Colon Cancer: Screening, Staging, and Surgical Management

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Epidemiology

Epidemiology

- The American Cancer Society estimates there will be over 100,000 new cases of colon cancer in 2022
  - Colorectal cancer (CRC) is the most frequently diagnosed cancer in persons aged 65 to 74
- Higher incidence in industrialized countries
  - 3rd leading cause of death in US
  - Lifetime risk of developing CRC in US is 4.3%

Epidemiology

- Incidence and mortality of CRC have declined in the last 3 decades
  - More effective screening
  - Improved treatment modalities
- Declining incidence seen mostly in older adults
  - Masks the rising incidence seen in younger adults since the mid 1990s
  - Incidence in adults aged 40 to 49 years has increased by almost 15% from 2000-2002 to 2014-2016

Risk Factors for Colorectal Cancer

Major Risk Factors

- Personal or family history of colon cancer or adenomas
- Genetic predisposition
  - Familial Adenomatous Polyposis (FAP)
  - Lynch Syndrome
- Inflammatory bowel disease
  - Ulcerative colitis
  - Crohn's disease

Risk Factors for Colorectal Cancer

Minor Risk Factors

- History of abdominal radiation therapy
- African American Race
- Ashkenazi Jewish descent
- Obesity
- Alcohol and Tobacco consumption
- Lack of regular activity
- Diet low in fruit and vegetables
- Type 2 diabetes

Screening

Prevention

- Prevention is better than cure, especially for colon cancer
- Screening rates: ~ 67% in the US
- Colonoscopy with polypectomy is the most common used modality
- Over 20% cancers are metastatic at time of diagnosis
- Screening rates higher in patients with:
  - Insurance
  - Higher income
  - Higher education levels

USPS Taskforce Screening Recommendations

Population	Recommendation	Grade
Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years.	A
Adults aged 45 to 49 years	The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years.	B
Adults aged 76 to 85 years	The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small.	C

Multi-Society Task Force Ranking of Current Colorectal Cancer Screening Tests

- Tier 1
  - Colonoscopy every 10 years
  - Annual fecal immunochemical test
- Tier 2
  - CT colonography every 5 years
  - FIT–fecal DNA every 3 years
  - Flexible sigmoidoscopy every 5-10 years
- Tier 3
  - Capsule colonoscopy every 5 years

MSTF Recommendations for Persons With High-Risk Family Histories

- Family Colon Cancer Syndrome X
  - Colonoscopy every 3-5 years beginning 10 years before earliest age of diagnosis
- CRC or advanced adenoma in a single first-degree relative age ≥ 60 years
  - Begin screening at age 40 years

MSTF Recommendations for Persons With High-Risk Family Histories

- CRC or advanced adenoma in two first-degree relatives diagnosed at any age OR CRC or advanced adenoma in a single first-degree relative at age < 60 years
  - Colonoscopy every 5 years beginning 10 years before the age at diagnosis or age 40, whichever is earlier
- FAP
  - Annual colonoscopy starting at 12 years
- Lynch Syndrome
  - Every 1-2 years starting at 22-25 years

US Multisociety Task Force Recs – Surveillance

- Personal History of Cancer
  - 3-6 months after surgery in case of obstructive cancer
  - 1 year, then 3 years, then every 5 years
- Small rectal HP polyps
  - Every 10 years
- 1-2 sub-centimeter tubular adenomas
  - 5-10 years

US Multisociety Task Force Recs – Surveillance

- Patients with 3-10 adenomas, or 1 adenoma >1 cm, or any adenoma with villous features or HGD
  - 3 years
- Patients with >10 adenomas on a single examination
  - Less than 3 years
- Patients with sessile adenomas removed piecemeal
  - 2-6 months

Initial Evaluation and Staging

Key Concepts

- **Total colonic evaluation** prior to surgical intervention to exclude synchronous tumors that may alter surgical plan
- **Evaluation for metastatic disease by imaging** prior to surgical intervention, as it may alter treatment decisions
- **Preoperative carcinoembryonic antigen (CEA) level** should be obtained, as changes in CEA may indicate tumor recurrence
- **Tumor location** should be identified preoperatively
- **Tumor grade**, **lymphovascular invasion**, margin status, and immunohistochemical assessment of **mismatch repair proteins** have prognostic significance and should be routinely reported

Clinical Presentation

- Three common ways:
  - Asymptomatic lesion found through screening
    - 30% of CRC are found on screening with absence of symptoms
  - Vague signs/symptoms leading to investigation
    - Change in bowel habits, fatigue, weight loss, anemia, bleeding
  - Emergently with perforation or obstruction
- 20-25% of CRC is metastatic at diagnosis
  - Liver, lungs, peritoneal surfaces

Preoperative Evaluation

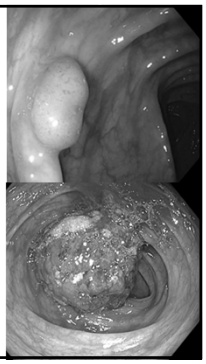
- Complete history and physical
  - Duration and severity of symptoms
    - Obstructive?
- Family history
  - Colon cancer
  - Inherited syndromes
- Other medical comorbidities
  - Assess readiness for surgery

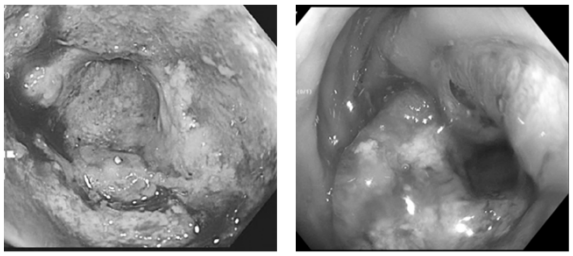
Coexisting Medical Conditions

- Identify factors that may affect ability to undergo surgery or treatment
  - Preoperative optimization
- EKG for older patients and those with cardiac risk factors
  - h/o MI, angina, valvular disease, arrhythmias, heart failure
- Pulmonary factors: COPD, obesity, OSA, pulmonary HTN, recent URI, smoking
  - Consider PFTs and baseline ABG

Colonoscopy

- Evaluation of the entire colon ***essential***
  - Identify synchronous cancers or polyps
    - 5% rate of synchronous cancer
    - May change surgical approach
  - Localize the lesion
    - Tattoo
- CT colonography, contrast enema or intraoperative colonoscopy can be performed if unable to undergo completion colonoscopy



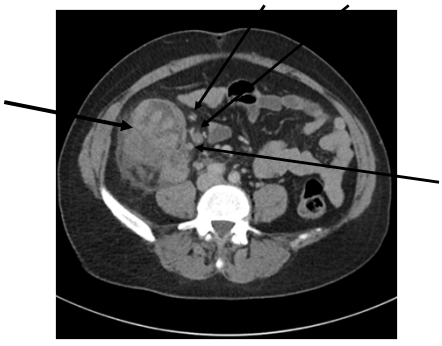


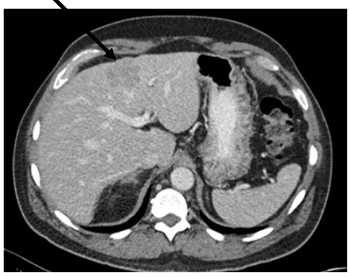
Labs

- Preoperative CBC, BMP, type and screen
  - LFTs not required – not sensitive for liver metastasis
  - Nutritional panels for those at risk
- CEA
  - Glycoprotein involved in intracellular adhesion produces by goblet and columnar cells
  - Overexpressed in a variety of cancers including CRC
  - Can be elevated in benign disease – heavy smokers, pancreatitis, IBD
  - Elevated level after resection may be first sign of recurrence or metastatic disease
  - Preoperative level >5ng/mL has worse prognosis stage for stage

Radiographic Evaluation

- CT Chest/abdomen/pelvis with PO and IV contrast
  - Cost effective initial imaging
  - Provides information regarding lymph nodes, liver and lung metastasis
  - Helpful for OR planning
    - Involves local structures? → plan for en bloc resections
- MRI liver superior to CT for small indeterminate lesions, if needed
- PET/CT
  - Usually not used as first line staging
  - Best use is in recurrent disease

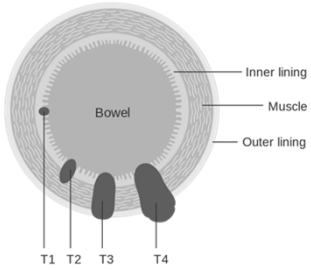




Staging

Staging of Colon Cancer

- Based on TNM staging system
  - Tumor depth
  - Nodal involvement
  - Distant metastasis



American Joint Committee on Cancer Staging

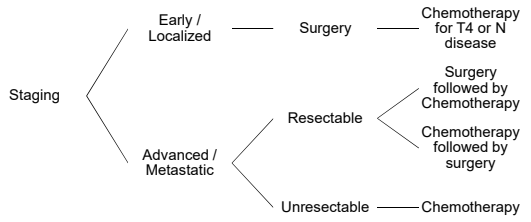
AJCC stage	TNM stage	TNM stage criteria
Stage 0	Tis N0 M0	Tis: Tumor confined to mucosa; cancer-*in-situ*
Stage I	T1 N0 M0	T1: Tumor invades submucosa
	T2 N0 M0	T2: Tumor invades muscularis propria
Stage II-A	T3 N0 M0	T3: Tumor invades subserosa or beyond (without other organs involved)
Stage II-B	T4a N0 M0	T4a: Tumor perforates the visceral peritoneum
Stage II-C	T4b N0 M0	T4b: Tumor invades adjacent organs
Stage III-A	•T1-2 N1 M0 or •T1, N2a, M0	•N1: Tumor cells in 1 to 3 regional lymph nodes •N2a: Tumor cells in 4 to 6 regional lymph nodes
Stage III-B	•T3-4a, N1 M0 or •T2-3, N2a, M0 or •T1-2 N2b M0	•N1: Tumor cells in 1 to 3 regional lymph nodes •N2a: Tumor cells in 4 to 6 regional lymph nodes •N2b: Tumor cells in 7 or more regional lymph nodes
Stage III-C	•T4a N2a M0 or •T3-4a N2b M0 or •T4b N1-2, M0	•N2a: Tumor cells in 4 to 6 regional lymph nodes •N2b: Tumor cells in 7 or more regional lymph nodes •N1-2: Tumor cells in at least one regional lymph node
Stage IVa	any T, any N, M1a	M1a: Metastasis to 1 other part of the body beyond the colon, rectum or regional lymph nodes
Stage IVb	any T, any N, M1b	M1b: Metastasis to more than 1 other part of the body beyond the colon, rectum or regional lymph nodes
Stage IVc	any T, any N, M1c	M1c: Metastasis to the peritoneal surface

Completeness of Resection

- R0—complete tumor resection with negative margins
- R1—incomplete tumor resection with microscopic involvement of the margin
- R2—incomplete tumor resection with gross residual disease that was not resected

Management of Colon Cancer

Simplified Treatment Overview – Colon Cancer



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General Management Concepts

- Treatment modalities:
  - Local disease – surgery
  - Lymphatic metastasis – surgery
  - Distant metastasis – chemotherapy
  - Targeted metastatic disease – surgery, liver-directed therapy, etc.
- Endoscopic stenting of an obstructing colon cancer is an effective bridge to surgery **within 72 hours**
- First-line therapy for patients with metastatic colon cancer and an asymptomatic primary tumor is chemotherapy

Surgical Management Concepts

- Principles of an oncologic resection:
  - Total mesocolic resection
    - Dissection of the visceral fascia from the parietal fascia of the RP with central ligation of the primary vasculature
      - Increased lymph node harvest
      - Longer vascular ligation
      - Increased resection of extranodal tumor deposits
      - Increased upstaging
  - Ligation of the primary vessel at its origin
  - Wide mesenteric resection with >12 lymph nodes
  - At least a 5 cm resection margin

Surgical Management Concepts

- There is no difference in cancer-related outcomes for open and laparoscopic resections
- Anastomotic assessment for left-sided anastomosis is associated with a decreased leak rate
- Surgical resection is the most effective therapy for patients who present with obstructing colon cancers
- Perforated cancers should be treated with an oncologic resection

Lap vs. Open – Colon Cancer

- COST Trial – non-inferiority trial of 862 patients
  - Laparoscopic group: shorter LOS and fewer days of intravenous and oral analgesics
  - No difference in intraoperative complications, 30-day morbidity, or hospital readmission rates
  - No difference in the 3-year recurrence or overall survival rates

Lap vs. Open – Colon Cancer

- MRC CLASICC Trial – 413 patients randomized 2:1 into laparoscopic and open arms
  - No statistical difference in LOS, ROBF, rate of curative resection, complications, and quality of life measures
  - 3 year disease free survival and overall survival similar
  - Conversion from laparoscopy to open for patients with colon cancer was associated with a worse overall survival and disease-free survival

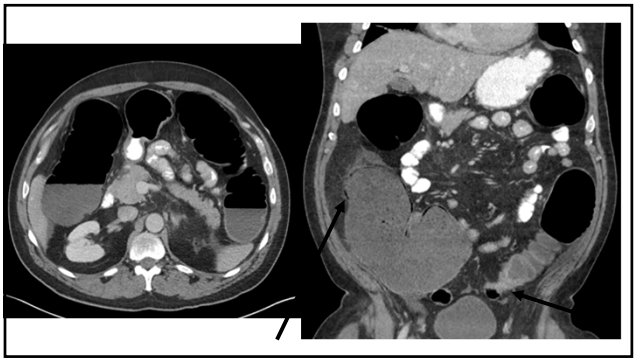
Lap vs. Open – Colon Cancer

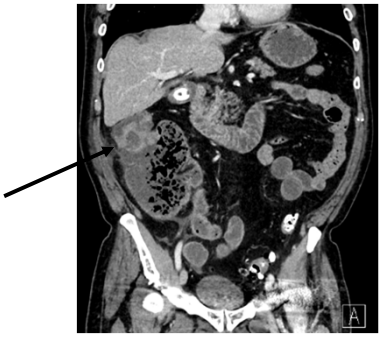
- COLOR Trial – prospective, randomized, non-inferiority trial 0f 1076 patients
  - No difference in lymph node harvest or overall morbidity
  - Operative times, conversions, and complications were lowest in the high-volume centers and were highest in the low-volume centers

Surgical Management of Specific Subpopulations

Obstructing Colon Cancers

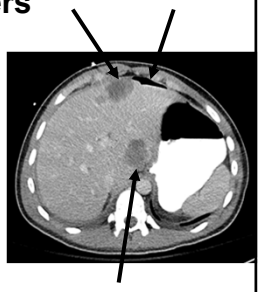
- Worse outcomes for patient presenting with obstruction
  - Often T3 or T4 at diagnosis
- No well-established guidelines
  - Proximal diversion → doesn't treat primary
  - Resection of primary → significant morbidity, high stoma rate
    - 60% morbidity: wound complications, deep organ space infections, respiratory complications, and intensive care unit admissions most common
  - Stent → appealing for bridging, but risk of perforation, migration and bleeding
- Surgical approach depends on patient condition





Perforated Colon Cancers

- Challenging to address sepsis and oncologic principles
- Acute septic injury has the greatest impact on short-term outcomes, which in turn impacts the long-term outcome of the cancer
- Overall, the worst of the worst:
  - Much higher operative mortality and higher 5-year local recurrence and peritoneal carcinomatosis rates
  - More likely to get a stoma
  - More likely to have metastatic disease on presentation
- If possible, perform oncologic based resection



Management of Metastatic Disease

Metastatic Colon Cancer

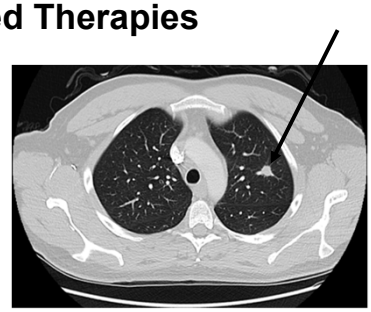
- Symptomatic → resect or divert
  - Bleeding or obstruction
- Asymptomatic → chemotherapy
  - Rationale: patients will succumb from metastatic disease before primary disease becomes symptomatic
  - Benefits:
    - Down-staging of primary disease
    - Minimize progression of symptoms of primary disease
    - Improve overall survival

Liver Directed Therapies

- Ablation
- Stereotactic Body Radiation Therapy (SBRT)
- Selective Internal Radiation Therapy (SIRT)
  - Yttrium-90 (y-90) – radioactive tagged resin or microspheres that are lodged in the arterioles feeding liver metastases
- Transarterial Chemoembolization (TACE)
  - Occlusion of selected hepatic artery branches, allows for maximum exposure of liver-directed chemotherapy to the ischemic environment formed within the targeted metastases
- Hepatic artery infusion pump
- Hepatectomy

Lung Directed Therapies

- Ablation
- Cryotherapy
- Stereotactic Body Radiation Therapy (SBRT)
- Lung metastectomy
  - Lobectomy
  - Wedge resection



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Colon Cancer Treatment

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Goals of Therapy

- Surgical resection is the only curative treatment for locoregional colon cancer
- Disease recurrence is thought to arise from clinically occult micrometastases that are present at the time of surgery
- Goal of postoperative (adjuvant) therapy is to eradicate these micrometastases, thereby increasing the cure rate

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Timing of Adjuvant Therapy

- Once recovered from surgery
- Most trials recommend starting within 6-8 weeks of surgery
- Worse overall and event-free survival with a delay beyond 8 weeks
- One study suggesting worse overall survival with a delay beyond 12 weeks
- Ideal – aim for within 8 weeks of surgery

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Stage of colon cancer for which adjuvant therapy is indicated

- Stage I – no indication
- Stage III – node positive, adjuvant therapy is definitely indicated if patient performance status and co-morbidities allow
  - an approximately 30 percent relative reduction in the risk of disease recurrence and a 22 to 32 percent relative reduction in mortality
  - Some new data regarding how much therapy is needed for stage III
- Stage II – less straight forward

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Fit Patients with Stage III Colon Cancer

- Oxaliplatin-based regimens recommended for fit patients with stage III disease
- Less data for patients >70 years
- Fluoropyrimidines (5FU and capecitabine) alone are ineffective in patients with **deficient mismatch repair deficiency** or **microsatellite instability**

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FOLFOX every 14 days

Drug	Dose and route	Given on days
Oxaliplatin	85 mg/m^2 IV	Day 1
Leucovorin	400 mg/m^2 IV	Day 1
Fluorouracil (FU)	400 mg/m^2 IV bolus	Day 1
FU	2400 mg/m^2 IV	Day 1 over 46 hours

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Common side effects of FOLFOX

- Febrile neutropenia (1.8%)
- Grade 3 or 4 diarrhea (10.8%)
- Peripheral sensory neuropathy developed in 92% of patients receiving FOLFOX - due to oxaliplatin
- Neuropathy severe (grade 3) in 13 % and generally reversible but not always so

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CAPOX (XELOX)

- Capecitabine (oral fluoropyrimidine) in combination with oxaliplatin every 21 days may be more toxic than FOLFOX

Drug	Dose and route	Given on days
Oxaliplatin	130 mg/m^2 IV	Day 1
Capecitabine	850 mg/m^2 per dose, by mouth	Evening of day 1 to morning of day 15

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Optimal Duration of Adjuvant Therapy

- 6 months has been the standard based on MOSAIC and NSABP C-07 trials
- **International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration** (6 separate randomized trials of 6 versus 3 months of adjuvant oxaliplatin-based therapy)

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Conclusions from IDEA Analysis

- Noninferiority of 3 months vs 6 months of adjuvant chemotherapy for all stage III colon cancers was not confirmed in terms of 5-year overall survival
- However, there was an absolute 0.4% difference in OS for all stages
- 82.4% for 3 months vs 82.8% for 6 months
- A subset analysis suggested that CAPOX was better than FOLFOX for 3 months

Stage II Colon Cancer

- Less certain benefit for adjuvant therapy
- QUAZAR (5FU/LV =/- levamisole) – trend towards benefit
- Adjuvant Colon Cancer End Points (ACCENT) collaboration – included 9 trials & showed an absolute benefit in overall survival of 5% which was not statistically significant
- Numerous meta-analyses have shown no statistically significant survival benefit from adjuvant therapy for stage II disease
- No benefit from addition of oxaliplatin in MSS stage II colon cancer

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High-Risk Stage II Colon Cancer – features associated with worse prognosis

- T4 primary
- high-grade/poorly differentiated histology (including signet ring and mucinous tumors)
- lymphovascular invasion (LVI)
- perineural invasion
- bowel obstruction or perforation
- close, indeterminate, or positive margins;
- inadequately sampled lymph nodes (less than 13 in the surgical specimen)
- a high preoperative serum carcinoembryonic antigen (CEA) level
- occult nodal micrometastases, as detected by molecular or immunohistochemical methods

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Data is controversial for high-risk stage II

- In the MOSAIC trial FOLFOX versus FU/LV), there was a trend toward improved DFS with FOLFOX (82 v 75%) in subgroup of stage II patients with high-risk tumors (clinical T4, poorly differentiated, perforation, obstruction, or <10 nodes in the surgical specimen)
- Several other studies negative but retrospective studies showed possible benefit
- Most guidelines (ASCO, NCCN) suggest considering adjuvant chemo for high-risk stage II
- EXCEPTION: MSI high tumors
  - Low risk stage II – no chemo, 5FU potentially harmful
  - High risk stage II – need oxaliplatin with 5FU for benefit

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Other Adjunctive Therapies

- Aspirin – inhibits cyclooxygenase-2
- Data for benefit for aspirin is based on observational studies
- Nurses Health Study: aspirin users had a significant 29% lower cancer-specific mortality and a 21% lower overall mortality than nonusers
- Aspirin for Dukes C and High-Risk Dukes B Colorectal Cancers study [ASCOLT] – results still pending
- Phase III Alliance 80702 trial of addition of celecoxib vs placebo for 3 years to adjuvant FOLFOX
  - No significant improvement in disease-free survival with celecoxib

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Vitamin D

- Low vitamin D levels associated with worse prognosis
- In phase III Cancer and Leukemia Group B (CALGB) Alliance 89803 trial comparing adjuvant chemotherapy with weekly fluorouracil/leucovorin with or without irinotecan, those in the highest quintile of predicted vitamin D score had significantly improved overall survival compared with those in the lowest quintile (multivariable adjusted hazard ratio for death 0.55, 95% CI 0.38-0.80)
- Alliance study testing addition of vitamin D to chemotherapy in metastatic patients

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Exercise

- Higher levels of physical activity may reduce CRC-specific and overall mortality
- Three studies found that higher levels of physical activity after diagnosis were associated with a reduced risk of CRC-specific mortality, ranging from 43 to 61%
- Generally we recommend a minimum of 30 mins of moderate activity e.g. walking, 5 days per week

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Chemotherapy for Metastatic Colon Cancer

- Goals of therapy:
  - prolong survival
  - improve symptoms
  - Shrink isolated metastatic disease in liver or lungs to make it resectable
- Median overall survival for patients with metastatic colon cancer is 3 years
- Molecular profile of the tumor may influence prognosis
- Performance status influences choice of therapy

Chemotherapy for Metastatic Colon Cancer

- Molecular profiling and side of tumor (right vs left colon cancer) frequently influences therapy options
- Basic profiling should include:
  - **Mismatch repair proteins** – MLH1, MSH2, MSH6, PMS2 or microsatellite status (deficient proteins in 3.5 to 6.5% of metastatic CRC)
  - **KRAS** (mutations in 45%)
  - **NRAS** (mutations in 5 to 8%)
  - **BRAF V600E** (mutation in 5 to 12% of mCRC and 15 to 25% are also MSI high)
  - **HER-2** (amplification or HER-2 overexpression in 3 to 5%)
  - **TRK fusion** (0.5 to 1%)
- More extensive profiling and calculation of **tumor mutation burden** (high in 5%) is possible

First-Line Options for Metastatic Colon Cancer

- **FOLFIRI** (5FU, LV, irinotecan) + **bevacizumab** (anti-VEGF) or **FOLFOX** + **bevacizumab** may be used for all types of mCRC independent of molecular subtype
  - Response rates 53.6%
  - Median OS 24.5 months
- **FOLFOXIRI** (5FU/LV, oxaliplatin & irinotecan) + **bevacizumab**
  - RR 64.5%
  - Median OS 28.9 months

Cremolini et al, J Clin Oncol. 2020

Agents targeting EGFR

- **Cetuximab** and **panitumumab** target EGFR
- Only effective in **RAS wild type tumors** – pts with KRAS or NRAS mutations do not benefit
- Lack of benefit if concurrent **BRAF V600E mutation**
- Benefit seen in **left sided tumors**
- May be give with **FOLFOX** or **FOLFIRI**

Immunotherapy for Metastatic CRC

- PD-1 inhibitor **pembrolizumab** is approved for first-line therapy of MSI high/dMMR mCRC
- KEYNOTE 177 trial of first-line pembrolizumab compared to chemotherapy showed
  - ORR 44% vs 33%
  - Median PFS 16.5 months vs 8.2 months
  - Better quality of life
- mCRC with **high tumor mutation burden** (≥10 mutations per megabase) may also respond to pembrolizumab

- Molecular profiling may influence therapy options following progression on first- or second-line therapy

BRAF V600E mutated, RAS wild-type mCRC

- Phase III BEACON trial (mCRC after progression on first- or second-line therapy)
- **Cetuximab** plus **encorafenib** with or without **binemetinib** was superior to FOLFIRI plus cetuximab
- Median OS 9.3 vs 5.9 months
- No OS difference with addition of binemetinib to encorafenib and cetuximab

HER-2 Overexpression

- Lapatinib and trastuzumab (HERACLES study)
  - RR 30%, stable disease 44%
- Pertuzumab and trastuzumab (MyPathway study)
  - 26% RR
- Fam-trastuzumab deruxtecan (DESTINY-CRC01 study)
  - RR 45%
  - Median duration of response 7 months
  - Median PFS 6.9 months

TRK Fusion

- **Tropomyosin receptor kinase** (TRK) **fusion-positive** mCRC may respond to **larotrectinib** or **entrectinib** after progression on first and second-line therapy

Systemic therapy to convert unresectable liver metastases to resectable

- 12-33% of patients treated initially **unresectable liver metastases** were converted to **resectable (R0)** after responding to systemic therapy
- Usually use FOLFOX or FOLFIRI
- 5-year survival rate of 30 to 35% seen in this setting

Conclusion

- All stage III and certain high risk stage II colon cancer patients are eligible for adjuvant chemotherapy
- Molecular profiling may influence therapy options for metastatic disease
- Toxicity of therapy needs to be considered
- Personalized therapy has improved prognosis