Changing World of Colon Cancer

1. Williamson B. Strum MD
2. 15 December 2010

Colorectal Cancer 2010
- 148,970 projected cases in the US 2010
- More than 51,000 deaths projected 2010
- Third most common CA: Second leading cause of death due to cancer in the US
- CA in Women: CRC 5.2%, lung 6%, breast 12% - lifetime risk
- CA in Men: CRC 5.7%, lung 8%, prostate 17% - lifetime risk

Colorectal Cancer
Goal:
- Eliminate the disease
- Primary prevention
- Secondary prevention
Acknowledgements

- Cancer Registry: Sandy Sandbakken, Sharon Piazza, RN, Karen Reid, LVN
- Biostatistics: James Koziol, PhD
- GI Fellows: Carrie Frenette, Emily Singh, Frank Tsai, Andrew Cummins
- IM Resident: Khai Nguyen
- Private donations to the Scripps Clinic CRC research program

Age/Frequency - CRC–FH + / FH – 921 Pts Green Hospital

Distribution of CRC in 921 Pts Green Hospital

Incidence rates/100k 2002-2006

Mortality rates/100k 2002

Mortality rates/100k 2002-2006

3636--4040
Primary Prevention

- High fiber, low fat diets
- Folate, Vit B6, E, C, b-carotene, omega-3, selenium, etc
- HRT
- Calcium/ Vit D
- Aspirin

Folic acid and CRC/adenomas

- Random studies suggested low folate intake by alcoholics increased risk of CRC
  - Nurses Health Study JNCI 1993 - >400ug vs <200ug found RR 0.69 for CRC (CI 0.54-0.93) and similar for adenomas

HRT

- Women’s Health Initiative NEJM 2006 – Estrogen plus progestin (study stopped in 2002)
  - RR 0.83 (0.43-0.92)
  - Breast CA increased; C-V dz increased

Calcium and CRC

- 10 Cohort studies JNCI 2004 –
  - RR 0.78 (CI 0.69-0.88)
- Women’s Health Initiative NEJM 2006
  - 36,282 post-menopausal
  - ½ -1 gm calcium/ 400 units Vit D vs placebo
- High fiber diet
- No difference after 7 years

? Dose and duration too short
Aspirin and CRC/Adenomas

- 2 RCTs - Reduction in adenoma recurrence
  - Placebo 47%
  - 81mg 38%
  - 325mg 45%
  - Placebo 27%
  - 325mg 17%

Aspirin and CRC/Adenomas

- Women’s Health Study JAMA 2005
  - 100mg qod - 10 year F/U = No effect.
- Nurses Health Study JAMA 2005
  - 82,911 nurses/ 962 w/ CRC
  - >650mg/wk-10 yrs - RR 0.77 (CI .67-.88)
- High dose; > 10 yr duration

ASA Study – Lancet, Dec 2010

- 25,000 pts treated with 75 mg ASA for IHD
- F/u for 20 yrs
- Reduction in cancers 25%,
- began after 7-8 yrs

Reduction in Cancers – Lancet 2010

- Reduction in Cancers
- Colon 40%
- Lung 30%
- Esophagus 60%
- No Reduction
- Rectum
- Pancreas
- Prostate
- Bladder
- Kidney
- Brain
- Blood
- (Breast – insuffic data)

Life Style Issues

- Folate supplements – may be harmful
- Smoking, obesity – harmful
- Fiber, Vit B6, Vit D – no benefit
- ASA, (Calcium) – may be helpful

Life Style - modifications

- 1. No smoking
- 2. Regular exercise
- 3. Avoid excess red meat, refined grains
- 4. Low fat diet
- 5. High fruits and vegetables
  - Does not preclude screening!
Secondary Prevention CRC Screening

- Indirect tests
  - FOBT, DNA
- Structural tests
  - FLSI, DCBE, CTC, OC

Early vs. Late Stage % Survival

- Stage I - 93%
- Stage IIA - 85%
- Stage IIB - 55-65%
- Stage IIIA - 45-55%
- Stage IIIB - 33-45%
- Stage IIIC – 25-35%
- Stage IV – 8%

FOBT

- PCP Survey
- 31% in-office
- 41% in-office and take home
- Sensitivity
- 5% advanced neoplasm
- 9% cancer
- Mortality reduction – 15-33%
Analysis of Mutations in DNA Isolated From Plasma and Stool of Colorectal Cancer Patients

Frank Oehl, Kristin Schmidt, Kristine H. Durkee, Kent J. Moore, Steve N. Codoni, Anthony P. Diller, Kenneth W. Kinzler, and Bert Vogelstein

The Ludwig Center for Cancer Genetics and Therapeutics, Howard Hughes Medical Institute and Sidney Kimmel Cancer Center, and the Institutions, Johns Hopkins Medical Institutions, Baltimore, Maryland. *Eaton Sorensen Corp., Marlborough, Massachusetts. Published Online September 27, 2008

GASTROENTEROLOGY 2008;135:489-498

ONE-TIME FLEX SIG REDUCES CRC INCIDENCE AND MORTALITY

Atkin WS, Edwards R, Kralj-Hans I, et al. (Department of Surgery and Cancer, Imperial College of London, St. Mary’s Campus, UK). Once-only flexible sigmoidoscopy

Screening in prevention of colorectal cancer: a multicentre randomised controlled trial.


CRC misses – Scripps Clinic 2000-2005

- 379 pts with CRC – 421 exams
  - FS – 50% (30/60) – (23% within reach)
  - BE – 20% (16/79)
  - OC – 9% (25/282)

Frenette/Strum J Gli CA 2007

Bottom line

- 23/25 fecal DNA samples + (92%)
- 8/16 plasma DNA samples + (50%)
- Technique-superior to others (90% vs 60%)
- DNA stabilization
- Remove PCR inhibitors
- Remove bacterial DNA

ONE-TIME FLEX SIG REDUCES CRC INCIDENCE AND MORTALITY

- 170,000 Pts in UK
- Median f/u of 11.2 yrs
- Reduced CRC 23% (NNS-191 pts)
- Reduced Mortality 43% (NNS-489 pts)

Lancet 2010;375:1624–1633

CTC
Solitary 16-mm Pedunculated Cecal Polyp in a 55-Year-Old Man at Average Risk for Colorectal Neoplasia


A 67-year-old woman presented with a three-month history of abdominal pain, weight loss, and rectal bleeding. CT Colonography Detects Unsuspected Extracolonic Cancers

- Study of 10,000 adults found that 1 in every 200 asymptomatic people screened with computed tomographic (CT) colonography, or virtual colonoscopy, had clinically unsuspected malignant cancer and more than half of cancers were extracolonic.
- Radiology, April 2010.

CT Colonography

- Advantages:
  - No sedation
  - Multiple views/ views are stored
  - Extra-colonic diagnoses (eg: AAA, mass lesions, abn calcif, etc.)
  - (Future - ? No prep needed)
- Disadvantages – polyp found: another procedure - Re-prep

Optical Colonoscopy
Optical colonoscopy
- NPS – 76-90% redux in CRC NEJM 1993
- Italian Adenoma Study – 80% redux
- US 3 Chemoprevent and 2 Dietary – up to 4X CRC rate of NPS; no reduction in CRC incidence compared to SEER data.

Screening Colonoscopy-Scripps
- 4,967 cases, 2005-2006:
  - 27.4% (1,361) had at least 1 polyp
  - 19% (930) had at least 1 adenoma
  - 5% (249) had at least 1 adv adenoma
  - 0.16% (8) had cancer (1 per 620 pts)

Impact of Gender by Age

Best Test?

Indications for VC
- Patient preference
- Medical contraindication to OC
- Failed OC
CT Colonography Accuracy compared to OC

- 2,531 pts with CTC followed by OC
- CTC discovered 90% of Adv Adenomas

*Johnson et al, NEJM 2008*

Adenomas

- Small and Diminutive

CT Colonography

- Current radiology guidelines recommend that lesions ≥ 6 mm be reported and f/u with CTC in 3 yrs
- Lesions ≤ 5 mm be ignored

CT Colonography

- Lesions ≤ 5 mm?

*Taylor SA. Radiology 2006.*

U.S. Consensus Guidelines for Colonoscopic Surveillance after Polypectomy

<table>
<thead>
<tr>
<th>Polyp Size</th>
<th>Hyperplastic</th>
<th>Non-adenomatous</th>
<th>Tubular Adenoma</th>
<th>Villous Adenoma</th>
<th>villous + villous adenoma</th>
<th>息肉</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 mm</td>
<td>320</td>
<td>49</td>
<td>551</td>
<td>86</td>
<td>17</td>
<td>2</td>
<td>395</td>
</tr>
<tr>
<td>6-9 mm</td>
<td>40</td>
<td>5</td>
<td>131</td>
<td>47</td>
<td>19</td>
<td>0</td>
<td>145</td>
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<tr>
<td>&gt; 10 mm</td>
<td>10</td>
<td>3</td>
<td>31</td>
<td>23</td>
<td>14</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
<td>61</td>
<td>713</td>
<td>156</td>
<td>50</td>
<td>5</td>
<td>870</td>
</tr>
</tbody>
</table>


Size and Pathology of Polyps
Low power adenocarcinoma

Positive node

Horizon

MISS RATES

Studies of CRC Misses

- Back-to-back OC – 6% for Adv Aden
- R-sided CA – 4% (? 8% entire colon)
- OC > BE 8-52% for Adv Aden
- CT <> OC - 10-17% for Adv Aden

Rex et al. GE 1997;112:24-8.
Bressler et al. GE 2007;132:90-102.
Reasons for failure
- Not examining the entire colon (30/71)
- Inaccurate observation (25/71)
- Premature dismissal of inadequate exam (11/71)
- No F/U of advanced lesions (5/71)

Quality Assurance
- Exam the entire colon
- Extra diligence with all exams
  - Minimum of 6 min on withdrawal
  - Establish adenoma detection rate (20%)
  - Change pt positions, if needed/ add water, etc
  - Use supplementary instruments, if needed
  - Repeat with additional prep/anesthesia
  - F/U advanced villous lesions 2-6 months


Barriers to Screening
1. Access
2. Money
3. Ethnic
4. Cultural

Figure 3. Colorectal cancer screening by race/ethnicity, years of education, and insurance status, 2003-2005. Colorectal cancer screening refers to an FOBT within the past year or a lower endoscopy within the past 10 years. Groups have been combined (years of education, 13+) due to small sample sizes. Source: National Health Interview Survey 2003 and 2005, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006. Reprinted with permission from the American Cancer Society.
Multistep genetic model of colorectal carcinogenesis. (Pino and Chung, GE 2010)

Molecular Pathway to Colorectal Cancer
- Four pathways
  - Chromosomal instability, CIN
  - Microsatellite instability, MSI
  - CpG Island Methylator Phenotype, CIMP
  - Serrated Neoplastic

Molecular Pathway to Colorectal Cancer
- Multiple genes involved (minimum of 7; up to 80)
- Slow, gradual process (10 years)

Molecular diagnostics
- Epidermal Growth Factor Receptor
  - 1. Soluble protein with trophic effects
  - 2. CRCs signal thru EGFR
  - 3. Signaling is mediated by activating MAPK and PI3K cascades
  - 4. Mutations in these and KRAS and PI3K: do not respond to anti-EGFR therapy

Pharmacogenomic application
- KRAS and BRAF mutations detected by PCR = resistance to cetuximab
- High expression of ERCC1,TS = resistance to FOLFOX, sensitivity to FOLFIRI
- High expression of VEGFR2 = sensitivity to anti-angiogenic rx

Hyperplastic polyps
- Hyperplastic
- Traditional serrated adenoma
- Sessile serrated adenoma
- Mixed
Hyperplastic Polyposis Syndrome (HPS)
- >5 HP polyps prox to R-S, 2 ≥10mm
- Any # of HP polyps if 1st degree rel with HPS
- ≥30 HP throughout the colon
- Increased risk for CRC?

Serrated Adenoma
- Saw-toothed growth pattern
- Epithelial dysplasia (intraepithelial neoplasia)
- Mechanism for tumorigenesis – methylation of multiple CpG islands

Genetic Alterations in Serrated Adenomas
- CpG island methylation phenotype (CIMP)
- High frequency - K-ras, BRAF oncogene activation
- Low frequency - APC

Hereditary Colorectal Cancer Syndromes
- Nonpolyposis (Lynch Syndrome)
  - HNPCC
  - Attenuated HNPCC
- Polyposis (multiple adenomas)
  - Familial adenomatous polyposis (FAP)
    - Severe colonic polyposis +/- CRC
  - Attenuated FAP (AFAP)
    - Less severe colonic polyposis +/- CRC
  - MYH-associated polyposis (MAP)
    - Varying degrees of colonic polyposis +/- CRC

Populations of CRC (GHSC)
- 13% FH of CRC
- 87% No FH
Fam Hx – We can do better!

“There is no disease which runs in the family.”

Taking of Fam Hx

“No disease which runs in the family” does not take into account a host of outcomes:

- Accidents: both parents died in a crash at age 32.
- Homicide, suicide, fatal diseases - at early age.
- Unknown outcome: adopted, abandoned, etc.

Taking of Fam Hx

Must knows:

- Ages and fates of biological parents
- Ages and fates of brothers and sisters
- If serious diseases are present, extend to second degree relatives

Fam Hx

Refer to appropriate specialty
Refer to Cancer Genetic Program Coordinator

Additional Changes

- Improved endoscopic images: NBI, chromo, HD, Third eye retroscope, etc
- Video Capsule Colonoscopy

Soetikno et al 2008
Future

- Video Capsule Colonoscope:
- Where Will We Be in 2015?

Ramzi Eliaikim, GE 2010, Haifa, Israel

Take Home Points

- Second leading cause of cancer deaths
- 5.5% lifetime risk; improved risk scores needed
- Adenomas are precursors and grow slowly
- Curable if found early
- Take a detailed hx
- Employ the most sensitive dx technique
- Miss rates for CA/AA - 2-4% range/5yrs
- 10-year F/U must assume slight risks

What will tomorrow bring?

- Blood/fecal test for mutated colon DNA
- Colonoscopy with fewer/no misses
- CTC with no prep necessary
- Video Capsule Colonoscopy
- Molecular diagnostics for Rx
- Improved risk stratification
- Exam available for every eligible pt
Thank you for your attention