Colorectal Cancer

Colorectal Cancer

ADENOCARCINOMA = 90%

Colon Cancer

Above peritoneal reflection

Rectal Cancer

Below peritoneal reflection
Above anal verge

Colon Cancer Presentation

Right Sided: SBO, anemia
Left Sided: LBO, cramping, bloody stools

Histology

Tumor grade based on gland formation
1 = well formed glands
4 = undifferentiated glands

Adenocarcinoma Sub-Types

Mucinous/Colloid (>50% mucinous)
Signet-Ring (>50% signet-ring)
Medullary

Tumors can produce mucin
* If mucin is >50% of tumor volume = mucinous
* When mucin displaces nuclei laterally = signet ring

Colorectal Cancer

Screening:

Screening Modalities:
- Colonoscopy Q10 years (preferred)
- Flex Sigmoidoscopy Q5 years
- CT scan Q5 years
- FOBT Q1 year

General Screening Guidelines:
- Start at 45 yo
- Continue until 10 years prior to anticipated death

Special Screening Guidelines:
- Family history (10 yrs prior to earliest dx or 40 yo, Q5 years)
- CF (40 yo)
- Lynch/HNPCC (20-25 yo, Q3 years)
- IBD (8 years after dx, Q1-3 years)
- FAP (10 yo)

Work Up:

Work Up Colon Cancer:
- Colonoscopy
- CT CAP

Work Up Rectal Cancer:
- Rigid Proctoscopy
- Pelvic MRI/Endorectal US

IHC: CK20+, CDK2+, CK7-,

GI Tumor Markers:
- CEA
- CA19-9
- AFP

Colorectal Cancer

Clinical Risk Factors

Risk Factors
- IBD
- Smoking
- ETOH
- Obesity

High Risk Polyps
- Adenomas
- > 1 cm
- Villous, Tubulovillous
- Sessile
- High-grade dysplasia

Genetic Risk Factors

Mismatch Repair Mutation = MMR
- MMR deficient (dMMR) → Microsatellite Instability High (MSI-H)
- Responds better to immunotherapy

BRAF
- BRAF mutation → hypermethylation of MMR → MSI
- Poor prognosis

Lynch Syndrome/Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
- Syndrome = colon, endometrial, uroepithelial, pancreatic, CNS, etc
- MLH1, MSH2/6, PMS2 → dMMR → MSI-H
- Associated w/ Signet Cell, aggressive variant

Familial Adenomatous Polyposis
- APC mutation

Inherited Polyposis Conditions
- Juvenile Polyposis, Peutz-Jeghers

Colorectal: Staging & Prognosis

Staging

T1
T0 = carcinoma in situ
T1 = submucosa
T2 = muscularis propria
T3 = peri-colorectal
T4 = visceral peritoneum, adjacent organs

N
N1 = 1-3 LN (includes “tumor deposits”)
N2 = 4+ LN

M
M1 = distant mets, includes peritoneum

Stage
Stage I = T1-2, N0
Stage II = T3-4, N0
Stage III = T1-4, N1-2
Stage IV = M+

Colon Cancer Prognosis

Stage I-II: Curative >85%

Stage IV: 5Y OS 15%

Colon Cancer: Localized Treatment

Stage I CRC (T1-2, N0)

Surgery + Observation

Post-surgery local recurrence < 5%
Most recur year 1-3

Colon Cancer: Localized Treatment

Stage II CRC (T3-4, N0)

Surgery +/- Adjuvant Chemotherapy

T3N0

+/- Chemotherapy

MSI-H = NO benefit to chemo
MSI-L = YES benefit with chemo

T4N0

+ Chemotherapy

5FU/Leucovorin
Capecitabine

* NO oxaliplatin if N0

Colon Cancer: Localized Treatment

Stage III CRC (N+)

Low Risk
T1-3, N1 (<3 LN)

3 Months Chemotherapy
CAPOX

CAPOX = capecitabine + oxaliplatin

High Risk
T4, N2 (>3 LN)

6 Months Chemotherapy
FOLFOX or CAPOX

FOLFOX = 5FU + oxaliplatin
CAPOX = capecitabine + oxaliplatin

* Stage III > 70 yo: no benefit to oxaliplatin

Colon Cancer: Front-Line Metastatic Treatment

Front-Line

FOLFOX
5FU + Oxaliplatin

CAPOX
Capecitabine + Oxaliplatin

FOLFIRI
5FU + Irinotecan

FOLFOXIRI
5FU + Oxaliplatin + Irinotecan

Principles of Front-Line Regimen Selection

1. Avoid Neuropathy
Consider starting with regimen without oxaliplatin to spare neuropathy

2. Balance Toxicity with OS benefit
FOLFOXIRI has better OS but is more toxic

3. Order is less important
Can give FOLFOX after FOLFIRI or vice versa

4. Add biologic agent (EGFR or VEGF inhibitor)
Left sided = add EGFR
Right sided = add VEGF

4. Utilize maintenance therapy
Such as biologic or capecitabine

Colon Cancer: Front-Line Metastatic Treatment

Front-Line

FOLFOX
5FU + Oxaliplatin

CAPOX
Capecitabine + Oxaliplatin

FOLFIRI
5FU + Irinotecan

FOLFOXIRI
5FU + Oxaliplatin + Irinotecan

Targeted Therapy for Special Populations

Left-Sided Colon Cancer
Add cetuximab (EGFR Inhibitor)

Right-Sided Colon Cancer
Add bevacizumab (VEGF Inhibitor)

KRAS/NRAS Mutated
No EGFR biologic therapy

dMMR/MSI-High
Pembrolizumab
Nivolumab/Ipilimumab
* CPI monotherapy front line if dMMR

Colon Cancer: Front-Line Metastatic Treatment

Front-Line

FOLFOX
5FU + Oxaliplatin

CAPOX
Capecitabine + Oxaliplatin

FOLFIRI
5FU + Irinotecan

FOLFOXIRI
5FU + Oxaliplatin + Irinotecan

+/- EGFR or VEGF Inhibitors:
EGFR = Cetuximab
VEGF = Bevacizumab

Notable Side Effects

5FU/Capecitabine → Hand-foot Syndrome (palmar-plantar erythrodysesthesia), mucocutaneous/stomatitis, diarrhea, Prinzmetal angina, mild alopecia, NASH

Oxaliplatin → Neuropathy, nephropathy, ototoxicity, cold hypersensitivity

Irinotecan → Watery secretory diarrhea, mild alopecia, NASH

Bevacizumab → HTN, stroke, MI, poor wound healing

Cetuximab → Diarrhea/electrolyte abnormalities, acne

Colon Cancer: Front-Line Metastatic Treatment

Front-Line

FOLFOX
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Administration

5FU → 48H IV infusion (pts go home w/ pump)
Metabolism affected by DPYD mutation

Capecitabine → PO, 2 weeks on/1 week off
Absorption affected by PPI

Oxaliplatin → IV, Dose reduce renal disease

Irinotecan → IV, Can’t give bilirubin > 2

Colorectal Cancer: Second-Line Metastatic Treatment

Second-Line

1. **Targeted Therapy →**

2. **Trifluridine/Tipiracil (Lonsurf)**

3. **Regorafenib**

   More side effects than lonsurf

Targeted Therapy for Special Populations

dMMR/MSI-High

Pembrolizumab (1st line/2nd line)
Nivolumab/ipilimumab (1st line/2nd line)

BRAFV600E Mutated

Encorafenib + cetuximab (2nd line)
Dabrafenib + trametinib (2nd line)

HER2 Mutated

Trastuzumab
Lapatinib

Rectal Cancer

Stage I

Surgery
T1-T2N0

Small (T1, <3 cm)
Local Excision alone

Distal 1/3 Rectum
= Abdominoperineal Resection (APR)

Proximal 2/3 Rectum
= Low Anterior Resection (LAR)

Stage II-III

Neoadjuvant ChemoRT + Surgery + Adjuvant Chemo
Trimodal Approach (*can also get total neoadjuvant therapy)

Neoadjuvant ChemoRT
5FU/RT

Surgery

Adjuvant Chemotherapy
FOLFOX
CAPOX

* Order of trimodal therapy can change. Ex: chemoRT → chemo → surgery

Stage IV

Systemic therapy = stage IV CRC (FOLFOX + Bevacizumab)
* oligometastatic disease is curable

Anal Cancer

General

Risk
Associated with HPV

Pathology
Mostly squamous, rarely adenocarcinoma

Stage I

No sphincter involvement and Well Differentiated
Surgery = Abdominoperineal Resection (APR)

Yes sphincter involvement or Poorly Differentiated
ChemoRT

Stage II-III

ChemoRT
5FU/mitomycin + RT
* Cisplatin can replace mitomycin if contraindication

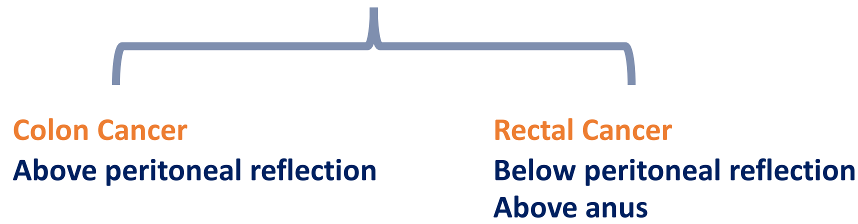
Recurrence = disease 26 weeks post-tx
Repeat surgical resection

Stage IV

Chemotherapy or Immunotherapy
No standard treatment: Carboplatin/paclitaxel or Pembrolizumab, Nivolumab

Colorectal Cancer Reference Handout

Colorectal Cancer



Colon Cancer
Above peritoneal reflection

Rectal Cancer
Below peritoneal reflection
Above anus

Staging

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Colon Cancer Tx Early Stage

Stage I CRC (T1-2, N0)

Surgery + Observation

Stage II CRC (T3-4, N0)

Surgery +/- Chemotherapy

T3N0
+/- Chemo
MSI-H = NO benefit to chemo
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T4N0
+ Chemo
5FU/Leucovorin
Capecitabine

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Colorectal Cancer Tx Metastatic

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3. **Order is less important**
4. **Add biologic agent (EGFR or VEGF inhibitor)**
4. **Utilize maintenance therapy**

Second-Line

Targeted Therapy →
if indicated

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Regorafenib
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Trastuzumab
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Rectal Cancer

Pathology
Mostly adenocarcinoma
Squamous rectal tx as anal

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Below peritoneal reflection
Above anus

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Stage II-III

Neoadjuvant ChemoRT + Surgery + Adjuvant Chemo
Trimodal

1. **Neoadjuvant ChemoRT (5FU/RT)**
2. **Surgery**
3. **Adjuvant Chemotherapy (FOLFOX or CAPOX)**

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FOLFOX + Bevacizumab
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