Objectives

- Overview
- Diagnostic innovation
- Management of benign/early lesions
  - Endoscopic techniques
  - Transanal endoscopic microsurgery (TEM)
- Chemoradiation.
  - When, Why, How much
- Radical Surgery
  - Laparoscopy
  - Robotic surgery

Worldwide Colorectal Cancer Statistics

- Estimated for 2008
  - 1,233,700 new cases
    - 663,600 male
    - 570,100 female
  - 608,700 deaths
    - 320,600 male
    - 288,100 female
- 4th most common incidence
- 3rd most cause of cancer death

U.S. Colorectal Cancer Statistics

- Estimated for 2010
  - 102,900 new cases
    - 6,610 in IL (2007)
    - 51,370 deaths
    - 2,560 in IL (2007)
- 5-year survival 66%
  - 1999-2005
- Lifetime Risk:
  - Men: 1 in 17
  - Women: 1 in 18

Epidemiology of Colorectal Cancer: New Cases Are Declining

Kris et al. JCO 2010

**Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population**
Death rates by site in the US from 1930-2005 for (A) men and (B) women.

Stage I: >90% 5-Year Survival

Stage II: 45-90% 5-Year Survival

Stage III: 20-65% 5-Year Survival

Stage IV: 10% 5 Year Survival

Colon Cancer Develops in a Sequential Process

Risk Factors for Getting CRC
- Age (>90% are >50 years old)
- Family History (CRC or polyps)
- Obesity
- High-fat or low-fiber diet
- Genetics (Host)
  - Familial polyposis (FAP)
  - Hereditary nonpolyposis colorectal cancer (HNPCC)
  - Ulcerative colitis (chronic inflammation)

(American Cancer Society, Facts & Figures 2005)

Familial Adenomatous Polyposis
- Autosomal Dominant Inheritance
- Results from Mutation in the APC (chromosome 5q21-q22) Gene
- Patients Develop Hundreds of Thousands of Polyps starting age 16
- Cancer risk is 100% (usually by age 39)
- Start Screening at age 12 (can consider genetic testing first)
- If Polyps Found-Colectomy

Familial Adenomatous Polyposis

FAP

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
- Autosomal Dominant
- Problem with one of the Mismatch Repair Genes (MMR-Chromosomes 2, 3, 7)
- Risk of Cancer 70-90% (usually by the age of 45)
- Usually Right Sided
- Usually Poorly Differentiated
- Often do not arise from a polyp
- Heavy Lymphoid Reaction Seen on Path

HNPCC: How to Diagnose and How to Screen
- Amsterdam Criteria (3-2-1 rule)
  - Three Relatives with HNPCC associated cancer
    - (CRC, endometrial, small bowel, renal pelvis)
    - One should be a first degree relative of the other two
  - CRC Affecting two generations
  - One or more relatives younger than 50 at diagnosis
- Screening:
  - Begin at age 25 or 10 years younger than the youngest affected relative
  - Colonoscopy every 2 years than yearly after the age of 40
Screening the General Population: How to Screen

- Stool-based tests
  - Guaiac-based fecal occult blood test (gFOBT)
  - Immunochemical-based fecal occult blood test (iFOBT), also known as fecal immunochemical test (FIT)
  - Stool DNA panel (sDNA)
- Endoscopic and radiologic examinations
  - Flexible sigmoidoscopy (FS or FSIG)
  - Optical colonoscopy
  - Double contrast barium enema (DCBE)
  - CT colonography (CTC, formerly referred to as "virtual colonoscopy")

Screening the General Population: How and Who to Screen

United States Preventive Services Task Force (USPSTF)

Three Options starting at age 50:
- Annual fecal occult blood test (FOBT) with a sensitive test
- Flexible sigmoidoscopy every 5 years, with sensitive FOBT every 3 years
- Colonoscopy every 10 years

Screening the General Population: How and Who to Screen

- Patient with one first degree relative with colon cancer (diagnosed after 50)
  - Same as above but begin at age 40
- Two first degree relatives or one first degree diagnosed younger than 50
  - Colonoscopy every 3-5 years beginning at age 40 or 10 years younger than the youngest affected relative

What do you do with the results from screening?

- Hyperplastic Polyp - Nothing…routine screening
- Adenomatous polyp
  - If no colonoscopy then needs one
  - Multiple or one larger than 1 cm-repeat colon in 3 years
  - Carcinoma in the polyp (CIS)-repeat colon in 3-5 years
  - Only one small adenoma-colon every 5 years
- Cancer-The subject of the rest of this talk

Prognostic Factors If You Have Colorectal Cancer

- Stage (TNM):
  - Tumor penetration
  - Node involvement
  - Metastases
- Clinical Factors:
  - Bowel perforation
  - Elevated pretreatment CEA
- Tumor Genetics:
  - Microsatellite instability
Overview of Treatment

- **Stage I** - Surgery. Hemicolecotomy
- **Stage II** - Surgery. Chemotherapy controversial.
  - Lean toward it in T4 patients and patients who present with obstruction, angiolymphatic invasion, or inadequate lymph node sampling (<10-12 lymph nodes removed)
  - Microsatellite instability (MSI)
- **Stage III** - Survival and QOL advantage to adjuvant (after surgery) chemo
- **Stage IV** - Survival and QOL advantage to chemo. Surgery for palliation and sometimes for cure.

Diagnostic Modalities

- **Standard Colonoscopy**

Diagnostic Modalities

- **Virtual colonoscopy**

Diagnostic Modalities

- **Image Enhanced Methods**
  - Chromoendoscopy
  - Narrow Band Imaging
  - Autofluorescence
  - Probe-Based Spectroscopy

Management of benign/early lesions

Combined Laparoscopic-Endoscopic Resections (CLER)

- A total of 146 consecutive patients underwent CLER for 154 lesions, and 120 (82%) patients underwent local excision
  - laparoscopy-assisted endoscopic resection,
  - endoscopy-assisted wedge resection
  - endoscopy-assisted transluminal resection
  - 26 (18%) patients received endoscopy-assisted segmental colon resection.
- Conversion rate was 5%
  - Intraop complications 2 patients (1%)
- Major postoperative complications—5 patients (3%), local recurrence rate of 0.9%


Risk of Lymph Node Metastases

- Haggitt level 1, 2, and 3 is low 1-3%
- Level 4, sessile, Kudo classification

DEFINITION

Transanal Endoscopic Microsurgery – (TEM)

TEM is a minimally invasive approach that allows the surgeon to access the lower, mid and upper rectum to remove polyps or early carcinomas locally, full thickness without having to make an incision in the abdomen.

TEM was introduced by Dr. Buess from Germany who developed the technique with Richard Wolf.
SET UP

PATIENT POSITIONING

The exact localization of the tumor is important for the correct positioning of the patient on the OR table.

IMPORTANT:
View of the operations field is always at 6 o'clock (down) !!!

PATIENT POSITIONING

Positioning of the patient according to localization of tumor

1. Supine position – posterior tumor
2. Prone position – anterior tumor
3. Right or left lateral decubitus position – tumor located on right or left wall of rectum

SET UP
### RESULTS

#### TEM FOR BENIGN DISEASE

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>RR (%)</th>
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<tbody>
<tr>
<td>Guerrieri (2006)</td>
<td>588</td>
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<td>Bretagnol (2007)</td>
<td>148</td>
<td>7.6</td>
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<tr>
<td>Tsai (2010)</td>
<td>120</td>
<td>5.0</td>
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<tr>
<td>McCloud (2006)</td>
<td>75</td>
<td>4.3</td>
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#### TEM FOR T1 CANCERS

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<th>No. of patients</th>
<th>LR (%)</th>
</tr>
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<tbody>
<tr>
<td>Borschitz (2006)</td>
<td>Low Risk 89</td>
<td>6</td>
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<tr>
<td></td>
<td>High Risk 21</td>
<td>39</td>
</tr>
<tr>
<td>Heintz (1998)</td>
<td>Low Risk 46</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>High Risk 12</td>
<td>33</td>
</tr>
<tr>
<td>Tsai (2010)</td>
<td>51</td>
<td>9.8</td>
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</table>

#### TEM FOR > T1 CANCERS

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>LR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borschitz (2007)</td>
<td>T2 Low Risk 29</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>T2 High Risk 8</td>
<td>67</td>
</tr>
<tr>
<td>Tsai (2010)</td>
<td>T2 17</td>
<td>23.5</td>
</tr>
<tr>
<td></td>
<td>T3 4</td>
<td>100</td>
</tr>
</tbody>
</table>
TEM vs. TAE

- 42 TEM - 129 TAE
- 52 TAE (40%) <5 cm from AV vs. 1 TEM (2%) (p=0.0001)
- Positive surgical margins 2% TEM vs. 16% TAE (p=0.017)
- Tumors ≥5 cm from AV estimated 5-year DFS rate similar: TEM (84.1%) vs. TAE (76.1%) (p=0.651).
- Multivariate analysis independent predictors of LR, DFS:
  - Tumor distance from the anal verge
  - Resection margin status
  - T stage
  - Use of adjuvant therapy

TREATMENT ALGORYTHMS

Rectal Mass

![Rectal Mass Diagram](image1)

Chemo/Radiation

![Chemo/Radiation Diagram](image2)

Chemo Options for Colorectal Cancer: A Timeline

![Timeline Diagram](image3)
Adjuvant Therapy Conclusions

• 5FU based therapy for 6 months provides the majority of benefit stage III-II
• Oxaliplatin has a survival advantage in stage III colon cancer patients with a NNT of about 25 to save 1 life
• Negative trials with irinotecan, bevacizumab, cetuximab

STAGE II Controversy

-- 5-FU chemotherapy has a small survival advantage in Stage II patients…but
-- Stage II Patients with MSI-H tumors probably don’t need any therapy and therapy may be harmful
-- High risk stage II patients likely do benefit from 5-FU (and oxaliplatin?) therapy

STAGE II Controversy

-- What About T3N0 with MSS Tumor?
  • Recurrence score Oncotype Dx?
  • Treat with 5-FU or capecitabine alone-Probably
  • Don’t Treat-Possible
  • Treat with FOLFOX—Probably not

Personalized Therapy for Rectal Cancer

• Depth of invasion
  -- T1: Local excision
  -- T2: Radical surgery
  -- T3-T4: Neo-adjuvant therapy

• Nodal status
  -- N+: Neo-adjuvant therapy

• Distant spread
  -- M1: Neo-adjuvant therapy vs. palliative therapy

Combined Modality Therapy in Rectal Ca: Is it Necessary for Everyone?

• Local Recurrence
  -- Less of a problem
  -- Experienced centers demonstrating <10% LR
• Survival is dictated by distant metastasis
  -- Can we treat micrometastatic disease earlier in the treatment course?
• Not all Stage II and III patients are high risk
• Observations in Stage IV patients demonstrate that primary tumors respond to systemic chemotherapy

Current US Treatment Paradigm for Stage II and III Rectal Cancer

6 weeks recovery
5.5 Weeks CMT with 5FU

6 weeks recovery
Rectal Surgery

Adjuvant Chemo

18-20 weeks until start of systemic chemotherapy

Combined Modality Therapy: Is it Necessary for Everyone?

• Local Recurrence
  -- Less of a problem
  -- Experienced centers demonstrating <10% LR
• Survival is dictated by distant metastasis
  -- Can we treat micrometastatic disease earlier in the treatment course?
• Not all Stage II and III patients are high risk
• Observations in Stage IV patients demonstrate that primary tumors respond to systemic chemotherapy

Rectal Cancer Pooled Analysis: Risk Groups

<table>
<thead>
<tr>
<th>Risk of relapse</th>
<th>Stage</th>
<th>5 year OS</th>
<th>5 year DFS</th>
<th>Local Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>T1-2N0</td>
<td>90%</td>
<td>90%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>T2-3N1</td>
<td>83%</td>
<td>74%</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>T3N0</td>
<td>74%</td>
<td>66%</td>
<td>8</td>
</tr>
<tr>
<td>Moderate High</td>
<td>T1-2 N2</td>
<td>69%</td>
<td>62%</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>T4N0</td>
<td>65%</td>
<td>54%</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>T3N1</td>
<td>61%</td>
<td>50%</td>
<td>11</td>
</tr>
<tr>
<td>High</td>
<td>T3N2</td>
<td>48%</td>
<td>39%</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>T4N1</td>
<td>33%</td>
<td>30%</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>T4N2</td>
<td>38%</td>
<td>30%</td>
<td>19</td>
</tr>
</tbody>
</table>

MSKCC Pilot Study 07-021
Preoperative Chemotherapy
Selective use of Chemoradiation

5.5 Weeks CMT with 5FU → Rectal Surgery → Chemotherapy

MSKCC 07-021 Schema

5.5 Weeks of CMT
No Response
FOLFOX6 Bev4
Response → TME Surgery → Adjuvant Chemo

MSKCC 07-021 Overall Survival
Median FU: 44 mo
Median OS: 57 mo
3 year OS 97%
(95% CI: 91-100)

MSKCC 07-021 Disease Free Survival
Median FU: 44 mo
Median DFS: 57 mo
3 year DFS 90%
(95% CI: 79-100)

PROSPECT Study Schema

“Standard Arm”
5FU CMT → TME → FOLFOX x 8

“Selective Arm”
Response ≥20%
FOLFOX x 6

Response <20%
5FU CMT → TME → FOLFOX x 4

Radical Surgery
Level 1 evidence supports the practice of laparoscopic colectomy

Guidelines 2000 for Colon and Rectal Cancer Surgery.
JNCI 93(8): 583-596, 2001

Principles of Colon Cancer Surgery
Surgical Guidelines – Colon and Rectal Cancer

Thorough abdominal exploration
  – Liver
  – Peritoneal surfaces
  – Omentum
  – Ovaries
  – Local tumor site (R/O fixation)
  – Lymphatics

Lymphovascular Ligation
  – Level of origin of primary feeding vessel
  – Suspicious positive nodes should be removed when feasible
  – 12 nodes

Bowel Margins
  – >=5 cm proximally and distally

En Bloc Resection
  – Should be performed for tumors adherent to local structures

Inadvertent Perforation
  – Increases risk of recurrence
  – Should be avoided

No-touch technique
  – Little evidence to support

Ovaries with tumor should be removed

Laparoscopic Resection
  – Clinical trials indicated for rectal cancer
COST Laparoscopic Trial
Primary Hypothesis

- That Disease-Free Survival and Overall Survival are not inferior for Laparoscopic Colectomy compared with Open Colectomy

COST Laparoscopic Trial
Study Aims

To test differences in
- Cancer outcomes
- Safety
- Patient-related benefits

COST 5-yr Overall Survival – All Stages

![Overall Survival Graph]

\[P-value = 0.93\]

COST 5-yr Disease Free Survival – All Stages

![Disease-Free Survival Graph]

\[P-value = 0.94\]

COSTSG 5 year data
Stage III Subset Analysis

Overall Survival

![Overall Survival Graph]

\[P-value = 0.42\]

Disease-Free Survival

![Disease-Free Survival Graph]

\[P-value = 0.43\]

COST Laparoscopic Trial
5-year Cancer Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Open (n=428)</th>
<th>LAC (n=435)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>75%</td>
<td>77%</td>
<td>0.94</td>
</tr>
<tr>
<td>Disease-Free Survival</td>
<td>69%</td>
<td>69%</td>
<td>0.96</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td>2.6%</td>
<td>2.3%</td>
<td>0.79</td>
</tr>
<tr>
<td>Overall Rates of Recurrence</td>
<td>21.8%</td>
<td>19.4%</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Annals of Surgery 246(4), October 2007
COST Laparoscopic Trial
Sites of First Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Open n=428</th>
<th>LAC n=435</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Wound</td>
<td>0.5%</td>
<td>0.9%</td>
<td>0.43</td>
</tr>
<tr>
<td>Liver</td>
<td>5.8%</td>
<td>5.5%</td>
<td>0.82</td>
</tr>
<tr>
<td>Lung</td>
<td>4.6%</td>
<td>4.6%</td>
<td>0.95</td>
</tr>
<tr>
<td>Other</td>
<td>8.4%</td>
<td>6.1%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

COST Laparoscopic Trial
Conclusions – Primary Analysis

- No differences in:
  - Overall survival
  - Disease-free survival
  - Wound recurrences
- Consistent with:
  - Barcelona Trial (n=219)
  - Meta-analysis of Trans-Atlantic Group (n=1765)

COST Laparoscopic Trial
Summary

Level 1 evidence supports the practice of laparoscopic colectomy

Future Directions

Laparoscopic-Assisted Rectal Resection

Laparoscopic Resection of Rectal Cancer
Differences From Colon Cancer

- Neoadjuvant therapy
- Sphincter preservation
- Anastomotic complications
- Local recurrence rates

ACOSOG Z6051
A Phase III Prospective Randomized Trial Comparing Laparoscopic-assisted Resection versus Open Resection for Rectal Cancer
Robotic Surgery

- An imprecise term
- Has been widely used by both the medical and lay press
- Now generally accepted by the medical community
- Surgical technology that places a computer-assisted electromechanical device in the path between the surgeon and the patient
- Scientifically accurate term: “remote telepresence manipulators”
- Available technology does not generally function without the explicit and direct control of a human operator


The da Vinci Surgical System

The da Vinci Surgical System

Vision System

- 3D Vision System
  - Dual lens endoscope
- High-Resolution Image Processing
  - Edge enhancement
  - Noise reduction
  - No flicker or cross-fading
- Camera stability
  - Camera control through the hand controls and foot pedals

Surgeon Console

Mechanical Manipulators

- 7 degrees of freedom
- 90 degrees of articulation
- Finger tip control
- Motion scaling and tremor reduction

EndoWrist Technology
Advantages Over Laparoscopy

• Stabilization of instruments within the surgical field
• Mechanical advantages over traditional laparoscopy (strength and dexterity)
• Tremor reduction and motion scaling
• Improved ergonomics for the operating surgeon
• Superior visualization including three-dimensional imaging of the operative field

Disadvantages Compared to Laparoscopy

• Lack of haptics (sense of touch)
• Large size of the devices
• Instrumentation limitations
• Inflexibility of certain energy devices
• Problems with multi-quadrant surgery

Robotic Surgery in Rectal Cancer

• Ideally suited for operations in limited working space
• Mechanical advantages (strength and articulation)
• Positioning “over” the patient
• Surgeon comfort

Worldwide Experience

• S. H. Baik and colleagues: Seoul, Korea
  • 36 patients randomized to laparoscopic or robotic TME

### Follow-Up After Treatment

- Clinic visits every 3 months for first 3 years and every 6 months up to year 5 with CEA levels at every visit
- CT Scans every year for the first 3 years
- Colonoscopy within 3 years after diagnosis (assuming full colonoscopy and no polyps within 1 year of surgery) and then every 3-5 years if that one is normal
- Exercise (walk one hour a day 6 days/week)
- Daily Low Dose Aspirin
- Vitamin D
Conclusion

• Innovations in every field
• Early diagnosis improves outcomes
• Personalized medical management to eliminate unnecessary toxicity
• Minimally invasive approaches widely available to improve surgical outcomes

Questions

"You don't need a colonoscopy, but I'm sending you for one because, quite frankly, I don't like you."