PREVALENCE:
- 2nd most common
  - Men: prostate > colorectal
  - Women: breast > colorectal
- 2nd most lethal (10-year survival)

RISK FACTORS:
- Age: 90% after age > 50
- Family history
  - 20% with 1st degree family history
  - 5% with hereditary genetic syndromes
- Comorbidities
  - Inflammatory bowel disease
  - Colorectal polyps
- Lifestyle factors?

SYMPTOMS:
- Most patients symptomatic at presentation
  - Rectal bleed, bowel changes, diarrhea
  - Iron deficiency anemia
  - Bowel obstruction (due to narrowing of bowel lumen)
  - Palpable rectal or abdominal mass
  - Appetite + weight loss, low energy
  - If cancer spreads to liver: jaundice, RUQ pain, abdominal distention
- Early recognition of symptoms can prompt investigation and appropriate intervention

DIAGNOSIS:
- Colonoscopy: identify primary cancer, biopsy
- CT scan of abdomen, pelvis
- X-ray or CT of chest

PROGNOSIS:
- Non-metastatic cancer removed by surgery
  - Most effective treatment of cancer
- Recurrence depends on:
  - Disease stage
  - Depth of local tumor invasion
  - # of regional lymph nodes involved
  - Grade of tumor
  - Cancer cells in blood and/or lymphatic vessels near tumor
  - Bowel obstruction and/or perforation
- Patients with metastases or who have residual disease after surgery are usually incurable
- Prognosis determined by amount of disease and whether disease is responsive to txt

RESECTABLE VS. UNRESECTABLE CANCER:

Resectable	• **Colon cancer:** removing primary tumor and adjacent mesentery, plus nearby lymph nodes • **Rectal cancer:** removal of cancer and entire rectal mesentery
Unresectable	• Most common metastatic sites: liver, lungs, peritoneum • Survival ~ 8 months without treatment • Recent advances have improved survival to ~ 20 months with combination regimens

SCREENING:
- Most provinces have population-based screening programs for colorectal cancer
- Screening of asymptomatic individuals can help detect colorectal cancers at an earlier stage, more likely to be curable
  - 5-year survival: localized = 90% ; regional (incl. lymph nodes = 70%), metastatic = 10%
- Screening for average risk individuals to start at age 50, with a fecal screening test every 1-2 years
  - **Fecal immunochemical test (FIT)** detects occult blood in stool due to microscopic bleeding from colorectal cancers
    - Uses antibodies specific for human hemoglobin or other blood components
    - Non-invasive; can be carried out by individuals at home
    - No pre-test dietary restrictions, simple stool sample collection procedures
    - Not specific to cancer bleeding, false positive from other GI conditions
    - Test kit from screening programs, primary care physicians, or community pharmacists
      - Pharmacists are accessible, and can increase awareness, facilitate stress and educate to alleviate the fear
- If abnormal fecal test results, colonoscopy recommended
  - Highly specific and sensitive, plus allowing tissue sampling or polyps removal

PREVENTION:

Lifestyle factors	BAD	• Diets rich in fat, red or processed meat • Smoking, excessive alcohol • Obesity, physical inactivity
	GOOD	• Diets with high fibre, fruit, veggies, cereal fibre, whole grains, poultry, fish

Aspirin, NSAID		• NSAIDs can reduce development of GI neoplasia, probably thru inhibition of COX-2
		  ○ COX-2 overexpression found in colorectal cancer (85%) and adenoma (50%)
		  ○ COX-2 can be mutagenic and tumorigenic, partly by increasing survival of abnormal cells and genetic changes
		• NSAIDs may reduce tumor growth via non-COX inhibition
		• ASA and NSAIDs may reduce incidence of colorectal cancers and adenomas
		  ○ ASA doses used were higher than those used for CVD
		  ○ Uncertainties re: optimal dosing & duration of ASA, risk of long-term toxicities
		• Evidence inconsistent, unclear whether chemoprevention would reduce mortality
		  ○ Chemoprevention with ASA and other NSAIDs not currently recommended except in specific high-risk individuals

Ca +/- Vit D		• Daily elemental calcium 1200 mg reduced recurrence of adenoma in patients with history of benign adenoma ○ Unclear if this would reduce risk of colorectal cancer • No reduction in colorectal cancer in women taking elemental calcium 1000 mg and vitamin D 200 units daily

DRUG THERAPY IN COLORECTAL CANCER:

	RESECTABLE	UNRESECTABLE

Role of drug therapy	• Helps surgery (*adjuvant* therapy)
	  ○ Stage III colon cancer
	  ○ Stage II-II rectum cancer
	• Kills subclinical cancer not detected or resected
		• Instead of surgery
		• Kills clinical cancer spread throughout the body (metastatic)
		• Non-curative (palliative) therapy

Goals of drug therapy	• Surgery cures (cancer not detectable) • Adjuvant therapy kills subclinical cancer to prevent recurrence • May increase **survival**	• Non-curable (no therapy kills all cancer cells) • Non-curative therapy kills clinical cancer to delay progression of cancer • May increase **survival** and/or improve **symptoms** (QOL?)
Monitoring	• Physical exam • Radiologic imaging (incl. of liver) • Tumor marker • Colonoscopy	• Physical exam • Radiologic imaging • Tumor marker

TYPES OF DRUG THERAPY:

Chemo-therapy	Cytotoxic	• Fluorouracil, capecitabine (PO): cell-cycle specific
		  ○ Antimetabolite, inhibits thymine synthesis
		• Oxaliplatin: genotoxic (DNA damaging)
		• Irinotecan: cell-cycle specific
		  ○ DNA replication & typology (topoisomerase I)

	Mono or combo therapy	• Combination reduces likelihood of drug resistnace
Molecular targeted therapy	Anti-angiogenic (VEGF)	• Bevacizumab
	Anti-EGFR	• Panitumumab, cetuximab

PHARMACOTHERAPY:

Fluorouracil, capecitabine	MOA	• Inhibits DNA synthesis o Leucovorin stabilizes active fluorouracil metabolite of fluorouracil
	ADRs	• Neutropenia, thrombocytopenia, anemia • Diarrhea • Store mouth, mucositis (alleviated by ice chips) • Hand-foot syndrome (soreness, redness and peeling of skin in palms & soles of feet)
Oxaliplatin	MOA	• Inhibits DNA replication and transcription by cross-linking DNA strands
	ADRs	• Neutropenia, thrombocytopenia, anemia • Reversible numbness and tingling of hands and feet (peripheral sensory neuropathy) o Cumulative dose-dependent • Unusual sensitivity to cold temp (painful spasms of throat induced by inhaling cold air or ingesting cold liquids) • Nausea and vomiting (less than cisplatin)
Irinotecan	MOA	• Inhibits DNA replication and transcription o Binds to topoisomerase I that separates DNA strands

	ADRs	• Neutropenia, thrombocytopenia, anemia
		• Nausea, vomiting
		• Diarrhea
		  o Early-onset diarrhea (< 24) hours: transient and not severe
		  ▪ Due to increased cholinergic activities
		  ▪ Responds to atropine
		  o Late onset diarrhea: prolonged and severe
		  ▪ Due to toxic metabolite in gut lumen
		  ▪ Requiring rehydration, electrolyte replacement and high dose loperamide (up to 24 mg a day)

Bevaclizumab	**MOA**	• Anti-vascular endothelial growth factor (VEGF) • Anti-angiogenesis (new blood vessels)
	ADRs	• Hypertension, proteinuria o Hold dose • Wound healing complications, hemorrhage, GI perforation • Arterial thromboembolism
Panitumumab	**MOA**	• Anti-epidermal growth factor receptor (EGFR)
	ADRs	• Acneigorm rash o Use topical clindamycin and hydrocortisone, oral minocycline • Hypomagnesemia • Infusion reaction

USE OF DRUGS:

Adjuvant *Combination chemotherapy*	Colon	Standard – 6 months of fluorouracil, leucovorin, oxaliplatin (FOLFOX)
	Rectum	Pre-operatively or post-operatively • Neoadjuvant radiation, followed by adjuvant FOLFOX • Adjuvant chemoradiation +/- further adjuvant FOLOX
Non-curative therapy *Combination chemotherapy + molecular targeted therapy*	Fluororuracil, leucovorin, irinotecan (FOLFIRI) plus bevacizumab • If irinotecan contraindicated, FOLFOX plus bevacizumab • Capecitabine alternative to fluorouracil if IV access an issue • If too frail, single agent fluorouracil, capecitabine, etc	