Colon 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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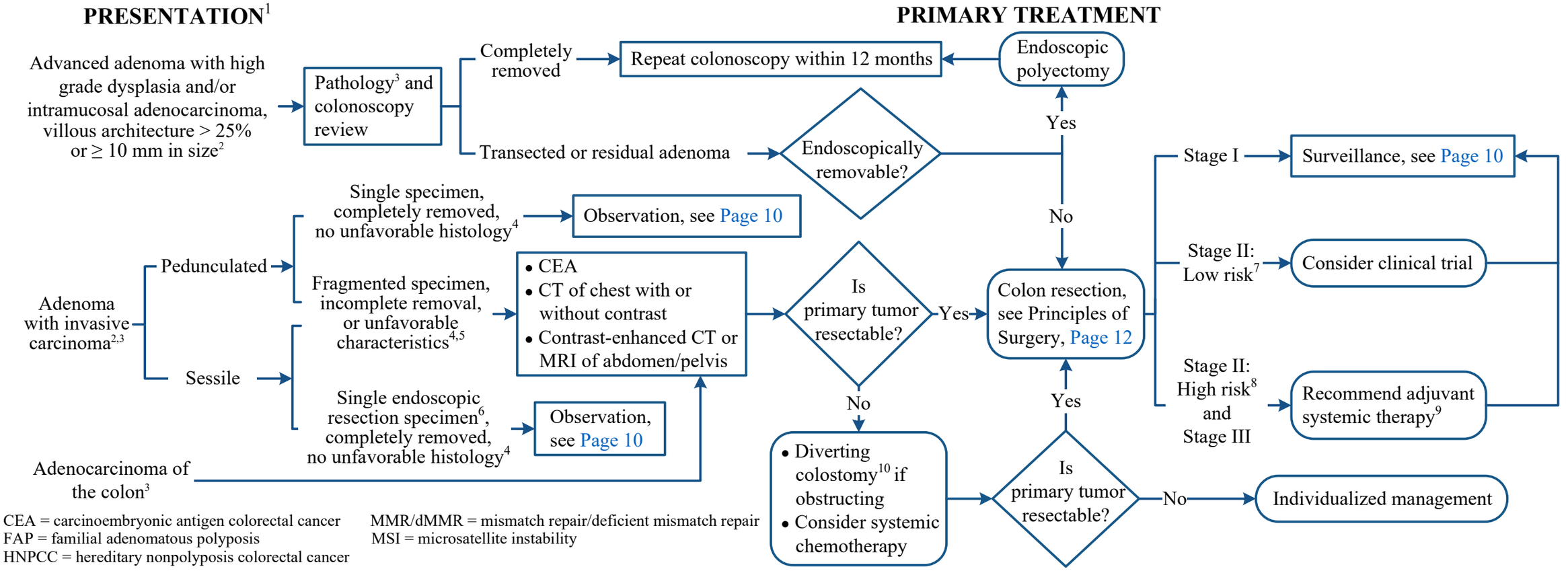
Note: Consider Clinical Trials as treatment options for eligible patients. Initial evaluation should include assessment of family history for HNPCC, FAP, or other less common germline mutations associated with colorectal cancer.



CEA = carcinoembryonic antigen colorectal cancer
FAP = familial adenomatous polyposis
HNPCC = hereditary nonpolyposis colorectal cancer
MMR/dMMR = mismatch repair/deficient mismatch repair
MSI = microsatellite instability

[1] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[2] Refer to Principles of Endoscopic Therapy
[3] Consider MD Anderson approved GI biomarkers including immunohistochemistry for MMR protein expression or MSI analysis by PCR
[4] Unfavorable pathology characteristics: • Poor differentiation • Lymphatic, vascular or perineural invasion • Tumor budding • Transection of carcinoma • Resection margin ≤ 1 mm
[5] In the absence of unfavorable characteristics, CT of chest with or without contrast and contrast enhanced CT or MRI of abdomen and pelvis is optional
[6] 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. See Page 11 for Principles of Endoscopic Therapy.
[7] Low-risk defined by absence of high-risk features (see footnote 8) or dMMR
[8] 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
[9] Refer to Page 14 for Principles of Adjuvant Systemic Therapy
[10] Endoscopic stent decompression may be considered in selected circumstances without adjacent angulation. Stents should not be deployed in the rectum.

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Colon Cancer

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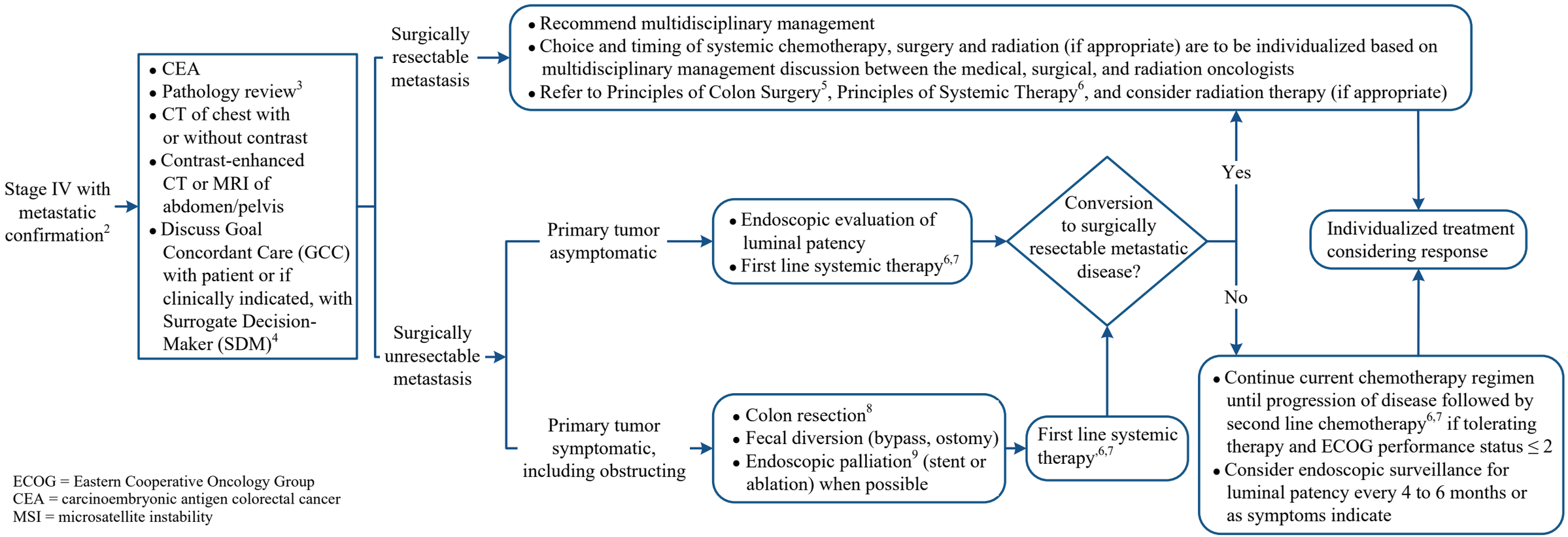
PRESENTATION[1] AND EVALUATION

PRIMARY TREATMENT



ECOG = Eastern Cooperative Oncology Group
CEA = carcinoembryonic antigen colorectal cancer
MSI = microsatellite instability

[1] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[2] See Page 4 for Stage IV with carcinomatosis
[3] 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.
[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).
[5] See Page 12 for Principles of Colon Surgery
[6] See Page 14 for Principles of Systemic Therapy
[7] See Page 6 or 7 for Systemic Therapy for Advanced or Metastatic Disease as indicated
[8] If the potential for resectability of metastases remains, extent of resection should be curative, rather than palliative
[9] Refer to Page 11 for Principles of Endoscopic Therapy

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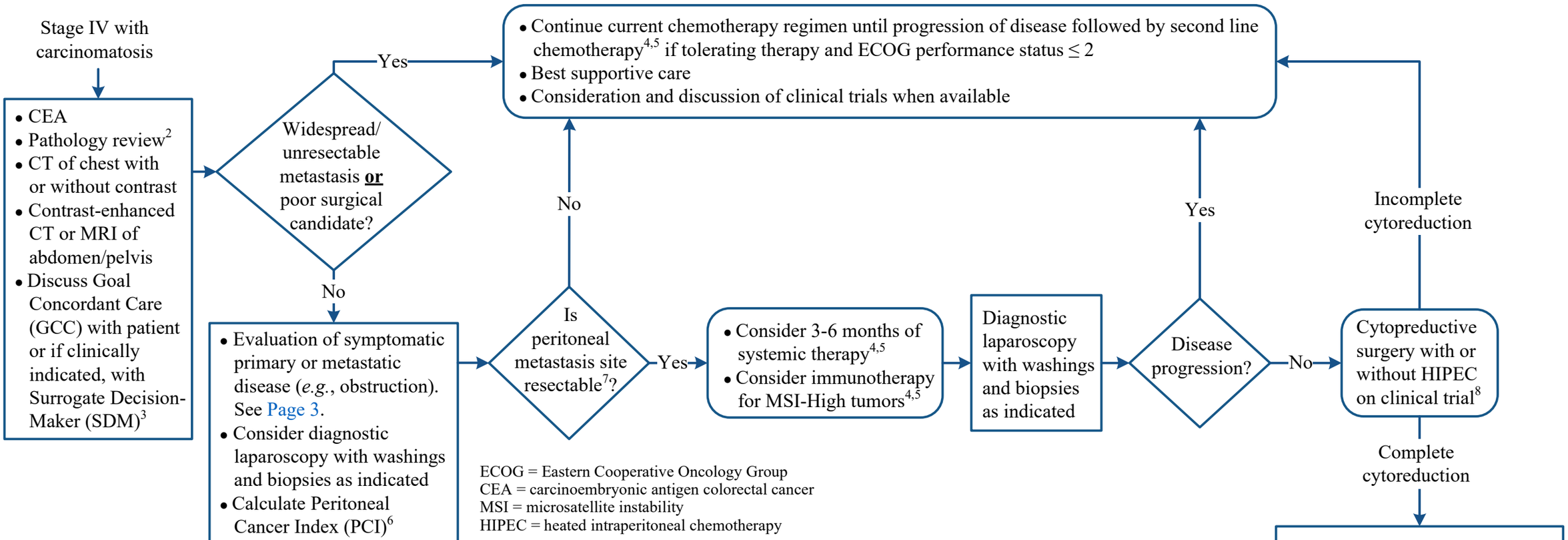
PRESENTATION[1] AND EVALUATION

TREATMENT AND EVALUATION



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.
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[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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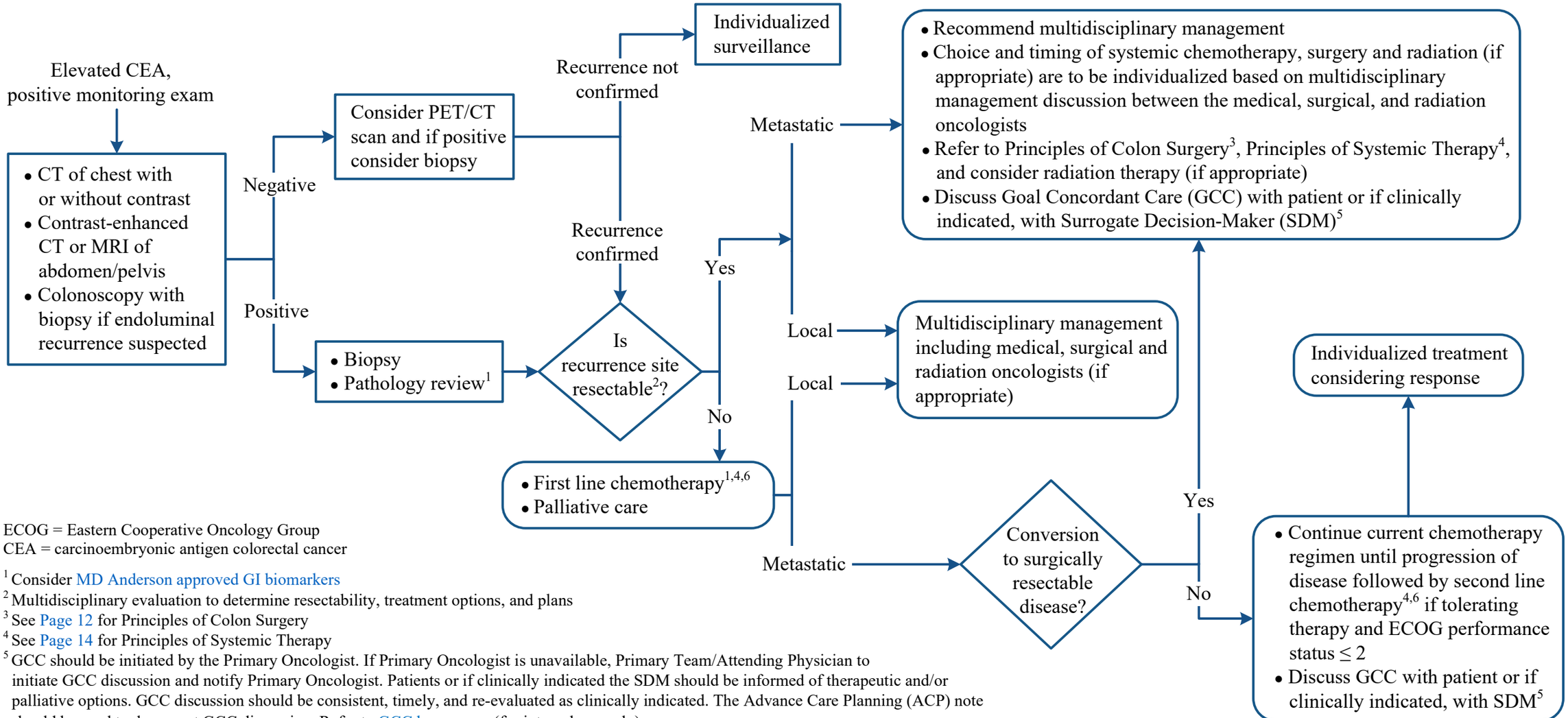
EVALUATION AND MANAGEMENT OF SUSPECTED OR DOCUMENTED RECURRENT COLON CANCER



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

[1] Consider MD Anderson approved GI biomarkers
[2] Multidisciplinary evaluation to determine resectability, treatment options, and plans
[3] See Page 12 for Principles of Colon Surgery
[4] See Page 14 for Principles of Systemic Therapy
[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 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).
[6] See Page 6 or 7 for Systemic Therapy for Advanced or Metastatic Disease as indicated

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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]
- 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**
- Re-challenge 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
CapeOx = capecitabine[4,5] and oxaliplatin
dMMR = deficient mismatch repair
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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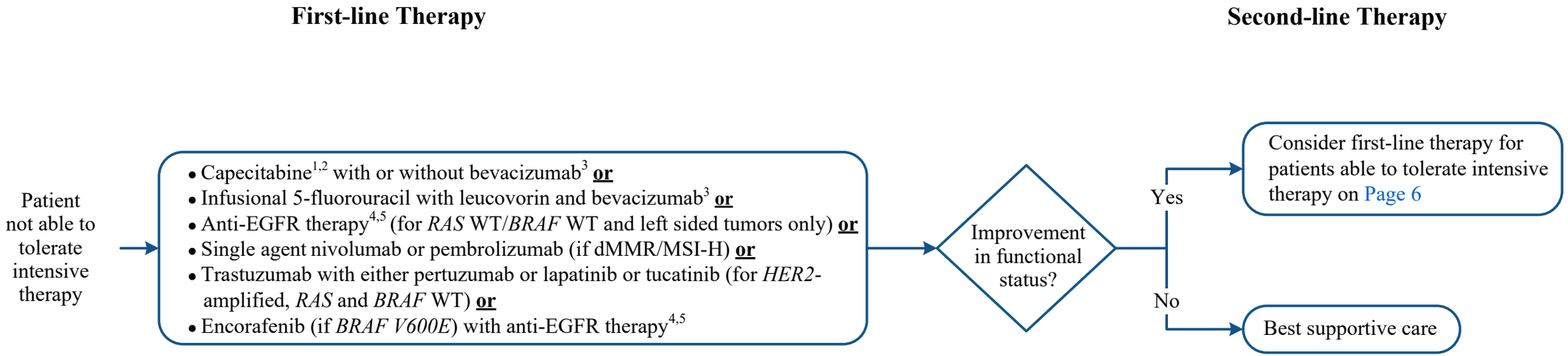
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE



anti-EGFR = cetuximab or panitumumab
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Colon Cancer

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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 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

Note: Consider Clinical Trials as treatment options for eligible patients. Initial evaluation should include assessment of family history for HNPCC, FAP, or other less common germline mutations associated with colorectal cancer.

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.

Colon Cancer

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OBSERVATION/SURVEILLANCE[1,2]

Stage 1 (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]	• Physical exam: every 6-12 months for 3 years • CEA: 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 (low risk[4])	• Physical exam: every 6 months for up to 5 years • CEA: 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 (high risk[4]) and Stage III	• 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 circulating tumor DNA testing every 3 months for 2-3 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	• 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 ~~3~~ 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 circulating tumor DNA testing every 3 months for 2-3 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 dictated by primary site, response and site of metastasis if clinically appropriate.

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] 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] 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)].

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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.

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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

- Hereditary Non-polyposis Colorectal Cancer (HNPCC) associated carcinoma
  - Individualized treatment may include tumor directed segmental resection or subtotal colectomy with ileo-rectal anastomosis. In selected 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. Initial evaluation should include assessment of family history for HNPCC, FAP, or other less common germline mutations associated with colorectal cancer.

PRINCIPLES OF COLON SURGERY - METASTASES

Liver

- 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. Initial evaluation should include assessment of family history for HNPCC, FAP, or other less common germline mutations associated with colorectal cancer.

PRINCIPLES OF SYSTEMIC THERAPY

- Identify the primary site of tumor when treatment naïve
- Anti-EGFR therapy is contraindicated in the setting of right sided primary tumors in treatment naïve patients
- The presence of microsatellite instability (MSI-H) status regardless if due to somatic or germline mutation may benefit from immune checkpoint inhibition
- 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
  - Consider 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
  - Consider 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* mutation indicates anti-EGFR resistance
- 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

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
  - All patients with dMMR undergoing adjuvant therapy should receive a fluoropyrimidine in combination with oxaliplatin
- 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

SUGGESTED READINGS

Abdalla, E., Vauthey, J. N., Ellis, L., Ellis, V., Pollock, R., Broglio, K., . . . Curley, S. (2004). Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Annals of Surgery, 239*(6), 818-827. https://doi.org/10.1097/01.sla.0000128305.90650.71

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

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

Amado, R., Wolf, M., Peeters, M., Van Cutsem, E., Siena, S., Freeman, D., . . . Chang, D. (2008). Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *Journal of Clinical Oncology, 26*(10), 1626-1634. https://doi.org/10.1200/JCO.2007.14.7116

André, T., Boni, C., Mounedji-Boudiaf, L., Navarro, M., Tabernero, J., Hickish, T., . . . Tabah-Fisch, I. (2004). Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *The New England Journal of Medicine, 350*(23), 2343-2351. https://doi.org/10.1056/NEJMoa032709

André, T., Boni, C., Navarro, M., Tabernero, J., Hickish, T., Topham, C., . . . de Gramont, A. (2009). Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *Journal of Clinical Oncology, 27*(19), 3109-3116. https://doi.org/10.1200/JCO.2008.20.6771

André, T., Shiu, K., Kim, T., Jensen, B., Jensen, L., Punt, C., . . . Diaz., L. (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*(Suppl 18), LBA4. https://doi.org/10.1200/JCO.2020.38.18_suppl.LBA4

Bertelsen, C., Neuenschwander,, A. U., Jansen, J. E., Wilhelmsen, M., Kirkegaard-Klitbo, A., Tenma, J. R., . . . Gogenur, I. (2015). Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: A retrospective, population-based study. *The Lancet Oncology, 16*(2), 161-168. https://doi.org/10.1016/S1470-2045(14)71168-4

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

Chang, G., Kaiser, A., Mills, S., Rafferty, J., & Buie, W. (2012). Practice parameters for the management of colon cancer. *Diseases of the Colon & Rectum, 55*(8), 831-843. https://doi.org/10.1097/DCR.0b013e3182567e13

Chang, G., Rodriguez-Bigas, M., Skibber, J., Moyer, V. (2007). Lymph node evaluation and survival after curative resection of colon cancer: Systematic review. *Journal of the National Cancer Institute, 99*(6), 433-441. Retrieved from http://search.proquest.com/docview/19984164/

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. *JAMA, 302*(21), 2338-2344. https://doi.org/10.1001/jama.2009.1755

Clinical Outcomes of Surgical Therapy Study Group. (2004). A comparison of laparoscopically assisted and open colectomy for colon cancer. *The New England Journal of Medicine*, *2004*(350), 2050-2059. https://doi.org/10.1056/NEJMoa032651

Continued on next page

SUGGESTED READINGS - continued

Colon Cancer Laparoscopic or Open Resection Study Group. (2009). Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *The Lancet Oncology, 10*(1), 44-52. https://doi.org/10.1016/S1470-2045(08)70310-3

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

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

Douillard, J. Y., Siena, S., Cassidy, J., Tabernero, J., Burkes, R., Barugel, M., . . . Gansert, J. (2010). Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: The PRIME study. *Journal of Clinical Oncology, 28*(31), 4697-4705. https://doi.org/10.1200/JCO.2009.27.4860

Drilon, A., Laetsch, T. W., Kummar, S., Dubios, S. G., Lassen, U. N., Demetri, G. D., . . . Hyman, D. M. (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

Falcone, A., Cremolini, C., Antoniotti, C., Lonardi, S., Ronzoni, M., Zaniboni, A., . . . Loupakis, F. (2015). FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as initial treatment for metastatic colorectal cancer (TRIBE study): Updated survival results and final molecular subgroups analyses. *Annals of Oncology, 26*(Suppl 6), vi1. https://doi.org/10.1093/annonc/mdv335.02

Flejou, J. F., André, T., Chibaudel, B., Scriva, A., Hickish, T., Tabernero, J., . . . Gramont, A. D. (2013). Effect of adding oxaliplatin to adjuvant 5-fluorouracil/leucovorin (5FU/LV) in patients with defective mismatch repair (dMMR) colon cancer stage II and III included in the MOSIAC study. [Abstract]. *Journal of Clinical Oncology, 31*(Suppl 15), 3524. https://doi:10.1200/jco.2013.31.15_suppl.3524

Folprecht, G., Seymour, M., Saltz, L., Douillard, J. Y., Hecker, H., Stephens, R., . . . Kohne, C. H. (2008). Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: Combined analysis of 2,691 patients in randomized controlled trials. *Journal of Clinical Oncology, 26*(9), 1443-1451. https://doi.org/10.1200/JCO.2007.14.0509

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

Grothey, A., Sobrero, A., Shields, A., Yoshino, T., Paul, J., Taieb, J., . . . Iveson, T. (2018). Duration of adjuvant chemotherapy for stage III colon cancer. *The New England Journal of Medicine, 378*(13), 1177-1188. https://doi.org/10.1056/NEJMoa1713709

Haggitt, R., Glotzbach, R., Soffer, E., & Wruble, L. (1985). Prognostic factors in colorectal carcinomas arising in adenomas: Implications for lesions removed by endoscopic polypectomy. *Gastroenterology, 89*(2), 328-336. https://doi.org/10.1016/0016-5085(85)90333-6

Continued on next page

SUGGESTED READINGS - continued

Haller, D., Tabernero, J., Maroun, J., de Braud, F., Price, T., Van Cutsem, E., . . . Schmoll, H. (2009). First efficacy findings from a randomized phase 1II trial of capecitabine plus oxaliplatin versus bolus 5-FU/LV for stage III colon cancer (NO16968/XELOXA study). *European Journal of Cancer Supplements, 7*(3), 4. https://doi.org/10.1016/S1359-6349(09)72033-6

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

Hassan, C., Zullo, A., Risio, M., Rossini, F. P., & Morini, S. (2005). Histologic risk factors and clinical outcome in colorectal malignant polyp: a pooled-data analysis. *Diseases of the Colon & Rectum, 48(*8), 1588-1596. https://doi.org/10.1007/s10350-005-0063-3

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

Hendriks, J., Romijn, S., Van Putte, B., Eyskens, E., Vermorken, J., Van Marck, E., & Van Schil, P. E. (2001). Long-term results of surgical resection of lung metastases. *Acta Chirurgica Belgica, 101*(6), 267-272. Retrieved from https://www.tandfonline.com/loi/tacb20

Hurwitz, H., Fehrenbacher, L., Novotny, W., Cartwright, T., Hainsworth, J., Heim, W., . . . Kabbinavar, F. (2004). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *The New England Journal of Medicine, 350*(23), 2335-2342. https://doi.org/10.1056/NEJMoa032691

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

Irshad, K., Ahmad, F., Morin, J., & Mulder, D. (2001). Pulmonary metastases from colorectal cancer: 25 years of experience. Canadian Journal of Surgery, 44(3), 217-221. Retrieved from http://canjsurg.ca/wp-content/uploads/2014/03/44-3-217.pdf

Kikuchi, R., Takano, M., Takagi, K., Fujimoto, N., Nozaki, R., Fujiyoshi, T., & Uchida, Y. (1995). Management of early invasive colorectal cancer. *Diseases of the Colon & Rectum, 38*(12), 1286-1295. https://doi.org/10.1007/BF02049154

Kopetz, S., Grothey, A., Yaeger, R., Van Cutsem, E. , Desai, J., Yoshino, T., . . . Tabernero, J. (2019). Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. The *New England Journal of Medicine, 381*(17), 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). J*ournal of Clinical Oncology, 35*(Suppl 4S), 520. https://doi.org/10.1200/JCO.2017.35.4_suppl.520

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. T*he 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

Maughan, T., Adams, R., Smith, C., Seymour, M., Wilson, R., & Meade, A. (2010). Oxaliplatin and fluoropyrimidine chemotherapy plus or minus cetuximab: The effect of infusional 5-FU or capecitabine on the outcomes of the MRC COIN trial in advanced colorectal cancer (ACRC). In American Society of Clinical Oncology 2010 Gastrointestinal Cancers Symposium, Orlando, FL.

Continued on next page

SUGGESTED READINGS - continued

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

Meric-Bernstam, F., Hurwitz, H., Raghav, K. P. S., McWilliams, R. R., Fakih, M., VanderWalde, A., . . . Hainsworth, J. (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

Meyerhardt, J., Mangu, P., Flynn, P., Korde, L., Loprinzi, C., Minsky, B., . . . Benson III, A. (2013). Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *Journal of Clinical Oncology, 31*(35), 4465-4470. https://doi.org/10.1200/JCO.2013.50.7442

Lim, S., Feig, B., Wang, H., Hunt, K., Rodriguez-Bigas, M., Skibber, J., . . . Chang, G. (2008). Sentinel lymph node evaluation does not improve staging accuracy in colon cancer. *Annals of Surgical Oncology, 15*(1), 46-51. https://doi.org/10.1245/s10434-007-9629-8

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, 37*(35), 3401-3411. https://doi.org/10.1200/JCO.19.01340

National Comprehensive Cancer Network. (2022). *Colon Cancer* (NCCN Guideline Version 1.2022). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

Nelson, H., Petrelli, N., Carlin, A., Couture, J., Fleshman, J., Guillem, J., . . . Sargent, D. (2001). Guidelines 2000 for colon and rectal cancer surgery. *Journal of the National Cancer Institute, 93*(8), 583-596. https://doi.org/10.1093/jnci/93.8.583

Nordlinger, B., Quilichini, M. A., Parc, R., Hannoun, L., Delva, E., & Huguet, C. (1987). Surgical resection of liver metastases from colo-rectal cancers. *International Surgery, 72*(2), 70-72. Retrieved from http://search.proquest.com/docview/77615926/

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

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. J., 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

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

Continued on next page

SUGGESTED READINGS - continued

Peeters, M., Price, T., & Hotko, Y. (2010, January). Randomized phase III study of panitumumab (pmab) with FOLFIRI versus FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer (mCRC): Patient-reported outcomes. *In Program and Abstracts of the 2010 ASCO Gastrointestinal Cancers Symposium,* Orlando, FL.

Popat, S., Hubner, R., & Houlston, R. (2005). Systematic review of microsatellite instability and colorectal cancer prognosis. *Journal of Clinical Oncology*, *23*(3), 609-618. https://doi.org/10.1200/JCO.2005.01.086

Primrose, J. N., Falk, S., Finch-Jones, M., Valle, J. W., Sherlock, D., Hornbuckle, J., . . . Bridgewater, J.A. (2013) A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild-type patients with operable metastases from colorectal cancer: The new EPOC study. [Abstract]. *Journal of Clinical Oncology, 31*(Suppl 15), 3504. https://doi:10.1200/jco.2013.31.15_suppl.3504

Primrose, J., Perera, R., Gray, A., Rose, P., Fuller, A., Corkhill, A., . . . Mant, D. (2014). Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: The FACS randomized clinical trial. *JAMA, 311*(3), 263-270. https://doi.org/10.1001/jama.2013.285718

Regnard, J. F., Grunenwald, D., Spaggiari, L., Girard, P., Elias, D., Ducreux, M., . . . Levasseur, P. (1998). Surgical treatment of hepatic and pulmonary metastases from colorectal cancers. *The Annals of Thoracic Surgery, 66*(1), 214-218. https://doi.org/10.1016/S0003-4975(98)00269-0

Rena, O., Casadio, C., Viano, F., Cristofori, R., Ruffini, E., Filosso, P., & Maggi, G. (2002). Pulmonary resection for metastases from colorectal cancer: Factors influencing prognosis. Twenty-year experience. *European Journal of Cardio-Thoracic Surgery, 21*(5), 906-912. https://doi.org/10.1016/S1010-7940(02)00088-X

Renfro, L., Shah, M., Allegra, C., Andre, T., De Gramont, A., Sinicrope, F., . . . Sargent, D. (2015). Time-dependent patterns of recurrence and death in resected colon cancer (CC): Pooled analysis of 12,223 patients from modern trials in the ACCENT database containing oxaliplatin. *Journal Of Clinical Oncology, 33*(Suppl 15), 3593. https://doi.org/10.1200/jco.2015.33.15_suppl.3593

Ribic, C., Sargent, D., Moore, M., Thibodeau, S., French, A., Goldberg, R., . . . Gallinger, S. (2003). Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *The New England Journal of Medicine, 349*(3), 247-257. https://doi.org/10.1056/NEJMoa022289

Rosati, G., Ambrosini, G., Barni, S., Andreoni, B., Corradini, G., Luchena, G., . . . Fossati, R. (2016). A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. *Annals of Oncology, 27*(2), 274-280. https://doi.org/10.1093/annonc/mdv541

Sagar, J. (2011). Colorectal stents for the management of malignant colonic obstructions. *Cochrane Database of Systematic Reviews*, *11*, CD007378. https://doi.org/10.1002/14651858.CD007378.pub2.

Sakamoto, T., Tsubota, N., Iwanaga, K., Yuki, T., Matsuoka, H., & Yoshimura, M. (2001). Pulmonary resection for metastases from colorectal cancer. *Chest, 119*(4), 1069-1072. https://doi.org/10.1378/chest.119.4.1069

Sammour, T., Malakorn, S., Thampy, R., Kaur, H., Bednarski, B. K., Messick, C. A., . . . You, Y. N. (2020). Selective central vascular ligation (D3 lymphadenectomy) in patients undergoing minimally invasive complete mesocolic excision for colon cancer: Optimizing the risk-benefit equation. *Colorectal Disease, 22*(1), 53-61. https://doi.org/10.1111/codi.14794

Sargent, D., Sobrero, A., Grothey, A., O'Connell, M., Buyse, M., Andre, T., . . . de Gramont, A. (2009). Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. *Journal of Clinical Oncology, 27*(6), 872-877. https://doi.org/10.1200/JCO.2008.19.5362

Sargent, D. J., Marsoni, S., Thibodeau, S., Labianca, R., Hamilton, S., Torri, V., . . . Gallinger, S. (2008). Confirmation of deficient mismatch repair (dMMR) as a predictive marker for lack of benefit from 5-FU based chemotherapy in stage II and III colon cancer (CC): A pooled molecular reanalysis of randomized chemotherapy trials. *Journal of Clinical Oncology, 26*(Suppl 15), 4008. https://doi.org/10.1200/jco.2008.26.15_suppl.4008

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SUGGESTED READINGS - continued

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

Shaukat, A., Kaltenbach, T., Dominitz, J. A., Robertson, D. J., Anderson, J. C., Cruise, M., . . . Rex, D. K. (2020). Endoscopic recognition and management strategies for malignant colorectal polyps: Recommendations of the US Multi-Society Task Force on colorectal cancer. *Gastroenterology, 159*(5), 1916-1934. https://doi.org/10.1053/j.gastro.2020.08.050

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

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

Tanaka, S., Kashida, H., Saito, Y., Yahagi, N., Yamano, H., Saito, S., . . . Tajiri, H. (2020). Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Digestive Endoscopy, 32*(2), 219-239. https://doi.org/10.1111/den.13545

Twelves, C. (2006). Xeloda® in Adjuvant Colon Cancer Therapy (X-ACT) trial: Overview of efficacy, safety, and cost-effectiveness. *Clinical Colorectal Cancer*, *6*(4), 278-287. 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. (2008). 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

Van Cutsem, E., Twelves, C., Cassidy, J., Allman, D., Bajetta, E., Boyer, M., . . . Harper, P. (2001). Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. *Journal of Clinical Oncology, 19*(21), 4097-4106. https://doi.org/10.1200/JCO.2001.19.21.4097

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

West, N., Hohenberger, W., Weber, K., Perrakis, A., Finan, P., & Quirke, P. (2009). Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *Journal of Clinical Oncology, 28*(2), 272-278. https://doi.org/10.1200/JCO.2009.24.1448

Wille-Jørgensen, P., Syk, I., Smedh, K., Laurberg, S., Nielsen, D. T., Petersen, S. H., . . . Sørensen, H. T. (2018). Effect of more vs less frequent follow-up testing on overall and colorectal cancer-specific mortality in patients with stage II or III colorectal cancer: The COLOFOL randomized clinical trial. *JAMA, 319*(20), 2095-2103. https://doi.org/10.1001/jama.2018.5623

Winawer, S., Zauber, A., Ho, M., O'Brien, M., Gottlieb, L., Sternberg, S., . . . Stewart, E. (1993). Prevention of colorectal cancer by colonoscopic polypectomy. *The New England Journal of Medicine, 329*(27), 1977-1981. https://doi.org/10.1056/NEJM199312303292701

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