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MD Anderson Cancer Center
Making Cancer History®

Bottom's Up: An Overview of Colorectal Cancer

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Disclosures

I have relevant relationships with ineligible companies to disclose with the past 24 months.

- Carevive Systems, Inc., Consulting

Learning Objectives

- Describe the incidence and mortality rate of colorectal cancer in the United States.
- Understand the pathophysiology of colorectal cancer.
- Describe non modifiable and modifiable risk factors for colorectal cancer.
- Understand colorectal cancer screening guidelines.
- Describe the common signs and symptoms associated with colorectal cancer.
- Explain the TNM staging for colorectal cancer and explain the impact of stage on prognosis.
- Describe appropriate clinical work up for colon and rectal cancer.
- Understand the treatment for colorectal cancer including common surgical approaches and common chemotherapy regimens.
- Recognize the common side effects of chemotherapy used for colorectal cancer.
- Understand post treatment surveillance guidelines and survivorship care for the colorectal cancer patient.

Case Study

51 y/o F underwent EGD and colonoscopy for work up of post-prandial cramping and increase in bowel frequency. Notable findings include an ulcerated and fungating circumferential mass in the ascending colon, biopsies taken.

An additional small polyp in the rectum was removed via polypectomy.

Pathology

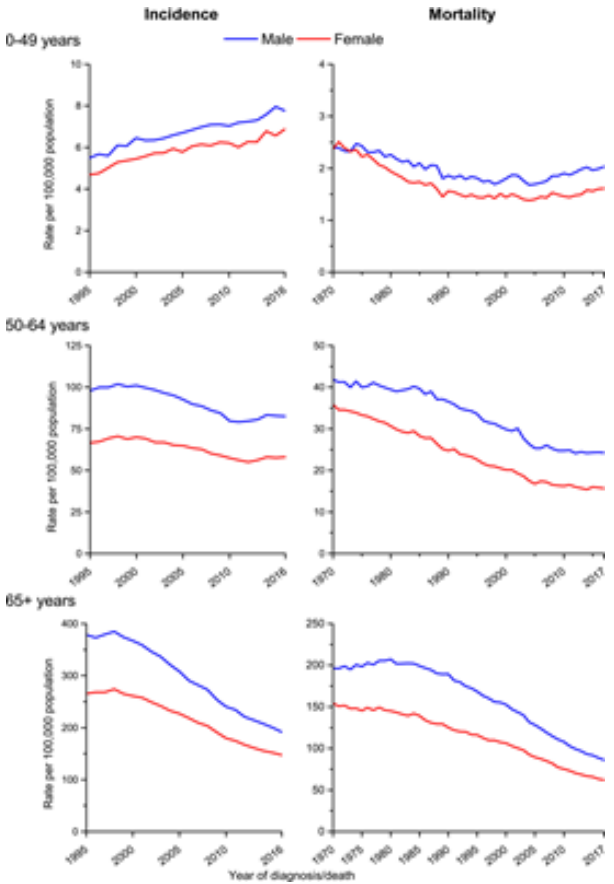
- Ascending colon: moderately differentiated adenocarcinoma arising in a villous adenoma with high grade dysplasia
- Rectum: invasive moderately differentiated adenocarcinoma rising in a tubulovillous adenoma with invasion into the submucosa and negative polypectomy margins measuring <1 cm.

Colorectal cancer is the third most common cancer diagnosed and the third leading cause of cancer death in the US for both men and women.

Epidemiology

- Estimated approximately 151,000 new cases in US in 2022
- Estimated 53,000 deaths in 2022
- Decreasing death rates in the last several decades due to improvements in screening, prevention, and treatment
  - Over 1.5 million colorectal cancer survivors in the US
  - Increasing incidence and death rates of 2% per year from 2012 and 2016 among people younger than 50

Trends in Colorectal Cancer Incidence (1995 to 2016) and Mortality (1970 to 2017) Rates by Age and Sex, United States.



Source: Incidence: NAACCR, 2019; Mortality: NCHS, 2019.

Colon cancer usually arises from adenomatous polyps or flat dysplasia. Majority are carcinomas with 90% adenocarcinomas.

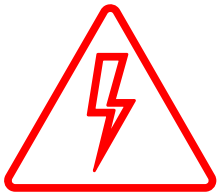
Pathophysiology

90% of all CRC are adenocarcinomas and typically arise from adenomatous polyps

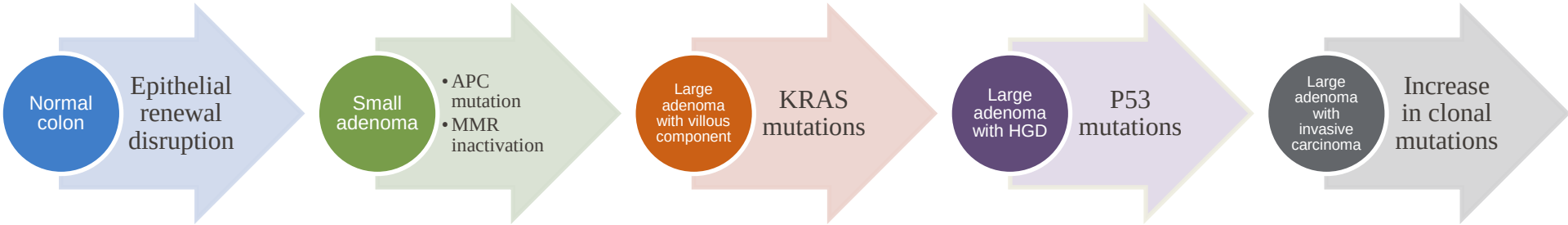
- Tubular Adenoma

- Tubulovillous adenoma

- Villous adenoma



Molecular pathogenesis



Hereditary Syndromes

- Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch Syndrome
- Familial Adenomatous Polyposis (FAP)

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- Ascending colon: **moderately differentiated adenocarcinoma** arising in a **villous adenoma** with high grade dysplasia
- Rectum: invasive **moderately differentiated adenocarcinoma** arising in a **tubulovillous adenoma** with invasion into the submucosa and negative polypectomy margins measuring <1 cm.
- **MMR intact/MSI-stable**

Family history: + uterine cancer (sister), + bile duct cancer (brother)

Risk Factors

Non-modifiable risk factors

- Age >50
- Family history of colorectal cancer
- Personal history of adenomatous polyps
- Inherited syndromes – Familial adenomatous polyposis (FAP), Hereditary nonpolyposis colorectal cancer (HNPCC)
- African American and Ashkenazi Jewish descent
- Inflammatory bowel disease: Ulcerative colitis > Crohn disease

Modifiable risk factors

- Obesity
- Type 2 diabetes mellitus
- Sedentary lifestyle
- Diets high in red and/or processed meat and low in fiber
- Smoking
- Heavy alcohol use

Screening for colorectal cancer in an average-risk adult should begin at age 45.

Colorectal Cancer Screening

- Screening is recommended for **average** risk adults ≥45
- Average Risk Screening:
  - No personal history of CRC, IBD, pre-malignant polyps (adenoma or SSP), high-risk genetic syndrome, or cystic fibrosis
  - No family history of CRC or advanced pre-malignant polyp
- Screening for adults **76-85** is individualized based on life expectancy and risk/benefit of comorbidities
- Not recommended for adults > **85**

Colorectal Cancer Screening

Screening Modalities and Frequency for **Average Risk** Adults

	Screening Modality	Frequency
Visual Examination	Colonoscopy	Every 10 years
	Flexible Sigmoidoscopy	Every 5 years
	CT Colonography (Virtual)	Every 5 years
Stool based tests	Highly sensitive fecal immunochemical test (FIT) or guaiac based (gFOBT)	Yearly
	Multi-targeted stool DNA test	Every 3 years

*Frequency is based upon normal results

.

Colorectal Cancer Screening

Colonoscopy Screening Recommendations and Frequency for **Increased Risk** Adults

Family History:	**Initiation of Screening**	**Frequency**
First degree relative with CRC	Age 40 or 10 years younger than diagnosis	Every 5 years
First degree relative with advanced adenoma	Age 40 or age of onset of adenoma	Every 5 – 10 years
Personal History:		
IBD	8 years after the onset of symptoms	Every 1-3 years
CRC	1 year after diagnosis	Every 3-5 years
Pre-malignant polyps		Varies

High Risk Adults: HNPCC or personal or family history of polyposis syndromes

Case Study

51 y/o F underwent EGD and colonoscopy for work up of post-prandial cramping and increase in bowel frequency.

Notable findings:

- Adenocarcinoma at the ascending colon
- Adenocarcinoma in the rectum s/p polypectomy

MMR intact/MSI-stable

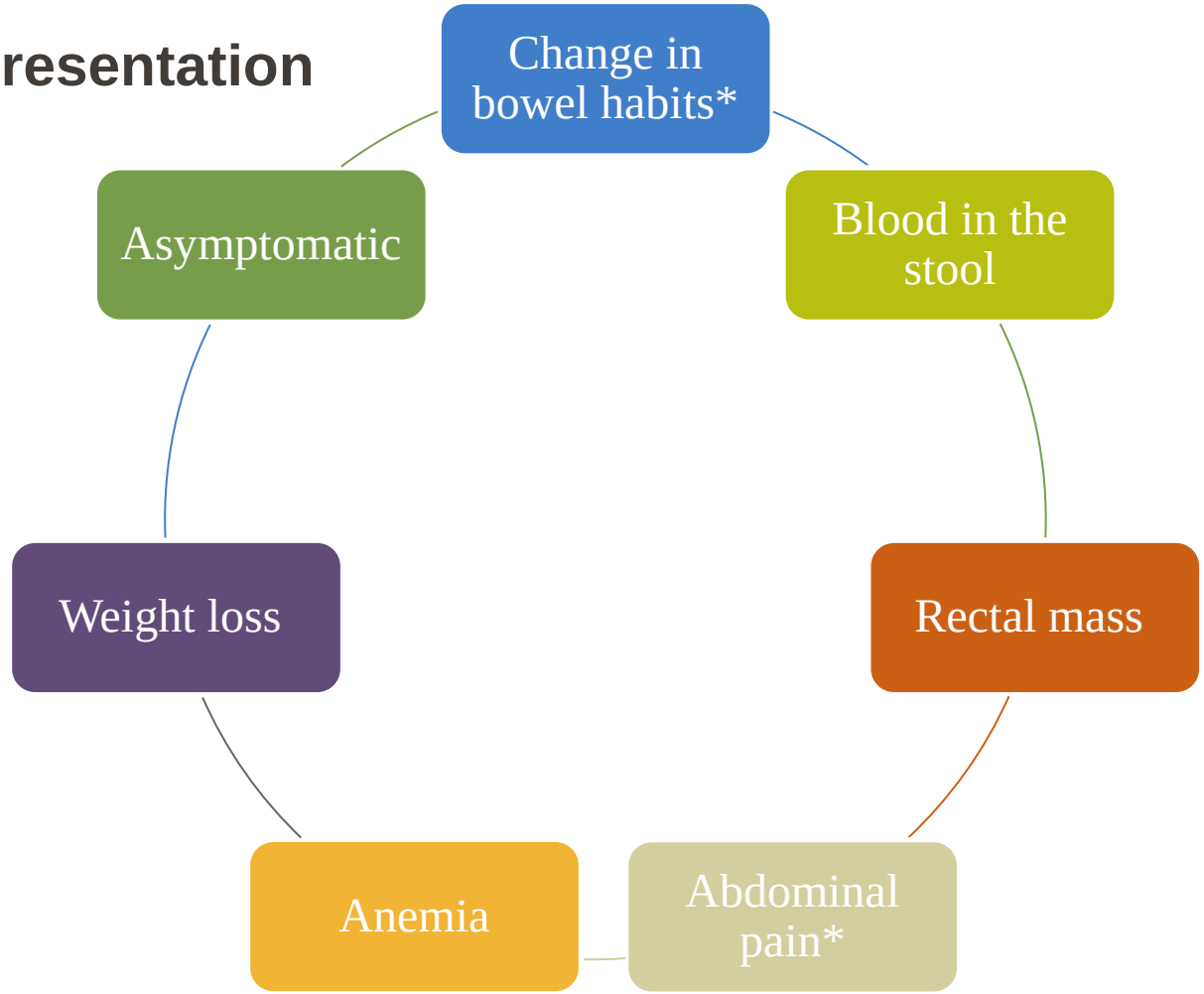
Family history: + uterine cancer (sister), + bile duct cancer (brother)

→Genetic testing completed and **negative for Lynch Syndrome**

At what age should our patient's first-degree relatives begin screening?

The clinical presentation of a patient with colorectal cancer is dependent on stage and location of disease. Change in bowel habits is the most common presentation.

Clinical Presentation



Colorectal Cancer Work Up

Clinical Work Up and Pre-Treatment Staging Evaluation – Colon Cancer:

- Biopsy with pathologic tissue review
  - Microsatellite instability (MSI) status and mismatch repair (MMR) testing
  - Molecular profiling indicated for metastatic disease
- Complete colonoscopy
- CBC, CMP, and CEA (tumor marker)
- Baseline CT chest, abdomen, and pelvis with IV and oral contrast
  - If contrast is contraindicated → abdominal/pelvic MRI with contrast and non contrast chest CT
- Physical examination with evaluation of performance status

Molecular Profiling

PCR for microsatellite instability/MSI-high vs. IHC stain for deficient mismatch repair

Tissue vs. blood-based genomic profiling

- KRAS, NRAS, HRAS
- BRAF V600E
- HER2/neu amplification

	Tissue	Blood-based ctDNA
Advantages	• Large number of genes and alterations • Includes TMB and MSI	• Mutational status in the absence of tissue availability • Predictive of recurrence
Disadvantages	• Limited availability of tissue • Longer for results	• Smaller panel of genes • Dependent on presence of detectable ctDNA, potential for false negatives

Colorectal Cancer Work Up

Additional work up for Rectal Cancer

- As per colon cancer
- Local regional staging with MRI pelvis rectal protocol:
  - Determine clinical T, N status
  - High risk features (tumor deposits, vascular invasion, involvement of the mesorectal fascia)
- Baseline sigmoidoscopy by surgeon
  - Essential for surgical decision making

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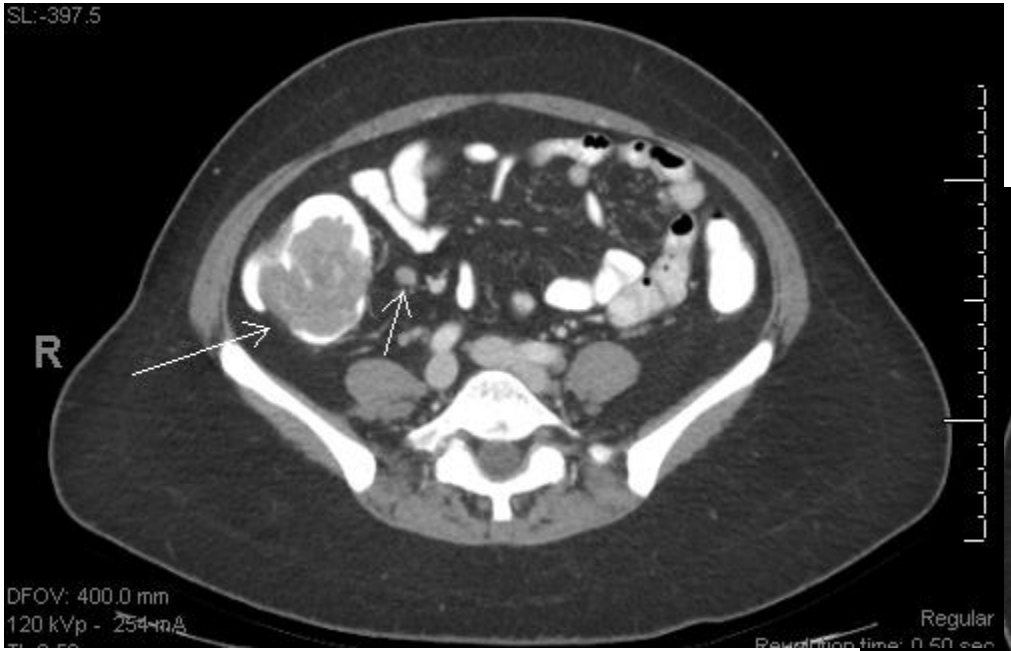
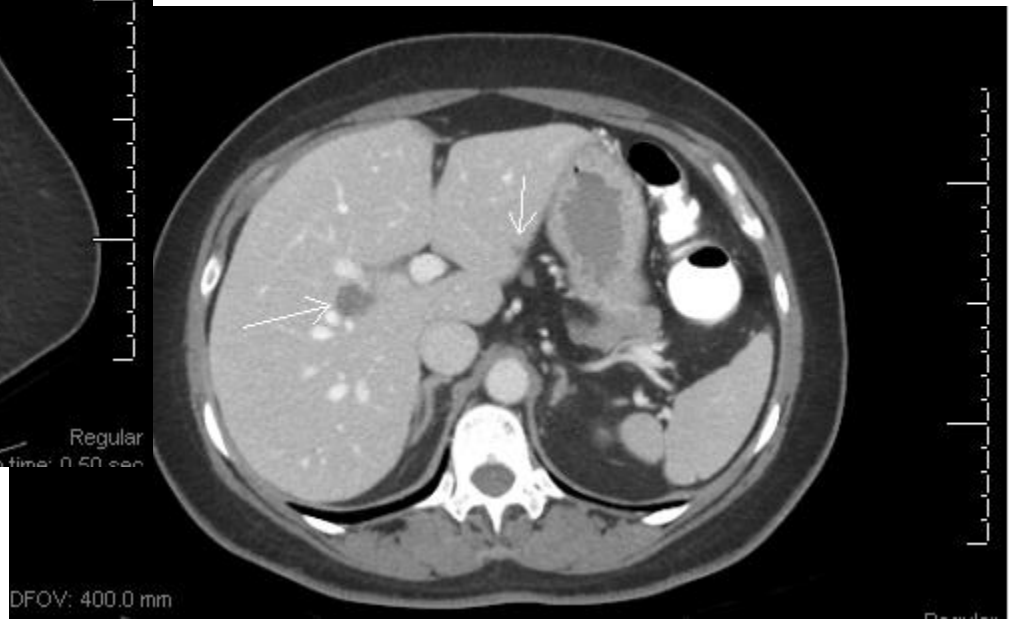
Family history: + uterine cancer (sister), + bile duct cancer (brother)

Genetic testing completed and **negative for Lynch Syndrome**

After endoscopy with biopsy and pathologic review, what is the next study in our patient's diagnostic work up?

Case Study





Colorectal cancer is staged based on the TNM staging system.

Colorectal Cancer Staging

- Colorectal Cancer staging based on tumor, node, metastases (TNM) staging system of the American Joint Committee on Cancer (AJCC)
  - T: Depth of tumor invasion into layer of colon or rectal wall
  - N: Presence or absence of regional lymph nodes
  - M: Presence of distant metastases
- Provides a framework for discussing therapy and prognosis
- Radiographic, endoscopic, and intra-op findings can provide clinical stage cTNM
- Histologic examination of resected specimen from surgery for pathologic stage, pTNM

AJCC Colorectal Cancer Staging 8th Edition

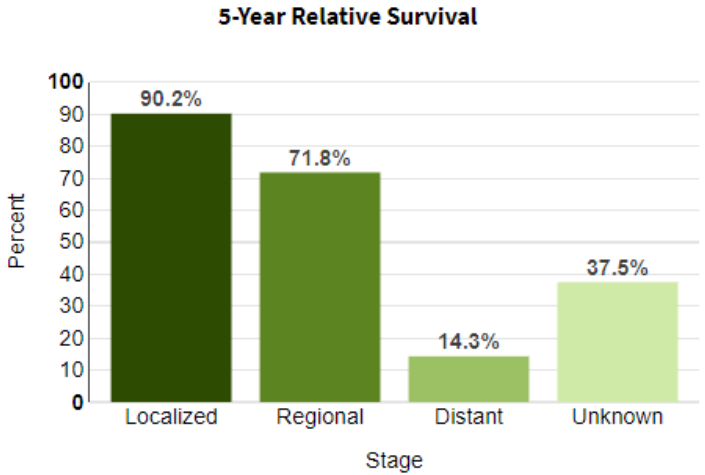
Tumor (T)		Regional Lymph Nodes (N)		Metastasis (M)	
T	Criteria	N	Criteria	M	Criteria
Tx	Tumor not assessed	Nx	Regional LNs not assessed	M0	No mets by imaging
T0	No tumor	N0	0 LNs	M1	Metastasis to 1 or more sites or peritoneal metastasis
Tis	Carcinoma in situ, intramucosal carcinoma	N1	1-3 LNs are positive or any number of tumor deposits are present	M1a	Metastasis to 1 site or organ without peritoneal metastasis
T1	Tumor invades submucosa	N1a	1 LN is positive	M1b	Metastasis to 2 or more sites without peritoneal metastasis
T2	Tumor invades the muscularis propria	N1b	2-3 LNs are positive	M1c	Metastasis to the peritoneal surface alone or with other metastases
T3	Tumor invades through muscularis propria into pericolorectal tissues	N1c	0 LNs are positive, tumor deposits are present		
T4a	Tumor invades visceral peritoneum	N2	4 or more NSs are positive		
T4b	Tumor directly invades or adheres to adjacent organs or structures	N2a	4-6 LNs are positive		
		N2b	7 or more LNs are positive		

AJCC Prognostic Stage Groups for Colorectal Cancer

Stage	T	N	M
Stage I	T1-T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

Prognosis

Stage at diagnosis is the most important determinate of prognosis



SEER 18 2010–2016, All Races, Both Sexes by SEER Summary Stage 2000

Case Study

Adenocarcinoma at the ascending colon

- Stage IVa, cTxNxM1a

Adenocarcinoma in the rectum s/p polypectomy

- Stage I, pT1NxM0

Colorectal cancer management varies by stage, but the only curative treatment modality is complete surgical resection.

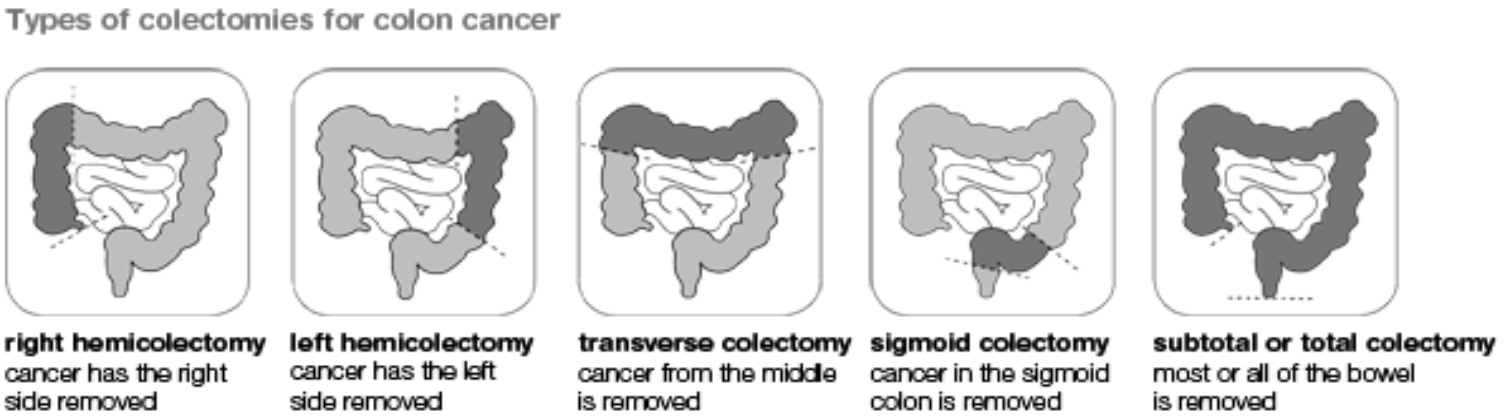
Colorectal Cancer Management

Malignant Polyp:

- Defined as polyp with cancer invading into submucosa (pT1)
- Endoscopic removal is sufficient for pedunculated or sessile polyps that have be removed in one piece **without high risk features**.
- Polyps with one or more high risk features should undergo complete staging and then surgery due to higher risk of lymph node metastases

Colon Cancer Management : Stage I-III

- Colectomy with regional lymphadenectomy is the only curative treatment modality
  - Consideration of neoadjuvant chemotherapy for patients with cT4b or bulky nodal disease
- The extent of the resection depends upon the location of the tumor



Adjuvant Chemotherapy for Colon Cancer

Stage I pT1-T2, N0	Stage II pT3-T4, N0	Stage III T any, N +
No adjuvant therapy indicated Observation only	Discussion regarding risks of therapy compared to benefits Comorbidities and overall life expectancy Consider therapy for presence of poor prognostic features • Poorly differentiated histology • Lymphovascular invasion • Perineural invasion • Bowel obstruction or perforation • Margin status • Inadequate lymph node sampling No indication for MSI-high tumors	Adjuvant chemotherapy indicated • Start 4-6 weeks after surgery Low risk T1-T3, N1 • 3 months CAPEOX or 3-6 months FOLFOX High risk T4, N1-2 • 6 months FOLFOX or 3-6 months CAPEOX

Rectal Cancer Management

Stage I Rectal Cancer

- cT1, N0: transanal local excision if applicable
  - Advantages: Minimal morbidity, rapid post op recovery
  - Disadvantages: Absence of pathologic staging of regional LNs
- cT1-T2, N0: transabdominal resection
  - High risk of lymph node metastases with T2 (10% or higher)

Rectal Cancer Management

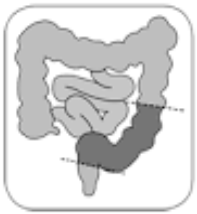
Surgical Approaches

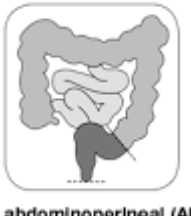
Total mesorectal excision (TME) is recommended for all rectal surgeries

- Includes removal of mesorectum and associated lymph nodes and blood vessels

Surgical procedures include both sphincter sparing and non sphincter sparing operations and depend on the location of the tumor:

- Sphincter sparing: Low anterior resection (LAR)
- Non sphincter sparing: Abdominoperineal resection (APR) with permanent colostomy



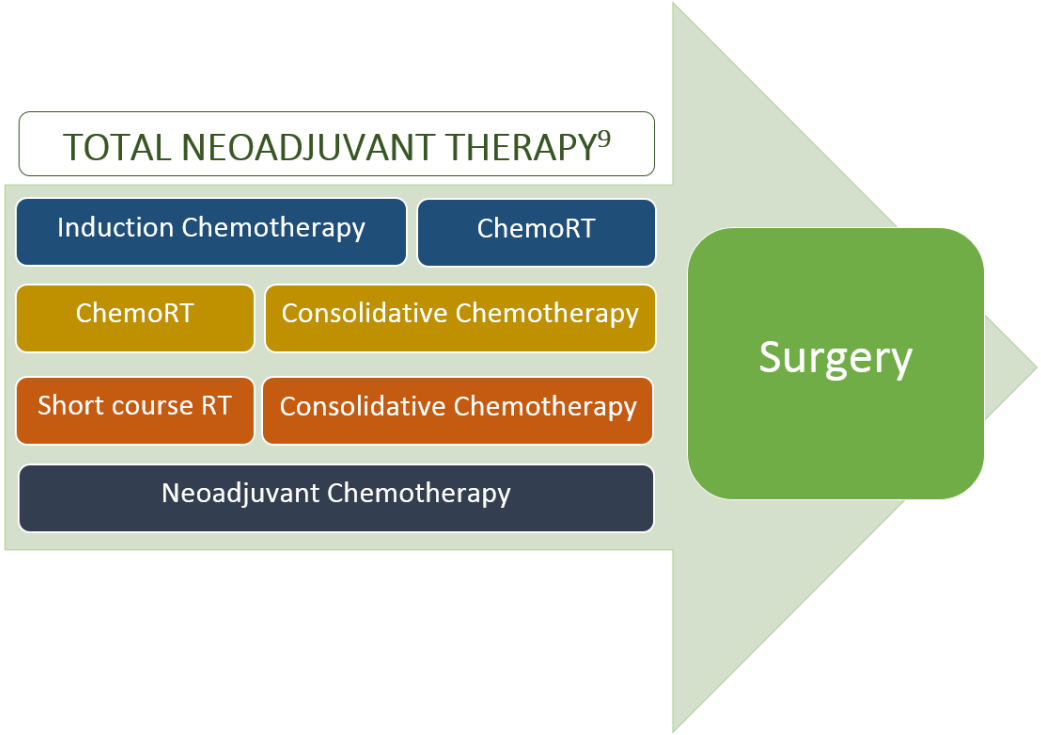


Rectal Cancer Management

Stage II & III

Benefits

- Higher pCR rates
- Longer DFS
- Improvement in OS
- Decreased risk of distant mets



Mainstay of treatment for stage IV colorectal cancer is palliative chemotherapy.

Colorectal Cancer Management: Stage IV

Principles of therapy

- Chemotherapy alone is incurable
- Consider metastectomy for limited disease
- Frequent monitoring during therapy for toxicities and response
  - Changes in therapy indicated for dose-limiting toxicities or progression
- Molecular profile of tissue aids in treatment selection

Stage IV Colorectal Cancer Management

First Line

FOLFOX or CAPEOX + bevacizumab

FOLFIRI + bevacizumab

FOLFIRINOX + bevacizumab

FOLFOX + cetuximab or panitumumab (RAS/RAF WT)

FOLFIRI + cetuximab or panitumumab (RAS/RAF WT)

*Nivo +/- ipi or pembrolizumab (MSI-high/dMMR)

Second Line

FOLFOX or CAPEOX + bevacizumab

FOLFIRI + bevacizumab

FOLFIRINOX + bevacizumab

FOLFOX + cetuximab or panitumumab (RAS/RAF WT)

FOLFIRI + cetuximab or panitumumab (RAS/RAF WT)

*Nivolumab or pembrolizumab (MSI-high/dMMR)

*Encorafenib + cetuximab or panitumumab (BRAF V600E mut)

*HER2 inhibitors (HER2 amp, RAS/RAF WT)

Third line and beyond

Regorafenib

Trifluridine + tipiracil +/- bevacizumab

*Nivolumab or pembrolizumab (MSI-high/dMMR)

*Encorafenib + cetuximab or panitumumab (BRAF V600E mut)

*HER2 inhibitors (HER2 amp, RAS/RAF WT)

Colorectal Cancer Management: Stage IV

Regimen	Indication	Molecular Profile
5FU + Oxaliplatin (FOLFOX) Capecitabine + Oxaliplatin (CAPEOX)	First or second line	N/A
5FU + Irinotecan (FOLFIRI)	First or second line	N/A
5FU + Irinotecan + Oxaliplatin (FOLFOXIRI)	First line *only if excellent performance status	BRAF V600E mutation
Bevacizumab	Added to chemotherapy in first or second line	N/A
Cetuximab or panitumumab	Added to chemotherapy in first or second line	RAS wild-type
Encorafenib + (cetuximab or panitumumab)	Second line	BRAF V600E mutation
Pembrolizumab or Nivolumab +/- ipilumumab	First or Second line	MSI-high or Deficient MMR
HER2 inhibitors	Second line	HER2 amplification and RAS wild-type
Regorafenib	Following progression through all available regimens	N/A
Trifluridine/Tipiracil	Following progression through all available regimens	N/A

Common Side Effects of Treatment

General side effects

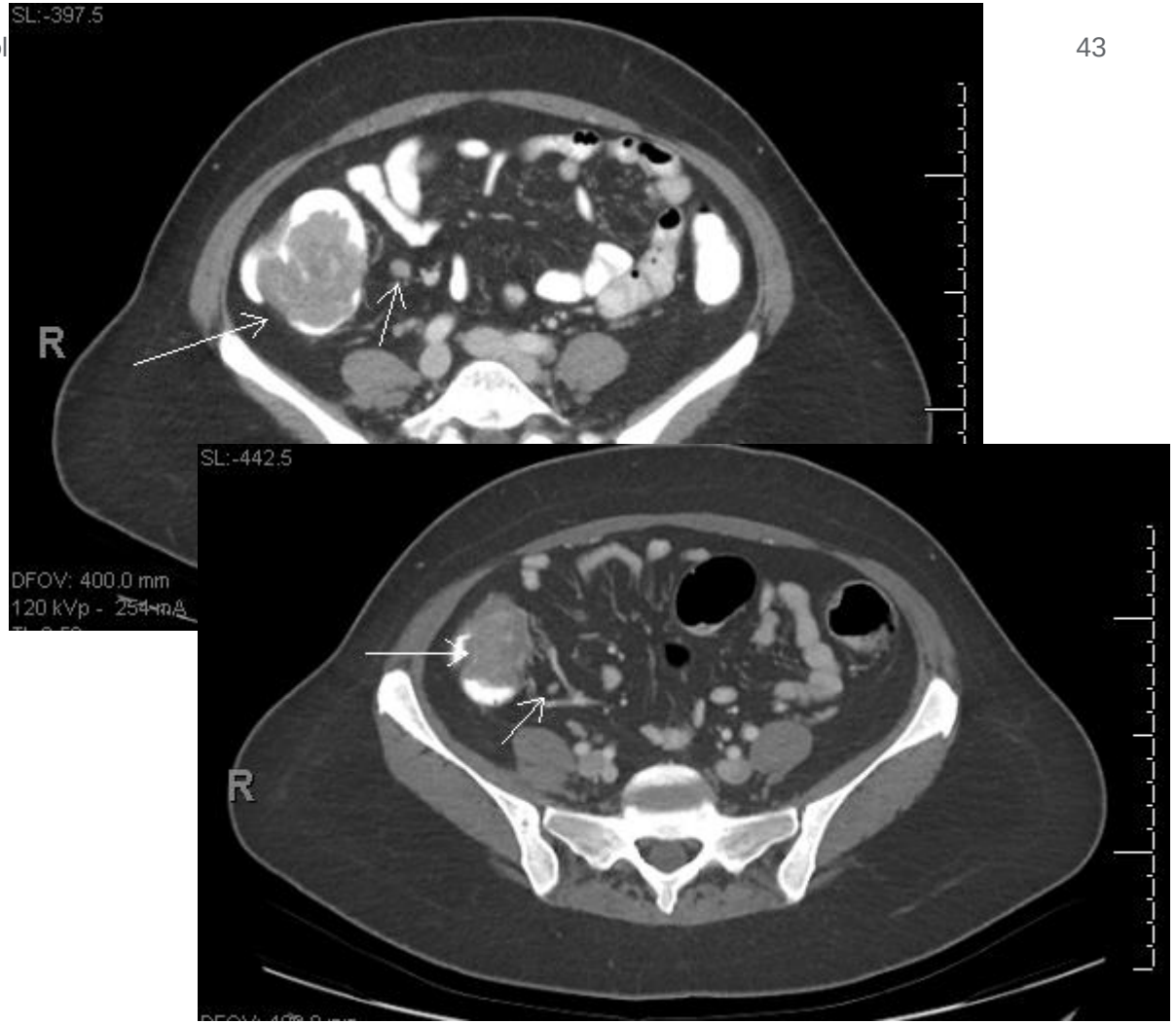
- Nausea/vomiting
- Low blood counts – white blood cells, hemoglobin/hematocrit, platelets
- Fatigue
- Appetite loss
- Infertility

Specific side effects

Agent	Side Effects
5FU Capecitabine	Mucositis Hand-foot syndrome
Oxaliplatin	Cold sensitivity, peripheral neuropathy Thrombocytopenia
Irinotecan	Diarrhea
Bevacizumab	Hypertension Impaired wound healing
Cetuximab Panitumumab	Acneiform rash
Nivolumab Pembrolizumab Ipilimumab	Can affect any organ system that is subject to immune infiltration and inflammation Dermatitis, colitis, pneumonitis, hepatitis
Encorafenib	Anemia
Trastuzumab Pertuzumab	Cardiomyopathy
Regorafenib	Hand-foot syndrome
Trifluridine/Tipiracil	Neutropenia

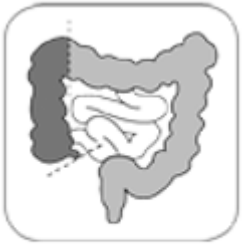
Case Study

Patient initiates FOLFOX + bevacizumab x2 months prior to surgical resection



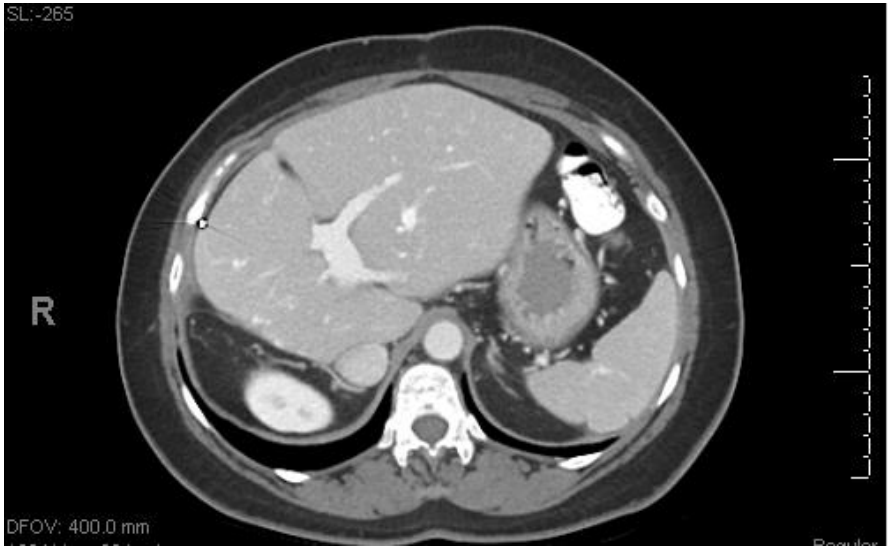
Case Study

Surgery: right hemicolectomy and regional lymphadenectomy



right hemicolectomy
cancer has the right side removed

Right portal vein embolization



Surgery: right hepatectomy, cholecystectomy, and partial left hepatectomy

Case Study

Patient initiates FOLFOX (5-FU + oxaliplatin) with bevacizumab x2 months followed by right hemicolectomy, right hepatectomy and partial left hepatectomy with curative intent and another 4 months FOLFOX.

What would be the anticipated side effect profile of this regimen?

After curative intent surgery and treatment, patients should undergo routine surveillance for detection of recurrence as part of comprehensive survivorship care.

Principles of Survivorship Care

Surveillance for recurrence and screening for other cancers

Management of long-term effects of disease and/or treatment

- Emotional distress
- Pain
- Neuropathy
- Sexual dysfunction and infertility
- Chronic bowel changes, incontinence, and management of an ostomy

Routine health care and promotion of healthy lifestyle

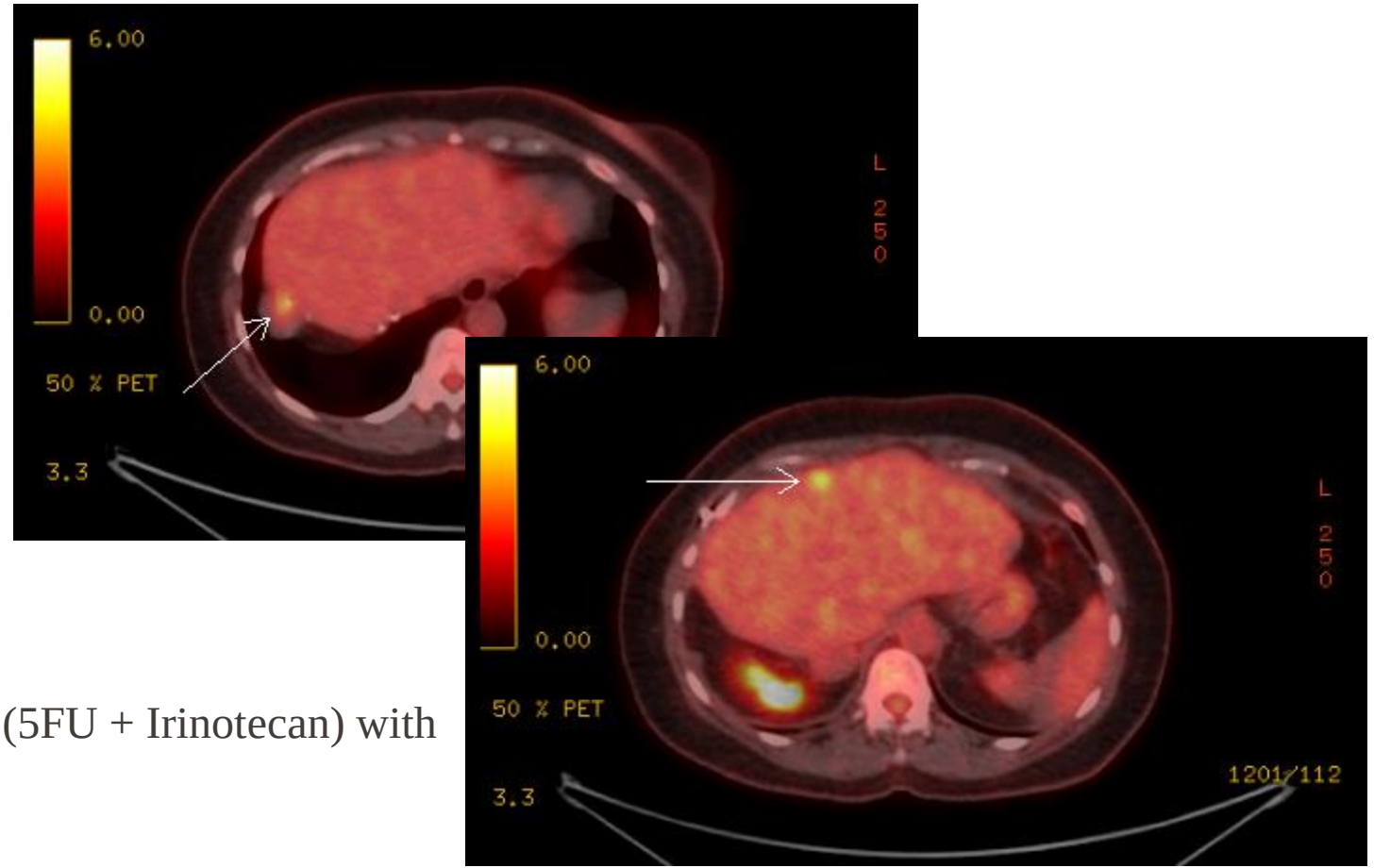
Preventative care

Survivorship Care: Colorectal Cancer Surveillance

Stage I	Stage II-III	Stage IV
Colonoscopy 1 year after surgery Repeat every 3-5 years	Colonoscopy 1 year after surgery Repeat every 3-5 years	Colonoscopy 1 year after surgery Repeat every 3-5 years
Rectal cancer s/p local excision • Flexible sigmoidoscopy with EUS or MRI pelvis every 3-6 months x 2 years, then every 6 months for a total of 5 years	H&P + CEA every 3 - 6 months x 2 years, then every 6 months for a total of 5 years CT CAP every 6-12 months x 5 years	H&P + CEA every 3 - 6 months x 2 years, then every 6 months for a total of 5 years CT CAP every 3-6 months x 2 years, then every 6-12 for total of 5 years

Case Study

3 years later…



Initiated FOLFIRI (5FU + Irinotecan) with bevacizumab

Survivorship Care: Long-Term Effects

Emotional distress

Pain

Neuropathy

- Duloxetine indicated for painful neuropathy

Sexual dysfunction and infertility

Chronic bowel changes, incontinence, and management of an ostomy

- Antidiarrheals
- Bulk-forming agents
- Dietary modifications
- Pelvic floor rehab
- Referral to ostomy nurse and/or ostomy support group

Survivorship Care: Healthy Lifestyle and Prevention Strategies

Age- and gender-appropriate cancer screenings

Physical activity ≥30 minutes moderate-intensity on most days and healthy weight

Diet low in saturated fats, red and processed meats; emphasis on plant sources

Limit/eliminate alcohol and smoking

Consider daily ASA

Key Takeaways and Pearls

- **Colorectal cancer is the third most common cancer diagnosed and the third leading cause of cancer death in the US for both men and women.**
- **Colon cancer usually arises from adenomatous polyps or flat dysplasia. Majority are carcinomas with 90% adenocarcinomas.**
- **Screening for colorectal cancer in an average-risk adult should begin at age 45.**
- **The clinical presentation of a patient with colorectal cancer is dependent on stage and location of disease. Change in bowel habits is the most common presentation.**
- **Colorectal cancer is staged based on the TNM staging system.**
- **The primary treatment for early stage, locally advanced, and non metastatic colon cancer is surgery.**
- **The mainstay of treatment for stage IV colorectal cancer is palliative chemotherapy.**
- **After curative intent surgery and treatment, patients should undergo routine surveillance for detection of recurrence and comprehensive survivorship care.**

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Resources

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