvant therapy should begin within 4 to 8 weeks after surgery, unless postoperative complications warrant a delay

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Advance Care Planning (ACP) Conversation Workflow (ATT1925)

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DEVELOPMENT CREDITS

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