COLORECTAL CANCER

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Objectives

- Understand the pathophysiology of CRC
- Evaluate common presentations of suspected CRC
- Management of CRC
- Management of Anal Canal SCC

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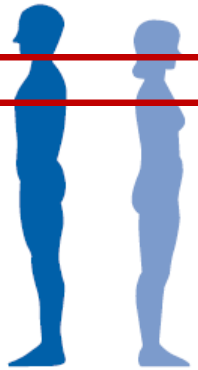
The Problem

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2019 Estimates

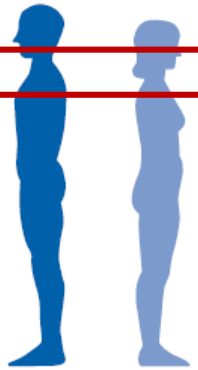
Estimated New Cases

Male			Female		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	7%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	5%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All sites	**870,970**		**All sites**	**891,480**	



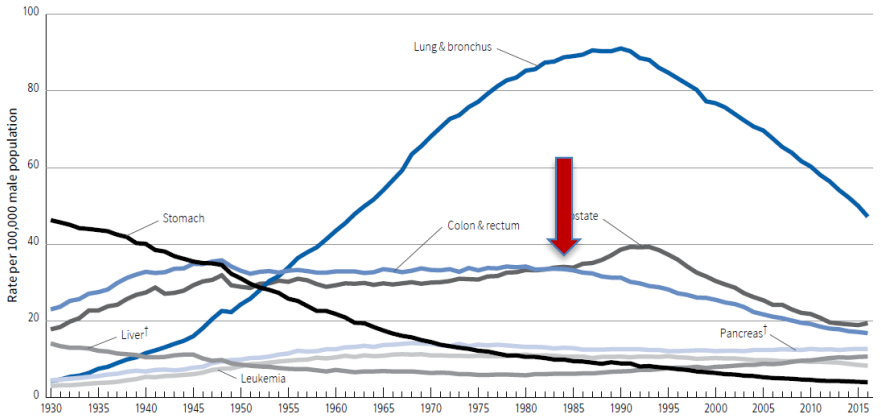
Estimated Deaths

Male			Female		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All sites	**321,670**		**All sites**	**285,210**	



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

Figure 1. Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2016

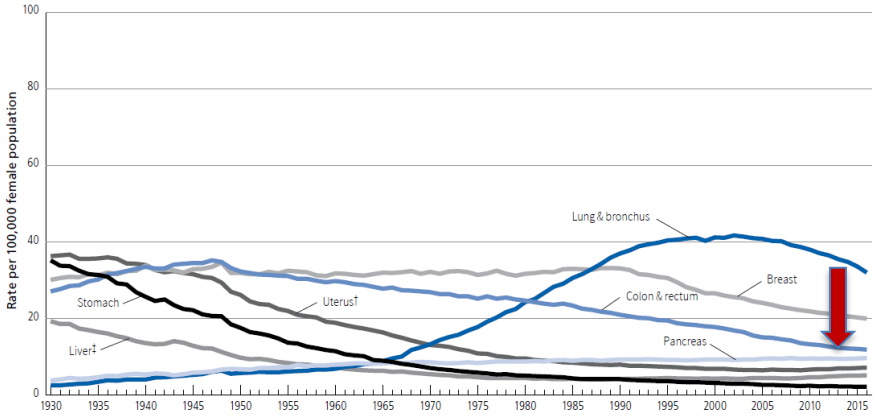


*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2016, National Center for Health Statistics, Centers for Disease Control and Prevention.

Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2016

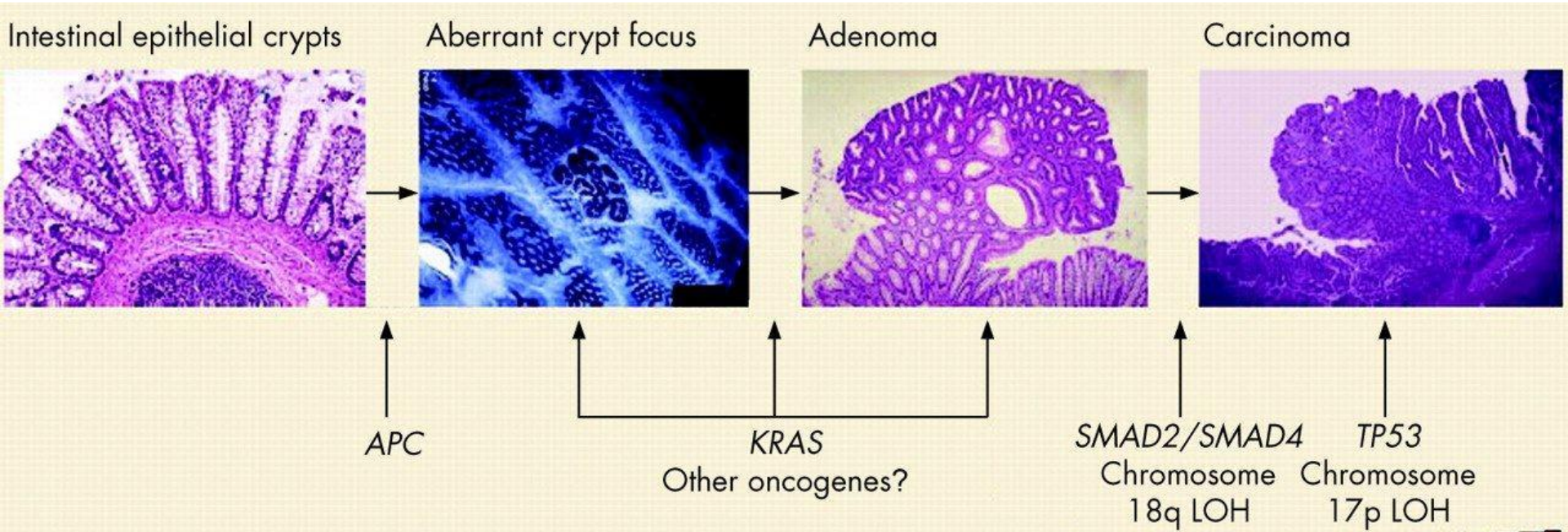


*Per 100,000, age adjusted to the 2000 US standard population. Rates exclude deaths in Puerto Rico and other US territories. †Uterus refers to uterine cervix and uterine corpus combined. ‡The mortality rate for liver cancer is increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, colon and rectum, and uterus are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2016, National Center for Health Statistics, Centers for Disease Control and Prevention.

The ‘Suspected’ Cause - Pathogenesis



- **Chromosomal instability**
- ***Microsatellite instability pathway***
  - inactivation of DNA mismatch repair proteins
- ***CpG island methylator pathway (CIMP)***
  - underlies MSI associated with MLH1 hypermethylation

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Staging

Colorectal cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres¶ to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres¶ to adjacent organs or structures

* Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (ie, respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

¶ Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classification should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.

Regional lymph nodes (N)

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Staging

N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the: • Subserosa • Mesentery • Nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Distant metastasis (M)

M category	**M criteria**
M0	No distant metastasis by imaging, etc; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

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When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB
T2-T3	N2a	M0	IIIB
T1-T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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UpToDate®

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Clinical Vignette

- 45 yo female undergoes a Rt hemicolectomy for a large non obstructive T3 poorly differentiated adenocarcinoma. No LVI or PNI. 0/35 LN. Margins –ve.

Here to discuss adjuvant therapy:

Which statement is accurate

- RAS mutation Analysis can guide adjuvant therapy decision
- Stage II MSI high tumors have an excellent prognosis and don't req adjuvant Rx
- Most cases of MSI-H tumors occur as a manifestation of Lynch syndrome

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Management

- Stage I: surgery alone
- Stage II:
  - low risk vs. high risk

  Surgery +/- Adjuvant chemo
- Stage III: Surgery plus adjuvant chemotherapy
- Stage IV: Palliative Chemotherapy (except oligometastatic disease)

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Stage II

- High Risk:
  - T4 primary
  - Inadequately sampled lymph nodes (less than 13 in the surgical specimen)
  - Bowel obstruction or perforation
  - High-grade/poorly differentiated histology
  - Lymphovascular invasion (LVI)
  - Perineural invasion (PNI)
  - Close, indeterminate, or positive margins
  - High preoperative serum carcinoembryonic antigen (CEA) level

What about MSI and Stage II

- MSI-H:
  - Hypermutability that occurs due to a deficiency in the DNA MMR
  - DNA Replication with accumulated errors
  - Microsatellites aka repeated sequences of DNA
  - MSI can be
    - Sporadic-15%; due to hypermethylation of the MLH1 gene promoter
    - Genetic-Lynch syndrome; germline mutation in MLH1, MSH2, MSH6, PMS2

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- MSI-H (IHC or PCR) portends to a better prognosis and don't respond to 5-FU based regimens*
- Popat et al# in a systematic review of 32 studies of CRC demonstrated that MSI-H pts derived no benefit from adjuvant FU-containing chemotherapy
- Sargent et al^ demonstrated that MSI-H pts treated with chemotherapy was associated with a reduced OS

*Ribic CM, NEJM,2003; #Popat S, JCO,2005;^Sargent DJ, JCO 2010

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Stage IV

Palliative intent, ECOG - IMPORTANT

- 5FU (or capecitabine) and Oxaliplatin
- 5FU (or capecitabine) and Irinotecan
- YES-BEVACIZUMAB, CETUXIMAB, PANITUMUMAB, ziv-AFLIBERCEPT, RAMUCIRUMAB, REGORAFENIB, TAS-102, Checkpoint inhibitors(MSI-H)
- NO Radiation except for palliation

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Adjuvant therapy

- 5FU (or capecitabine) and Oxaliplatin

- **NO** BEVACIZUMAB, CETUXIMAB, PANITUMUMAB, ziv-AFLIBERCEPT, RAMUCIRUMAB

- **NO** Radiation unless its rectal cancer OR Positive Margins

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What about CEA?

- Causes for elevated CEA in an individual without cancer
  - Biliary disease
  - Hepatic injury
  - Pulmonary infections
  - Smokers
  - Bowel disease

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Newer biomarkers

- Holy grail of onco-monitoring
- Several modalities of testing incl:
  - Quantitatively or structurally-altered proteins
  - Cancer-associated autoantibodies
  - Cell-free nucleic acids (cfNAs)
  - Circulating tumor cells (CTCs)
  - Cancer derived extracellular vesicles (EVs)

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Clinical Vignette

- A 58-year-old man undergoes follow-up evaluation for cancer of the ascending colon diagnosed 3 weeks ago.
- Colonoscopy at that time revealed a fungating mass in the ascending colon.
- Biopsy revealed adenocarcinoma, and additional studies showed no evidence of metastatic disease.

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- Right hemicolectomy was performed.
- The pathology report showed a 4-cm primary adenocarcinoma with clear margins at resection, full-thickness penetration through the colonic wall into pericolonic fat, and 4/21 lymph nodes involved.
- Medical history is otherwise unremarkable, and the patient takes no medications.

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Which of the following is the most appropriate management at this time?

- A Leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX)
- B Radiation therapy
- C Radiation therapy and capecitabine followed by capecitabine plus oxaliplatin (CAPOX)
- D Observation
- E CAPOX

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Clinical Vignette

- A 58-year-old man undergoes follow-up evaluation for bleeding PR.
- Colonoscopy at that time revealed a mass 6 cm from the anal verge.
- Biopsy revealed adenocarcinoma.
- MRI Pelvis demonstrated multiple perirectal LN's and additional studies showed no other evidence of metastatic disease.

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Which of the following is the most appropriate management at this time?

- A Leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX)
- B Radiation therapy
- C Radiation with concurrent capecitabine
- D Observation
- E Surgery

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Anal Cancer

- 2.5% of all Digestive Cancers
- <8500 new cases estimated for 2019
- Increased in incidence over the last 3 decades
- SCC is the most common histology

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Etiology

Higher incidence noted with :

- Infection with human papillomavirus (HPV)
- Lifetime number of sexual partners
- Genital warts
- Cigarette smoking
- Receptive anal intercourse
- Infection with HIV

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Management

- T1 (<1cm): surgery alone (no RCT comparing this with CRT)
- Localized:
  - Chemo (5FU and mitomycin C) with concurrent RT)
- Metastatic
  - Palliative systemic therapy

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Questions?

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