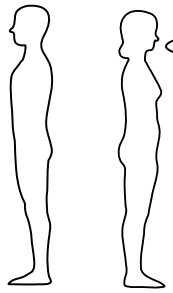
# Screening and Treatment of Colon Cancer

**Maher Azzouz, MD**
**Associate Professor of Medicine**
**Ohio State University**
**James Cancer Center**

## 2008 Estimated US Cancer Deaths*

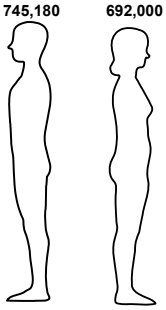
| Men | | Women | |
|---|---|---|---|
| Lung & bronchus | 31% | 26% | Lung & bronchus |
| Prostate | 10% | 15% | Breast |
| Colon & rectum | 8% | 9% | Colon & rectum |
| Pancreas | 6% | 6% | Pancreas |
| Liver & intrahepatic bile duct | 4% | 6% | Ovary |
| Leukemia | 4% | 3% | Non-Hodgkin lymphoma |
| Esophagus | 4% | 3% | Leukemia |
| Urinary bladder | 3% | 3% | Uterine corpus |
| Non-Hodgkin lymphoma | 3% | 2% | Liver & intrahepatic bile duct |
| Kidney & renal pelvis | 3% | 2% | Brain/ONS |
| All other sites | 24% | 25% | All other sites |




ONS=Other nervous system.
Source: American Cancer Society, 2008.

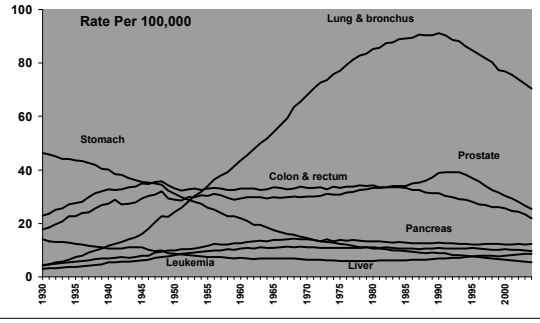
## 2008 Estimated US Cancer Cases*

| Men | | Women | |
|---|---|---|---|
| Prostate | 25% | 26% | Breast |
| Lung & bronchus | 15% | 14% | Lung & bronchus |
| Colon & rectum | 10% | 10% | Colon & rectum |
| Urinary bladder | 7% | 6% | Uterine corpus |
| Non-Hodgkin lymphoma | 5% | 4% | Non-Hodgkin lymphoma |
| Melanoma of skin | 5% | 4% | Thyroid |
| Kidney & renal pelvis | 4% | 4% | Melanoma of skin |
| Oral cavity | 3% | 3% | Ovary |
| Leukemia | 3% | 3% | Kidney & renal pelvis |
| Pancreas | 3% | 3% | Leukemia |
| All Other Sites | 20% | 23% | All Other Sites |



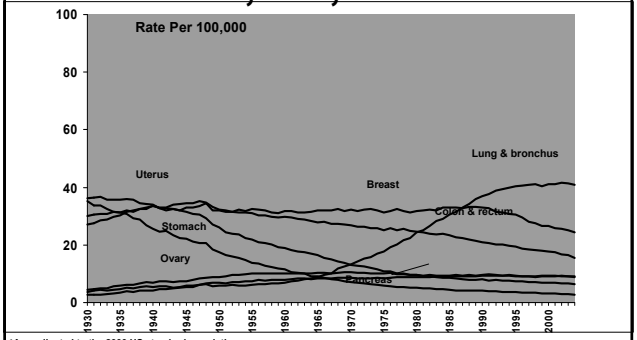

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2008.

## Cancer Death Rates* Among Men, US,1930-2004



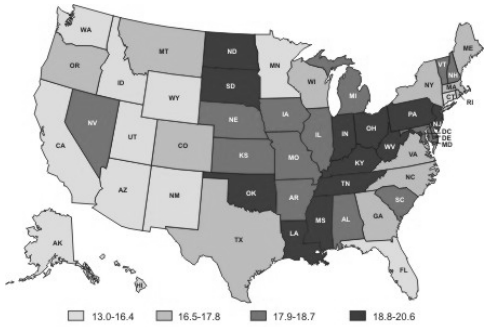

*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2004, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

## Cancer Death Rates* Among Women, US,1930-2004

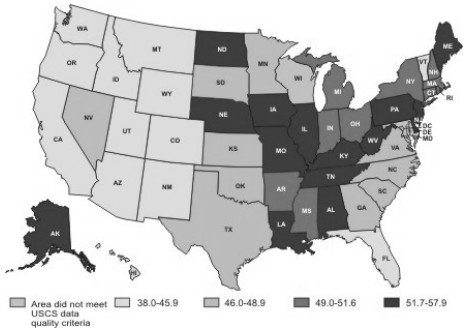



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2004, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

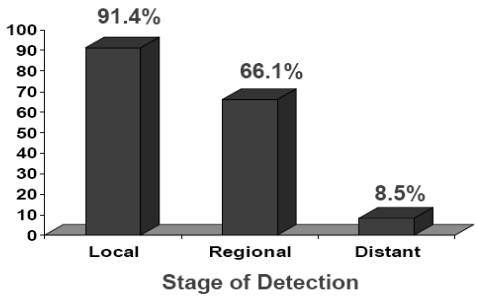
## Colorectal Cancer Death Rates,* by State, 2005†



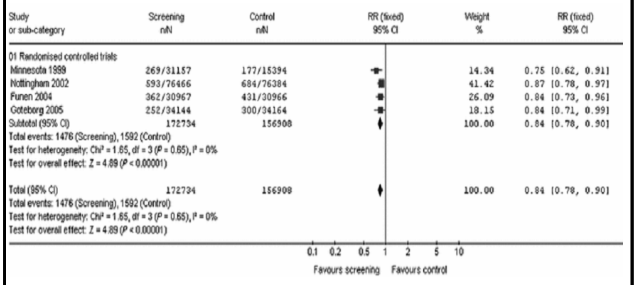

## Colorectal Cancer Incidence Rates,* by State, 2005†




## Survival by Stage of Detection



# FOBT and Effect on Mortality




Am J Gastroenterol. 2008;103(6):1541-1549

# Risk Factors for Colon Cancer

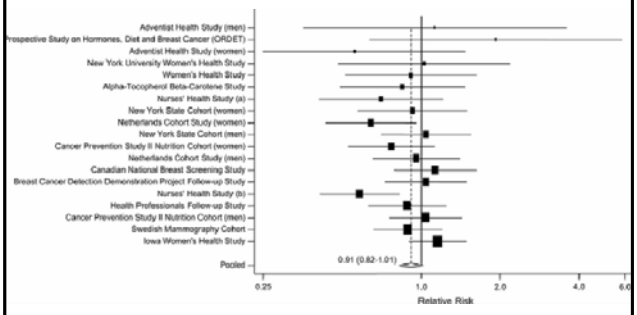
**Factors that may contribute to increased risk:**

- **Lack of regular physical activity**
- **Diet high in saturated fats, such as red meat** (RR 2.1 – 4.0)
- **Low fruit and vegetable intake**
- **A low-fiber and high-fat diet**
- **Overweight and obesity**
- **Alcohol consumption**
- **Tobacco use**
- **Diabetes**
- **Pelvic Radiation**

# Risk Factors for Colon Cancer

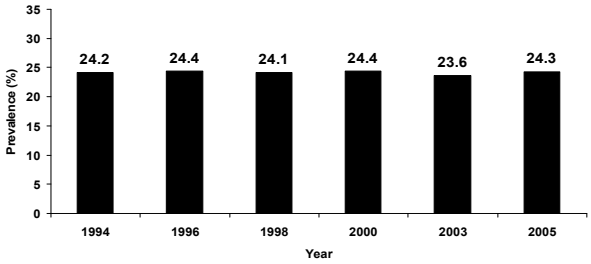
- **Personal history of adenomatous polyps**
- **Advancing age**
  - **CRC: 90% occur in people aged 50 or older**
  - **Adenomatous Polyps 33% at age 50**
    **70% at age 70**
- **A family history of CRC or colorectal polyps**
- **Inflammatory bowel disease**
- **Certain hereditary syndromes**
  - **HNPCC, FAP, Uterine/Ovarian cancer in a young patient**

# Fruits, Vegetables, and Colon Cancer Risk




J Natl Cancer Inst. 2007;99(19):1471-1483

## Trends in Consumption of Five or More Recommended Vegetable and Fruit Servings for Cancer Prevention Adults 18 and Older, US, 1994-2005




Note: Data from participating states and the District of Columbia were aggregated to represent the United States. Source: Behavioral Risk Factor Surveillance System CD-ROM (1984-1995, 1996, 1998) and Public Use Data Tape (2000, 2003, 2005), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 1997, 1999, 2000, 2001, 2004, 2006.

## FOBT: Mortality Reduction

Potential Mortality Reduction

Adherence at Every level: 100% → 40%

IF adherence to initial test: 75%

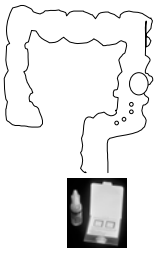
IF adherence to repeat test after (-) test: 67%

IF rate of colonoscopy after (+) test: 75%

→ < 20%

Effective – but only in a program of repeat testing

## FOBT- One-time Testing



% of patients with cancer who have (+) test — 33- 60%

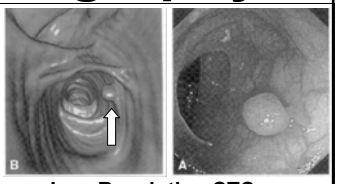
% of patients with serious Polyps who have (+) test — 11- 50%



More than 50% of patients with serious polyps will not be detected with one test !!!

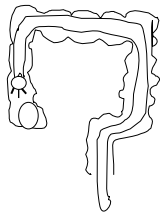
## CT Colonography

- Inter-observer variability
- Detection of flat polyps
- Bowel Prep
- Radiation
- Extracolonic findings
- Intervals uncertain:
  - ✓ After negative exam
  - ✓ After exam with small polyps



Low Resolution CTC

# Colonoscopy



**Evidence: Cohort Studies**

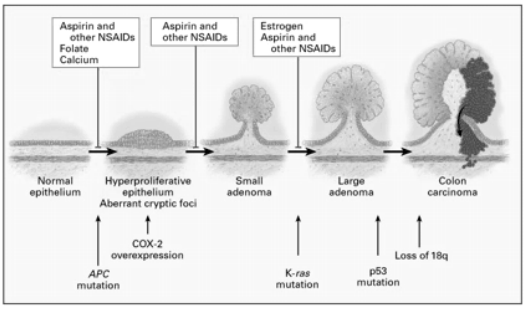
**Efficacy: Uncertain, but extrapolated from FOBT and Sig studies**

**Quality in practice: unknown**

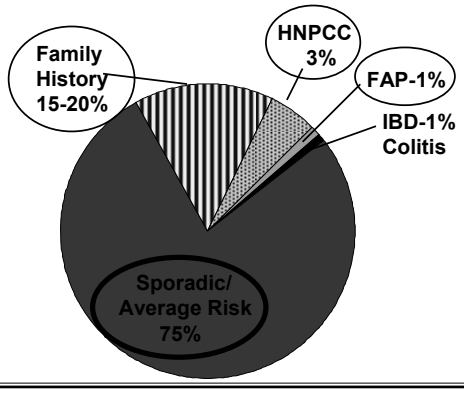
**Program performance: unknown**

**National colonoscopy study (Winawer)**

# Chromosomal Instability (CIN)




# Risk Factors for CRC

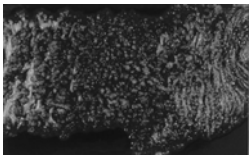



# Familial Adenomatous Polyposis (FAP)

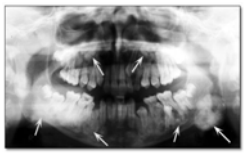
- **FAP accounts for 1% of CRC**
- **Hundreds to thousands of colon polyps**
- **Penetrance is 100% (All polyps will develop cancer)**
- **Colorectal cancer usually occurs by age 40**
- **Yearly screening at age 12**

| Gastrointestinal Lesions | Extraintestinal Features |
|---|---|
| •Gastric adenomas | •Brain Tumors |
| •Fundic Gland polyps | •Osteomas |
| •Duedenal,Ampullary adenoma | •Desmoid Tumors |
| •Jejunoileal adenomas | •Epidermal Cysts |
| •Colorectal Cancer | •Congenital hypertrophy of the retinal pigment epithelium CHRPE |

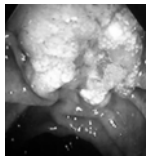
## Familial Adenomatous Polyposis (FAP)



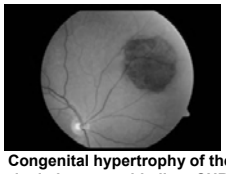
Colon Adenomas



Osteomas



Duedenal adenoma



Congenital hypertrophy of the retinal pigment epithelium CHRPE

# Familial adenomatous polyposis (FAP)

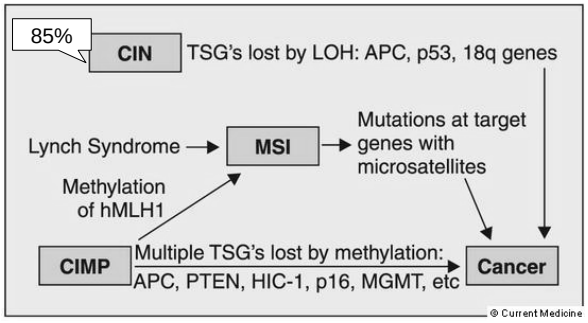
- APC gene mutations on chromosome 5q21
- Autosomal dominant disease
- Genetic testing is available
- Counseling and informed consent
- Colectomy in late teens in gene carriers
- Screening to include upper GI tract
- Decreased screening in non carriers

- Attenuated FAP: people have fewer polyps

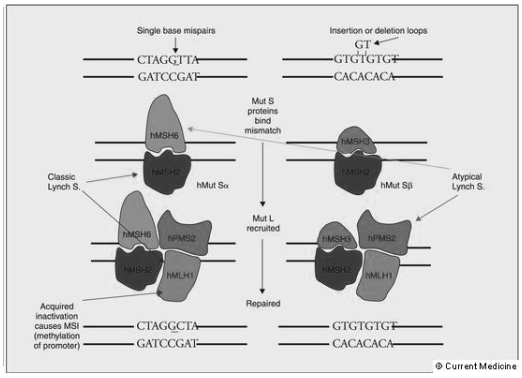
# Familial adenomatous polyposis (FAP)

- APC gene mutations on chromosome 5q21
- Autosomal dominant disease
- Genetic testing is available
- Counseling and informed consent

## Microsatellite Instability (MSI)



# DNA mismatch repair (MMR)



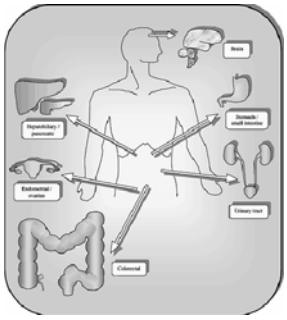

# The modified Amsterdam criteria for Lynch syndrome

| |
|---|
| **Three or more family members**<br>**colorectal cancer, or a Lynch syndrome phenotype cancer**<br>(endometrial cancer, gastric cancer, ovarian cancer, cancer of the urinary tract, small intestinal cancer, and brain tumors) |
| **One is a first degree relative of the other two** |
| **At least two generations are involved** |
| **Familial adenomatous polyposis is excluded** |
| **One person with cancer less than 50 years of age** |

**Familial colorectal cancer, syndrome X**
lack microsatellite instability MSI
lack of mutation in DNA mismatch repair gene

# Hereditary Colorectal Cancer Syndromes: HNPCC

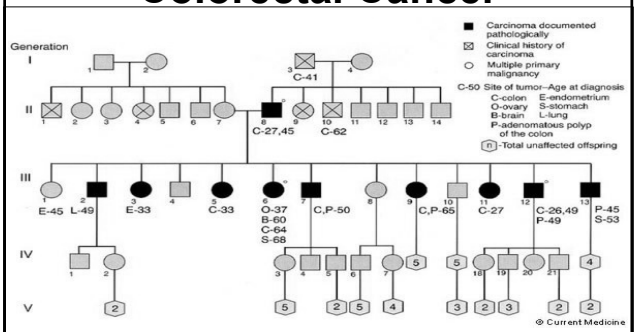
- **Lynch syndrome: 5% to 10% of all CRC**
- **Autosomal Dominant Disease**
- **Mismatch Repair gene mutation**
- **The risk of CRC**
  - **70% to 90%,**
  - **Average age of 45**
  - **Proximal Location**
- **Extraintestinal cancers**
- **Genetic testing for HNPCC genes is available**



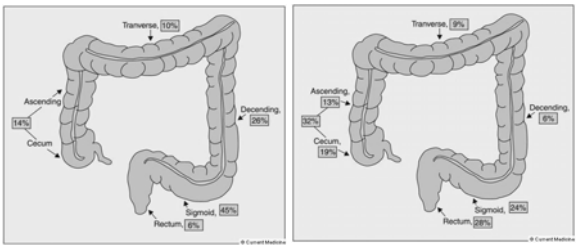
# Revised Bethesda Criteria Screen for Microsatellite Instability (MSI)

| |
|---|
| **CRC in a patient who is ≤ 50 years of age** |
| **Presence of CRC or other Lynch syndrome-associated tumors, regardless of age** |
| **CRC with the MSI-H histology diagnosed in a patient who is ≤ 60 years of age** |
| **CRC in one or more first-degree relatives with an HNPCC-related tumor, one of the cancers diagnosed ≤ 50 years** |
| **CRC in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age** |

# Inheritance in Family with Hereditary Nonpolyposis Colorectal Cancer

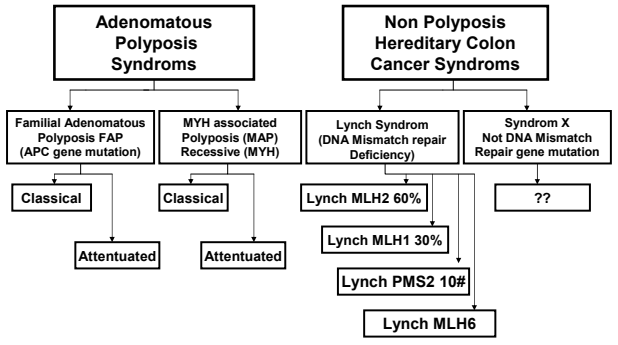



# Distribution of Polyps and Cancer




**Adenomatous Polyps** | **Cancer**

# Hereditary Colorectal Cancer




# ACS Screening Recommendations 2008

| | |
|---|---|
| • Colonoscopy (Gold Standard) | Every 10 years |
| • Flexible Sigmoidoscopy and FOBT | Every 5 years |
| • CT colonography | Every 5 years |
| • Flexible Sigmoidoscopy | Every 5 years |
| • Double Contrast Barium Enema | Every 5 years |
| • FOBT or FIT | Annually |
| • A stool DNA test | Interval uncertain |

**All positive tests must be followed up with a colonoscopy**

## ACS Screening Recommendations 2008

- Colonoscopy (Gold Standard) — Every 10 years
- Flexible Sigmoidoscopy and FOB — Can detect Precancerous polyps and early cancer
- CT colonography — Every 5 years
- Flexible Sigmoidoscopy — Every 5 years
- Double Contrast Barium Enema — Every 5 years
- FOBT or FIT — Annually
- A stool DNA test — Interval uncertain

All positive tests must be followed up with a colonoscopy

## Colorectal Cancer Screening Guidelines 2008

### Average Risk

- Age ≥ 50
- No History of Adenoma
- No History of IBD
- Negative Family History


## ACS Screening Recommendations 2008

- Colonoscopy (Gold Standard) — Every 10 years
- Flexible Sigmoidoscopy and FOB — Can detect Precancerous polyps and early cancer
- CT colonography — Every 5 years
- Flexible Sigmoidoscopy — Every 5 years
- Double Contrast Barium Enema — Every 5 years
- FOBT or FIT — Annually
- A stool DNA test — Can detect early cancer


## Colorectal Cancer Screening Guidelines 2008

### Average Risk

- Age ≥ 50
- No History of Adenoma
- No History of IBD
- Negative Family History

→

- Screening at 50 years
- Repeat every 10 years if negative
- Repeat 3-5 years if polyps are found

# Colorectal Cancer Screening Guidelines 2008

## Increased Risk

**I. Personal History**

- Adenomatous Polyps
- Cancer
- Endometrial/Ovarian Cancer ≤60
- Inflammatory Bowel Disease

# Colorectal Cancer Screening Guidelines 2008

## Increased Risk

**II. Family History**

- One 1st degree relative with CRC
- Two 2nd degree relative with CRC
- Clustering of CRC or HNPCC related cancer

# Colorectal Cancer Screening Guidelines 2008

## Increased Risk

**I. Personal History**

- Adenomatous Polyps
- Cancer
- Endometrial/Ovarian Cancer ≤60
- Inflammatory Bowel Disease

→ Repeat in 3-5 years

→ Repeat within 1 year

→ Start at age 40 years

→ Start 8-10 years after on set

# Colorectal Cancer Screening Guidelines 2008

## Increased Risk

**II. Family History**

- One 1st degree relative with CRC
- Two 2nd degree relative with CRC
- Clustering of CRC or HNPCC related cancer

→

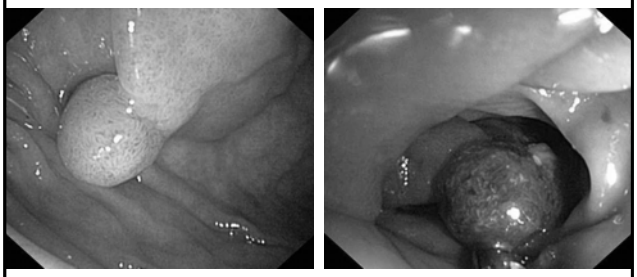
- Start Screening at age 40 or 10 years prior to the earliest CRC case in the family
- Repeat every 5 years

# Colorectal Cancer Screening Guidelines 2008

**Increased Risk**

**III. Hereditary**
- CRC age ≤ 50
- Multiple HNPCC related cancer
- HNPCC cancer with family history of CRC or HNPCC cancers
- FAP
- Lynch Syndrome
- Other polyposis syndromes

# Adenomatous Polyps



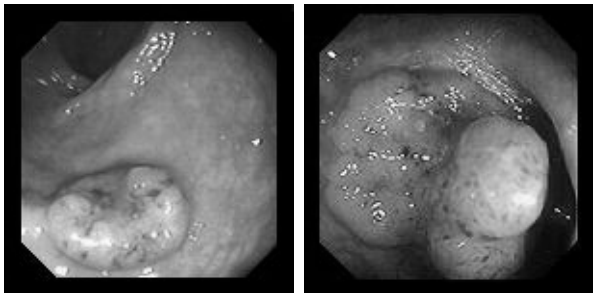
# Colorectal Cancer Screening Guidelines 2008

**Increased Risk**

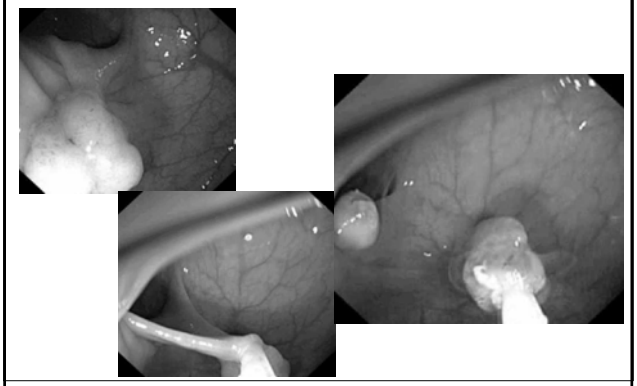
**III. Hereditary**
- CRC age ≤ 50
- Multiple HNPCC related cancer
- HNPCC cancer with family history of CRC or HNPCC cancers
- FAP
- Lynch Syndrome
- Other polyposis syndromes

- Early specific Screening
- Upper GI tract screening
- Non GI cancer screening
- Consider genetic testing and counceling

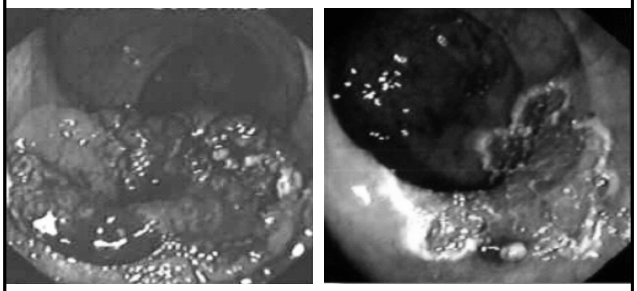
# Malignant Polyp



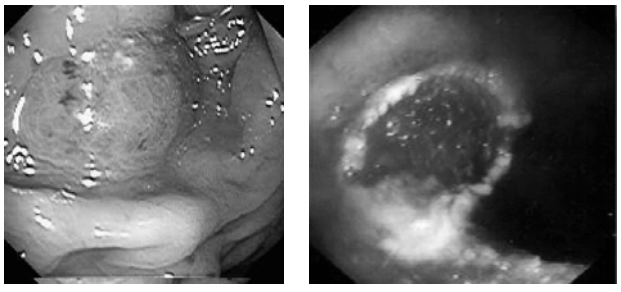
## Adenomatous Polypectomy



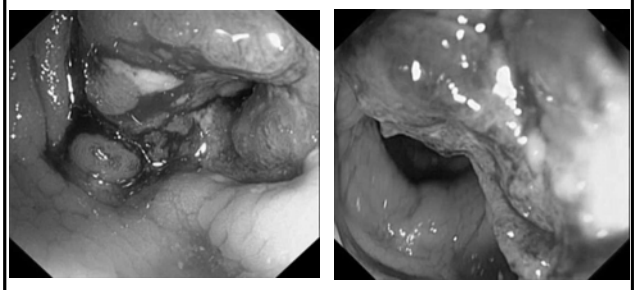
## Mucosectomy for T1



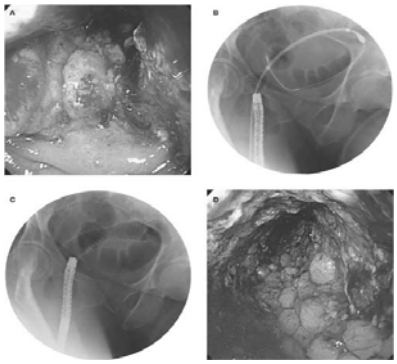
## Mucosectomy for T1



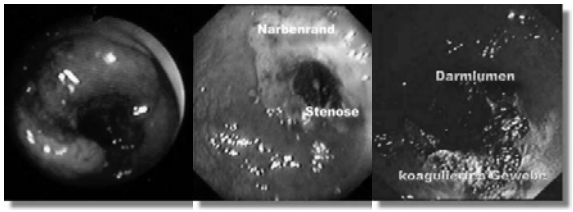
## Obstructing Cancer



## Self Expandable Metal Stent

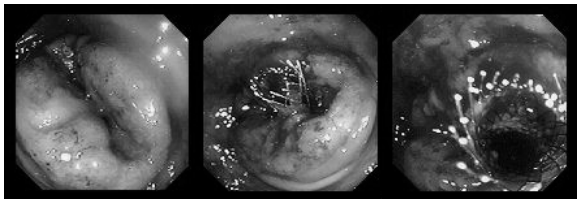


## Ablation Therapy




Argon-plasma-coagulation

## Self Expandable Metal Stent



## Cost-effectiveness (Cost/Year of Life Saved)

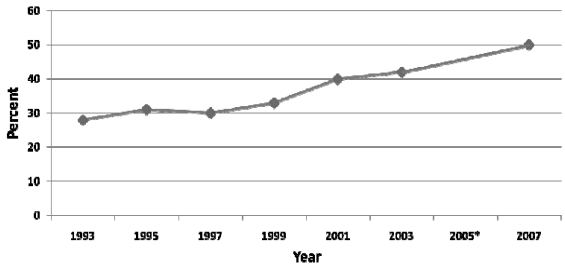
| | |
|---|---|
| • Mandatory motorcycle helmets | $2000.00 |
| • Colorectal cancer screening | $25,000.00 |
| • Breast cancer screening | $35,000.00 |
| • Dual airbags in cars | $120,000.00 |
| • Smoke detectors in homes | $210,000.00 |
| • School bus seat belts | $1,800,000.00 |

# Future Of Screening for CRC

**A recent CDC study demonstrated that:**

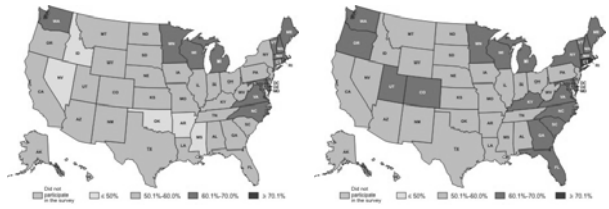
- **Approximately 41.8 million average-risk people aged 50 or older have not been screened for colorectal cancer according to national guidelines.**
- **The U.S. health care system has enough capacity to conduct widespread screening of the unscreened population, using FOBT and diagnostic colonoscopy for those with a positive FOBT.**
- **Widespread screening with flexible sigmoidoscopy or colonoscopy may take up to 10 years, depending on the proportion of available capacity used for colorectal cancer screening**

# Trend in the prevelance of persons 50 and older reported having had a Sigmoidoscopy/Colonoscopy over the past 5 years in Ohio




Ohio Behavioral Risk Factor Surveillance System, Ohio Department of Health, 2008

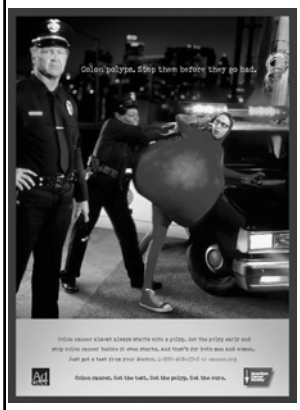
# Behavioral Risk Factor Surveillance System (BRFSS) in the US



**2004** **2006**

# ACS Colorectal Cancer Objectives

- **By 2015, reduce the age-adjusted incidence rate of colorectal cancer by 40%**
- **By 2015, reduce the age-adjusted mortality rate of colorectal cancer by 50%**
- **By 2015, increase to 75% the proportion of people aged 50 and older who have colorectal screening consistent National guidelines**




**Ohio**

***Senate Bill 50/House Bill 266 (Cancer Screening Coverage Legislation)***

**National**

***Senate Bill 710/House Representative Bill 1520 (Eliminate Colorectal Cancer Act)***

# Physician Intervention

**The positive impact of a doctor's advice has been demonstrated in studies of cancer screening behavior for several cancers:**

1. **Having a received a physician's recommendation for a flexible sigmoidoscopy makes it more likely that an individual will be screened for CRC.**
2. **More preventive health visits also increase the likelihood of screening.**
3. **Having seen a physician within the prior year is one of the strongest predictors of receipt of CRC screening.**

1.Zapka JG, Puleo E, Vickers-Lahti M, Luckmann R. Healthcare system factors and colorectal cancer screening. AM J Prev Med. 2002
2.Ouyang DI, Chen JJ, Getzenberg RH, Schoen RE, Noninvasive testing for colorectal cancer: a review. Am J Gastroenterol. 2005, June
3.Seef LC, Nadel MR, Klabunde CN, Thompson T, Shapiro JA, Vernon

# Strategies to Increase CRC Screening

1. **Increase Public Awareness: Increase individual awareness of personal risk and stimulate action.**
2. **Affect Physician Behavior Change: Reach out to physicians individually and through systems to provide screening advice, support and resources.**
3. **Advocate for Coverage: Advocate for state and federal policies to increase access to breast and colon cancer screening.**
4. **Collaboration: Collaborations provide access to large numbers of people, physicians, and policy decision-makers. They include:**
   - **Physicians**
   - **Health Plans**
   - **Employers**
   - **Health Care Systems**
   - **Influencers (Trade and Accreditation Orgs.)**

# Conclusion

**"The barrier to reducing the number of death from colorectal cancer is not a lack of scientific data but a lack of organizational, financial, and societal commitment."**

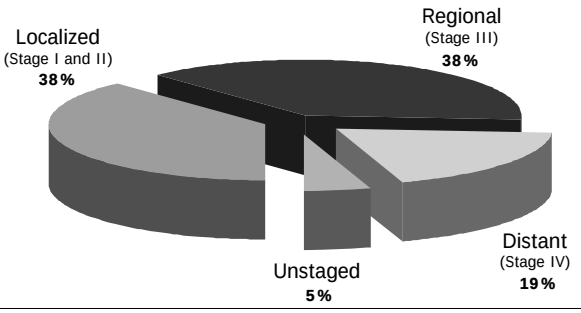
**Daniel K. Podolsky, MD (NEJM 7/20/00)**

# Therapeutic and Surveillance Strategies in Colorectal Cancer

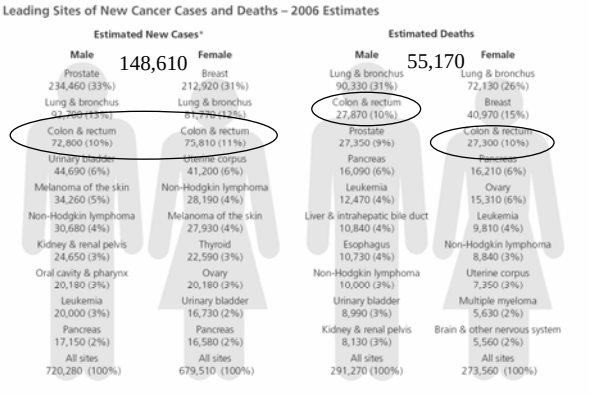

## Tanios Bekaii-Saab ,MD

**Assistant Professor of Medicine and Pharmacology**
**Ohio State University**
**James Cancer Hospital**

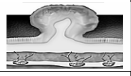
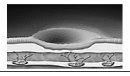
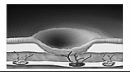
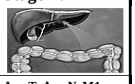

# CRC Stage at Diagnosis




Ries et al (eds). *SEER Cancer Statistics Review, 1975-2000.*
National Cancer Institute. Bethesda, MD. At: http://seer.cancer.gov/csr/1975_2000.



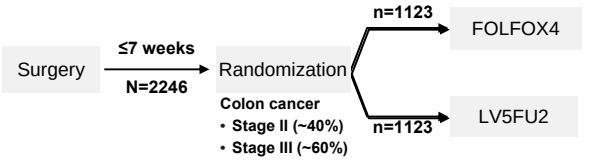

# AJCC Staging Guidelines for CRC

| | Stage I | Stage II | Stage III | Stage IV |
|---|---|---|---|---|
| **Disease development** |  |  |  |  |
| **Staging** | **T1, N0, M0**<br>**T2, N0, M0** | **A: T3, N0, M0**<br>**B: T4, N0, M0** | **A: T1-2, N1, M0**<br>**B: T3-4, N1, M0**<br>**C: Any T, N2, M0** | **Any T, Any N, M1** |
| **Definition** | **Invades submucosa (T1)/ muscular propria (T2)** | **Invades subserosa, nonperitonealized pericolic/perirectal tissues (T3) invades other organs or structures/visceral peritoneum (T4)** | **Involves 1-3 (N1) or more (N2) lymph nodes** | **Involves distant metastases** |
| **Usual treatment** | **Surgery** | **Surgery ± chemotherapy** | **Surgery + chemotherapy** | **Chemotherapy ± surgery** |

*AJCC Cancer Staging Manual, Sixth Edition.*
National Comprehensive Cancer Network *Clinical `Practice Guidelines in Oncology:* Colon Cancer. v.1.2004.
Image adapted from http://www.exactsciences.com/pregen26/professionals/about_hnpcc/_index.htm#: Accessed 1/16/04.

# Stage II and III Colorectal Cancer: A Closer Look

## MOSAIC Phase III Trial




LV5FU2= 5 - Fluorouracil + Leucovorin
FOLFOX4 = LV5FU2 + Oxaliplatin

- **Primary end point: disease-free survival (DFS)**
- **Secondary end points: overall survival (OS), safety**

## Increasing Negative Lymph Node count in Stage III CRC is independently associated with improved long term outcome

5-Year Cumulative Survival

| # Negative Nodes | Stage IIIA | Stage IIIB | Stage IIIC |
|---|---|---|---|
| ≤ 3 nodes | 86.5% | 56.3% | 39.0% |
| ≥ 13 nodes | 87.6% | 73.3% | 60.8% |

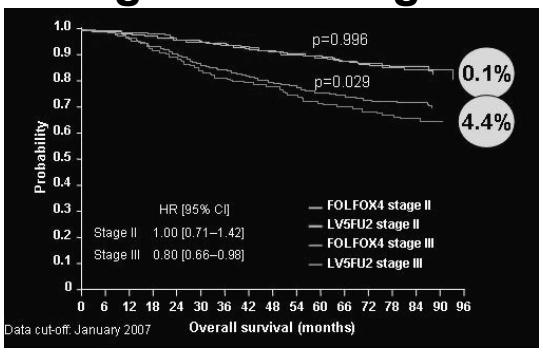
Baxter et al , ASCO GI 2006 , abs 219

## MOSAIC: Summary

| | FOLFOX4 | LV5FU2 | *P* |
|---|---|---|---|
| N (overall) | 1123 | 1123 | -- |
| 5-year DFS (overall) | 73.3 | 67.4 | 0.003 |
| n (stage III) | 672 | 675 | -- |
| 5-year DFS (stage III) | 66.4% | 58.9% | .0.78 |

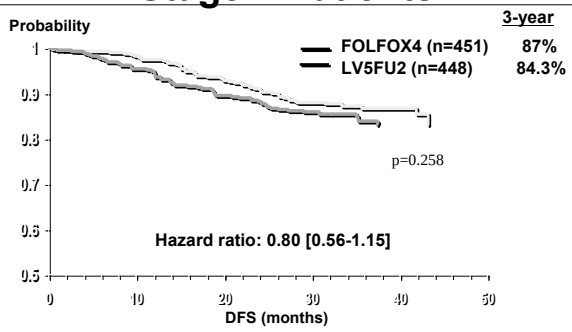
De Gramont et al, ASCO 2007; Abs 4007

# Overall Survival: Stage II and Stage III




De Gramont et al, ASCO 2007; Abs 4007

# MOSAIC – Disease-Free Survival: Stage II Patients




**20% risk reduction for stage II patients in the FOLFOX4 arm**

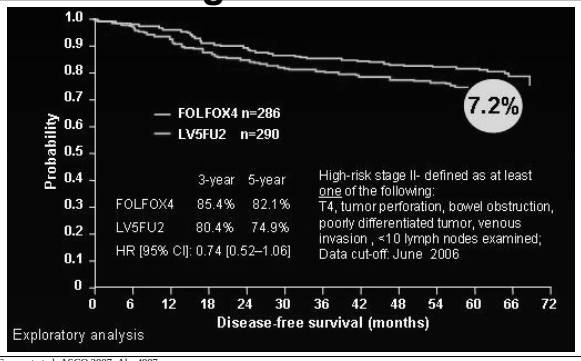
De Gramont et al, ASCO 2007; Abs 4007

# ASCO Recommendations: Stage II Disease

- **Routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer is NOT recommended**
- ***Subsets* of patients in whom adjuvant therapy can be considered include those with:**
  - ✓ **Inadequately sampled lymph nodes**
  - ✓ **Poorly differentiated histology**
  - ✓ **T4 lesions**
  - ✓ **Perforation**

Benson et al. *J Clin Oncol* 2004

# Disease-Free Survival: High-Risk Stage II Patients




De Gramont et al, ASCO 2007; Abs 4007

# Stage II Colon Cancer

- Most large cooperative group studies have failed to demonstrate survival benefit due to:
  - ✓ Insufficient number of patients in earlier trials
  - ✓ Relatively good prognosis in stage II disease
- Many patients needed to detect treatment benefit

| | Survival | ARR* | No. of patients |
|---|---|---|---|
| At 3 years | 85% | 2.5% | 8,000 |
| At 5 years | 75% | 4% | 4,700 |

** ARR: absolute risk reduction*

# Surveillance Strategies in Stage II and III Colorectal Cancers

# Stage II Colorectal Cancer

- May need to identify subsets of patients who might benefit:
  - Genomic markers - 18q, microsatellite instability (MSI), p53, thymidylate synthase (TS), TGF-β, methylation (CIMP), et al
- New protocols examining stage II role of markers
  - Eastern Cooperative Oncology Group (ECOG): Evaluating role of thymidylate synthase (TS) as indicator of prognosis – need for adjuvant chemotherapy for stage II

# Patterns of Recurrence

- 85% of colon cancer recurrences are diagnosed in the first 3 years after surgical resection.
- Most of the recurrences involve the liver

# History and Physical

- Lack of outcome data
- Frequency : Every 3-6 months for 3 years , then every 6 months for years 4 and 5 and then yearly.
- Only 20% of all recurrences are found on the basis of a H&P
- 45% of recurrences within the first 3 years occur between visits and tests

# CT Scanning

- Candidates for CT scanning include:
  - ✓ High risk patients ( T4 , N+ … )
  - ✓ Patients who would be candidates for liver resection
- Every year for 3 years after surgery
- 3 metanalysis showed a survival benefit for patients with " liver" imaging ( 25% lower mortality).

# Laboratory Data

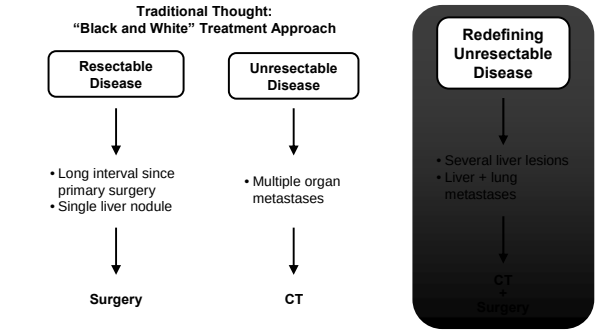
- Lack of specificity and sensitivity for a routine CBC testing or LFTS
- CEA should be tested every 3 months for at least 3 years from diagnosis.
  - ✓ If CEA is elevated , retesting is warranted. If still increasing , then further evaluation needs to be performed.
  - ✓ Institution of chemotherapy should never be based on an elevation of CEA.
  - ✓ Of note that 20-30% of all asymptomatic recurrences are not associated with CEA elevations
  - ✓ Nearly 80% of all colorectal recurrences are found based on an elevated CEA

# Colonoscopy

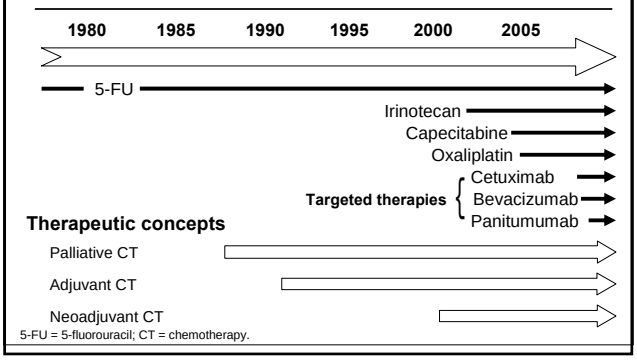
- At the time of surgery , the patients should have complete visualization of their large bowel to rule out any metachronous lesions.
- Studies are conflicting about the value of periodic examinations.
  - ✓ In one study by Juhl et al only 1/56 recurrences was in the anastomotic site whereas another study showed 3/17 to be at the anastomotic site
- Each patient should have a post-operative colonoscopy to document cancer and polyp-free colon.
- Frequency : 1$^{st}$ year after surgery, then at 3 years and finally at 5 years

# Stage IV Colorectal Cancer

## Making More Patients Eligible Candidates for Surgery




## Advances in the Treatment of Colorectal Cancer



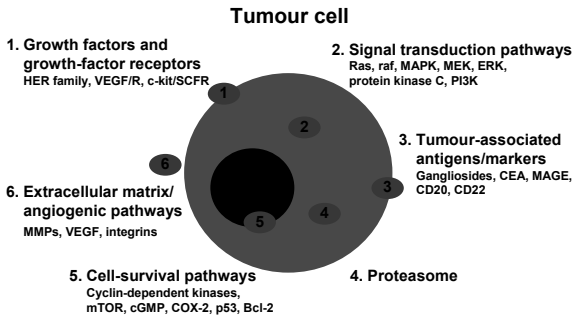

5-FU = 5-fluorouracil; CT = chemotherapy.

# The Role Of Cytotoxic Therapy

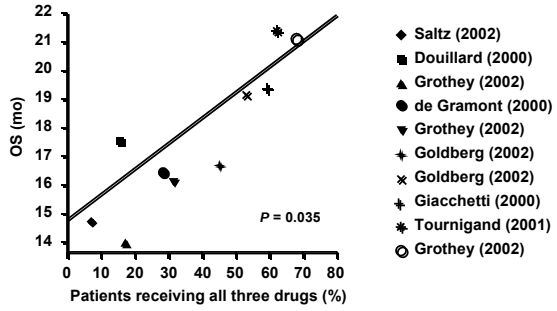
# Considerations for Therapeutic Agents

- Goal: Expose patients to all active agents over time (Irinotecan, Oxaliplatin and 5FU)
- Balance efficacy and toxicity, and tailor to patient needs and status
- Determine in which patients specific agents would be preferred (considering patient's co-morbidities, occupation, psychological status, etc.)
- Optimal duration of use to extend the line of treatment

# Biological targets for cancer therapy

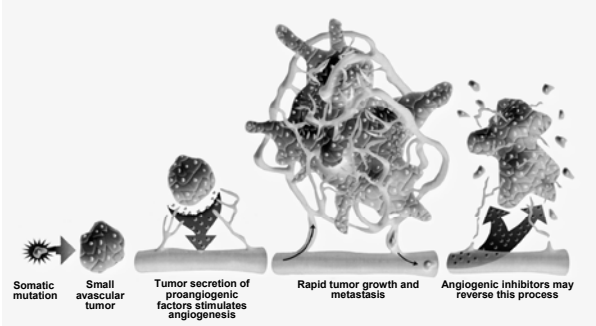



## Median OS Correlates With Availability of all Drugs Effective in Advanced CRC

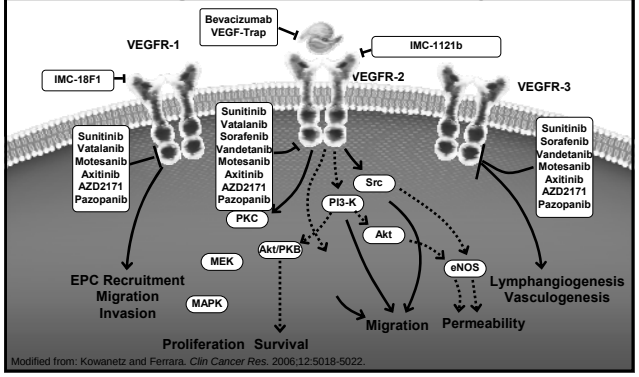



Hobday TJ, Goldberg M. *Clin Colorectal Cancer*. 2002;2:161-169.

# The Angiogenic Switch and Antiangiogenic Therapy

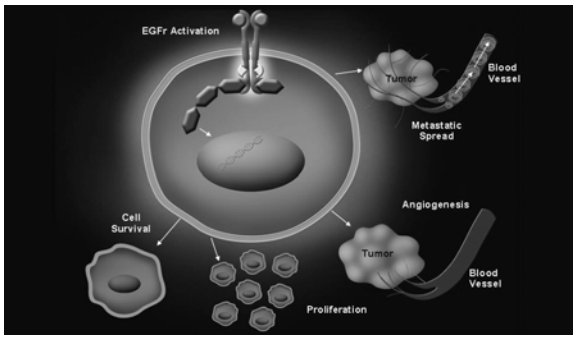


# Anti-VEGF Approaches and Agents: Summary

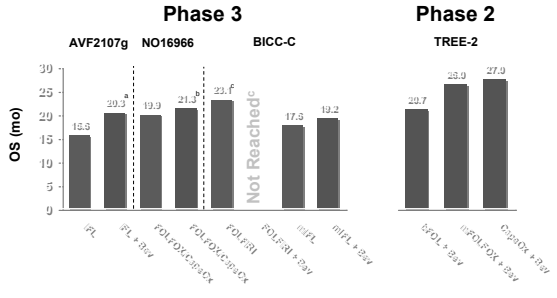



Modified from: Kowanetz and Ferrara. *Clin Cancer Res.* 2006;12:5018-5022.

# EGFr Activation Enhances Pathways Important for Tumor Cell Growth



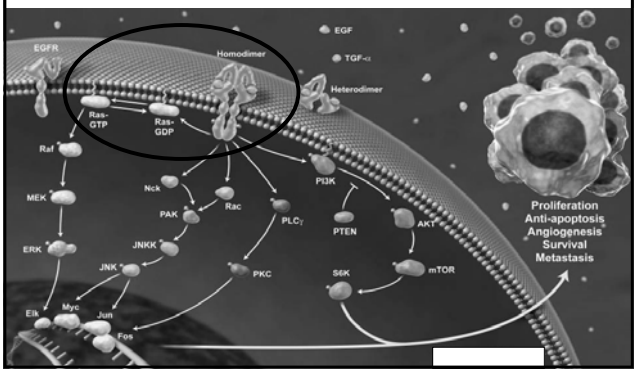

# First-Line Bevacizumab in MCRC: Overall Survival




[a]$P<0.001$; [b]$P=0.0769$; [c]$P=0.01$ vs mIFL + Bev.

Fuchs et al. ASCO, 2007. Abstract 4027; Hochster et al. ASCO, 2006. Abstract 3510; Hurwitz et al. *N Engl J Med*. 2004;350:2335; Saltz et al. ASCO GI, 2007. Abstract 238.

# EGFR Activation and Downstream Signaling Pathways



# NCIC CTG CO.17: Cetuximab vs. BSC

REGISTER

EGFR testing by IHC

RANDOMIZE

1:1

Failed or intolerant to all recommended therapies

- Cetuximab* + BSC
- BSC alone

Disease Progression or Unacceptable Toxicity

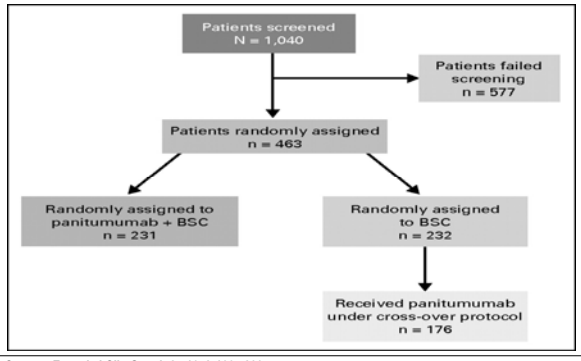
* Cetuximab 400 mg/m$^2$ IV week 1 then 250 mg/m$^2$ IV weekly

**Primary:**
Overall Survival

**Secondary:**
Progression Free Survival
Objective Response Rate (RECIST criteria)
Safety
Quality of Life

**Stratification:**
- Centre
- ECOG PS (0 or 1 *vs.* 2)

# Panitumumab vs. BSC




Van Cutsem, E. et al. J Clin Oncol; 25:1658-1664 2007

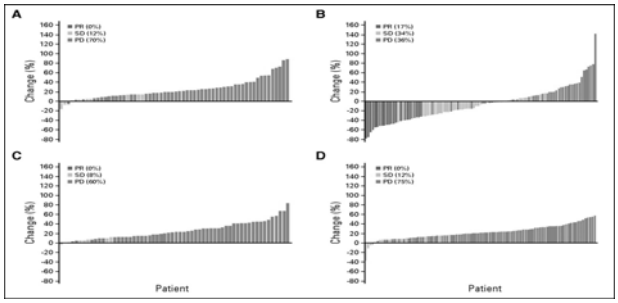


JOURNAL OF CLINICAL ONCOLOGY

# NCIC CTG CO.17 : Initial and Retrospective Results

| | ITT Population | | K-ras Wild Type | | K-ras Mutation | |
|---|---|---|---|---|---|---|
| | BSC | | BSC | | BSC | |
| | + Cetuximab | - Cetuximab | + Cetuximab | - Cetuximab | + Cetuximab | - Cetuximab |
| # of Patients | 287 | 285 | 117 | 113 | 81 | 83 |
| Overall Response Rate | 8% p<0.001 | 0% | 12.8% | 0% | 1.2% | 0% |
| Median PFS | 1.9 mos Hazard Ratio: 0.68 p<0.0001 | 1.8 mos | 3.8 mos Hazard Ratio: 0.40 p<0.0001 | 1.9 mos | 1.8 mos Hazard Ratio: .99 p=.96 | 1.8 mos |
| Median OS | 6.1 mos Hazard Ratio: 0.77 p=0.0046 | 4.6 mos | 9.5 mos Hazard Ratio: 0.55 p<0.0001 | 4.8 mos | 4.5 mos Hazard Ratio: .98 p=.89 | 4.6 mos |

**Waterfall plots showing maximum percent decrease in target lesions**

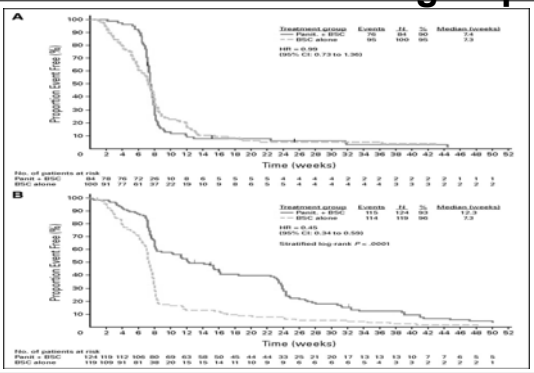



**(A) Patients receiving panitumumab, mutant *KRAS*. (B) Patients receiving panitumumab, wild-type (WT) *KRAS*. (C) Best supportive care (BSC) patients, mutant *KRAS*. (D) BSC patients, WT *KRAS*. Percentages are best response within each *KRAS* group, excluding missing or nonassessable postbaseline tumor assessments. PR, partial response (gray); SD, stable disease (yellow); PD, progressive disease (blue).**

Amado, R. G. et al. J Clin Oncol; 26:1626-1634 2008

JOURNAL OF CLINICAL ONCOLOGY

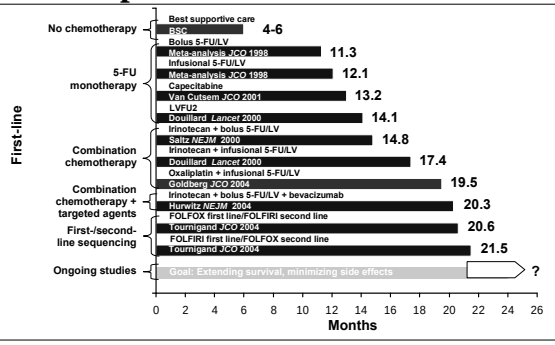
# Progression-free survival by treatment within KRAS groups




Amado, R. G. et al. J Clin Oncol; 26:1626-1634 2008

JOURNAL OF CLINICAL ONCOLOGY

# Treatment Evolution in mCRC and Impact on Median Survival




NOTE: This graph is not meant to represent a comparison of studies.

Adapted from Grothey A, et al. *J Clin Oncol*. 2004;22:1209-1214; Venook A. *Oncologist*. 2005;10:250-261; Tournigand C, et al. *J Clin Oncol*. 2004;22:229-237; Hurwitz H, et al. 2004;350:2335-2342.