Clinical Colorectal Cancer

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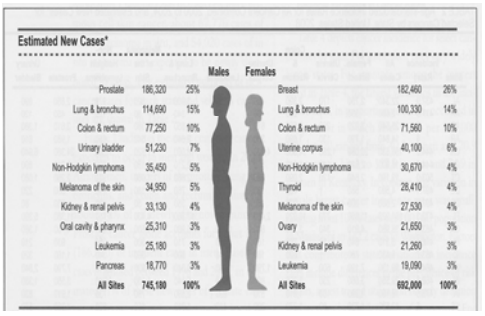
COLON CANCER

1. Epidemiology
2. Risk factors
3. Manifestations
4. Treatment

1. EPIDEMIOLOGY

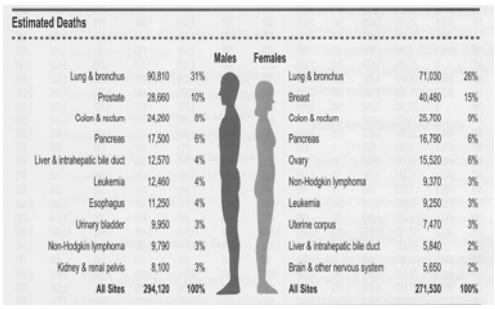
- Colorectal cancer is the third most common cancer in the United States
- About 150,000 new cases/year
- Most cases in people over 50

Colorectal Cancer Incidence, 2008

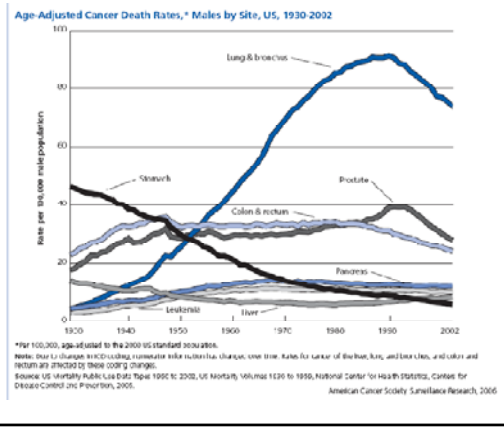


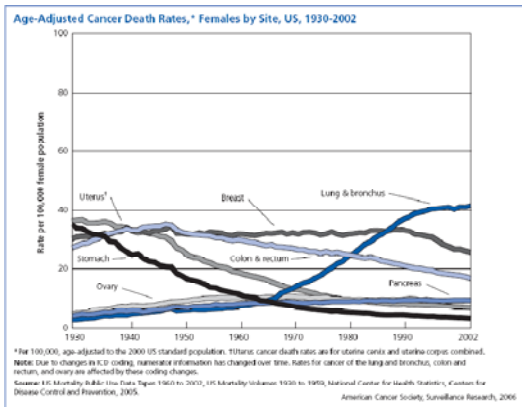
Estimated New Cases*				Males	Females			
Prostate	186,320	25%				Breast	182,460	26%
Lung & bronchus	114,690	15%				Lung & bronchus	100,330	14%
Colon & rectum	77,250	10%				Colon & rectum	71,560	10%
Urinary bladder	51,230	7%				Uterine corpus	40,100	6%
Non-Hodgkin lymphoma	35,450	5%				Non-Hodgkin lymphoma	30,670	4%
Melanoma of the skin	34,950	5%				Thyroid	28,410	4%
Kidney & renal pelvis	33,130	4%				Melanoma of the skin	27,530	4%
Oral cavity & pharynx	25,310	3%				Ovary	21,650	3%
Leukemia	25,180	3%				Kidney & renal pelvis	21,260	3%
Pancreas	18,770	3%				Leukemia	19,090	3%
All Sites	**745,180**	**100%**				**All Sites**	**692,000**	**100%**

Colorectal Cancer Deaths, 2008



Estimated Deaths				Males	Females			
Lung & bronchus	90,810	31%				Lung & bronchus	71,030	26%
Prostate	28,660	10%				Breast	40,480	15%
Colon & rectum	24,260	8%				Colon & rectum	25,700	9%
Pancreas	17,500	6%				Pancreas	16,790	6%
Liver & intrahepatic bile duct	12,570	4%				Ovary	15,520	6%
Leukemia	12,460	4%				Non-Hodgkin lymphoma	9,370	3%
Esophagus	11,250	4%				Leukemia	9,250	3%
Urinary bladder	9,950	3%				Uterine corpus	7,470	3%
Non-Hodgkin lymphoma	9,790	3%				Liver & intrahepatic bile duct	5,840	2%
Kidney & renal pelvis	8,100	3%				Brain & other nervous system	5,650	2%
All Sites	**294,120**	**100%**				**All Sites**	**271,530**	**100%**





EPIDEMIOLOGY

- Incidence rates high in U.S., Europe, Australia
- Increasing in Japan
- Low in China, Africa

EPIDEMIOLOGY

- Changes in incidence rates over time and with migration may indicate role of environmental factors

2. RISK FACTORS: Protective

- Folic acid
- Exercise
- NSAIDS
- ? Calcium/Vitamin D
- ? Fiber

NSAIDS

1) Cox-1 and Cox-2 inhibition
   - -Aspirin, Ibuprofen
   - -Bleeding risk
2) Selective Cox-2 inhibition
   - -Rofecoxib (Vioxx), -Celecoxib (Celebrex)
   - -Thrombosis risk

RISK FACTORS: Increased risk with…

-Advanced age

-Inflammatory bowel disease

-Consumption of high-fat diet

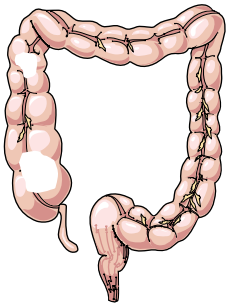
-Personal or family history of colon cancer

FAMILIAL SYNDROMES

- HNPCC
  - Hereditary non-polyposis colon cancer
- APC
  - Adenomatous polyposis coli
- Both usually autosomal dominant

HNPCC (Lynch Syndrome)
Hereditary Non-Polyposis Colon Cancer

- 2-5% of colon cancers
- Caused by mutations in mismatch repair genes
- Tend to present in the right colon
- Often associated with endometrial cancer in women
- Start screening at age 21



HNPCC Increases the Risk of Colorectal Cancer

	By age 50	By age 70
		
Population Risk	**0.2%**	**2%**
HNPCC Risk	**>25%**	**80%**

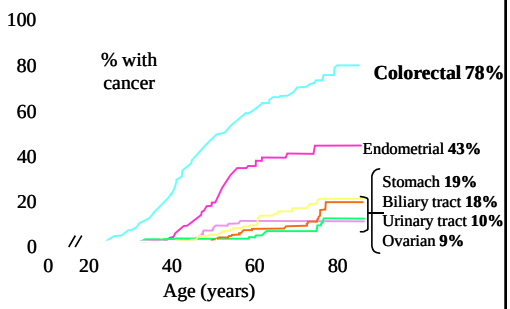
Gastroenterology **1996;110:1020-7**
Int J Cancer **1999;81:214-8**

HNPCC Increases the Risk of Endometrial Cancer

	By age 50	By age 70
		
Population Risk	**0.2%**	**1.5%**
HNPCC Risk	**20%**	**60%**

Gastroenterology **1996;110:1020-7**
Int J Cancer **1999;81:214-8**

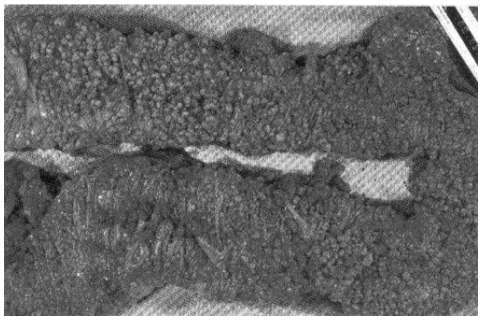
HNPCC: Cancer Risks

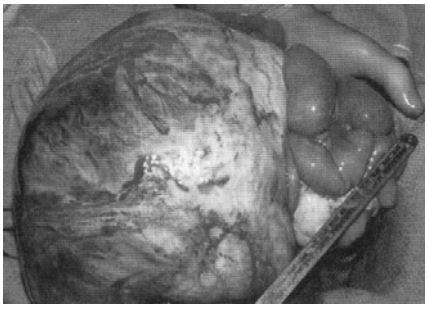


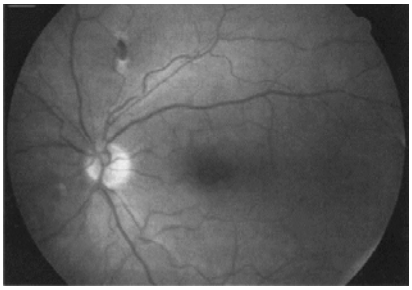
Aarnio M et al. *Int J Cancer* 64:430, 1995

APC
Adenomatous Polyposis Coli

- Less than 1% of colon cancers
- Caused by mutation of APC gene (5q21)
- Also associated with duodenal cancers, desmoid tumors, "CHRPE" (congenital hypertrophy of the retinal pigment epithelium)
- Start screening at puberty

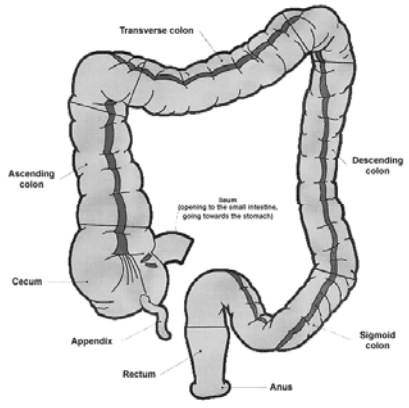






3. MANIFESTATIONS

1. Growth of cancer at primary site
2. Metastatic spread



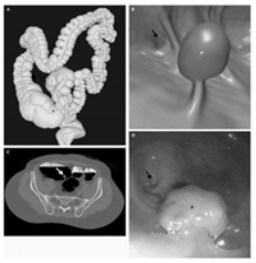
MANIFESTATIONS

1. Growth of cancer at primary site
   a. Asymptomatic/screening
   b. Right sided syndrome
   c. Left sided syndrome

MANIFESTATIONS

1. Growth of cancer at primary site
   i. Asymptomatic
      - Detected by screening test
        - Fecal occult blood
        - Sigmoidoscopy
        - Colonoscopy
        - "Virtual" colonoscopy
        - Molecular techniques

Virtual Colonoscopy



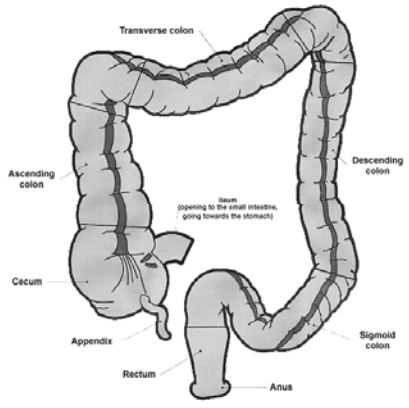
Pickhardt et al. NEJM. 349 (23): 2191. 2003

Screening summary

- Average risk: colonoscopy every 10 years over age 50
- Family history: colonoscopy 10 years before index case
- Dysplastic polyps: repeat colonoscopy after 3 years

Screening, continued…

- APC: annual flexible sigmoidoscopy starting at age 11, colectomy when polyps develop
- HNPCC: colonoscopy at age 21, then every 1-2 years
- Inflammatory bowel disease: start 8 years after pancolitis, 12 years after distal disease



MANIFESTATIONS

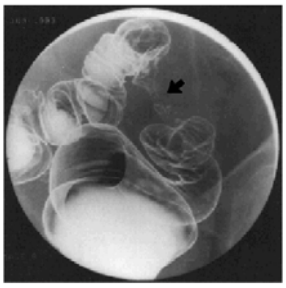
1. Growth of cancer at primary site
   ii. Right sided syndrome

   a) Ascending colon has thin wall, large diameter, distensible
   b) Liquid fecal stream
   c) Chronic blood loss results in iron deficiency anemia***
   d) Obstruction unlikely

MANIFESTATIONS

1. Growth of cancer at primary site
   iii. Left sided syndrome
      a) Descending colon wall thicker, less distensible
      b) More solid fecal stream
      c) Tumors tend to infiltrate
      d) Bright red blood more common
      e) Obstruction more common

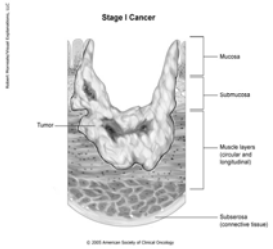
"Apple core lesion"



COMPARISON RIGHT AND LEFT SIDED COLON CANCERS

	Right	Left
Anemia	+++	+
Occult bleeding	+++	+
Gross bleeding	+	+++
Abd. Mass	++	+
Change in bowel habits	+	+++
Obstruction	+	+++

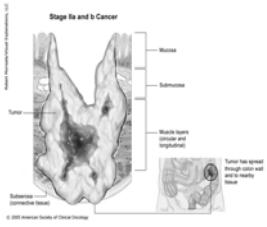
Stage 1 Colorectal Cancer



- 23% of colorectal CA
- Cancer has grown through the mucosa and invades the muscularis
- Treatment: surgery to remove the tumor and some surrounding lymph nodes
- Survival: 93%

Adapted from www.plwc.org, 2007

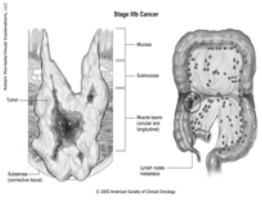
Stage 2 Colorectal Cancer



- 31% of colorectal CA
- Cancer grows beyond the muscularis of the colon or rectum but has not spread to the lymph nodes
- Treatment (colon): surgery +/- adjuvant chemotherapy
- Survival: 72 to 85%
- Treatment (rectal): surgery, radiation and chemo

Adapted from www.plwc.org, 2007

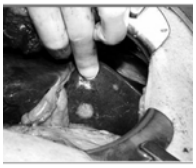
Stage 3 Colorectal Cancer



- 26% of colorectal CA
- Cancer has spread to the regional lymph nodes
- Treatment (colon): surgery and adjuvant chemotherapy
- Survival: 44 to 83%
- Treatment (rectal): surgery, radiation and chemotherapy

Adapted from www.plwc.org, 2007

Stage 4 Colorectal Cancer



- 20% of colorectal CA
- Cancer has spread to other areas of the body
- Treatment: chemotherapy. Consider surgery of primary lesion, especially if symptomatic
- Surgery to remove metastases (liver/lung) in carefully selected patients
- Survival: 8%

Source: UpToDate.com, 2007

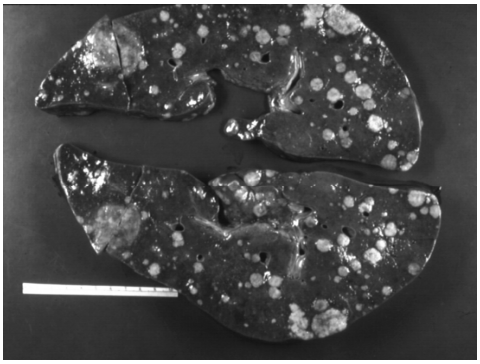
PROGNOSIS depends on…

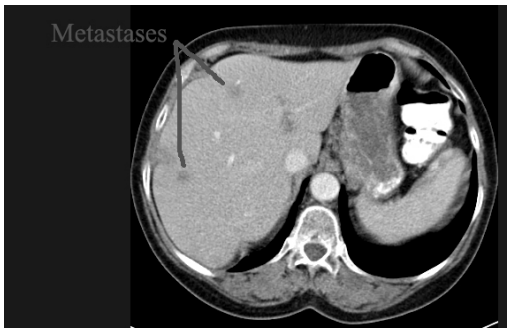
1. Histological features
   - poor differentiation
   -vascular invasion
2. Depth of invasion
3. Nodal involvement
4. Genetic alterations
   -18q LOH (bad), MSI (good), K-ras mutation (limits response to anti-EGFR antibodies)

MANIFESTATIONS

Metastatic Spread

1. Lymphatics
   Mesenteric nodes
   Virchow's node
2. Hematogenous spread
   Liver via portal circulation





LIVER METASTASES

MANIFESTATIONS

1. Pain (stretching capsule)
2. Hepatomegaly, nodularity
3. Elevated liver function tests

4. TREATMENTS

1. Surgery
   - -Localized disease (Stage I, II, III)
   - -Try to remove isolated metastases
2. Radiation therapy
   - -Rectal cancer-helps prevent local recurrence
3. Pharmaceuticals
   - -Stage III and IV disease

TREATMENT: Pharmaceuticals

1. 5-Fluorouracil
   - pyrimidine antimetabolite
2. Irinotecan
   - topoisomerase inhibitor
   - prevents re-ligation after cleavage of DNA by topoisomerase I
3. Oxaliplatin
   - alkylating agent, causes formation of bulky DNA adducts

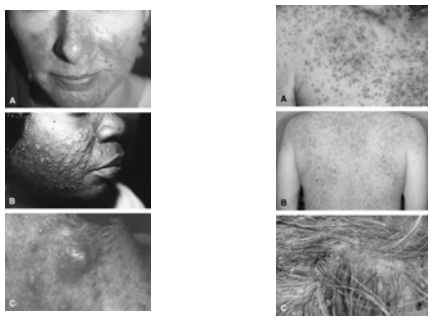
Exciting new biologics…

4. Bevacizumab
   - -Antibody against VEGF
   - -May block angiogenesis and also stabilize leaky vasculature
5. Cetuximab, Panitumomab
   - -Antibodies against EGFR
   - -Binds to EGF receptor on tumor cells, prevents dimerization and cell signaling

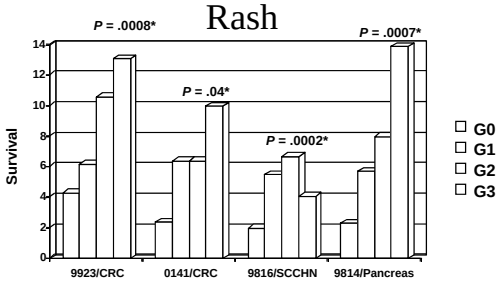
Bevacizumab toxicities

- Bleeding
- Thrombosis
- Hypertension
- Wound healing complications
- Half life about 3 weeks; wait at least 2 half-lives before major surgery

EGFR inhibition and rash



Correlating Survival With Skin Rash



* Log-rank *P* value, grade 0 vs. grades 1-3

Saltz L et al. *Proc Am Soc Clin Oncol* 2003; 22:204 (abstract 817)

Slide courtesy of Josep Tabernero, MD

Original Article

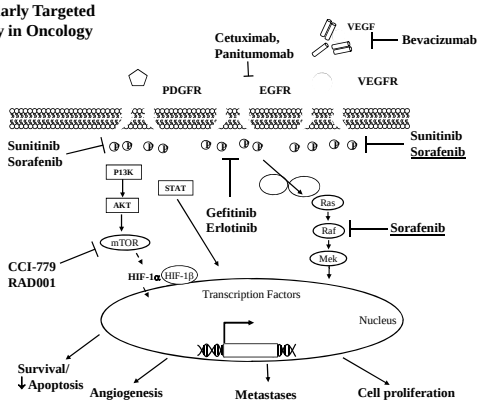
Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer

Eric Van Cutsem, M.D., Ph.D., Claus-Henning Köhne, M.D., Erika Hitre, M.D., Ph.D., Jerzy Zaluski, M.D., Chung-Rong Chang Chien, M.D., Anatoly Makhson, M.D., Ph.D., Geert D'Haens, M.D., Ph.D., Tamás Pintér, M.D., Robert Lim, M.B., Ch.B., György Bodoky, M.D., Ph.D., Jae Kyung Roh, M.D., Ph.D., Gunnar Folprecht, M.D., Paul Ruff, M.D., Christopher Stroh, Ph.D., Sabine Tejpar, M.D., Ph.D., Michael Schlichting, Dipl.-Stat., Johannes Nippgen, M.D., and Philippe Rougier, M.D., Ph.D.

N Engl J Med
Volume 360(14):1408-1417
April 2, 2009

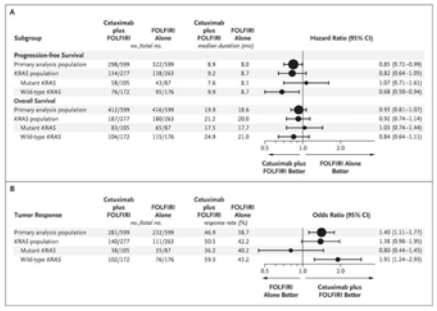
The NEW ENGLAND JOURNAL of MEDICINE

Molecularly Targeted Therapy in Oncology



Slide courtesy of Wells Messersmith, MD

Hazard Ratios for Progression-free and Overall Survival and Odds Ratios with Tumor Response, According to the Mutation Status of KRAS in the Tumor



Van Cutsem E et al. N Engl J Med 2009;360:1408-1417

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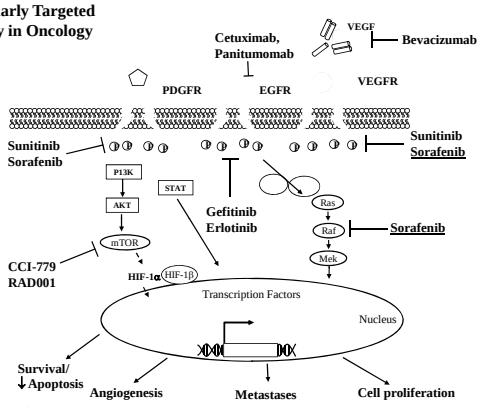


Slide courtesy of Wells Messersmith, MD

TREATMENT

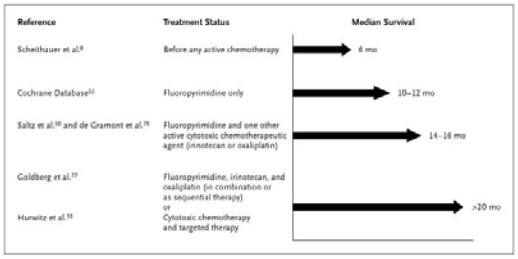
Pharmaceuticals

1. "Adjuvant" (after surgery)
   Curative goal in patients after complete resection
2. Palliation in patients with gross metastatic disease
3. "Neoadjuvant" (before surgery)
   Shrink tumors, then try to resect in limited metastatic disease

TREATMENT: Metastatic disease

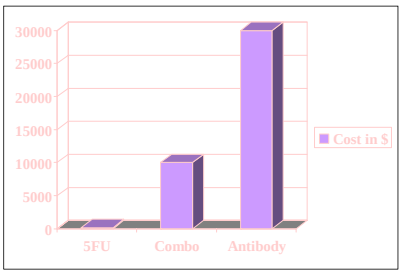
- Systemic chemotherapy now has improved survival for those with metastatic disease to about 2 years
- We now sometimes treat neoadjuvantly (before surgery), shrinking metastases and then surgically removing them
- This is important, because some of these "limited metastases" patients are cured!

Trends in the Median Survival of Patients with Advanced Colorectal Cancer



Meyerhardt, J. A. et al. N Engl J Med 2005;352:476-487

Estimated drug costs for eight weeks of treatment for metastatic colorectal cancer



Schrag, D. N Engl J Med 2004;351:317-319

Conclusions:

- Know HNPCC and APC—these may help you prevent cancers in others
- Understand how colon cancer commonly presents (right versus left-sided), and common sites of spread
- Think about colon (or other GI) cancer in an older person with iron-deficiency anemia—don't just give them iron!
- Don't give up on those with metastatic disease with new treatment options and occasionally cures

- My email:
- aas54@columbia.edu
- Many thanks to Tom Garrett for many slides!