Rationale for Laparoscopy and Minimally Invasive Surgical Methods (Scientific & Clinical) For Cancer: In Theory and In Practice

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Disclosures

- Olympus Corporation (investigator initiated research, consultant)
- Ethicon Endosurgery (stapling education)
Abdominal Surgery Methods
Before 1990

- Only 1 way into abdomen
- Via sizable incision over target area
- Provides direct access to organ in question
- Allows manual palpation & dissection
- Tumor/pathology resected
The Downside or “Cost” of Open Surgery

- **Access trauma**: abdominal wall (muscles, fascia, skin, etc)
- **Intra-abdominal trauma** (unavoidable)
- **Systemic response** (2° to trauma + wound healing)
- **Pain** (mostly related to abdominal wall trauma)
- **Need for wound healing at multiple sites**
- **Disruption of GI function**
Video Laparoscopy & Advanced Laparoscopic Methods

• Introduced in early 90’s
  – Paradigm shift
  – “Sea change”
• Radically changed the approach to majority of abdominal operations
Advantages of Laparoscopy

- Less abdominal wall trauma & injury
- Short term outcome
  - Less pain (→ less pain meds)
  - More rapid recovery
  - Fast return bowel function
  - Better ambulation
  - Shorter length of stay
  - Faster return to work
Advantages of Laparoscopy

- Long term
  - Fewer adhesions
  - Fewer bowel obstructions
  - Fewer incisional hernias
  - Better cosmesis

- Physiologic Benefits ??
- Oncologic benefits ??
- Cost benefits ???
Scientific Underpinning of Laparoscopy

• At the start, surprisingly little scientific support

• As regards new approaches & new techniques:
  – If feasible & logical then it will be attempted
  – “Better to beg for forgiveness rather than ask for permission.”
  – No group decision made as to when new procedure will be attempted
  – Market pressures (real or perceived) are huge
  – Data and scientific evaluation occur after initial adoption
Laparoscopic Cholecystectomy
(1st common general surgery procedure introduced)

- Video laparoscopy introduced
- Case reports & small series initially
- Rash of weekend courses
- Stampede to do first cases (vast majority of surgeons had minimal lap. experience)
- Overall results pretty good BUT
- Incidence of common duct injuries initially much higher than for open operation
Cholecystectomy

Short Term Clinical Results, MD & Patient Perception Drive Adoption

• By the time the basic science studies were done “the horse was out of the barn”
• Basic science studies found differences between open and laparoscopic responses to the surgery
  – Laparoscopy comes out on top
  – Clinical ramifications of these differences unclear
• Lap methods became “gold standard”
• Common duct injury rate dropped back down
Laparscopic Colectomy: A Unique Situation

• Lap. colectomy much more difficult than cholecystectomy
  – Requires bowel mobilization, devascularization, transection, & anastomosis
  – Takes 1-2 hours longer initially

• Most surgeons, after initial try, did not want to do lap. colons

• Issue of port wound tumor recurrences provided the rationale for not doing lap. ops.
Port Site Tumor Recurrences

- **Numeous anectodal reports** early on
- **Impression of many** that wound recurrences not seen after open cancer operations (not true).
- **Majority view:** Concern that CO2 pneumoperitoneum or other laparoscopic technique related factor was cause (disproved in time).
- **Alternate view:** Traumatization of the cancer (poor technique) was the cause. (current view)
Lack of Enthusiasm & Fear of Wound Tumor Recurrences

- Most colorectal surgeons desisted
- Small band of zealots embraced laparoscopy
- Randomized trials for cancer set up (3-7 years to complete studies)
- Provided window of time to do basic science studies
- Ultra-unique: Randomized trial data + basic science results preceded large scale adoption
Basic Science

Physiolgic Impact of Surgery: What to Assess?

- Immune Function
- Plasma protein changes that may impact
  - Physiology
  - Cancer cell growth
  - Angiogenesis
- Plasma’s impact on in vitro tumor growth & endothelial cell growth (angiogenesis)
Does Immune Function After Surgery Matter? YES

- Immunosuppressed populations have higher complication rates
- Anergic patients fare worse
  - Higher infection & mortality rates
  - Lower cancer resectability rates
- Transfused cancer patients do worse
Less Immunosuppression after Laparoscopic Surgery: Evidence*

- Both animal and human studies
- Less marked changes in immunomodulator levels
- Lymphocytes more readily stimulated
- Greater Th-1/Th-2 ratio post op
- Macrophage & PMN marker studies: systemic vs peritoneal (hard to interpret)
- Preserved DTH responses postoperatively

* Short lived 1-2 day differences for most parameters
Delayed Type Hypersensitivity

- Assesses immune systems ability to recognize pathogen it has seen in past
- Ability to respond is verification that immune system is working
Periop DTH Testing

• Preop test to determine size of baseline response (area of wheal)
• Repeat test day of surgery
• Repeat test Postop day 3
• Size of response thought to be rough measure of immune systems functional status
Percentage change in DTH response from preoperative baseline*

Less immunosuppression after laparoscopic vs open colectomy

- Differences are small and short lived.
- Clinical importance unclear
- May contribute to:
  
  • Significantly lower rate of wound complications (odds ratio 0.65; p=0.01)*
  • Incidence post-op complications significantly lower (18.2%) vs open (23%) P=0.02**
  • Oncologic significance unclear

*Schwenk et al. Cochrane Systematic Reviews 2006 No. 3 ISSN 1464-780X
Short Term Cytokine Changes: Lap vs Open Colectomy

- Less marked acute phase inflammatory response
  - IL-6, CRP, TNF-α, IL-8, IL-10 * ** + ++
  - Granulocyte elastase ++

- Serum levels significantly higher after open procedure

- Duration 18-36 hours at most

- Suggests open op more stressful

- Clinical significance unclear

* Ordemann et al. Surg Endosc DOI:1007/s004640090032
Long Duration Changes: Lap Vs Open

- Significantly higher levels of VEGF, ANG-2, PLGF, sVCAM, MMP-3, MCP-1, etc. X 2-5 weeks * **
- Pro-angiogenic
- May stimulate tumor angiogenesis in residual metastases
- Longer duration blood composition changes similar for Lap & Open methods

Linking Surgical Trauma and Tumor Growth

Blood Borne Metastases Model: Methods*

- **Tail vein injection** of $1 \times 10^5$ TA3Ha cells after procedure

- **Groups**: Laparoscopic cecectomy  
  Open cecectomy  
  Anesthesia control

- Mice sacrificed on postoperative day 14

- Surface lung metastases counted

Number of Lung Metastases Following Open Cecal Resection

![Box plot showing the number of lung metastases following different methods of cecal resection.](chart.png)
1. To determine if major abdominal surgery carried out via open or laparoscopic means was associated with alterations in the composition of plasma such that \textit{in vitro} tumor growth would be enhanced.

2. To identify the responsible factor(s).

# Human Plasma Factor Study:

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Open Surgery Patients

BrdU+ (proliferating) cells, %

- PreOP plasma
- POD1 plasma

Added to HT29 cell cultures
Endoscopic Surgery Patients

PreOP plasma

POD1 plasma

Added to HT29 cell cultures

BrdU+ (proliferating) cells, %
Barcelona Trial Interim Results: Cancer-related Survival* **

Laparoscopic-assisted group

Open group

* Kaplan-Meier method
Colon Cancer: Randomized trials

- Serious concerns over safety of laparoscopic methods for cancer
- Multi-center randomized trials started
- Colon cancer first, then rectal cancer
- Hypothesis: Laparoscopic method is not inferior to open method as regards DFS, OS
Laparoscopic vs Open Colectomy for Cancer: Randomized Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>C.O.S.T. (American)</td>
<td>863</td>
</tr>
<tr>
<td>C.O.L.O.R 1 (European)</td>
<td>1082</td>
</tr>
<tr>
<td>Classic (British)</td>
<td>794</td>
</tr>
<tr>
<td>COLOR 2 (European Rectal)</td>
<td>1044</td>
</tr>
<tr>
<td>COREAN (Korean Rectal Ca)</td>
<td>340</td>
</tr>
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</table>

All showed short term recovery benefits \((p < 0.05)\)
<table>
<thead>
<tr>
<th>Series</th>
<th>Laparosc.(%)</th>
<th>Open(%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COST</td>
<td>12</td>
<td>12</td>
<td>ns</td>
</tr>
<tr>
<td>COLOR 1</td>
<td>10 (0-41)</td>
<td>10 (0-42)</td>
<td>ns</td>
</tr>
<tr>
<td>Classic</td>
<td>12</td>
<td>13.5</td>
<td>ns</td>
</tr>
<tr>
<td>COLOR 2</td>
<td>13</td>
<td>14</td>
<td>ns</td>
</tr>
<tr>
<td>COREAN</td>
<td>17</td>
<td>18</td>
<td>ns</td>
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### Intermediate & LongTerm 3 & 5 Year Oncologic Outcome*

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<tr>
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<td>ND</td>
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<td>ND</td>
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<td>COLOR2 (rectal)</td>
<td>ND</td>
<td>ND</td>
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<td>COREAN (rectal)</td>
<td>ND</td>
<td>ND</td>
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* ND = No Difference
Morbid Obesity Surgery: Benefits of Lap vs Open Methods* **

- Less pain, shorter LOS
- Improved postop pulmonary function *
- Lower wound infection rate (1.2 vs 10%)*
- Initially leak rates, bleeding were higher in lap pts, but with time rates decreased
- Lower overall complication rates+
- Volume of cases done increased 6-8 X

Morbid Obesity: Mortality Decrease

• Open gastric bypass periop mortality between 1.9 to 4 %

• MIS methods associated mortality is 0.1 to 0.3%* ** (9 X lower vs 1998 mortality) +

• Attributed to significantly less robust cytokine / stress response in MIS vs Open patients

• ? role of increased volume of cases


Laparoscopic GYN vs Open Hysterectomy: NSQIP Review*

• N = 2076 patients
• MIS use rate: 2006, 16% → 2010, 48%
• Length of surgery: longer in lap. group
• LOS: Open 3.8 vs Lap 1.6
• Complications: significantly lower in Lap group

Basic Economics of Laparoscopy

- Cost of procedure is higher
  - Much OR equipment & devices are needed
  - Disposable cost higher
  - Lengthier op’s in general (more anesthesia, etc)
- Cost of postop hospitalization usually lower
  - Shorter length of stay
  - Lower wound complications & associated costs
- For multiple operations the complication rates and readmission rates are lower for MIS
- Overall, most studies show cost savings
Costs: Lap. Methods Vs Open

- **Ventral hernia repair**: Lap cheaper ($3451) when cost of complications considered*
- **Colectomy**: 90 day overall costs 1.26 x higher (p<0.05) in Open pts**
- **Hepatectomy/pancreatic resection**: Lap. cheaper (≈$4000) +
- **Gastric Bypass**: Lap cheaper ($2,500)++

Splinter Laparoscopic Methods

- Straight laparoscopic
- Laparoscopic-assisted
- Hand-assisted laparoscopy
- Single port laparoscopy
- Robotic laparoscopy

- Each method has its proponents
Robotic Laparoscopy: Advantages

• 3 D images (vs 2D for standard laparoscopy)
• Greater range of motion in robotic “wrists”
• Camera position is secured (no cameraman)
• 4th arm permits surgeon to assist themselves (less reliance on assistants)
• Surgeon sits at console (less taxing)
• In deep pelvis
• Suturing
• Easier to learn than laparoscopy
Robotic Laparoscopy: Disadvantages

- Robot (≈$2,000,000) + yearly maintenance ($150,000/robot)
- Devoted robotic tissue division tools, staplers (cost)
- Disposable robotic graspers, scissors, etc (cost)
- Loss of haptic feedback (how hard am I squeezing?)
- Added OR time (generally longer ops)
- Overall increased cost per case: ≈ $1,500 (colon), ≈ $2,000 (GYN)*

- Since op done alone, harder to train residents
- Once taught on robot must have robot to do case

Robotic Penetration

• Highest utilization rate in Urology
  – Prostate operation is ideal for robot
  – Number prostatectomies increased greatly

• Gynecology and Colon & rectal surgery

• Biggest proponents are surgeons with less straight laparoscopic experience

• If straight laparoscopic approach well established in field there is less penetration
Robotic Results:
Prostatectomy (no MIS alternative)

• Breakdown: Robotic, 85%; open, 14%; lap, 1%
• Many expert robotic GU surgeons (few straight lap G/U surgeons)
• Short term results are better than open
• Functional results same or ? Better (controversial)
• Long term oncologic results similar to open
• Utilization rates have plateaued
• Non-operative alternatives with similar efficacy (RT, hormonal Rx, observation)
Robotic Results
(where Laparoscopic alternative is present)

- Rectal cancer indication: Purported robotic advantage in pelvis $\rightarrow$ increased utilization
- Vs open operation, clear advantages
- Vs laparoscopic op’s (ROLAR, randomized):
  - No difference in quality of resection
  - No difference in short term outcome, LOS
  - Trend to lower conversion rate (obese males)
- Robot results best if used for all colorectal resections but if there is no advantage to patient & higher cost hard to justify
Gynecologic Robotic Surgery
(laparoscopic Vs Robotic)

- Robotic cases: significantly longer than lap*
- LOS: 7 hours shorter for Robotic*
- Costs: Higher for robotic ** +
- Complications: Bit higher for robotic +
- Use of robotics: Advised limiting use robotics to trial setting

Summary

• Laparoscopic methods are now the gold standard for:
  – cholecystectomy, appendectomy, colectomy, morbid obesity surgery, adrenalectomy, splenectomy, prostectomy, etc

• Scientific evidence (and sound clinical evidence) in support did not precede the introduction of these methods (except for colectomy)
Summary: Splinter Methods

- Numerous offshoot MIS methods
- Robotic laparoscopy has had most traction
- Less data available for splinter methods
- Robotic clinical results are equivalent to laparoscopic
- Costs are higher for robotics
- Unless clinical results (critical parameters such as survival in cancer pts) are superior & costs reasonable → limited growth
Summary: Scientific + Clinical Data (Laparoscopy)

- Less abdominal wall trauma
- Less marked acute inflammatory response & immunosuppression
- Less stimulation cancer growth (murine studies)
- Similar long term oncologic outcome (clinical)
- Short term clinical results (vs open):
  - Quicker return bowel function (colon)
  - Less pain, pain medication use
  - Shorter length of stay
  - Lower wound infection and hernia rates (colon)
Clinical Results (Real & Perceived) Drive Adoption

• Initial reports invariably show good results
• Community outcomes (multiple hospitals & many different surgeons) hard to come by and will always be worse than “champion’s” results
• Today: NSQIP Database, NCDB, National In Patient Sample Data Base provide more robust data more rapidly
Human Plasma Factor Study*

1. To determine if major abdominal surgery carried out via open or laparoscopic means was associated with alterations in the composition of plasma such that \textit{in vitro} tumor growth would be enhanced.

2. To identify the responsible factor(s).

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BrdU+ (proliferating) cells, %

Open Surgery Patients

PreOP plasma

POD1 plasma

Added to HT29 cell cultures
Endoscopic Surgery Patients

PreOP plasma

POD1 plasma

Added to HT29 cell cultures
Immunologic, Physiologic, and Oncologic Ramifications of Abdominal Surgery

Richard L. Whelan, MD
Section of Colon & Rectal Surgery
Presbyterian Hospital
Columbia University College of Physicians & Surgeons
New York, N.Y.
Decrease in the percentage of CD31+ T Cells after Colon Resection*

DTH Response

**Cognitive Phase**
- Antigen
- Antigen presenting cells

**Activation Phase**
- \( \text{TH}_1 \) helper lymphocyte
- Lymphokines
- Cell Activation
- Macrophage
- Cytotoxic T cells

**Effector Phase**
- Lysis of Infected Cells
- DTH
Serial DTH Testing Assesses Cell-Mediated Immune Function Over Time*

- Baseline DTH response determined preop
- Several postop challenges with same antigen
- Size of postop responses compared to baseline value for each animal
- Effect of surgery on DTH response thus measured
DTH Response After Open Colorectal Resection*

*P < 0.0005 vs. preop
**P < 0.0003 vs preop

n=17 patients

DTH Response After Laparoscopic Colorectal Resection

Laparoscopic Group

Sum-Total DTH Response in cm²

- Preop
- POD 0
- POD 3
DTH Results: MIS Colorectal Resection

Area of induration mm²

PreOP     POD2     POD5     PreOP     POD2     POD5
GMCSF     Placebo

n=18

Lymphocyte Microarray Studies

- Affymetrix oligonucleotide microarrays
- 22,000 unique genes assessed
- Murine study
- Laparotomy, C02 pneumo, & anesthesia alone
- ½ animals sacrificed at 12 and 24 hours
- Splenic T cells isolated & mRNA extracted
### Splenocyte Microarray 12 Hour Results: Versus Anesthesia Control Group*,+,**,

<table>
<thead>
<tr>
<th>Group</th>
<th># Genes ↑ Regulated</th>
<th># Genes ↓ Regulated</th>
<th>Total # Genes</th>
</tr>
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<tbody>
<tr>
<td>CO2 Pneumo</td>
<td>86</td>
<td>30</td>
<td>116</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>362</td>
<td>36</td>
<td>398</td>
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- Threshold difference between groups > 2 X expression
- Results validated with RT-PCR for 8 selected genes
- Sylla et al. submitted for publication
## Microarray Results at 24 Hours: Versus Anesthesia Control Group

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<th>Total # Genes</th>
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<td>133</td>
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<td>157</td>
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* Threshold difference between groups > 2 X expression
Where the Same Genes Effected? *

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<tr>
<th>Group</th>
<th># Genes 12 hours</th>
<th># Genes 24 hours</th>
</tr>
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<tbody>
<tr>
<td>Altered expression in both groups</td>
<td>60 (13%)</td>
<td>77 (39%)</td>
</tr>
<tr>
<td>Increased expression in <em>Open Group</em> only</td>
<td>338</td>
<td>80</td>
</tr>
<tr>
<td>Increased expression in <em>CO2 Group</em> only</td>
<td>59</td>
<td>41</td>
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* Threshold difference between groups > 2 X expression
Impact of Surgical Approach on Cancer Growth in Murine Studies

• Most studies suggest that laparotomy is associated with increased tumor growth than seen with CO2 pneumo
• Numerous cell lines assessed
• Differences observed been attributed to immune function differences
Murine Experiment: Tumor Establishment Study *

- Study Groups:
  Anesthesia control
  Laparoscopic-assisted cecectomy
  Open cecal resection

- **Low dose** flank injections of tumor cells on day of operation

- On POD 30 presence or absence of tumors determined

Lap.-assisted vs Open Cecectomy: Tumor Establishment by POD 30+

* p<0.01 vs control and open resection

** p<0.001 vs control

+ MMC Tumor Cell Line
Blood Borne Metastases Model: 
Methods*

- Tail vein injection of $1 \times 10^5$ TA3Ha cells after procedure
- Groups: Laparoscopic cecectomy
  Open cecectomy
  Anesthesia control
- Mice sacrificed on postoperative day 14
- Surface lung metastases counted

Number of Lung Metastases Following Open Cecal Resection

The graph shows the number of lung metastases following different types of cecal resection: AC, Lap-asst, and Open. The data is represented with box plots, indicating the distribution of metastases across these procedures.
Problems with Murine Studies vs Human Setting

- In mice, laparotomy alone or with cecetomy associated with higher tumor growth & establishment rates
- In humans, this does not seem to be the case
- The difference is the extent and magnitude of the intrabdominal trauma
- Intrabdominal trauma in major human cases is likely greater than access related trauma
- Regardless, in human setting cancer outcome is similar after MIS and Open resection
What is the Mechanism that Accounts for Tumor Growth Differences?

- Immunosuppression
- A surgery related serum factor? (cytokine, growth factor, protein, etc.)
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BrdU+ (proliferating) cells, %

PreOP plasma

 POD1 plasma
 Added to HT29 cell cultures
Endoscopic Surgery Patients

PreOP plasma and POD1 plasma were added to HT29 cell cultures. BrdU+ (proliferating) cells were analyzed.
Correlation of Increase in OS Plasma Mitogenic Activity & Incision Length*

*POD1 OS BrdU results at 48 hrs vs incision length
Levels of Intact IGFBP-3 on POD2

Intact IGFBP-3 ng/ml

Open

Laparoscopic
IGFBP-3

• Binds IGF-1 (cell growth factor)
• Induces apoptosis of most tumor cell lines
• Inhibits DNA synthesis of poorly differentiated cell lines
• Lower rates of adenoma formation noted in mice that overexpress IGFBP-3
• Prognostic indicator for prostate cancer, IBD, and colon cancer
Plasma Non Immune Protein Changes: Open $>$ Laparoscopic (1st 3 days)

- $\downarrow$ IGFBP-3 (tumor inhibitor, baseline $\uparrow$ levels)
- $\uparrow$ VEGF$_{165}$ (potent stimulator of angiogenesis)
- $\downarrow$ Ang 1/Ang 2 ratio (low ratio proangiogenic)
- $\uparrow$ MMP-9 (proangiogenic, degrades ECM, stroma)
- $\uparrow$ TIMP-1 (lower, shorter lived $\uparrow$ in lap pts.)
Other Short Term Protein Changes After Laparoscopic Surgery

- Soluble Tie-2
- HGF
- TGFβ
- FGF
- sVEGFR1
- sVEGFR2
- Clusterin
What About VEGF?

• Vascular Endothelial Growth Factor
• Most potent inducer of angiogenesis
• Critical to wound repair and healing.
• Critical for tumor growth beyond 2-3 mm*
• Huge effort underway by Pharmaceutical Companies to develop anti-VEGF and anti-angiogenesis therapies.
  – Avastin, VEGF Trap, Sunitinib, Vatalanib, etc.

Pre-resection Blood VEGF Levels

- Significantly higher in colon, gastric, renal cell, lung cancer patients.

- For colorectal cancer, correlation between VEGF level and:
  - Stage of Disease *** + ++
  - Survival * + ++

How Does Surgery Influence VEGF Levels?

- Wound fluid VEGF levels are increased*
- May be spillover into systemic circulation
- Increased blood VEGF levels may stimulate the growth of residual tumor microfoci and circulating viable tumor cells.

VEGF levels Open vs. Laparoscopic Colectomy for Cancer

* p<0.05 open POD1 vs preop, **p<0.05 open POD3 vs preop, pod1
***p<0.05 Lap POD3 vs preop

Cancer group: median VEGF levels
MIS Patients Only (n=69)

<table>
<thead>
<tr>
<th>OpDay</th>
<th>POD1</th>
<th>POD3</th>
<th>POD5</th>
<th>POD7-13</th>
<th>POD14-20</th>
<th>POD21-27</th>
<th>POD28+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>150</td>
<td>192.7</td>
<td>246</td>
<td>380.6</td>
<td>572.2</td>
<td>611.1</td>
<td>512.1</td>
</tr>
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P-value             0.3644     0.009     0.0012    0.0008    0.0098    0.0117   0.4648
Ang 1 and Ang 2

• Angiopoietin 1 (Ang 1) stabilizes mature blood vessels and inhibits VEGF initiated early angiogenesis

• Angiopoietin 2 (Ang 2) facilitates the angiogenic response to VEGF by preventing the Ang 1 response (blocks Tie2 receptor)

• Ratio of Ang 1/ Ang 2:
  – ↑ ratio inhibits VEGF-related angiogenesis
  – ↓ ratio facilitates VEGF-related angiogenesis
Plasma Ang1/Ang2 – Cancer Patients

- PO POD1 POD3 POD 7-13 POD 14-20 POD 21-27 POD 28+
- n = 96 n = 85 n = 60 n = 42 n = 10 n = 17 n = 24

+ : p = 0.0001 vs. PO
++ : p = 0.002 vs. PO
^ : p = 0.041 vs. PO
^^ : p = 0.0145 ns. PO
VEGF and Ang 2 Changes Persist for 2-4 Weeks

- Impact bloods ability to support angiogenesis
- More likely to influence cancer recurrence rates than short term changes
- We believe that open surgery is associated with similar changes
Plasma Contains Many Proteins

- Good number influence angiogenesis
- We have assessed only a handful
- Cannot draw conclusions regarding the net impact of surgery on plasma from such a limited survey
- Can determine the pre and postop plasma’s impact on *in vitro*
  - Tumor cell growth
  - Endothelial cell growth & behavior
What is the **Net** Effect of Postop Plasma in Regards to Angiogenesis?

- Target of angiogenesis related proteins is the endothelial cell (EC)
- Assess behavior of endothelial cells in culture when plasma is added to medium
- Preoperative & postop EC cultures
- Branch point (microtubule) formation
- Invasiveness and migration in culture
In vitro Endothelial Cell Migration Assay: Preop vs POD 7-13

- PreOp
  - Median: 98.7
  - n = 24

- POD 7-13
  - Median: 132.1
  - n = 24

+ : p=0.005 vs. PreOp.
In vitro Endothelial Branch Point Formation: Preop vs POD 7-13

$n = 24$
Median: 51.15

$n = 24$
Median: 62.950

$+p=0.039$ vs. PreOp.
In vitro EC Culture Assays
Significantly Greater Results Postop ?

<table>
<thead>
<tr>
<th>Vs Preop Plasma</th>
<th>BPF</th>
<th>Migration</th>
<th>Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD 7-13 (n=30)*</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>POD 14-20 (n=26)**</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* Mean sampling day = 11
** Mean sampling day = 17.5
+ Extent of change between pre and post op results is 17 - 25 %
Summary: Early Postoperative Period

• Detrimental surgery-related alterations:
  – Immunosuppression
  – Serum protein changes
  – Proangiogenic state

• Changes occur after both open & closed surgery

• Tumor growth may be accelerated

• Potentially dangerous window

• Strengthens case for early adjuvant & neoadjuvant treatment
Typical Time and Treatment Line for Patient with Resectable Cancer

Preop Period

Postop Period

Neoadjuvant Therapy

Operation

Adjuvant Therapy

(Months)
Early Adjuvant & Neoadjuvant Treatment Options

• Immunotherapy
• Conventional chemotherapy
• Angiogenesis inhibitors
• Monoclonal Ab’s
• Alternative therapies
Drugs Being Evaluated

- GMCSF (human study completed)
- Erbitux (human study underway)
- CPG (animal studies done, human next)
- EGCG
- Pinocembrin
Summary

• Laparoscopic methods associated with significantly less changes as regards
  – Numerous cytokines and proteins
  – Immune function parameters
  – Gene expression changes
• Most are short lived changes, in general
• Murine studies suggest laparotomy vs laparoscopy is associated with increased tumor growth rates
• These results suggest cancer benefit for MIS methods
Summary
Blood Borne Metastases Model: Methods*

- Tail vein injection of $1 \times 10^5$ TA3Ha cells after procedure
- Groups: Laparoscopic cecectomy
  Open cecectomy
  Anesthesia control
- Mice sacrificed on postoperative day 14
- Surface lung metastases counted

Number of Lung Metastases Following Open Cecal Resection
Problems with Murine Studies vs Human Setting

• In mice, laparotomy alone or with cecetomy associated with higher tumor growth & establishment rates
• In humans, this does not seem to be the case
• The difference is the extent and magnitude of the intrabdominal trauma
• Intrabdominal trauma in major human cases is likely greater than access related trauma
Human Situation Regarding Abdominal Surgery

• Open and Closed methods are more alike than they are different in regards to cancer
• Intrabdominal trauma is similar
• Both methods are associated with increased rates of tumor growth after resection
• Will not cure cancer by using MIS methods alone
Duration & Magnitude of Surgery’s Effects

• Vast majority of surgery-related physiologic/immunologic changes are of short duration
  – Hours to days
  – May not have significance
  – May impact short term outcome
  – Less likely to impact oncologic outcome

• A few changes persist for 2-4 weeks
  – Proangiogenic blood protein changes
  – More likely to impact cancer outcome
  – Lap & Open surgery effects very similar
Murine Study Conclusions

- Open methods associated with clearly higher rates of tumor growth & establishment (vs CO2 pneumo)
Other Plasma Compositional Changes
(Proteins not associated with immune function)

• May prove more important than immune function differences
• Surgery alters the composition of the blood such that the plasma postop may stimulate tumor growth
• **Early PostOp:** Open surgery associated with greater changes than laparoscopic
• **Late PostOp:** Unclear if open & lap effects are different
Surgery Associated With Proangiogenic Plasma Protein Changes That Persist for 3-4 Weeks

• Most enduring changes found, to date
• Factors generated in wound ➔ blood
• Angiogenesis critical to both wound healing and tumor growth
• Sustained pro-angiogenic conditions may stimulate growth of tumor metastases
• Need to develop “close neoadjuvant” and “immediate adjuvant” strategies for cancer patients
Summary

• Less immunosuppression after lap. surgery
• Most changes short lived and of ? significance
• Individual parameters not tied to outcome, however
• Overall, morbidity and wound complications lower after laparoscopic (?) immune related
• Regardless, would want to give patient benefit of the doubt (better preserved function)
• Other blood protein changes may be more important (angiogenesis)
• Need to find anti-cancer drugs for month prior and after surgery (bridge to standard adjuvant Rx)
Murine Experiment: Tumor Establishment Study *

- Study Groups:
  Anesthesia control
  Laparoscopic-assisted cecectomy
  Open cecal resection

- **Low dose** flank injections of tumor cells on day of operation

- On POD 30 presence or absence of tumors determined

Lap.-assisted vs Open Cecectomy: Tumor Establishment by POD 30

* p<0.01 vs control and open resection

** p<0.001 vs control

+ MMC Tumor Cell Line
Cochrane Evidence Based Review: Short Term Benefits of Laparoscopic vs Open Colectomy (All indications)* **

Main findings regarding laparoscopic method:

– Operative time longer
– Less pain, blood loss
– Shorter postoperative ileus, LOS
– Pulmonary function improved
– Incidence post-op complications lower (18.2%) vs open (23%) P=0.02
– Improved Quality of life x 1 month

*Schwenk et al. Cochrane Database of Systematic Reviews 2006 Issue 3 ISSN 1464-780X
** 25 Randomized control trials reviewed.
# Wound Infection Rates After Laparoscopic Colectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Pts.</th>
<th>Rate of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degiuli et al</td>
<td>108</td>
<td>1.8 %</td>
</tr>
</tbody>
</table>
Open (Big Incision) Surgery
Immune Function After Surgery. Does It Matter ??
Surgical Outcome: Anergic vs Immunocompetent Patients

- Significantly higher rate of postop sepsis and mortality
- Significantly lower resectability rates and higher recurrence rates in cancer patients
Importance of Immune Function: Impact of Blood Transfusions

- Transfusions in cancer patients undergoing curative open colectomy are associated with higher recurrence rates and a worse survival.
Surgery in Immunocompromised Patients

- Population:
  - Transplant patients
  - Pts. on immunosuppressive drugs
  - Disease-related immunosuppression
- Higher complication rates
- Higher mortality
What effect on immune function do laparoscopic and open procedures have?
Immune Function After Laparoscopy: Summary of Results

- Most studies suggest that laparoscopy is associated with less immunosuppression than open methods
- In many cases the differences are small and short lived
- Clinical importance uncertain
Less Immunosuppression after Laparoscopic Surgery: Evidence

- Both animal and human studies
- Serum levels of cytokines & proteins
- DTH responses
- Lymphocyte proliferation assays
- Lymphocyte subpop. & marker studies
- Macrophage / monocyte studies
- Microarray analysis of lymphocytes
Delayed-type Hypersensitivity Testing (DTH)

- Assesses cell-mediated immune function
- Most often used to establish anergy or immune competence
- Tests for prior exposure to specific infectious agent (ex. TB)
- Presence or absence of DTH response defines the anergic patients
DTH Response

Cognitive Phase

- Antigen
- Antigen presenting cells

Activation Phase

- TH$_1$ helper lymphocyte
- Lymphokines

Effector Phase

- Cell Activation
- DTH
- Macrophage
- Lysis of infected cells
- Cytotoxic T cells
Serial DTH Testing Assesses Cell-Mediated Immune Function Over Time*

- Baseline DTH response determined preop
- Several postop challenges with same antigen
- Size of postop responses compared to baseline value for each animal
- Effect of surgery on DTH response thus measured
Serial DTH Studies: Premise

Assumption of serial DTH studies:

• That cell-mediated immune function varies directly with size of DTH response

• A smaller DTH response after surgery will be associated with a diminished ability to respond immunologically
Human DTH Results:

- Cholecystectomy study
- Non randomized study
- 8 open & 8 laparoscopic patients
- Decreased response to PHA 24 hours post op in open patients only
Human Colectomy DTH Study*

- Prospective but not randomized study
- 23 laparoscopic and 17 open patients (well matched for indication and op)
- DTH response to panel of 6 antigens determined, total of 3 challenges
- Data difficult to interpret because multiple antigens were assessed

* Whelan et al. Surgical Endoscopy, publication pending
Immune Function Post Colectomy: Randomized Trial*

- 40 colorectal cancer patients
- Laparoscopic vs. open resection
- Several different immune parameters assessed
- WBC, CD4, CD8, HLA-DR, IL-6,
- PBMC cytokine elaboration

* Ordemann et al. Surg Endosc DOI:1007/s004640090032
Ordemann et al: Results

- Significantly greater WBC increase after open vs closed colectomy (POD 1-4)
- No change in number of CD4+ and CD8+ or in ratio
- Decreased monocyte HLA-DR expression in both groups
- Open HLA-DR result significantly less than closed result on POD 4
- IL-6 significantly higher in open group shortly after surgery
• Randomized 26 patients with colon cancer
• Assessed systemic and peritoneal cytokine and immune response
• Parameters assessed: IL-6, IL-8, TNF, CRP, HLA-DR expression
• Serum & fluid from the peritoneal cavity obtained and studied
Siestes et al Study of Immune Function: Systemic Results

- Significant differences in IL-6 and IL-8 levels 2 hours after surgery
- Leukocyte counts and monocyte HLA-DR expression normalized more rapidly after laparoscopic resection
- Small and short lived differences in favor of the laparoscopic group found
• Prospective study of 42 patients with either Crohn’s Disease or Neoplasms
• Serum levels of IL-6, IL-10, C-RP, and granulocyte elastase determined
• Significantly smaller increases in all 4 parameters noted in laparoscopic patients
• Greatest differences were in IL-6 & granulocyte elastase
• Differences were short lived
What Can We Study?

• Blood
  – Plasma or serum (proteins, etc)
  – Harvested cells (lymphocytes, PMN’s, PBMC’s, etc)
  – In vitro studies
    • assess function of harvested cells
    • impact of plasma on growth of cell cultures

• DTH studies (ex. PPD, mumps, candida)

• Clinical outcome (short term, long term)
Does Surgery Have an Impact on Postoperative Tumor Growth?

• What are the consequences, from an oncologic point of view, of a laparotomy?

• Tumor cells remain in the body after resection in 40+ %

• Is the host environment different after surgery?
Increased Tumor Growth After Laparotomy

- Cole WH. Journal Surg Oncology 1985;30:139-44
Murine Experiment: Tumor Establishment Study *

- Study Groups:  
  Anesthesia control  
  Laparoscopic-assisted cecectomy  
  Open cecal resection

- **Low dose** flank injections of tumor cells on day of operation

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  Open cecectomy
  Anesthesia control
- Mice sacrificed on postoperative day 14
- Surface lung metastases counted

Number of Lung Metastases Following Open Cecal Resection
What is the Mechanism that Accounts for these Differences?

- Immunosuppression
- A surgery related serum factor? (cytokine, growth factor, protein, etc.)
Human Plasma Factor Study*

1. To determine if major abdominal surgery carried out via open or laparoscopic means was associated with alterations in the composition of plasma such that *in vitro* tumor growth would be enhanced.

2. To identify the responsible factor(s).

## Human Plasma Factor Study:

<table>
<thead>
<tr>
<th>Operation Performed</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Colectomy</td>
<td>32</td>
</tr>
<tr>
<td>Cancer</td>
<td>20</td>
</tr>
<tr>
<td>Benign disease</td>
<td>12</td>
</tr>
<tr>
<td>Closed Colectomy</td>
<td>31</td>
</tr>
<tr>
<td>Cancer</td>
<td>22</td>
</tr>
<tr>
<td>Benign</td>
<td>9</td>
</tr>
<tr>
<td>Open Gastric bypass</td>
<td>13</td>
</tr>
<tr>
<td>Closed Gastric bypass</td>
<td>8</td>
</tr>
</tbody>
</table>
Open Surgery Patients

BrdU+ (proliferating) cells, %

PreOP plasma

POD1 plasma

Added to HT29 cell cultures
Endoscopic Surgery Patients

PreOP plasma

POD1 plasma

Added to HT29 cell cultures

BrdU+ (proliferating) cells, %
Correlation of Increase in OS Plasma Mitogenic Activity & Incision Length*

*POD1 OS BrdU results at 48 hrs vs incision length
Levels of Intact IGFBP-3 on POD2

Intact IGFBP-3 ng/ml

Open                  Laparoscopic
• Binds IGF-1 (cell growth factor)
• Induces apoptosis of most tumor cell lines
• Inhibits DNA synthesis of poorly differentiated cell lines
• Lower rates of adenoma formation noted in mice that overexpress IGFBP-3
• Prognostic indicator for prostate cancer, IBD, and colon cancer
Results: MMP-9 ELISA and WB

MMP-9 WB analysis

*\( p < 0.003 \)

rhMMP-9: Lane 1
Plasma MMP-9: Lanes 2,3

MMP-9, ng/ml

Open Surgery | Laparoscopic Surgery

Pre-OP | POD1 | POD2 | POD3
Results: TIMP-1 ELISA

**p<0.0003**

* p<0.01

TIMP-1, ng/ml

<table>
<thead>
<tr>
<th></th>
<th>Pre-OP</th>
<th>POD1</th>
<th>POD2</th>
<th>POD3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Vascular Endothelial Growth Factor

- Most important angiogenesis promoter
- Wounds require VEGF to heal
- Tumors also need VEGF to grow > 2mm
- Blood VEGF levels preop correlate with stage of disease and prognosis
- Anti-angiogenesis agents coming onto market (Avastin is first)
- What does surgery do to VEGF levels??
VEGF levels Open vs. Laparoscopic Colectomy for Cancer*

*Open vs Lap or Preop, p<0.0001
** Mean incision size: open 19.9 cm, closed 5.1 cm
(n= 140 pts [70 laparoscopic, 69 open])

*Belizon et al. Annals Surg (publication pending)
VEGF levels Open vs. Laparoscopic Colectomy for Benign Disease*

* Open vs Lap, p<0.05
** Mean incision size: open 4.5 cm, closed 21 cm)
(n= 40; 20 open & 20 lap.-assisted pts.)

*Belizon et al. Annals Surg (publication pending)
VEGF levels Open vs. Laparoscopic Gastric Bypass*

* Open vs Lap, p<0.05
** Mean incision size: 22 cm
(n=40; 20 open & 20 lap.-assisted pts.)

*Belizon et al. Annals Surg (publication pending)
Figure 2: VEGF Levels Cancer Patients

*Op day VS. POD#5, p=0.003
**Op day VS. POD7-14, p=0.0026
Conclusions

• Open surgery alters the plasma composition more so than laparoscopic surgery.
• Both open and closed methods have profound effect on VEGF levels (open > ?)
• Are the differences between open and closed methods enough to effect oncologic outcome???
• Regardless, we must develop neoadjuvant and immediate adjuvant therapies for cancer patients.
• The 1\textsuperscript{st} month after surgery is a \textit{dangerous} time for cancer patients.
Conclusions

• Motivation for doing laparoscopic colectomy for cancer may be to diminish the plasma compositional changes.
• Additional studies are ongoing
• Replacement of IGFBP-3 may lessen the negative oncologic impact of open surgery
• Block VEGF postoperatively? (GMCSF)
• Erbitux?
• Desiccation of peritoneum may play a role in stress response. (? role humidification, warming of CO2 gas)
Conclusion

• Perioperative immunomodulation with GMCSF – preliminary results soon
• Microarray studies ongoing
• Other serum proteins being studied
• The choice of surgical access method may have an impact on the long term oncologic outcome.
Perioperative Adjuvant Therapies?

- Early postop period is window of opportunity
- Immune stimulating drugs (GMCSF, FLT-3, etc)
- Tumor vaccines
- H-2 blockers
- IGFBP-3 protease inhibitors
Thanks & Acknowledgement

Many of the studies whose results were presented were carried out with PEER reviewed grants from SAGES, the Columbia MASC, and other organizations via USSC/ TYCO Educational Grants and Center of Excellence funding
<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>n</th>
<th>Age Yrs.</th>
<th>Plasma Mitogenic Activity</th>
<th>Cell Counts (x10^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BrdU+cells, %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PreOP</td>
<td>POD1</td>
</tr>
<tr>
<td>OS, All Patients</td>
<td>45</td>
<td>56.6±15.8</td>
<td>34.2±17.9</td>
<td>42.4±19.*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.6±1.6</td>
<td>7.0±1.8*</td>
</tr>
<tr>
<td>LS, All Patients</td>
<td>39</td>
<td>59.8±19.3</td>
<td>37.2±18.1</td>
<td>36.6±18.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.2±1.3</td>
<td>5.1±1.7</td>
</tr>
<tr>
<td>OS, Colon Cancerª</td>
<td>20</td>
<td>65.4±12.6</td>
<td>30.5±19.1</td>
<td>36.3±18**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.4±1.7</td>
<td>6.7±1.8*</td>
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<tr>
<td>LS, Colon Cancerª</td>
<td>22</td>
<td>63.9±17.6</td>
<td>32.6±19.9</td>
<td>31.6±18.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.9±1.4</td>
<td>4.8±1.7</td>
</tr>
</tbody>
</table>

*P<0.05; **P<0.005 PreOP versus POD1 •p<0.05 compared to identical OS subgroup. ¶Insufficient n for a statistical analysis.

* Patients with colon cancer stage I-III were included; distribution of stages was comparable in OS and LS groups.
## Mitogenic Activity of OS and LS POD 1 Plasma

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>n</th>
<th>Age Yrs.</th>
<th>BrdU+cells, % PreOP</th>
<th>BrdU+cells, % POD1</th>
<th>Cell Counts (x10^5) PreOP</th>
<th>Cell Counts (x10^5) POD1</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, Obesity</td>
<td>13</td>
<td>43.1±10.9</td>
<td>48.5±7.8</td>
<td>56.7±6.4**</td>
<td>6.7±0.6</td>
<td>7.8±0.8**</td>
</tr>
<tr>
<td>LS, Obesity</td>
<td>8</td>
<td>38.9±14.7</td>
<td>47.0±14.9</td>
<td>42.1±15.9</td>
<td>5.9±1.3</td>
<td>5.8±1.6</td>
</tr>
<tr>
<td>OS, Colon Adenoma</td>
<td>8</td>
<td>50.2±15.0</td>
<td>23.7±14.3</td>
<td>33.8±22.3*</td>
<td>4.3±1.5</td>
<td>6.3±3.0*</td>
</tr>
<tr>
<td>LS, Colon Adenoma</td>
<td>5</td>
<td>74.8±8.3</td>
<td>49.6±8.7</td>
<td>56.5±16.5¶</td>
<td>5.4±1.0</td>
<td>5.8±1.9 ¶</td>
</tr>
</tbody>
</table>

*P<0.05; **P<0.005 PreOP versus POD1 ¶¶Insufficient n for a statistical analysis.
What is Responsible for the Increased Tumor Growth after Laparotomy?

Two leading hypotheses

1. The incision*

2. Exposure of peritoneal cavity to air** +

Old Wives’ Tales

If a cancer patient has surgery, afterward, the tumor will grow faster and spread more rapidly.
What Accounts for the Differences in Tumor Growth?

- Increased tumor cell turnover?
- Decreased tumor cell death?
Tumor Cell Proliferation and Apoptosis* after Surgery*

- Groups:
  - Anesthesia control
  - CO2 pneumo
  - Sham laparotomy
- High dose flank tumor cell injections on day of surgery
- Tumors harvested on POD 14
- Cell proliferation and apoptotic rates determined

+ Apoptosis = programmed cell death
Figure 4: Comparison of Proliferative Rates and Apoptotic Rates on POD 14

Counts/hpf

- Control
- Insufflation
- Open

PCNA
Apoptosis

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>n</th>
<th>Age Yrs</th>
<th>Cells recovered from culture x10^5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PreOP</td>
</tr>
<tr>
<td>OS, Colon Adenoma</td>
<td>8</td>
<td>50.2 ± 15.0</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>LS, Colon Adenoma</td>
<td>4</td>
<td>74.8 ± 8.3</td>
<td>5.4 ± 1.0</td>
</tr>
<tr>
<td>OS, Diverticulitis</td>
<td>5</td>
<td>69.2 ± 6.2¶</td>
<td>5.7 ± 1.6</td>
</tr>
<tr>
<td>LS, Diverticulitis</td>
<td>4</td>
<td>60.8 ± 17.6¶</td>
<td>4.9 ± 0.7</td>
</tr>
</tbody>
</table>

*P<0.05 PreOP versus POD1 using Wilcoxon’s matched-pairs signed-ranks test.
*p<0.05 compared to identical OS subgroup. ¶Insufficient n for a statistical analysis.
Critical Outcome Parameters for Curative Cancer Surgery

- 5 year survival
- Local and distant recurrence rates
Laparoscopic Colectomy for Cancer: Technical Issues

Richard L. Whelan
Columbia University
New York Presbyterian Hospital
Surgical Technique Considerations

- Anchor all ports
- Do not touch tumor
- Rely on gravity and position changes
- Grasp epiploica or mesentery
- Atraumatic graspers
- Localize tumors preoperatively (tattoo)
Cancer Technique

- Ultrasound liver
- Devascularize early
- As radical as you need to be
- Wound protection or bag
- Tumoricidal irrigation
  - Betadine (dilute)
  - Taurolidine
Rectal Surgery

• TME technique
• Wide mobilization and resection
• Distal stapling a problem in some
• Hybrid method an option
  – Intentional small incision (8-11cm)
  – Anastomosis and distal transection
Laparoscopic Colectomy for Cancer: Issues

- Adequacy of resection
- Port site tumors
- Short term
- Long term oncologic results
- Randomized trial
## Randomized Colectomy Trials: Adequacy of Resection

<table>
<thead>
<tr>
<th>Trial</th>
<th>LAR versus Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI/COST</td>
<td>NSD +</td>
</tr>
<tr>
<td>Milsom *</td>
<td>NSD</td>
</tr>
<tr>
<td>Lacy**</td>
<td>NSD</td>
</tr>
</tbody>
</table>

* NSD = no significant difference
* * Cleveland Clinic Trial
* *** Barcelona Trial
Port Site Tumor Recurrences

- At port site or “assisted” incision

- Over 89 reported to date *

- Colon, gallbladder, lung, & ovarian

- Most in Duke’s C patients but some in Duke’s A & B-1 patients

- True incidence unknown

Do Wound Tumors Develop After Open Surgery?

Yes

- Two large reviews of open colectomy patients have been carried out

- More than 1000 patients in each

- 0.6% to 0.8% incidence of abdominal wound tumors

* Hughes et al. Dis Col Rectum 1983;26:571
Most Recent Human Laparoscopic Colectomy Results

- Incidence between 0 and 1.2 %
  (CPMC rate = 0.7 %, 1 case)

- Review of literature by Wexner
  (17 studies) found mean incidence of 1 %

- Anticipated very high port tumor rates have not been reported
Etiology of Port Wound Tumors: Direct Route of Spread Most Likely

Prerequisites for tumor formation

- Liberated viable tumor cells
- Mode of transportation to wound
- Receptive wound environment for tumor growth
Wound Tumors: Possible Contributing Etiologic Factors

- Tumor stage
- Biology of the tumor
- Operating environment (C02 pneumo)
- Technique
Port Wound Tumors: Possible Etiologic Role of CO₂ Pneumo

- Aerosolization of tumor cells? (NO)
- Desufflation related transport of liberated cells?
- CO₂ as stimulator of tumor cell growth? May play a minor role.
The Role of Technique in Port Wound Tumor Formation

- Controversial

- Discrepancy in results between various centers suggests that technique is an important variable

- Perforated cancers have worse outcome

- Bad technique should increase chances of local recurrences
Study of Technique: Murine Splenic Tumor Model

- Isolated splenic tumors established via splenic injection
- “Primary” tumor resected via splenectomy under a variety of conditions 10 days later
- Allows assessment of technique

- Studied 2 variables:
  - Presence or absence of pneumo
  - Poor surgical technique

- Three ports placed in all animals at start of procedure

- Splenectomy carried out extracorporeally via subcostal incision in all animals
Tumor Capsule Crushed Before Splenectomy in Half the Animals

Non-Crush Group  Crush Group
Half the Animals of Each Group: Underwent CO₂ Pnuemo

CO₂ pneumo: 5 mmHg for 15 min.
Comparison of Tumor Implantation at Trocar Sites

- **p (χ²):**
  - No Pneumo v. Pneumo: NS
  - No Pneumo v. *: p < 0.001
  - Pneumo v. **: p < 0.001

<table>
<thead>
<tr>
<th>Group</th>
<th>Frequency of Tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pneumo</td>
<td>10.9</td>
</tr>
<tr>
<td>Pneumo</td>
<td>13.8</td>
</tr>
<tr>
<td>Crush No Pneumo</td>
<td>35</td>
</tr>
<tr>
<td>Crush Pneumo</td>
<td>41.2</td>
</tr>
</tbody>
</table>
Second Splenic Tumor Model Study

- Compared laparoscopic-assisted to open splenectomy
- Spleen mobilized laparoscopically
- 3 ports & subcostal incision for all
- Splenectomy via subcostosal wound
- Study done in 4 different trials
- Single surgeon
Port Site Tumor Recurrence Rate in a Murine Model Decreased With Increased Experience

p = 0.003  p = NS  p = NS  p = NS
Summary of Port Site Data

- Technique appears to be the most important variable

- Human incidence in same range as for open incisional recurrences (1%)

- Port wound tumors are local recurrences

- Irrigation with tumoricidal agents further lowers incidence
Lumley et al

- **Survival data**
  - Stage A: 91 %
  - Stage B: 83 %
  - Stage C: 74 %

- **Recurrence data**
What Accounts for the Differences in Tumor Growth?

- Increased tumor cell turnover?
- Decreased tumor cell death?
Tumor Cell Proliferation and Apoptosis* after Surgery*

- Groups:
  - Anesthesia control
  - CO2 pneumo
  - Sham laparotomy
- High dose flank tumor cell injections on day of surgery
- Tumors harvested on POD 14
- Cell proliferation and apoptotic rates determined

+ Apoptosis = programmed cell death
Figure 4: Comparison of Proliferative Rates and Apoptotic Rates on POD 14
Human Lap. Vs Open Colectomy Study
Percentage Change in DTH Response from Preoperative Baseline*

* * p < 0.05

OS: Correlation between the Decrease in CD3+CD31+ Cells and the Length of Incision

The graph shows a scatter plot with the decrease in the percentage of CD31+ T cells on the y-axis and the length of incision on the x-axis. The data points suggest a trend indicating a correlation between the decrease in CD31+ T cells and the length of the incision.
Identification of Lung Metastases
What Accounts for the Differences in Tumor Growth?

- Increased tumor cell turnover
  AND

- Decreased tumor cell death
Increased Tumor Growth After Laparotomy

- Mouse mammary carcinoma (MC-2)
- Melanoma B-16 * **
- Colon 26 (C-26 adenocarcinoma)*
- CC531 tumor line+
- TA3Ha

IGF-BP3 Western Blot Analysis

- Adding IGFBP-3 to POD 1 plasma < ‘s tumor growth
- Adding Ab to IGFBP-3 to Preop plasma > growth
Figure 2: VEGF Levels Cancer Patients

*Op day VS. POD#5, p=0.003
**Op day VS. POD7-14, p=0.0026
Does Immune Function Impact Short Term Outcome Parameters ??

• Less pain ?
• Better pulmonary function ?
• Quicker resolution of ileus ?

What About Non-oncologic Long Term Outcome measures ??

• Fewer SBO admissions ?
• Fewer Reops for SBO ?
Role of CD31 Surface Protein in T Lymphocyte Function

- T-cells migrating from circulation to periphery express the CD 31 protein
- CD 31 involved in T cell transendothelial trafficking*
- An indicator of T cell activation**

Immunocompetent Mice

Tumor Size After Lap-assisted vs Open Cecectomy (POD 12) * **

* MC-2 MMC tumor cells injected into flank day of surgery
** Allendorf et al. Surg Endosc 1998;12(8)1035-1038
Tumor Mass on POD 12: Nude Mice

![Graph showing tumor mass measurements for AC, INS, and LAP groups with statistical significance notes.

AC: n=32
INS: n=32
LAP: n=24

* p< 0.015 vs INS, p< 0.03 vs LAP]
Decrease in the percentage of CD31+ T Cells after Colon Resection*

Ang 1 & 2 Modulate VEGF Mediated Angiogenesis

Plasma Ang1 /Ang 2 Ratio

PO POD1 POD3

Ang1/Ang2

Lap

Open

p=0.032

p=0.015
Levels of Intact IGFBP-3 on POD2* **
(Insulin-like Binding Protein-3)

* Tumor growth inhibitor
PDGF-bb levels Open vs. Laparoscopic Colectomy for Cancer

- PDGF-bb pg/ml
- Preop
- POD#2
- POD#3

n=48 open
n=44 closed

Open vs. Laparoscopic Colectomy for Cancer
Surgical Outcome: Anergic vs Immunocompetent Patients

- Significantly higher rate of postop sepsis and mortality
- Significantly lower resectability rates and higher recurrence rates in cancer patients
Importance of Immune Function: Impact of Blood Transfusions

• Transfusions in cancer patients associated with higher recurrence rates and a worse survival.
Surgery in Immunocompromised Patients

- Population:
  - Transplant patients
  - Pts. on immunosuppressives drugs
  - Disease-related immunosuppression

- Higher complication rates
- Higher mortality
Impact of T cells on Tumor Growth After Laparotomy or CO2 Pneumo***

- Surgery stimulates tumor growth
- Nude mice (no T cells) vs immunocompetent mice
- Laparotomy vs. CO2 pneumo
- High dose tumor injections postop
- POD 12 tumors excised & weighed

** Allendorf et al. Surgical Endoscopy 1999;13:233-235
Tumor Growth After Surgery in Immunocompetent Vs Nude Mice

Immunocompetent mice

T-cell deficient mice
How is immune function altered after laparoscopic and open procedures?
Delayed-type Hypersensitivity Testing (DTH)

- Assesses cell-mediated immune function

- Most often used to establish anergy or immune competence

- Tests for prior exposure to specific infectious agent (ex. TB)

- Presence or absence of DTH response defines the anergic patients
DTH Response

**Cognitive Phase**
- Antigen
- Antigen presenting cells

**Activation Phase**
- TH₁ helper lymphocyte
- Lymphokines

**Effector Phase**
- Cell Activation
- DTH
- Macrophage
- Lysis of Infected Cells
- Cytotoxic T cells

**Diagram Notes**
- APC (Antigen Presenting Cell)
- TN (T Helper 1)
- Lymphokines
- Cytotoxic T cells
Serial DTH Testing Assesses Cell-Mediated Immune Function Over Time*

- Baseline DTH response determined preop
- Several postop challenges with same antigen
- Size of postop responses compared to baseline value for each animal
- Effect of surgery on DTH response thus measured
DTH Response After Laparoscopic Colorectal Resection

Laparoscopic Group

Sum-Total DTH Response in cm²

n=23 patients
Lymphocyte Microarray Studies

- Affymetrix oligonucleotide microarrays
- 22,000 unique genes assessed
- Murine study
- Laparotomy, C02 pneumo, & anesthesia alone
- ½ animals sacrificed at 12 and 24 hours
- Splenic T cells isolated & mRNA extracted
<table>
<thead>
<tr>
<th>Group</th>
<th># Genes 12 hours</th>
<th># Genes 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered expression in both groups</td>
<td>60 (13%)</td>
<td>77 (39%)</td>
</tr>
<tr>
<td>Increased expression in <em>Open Group</em> only</td>
<td>338</td>
<td>80</td>
</tr>
<tr>
<td>Increased expression in <em>CO2 Group</em> only</td>
<td>59</td>
<td>41</td>
</tr>
</tbody>
</table>

* Threshold difference between groups > 2 X expression
Clinical Significance of Immune Function Differences is Uncertain

• Further studies needed
• Need to document clinical benefits
• There is no conclusive evidence, however, …
• There is some suggestive evidence
## Cancer Recurrence & Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. pts.</th>
<th>Oncologic Results</th>
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<tbody>
<tr>
<td>COST</td>
<td>863</td>
<td>No Difference</td>
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<tr>
<td>COLOR</td>
<td>1248</td>
<td>No Difference</td>
</tr>
<tr>
<td>Meta-Analysis</td>
<td></td>
<td>No Difference</td>
</tr>
<tr>
<td>Lacy et al</td>
<td>208</td>
<td>Lap. Benefit</td>
</tr>
</tbody>
</table>
Cochrane Evidence Based Review: Short Term Benefits of Lap. vs Traditional Colectomy (All indications)* **

Main findings regarding laparoscopic methods

– Lower blood loss
– Lower intensity of pain
– Shorter postoperative ileus
– Pulmonary function improved

– Incidence post-op complications significantly lower (18.2%) vs open (23%) \( P=0.02 \)

*Schwenk et al. Cochrane Database of Systematic Reviews 2006 Issue 3 ISSN 1464-780X
** 25 Randomized control trials reviewed.
Meta-Analysis of 17 Randomized Colectomy Trials (4013 Operations)*

- No difference in leak rate or overall morbidity found
- *Significantly lower rate of wound complications noted in laparoscopic patients (odds ratio 0.65; p=0.01)*
- Could better preserved immune function contribute to these findings?

Does Immune Function Impact Short Term Outcome Parameters ??

• Less pain ?
• Better pulmonary function ?
• Quicker resolution of ileus ?

What About Non-oncologic Long Term Outcome measures ??

• Fewer SBO admissions ?
• Fewer Reops for SBO ?
Microarray Results: Conclusions

- Open surgery has ↑ effect on gene expression
- Clinical importance unclear
- Human microarray study in progress (Cleveland Clinic, Ferguson Clinic, U Vermont, Columbia)
- May elucidate mechanism by which surgical trauma induces immunosuppression
- May lead to novel pharmacologic strategies to limit the deleterious immunologic side effects of surgery
What Can We Study?

• Blood
  – Plasma or serum
  – Harvested cells (lymphocytes, PMN’s, PBMC’s, etc)

• In vitro studies (assess harvested cells or the impact of plasma on growth of cell cultures)

• In vivo studies (rodent)
Problems with Murine Studies vs Human Setting

- In mice, laparotomy alone or with cecetomy associated with higher tumor growth & establishment rates
- In humans, this does not seem to be the case
- The difference is the extent and magnitude of the intrabdominal trauma
- Intrabdominal trauma in major human cases is likely greater than access related trauma
Human Situation Regarding Abdominal Surgery

- Open and Closed methods are more alike than they are different in regards to cancer
- Intrabdominal trauma is similar
- Both methods are associated with increased rates of tumor growth after resection
- Will not cure cancer by using MIS methods alone
Laparoscopic Surgery
Human Situation Regarding Abdominal Surgery

- No differences in cancer outcome in randomized trials
- Open and Closed methods are more alike than they are different in regards to cancer
- Intrabdominal trauma is similar
- Both methods are associated with increased rates of tumor growth after resection
- Will not cure cancer by using MIS methods alone
Abdominal Surgery Methods Before 1990

• Only 1 way into abdomen
• Via sizable incision ("open" method)
  – Direct exposure of organ in question
  – Allows manual palpation & dissection
• Upside: simple, direct
• Downside:
  – Painful (cut skin, fascia & muscle) → Pain meds
  – Short term morbidity (wound infections, dehiscence)
  – Long term morbidity (hernia, adhesions, SBO)
Laparoscopic Vs Open Colectomy: Post Hospitalization Costs*

- Straight forward benign pathology cases
- Hospital and outpatient health care utilization costs x 90 days determined
- Open methods cost: 1.26 X MIS cost
- Open patients return to work 2.78 days later
- At 1 year: Open methods associated with 1.16 x higher costs

ROLAR Results (Randomized study)*

- Laparoscopic vs Robotic laparoscopic methods for rectal cancer resection
- Preliminary results released
- No difference in pathologic assessment
- No difference in LOS, complications
- Trend: lower conversion rate in obese males
- Overall, showed the 2 methods yielded similar results
- No real benefit demonstrated

* Presentation, 2015 ASCRS Meeting, Boston, MA