THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

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.*

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.

PRESENTATION[1]

Advanced adenoma with high grade dysplasia, villous architecture greater than 25% or size greater than or equal to 10 mm (carcinoma *in situ*) → Pathology[2] and colonoscopy review

- Completely removed → Repeat colonoscopy within 12 months
- Transected or residual adenoma → Endoscopically removable?
  - Yes → Endoscopic polyectomy → Repeat colonoscopy within 12 months
  - No → Colon resection, see Principles of Surgery, Page 8

Adenoma with invasive carcinoma[2]

- Pedunculated
  - Single specimen, completely removed, no unfavorable histology[3] → Observation, see Page 7
  - Fragmented specimen, incomplete removal, or unfavorable characteristics[3] → • CEA • CT of chest/abdomen/pelvis (with and without contrast) or contrast-enhanced MRI of abdomen/pelvis → Is primary tumor resectable?
    - Yes → Colon resection, see Principles of Surgery, Page 8
    - No → • Diverting colostomy or stent if obstructing • Consider systemic chemotherapy → Is primary tumor resectable?
      - Yes → Colon resection, see Principles of Surgery, Page 8
      - No → Individualized management
- Sessile
  - Single EMR specimen[4], completely removed, no unfavorable histology[3] → Observation, see Page 7
  - Fragmented specimen, incomplete removal, or unfavorable characteristics[3] → • CEA • CT of chest/abdomen/pelvis (with and without contrast) or contrast-enhanced MRI of abdomen/pelvis → Is primary tumor resectable?
    - Yes → Colon resection, see Principles of Surgery, Page 8
    - No → • Diverting colostomy or stent if obstructing • Consider systemic chemotherapy → Is primary tumor resectable?
      - Yes → Colon resection, see Principles of Surgery, Page 8
      - No → Individualized management

Adenocarcinoma of the colon[2] → • CEA • CT of chest/abdomen/pelvis (with and without contrast) or contrast-enhanced MRI of abdomen/pelvis → Is primary tumor resectable?
- Yes → Colon resection, see Principles of Surgery, Page 8
- No → • Diverting colostomy or stent if obstructing • Consider systemic chemotherapy → Is primary tumor resectable?
  - Yes → Colon resection, see Principles of Surgery, Page 8
  - No → Individualized management

PRIMARY TREATMENT

Colon resection, see Principles of Surgery, Page 8

- Stage I → Surveillance, see Page 7
- Stage II
  - Low risk[5]:
    - Observation, see Page 7
    - Clinical trial
  - High risk[6,7]:
    - MSI analysis - patients with high levels of microsatellite instability (MSI-H) may derive no benefit from single agent 5-fluorouracil based therapy but may derive benefit from adjuvant FOLFOX (see references)
    - Consider adjuvant chemotherapy[8,9]
- Stage III
  - MSI analysis - patients with high levels of microsatellite instability (MSI-H) may derive no benefit from single agent 5-fluorouracil based therapy but may derive benefit from adjuvant FOLFOX (see references)
  - Consider adjuvant chemotherapy[7,8,9]
  - Consider clinical trial
  - Surveillance, see Page 7

EMR = endoscopic mucosal resection with submucosal elevation

[1] Lifestyle risk assessment: See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

[2] Consider MD Anderson approved GI biomarkers (Click here)

[3] Unfavorable pathology characteristics: • Poor differentiation • Lymphatic, vascular or perineural invasion • Transection of carcinoma or resection margin less than 3 mm • Sessile configuration of lesion

[4] 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 EMR followed by observation. Careful histopathologic review is prerequisite for this approach.

[5] Low-risk defined by absence of high-risk features (see footnote 6) or high levels of microsatellite instability (MSI-H)

[6] High-risk features for Stage II colon cancer: • Poor differentiation • Inadequate nodal sampling (less than 12 nodes) • Lymphatic, vascular or perineural invasion • T4 disease (invasion of serosa or other organ)

[7] In cases of tumor perforation, combination chemoradiation therapy to the tumor bed may be considered

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

[9] Consider MSI analysis because patient with MSI-H may not derive benefit from single agent 5-fluorouracil based therapy

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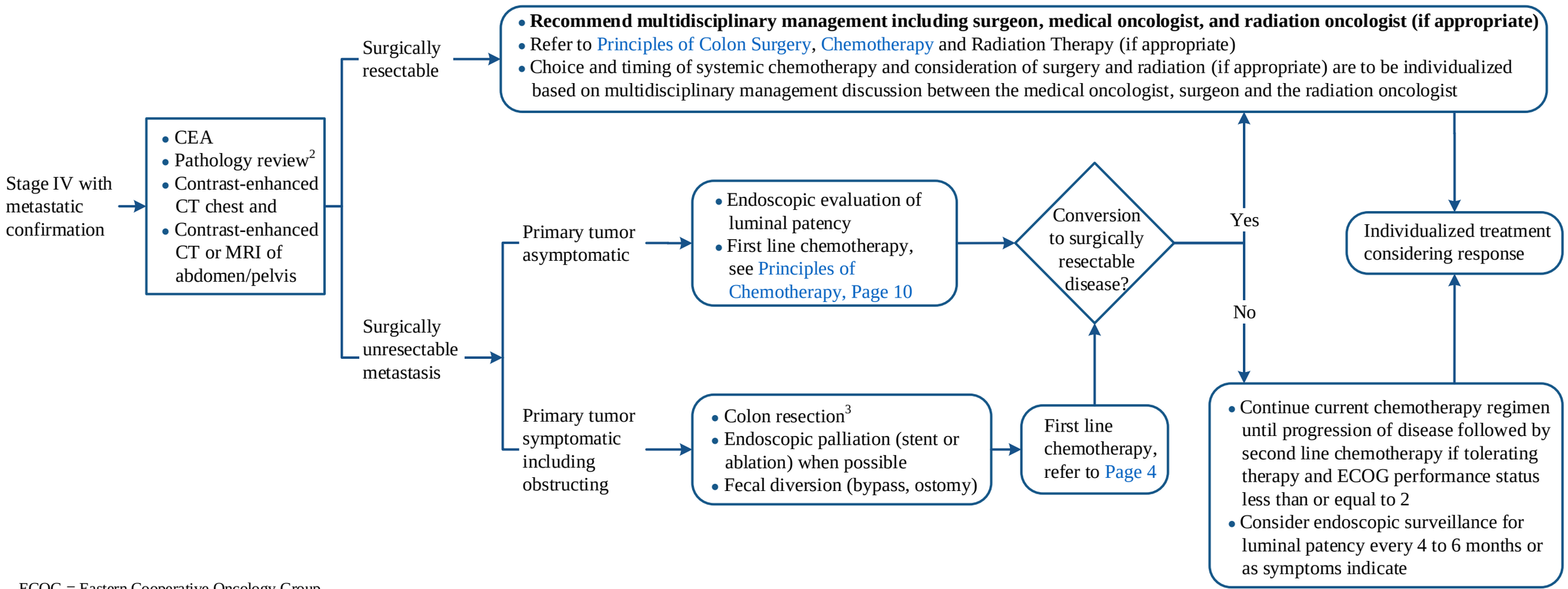
Colon Cancer

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.

PRESENTATION[1] **PRIMARY TREATMENT**



ECOG = Eastern Cooperative Oncology Group

[1]Lifestyle risk assessment: 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*, and MSI status. Refer to MD Anderson approved GI biomarkers (Click here)

[3]If the potential for resectability of metastases remains, extent of resection should be curative, rather than palliative

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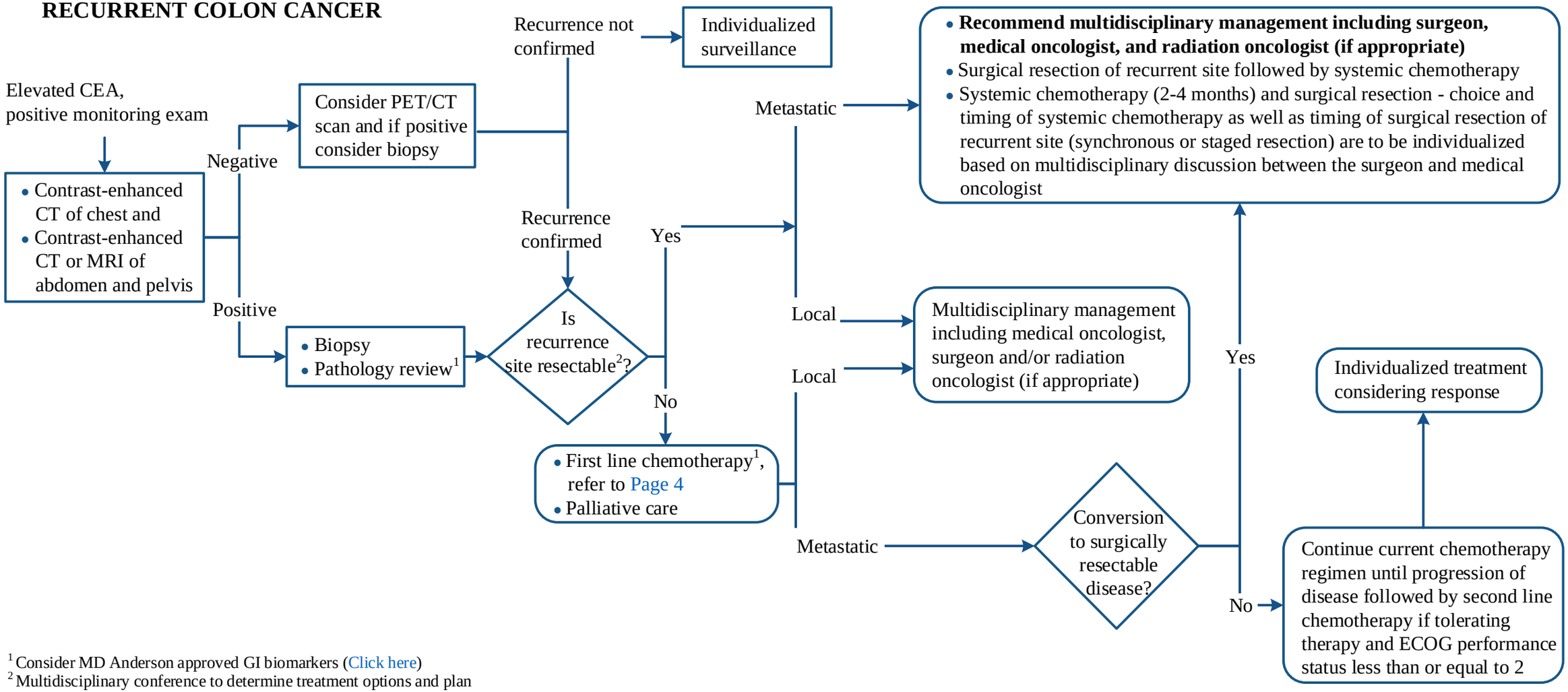
EVALUATION AND MANAGEMENT OF SUSPECTED OR DOCUMENTED RECURRENT COLON CANCER

PRIMARY TREATMENT



[1] Consider MD Anderson approved GI biomarkers (Click here)
[2] Multidisciplinary conference to determine treatment options and plan

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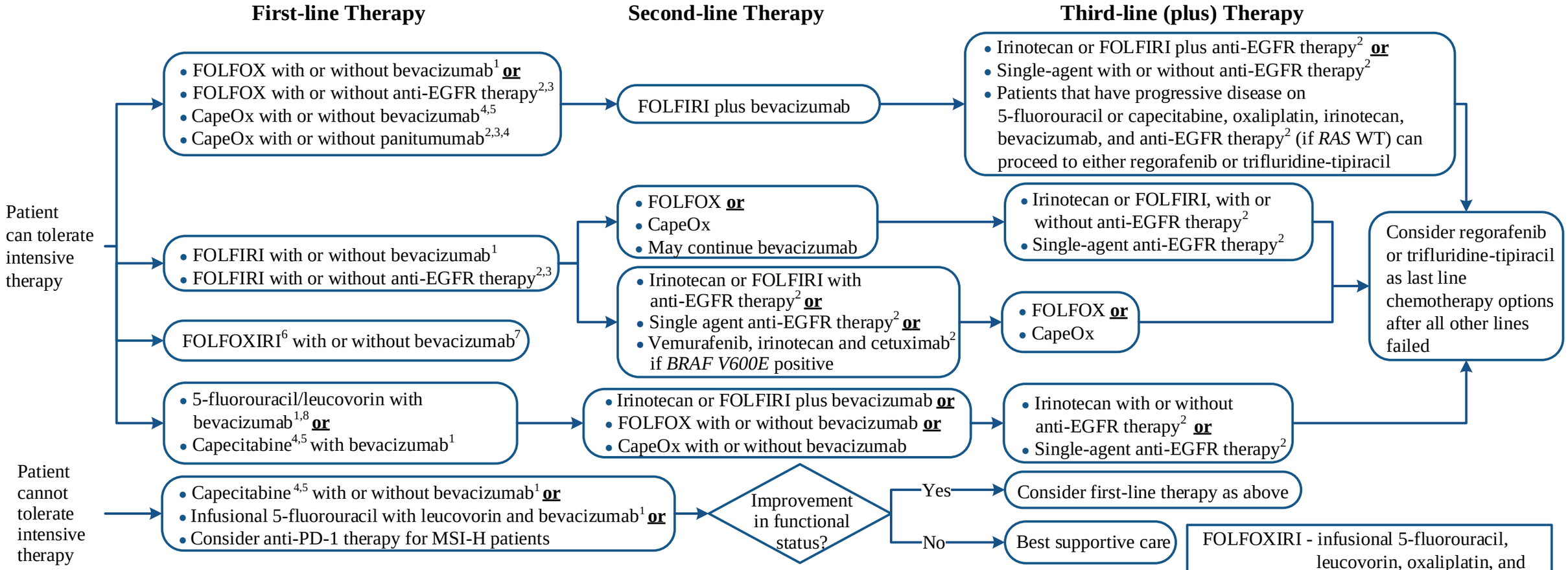
CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE



[1] Bevacizumab used in combination with IV 5-fluorouracil-based chemotherapy is approved for first-line therapy. 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 30-50 mL/minute will require dose reduction. All patients with a creatinine clearance of less than 30 mL/minute will not be eligible to receive capecitabine.
[5] If the patient is taking warfarin or phenytoin while on capecitabine, the patient must be monitored regularly due to potential drug-drug interaction
[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. Once progression, consider: • Clinical trial • *RAS* WT: irinotecan or FOLFIRI plus cetuximab or panitumumab • Regorafenib • Trifluridine-tipiracil
[8] A treatment option for patients not able to tolerate oxaliplatin or irinotecan

FOLFOXIRI - infusional 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan
FOLFOX - infusional 5-fluorouracil, leucovorin and oxaliplatin
FOLFIRI - infusional 5-fluorouracil, leucovorin and irinotecan
CapeOx - capecitabine[4,5] and oxaliplatin

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

CapeOx (XELOX)
- Oxaliplatin 100-130 mg/m^2 IV on Day 1
- Capecitabine 850-1000 mg/m^2 PO twice daily for 14 days
- With or without bevacizumab 7.5 mg/kg IV
- Repeat every 3 weeks
- With or without panitumumab* 9 mg/kg IV 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 2400 mg/m^2 over 46 hours IV continuous infusion
- With or without bevacizumab 5 mg/kg IV
- Repeat every 2 weeks
- With or without panitumumab* 6mg/kg IV every 2 weeks or cetuximab*

mFOLFIRI
- Irinotecan 180 mg/m^2 IV over 90 minutes on Day 1
- Leucovorin 400 mg/m^2 IV over 2 hours during irinotecan on Day 1
- 5-fluorouracil 400 mg/m^2 IV bolus, then 5-fluorouracil 2400 mg/m^2 over 46 hours IV continuous infusion
- With or without bevacizumab 5 mg/kg IV
- Repeat every 2 weeks
- With or without cetuximab* 400 mg/m^2 IV for the first infusion followed by 250 mg/m^2 weekly or 500 mg/m^2 IV every 2 weeks or panitumumab* 6 mg/kg IV 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 one to two months, then dose escalate as appropriate.)

Trifluridine-tipiracil
- Trifluridine-tipiracil 35 mg/m^{2}of trifluridine component (max 80 mg) PO twice per day on Days 1-5 and 8-12 of a 28 day cycle

5-Fluorouracil, Leucovorin or Capecitabine
- Capecitabine 1000 mg/m^2 PO twice daily for 14 days, every 3 weeks
- With or without bevacizumab 7.5 mg/kg IV every 3 weeks

or
- Leucovorin 400 mg/m^2 IV over 2 hours on Day 1
- 5-fluorouracil 400 mg/m^2 IV on Day 1, then 2400 mg/m^2 over 46 hours IV continuous infusion
- With or without bevacizumab 5 mg/kg IV
- Repeat 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

* A *RAS* mutation indicates resistance to cetuximab and panitumumab. (Refer to Principles of Chemotherapy on Page 10)

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.

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

Anti-EGFR therapy* plus Irinotecan

- Cetuximab* 400 mg/m^2 IV for the first infusion, then 250 mg/m^2 IV weekly
- Irinotecan 350 mg/m^2 IV every 3 weeks or 180 mg/m^2 IV every 2 weeks

or

- Cetuximab* 500 mg/m^2 IV every 2 weeks or panitumumab* 6mg/kg IV every 2 weeks
- With or without irinotecan 180 mg/m^2 IV every 2 weeks

Panitumumab*

- Panitumumab 6 mg/kg IV every 2 weeks
- Panitumumab 9 mg/kg IV every 3 weeks

FOLFOXIRI**

Consider dosing as FOLFIRINOX for toxicity

- Oxaliplatin 85 mg/m^2 IV Day 1
- Irinotecan 180 mg/m^2 IV Day 1
- 5-fluorouracil 2400 mg/m^2 IV continuous infusion over 46 hours
- Repeat every 2 weeks

***BRAF* Mutation**

- Vemurafenib 960 mg PO twice daily, irinotecan 180 mg/m^2 IV every 2 weeks, and anti-EGFR therapy with cetuximab* 500 mg/m^2 IV every 2 weeks

Microsatellite instability (MSI-H)

- Nivolumab 240 mg IV every 2 weeks
- Pembrolizumab 200 mg IV every 3 weeks

* A *RAS* mutation indicates resistance to cetuximab and panitumumab. (Refer to Principles of Chemotherapy on Page 10)
** Consider regimen only in patients with adequate ECOG. Check blood counts regularly. May be best used for neoadjuvant therapy.

Colon Cancer

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.

OBSERVATION/SURVEILLANCE[1,2]

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 3-6 months for 2 years, then every 6 months up to 3 years • CEA: every 3-6 months for 2 years, then every 6 months up to 3 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 3-4 months for 3 years, then every 6 months for 2 years • CEA: every 3-6 months for 2-3 years, then every 6 months up to a total of 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	• 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 3-6 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 • 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.

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 (less that 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. 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

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 intact.
- 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 laparoscopic colectomy as for open colectomy.
- Surgeon with experience performing laparoscopic colorectal operations.
- Tumors should be preoperatively localized by cross-sectional imaging or endoscopic localization with India ink 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).

Sentinel Node Biopsy

- The use of other than H&E staining is considered investigational.

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

- Involved adjacent organs should be resected en bloc.
- The competencies of resection should be evaluated and noted in the operative report.

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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 with or without intra-peritoneal hyperthermic chemotherapy may be considered in selected patients.

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 CHEMOTHERAPY

- 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.
- 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 CHEMOTHERAPY

- Capecitabine is equivalent to bolus 5-fluorouracil/leucovorin in Stage III patients.
- FOLFOX is superior for Stage III patients and is reasonable to be considered for high risk Stage II patients. It is not indicated for low risk Stage II patients.
  - In low risk (T1-3N1) patients, 3 months of CapeOx is non-inferior to 6 months of FOLFOX.
  - For all other patients, non-inferiority of 3 months versus 6 months for oxaliplatin based therapy has NOT been proven.
- Capecitabine may be considered in combination with oxaliplatin.
- Use of irinotecan-based regimen, such as FOLFIRI, is not recommended in the adjuvant setting.
- Patients with high levels of microsatellite instability (MSI-H) may derive no benefit from single agent 5-fluorouracil or capecitabine but may derive benefit from adjuvant FOLFOX.

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