Colorectal Cancer in 2006: New Developments

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Hereditary Colon Cancer and Genetic Testing

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Who is at High Risk for Hereditary Cancer?

Hereditary cancers account for a small but important proportion of all cancer.
Cancer arises when both copies of genes are inactivated.

2 normal genes → 1 damaged gene → 2 damaged genes → Tumor develops

In hereditary cancer, one damaged gene is inherited.

1 damaged gene → 2 damaged genes → Tumor develops
Colorectal Cancer

- Sporadic (~60%)
- Familial (~30%)
- Rare Syndromes (~4%)
- HNPCC (3-5%)
- FAP (~1%)
- MAP (~1%)

Cancer

1996;78:1149-67
Am J Med
1999;107:68-77
Gastroenterology
2000;119:837-53
Am J Path
2003;162:1545-8
Hereditary Colorectal Cancer (CRC) Syndromes

Nonpolyposis (few to no adenomas)
   HNPCC – CRC and/or endometrial cancer (EC)

Polyposis (multiple adenomas)
   FAP – Severe colonic polyposis +/- CRC
   AFAP – Less severe colonic polyposis +/- CRC
   MAP – Varying degrees of colonic polyposis +/- CRC
Features Suggestive of HNPCC

- Early onset colorectal cancer (<50y)
- Early onset endometrial cancer (<50y)
- Two or more HNPCC cancers in an individual or family*

*HNPCC cancers: colorectal, endometrial, gastric, ovarian, ureter/renal pelvis, biliary tract, small bowel, pancreas, brain, sebaceous adenoma
Features Suggestive of Adenomatous Polyposis Syndromes

- Multiple colorectal adenomas
- Colorectal cancer associated with multiple adenomas
- Possible extracolonic manifestations
  - Non-colonic polyps and cancers (i.e. duodenal, gastric)
  - Desmoid tumors, osteomas, soft tissue tumors, dental abnormalities, CHRPE
Is the cancer in my family hereditary?

- Risk Assessment appointment
  - understand cancer risk specific to your history
  - learn about screening, prevention and risk reduction
  - discuss the possibility of genetic testing
  - discuss the potential impact of genetic testing
What happens during the risk assessment appointment?

1. Collect family history information before appointment

2. Schedule an appointment with a health care provider to discuss your family history and determine if you are appropriate for genetic testing

3. Consider the pros and cons of genetic testing
What does genetic testing involve?

1. Genetic testing is performed on a small blood sample

2. Results are available in about 4 weeks and are discussed in person with health care provider

3. Consider options for screening and prevention, based on positive or negative results

4. Contact your health care provider periodically for updates
Costs

Risk Assessment Appointment
- Cost varies at each institution

Genetic Testing
- Most insurance companies are covering genetic testing
- Medicare and most major insurance carriers have established guidelines
Genetic Discrimination in Health Insurance is Illegal

- Health Insurance Portability and Accountability Act (HIPAA)
  - Prohibits group health plans from discriminating on the basis of genetic information
- Most states have enacted additional protections
Where Can I Learn More?

- Nicole Melby, RN, BSN
  757-673-5967
- Hereditary Colon Cancer Association-
  www.hereditarycc.org
- Colorectal Cancer Network
  www.colorectal-cancer.net
- Colon Cancer Alliance
  www.ccalliance.org
- Myriad Genetic Laboratories
  www.myriadtests.com
Overview

- Common, lethal and preventable
- Average lifetime risk ~ 5%
- Infrequent before age of 40
- 90% of cases occur after age 50
- 2nd leading cause of cancer death both sexes
- Approx. 52,000 deaths/yr in US
Why is Screening Effective?

- Most colon cancers develop gradually over many yrs.
- Most begin as small adenomatous polyps
- Polyps may grow then transform into malignancies and spread
- The usual progression takes at least 10 yrs
- Screening identifies polyp formers and those at risk
Screening vs. Surveillance

- Screening - Asymptomatic w/o risk factors
- Surveillance -
  - Previous polyps
  - Previous colon cancer
  - Significant family history
- Symptom evaluation
  - Blood, anemia, etc.
Determine the Risk

- Family history of CRC or polyps
  - 1\textsuperscript{st} or 2\textsuperscript{nd} degree relative?
  - Age of onset?
  - Number?
- Personal history of CRC or polyps
- Personal history of Inflammatory Bowel Disease
Screening Tests

- FOBT
- Flexible Sigmoidoscopy
- Air Contrast Barium Enema
- Colonoscopy
Colonoscopy—Expectations & Risk

- Evaluation of colon and removal of polyps can prevent colon cancer
- Allows inspection and treatment in 1 visit
- Low miss rate (no test is perfect)
- Requires bowel prep
- Sedation most commonly utilized
- Risk of perforation or major bleeding are ~1/1000 procedures
New Technologies

- Virtual colonoscopy
- Stool DNA testing
- Both would require colonoscopic intervention for positives
The Benefits of Minimally Invasive Surgery for Colon Cancer

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Tidewater Surgical Specialists - Colorectal Surgery Division
Director – Bon Secours Center for Colon & Rectal Diseases
Laparoscopic Surgery

- Revolution: minimally invasive surgery
- First cholecystectomy 1987
- Smaller incisions, decreased pain, shorter length of hospital stay, early return to regular activities
- Application to variety of abdominal operations
Laparoscopic Colectomy

- 1st Laparoscopic colectomy: 1990
- Spectrum of resections described
- Benefits similar as with other procedures
- Acceptable morbidity
- 2003: < 10% of all colectomies
LAPAROSCOPIC COLECTOMY

Clinical Outcomes of Surgical Therapy Study Group-COST

A Phase III Prospective Randomized Trial Sponsored by National Cancer Institute and NCI Cooperative Groups
LAPAROSCOPIC COLECTOMY TRIAL

Study Aims

To test differences in

- Cancer outcomes
  (Overall and Disease-Free Survival)
- Safety (morbidity; mortality)
- Patient-related benefits
  (quality of life; cost effectiveness)
LAPAROSCOPIC COLECTOMY TRIAL

Schema

Pt with 1° colon ACA → Stratify → Randomize

Open colectomy

Observation* (event monitoring)

Laparoscopic-assisted colectomy
872 Patients randomized

437 Assigned to open colectomy
  5 Received LAC

432 Received intervention as allocated

435 Assigned to LAC
  2 Refused any surgery

433 Received intervention as allocated
  5 Received intervention due to crossover

4 Included from analysis
  3 Metastatic disease identified preoperatively
  1 No local IRB approval

428 Included in analysis

3 Excluded from analysis
  2 Metastatic disease identified preoperatively
  1 Previous prostate cancer

435 Included in analysis
## Laparoscopic Colectomy: COSTST Trial - Recovery Benefits*

<table>
<thead>
<tr>
<th></th>
<th>Open*</th>
<th>LAC</th>
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</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>428</td>
<td>435</td>
</tr>
<tr>
<td><strong>Length of stay</strong></td>
<td>6 (5-7)</td>
<td>5 (4-6)</td>
</tr>
<tr>
<td><strong>Narcotics</strong></td>
<td>4 (3-5)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td><strong>Oral analgesic</strong></td>
<td>2 (1-3)</td>
<td>1 (1-2)</td>
</tr>
</tbody>
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*in days; median values;(interquartile range)
## LAPAROSCOPIC COLECTOMY
### COSTSG Trial - Morbidity/Mortality

<table>
<thead>
<tr>
<th></th>
<th>Open*</th>
<th>LAC *</th>
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<tbody>
<tr>
<td><strong>30-day mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no.(%)</td>
<td>4 (0.9)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>85 (20)</td>
<td>92 (21)</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>8 (2)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>80 (19)</td>
<td>81 (19)</td>
</tr>
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</table>

* * p=ns for all comparisons

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$n=428$  
$n=435$
Cumulative incidence of recurrence

All stages
- Open colectomy
- Laparoscopic colectomy

P = 0.32

Number at risk
- Open: 395, 345, 289, 240, 177, 109
- Laparoscopic: 414, 368, 311, 242, 185, 118

Years: 0, 1, 2, 3, 4, 5
Cancer Outcomes

- No differences in
  - Overall Survival
  - Disease-free survival
  - Wound recurrences
LAPAROSCOPIC COLECTOMY

Summary

- Safety
  - Equivalent morbidity
  - Equivalent mortality

- Patient Related Benefits
  - Faster recovery
  - Significant differences
Patients Now Have a Choice!
Traditional open colon surgery (skin incision) 6” - 12”

Laparoscopic colon surgery (Mini-laparotomy) 3” - 4”

THE SHORTEST DISTANCE BETWEEN A PATIENT AND RECOVERY
Laparoscopic Colorectal Surgery - Benefits -

- Smaller incision and scar
- Reduced operative trauma and stress
- Reduced post-op pain and narcotic use
- Early feeding
- Early return of bowel function
- Shorter hospital stay
- Diminished blood loss and morbidity
- Earlier return to work and activities of daily living
- Decreased physiologic and immunologic compromise
Laparoscopic Colon Resection

Summary
- Less pain
- Shorter hospital stay
- Faster recovery
- Why have colon surgery any other way???
Bon Secours Center for Colon and Rectal Diseases

- Harbour View Campus
- Nicole Melby
  - On-site Clinical Coordinator
  - 673-5970
Questions?

Thank You
Updates in Medical Oncology of Colon Cancer: Adjuvant Chemotherapy

James J. Stark, MD, FACP
Medical Director, Cancer Program
Maryview Medical Center

Professor of Medicine,
Eastern Virginia Medical School
Adjuvant Chemotherapy

- Given soon after surgery for cancer to try to eradicate tiny amounts of cancer that may have escaped the primary tumor before surgery
- Abundant animal experimental and human evidence of a substantial reduction in mortality using this approach
Adjuvant Chemotherapy for Colorectal Cancer

- Relatively late development
  - Only about 15 years of successful data, probably because of previously relatively weak drugs
  - Newer drugs have improved outcome at the cost of additional toxicity and a financial burden on the health care system
    - “FOLFOX” regimens most active, use Oxaliplatin, an expensive and toxic drug
Additional Factors Affecting Outcome

- Colorectal screening programs identify patients with earlier-stage disease
- Better surgical techniques
- Better pathological staging
  - The Will Rogers Phenomenon….
"When the Okies left Oklahoma and moved to California, they raised the average intelligence levels in both states."

-- Will Rogers, commenting on geographic migration during the economic depression of the 1930s.
Additional Factors Affecting Outcome

- Better surgical techniques
- Better pathological staging
  - The Will Rogers Phenomenon...

- As pathologists get better at finding lymph nodes, patients who would have been scored as "node negative" now have positive nodes and the prognosis of both groups improves

- Implications for data analysis....
As more patients get diagnosed early, have better surgery and have a better outcome, we need a better way to select which patients should not be treated with adjuvant chemotherapy: who doesn’t need treatment, and who won’t benefit from it.
Better Selection of Patients: Molecular Markers of Prognosis

- New technology can identify thousands of genes in a tiny specimen of tumor: c-DNA microarray technology
- Tumors can be analyzed retrospectively to see which gene mutations can predict for a good or bad outcome
- This approach has recently been taken in colorectal cancer...
The Eschrich Study:

Identified 43 genes out of 32,000 studied:

![Graph A](A) Good prognosis (n = 63)
Poor prognosis (n = 32)
Log-rank P < .001

![Graph B](B) Dukes’ B (32)
Dukes’ C (63)
Log-rank P = .118

Eschrich et al, JCO 23:3526, 2005
Another Variable: Microsatellite Instability

- Looks at ability of tumor genes to repair themselves
- 15% of colon cancers have “MSI” which means they cannot repair defective genes
- Leads to a relative inability of the tumor to survive additional mutations
- May be a marker for a better outcome…
Hazard ratios (HRs) of overall survival in studies of all stage II-III colorectal cancer associated with microsatellite instability

Final Variable: P-53 status

- P-53 is a tumor suppressor gene: helps us *not* to get cancer
- When altered (mutated) cancers may develop more easily and may be more aggressive
- Colon cancer specimens examined retrospectively for this gene...
Disease-free survival of 220 patients according to TP53 status (mutated v wild type)

Conclusions

- With better surgery and better staging colon cancer survival is better even without chemotherapy
- With newer drugs regimens are more effective but more toxic and much more expensive
- Decision on who to treat becomes very important
- Newer markers may predict outcome more precisely allowing better estimate of risk/reward ratio with chemo
- Patients with poorest predicted outcome will then get the most effective therapy
Any Questions?

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