

Colorectal Cancer Treatment

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Objectives:

- Describe signs, symptoms and red flags that would warrant evaluation of possible colon/rectal cancer.
- Discuss recommended surgical, chemotherapy and radiation treatment modalities as well as recommended follow up.
- Identify resources for patients and families dealing with colon/rectal cancer and survivorship



Signs and Symptoms

Early	Advanced
<ul style="list-style-type: none">No symptoms!!AnemiaChange in bowel habitsMelenaHematocheziaRectal bleedingChange in stool caliber	<ul style="list-style-type: none">Weight LossObstructionFistulaIncontinenceAbdominal Pain

Education!!!



Pathology-

The importance of tissue diagnosis

- ADENOCARCINOMA
- Melanoma
- Neuroendocrine
- Lymphoma
- GI stromal tumors
- Kaposi Sarcoma
- Anal Squamous Cell Carcinoma

All have different staging, treatment and prognosis.

Pathology-

Role in Prognosis and Treatment

- Determine the Stage, Grade, Margin and Lympho-vascular Invasion status.
- Determine the mutational status of the tissue:
 - KRAS
 - BRAF V600
 - Mismatch Repair (MMR)/Microsatellite Instability (MSI)

Natural History of Colorectal Neoplasia

Normal Colon

Small

Early Adenoma (Pre-cancer)

Intermediate

Late

Cancer

~10-15 years^{1,2}

Wasth et al., Clin Gastroenterol Hepatol (2005)
Wasth et al., Ann Surg (2005)
Blattman et al., Surg, Oncol, Hepatol, Gastroenterol, Oncol (2005) CC - 12

Think about Tumor Biology and Don't Panic!

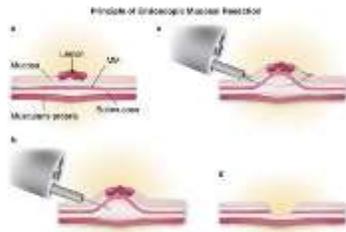
Provider effect on patients

- Stay calm, educate your patients
- Tumor biology is typically slow, therefore treatment is not typically emergent
- Verify pathology
- Verify staging
- Thorough Pre-op

Polyps



Endoscopic Mucosal Resection

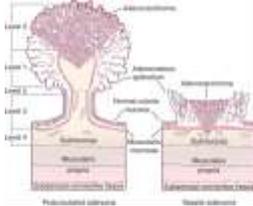


Polyps that require surgery

- Large sessile polyps >2 cm
- Sessile polyps in awkward locations where EMR is not ideal
- Ulcerated or depressed lesions
- Pedunculated polyps with concerning features (i.e. positive margins, poorly-diff)
- Invasive carcinoma in a sessile, depressed or Haggitt level 4 lesion

Polyps: Haggitt Classification

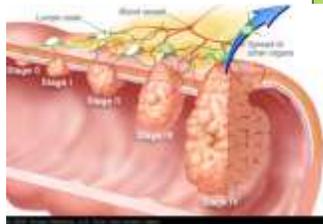
- **Level 0** Carcinoma in situ or intramucosal carcinoma. Not invasive.
- **Level 1** Carcinoma invading through muscularis mucosa into submucosa, but limited to the head of the polyp.
- **Level 2** Carcinoma invading the level of the neck of the adenoma.
- **Level 3** Carcinoma invading any part of the stalk.
- **Level 4** Carcinoma invading into the submucosa of the bowel wall below the stalk of the polyp, but above the muscularis propria.



What to do with a Mass or biopsy proven Cancer ?

Things to consider:

- Location
- Tattoo placement
- Pathology
- Sampling Errors
- Pre-op Staging
- Tumor Genetics*
- Family Screening



Colorectal Ca Pre-operative Staging Measures

- Carcinoembryonic Antigen (serum CEA)
- Chest X-Ray
- CT scan Abdomen/Pelvis with IV contrast
- Determine Tumor Gene Status (KRAS/BRAF)*
- Liver MRI vs Triple Phase CT ?
- PET/CT ? (not routine but recommended if any suspicious findings on CT scan or if serum CEA levels are elevated)
- Locoregional Staging for rectal Ca

Special Populations

- FAP
- Lynch
- Strong family history
- Ulcerative Colitis
- Tumor Genetics
- Elderly Patient

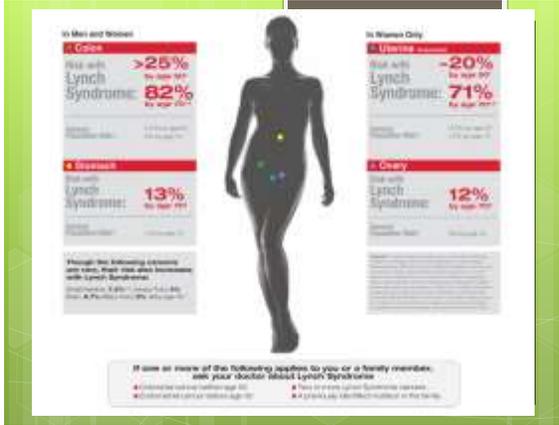
Familial Adenomatous Polyposis

- Compose 1% of all colorectal cancer
- Mutation in tumor suppressor gene APC
- Cancers develop as early as 15-20 years age
- 100% risk of cancer by age 40
- Recommend prophylactic surgery



Hereditary Nonpolyposis Colorectal Cancer (HNPCC) aka Lynch Syndrome

- Most common cause of inherited CRC
- Composes 2-4 % of colorectal cancers
- >80% chance lifetime risk of developing colon cancer
- Sporadic polyps
- Mutation in DNA mismatch repair genes
- This genetic alteration in MMR genes is termed microsatellite instability (MSI)



Tumor Genetics

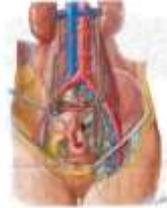
- KRAS, BRAF, and Microsatellite Instability
- Currently used primarily to guide systemic therapy regimens
- Does not typically change the surgical decision making unless there is already known metastasis.
- As targeted therapies advance it is possible that the future of tumor genetics may change the order sequence of first line therapy

Tumor Genetics

- KRAS mutation
 - present in about 35-50% of colorectal cancers
 - predictive of a very poor response to EGFR-inhibiting drugs panitumumab (Vectibix) and cetuximab (Erbix)
 - presence of the mutation has a worse prognosis
 - The use of cetuximab with chemo has shown significant efficacy with presence of the normal KRAS gene (aka wild-type KRAS)

Rectal Cancer

- Increased risk of local recurrence
- Invasion into adjacent structures
- Risk of permanent ostomy
- Increased morbidity
- Potential change in quality of life



Rectal Cancer – Surgery Alone vs Multimodal approach

- Surgery first
 - Early rectal cancers Tis-T2/N0 by preoperative method recommend surgery first
- Multimodal approach
 - > T3/N0 and higher.
 - >N1 disease and higher
 - close proximity to sphincters (patient wants to be considered for Sphincter sparing surgery)

Pre-Operative Locoregional Staging of Rectal Cancer

- Endoscopic Ultrasound
 - Aim: to assess T (tumor) stage and Nodal stage
 - Added benefit of revisualization of tumor, verify tattoo
 - Cons-operator dependent
- Pelvic MRI
 - Aim: to assess T (tumor) stage and Nodal stage
 - Added benefit of assessing CRM (tumor extension into mesorectum or adjacent structures). Objective information.
 - Cons- no consensus on sequencing protocol, not many radiologists not trained on how to read, difficult to stage after completion of radiation

Rectal Ca Multi-modality Approach

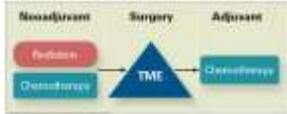


Figure 1. The Current Standard of Care for Rectal Cancer (Established in 2004, TME = total mesorectal excision)

XRT → Cool-off → Surgery → Chemo
 6 weeks ~6-12 weeks ~4 weeks ~6months

Neo-Adjuvant Chemoradiation

- Chemotherapy
 - Sensitizes the tumor to radiation
 - Oral Capecitabine (Xeloda) or
 - Infusional 5-FU (carry along pump)
- Radiation
 - Typically given M-F
 - 6 weeks
 - Total 5400 cGy

Considerations are given to start with Systemic Chemo for 12-16 weeks, followed by chemoradiation in patients with Advanced or metastatic disease

Morbidity and Impact on Quality of Life- Rectal CA

- XRT- nerve damage, incontinence, sexual dysfunction, radiation proctitis, skin burns
- Surgery- nerve damage, (ED/retrograde ejaculation), possible temporary vs permanent ostomy, surgical recovery
- Chemo- neuropathy, GI upset
- Long treatment protocol- depression, SI

Radiation Proctitis

- Acute or Delayed
- h/o prior XRT: GYN, Prostate, and anorectal
- Symptoms include:
 - Painful defecation
 - Bleeding
 - Urgency
 - Fistulas



Radiation Proctitis Treatment

- Fiber supplement
- Sulcrafate enemas
- Corticosteroids (Proctofoam HC)
- Formalin Painting
- Argon Plasma Coagulation (APC)
- Hyperbaric Oxygen Therapy

Surgical Techniques

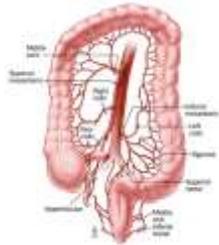
TEMS- Transanal endoscopic microsurgery

- Rectal polyps not amenable to EMR
- In situ disease
- Early T1
- Patients refusing formal surgery

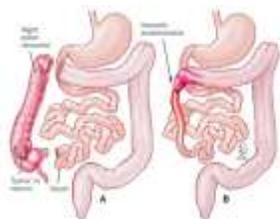


Surgical Approach

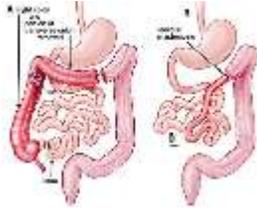
- Remove cancer with clear margins
- Resect adjacent draining lymph nodes (ideally 12)
- Reconstruct bowel (based on blood supply)



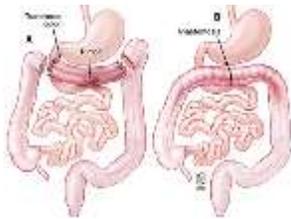
Right Hemicolectomy



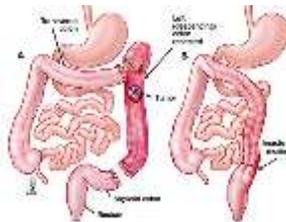
Extended Right-Hemicolectomy



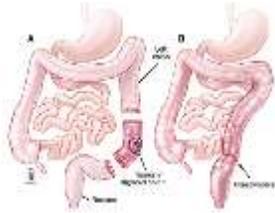
Segmental Colectomy



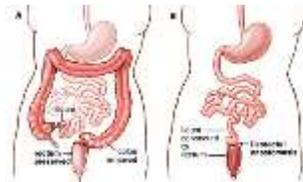
Surgical Approach Left Hemicolectomy



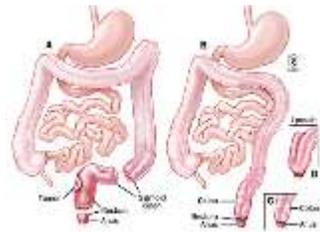
Surgical Approach Sigmoid Colectomy



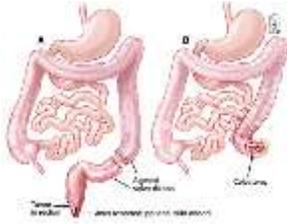
Subtotal Colectomy



Low Anterior Resection



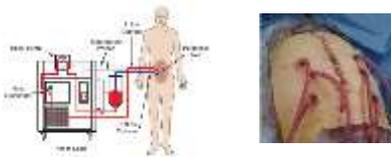
Abdominoperineal Resection



Laparoscopic Surgery vs Open

- No clear data to support advantage
- Laparoscopic –hand assisted
- Laparoscopic for rectal cancer- high risk of recurrence??
- Robotic surgery may be beneficial for deep pelvic resections.
- Operator dependent

Hyperthermic Intraperitoneal Chemotherapy- HIPEC



Typical Surgical Complications

- Wound Infection
- Anastomotic leak
- Ileus
- Hernia
- Peri-operative Risks
 - DVT/PE
 - Pneumonia
 - MI/CVA

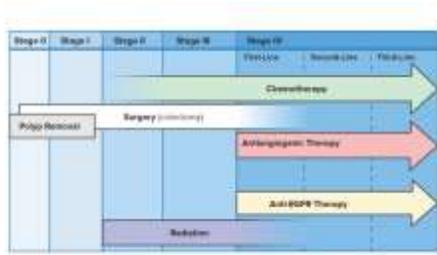
Quality Surgery and Outcomes

- Recommend at least sampling 12 nodes
- 5cm proximal and distal margins (except for distal rectal is 2cm)
- Circumferential resection margin aka radial margin is clear. (pre-op MRI can help with planning)

Adjuvant Therapies

TNM Staging for Colorectal Cancer, AJCC 8th ed, UICC 2017

AJCC 8th ed	TNM stage	TNM stage criteria for colorectal cancer
Stage 0	Tis, N0, M0	Tis: tumor confined to mucosa, cancer in situ
Stage I	T1-2, N0, M0	T1: tumor invades submucosa
Stage II	T2-4, N0, M0	T2: tumor invades muscularis propria
Stage III	T1-4, N1-3, M0	T3: tumor invades subserosa or beyond (within 200 or 250 μm of subserosa)
Stage IIIa	T1-3, N1, M0	T4: tumor invades adjacent organs or perforates the visceral peritoneum
Stage IIIb	T1-2, N1, M0	N1: Metastases to 1 to 3 regional lymph nodes, T1 or T2, A
Stage IIIc	T3-4, N1, M0	N2: Metastases to 4 to 3 regional lymph nodes, T3 or T4, B
Stage III	any T, any N2, M0	N2: Metastases to 4 or more regional lymph nodes, any T, C
Stage IV	any T, any N, any M1	M1: Distant metastasis, peritoneal, any T, any N, N, M1



Adjuvant Radiation

- Indications for post-surgery XRT:
 - Positive margins- pelvic or abdominal side wall
 - Intraoperative findings below peritoneal reflection
 - Recurrent disease: depends on location and if have received prior radiation to the targeted area.
- Possible sequelae include: colitis, proctitis, and stricture
- Typically performed shortly after surgery once patient has recovered.

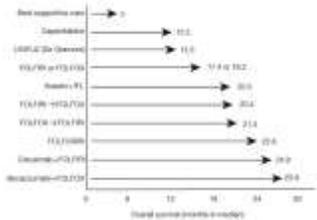
Adjuvant Systemic Therapy

- Chemotherapy options depend on KRAS/BRAF mutation presence and are tailored to each patient taking into account the patient's goals of treatment as well as ECOG status.
- Chemotherapy is given as either a single- agent or in combination.
- Can be combined with the use of monoclonal antibodies- directed at specific tumor signaling pathways and immunotherapies- that signal the body's natural defenses to attack the cancer cells.

Adjuvant Therapy- Systemic therapy with chemo

- Recommend for Stage IIB and above
 - T4
 - Obstructive lesions
 - Node positive
 - Known Mets
 - Perforated Tumors
- All Rectal Cancers Pre-operatively Staged T3 and greater

Systemic Chemotherapy for Colorectal Cancer



Common Regimens

- FOLFOX- (oxaliplatin plus short-term infusional FU and leucovorin)
- FOLFIRI -(irinotecan plus short-term infusional FU and leucovorin)
- FOLFOX/FOLFIRI + Bevacizumab
- FOLFOX + Panitumumab or Cetuximab (only for KRAS Wild-Type)
- Capecitabine single-agent (rectal, elderly)
- CAPOX (also called XELOX)

Typical Side Effects- Chemo

- | | |
|---|---|
| Capecitabine (Xeloda): <ul style="list-style-type: none">● "hand-foot syndrome" (acral erythema)● Diarrhea● Skin rash | Irinotecan (Camptosar) <ul style="list-style-type: none">● Diarrhea |
| Fluorouracil (5-FU) <ul style="list-style-type: none">● Mucositis● Nausea● Diarrhea | Folinic acid (Leucovorin) <ul style="list-style-type: none">● Rash |
| | Oxaliplatin (Eloxatin) <ul style="list-style-type: none">● neuropathy |

Antiangiogenic Therapy: Bevacizumab (Avastin)

- Monoclonal antibody that targets the vascular endothelial growth factor (VEGF)
- Not approved for use as single agent
- Improved overall outcome when used with Chemo regimen
- Significant Side Effects:
 - Bleeding
 - GI perforation
 - Nephrotic syndrome

Anti-EGFR Therapy

Panitumumab (Vectibix)

Cetuximab (Erbix)

- Monoclonal antibodies that target epidermal growth factor receptor (EGFR)
- Counters the protein that helps cancer cells grow
- Only used with KRAS wild-type (without mutation) tumors
- Tumors that are KRAS wild-type are not guaranteed to have a response
- Given as an infusion alongside chemo regimen
- SE: weakness, malaise, acneiform rash, nausea, infusion reaction

Immune checkpoint Inhibitors:

Pembrolizumab (Keytruda)

Nivolumab (Opdivo)

- IgG4 monoclonal antagonist antibody to PD-1
- Used for refractory stage IV colorectal tumors that are characterized as microsatellite instability-high or deficient mismatch repair
- Side Effects:
 - Rash, pneumonitis
 - Pancreatitis, transaminitis
 - Thyroiditis
- Promising for future clinical trials

Refractory Disease

- Regorafenib (Stivarga)
 - Kinase inhibitor
 - Can be taken as a pill
 - SE: hand-foot syn, diarrhea, fatigue,
- Trifluridine-tipiracil (TAS-102)
 - Oral cytotoxic
 - Still not well established

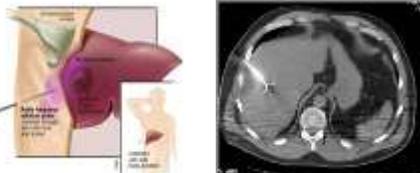
Prognosis for M-CRC

- Survivorship with metastatic disease depends on the extent of metastasis at time of diagnosis or recurrence
 - Single/few lesions vs multiple organ lesions.
- Roughly 1-5 years depending on ECOG status at time of metastasis and response to treatments. The newer agents have increased survival by about 30 months.

Management of Recurrent or Metastatic Disease

- Localized to colon → resection → systemic tx
- Consider PET/CT and restaging studies
- Single site vs multiple ?
- Systemic therapy (if patient is a candidate)
- Consider local therapies for single site disease after receiving maximal treatment effect with Chemo
 - RFA - Radiofrequency Ablation through the Interventional Radiology Department
 - SBRT (Stereotactic Body Radiation Therapy) through Radiation Oncology Department.

Adjuvant Therapy Radiofrequency Ablation



Cancer Survivorship

National Comprehensive Cancer Network (NCCN)
Clinical Practice Guidelines

- Serum CEA levels q3-6 months
- Surveillance CT scan annually x 3 years
- Surveillance colonoscopy annually x 3 years, depending on findings may progress to q 3-year and q 5-year intervals.
- Cancer Survivor should never go longer than 5 years without full colonoscopy - personal risk is 25% of developing a new primary lesion in their lifetime

Long term Sequelae

- XRT :
 - Radiation-induced fibrosis
 - Radiation proctitis/ cystitis/ colitis
 - Infertility
- Surgery
 - Loose stools
 - Hernia
 - ED/retrograde ejaculation/ incontinence
 - Possible need for permanent ostomy
- Chemo
 - Neuropathy
 - Lingering cytopenia

Loose Stools!- treatment

- Use supplemental Fiber to bulk!!
- Loperamide (Imodium)
- Diphenoxylate-atropine (Lomotil)
- Tincture of Opium
- Request for Ostomy Creation ?

Stealth Belt



Comprehensive Cancer Care

- Family counselling/screening
 - Ostomy training and counselling
 - Cancer Support Groups:
 - Colorectal Cancer Alliance
<https://www.ccalliance.org>
 - American Cancer Society
 - Psychosocial Needs/ Depression
 - Getting back into Life!
- Don't forget Lifelong cancer survivorship and continued surveillance



Treatments on the Horizon!

- Sending tumor tissue for next-generation tumor sequencing to determine if there are molecular drivers of tumor growth that we can target with treatment and that can determine treatment resistance.
- CAR-T: Immunotherapy which involves removing patient's own cells and engineering them to target tumor tissue has shown promise in colon cancer with mice. This type of therapy is now being used with lymphoma.
- Clinical Trials - national database through ClinicalTrials.gov.

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Questions???
