Colon Cancer

PRESENTATION

Stage IV with metastatic confirmation

- CEA
- Pathology review
- Contrast-enhanced CT chest
- Contrast-enhanced CT or MRI of abdomen/pelvis

PRIMARY TREATMENT

Surgically resectable

- Recommend multidisciplinary management including surgeon, medical oncologist, and radiation oncologist (if appropriate)
- Refer to Principles of Colon Surgery, Chemotherapy and Radiation Therapy (if appropriate)
- Choice and timing of systemic chemotherapy and consideration of surgery and radiation (if appropriate) are to be individualized based on multidisciplinary management discussion between the medical oncologist, surgeon, and the radiation oncologist

Primary tumor asymptomatic

- Endoscopic evaluation of luminal patency
- First line chemotherapy, see Principles of Chemotherapy, Page 10

Conversion to surgically resectable disease?

Yes

Individualized treatment considering response

No

Primary tumor symptomatic including obstructing

- Colon resection
- Endoscopic palliation (stent or ablation) when possible
- Fecal diversion (bypass, ostomy)

First line chemotherapy, refer to Page 4

Surgically unresectable metastasis

- Continue current chemotherapy regimen until progression of disease followed by second line chemotherapy if tolerating therapy and ECOG performance status less than or equal to 2
- Consider endoscopic surveillance for luminal patency every 4 to 6 months or as symptoms indicate

ECOG = Eastern Cooperative Oncology Group

1Lifestyle risk assessment: See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
2Confirm biomarker studies include expanded RAS, BRAF V600E, and MSI status. Refer to MD Anderson approved GI biomarkers (Click here)
3If the potential for resectability of metastases remains, extent of resection should be curative, rather than palliative

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.
EVALUATION AND MANAGEMENT OF SUSPECTED OR DOCUMENTED RECURRENT COLON CANCER

- Elevated CEA, positive monitoring exam

  Consider PET/CT scan and if positive consider biopsy

  - Contrast-enhanced CT of chest and abdomen and pelvis
  - Contrast-enhanced CT or MRI of abdomen and pelvis

  Biopsy, Pathology review

  Is recurrence site resectable?

  - Yes
    - Multidisciplinary management including medical oncologist, surgeon and/or radiation oncologist (if appropriate)
  - No
    - First line chemotherapy, refer to Page 4
    - Palliative care

Recurrence confirmed

Individualized surveillance

Recurrence not confirmed

Metastatic

Local

Yes

Individualized treatment considering response

Conversion to surgically resectable disease?

- Yes
  - Continue current chemotherapy regimen until progression of disease followed by second line chemotherapy if tolerating therapy and ECOG performance status less than or equal to 2
- No

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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.
Colon Cancer

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

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

First-line Therapy

- FOLFOX with or without bevacizumab\(^1\) or FOLFIRI with or without anti-EGFR therapy\(^2,3\)
- CapeOx with or without bevacizumab\(^4,5\)
- CapeOx with or without panitumumab\(^2,3,4\)
- FOLFOXIRI\(^6\) with or without bevacizumab\(^1\)
- 5-fluorouracil/leucovorin with bevacizumab\(^1,6\) or CapeOx with bevacizumab\(^1\)
- CapeOx\(^4,5\) with or without bevacizumab\(^1\)
- Infusional 5-fluorouracil with leucovorin and bevacizumab\(^1\) or Consider anti-PD-1 therapy for MSI-H patients

Second-line Therapy

- FOLFIRI plus bevacizumab
- FOLFOX or CapeOx
- May continue bevacizumab
- Irinotecan or FOLFIRI with anti-EGFR therapy\(^7\) or Vemurafenib, irinotecan and cetuximab\(^2\) if BRAF V600E positive
- Irinotecan or FOLFIRI plus bevacizumab or FOLFOX with or without bevacizumab

Third-line (plus) Therapy

- Irinotecan or FOLFIRI, with or without anti-EGFR therapy\(^2\)
- Patients that have progressive disease on 5-fluorouracil or capecitabine, oxaliplatin, irinotecan, bevacizumab, and anti-EGFR therapy\(^2\) (if RAS WT) can proceed to either regorafenib or trifluridine-tipiracil
- Irinotecan with or without anti-EGFR therapy\(^2\)
- Single-agent anti-EGFR therapy\(^2\)

- Consider regorafenib or trifluridine-tipiracil as last line chemotherapy options after all other lines failed

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 capcitabine.

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

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Approved by the Executive Committee of the Medical Staff on 06/26/2018.

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FOLFOXIRI - infusional 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan
FOLFIRI - infusional 5-fluorouracil, leucovorin and oxaliplatin
FOLFOX - infusional 5-fluorouracil, leucovorin and oxaliplatin
CapeOx - capcitabine\(^4,5\) and oxaliplatin
### CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

**CapeOx (XELOX)**
- Oxaliplatin 100-130 mg/m² IV on Day 1
- Capecitabine 850-1000 mg/m² 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/m² IV over 2 hours on Day 1
- Leucovorin 400 mg/m² IV over 2 hours on Day 1
- 5-fluorouracil 400 mg/m² IV bolus on Day 1, then 5-fluorouracil 2400 mg/m² over 46 hours IV continuous infusion
- With or without bevacizumab 5 mg/kg IV
- Repeat every 2 weeks
- With or without panitumumab* 6 mg/kg IV every 2 weeks or cetuximab*

**mFOLFIRI**
- Irinotecan 180 mg/m² IV over 90 minutes on Day 1
- Leucovorin 400 mg/m² IV over 2 hours during irinotecan on Day 1
- 5-fluorouracil 400 mg/m² IV bolus, then 5-fluorouracil 2400 mg/m² over 46 hours IV continuous infusion
- With or without bevacizumab 5 mg/kg IV
- Repeat every 2 weeks
- With or without cetuximab* 400 mg/m² IV for the first infusion followed by 250 mg/m² weekly or 500 mg/m² 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/m² of trifluridine component (max 80 mg) PO twice per day on Days 1-5 and 8-12 of a 28 day cycle

**5-Flourouracil, Leucovorin or Capecitabine**
- Capecitabine 1000 mg/m² PO twice daily for 14 days, every 3 weeks
- With or without bevacizumab 7.5 mg/kg IV every 3 weeks
- Leucovorin 400 mg/m² IV over 2 hours on Day 1
- 5-fluorouracil 400 mg/m² IV on Day 1, then 2400 mg/m² over 46 hours IV continuous infusion
- With or without bevacizumab 5 mg/kg IV
- Repeat every 2 weeks

**Irinotecan**
- Irinotecan 180 mg/m² IV over 90 minutes on Day 1
- Repeat every 2 weeks
- Irinotecan 300-350 mg/m² IV over 90 minutes on Day 1
- Repeat every 3 weeks

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* A RAS mutation indicates resistance to cetuximab and panitumumab. (Refer to Principles of Chemotherapy on Page 10)
CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

Anti-EGFR therapy* plus Irinotecan
- Cetuximab* 400 mg/m² IV for the first infusion, then 250 mg/m² IV weekly
- Irinotecan 350 mg/m² IV every 3 weeks or 180 mg/m² IV every 2 weeks
  or
- Cetuximab* 500 mg/m² IV every 2 weeks or panitumumab* 6mg/kg IV every 2 weeks
- With or without irinotecan 180 mg/m² 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/m² IV Day 1
- Irinotecan 180 mg/m² IV Day 1
- 5-fluorouracil 2400 mg/m² IV continuous infusion over 46 hours
- Repeat every 2 weeks

BRAF Mutation
- Vemurafenib 960 mg PO twice daily, irinotecan 180 mg/m² IV every 2 weeks, and anti-EGFR therapy with cetuximab* 500 mg/m² 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.
OBSERVATION/SURVEILLANCE 1,2

<table>
<thead>
<tr>
<th>Stage I 2,3</th>
<th>Physical exam: every 6-12 months for 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEA: every 6-12 months for 3 years</td>
</tr>
<tr>
<td></td>
<td>CT scan of chest and contrast-enhanced CT of abdomen/pelvis or MRI: every 12 months for 3 years 2</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Stage II (low risk) 4</td>
<td>Physical exam: every 3-6 months for 2 years, then every 6 months up to 3 years</td>
</tr>
<tr>
<td></td>
<td>CEA: every 3-6 months for 2 years, then every 6 months up to 3 years</td>
</tr>
<tr>
<td></td>
<td>CT scan of chest and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for 3 to 5 years 2</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Stage II (high risk) 4 and Stage III</td>
<td>Physical exam: every 3-4 months for 3 years, then every 6 months for 2 years</td>
</tr>
<tr>
<td></td>
<td>CEA: every 3-6 months for 2-3 years, then every 6 months up to a total of 5 years</td>
</tr>
<tr>
<td></td>
<td>CT of chest and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for 5 years 2</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Stage IV-NED</td>
<td>Individualized if on therapy</td>
</tr>
<tr>
<td></td>
<td>Physical exam: every 3-4 months for 2 years, then every 6 months for 3 years</td>
</tr>
<tr>
<td></td>
<td>Refer to GI endoscopy to evaluate patency of lumen every 3-6 months if primary tumor is intact (or sooner if clinically indicated)</td>
</tr>
<tr>
<td></td>
<td>CEA: every 3-4 months for 2 years, then every 6 months for 3 years, then annually</td>
</tr>
<tr>
<td></td>
<td>CT of chest and contrast-enhanced CT or MRI of abdomen/pelvis: every 3-4 months 2</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
</tbody>
</table>

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)).
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.
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.
Colon 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.
SUGGESTED READINGS


Continued on next page

Department of Clinical Effectiveness V11
Approved by the Executive Committee of the Medical Staff on 06/26/2018
SUGGESTED READINGS - continued


SUGGESTED READINGS - continued


SUGGESTED READINGS - continued


Suggested Readings - continued


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


DEVELOPMENT CREDITS

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

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