**EVALUATION**

- Advanced adenoma with high grade dysplasia, villous architecture greater than 25% or size greater than or equal to 10 mm (Carcinoma *in situ*)
  - Pathology1 and colonoscopy review
  - Completely removed → Repeat colonoscopy within 12 months
  - Transected or residual adenoma

- Adenoma with invasive carcinoma1
  - Pedunculated
  - Fragmented specimen, incomplete removal, or unfavorable characteristics2
  - Observation (see page 4)

- Sessile
  - Single specimen, completely removed, no unfavorable histology2
  - Observation (see Page 4)

- Adenocarcinoma of the colon1

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**PRIMARY TREATMENT**

- Endoscopic Polyectomy
  - Yes
  - Endoscopically removable?
    - Yes
      - Observation (see Principles of Surgery, Page 5)
    - No
      - Individualized management
  - No

- Colon resection
  - Is primary tumor resectable?
    - Yes
      - Diverting colostomy or stent if obstructing
      - Consider systemic chemotherapy
    - No
      - Consider adjuvant chemotherapy for 6 months7,8,9

- Surveillance (see page 4)

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2 Unfavorable pathology characteristics:
   - Poor differentiation
   - Lymphatic, vascular or perineural invasion
   - Transection of carcinoma or resection margin less than 3 mm
   - Lymphatic, vascular or perineural invasion

3 EMR: endoscopic mucosal resection with submucosal elevation

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 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 5) or high levels of microsatellite instability (MSI-H).

6 High-risk features for Stage I colon cancer:
   - Poor differentiation
   - Inadequate nodal sampling (less than 12 nodes)
   - 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 (5-FU)/leucovorin or 5-FU/leucovorin/oxaliplatin or capecitabine/oxaliplatin

9 Consider MSI analysis because patients with high levels of microsatellite instability (MSI-H) may derive no benefit from single agent 5-Fluorouracil (5-FU) based therapy but may derive benefit from adjuvant FOLFOX (see references)

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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 HNPCC, FAP, or other less common germline mutations associated with colorectal cancer.

EVALUATION

- Surgically resectable
- Stage IV with Metastatic confirmation
- CEA
- Pathology review
- Contrast-enhanced CT chest and abdomen/pelvis

PRIMARY TREATMENT

- 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, 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.

- Endoscopic evaluation of luminal patency
- First line chemotherapy (See Principles of Chemotherapy - Page 7)

Conversion to surgically resectable disease?

- Yes
  - Individualized treatment considering response

- No
  - 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

Primary tumor asymptomatic

- Primary tumor symptomatic including obstructing

Colon resection¹
- Endoscopic palliation (stent or ablation) when possible
- Fecal diversion (bypass, ostomy)

First line chemotherapy, refer to page 8

1 If the potential for resectability of metastases remains, extent of resection should be curative, rather than palliative.

2 ECOG = Eastern Cooperative Oncology Group
Elevated CEA
Positive monitoring exam

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

Consider PET/CT scan and if positive consider biopsy

Recurrence not confirmed

Individualized surveillance

Recurrence confirmed

Multidisciplinary management including medical oncologist, surgeon, and/or radiation oncologist (if appropriate)

- First line chemotherapy, refer to page 8
- Palliative care

Is recurrence resectable\(^1\)?

Yes

Conversion to surgically resectable disease\(^2\)

No

Individualized treatment considering response

Metastatic

Yes

Local

Multidisciplinary management including medical oncologist, surgeon, and/or radiation oncologist (if appropriate)

No

Local

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

Metastatic

Positive

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\(^1\) Multidisciplinary conference to determine treatment options and plan.

Colon Cancer

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**OBSERVATION/SURVEILLANCE**

| Stage II (Low Risk)       | Physical exam: every 3 - 6 months for 2 years, then every 6 months for 3 years |
|                          | CEA: every 3-6 months for 2 years, then every 6 months for 3 years |
|                          | CT scan of chest and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for 3 to 5 years |
|                          | Colonoscopy: at one year then (if normal) after 3 years and then once every 5 years. |

| Stage II (High Risk) and Stage III | Physical exam: every 3-4 months for 3 years, then every 6 months for 2 years |
|                                    | CEA: every 3 months for 3 years, then every 6 months for 2 years |
|                                    | CT of chest and contrast-enhanced CT or MRI of abdomen/pelvis: every 12 months for 5 years |
|                                    | Colonoscopy: at one year then after 3 years (if normal) then once every 5 years. |

| 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. |
|              | 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. |

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1. NOTE: Surveillance imaging with PET/CT alone is not recommended as primary imaging modality.
2. 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).
3. 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))
4. NED: No evidence of disease
PRINCIPLES OF COLON SURGERY

Extent of bowel resection
- A minimum of 5 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.

Lymphadenectomy
- A complete lymphadenectomy is essential for the treatment and prognosis of colon cancer. Lymphadenectomy should be complete, radical 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 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.
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.
PRINCIPLES OF CHEMOTHERAPY

- Capecitabine was shown to be at least equivalent to adjuvant 5-FU/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-FU/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.
- 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.
- Any RAS mutation indicates resistance to cetuximab and panitumumab. (See references for chemotherapy on page 12)

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.
- 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-FU or capecitabine but may derive benefit from adjuvant FOLFOX. (See references on page 12)
Colon Cancer

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

First – Line Therapy
- FOLFOX with or without bevacizumab or
- FOLOFO with or without anti-EGFR therapy or
- CapeOx with or without bevacizumab or
- CapeOx with or without anti-EGFR therapy or

Second – Line Therapy
- FOLFIRI plus bevacizumab

Patient can tolerate intensive therapy

Third – Line (plus) Therapy
- Irinotecan, FOLFIRI, with or without anti-EGFR therapy or
- Single-agent anti-EGFR therapy or

Patient cannot tolerate intensive therapy

- Capecitabine or Infusional 5-FU with leucovorin and bevacizumab

Improvement in functional status?

Yes
- Consider first-line therapy as above

No
- Best supportive care

FOLFOXIRI - infusional 5-FU, leucovorin, oxaliplatin, and irinotecan
FOLFOX - infusional 5-FU, oxaliplatin, and irinotecan
FOLFIRI - infusional 5-FU, leucovorin, and irinotecan
CapeOx - capecitabine and oxaliplatin

1 Bevacizumab used in combination with IV 5-FU-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 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.

4 If the patient is taking warfarin or phenytion while on capecitabine, the patient must be monitored regularly due to potential drug-drug interaction.

5 Best suited for surgically resectable patients. Once progresses, consider:
- Clinical Trial
- RAS WT: irinotecan or FOLFIRI plus cetuximab or panitumumab
- Regorafenib

6 A treatment option for patients not able to tolerate oxalipatin or irinotecan.

7 Consider regimen only in patients with adequate ECOG. Check blood counts regularly. May be best used for neoadjuvant therapy.
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### 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 (9mg/kg 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 (6mg/kg every 2 weeks) or cetuximab

#### mFOLFIRI
- Irinotecan 180 mg/m² 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 2,400 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 in first infusion followed by 250 mg/m² weekly or 500 mg/m² IV every 2 weeks) or panitumumab (6mg/kg every 2 weeks)

#### 5-Fluorouracil, 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)
- Or
- Leucovorin 400 mg/m² IV over 2 hours on Day 1
- 5-Fluorouracil 400 mg/m² 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.
- Or
- Irinotecan 300-350 mg/m² IV over 90 minutes on Day 1. Repeat every 3 weeks.

#### Anti-EGFR therapy¹ plus Irinotecan
- Cetuximab1 400 mg/m² first infusion, then 250 mg/m² weekly
- Irinotecan 350 mg/m² IV every 3 weeks or 180 mg/m² IV every 2 weeks.
- Or
- Cetuximab1 500 mg/m² every 2 weeks or panitumumab 6mg/kg every 2 weeks
- With or without irinotecan 180 mg/m² IV every 2 weeks.

#### Panitumumab1
- Panitumumab1 6 mg/kg IV every 2 weeks.
- Panitumumab1 9 mg/kg IV every 3 weeks.

#### Regorafenib
- Regorafenib 160 mg po daily for 21 days then 1 week off, one cycle is every 28 days.
- (Recommend to start at 120 mg po daily for 21 days then 1 week off for the first one – two months, then dose escalate as appropriate)

#### FOLFOXIRI²
- 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.

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¹ A RAS mutation indicates resistance to cetuximab and panitumumab. (See references for principles of chemotherapy on page 12)
² Consider regimen only in patients with adequate ECOG. Check blood counts regularly. May be best used for neoadjuvant therapy.
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SUGGESTED READINGS


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SUGGESTED READINGS


Lenz et al. (2014). CALGB/SWOG 80405: Phase III trial of FOLFIRI or mFOLFOX6 with bevacizumab or cetuximab for patients with expanded RAS analyses in untreated metastatic adenocarcinoma of the colon or rectum; ESMO.


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SUGGESTED READINGS

Primrose, J. N. (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 # 3504


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DEVELOPMENT CREDITS

This practice consensus 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 medical, radiation and surgical oncologists.

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