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

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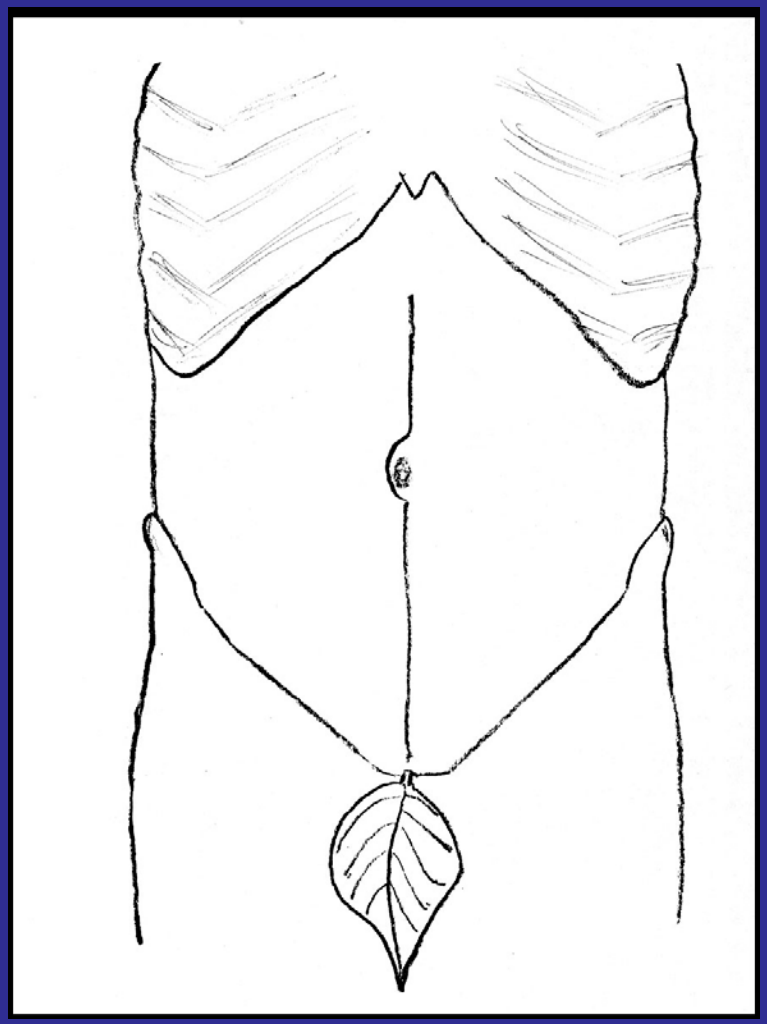
Disclosures

- 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

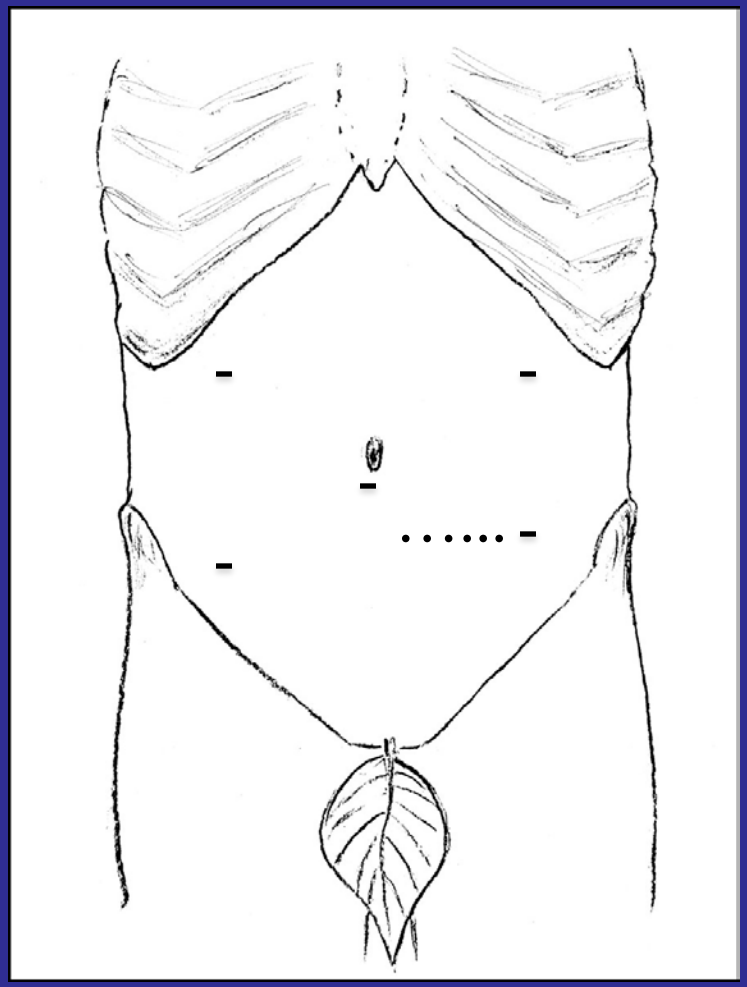


The Downside or "Cost" of Open Surgery

- 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

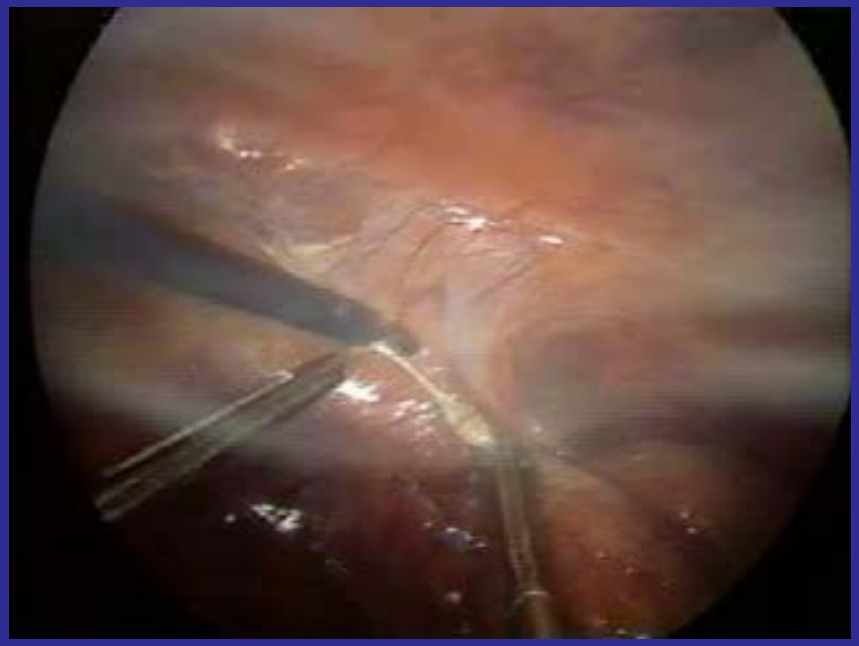
Video Laparoscopy & Advanced Laparoscopic Methods

- Introduced in early 90's
  - Paradigm shift
  - "Sea change"
- Radically changed the approach to majority of abdominal operations



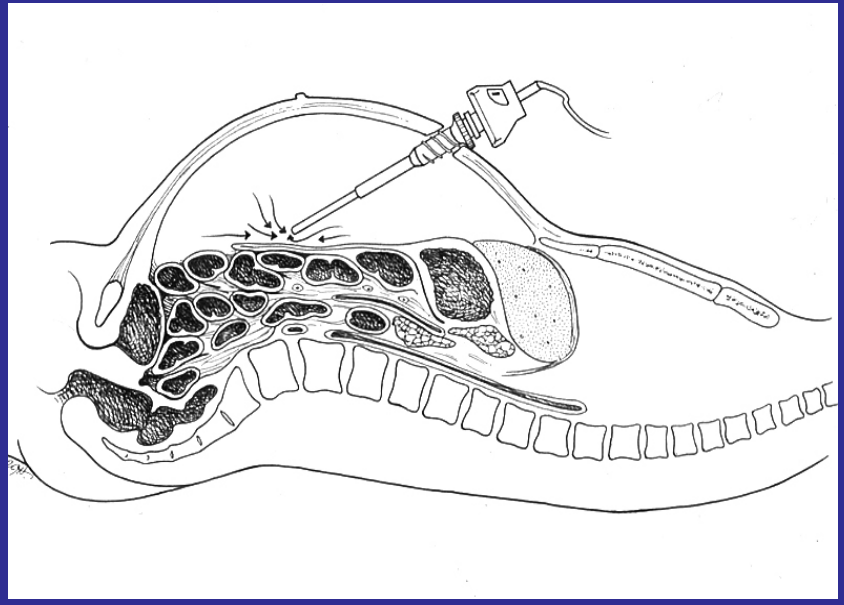
Advantages of Laparoscopy

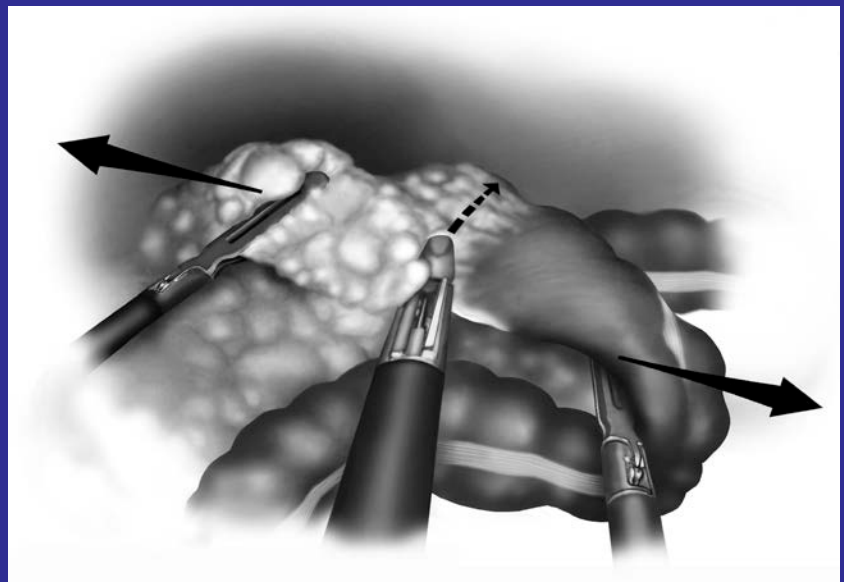
- Less abdominal wall trauma & injury
- Short term outcome
  - Less pain (→ less pain meds)
  - More rapid recovery
  - Fast return bowel function
  - Better ambulation
  - Shorter length of stay
  - Faster return to work



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

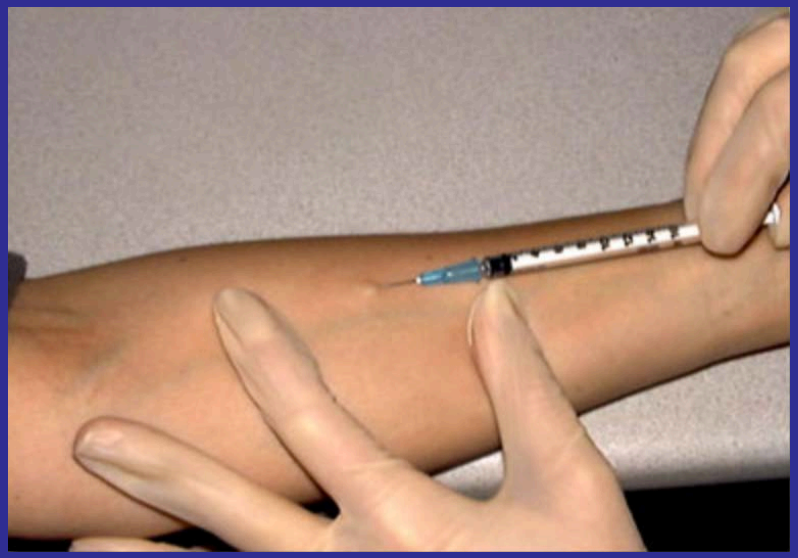
Less Immunosuppression after Laparoscopic Surgery: Evidence*

- 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

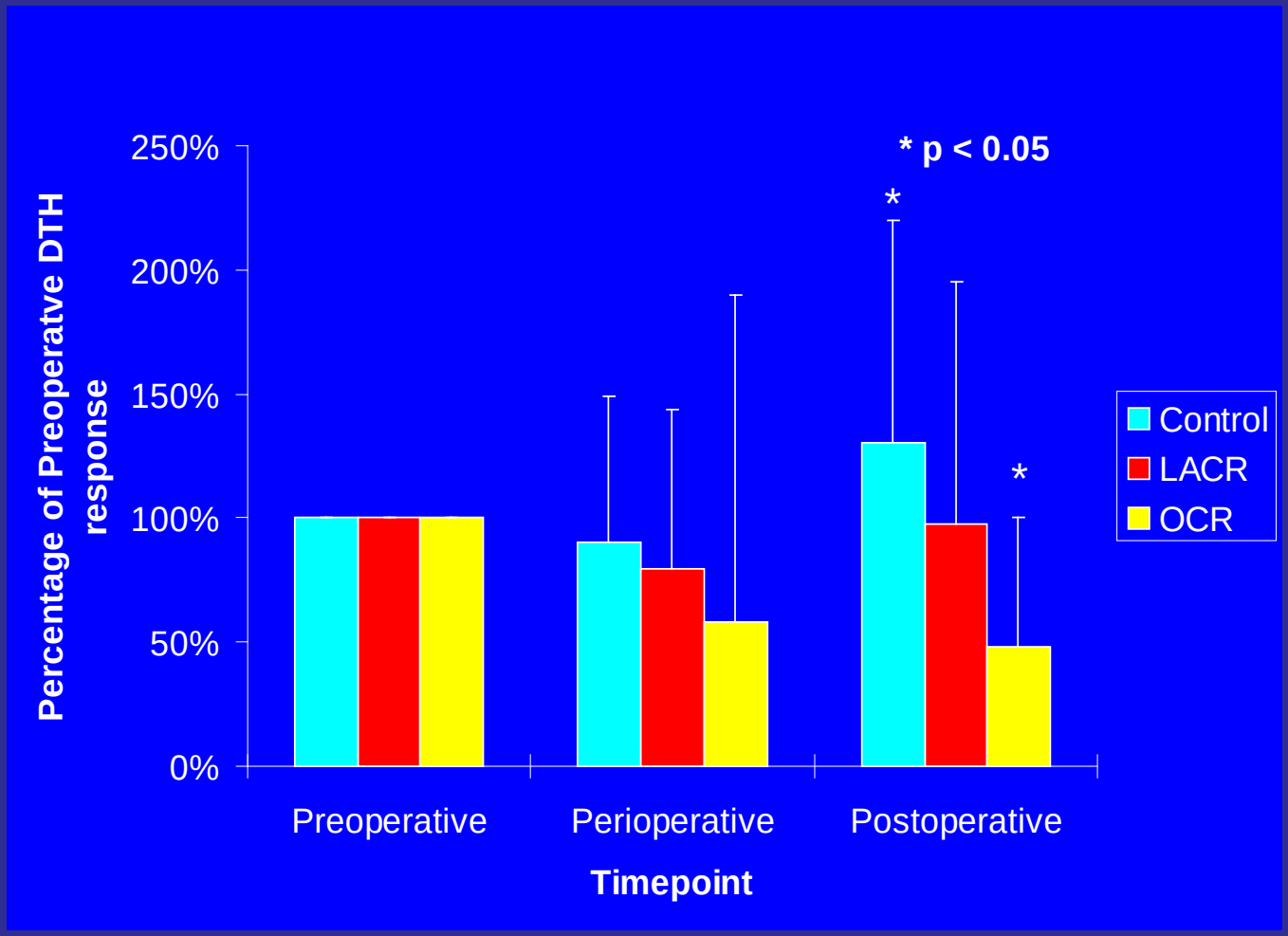
- Assesses immune systems ability to recognize pathogen it has seen in past
- Ability to respond is verification that immune system is working



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*



* Whelan et a. Surg Endosc 2003;17(6):972-978.

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

** Tjandra JJ et al. Colorectal Dis 2006;8:375-388.

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
**Harmon et al. Dis Colon Rectum 1994;37:754-759.
+Sietses et al. Dis Colon Rectum 2003 Feb;46(2):147-55.
++Hildebrandt et al. Surg Endosc. 2003;17(2):242-6.

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

* Kumara et al. Ann Surg. 2009 Jun;249(6):973-7.
**Kumara et al. Surg Endosc. 2011 Jul;25(7):2153-8.

Linking Surgical Trauma and > Tumor Growth

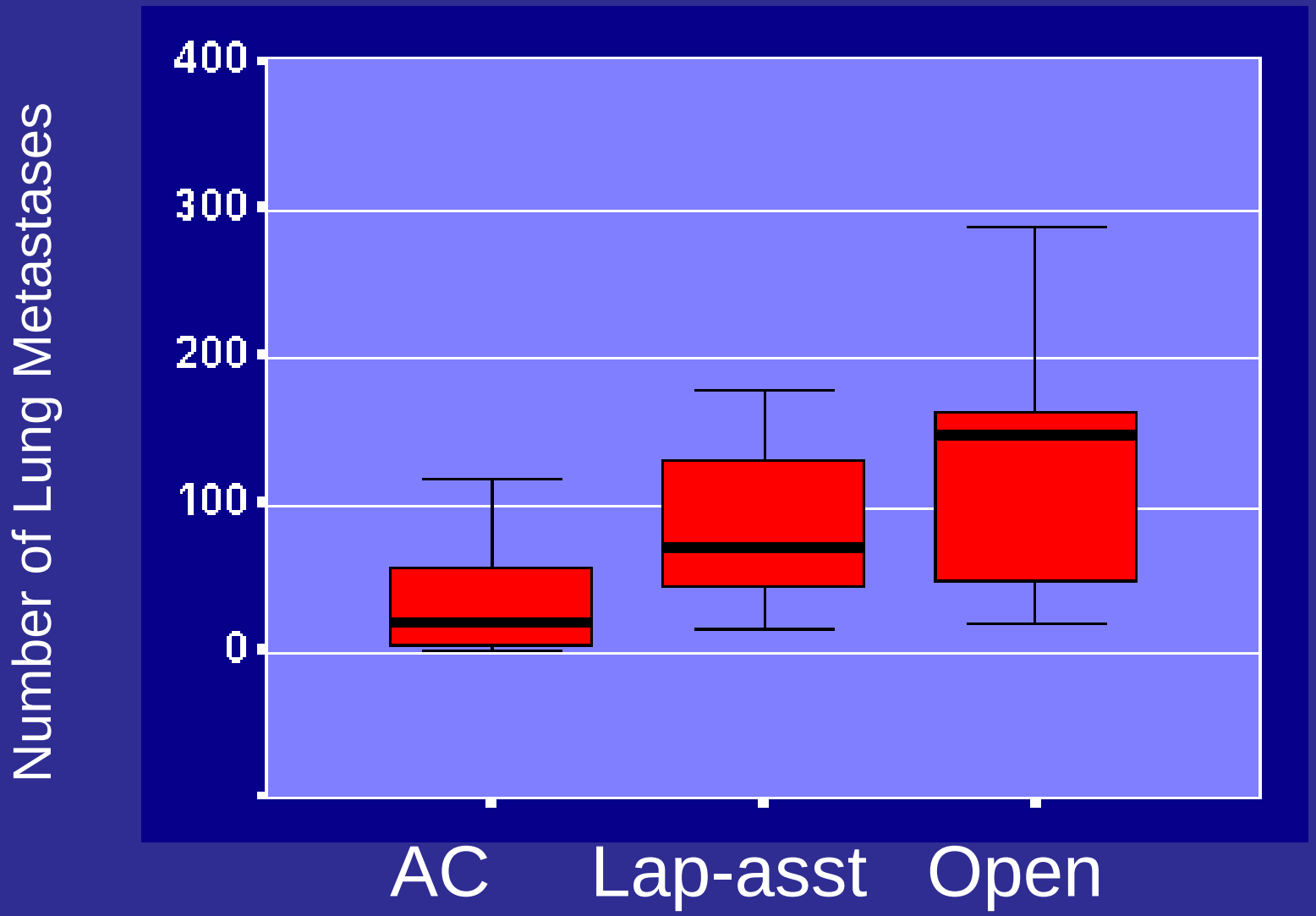
- Tagliabue E, et al. Europ J Cancer 2006;42:1057-1061.
- Spiegel DR. Lancet 2003;362:502.
- Tagliabue et al. Lancet 2003;362:527-533.
- Coffey JC, et al. Lancet Oncology 2003;4:760-768.
- Baum M, et al. Europ J Cancer 2005;41:508-515.
- Tyzzer E. J Med Research 1913;28:309-322.
- Jones F, et al. Monograph Rockefeller Inst Med Res 1914;1:404-412.
- Skipper D, et al. Int J Colorect Dis 1989;4:172-177.
- Abramovitch R, et al. Br J Cancer 1999;79:1392-96.
- Qadri SS, et al. Ann Thorac Surg. 2005 Sep;80(3):1046-50.

Blood Borne Metastases Model: Methods*

- Tail vein injection of $1x10^5$ TA3Ha cells after procedure
- Groups: Laparoscopic cecectomy
  Open cecectomy
  Anesthesia control
- Mice sacrificed on postoperative day 14
- Surface lung metastases counted

* Carter et al. Surgery 2003;134(3):432-6 .

Number of Lung Metastases Following Open Cecal Resection



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.

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* Kirman et al. Surgery 2002;132:186-92.

Human Plasma Factor Study:

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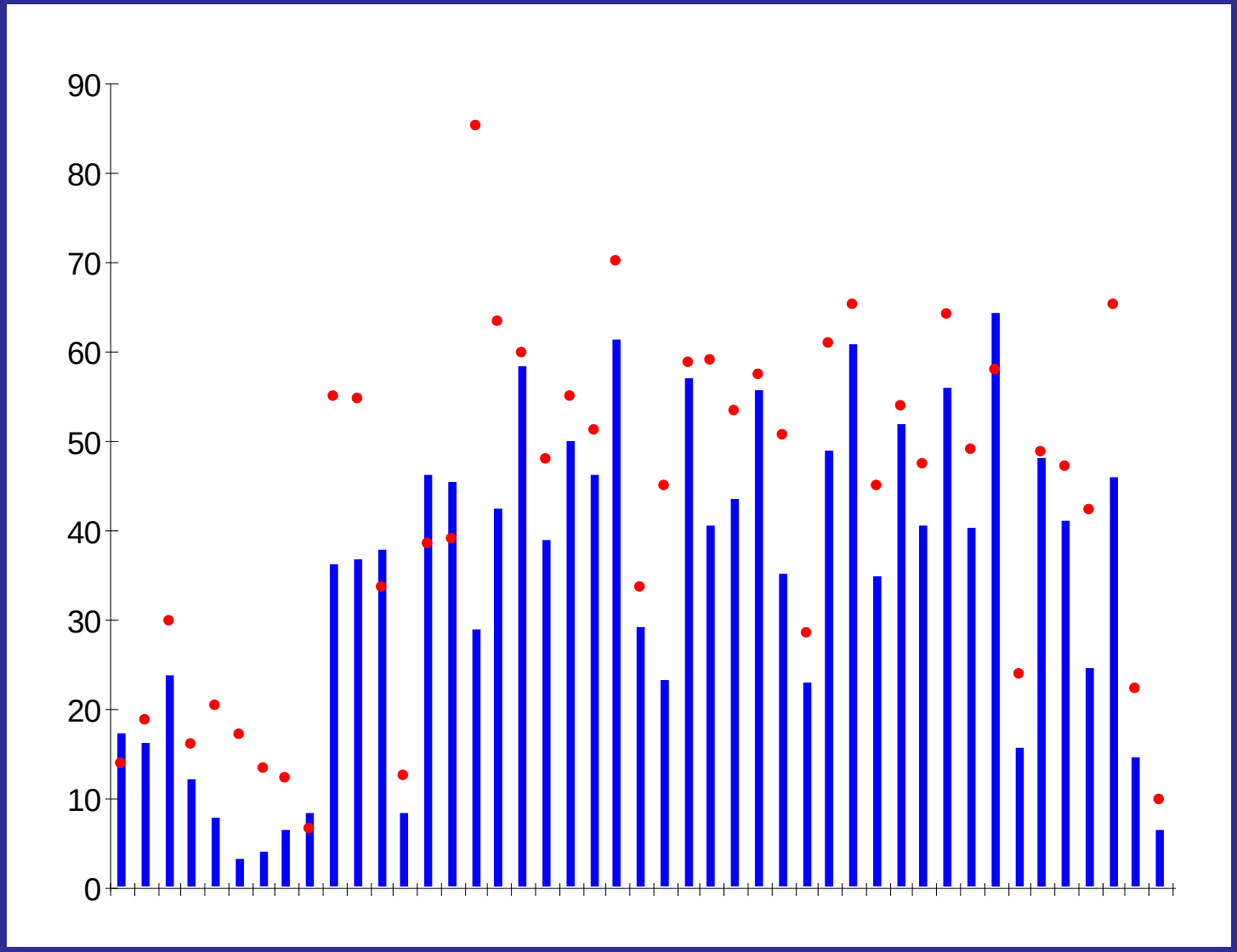
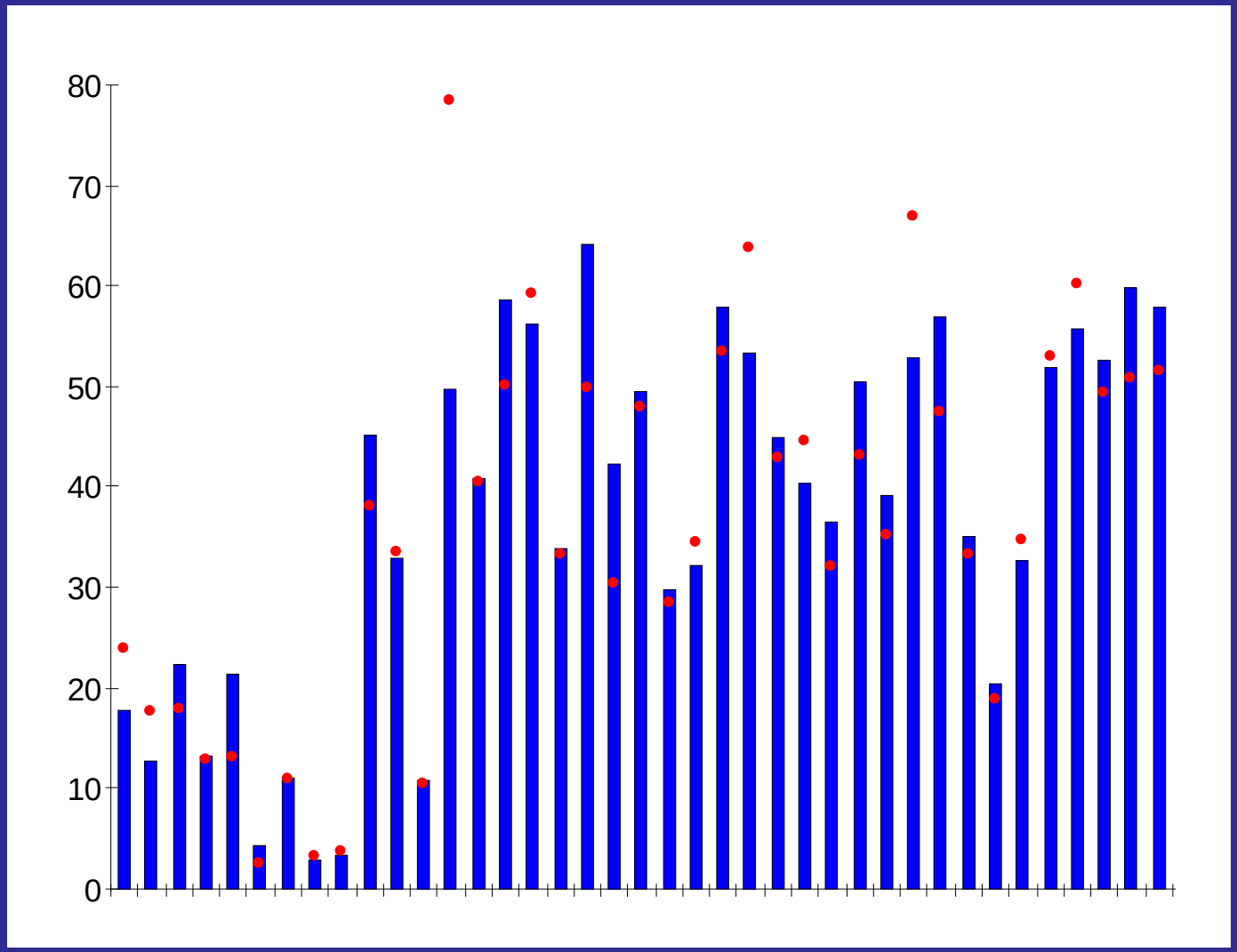
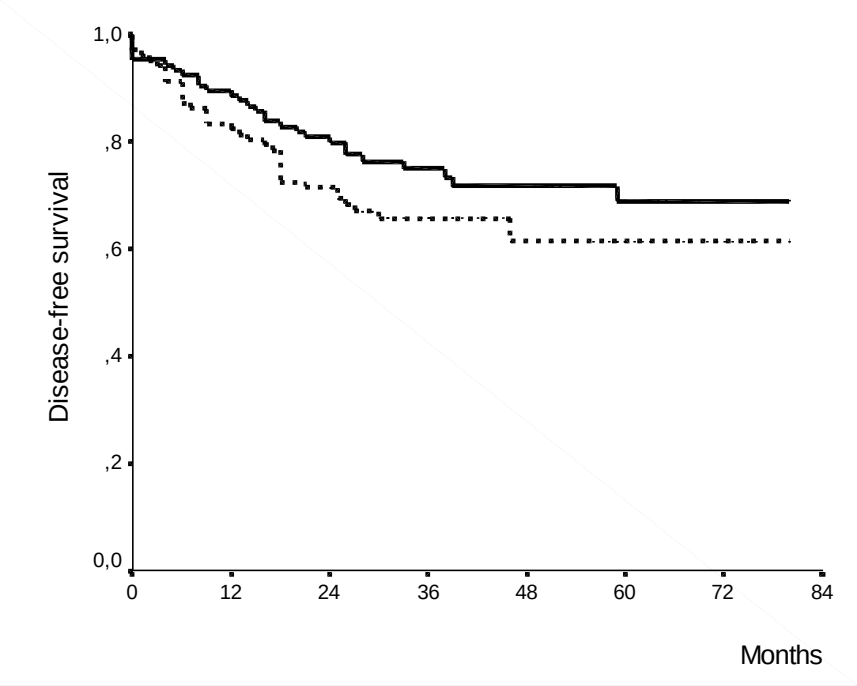
Open Surgery Patients



Endoscopic Surgery Patients



Barcelona Trial Interim Results: Cancer-related Survival* **



p=0.02

____ Laparoscopic-assisted group

……. Open group

*** Kaplan-Meier method**

****Lacy et al.** Lancet. 2002 Jun 29;359(9325):2224-9.

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

Trial	n
C.O.S.T. (American)	863
C.O.L.O.R 1 (European)	1082
Classic (British)	794
COLOR 2 (European Rectal)	1044
COREAN (Korean Rectal Ca)	340

All showed short term recovery benefits ($p \leq 0.05$)

Lymph Node Harvest (median)

Series	Laparosc.(%)	Open(%)	p value
COST	12	12	ns
COLOR 1	10 (0-41)	10 (0-42)	ns
Classic	12	13.5	ns
COLOR 2	13	14	ns
COREAN	17	18	ns

Intermediate & LongTerm 3 & 5 Year Oncologic Outcome*

Trial	DFS	OS
COST	ND	ND
COLOR 1	ND	ND
CLASSIC	ND	ND
COLOR2 (rectal)	ND	ND
COREAN (rectal)	ND	ND

* 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

*Nguyen et al. J Am Col Surg 2005;200(4):621-9

**Paxton JH, et al. Obes Surg. 2005 Jan;15(1):24-34.

+Nguyen NT, et al. J Am Coll Surg. 2007 Aug;205(2):248-55.

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

*Flum et al. N Engl J Med. 2009 Jul 30;361(5):445-54.
**Stroh et al. Obes Surg. 2009 Jan;19(1):105-12.
+Broderick RC, et al. Surg Endosc 2015 PMID: 25986426 [PubMed]

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

*Scalici J, et al. Gynecol Oncol. 2015 Mar;136(3):512-5

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)++

*Ecker BL, et al. Surg Endosc 2015 PMID: 26092027 [Epub]
** Cranshaw et al. JAMA Surg 2015;150(5):410-5.
+Limongelli P, et al. World J Gastroenterol. 2014 Dec 14;20(46):17595-602.
++Livingston EH, et al. Am J Surg. 2005 Nov;190(5):816-20.

Splinter Laparoscopic Methods

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

- Each method has its proponents

DaVinci Robot in OR

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

*Marino P, et al. Int J Gynecol Cancer, 2015;25(6):1102-8.

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 → 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

* Liu H et al. Cochrane Library, 2014, Issue 12

**Xie Y, et al. Curr Opin Obstet Gynecol. 2015 Feb;27(1):73-6.

+Wright JD et al. Obstet Gynecol. 2014 Nov;124(5):886-96.

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

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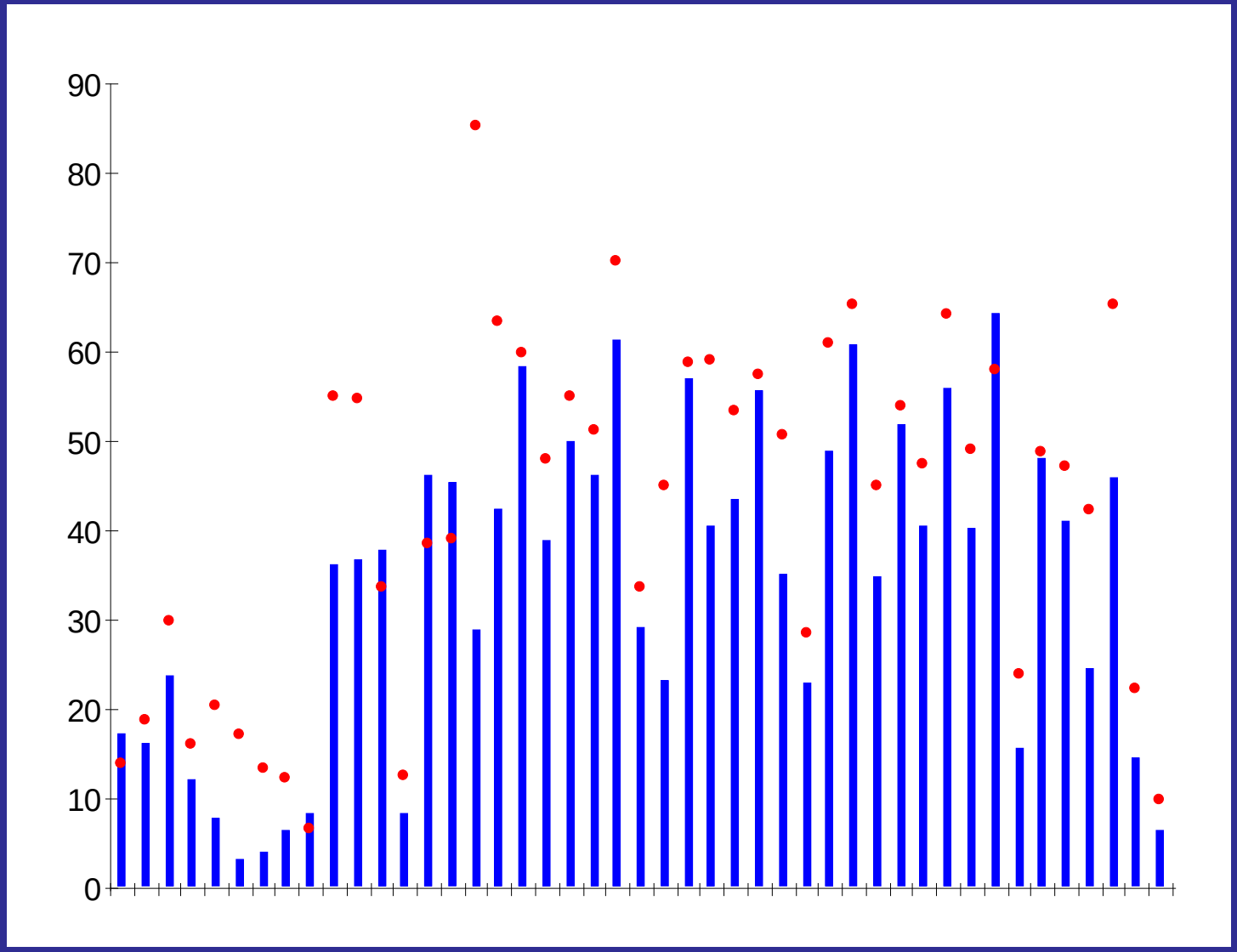

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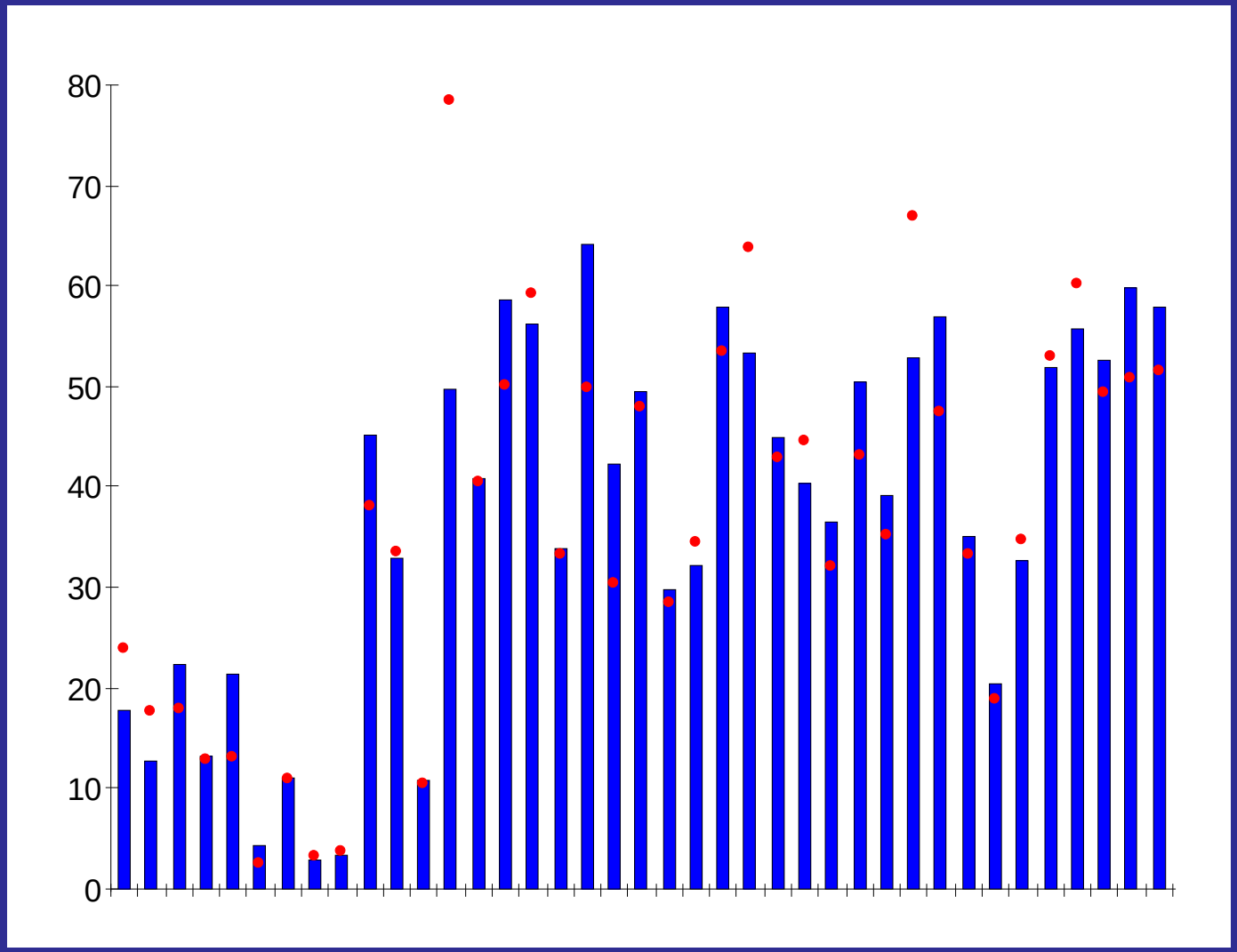

Advances in Colorectal Surgery Symposium - April 2008

Immunologic, Physiologic, and Oncologic Ramifications of Abdominal Surgery

Richard L. Whelan, MD
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Presbyterian Hospital
Columbia University College of Physicians & Surgeons
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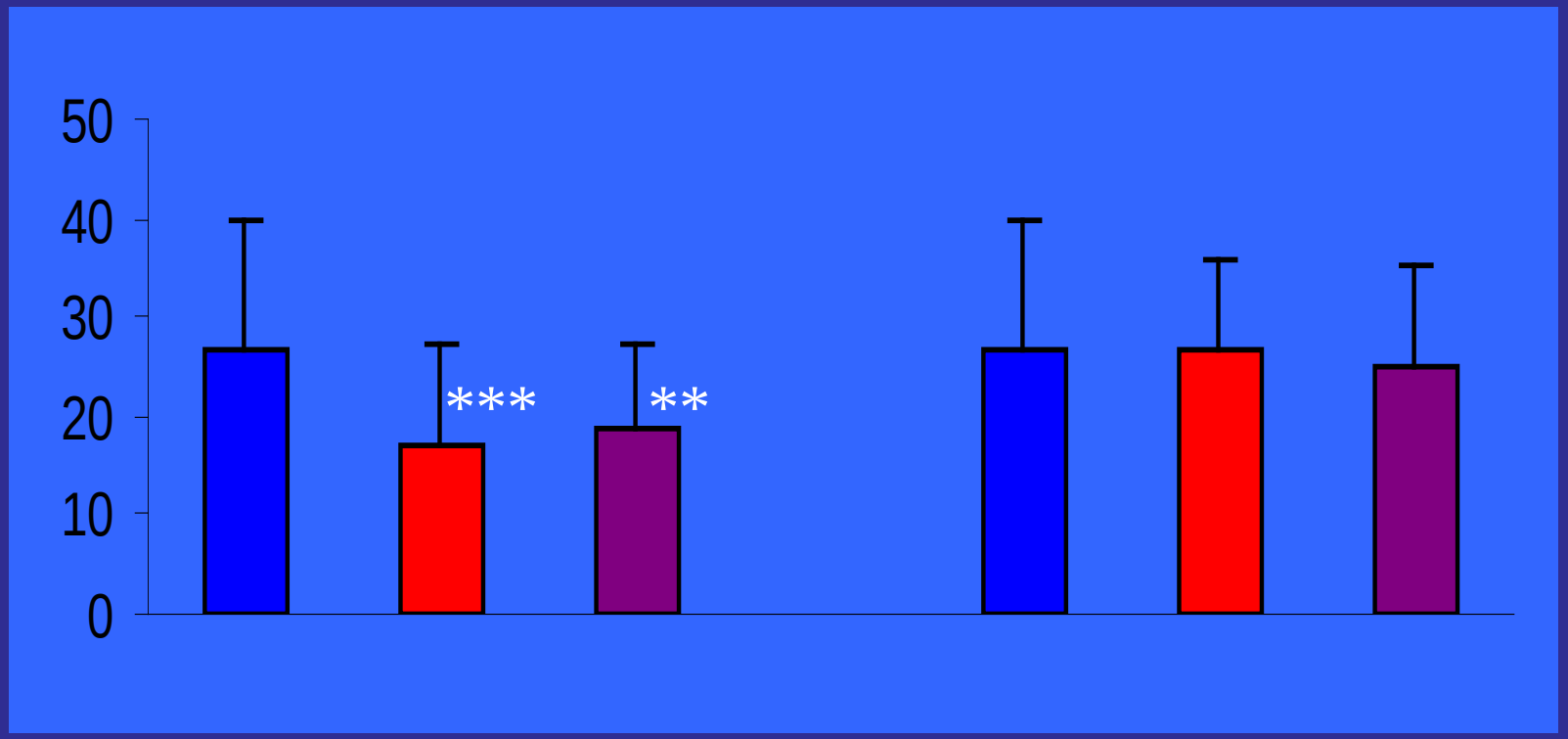
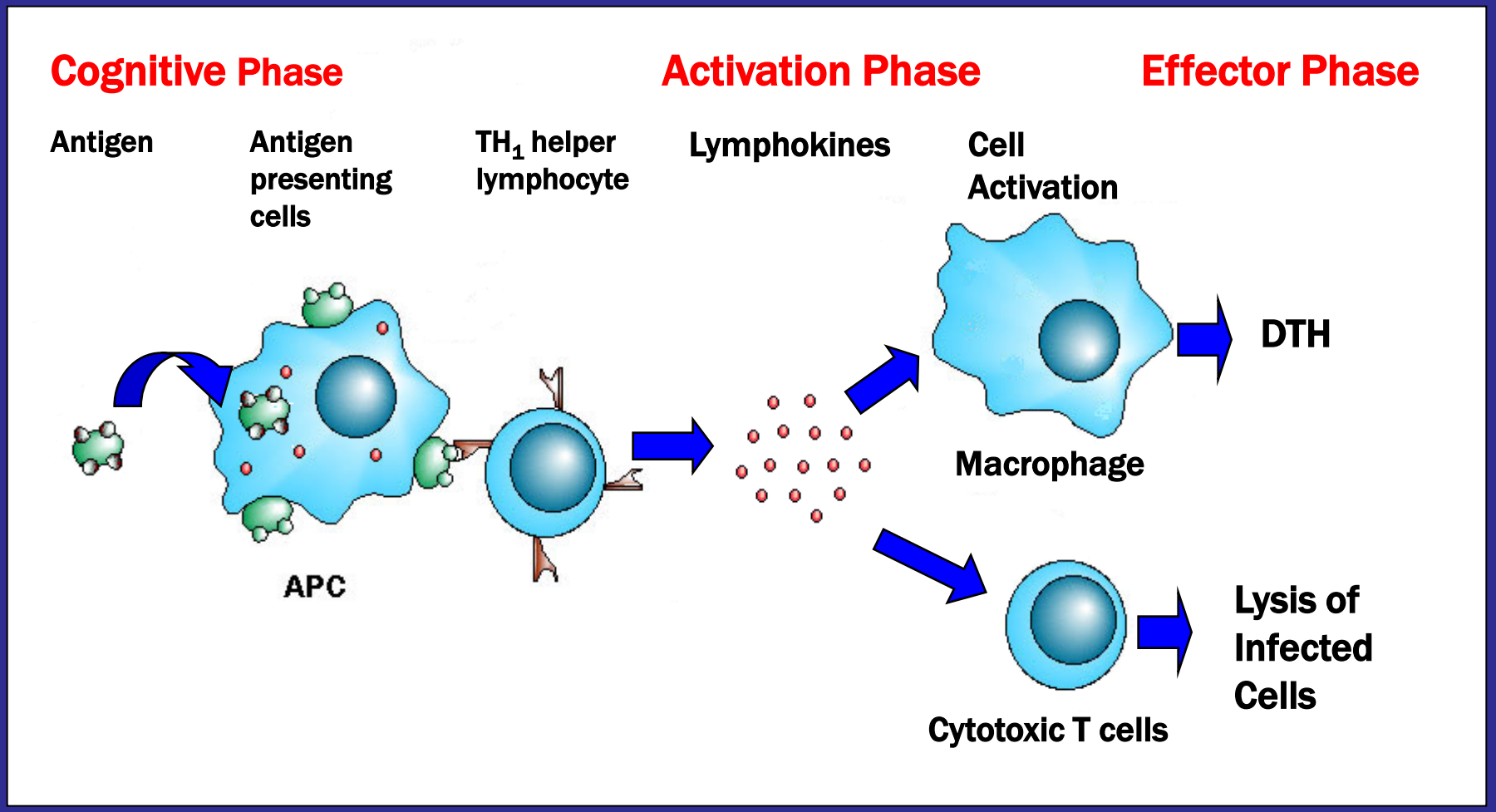
Decrease in the percentage of CD31+ T Cells after Colon Resection*



* Kirman et al. Surg Endosc 2003;DOI: 10.1007/s00464-002-8942-3.

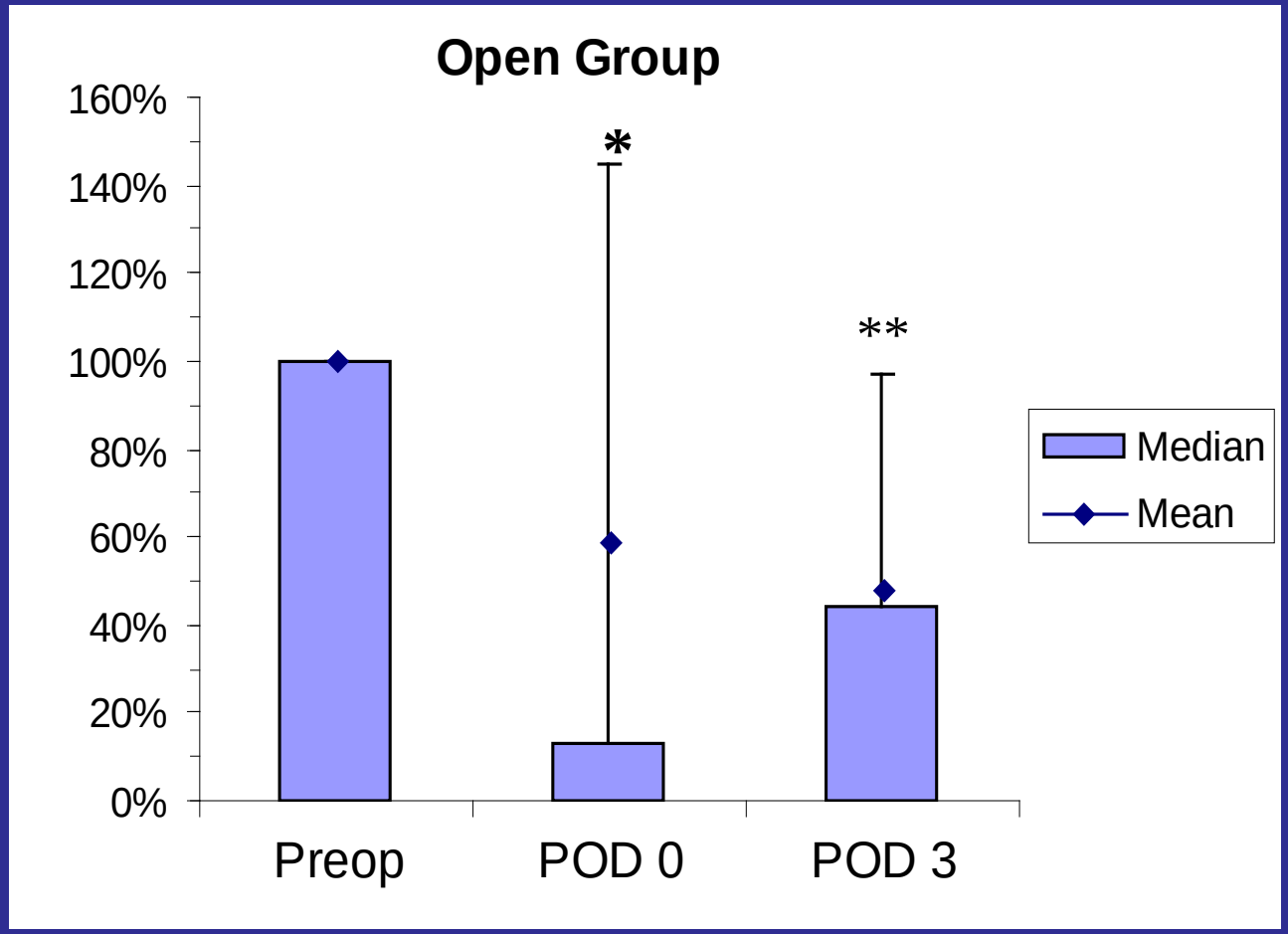
DTH Response



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*



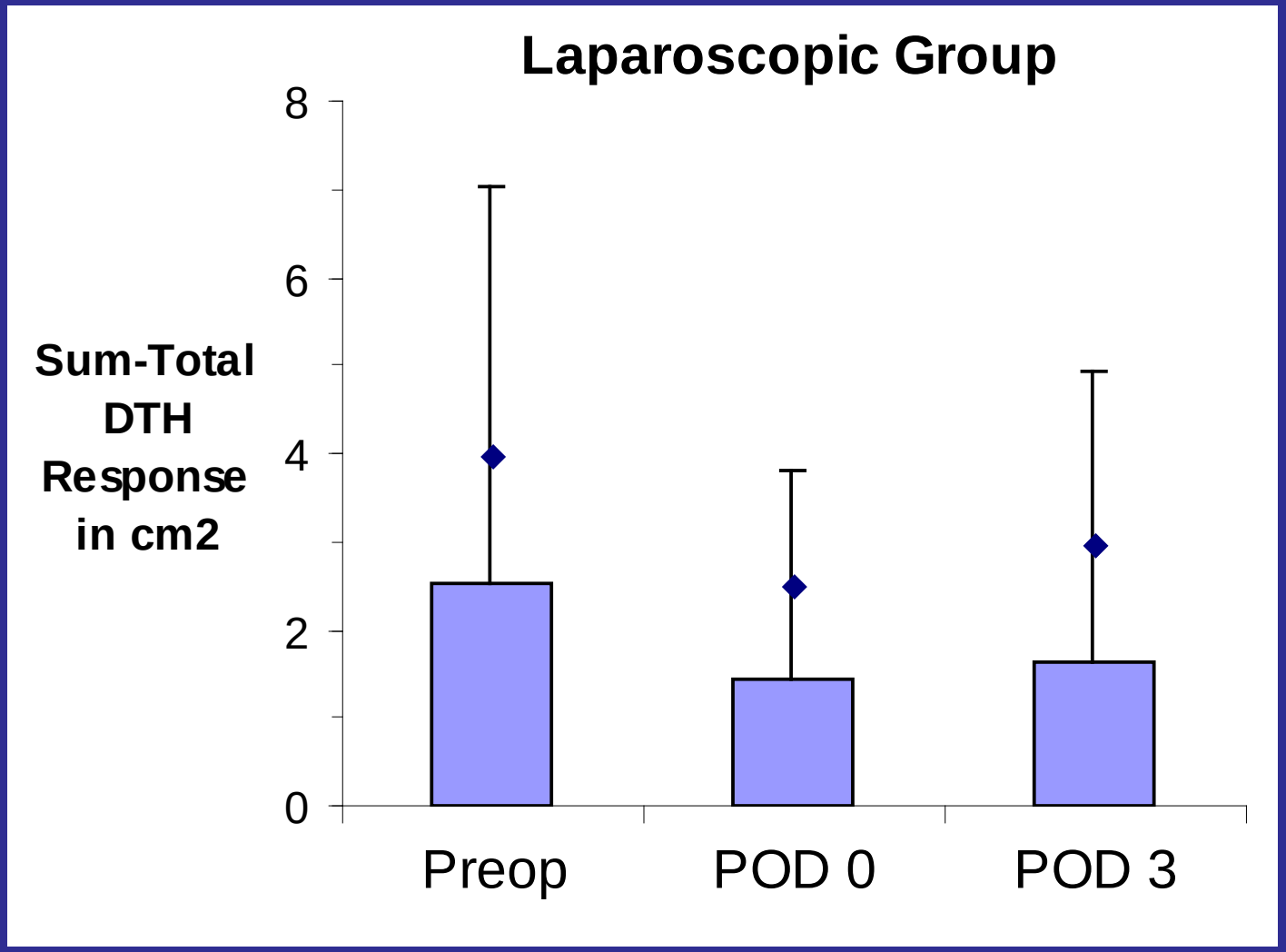
*$P < 0.0005$ vs. preop

**$P < 0.0003$ vs preop

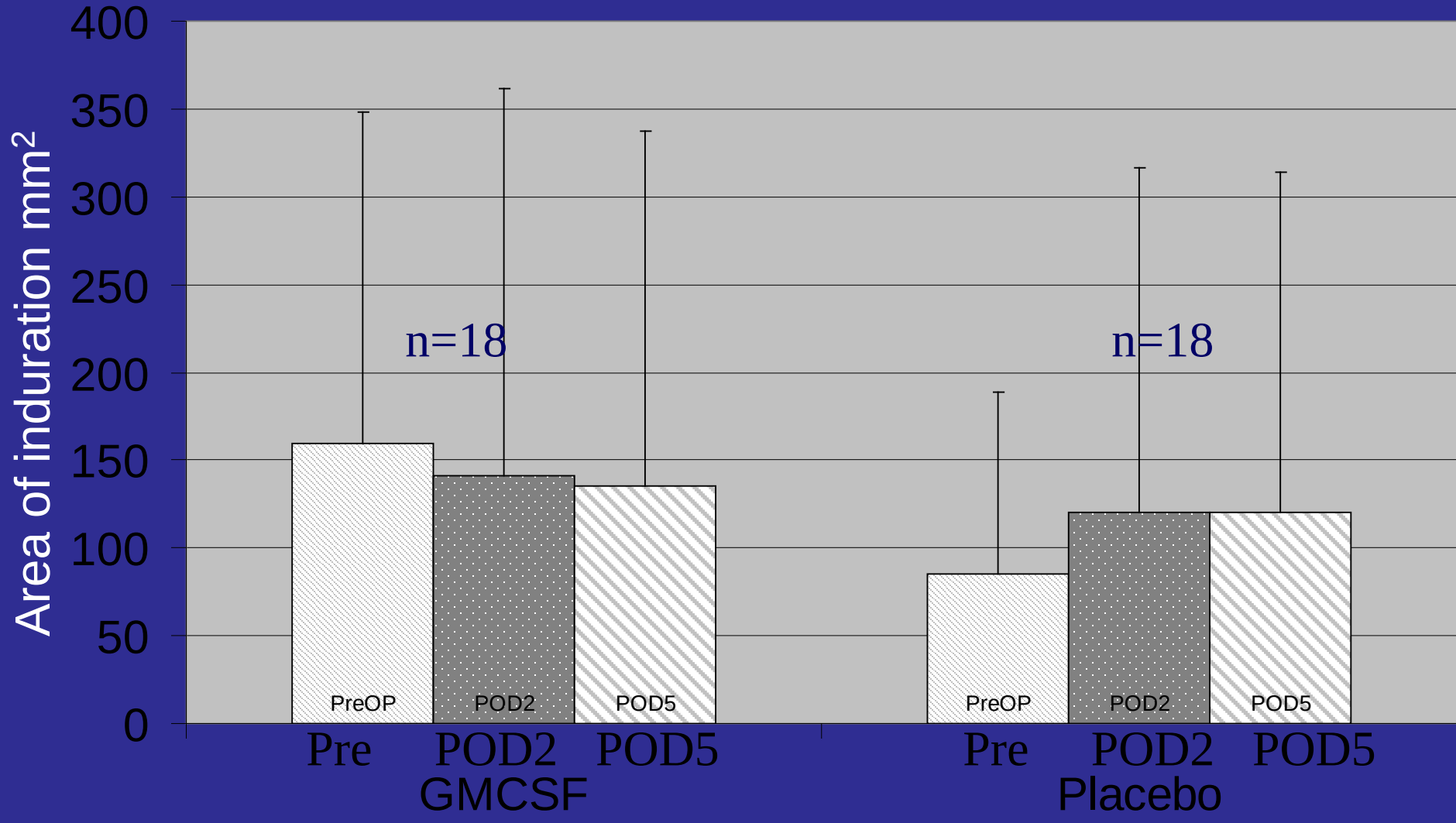
n=17 patients

* Whelan et al. Surg Endoscopy 2003;17(6):972-978

DTH Response After Laparoscopic Colorectal Resection



DTH Results: MIS Colorectal Resection



* Belizon et al. Europ J Surg Oncol. Pub.pending

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*,+,**

Group	# Genes ↑ Regulated	# Genes ↓ Regulated	Total # Genes
CO2 Pneumo	86	30	116
Laparotomy	362	36	398

•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*

Group	# Genes ↑ Regulated	# Genes ↓ Regulated	Total # Genes
CO2 Pneumo	118	14	132
Laparotomy	133	24	157

* Threshold difference between groups > 2 X expression

Where the Same Genes Effected ? *

Group	# Genes 12 hours	# Genes 24 hours
Altered expression in both groups	60 (13%)	77 (39%)
Increased expression in ***Open Group*** only	338	80
Increased expression in ***CO2 Group*** only	59	41

* 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 *

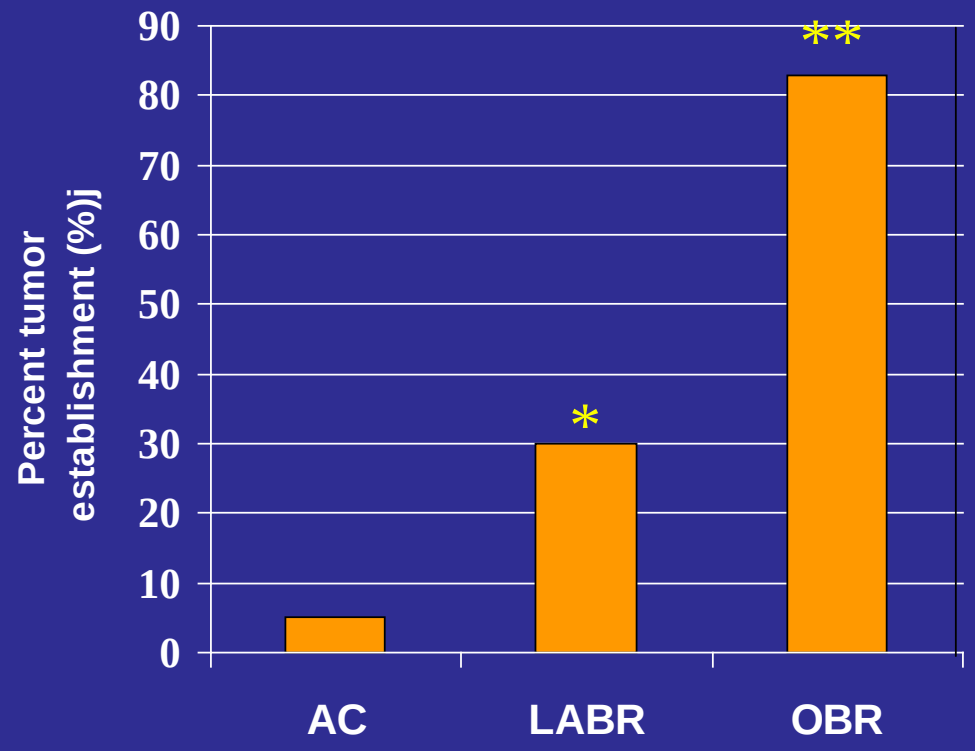
- Study Groups:
  - Anesthesia control
  - Laparoscopic-assisted cecectomy
  - Open cecal resection

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

- On POD 30 presence or absence of tumors determined

* Allendorf JD et al. Surgical Endoscopy 1998;12(8)1035-1038.

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*

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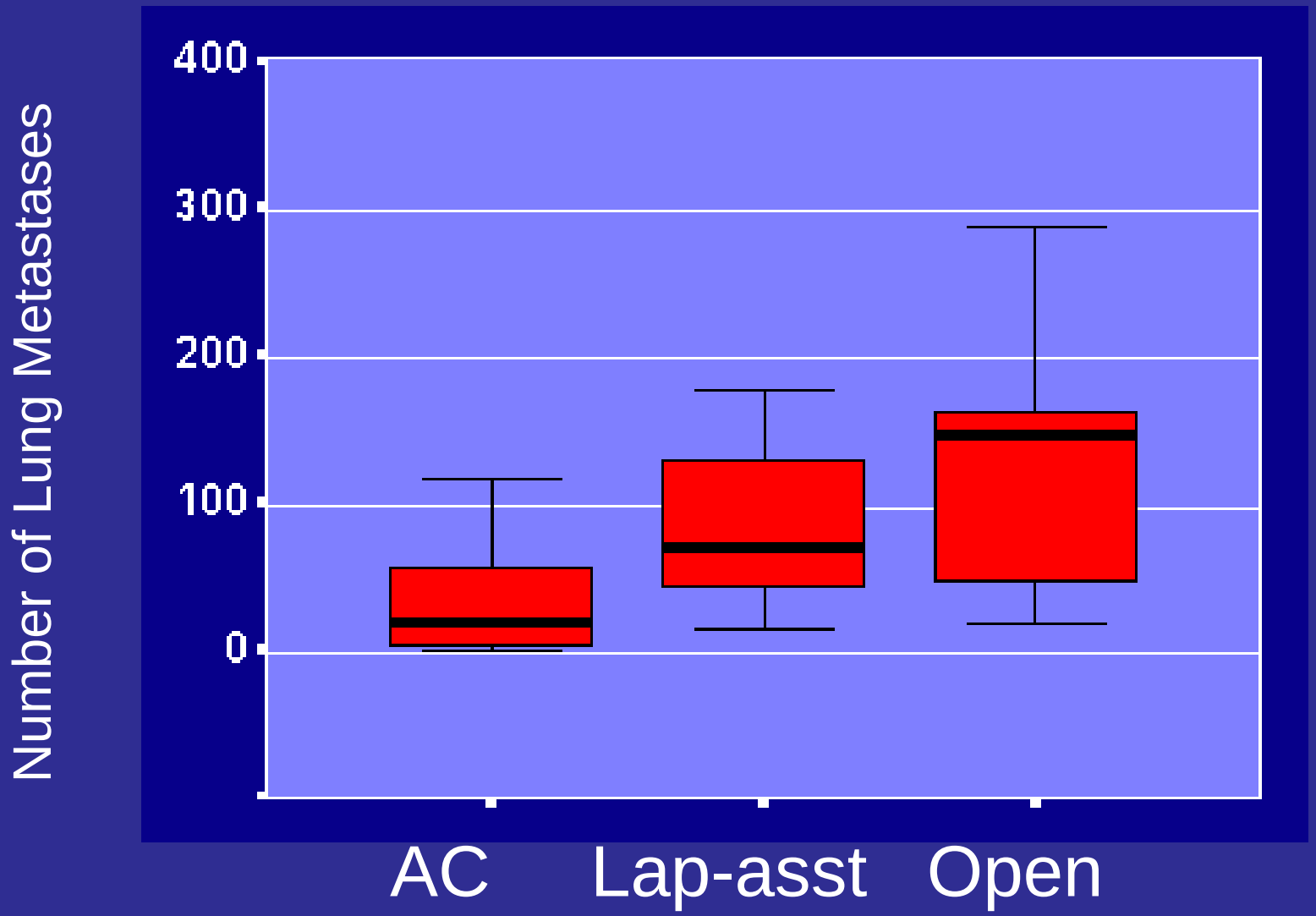

Problems with Murine Studies vs Human Setting

- 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.)

Human Plasma Factor Study*

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Human Plasma Factor Study:

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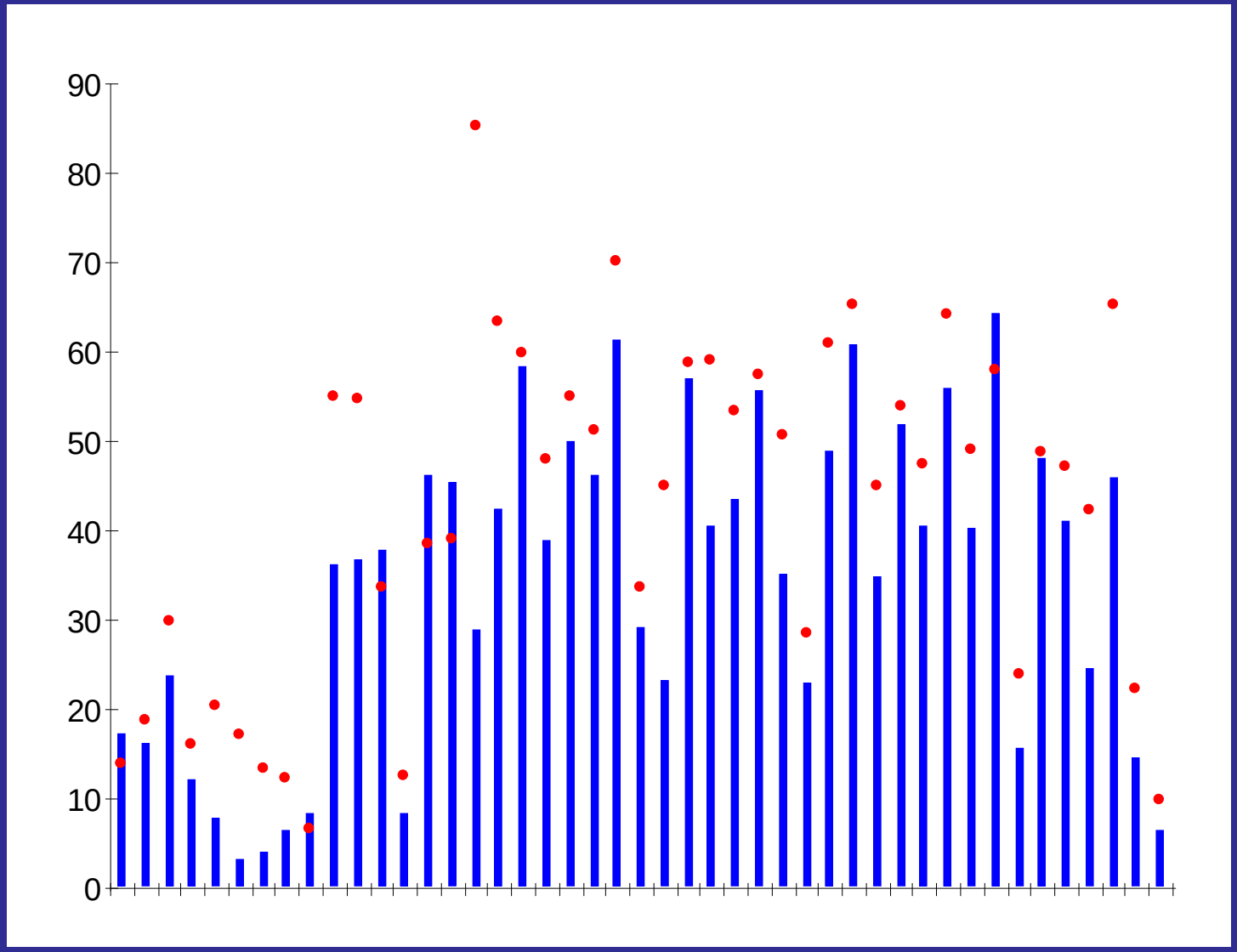
Open Surgery Patients



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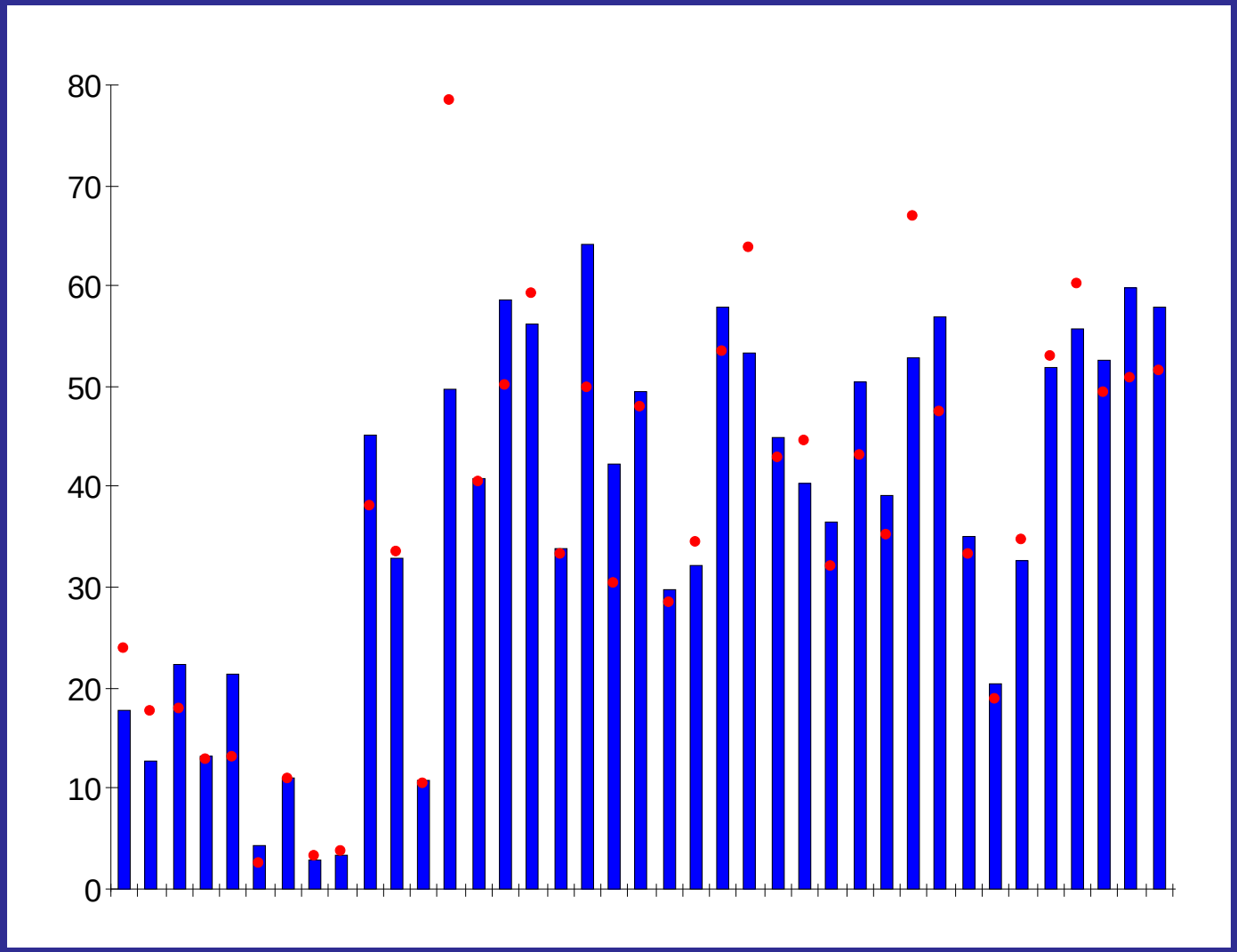
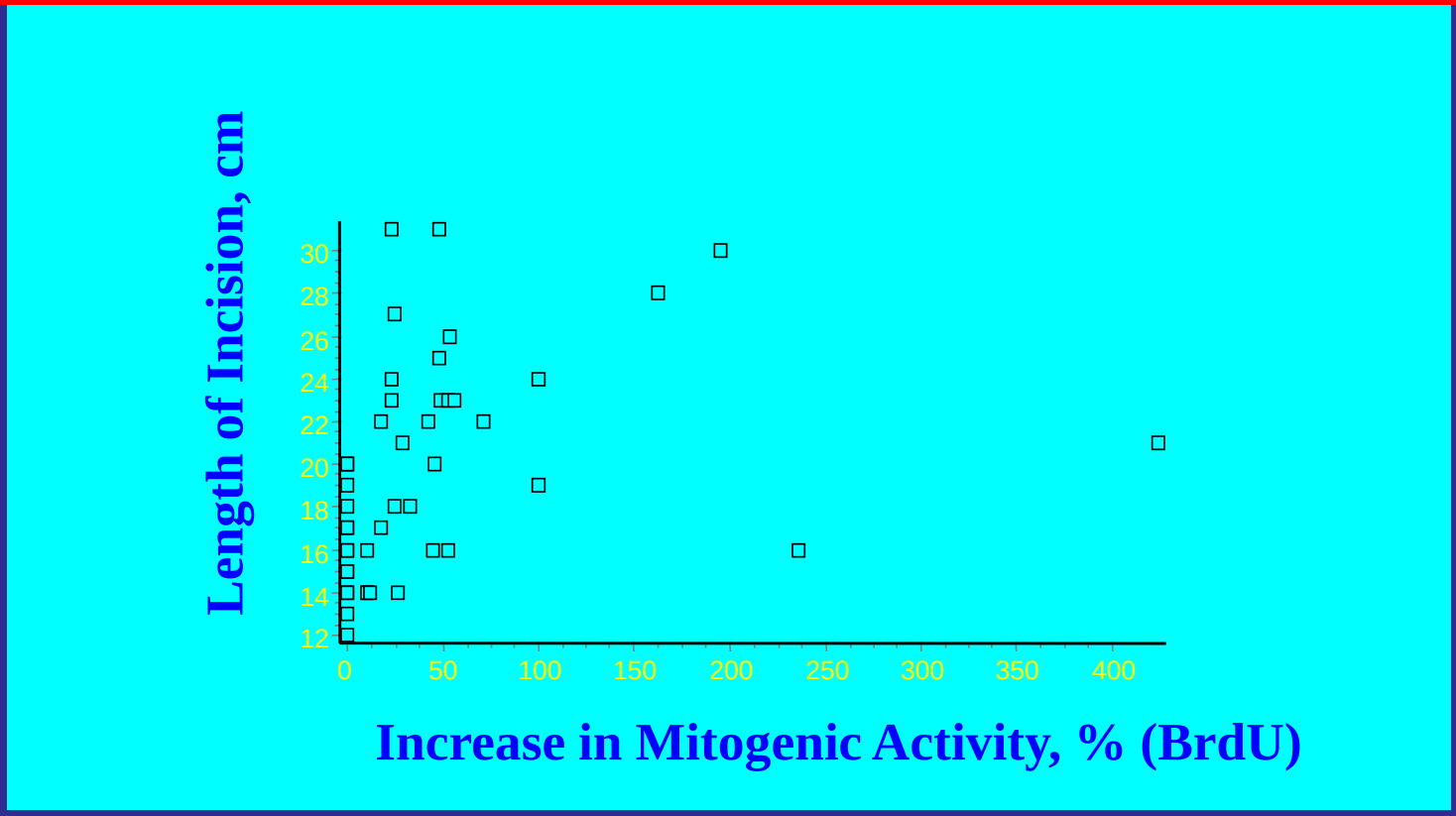


Correlation of Increase in OS Plasma Mitogenic Activity & Incision Length*



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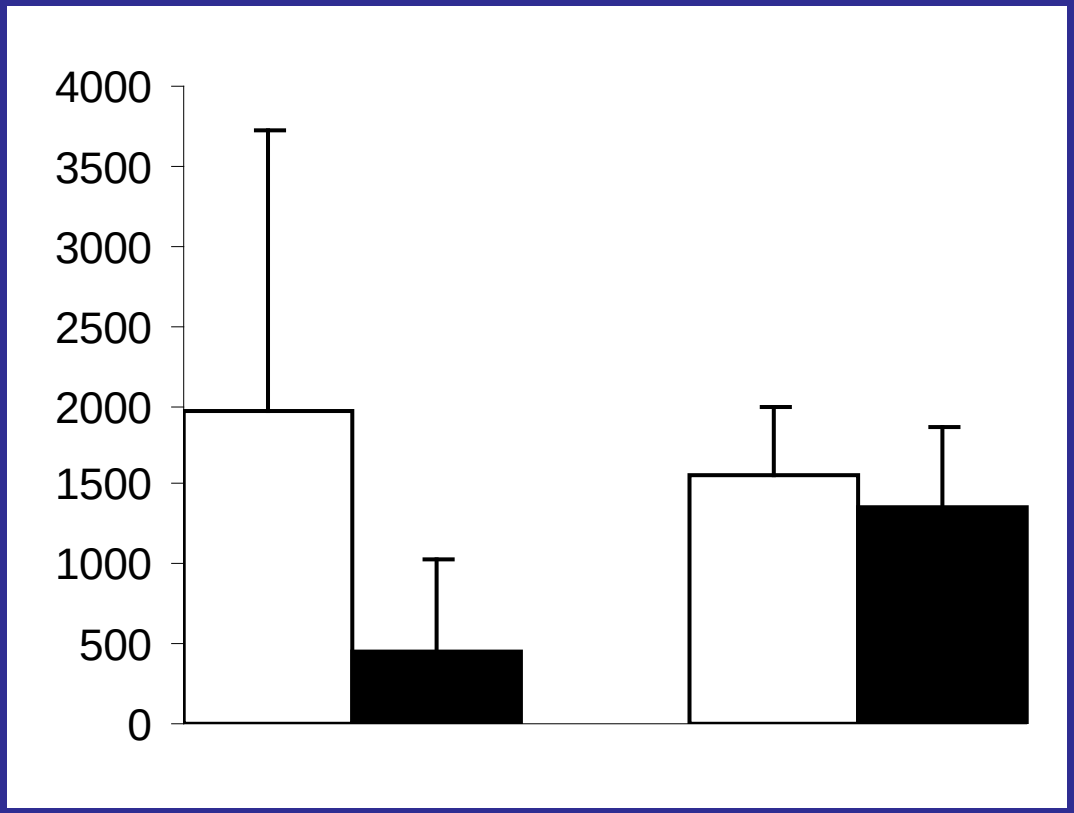
Levels of Intact IGFBP-3 on POD2

Intact IGFBP-3 ng/ml



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)

- ↓ IGFBP-3 (tumor inhibitor, baseline ↑ levels)
- ↑ $VEGF_{165}$ (potent stimulator of angiogenesis)
- ↓ Ang 1/Ang 2 ratio (low ratio proangiogenic)
- ↑ MMP-9 (proangiogenic, degrades ECM, stroma)
- ↑ TIMP-1 (lower, shorter lived ↑ 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.

*Werther K et al. Eur J Surg Oncol. 2000;26(7):657-62.

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 * + + +

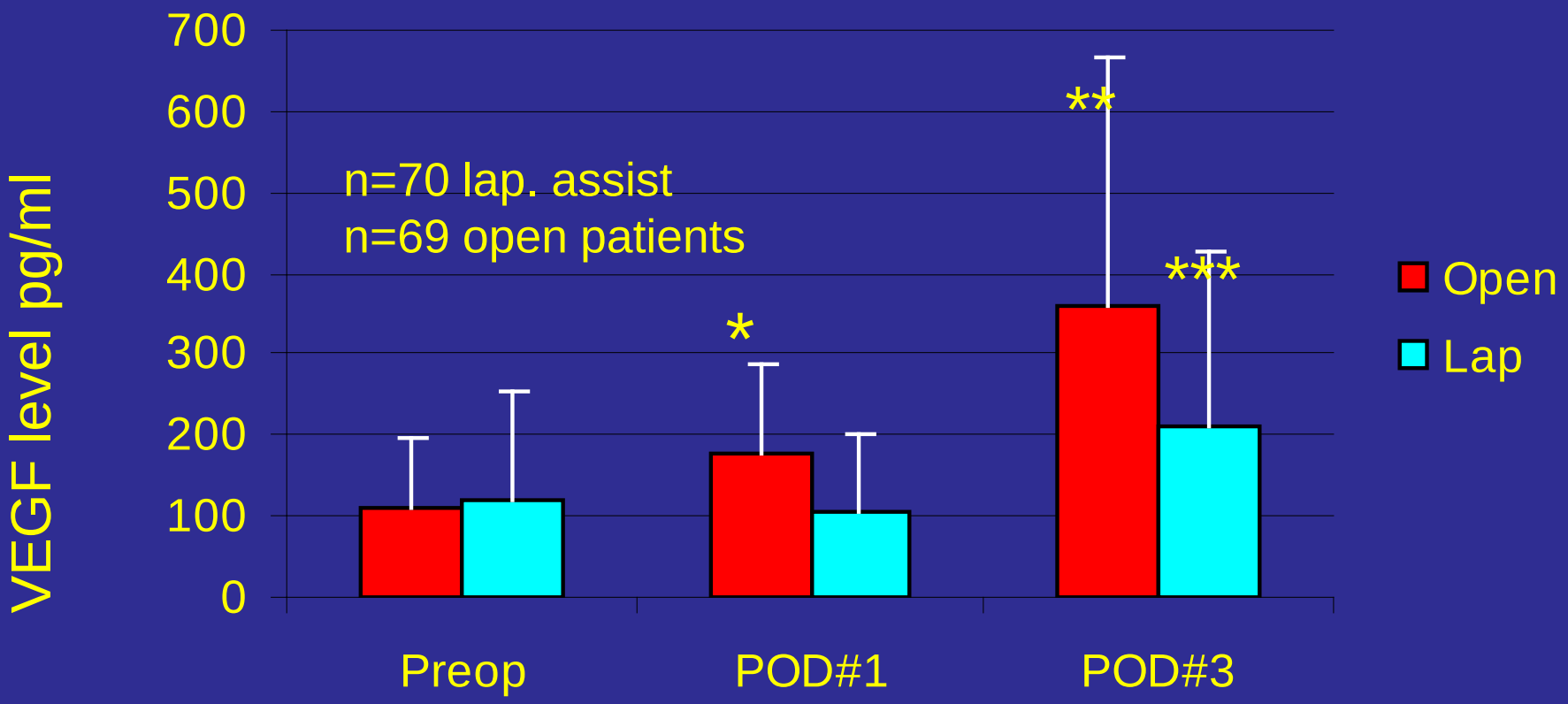
* Werther K, et al. Eur J Surg Oncol. 2000;26(7):657-62.
**Karayiannakis AJ, et al. Surgery 2002; 131(5): 548-55.
***Landriscina M et al. Br J Cancer, 1998; 78:765-70.
+ DeVita F, et al. Cancer 2004;100:270-278
++ Akbulut et al. Cytokine, 2002; 20(4):184-90.

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.

*Karayiannakis AJ et al. Eur Surg Res. 2003 Nov-Dec;35(6):492-6.

VEGF levels Open vs. Laparoscopic Colectomy for Cancer+

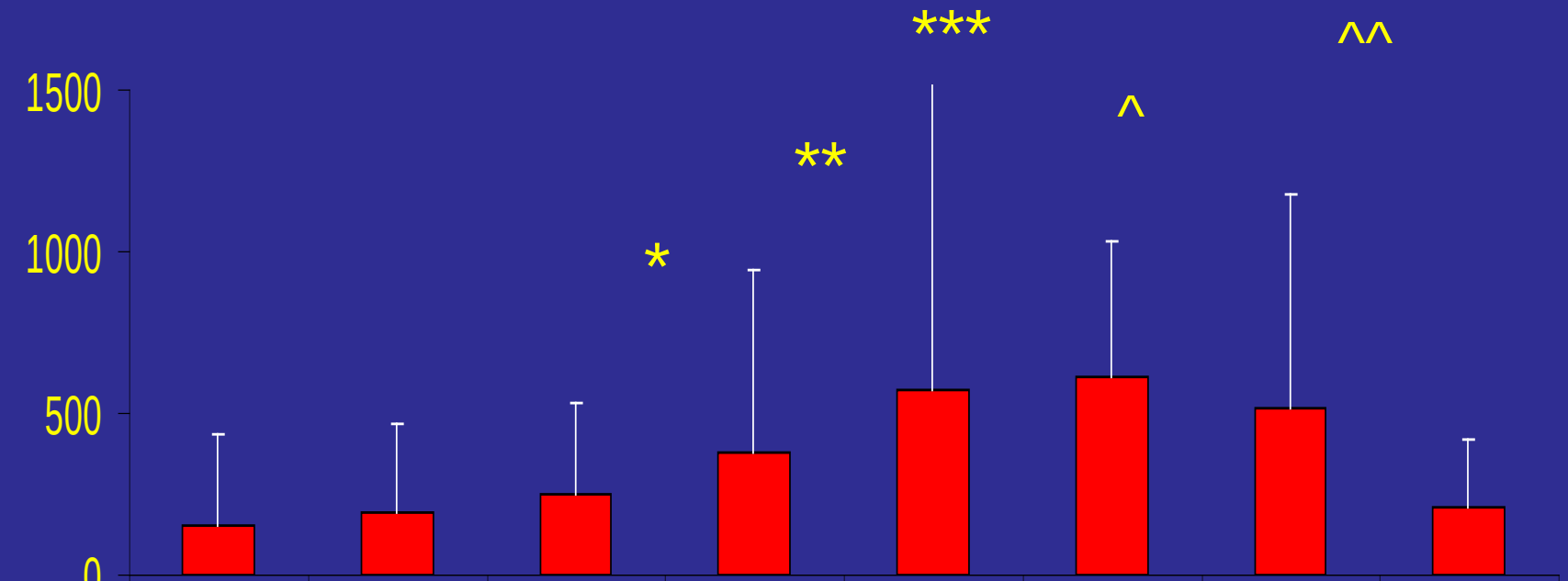


*** p<0.05 open POD1 vs preop, **p<0.05 open POD3 vs preop, pod1**

*****p<0.05 Lap POD3 vs preop**

+ Belizon et al. Annals Surgery 2006 Nov;244(5):792-8.

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

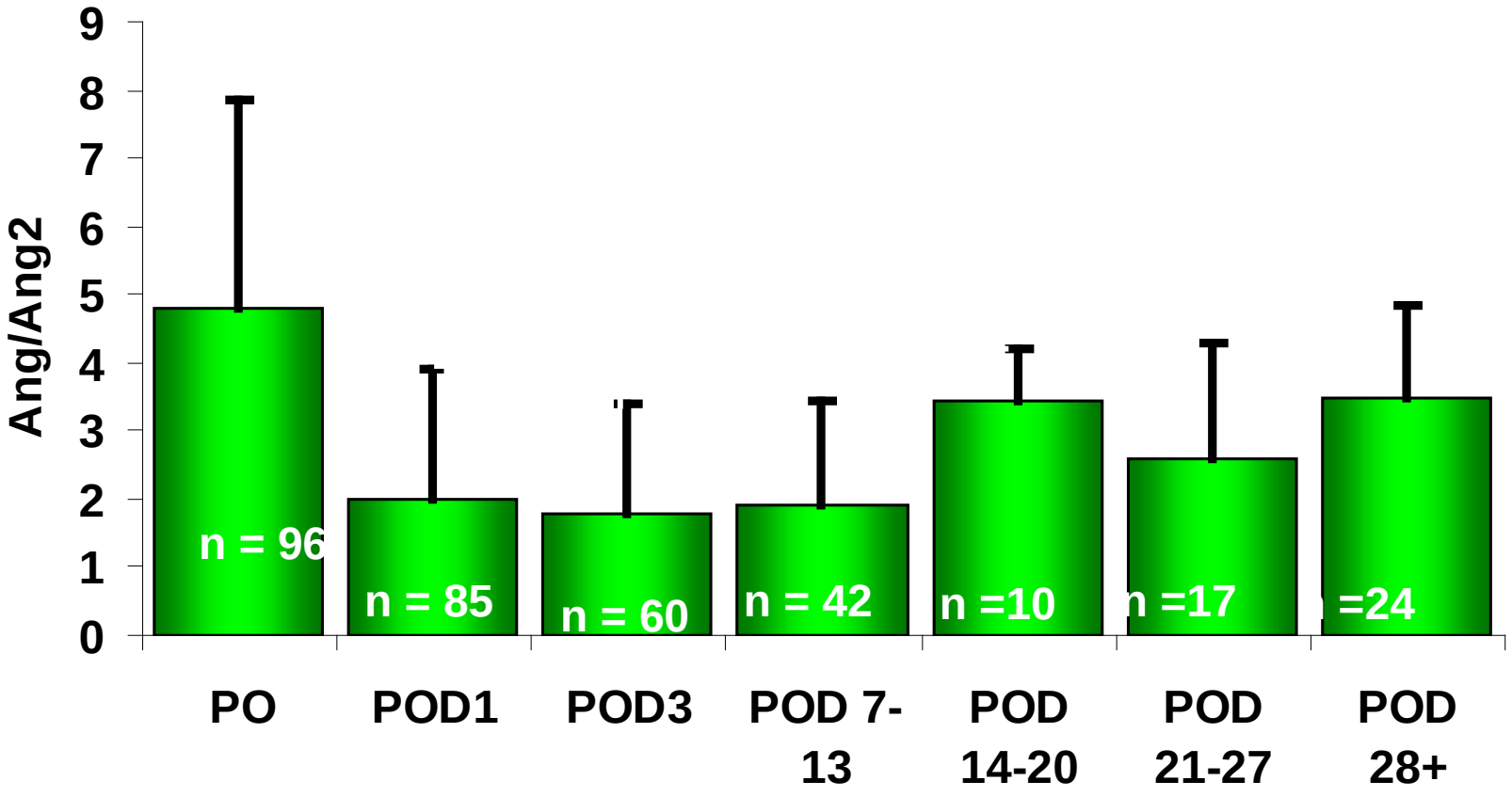


	OpDay	POD1	POD3	POD5	POD7-13	POD14-20	POD21-27	POD28+
Median	150	192.7	246	380.6	572.2	611.1	512.1	210.4
Pvalue		**0.3644**	**0.009**	**0.0012**	**0.0008**	**0.0098**	**0.0117**	**0.4648**

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



+ : p= 0.0001 vs. PO

++ : p= 0.002 vs. PO

Λ : p= 0.041 vs. PO

ΛΛ : 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

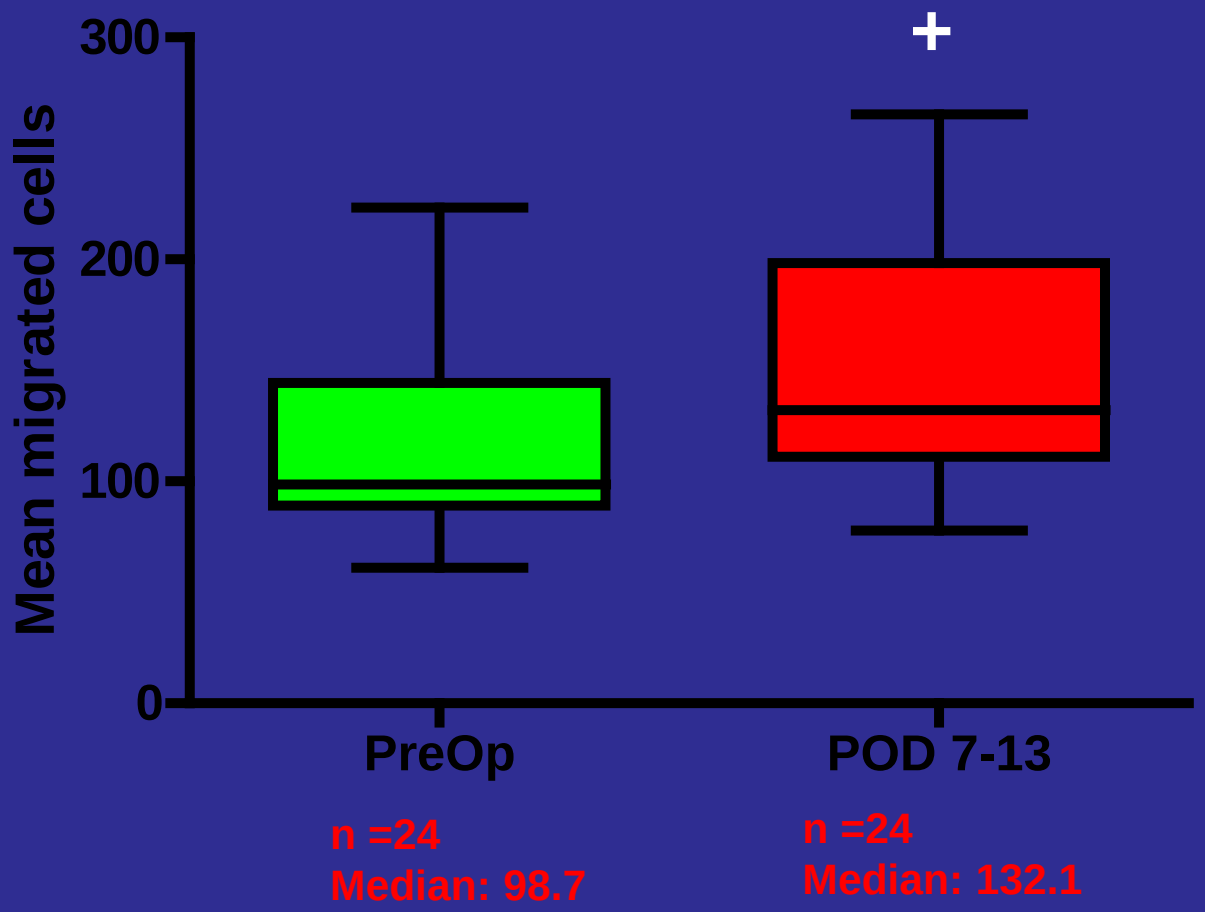
Plasma Contains Many Proteins

- 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 ?

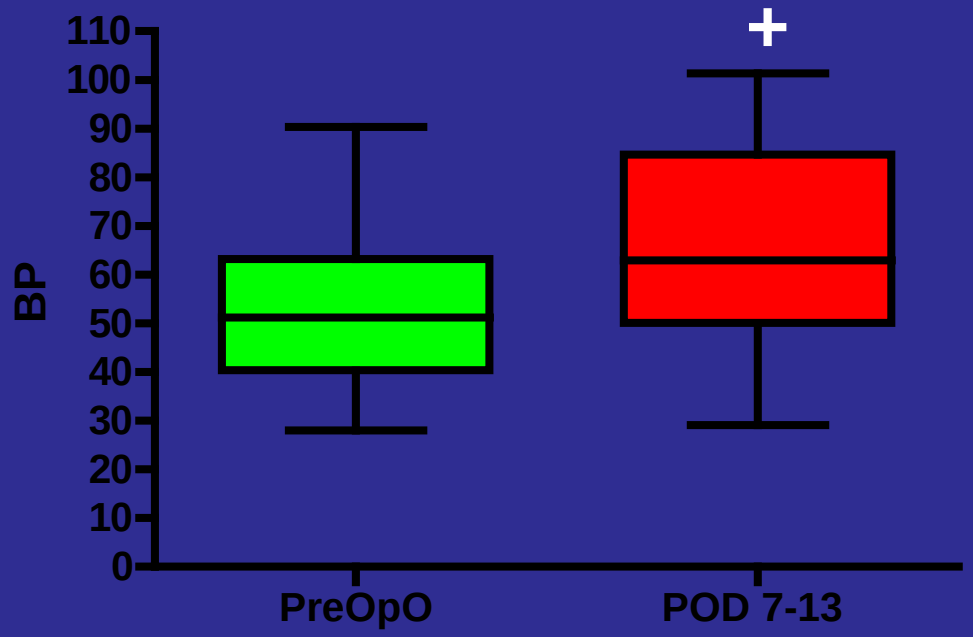
- Target of angiogenesis related proteins is the endothelial cell (EC)
- Assess behavior of endothelial cells in culture when plasma is added to medium
- Preoperative & postop EC cultures
- Branch point (microtubule) formation
- Invasiveness and migration in culture

In vitro Endothelial Cell Migration Assay: Preop vs POD 7-13



+ :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 ? +

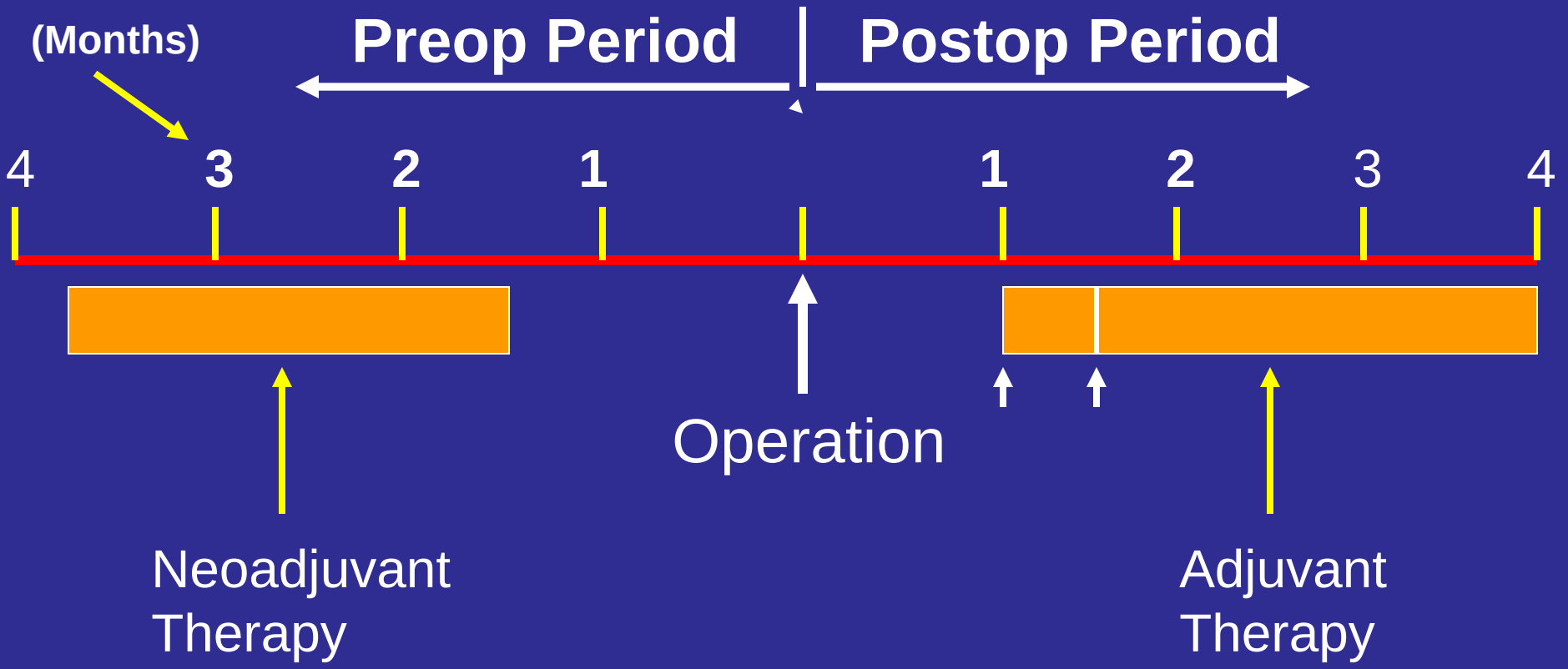
Vs Preop Plasma	BPF	Migration	Invasion
POD 7-13 (n=30)*	+	+	+
POD 14-20 (n=26)**	+	+	+

*** 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



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

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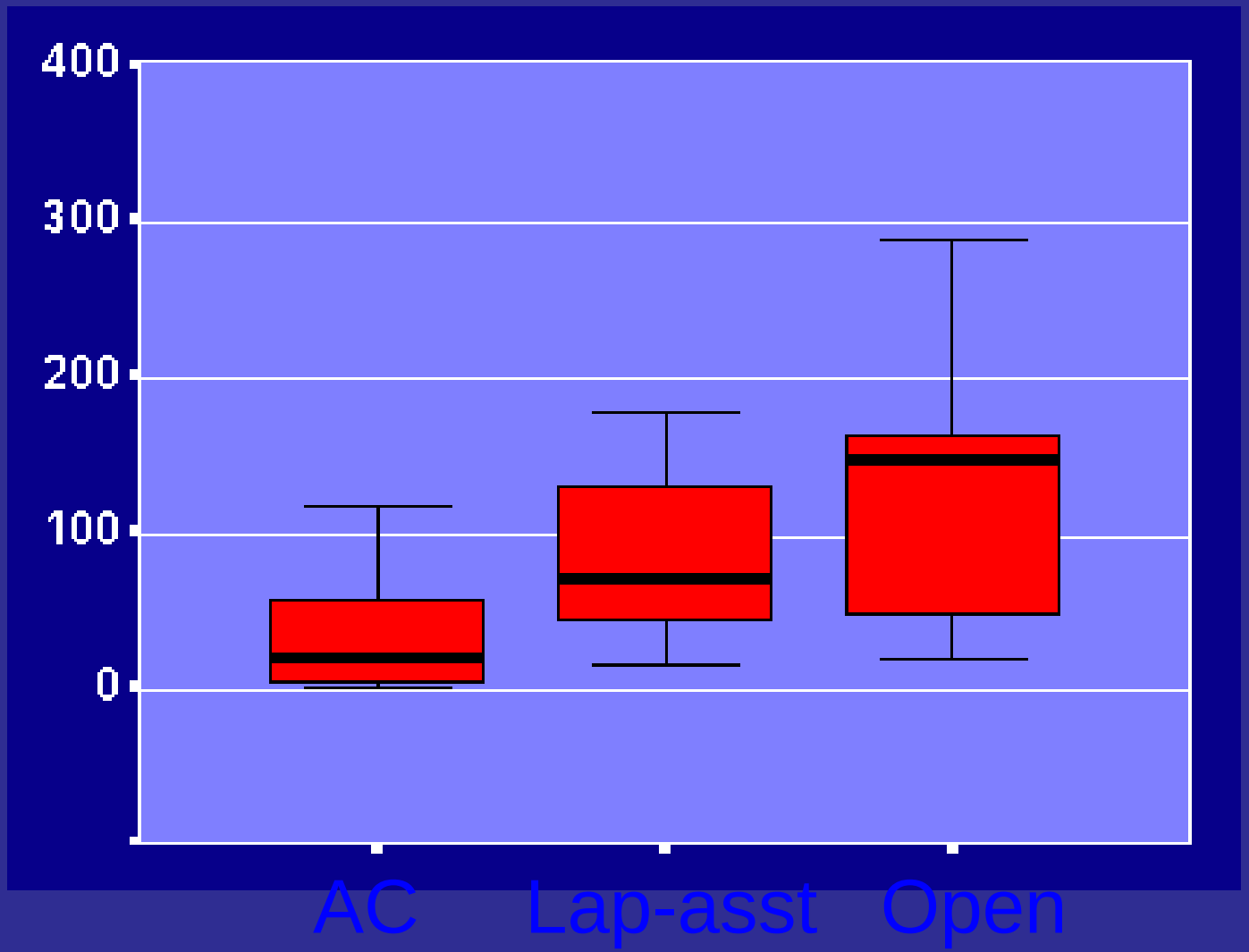

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Human Situation Regarding Abdominal Surgery

- 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

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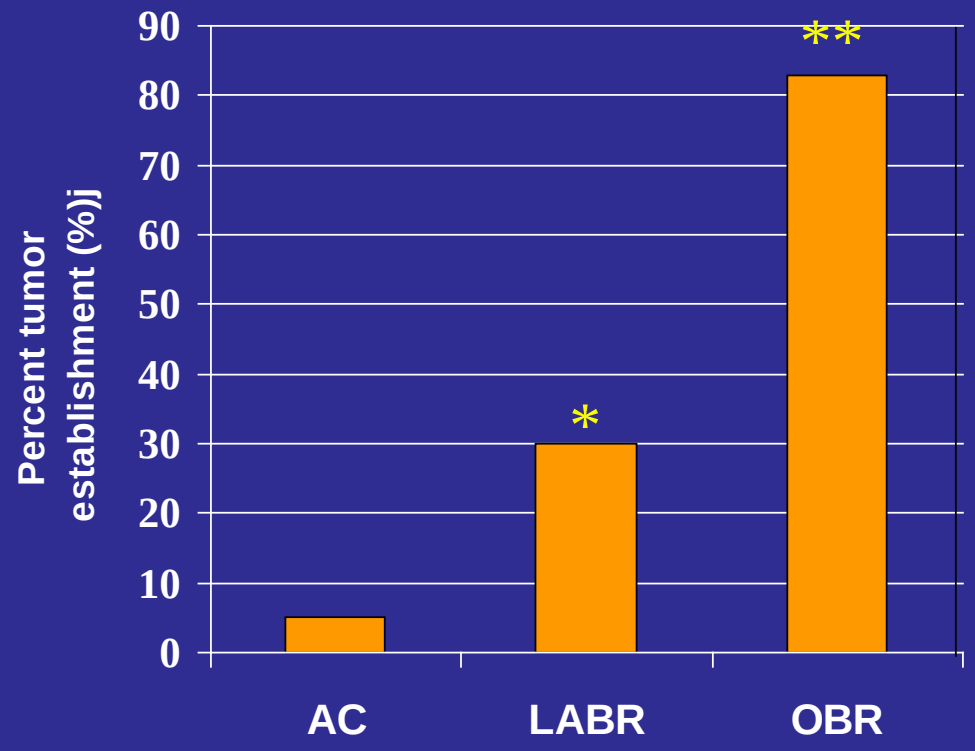


* p<0.01 vs control and open resection

** 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

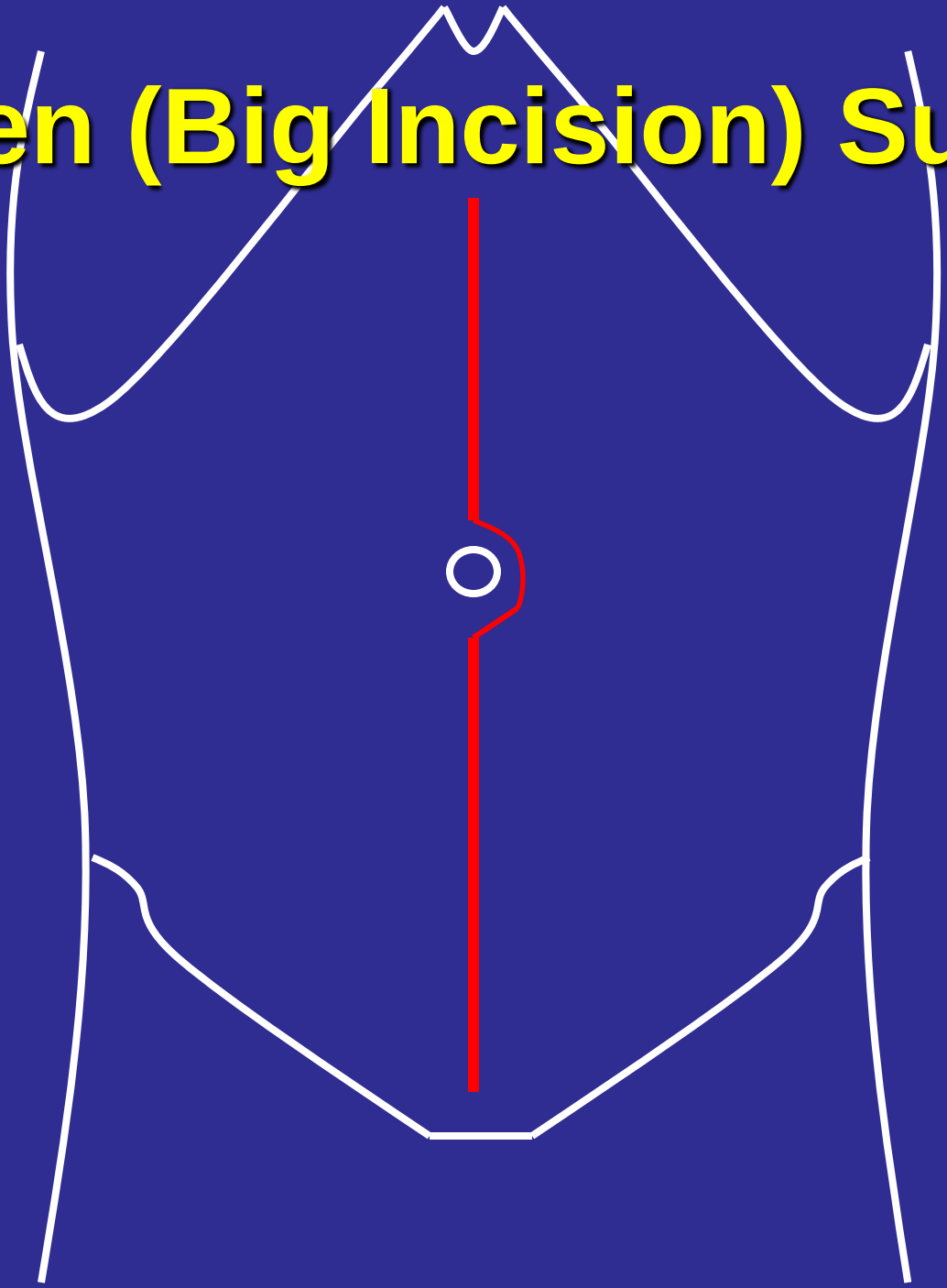
*Schwenk et al. *Cochrane Database of Systematic Reviews* 2006 Issue 3 ISSN 1464-780X

** 25 Randomized control trials reviewed.

Wound Infection Rates After Laparoscopic Colectomy

Author	No. Pts.	Rate of Infection
Degiuli et al	108	1.8 %

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 immunosuppresive 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)

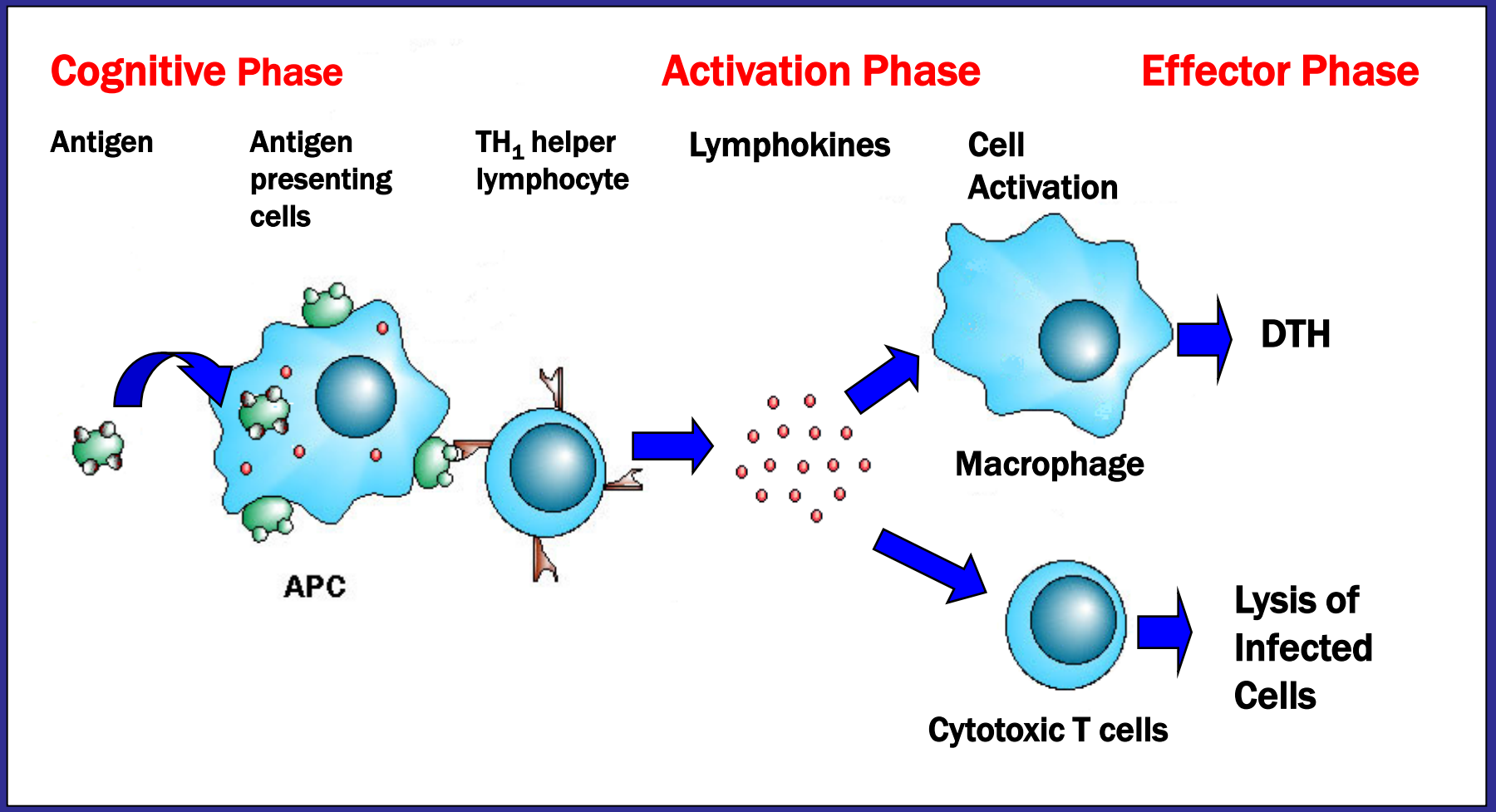
- Assesses cell-mediated immune function

- 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



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:
Kloosterman et al. Surg 1994;115:424-8.

- 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

Sietses et al. Dis Colon Rectum 2003 Feb;46(2):147-55.

- 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

Hildebrandt et al. Surg Endosc. 2003;17(2):242-6.

- 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

- Fisher B et al. Cancer 1959;12:929-932.
- Lewis MR et al. Arch Surg 1958;77:621-626
- Eggermont et al. Cancer Detect Prevent 1988:12:421-9.
- Cole WH. Journal Surg Oncology 1985;30:139-44
- Goshima et al. J Japan Surg Soc 1989;90:1245-50.
- Ratajczak et al. Proc Soc Exp Biol Med 1992;199:432-440.
- Kodama et al. Anticancer Res 1992;12:1603-16.
- Allendorf et al. Archives Surg 1995;130:649-53.
- Bouvy et al. Surg Endosc 1996;10:186.
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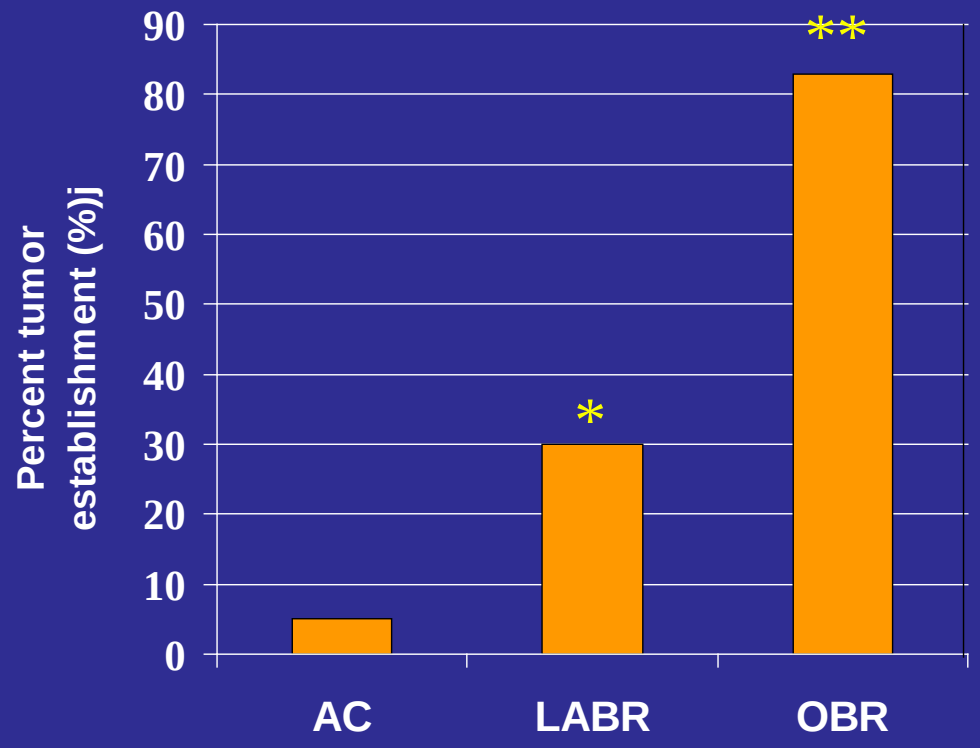

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* Wildbrett et al. Surgical Endoscopy 2002;16:889-94.

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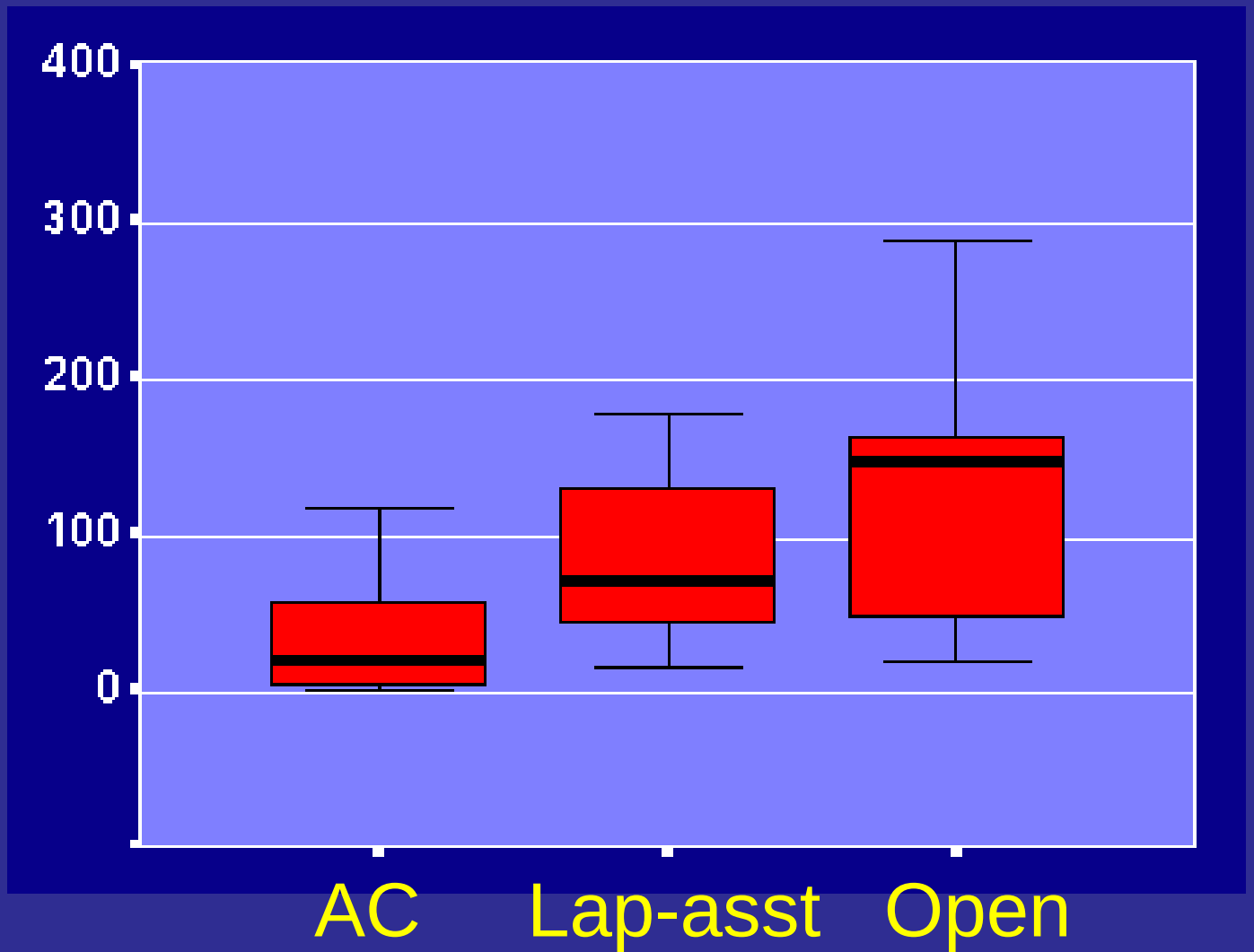

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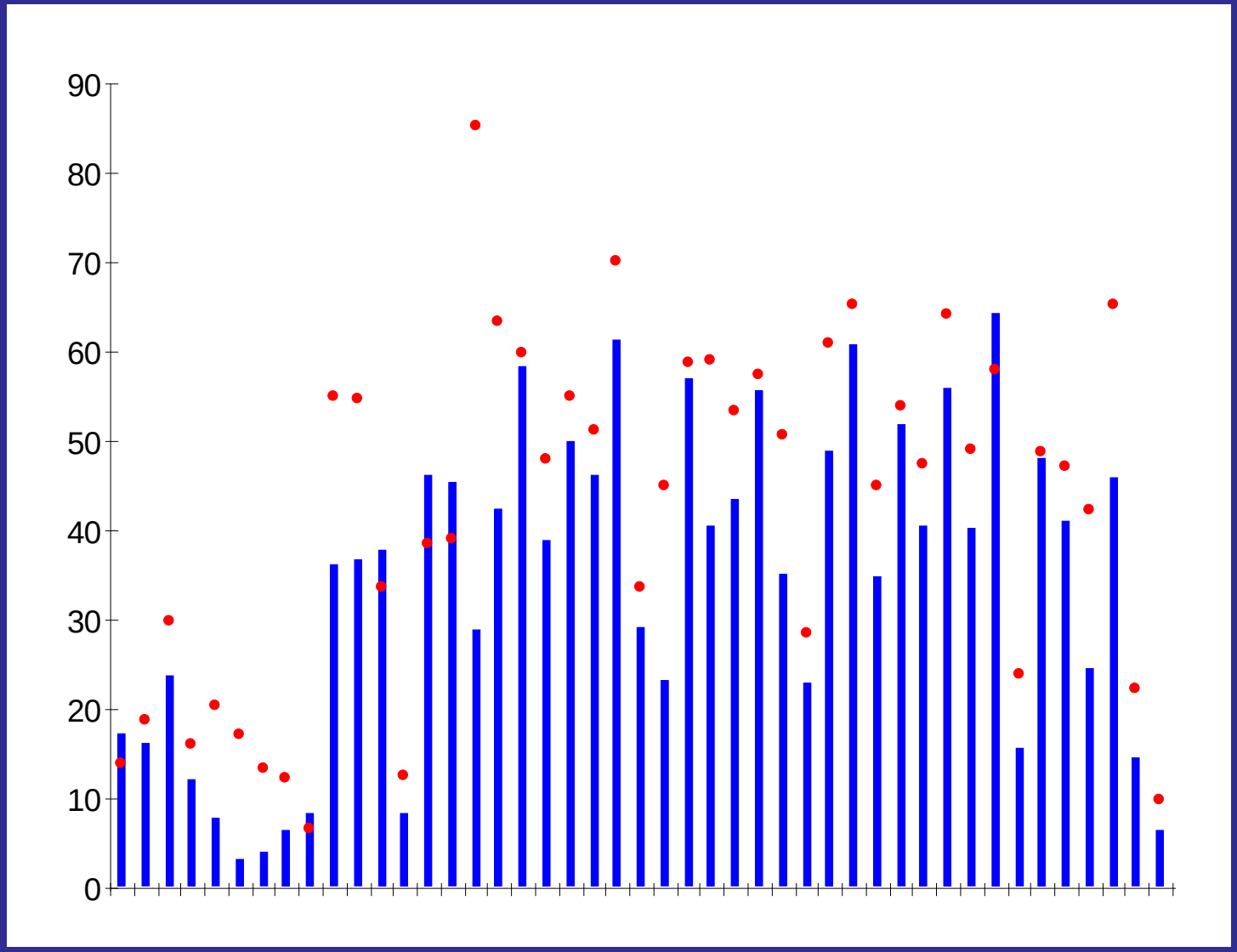

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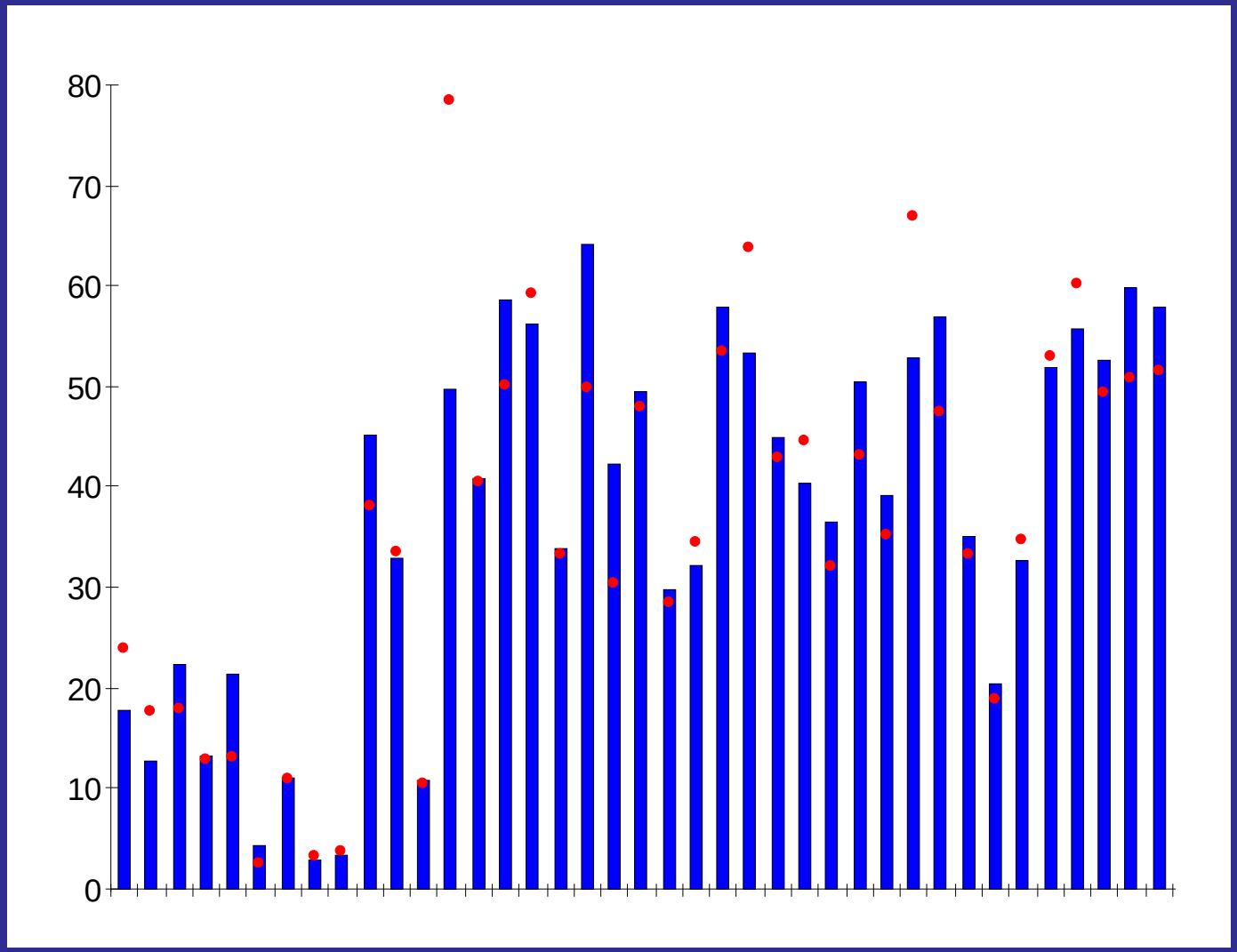

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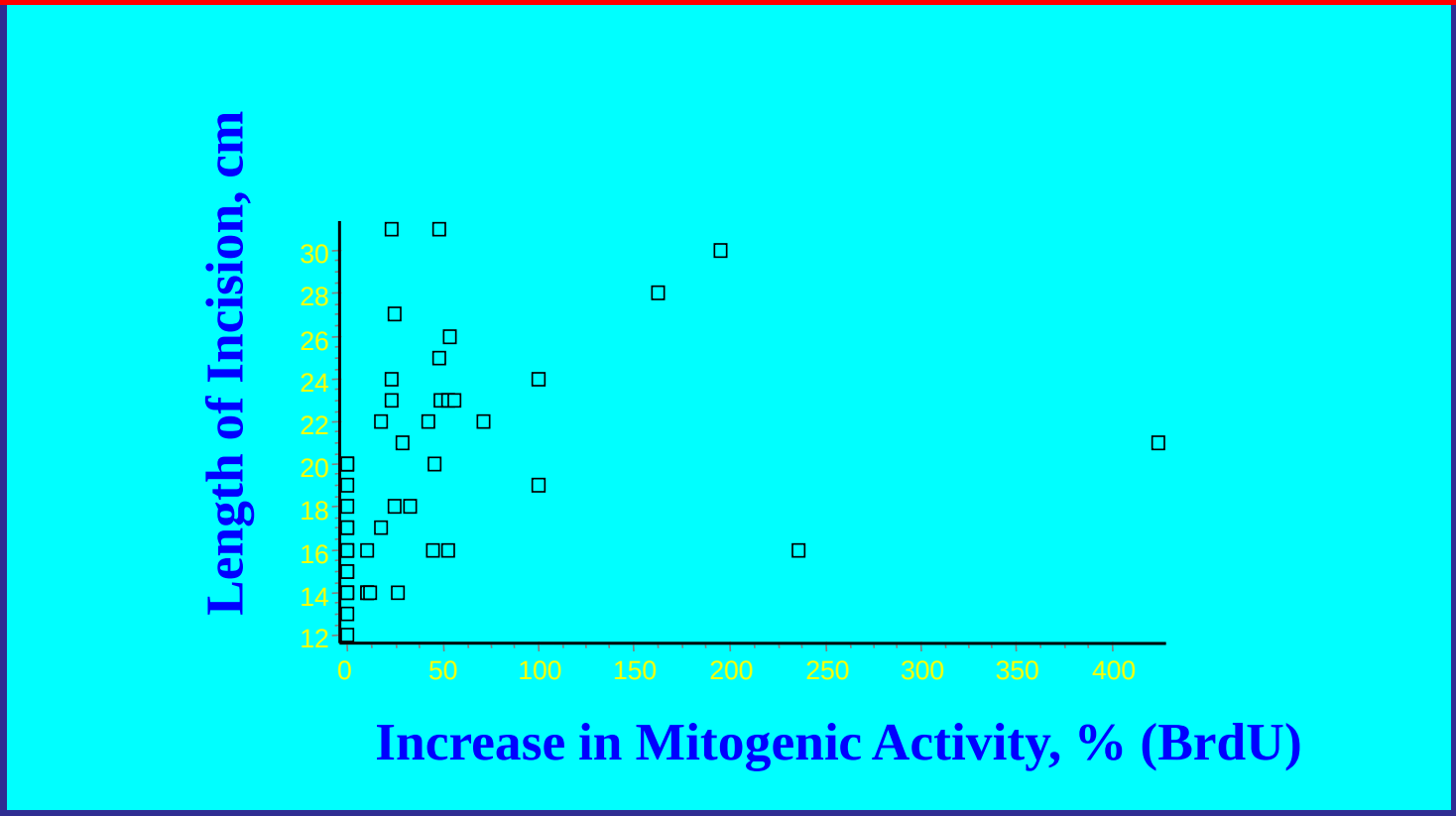

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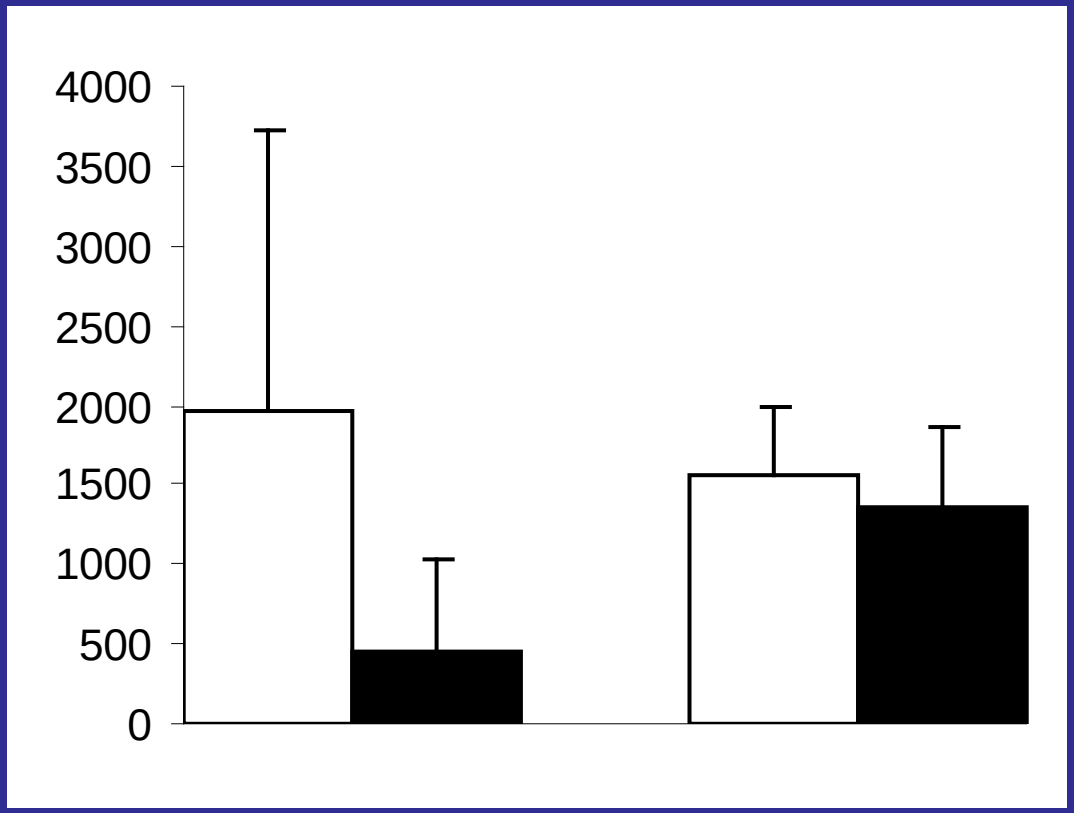
Levels of Intact IGFBP-3 on POD2

Intact IGFBP-3 ng/ml



IGFBP-3

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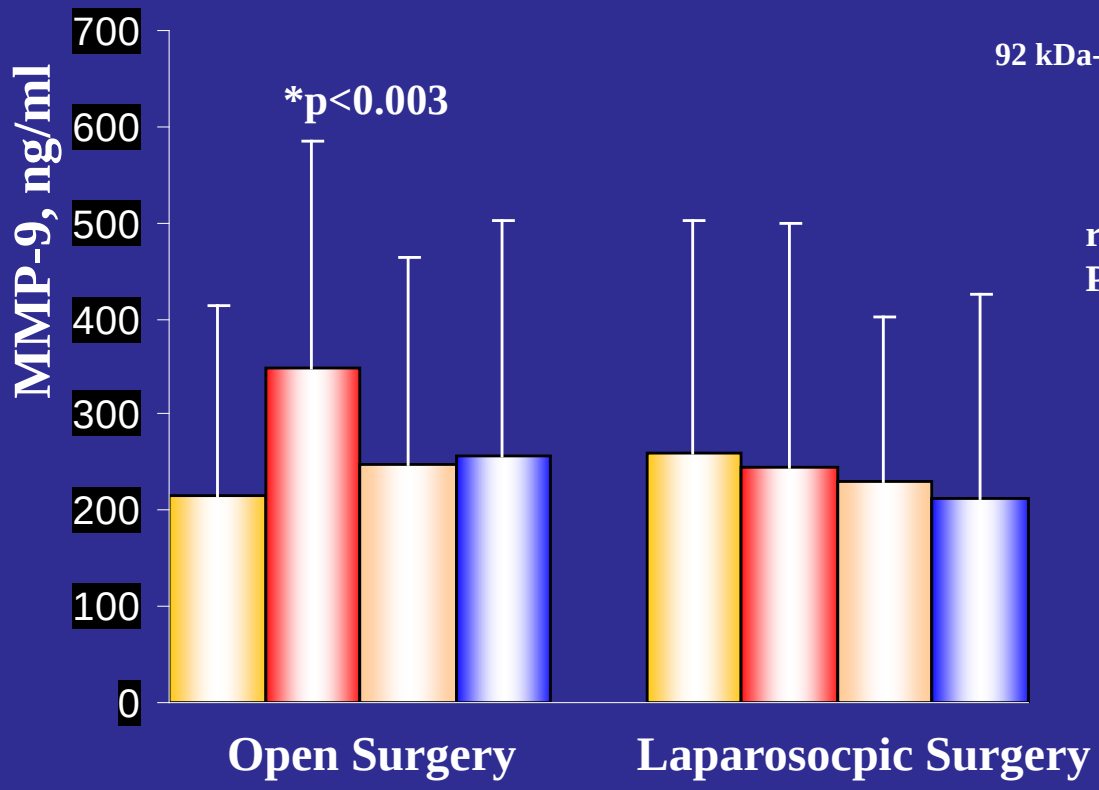
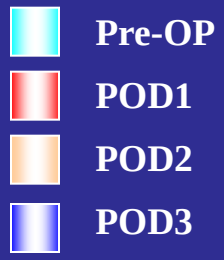
- Induces apoptosis of most tumor cell lines
- Inhibits DNA synthesis of poorly differentiated cell lines
- Lower rates of adenoma formation noted in mice that overexpress IGFBP-3
- Prognostic indicator for prostate cancer, ? IBD, and ? colon cancer

Results: MMP-9 ELISA and WB

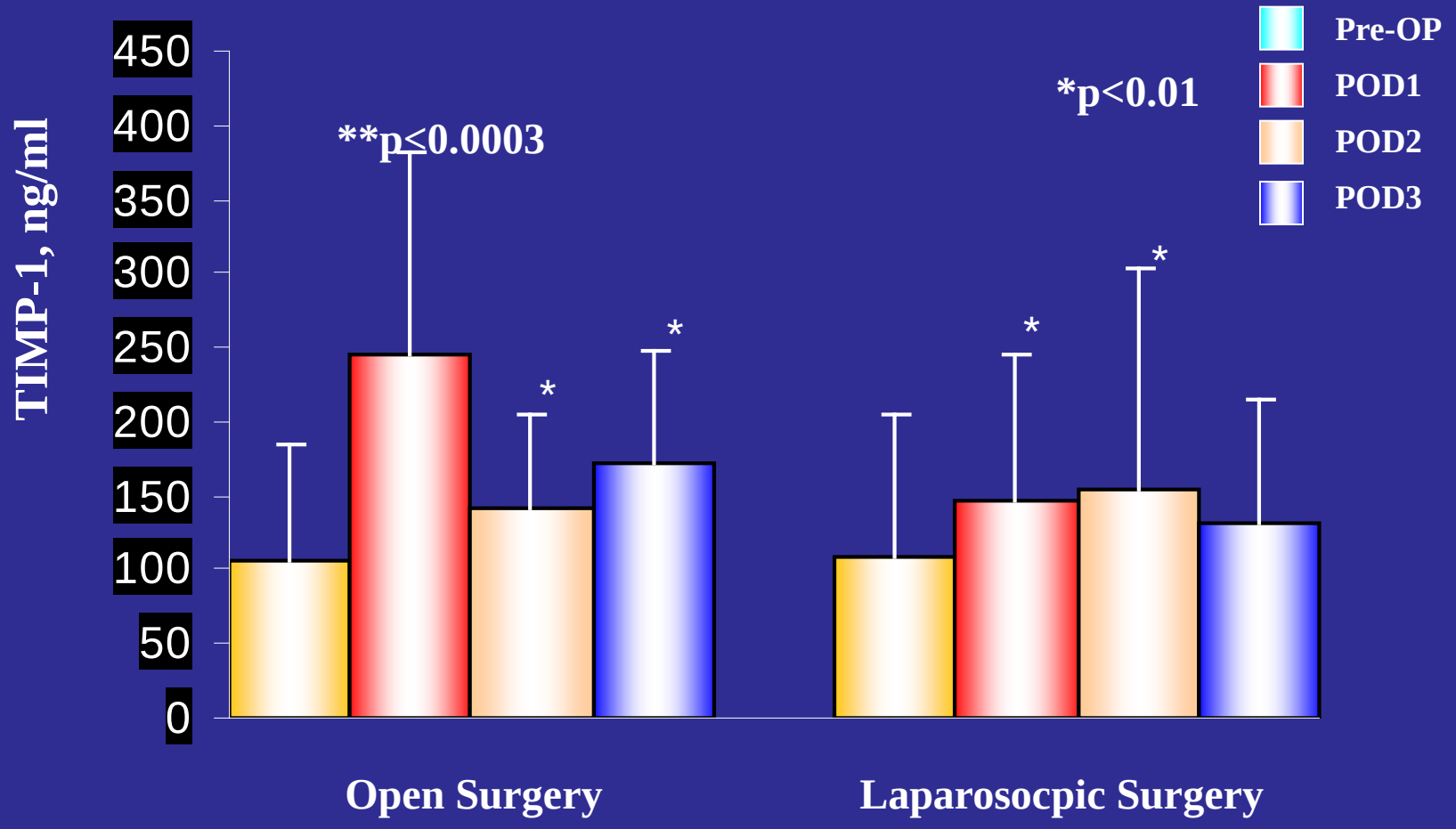


MMP-9 WB analysis

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



Results: TIMP-1 ELISA

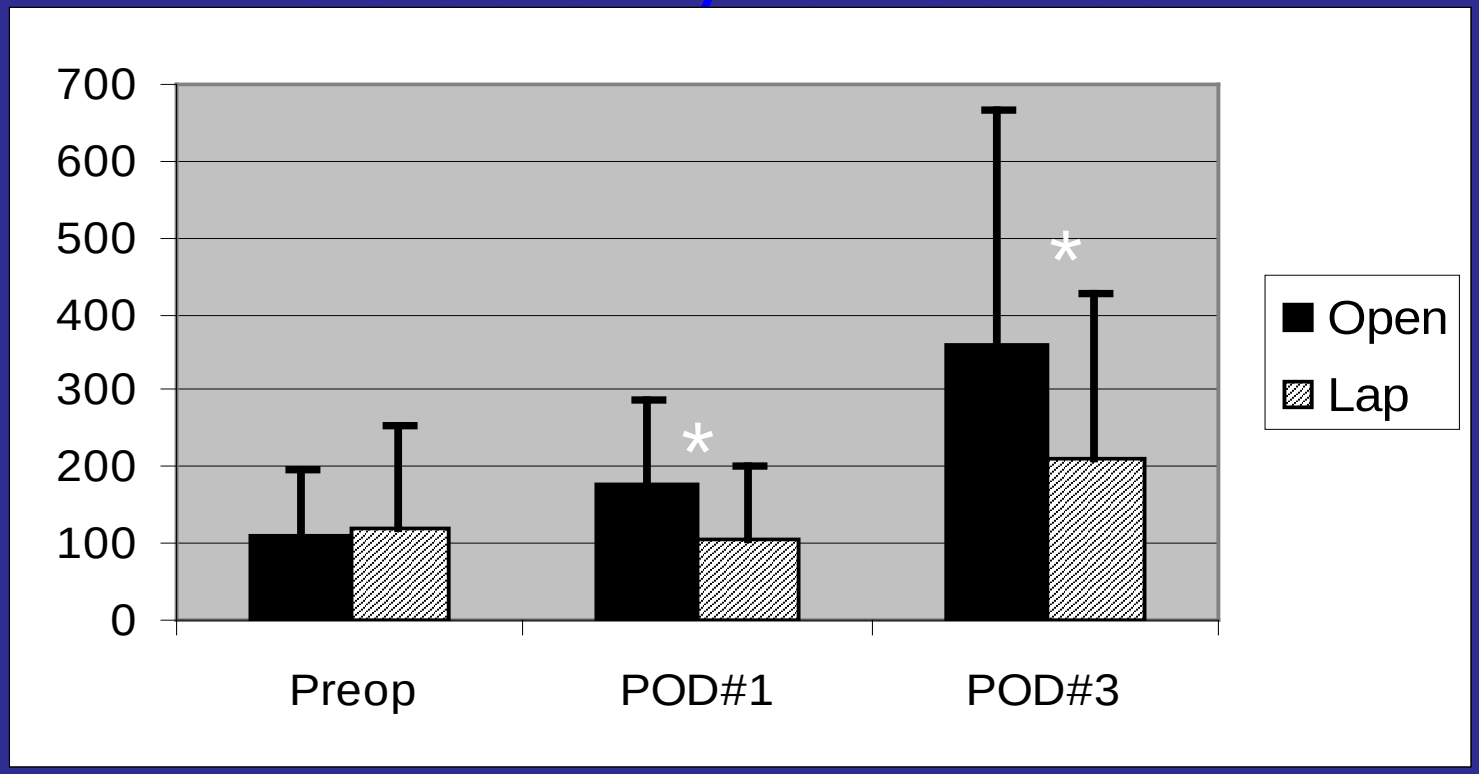


Vascular Endothelial Growth Factor

- 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-agniogenesis agents coming onto market (Avastin is first)
- What does surgery do to VEGF levels??

FIGURE #1

VEGF levels Open vs. Laparoscopic Colectomy for Cancer*



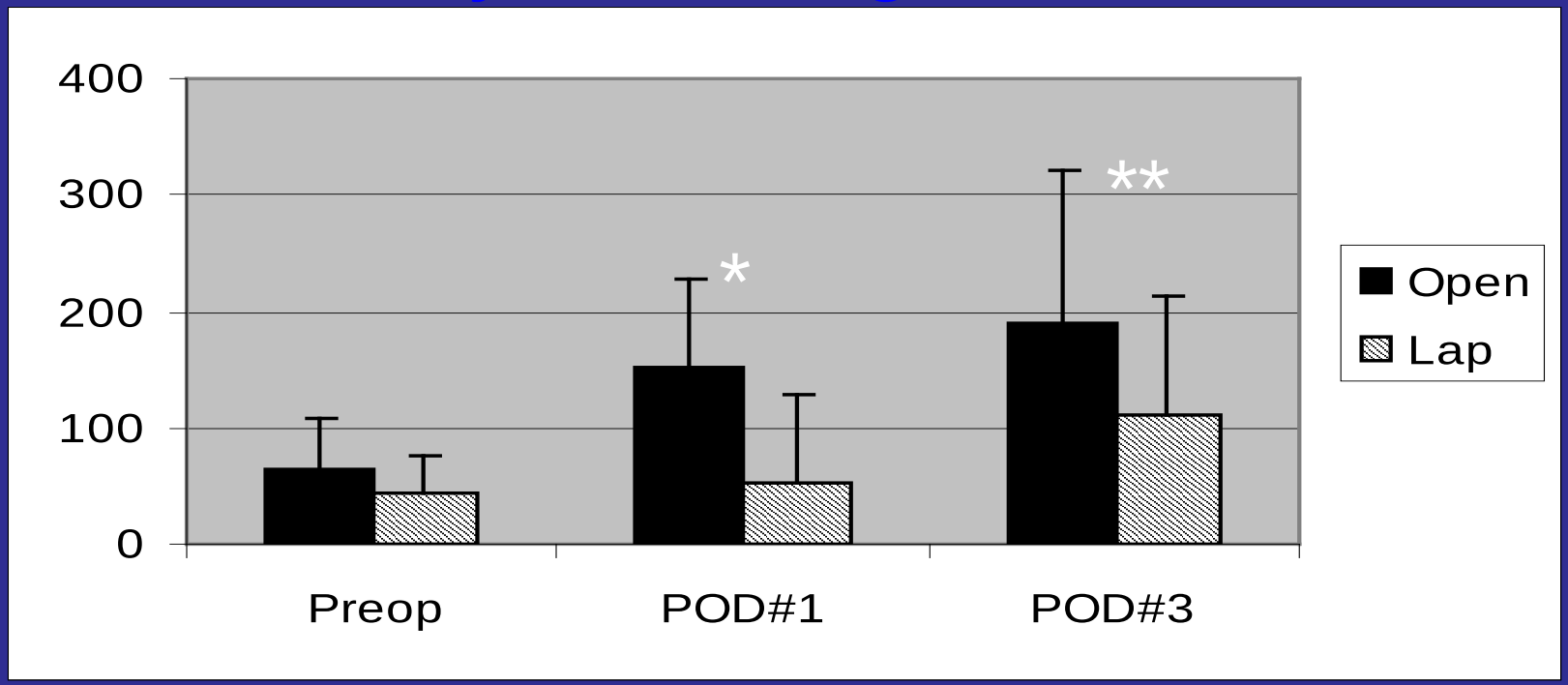
*Open vs Lap or Preop, p<0.0001

** 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)**

FIGURE #3

VEGF levels Open vs. Laparoscopic Colectomy for Benign Disease*

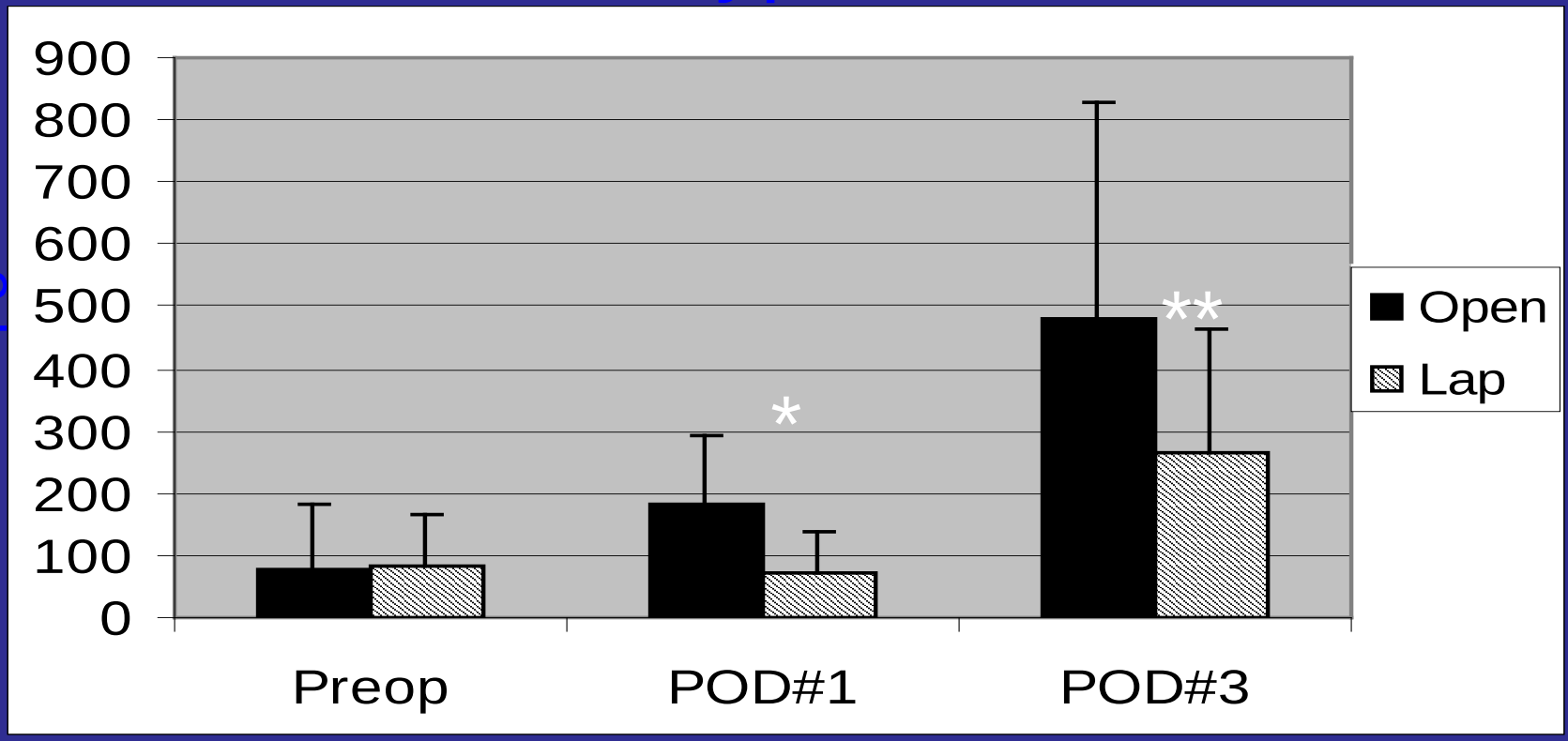


* Open vs Lap, p<0.05

** 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*



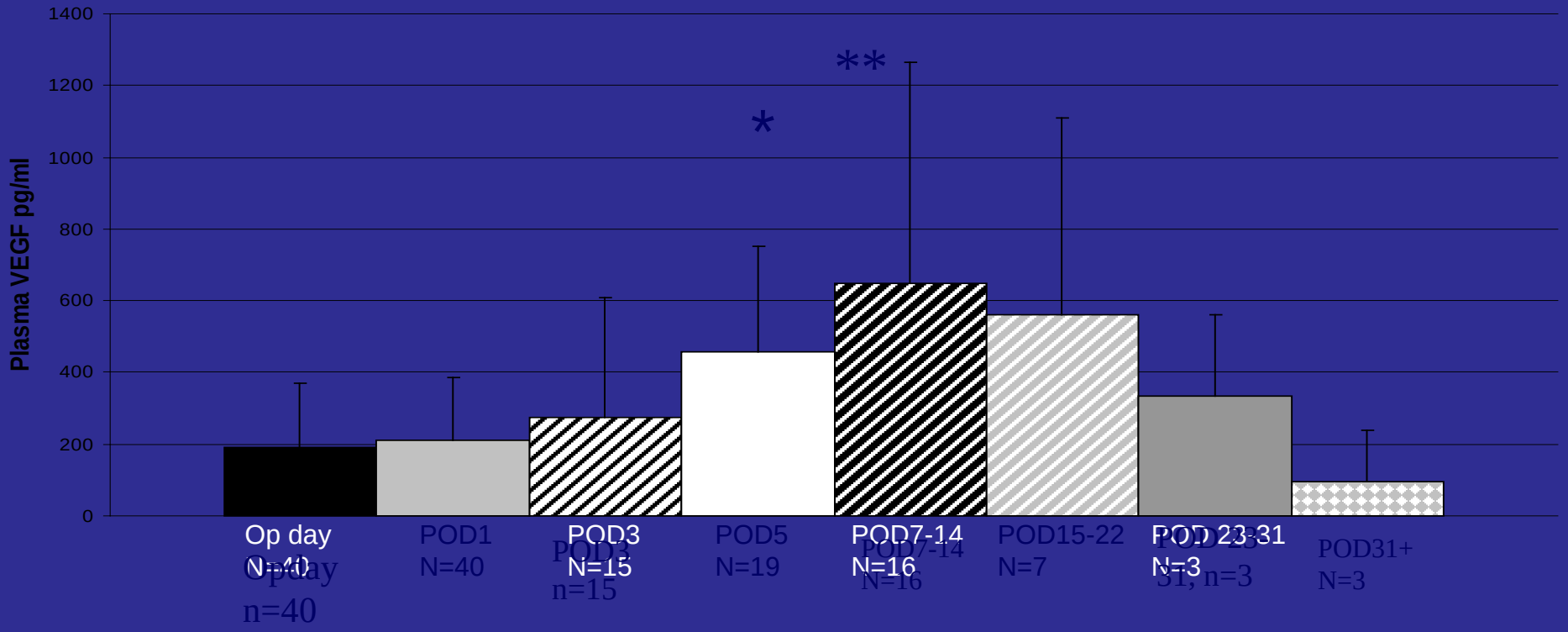
* Open vs Lap, $p<0.05$

** 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 1st month after surgery is a 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

Mitogenic Activity of OS and LS POD 1 Plasma

Patient Groups	n	Age Yrs.	Plasma Mitogenic Activity			
			BrdU+cells, %		Cell Counts (x10^5)	
			PreOP	POD1	PreOP	POD1
OS, All Patients	45	56.6±15.8	34.2±17.9	42.4±19.**	5.6±1.6	7.0±1.8**
LS, All Patients	39	59.8±19.3	37.2±18.1	36.6±18.9	5.2±1.3	5.1±1.7
OS, Colon Cancer[a]	20	65.4±12.6	30.5±19.1	36.3±18**	5.4±1.7	6.7±1.8**
LS, Colon Cancer[a]	22	63.9±17.6	32.6±19.9	31.6±18.4	4.9±1.4	4.8±1.7

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

[a] 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

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

*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** +

* Allendorf et al. Surg Endosc 1997;11:427-30

** Watson et al. Br J Surg 1995;82:1060-65

\+ Kobayashi et al. Arch Surg 1995;130:676.

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 ?

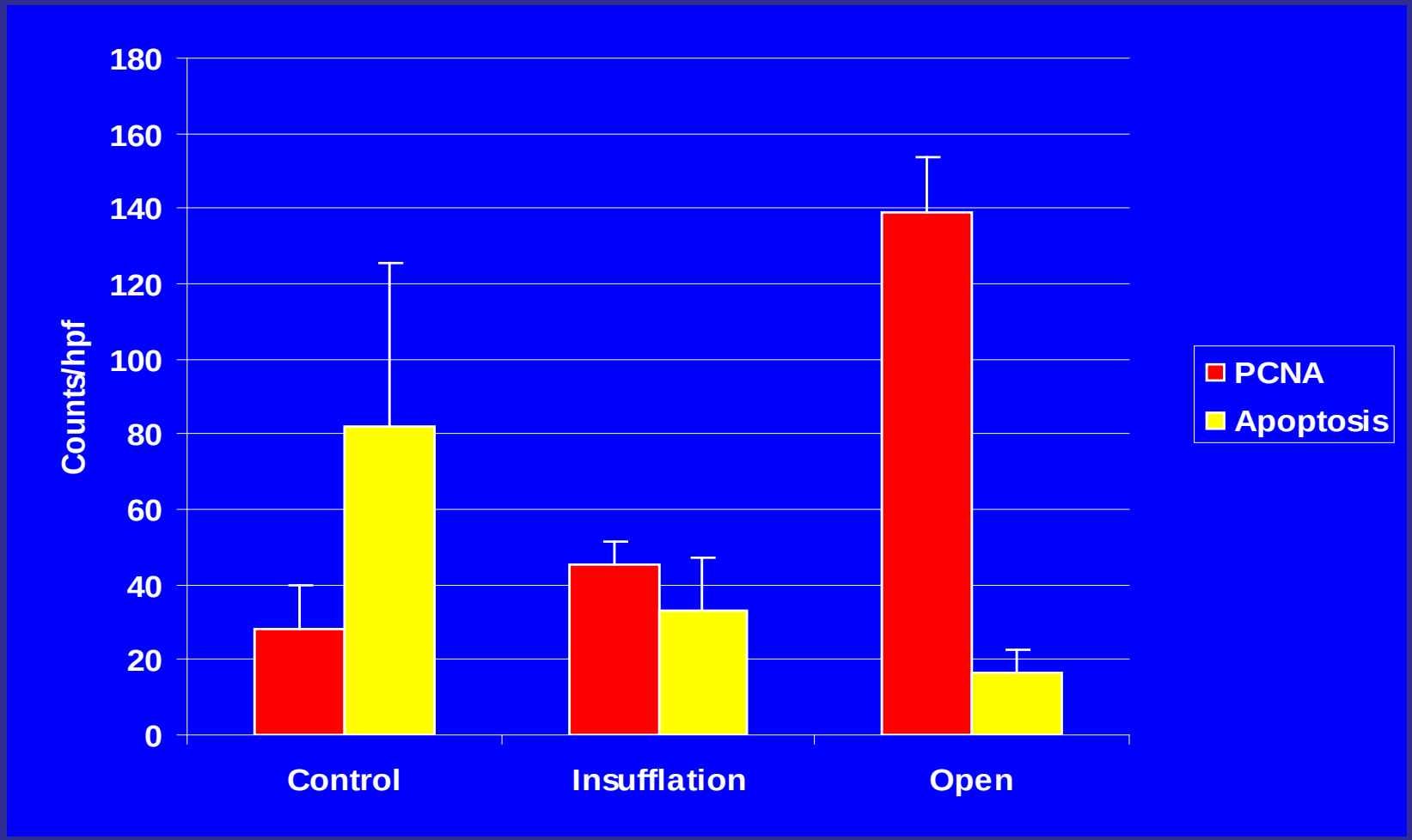
Tumor Cell Proliferation and Apoptosis[+] after Surgery*

- 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

* Lee et al. Surgical Endoscopy 1998;12(5):514.

Figure 4: Comparison of Proliferative Rates and Apoptotic Rates on POD 14



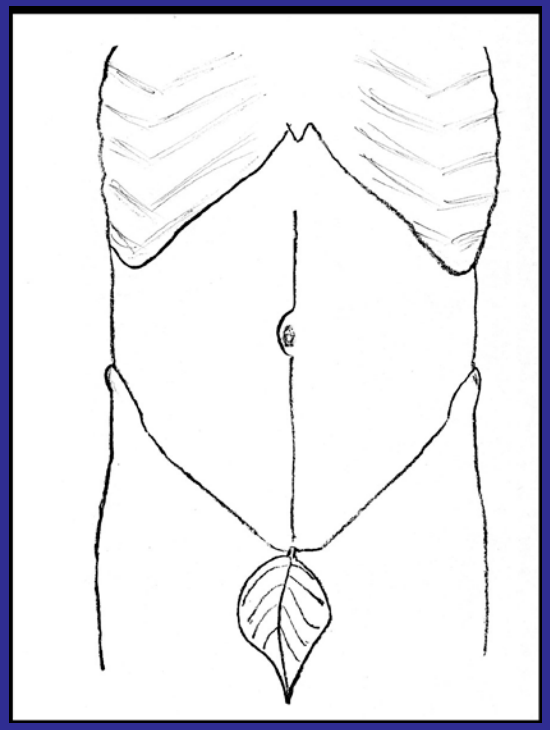
Mitogenic Activity of Plasma from Patients in OS and LS Groups: Adenoma and Diverticulitis. Cell Numbers.

Patient Groups	*n*	*Age Yrs.*	Cells recovered from culture x10^5	
			PreOP	POD1
OS, Colon Adenoma	8	50.2±15.0	4.3±1.5	6.3±3.0*
LS, Colon Adenoma	4	74.8±8.3·	5.4±1.0	5.8±1.9¶
OS, Diverticulitis	5	69.2±6.2¶	5.7±1.6	8.0±1.7¶
LS, Diverticulitis	4	60.8±17.6¶	4.9±0.7	5.0±0.8¶

*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 (tatoo)

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

Trial	LAR versus Open
NCI/COST	NSD +
Milsom *	NSD
Lacy**	NSD

+ 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

* Johnstone et al. J Clin Oncol 1996;14:1950-6

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

** Reilly et al. Dis Col Rectum 1996;39:200.

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 C02 Pneumo

- Aerosolization of tumor cells ? (NO)
- Desufflation related transport of liberated cells ?
- C02 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

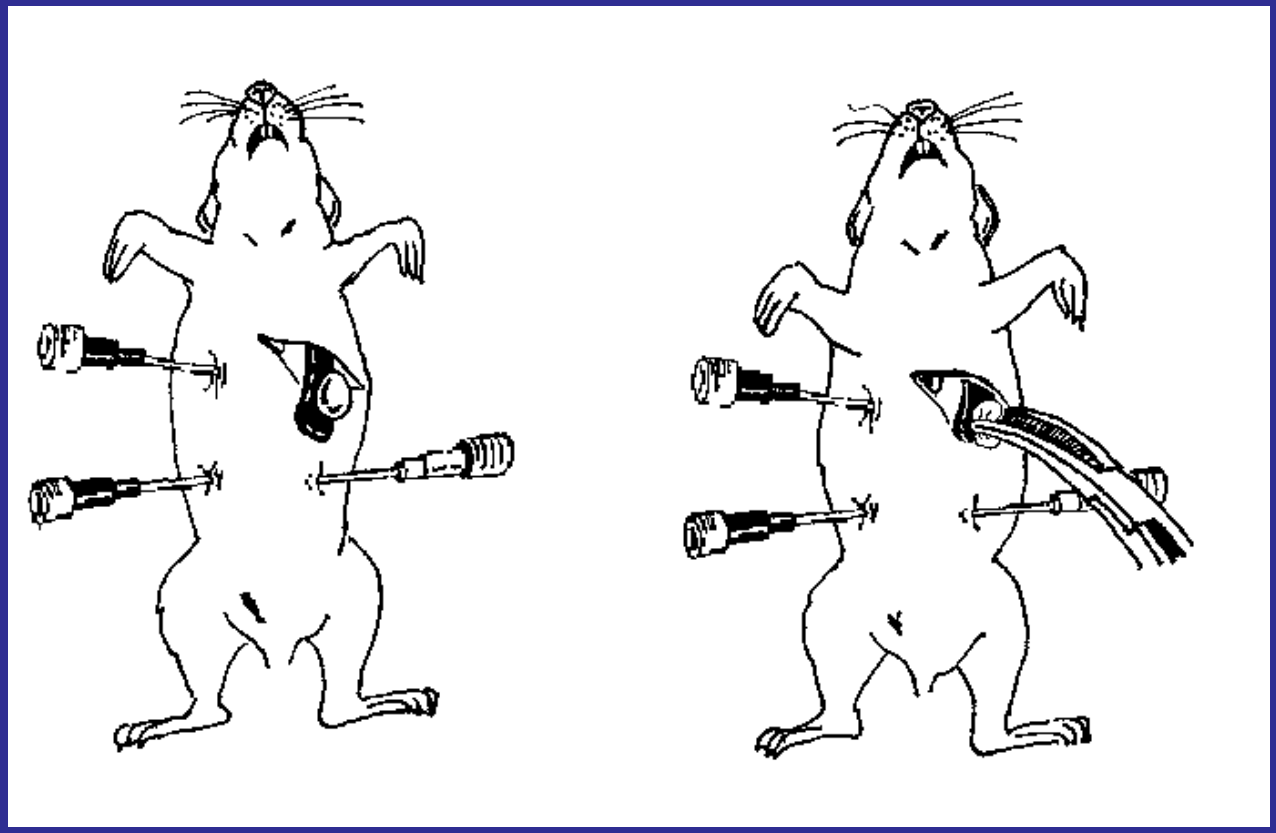
Study of Technique: Murine Splenic Tumor Model

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

First Port Tumor Experiment: Lee et al. Surg Endosc 1998;12(6)828.

- 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

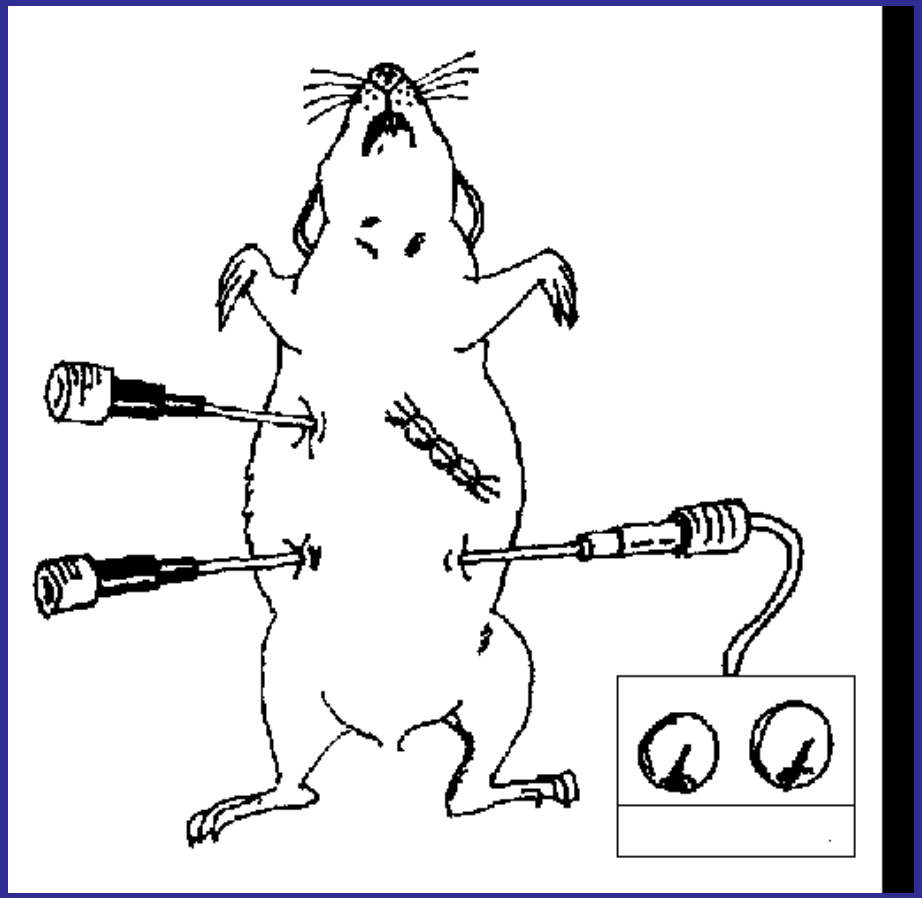
Tumor Capsule Crushed Before Splenectomy in Half the Animals



Non-Crush Group

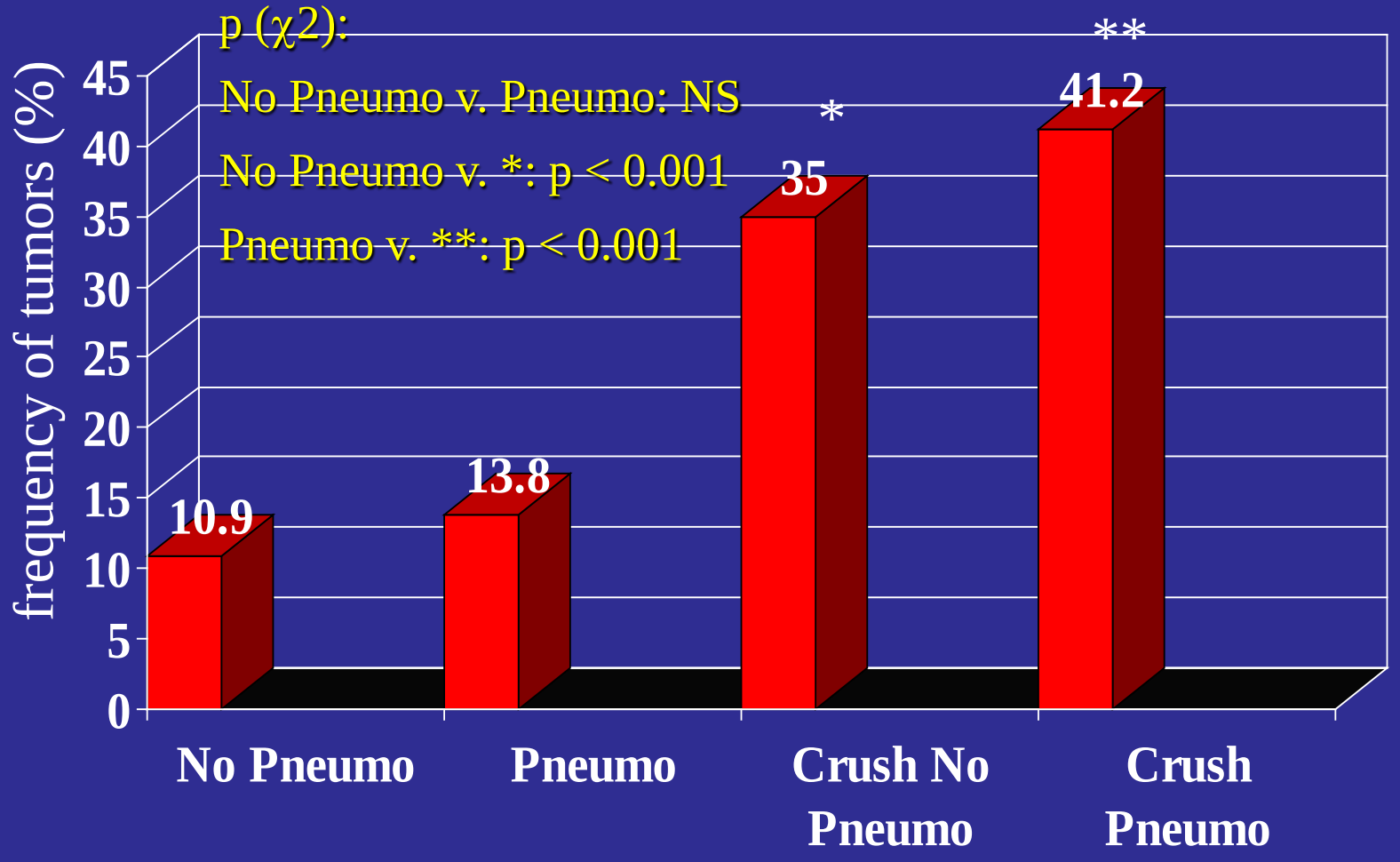
Crush Group

Half the Animals of Each Group: Underwent CO_2 Pnuemo



C02 pneumo: 5 mmHg for 15 min.

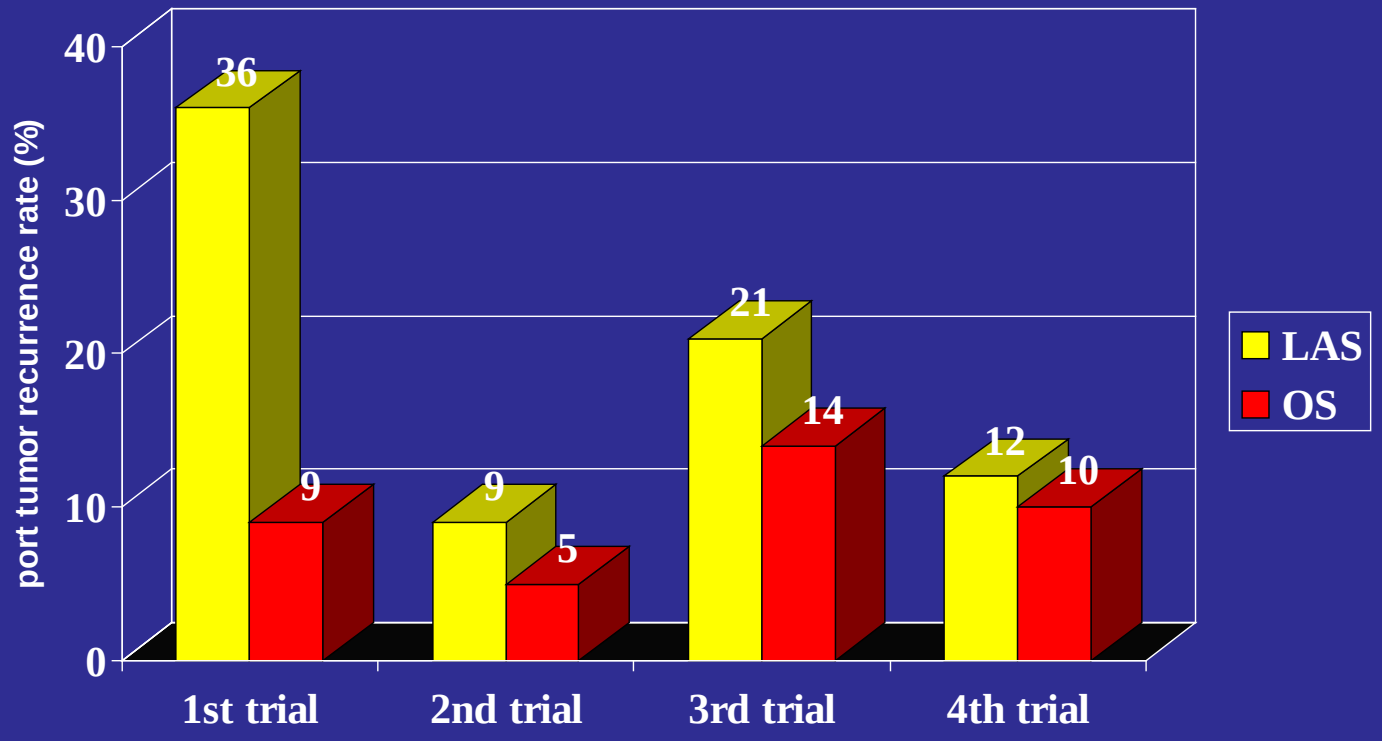
Comparison of Tumor Implantation at Trocar Sites



Second Splenic Tumor Model Study

- Compared laparoscopic-assisted to open splenectomy
- Spleen mobilized laparoscopically
- 3 ports & subcostal incision for all
- Splenectomy via subcostal 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 ?

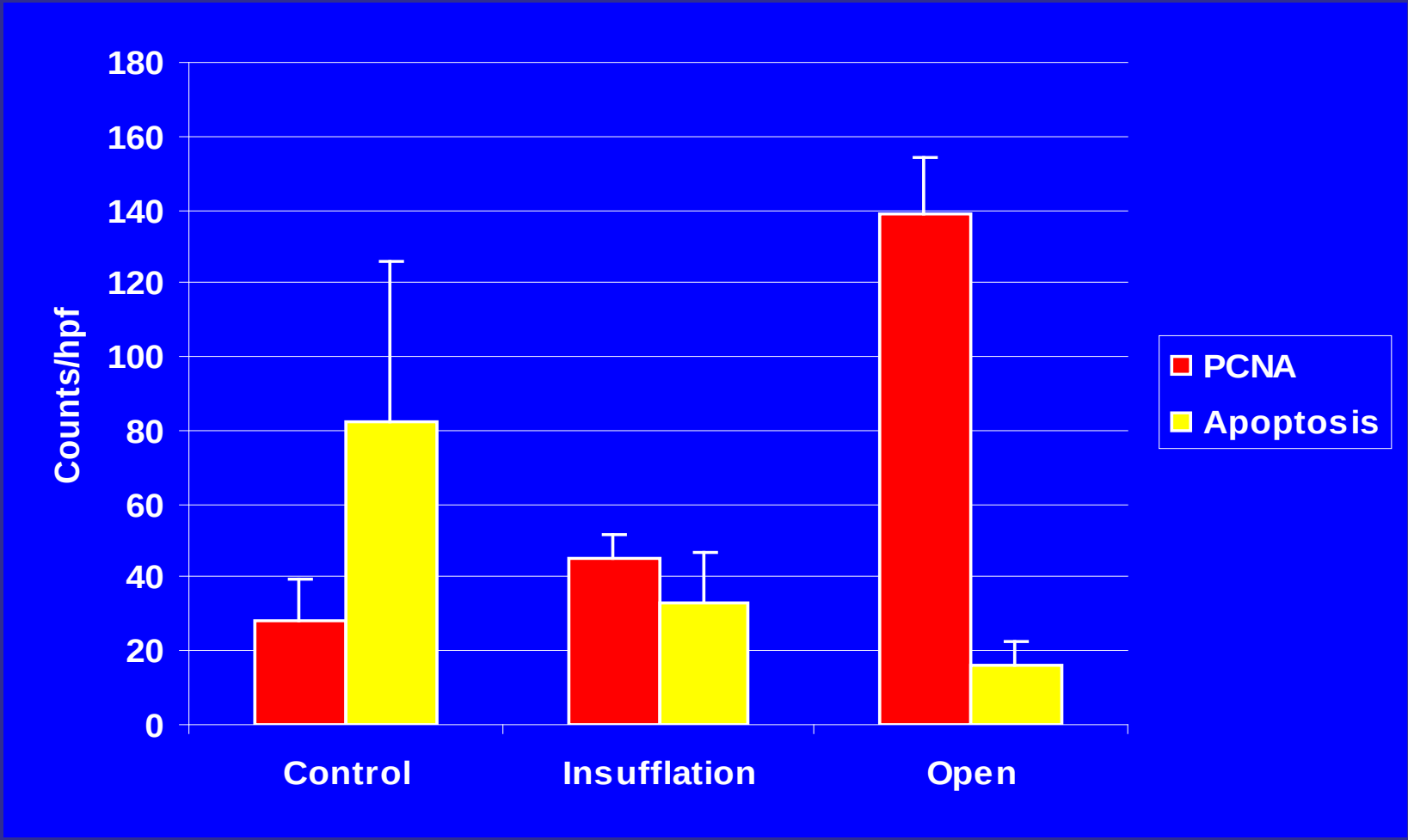
Tumor Cell Proliferation and Apoptosis[+] after Surgery*

- 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

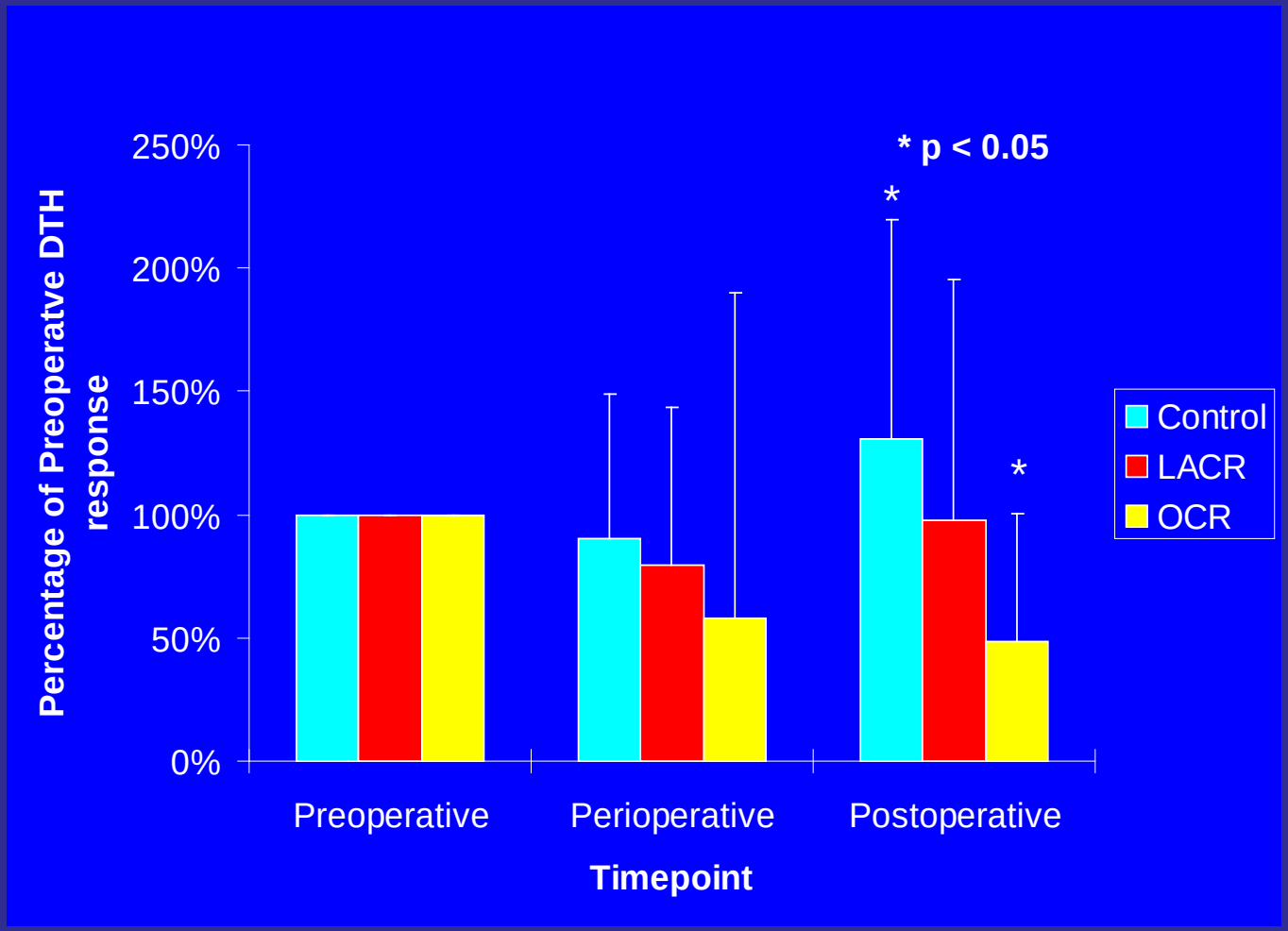
+ Apoptosis = programmed cell death

* Lee et al. Surgical Endoscopy 1998;12(5):514.

Figure 4: Comparison of Proliferative Rates and Apoptotic Rates on POD 14

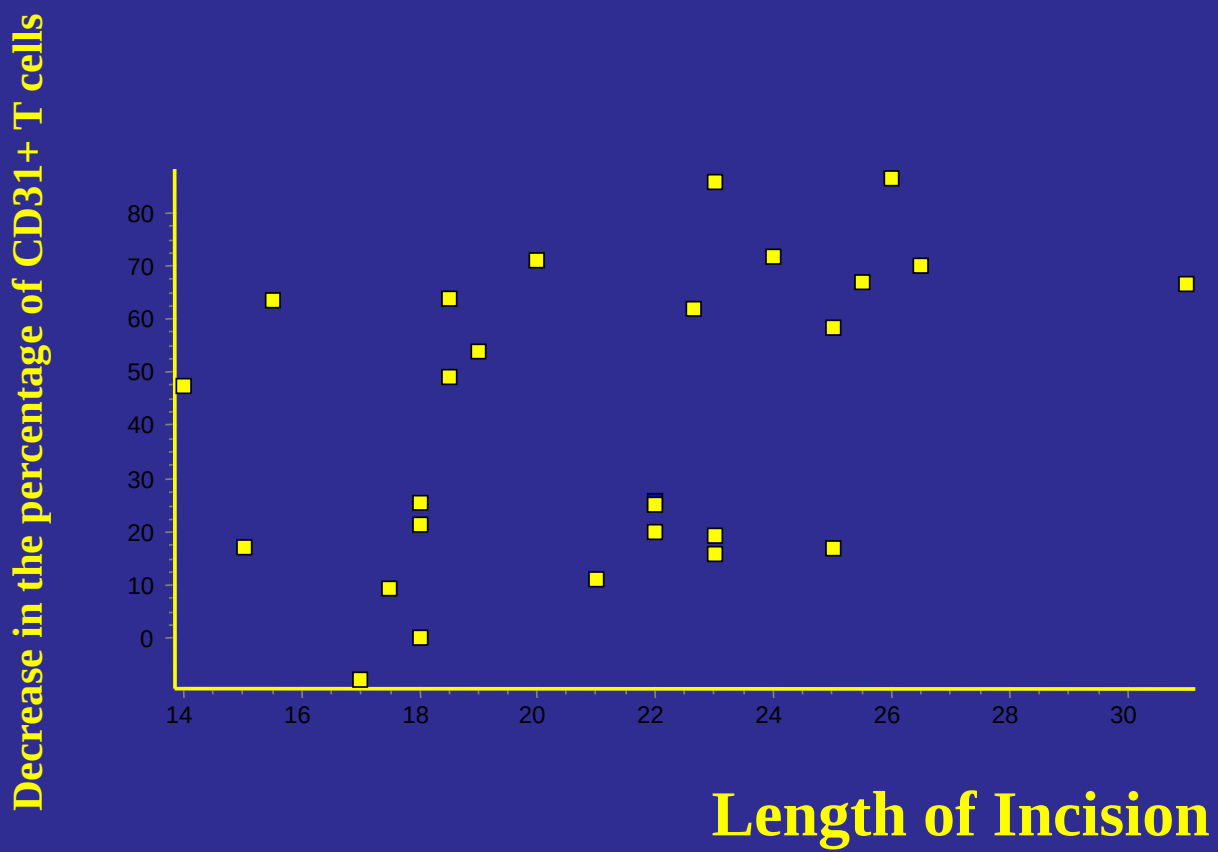


Human Lap. Vs Open Colectomy Study Percentage Change in DTH Response from Preoperative Baseline*

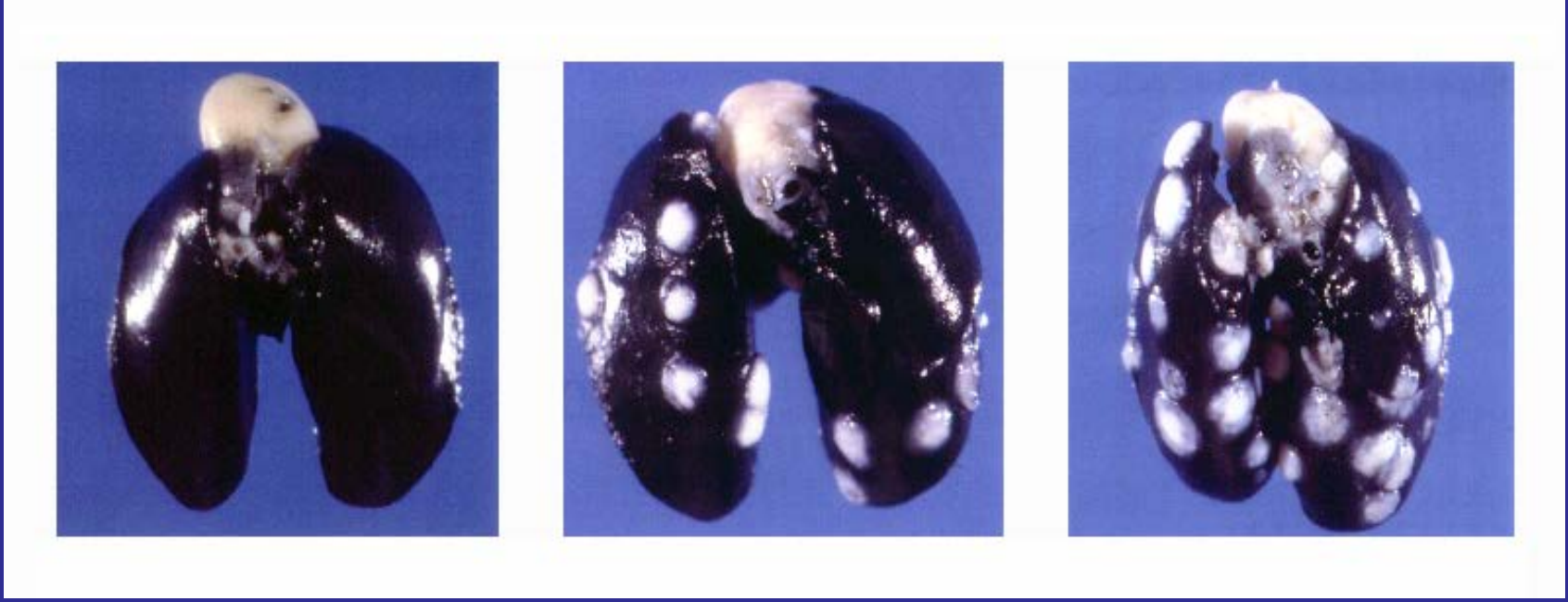


*Whelan et al. Surgical Endoscopy 1998;12(5):586

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

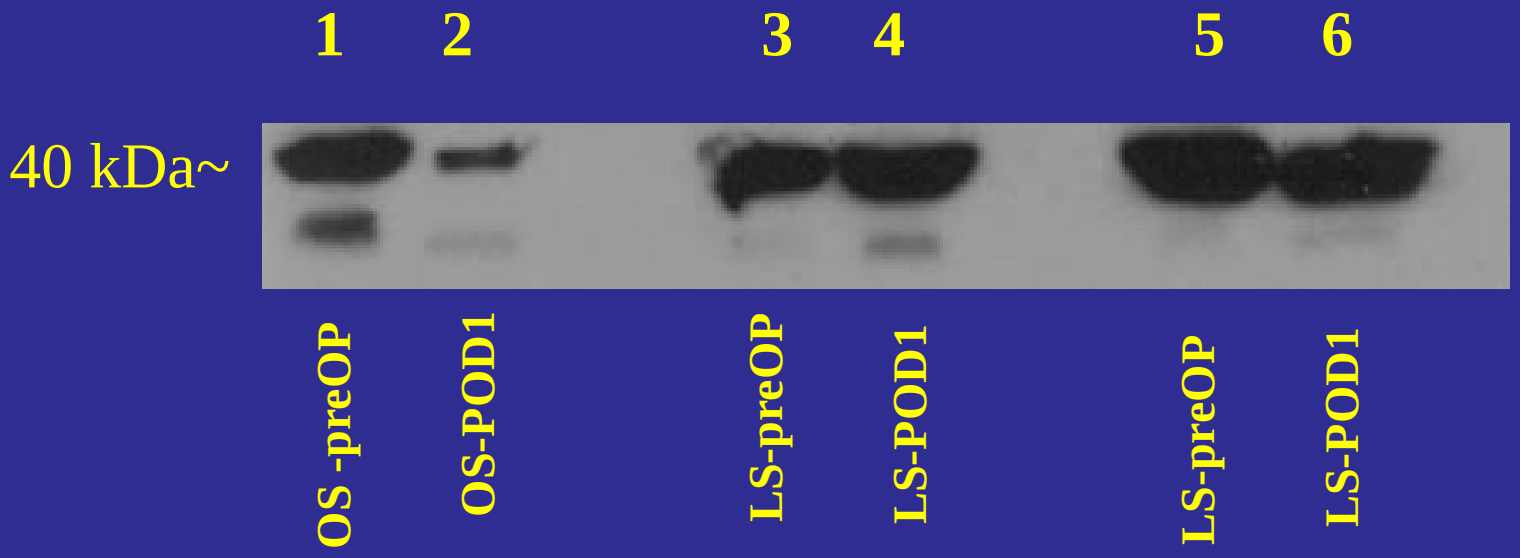
- Mouse mammary carcinoma (MC-2)
- Melanoma B-16 * **
- Colon 26 (C-26 adenocarcinoma)*
- CC531 tumor line+
- TA3Ha

* Southall et al. Dis Colon Rectum 1998;41:564-569.

**DaCosta et al. Br J Surg 1998;85:1439-42

\+ Bouvy et al. Surg Endo 1996;10:186

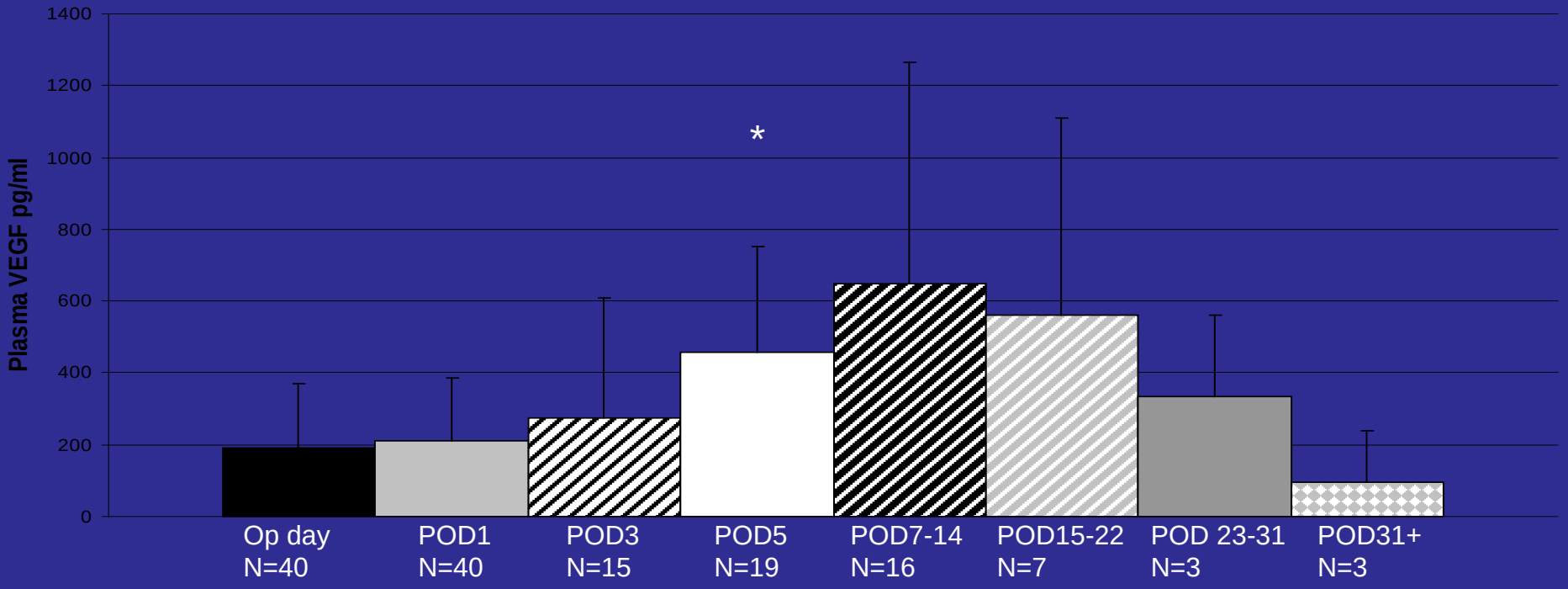
IGF-BP3 Western Blot Analysis



-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 ?

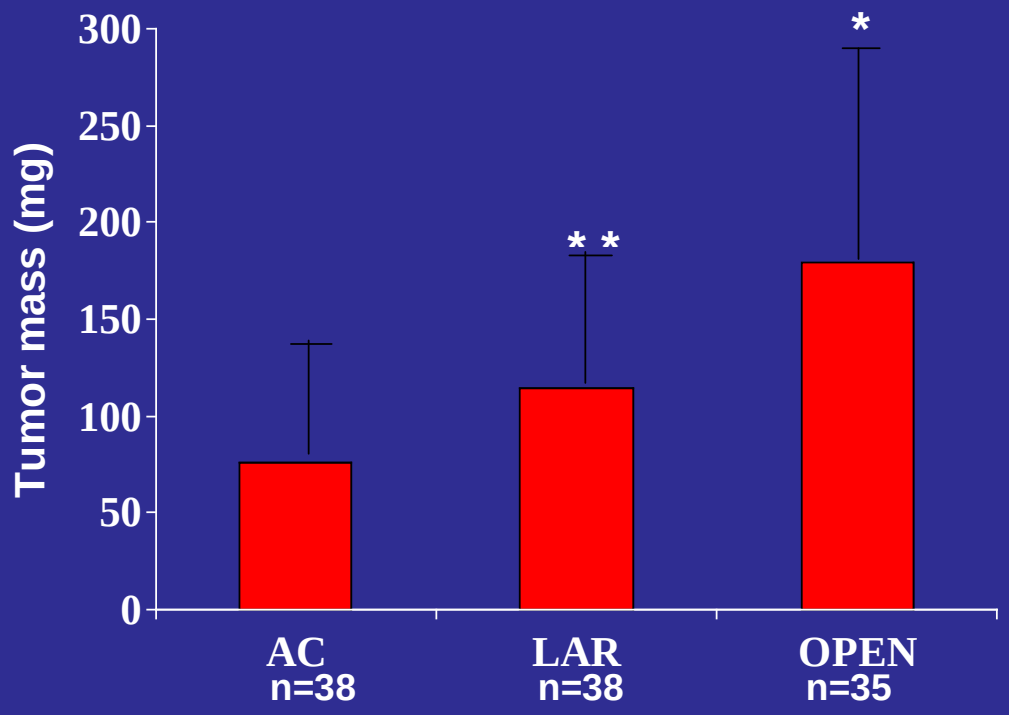
Role of CD31 Surface Protein in T Lymphocyte Function

- 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**

*** Prager E et al. J Immunol 2001 Feb 15;166(4):2364-71.**

****Brezinschek RI et al. J Immunol 1999;162:1677-84.**

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



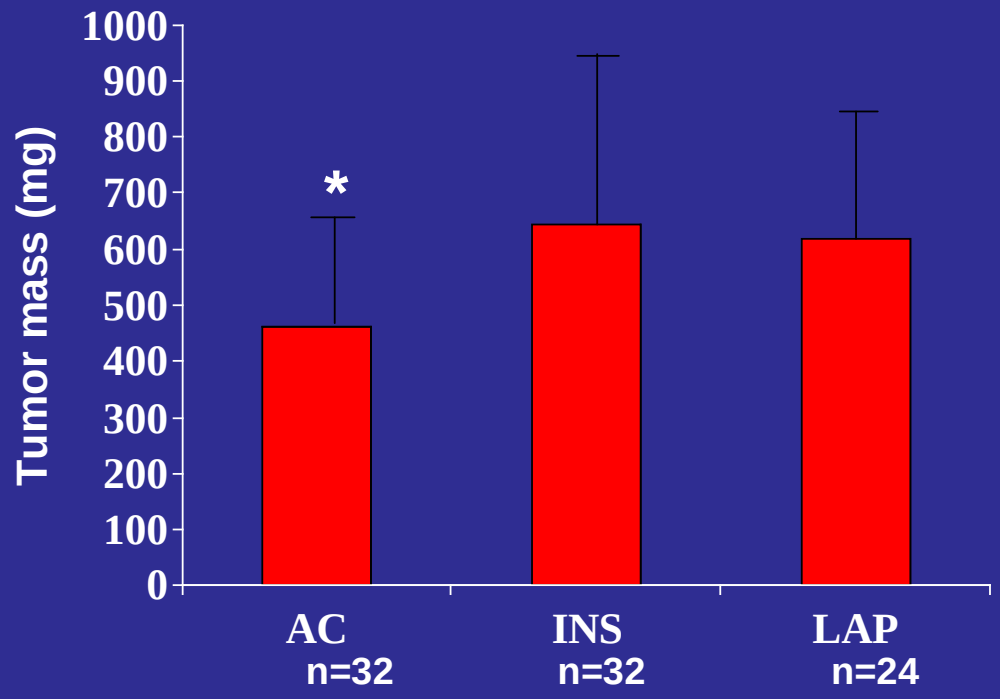
* p< 0.01 vs LAR,
p< 0.001 vs AC

** p< 0.02 vs AC

* MC-2 MMC tumor cells injected into flank day of surgery

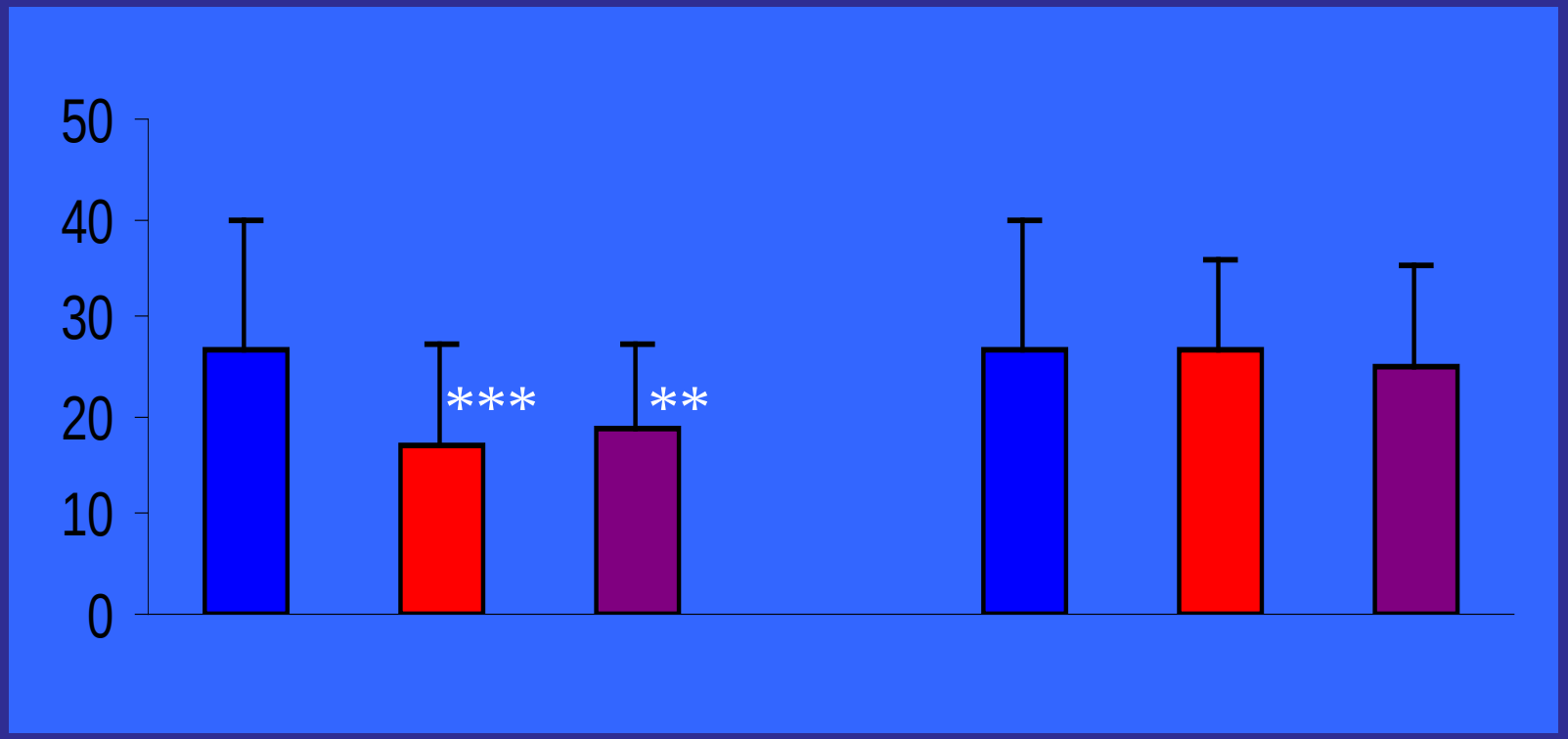
** Allendorf et al. Surg Endosc 1998;12(8)1035-1038

Tumor Mass on POD 12: Nude Mice



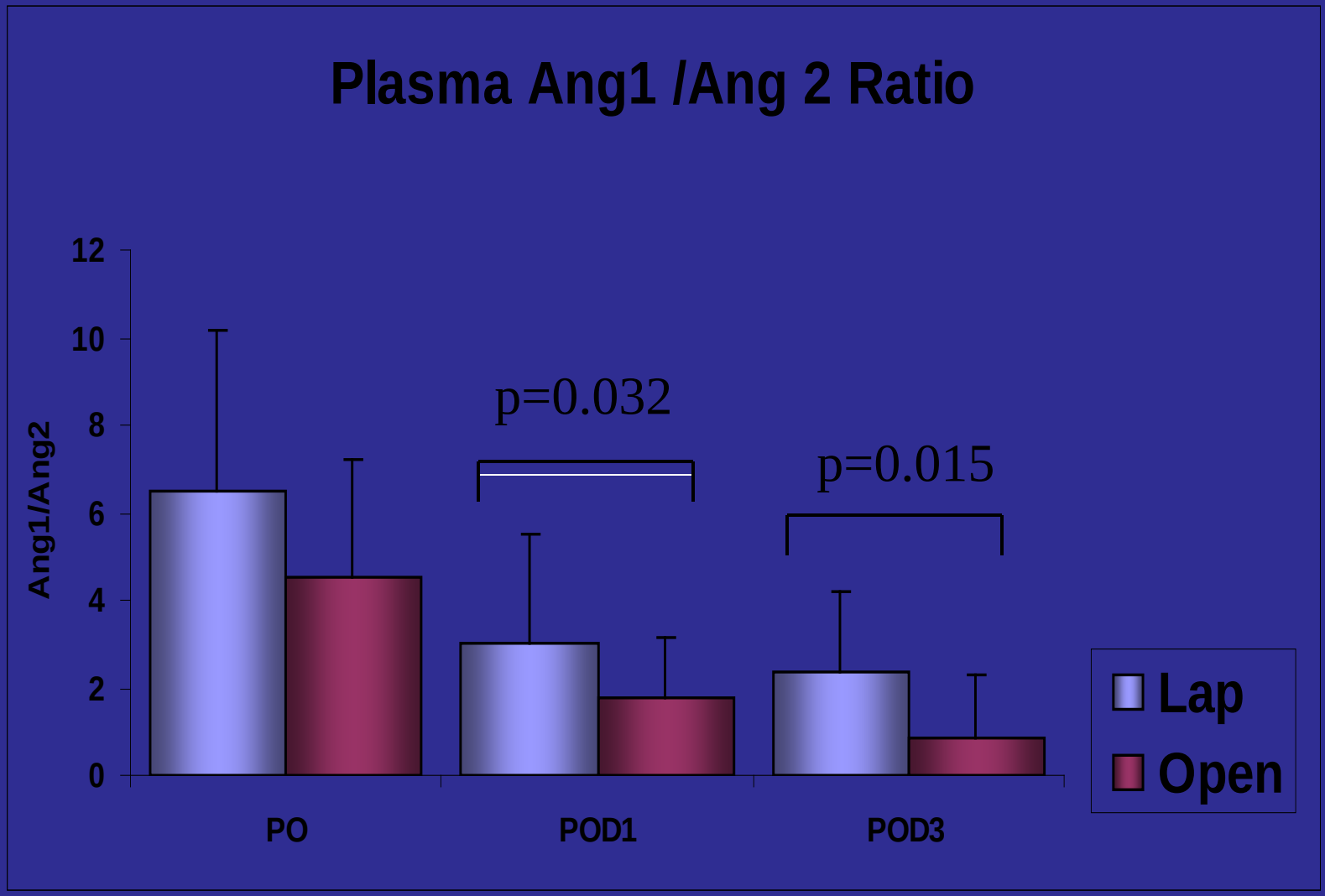
* p< 0.015 vs INS,
p< 0.03 vs LAP

Decrease in the percentage of CD31+ T Cells after Colon Resection*



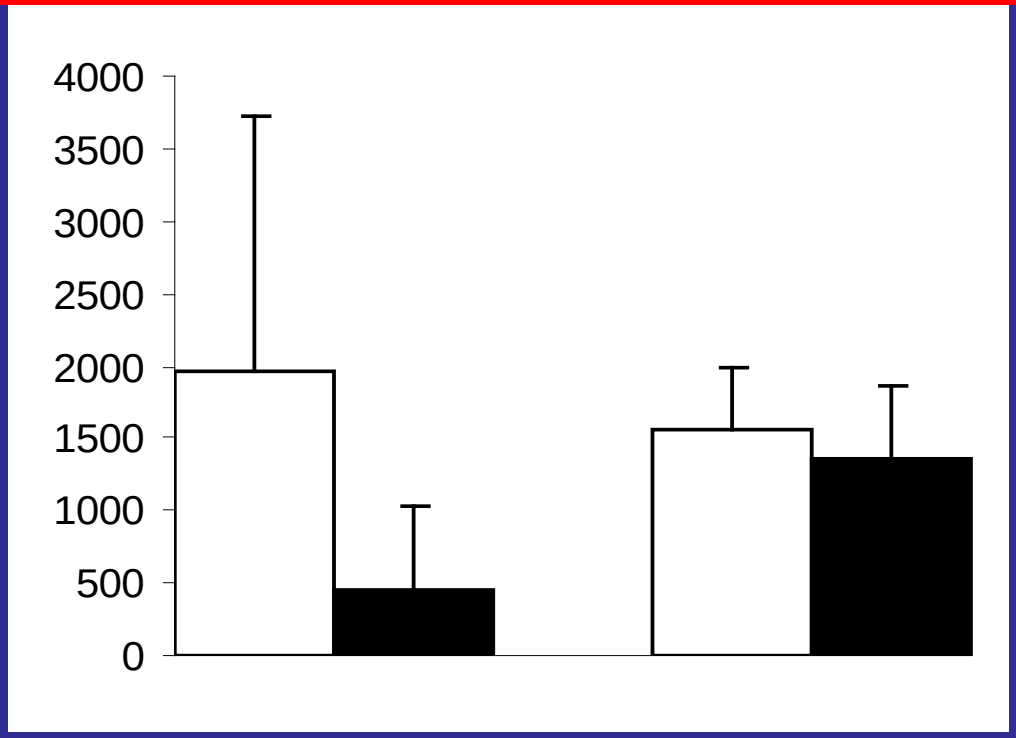
* Kirman et al. Surg Endosc 2003;DOI: 10.1007/s00464-002-8942-3.

Ang 1 & 2 Modulate VEGF Mediated Angiogenesis



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

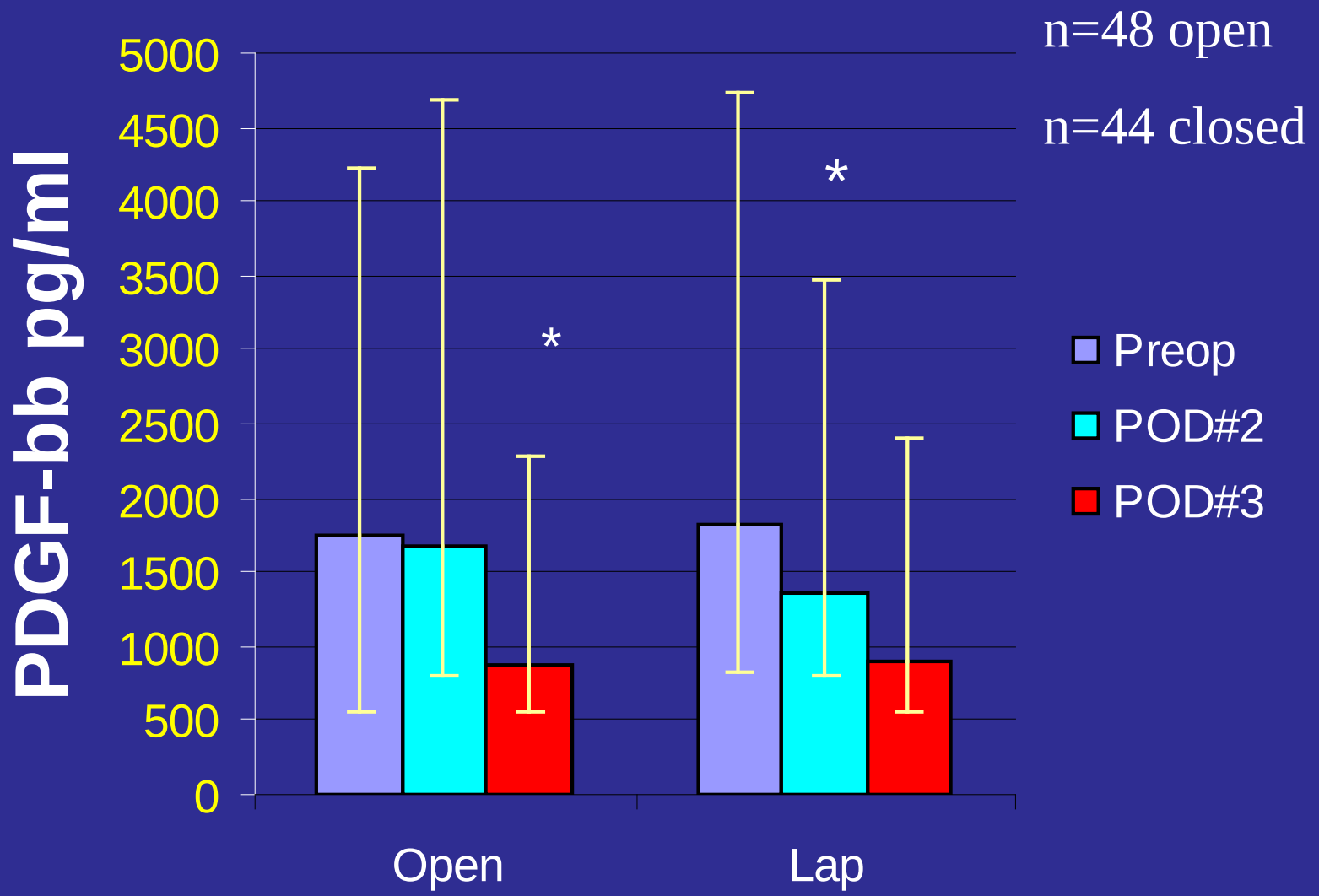
Intact IGFBP-3 ng/ml



* Tumor growth inhibitor

** Kirman et al. Surg Endosc 2003;19:55-59.

PDGF-bb levels 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

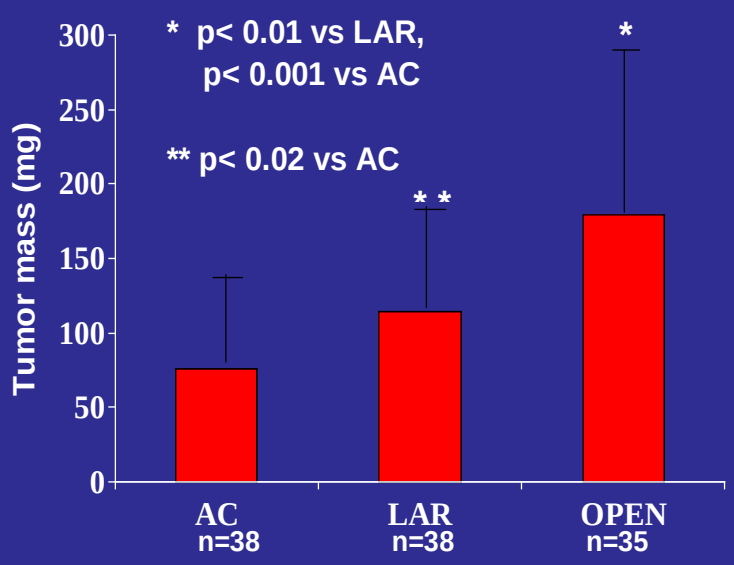
- Population:
  - Transplant patients
  - Pts. on immunosuppresive drugs
  - Disease-related immunosuppression
- Higher complication rates
- Higher mortality

Impact of T cells on Tumor Growth After Laparotomy or CO2 Pneumo***

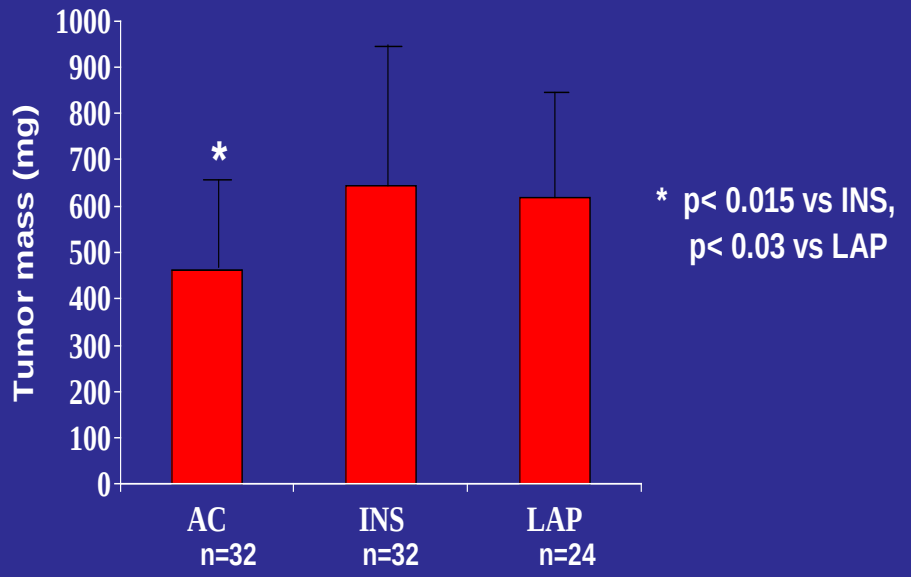
- Surgery stimulates tumor growth
- Nude mice (no T cells) vs immunocompetent mice
- Laparotomy vs. C02 pneumo
- High dose tumor injections postop
- POD 12 tumors excised & weighed

* Allendorf et al. Archives Surg 1995;130(6):649-53
** 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)

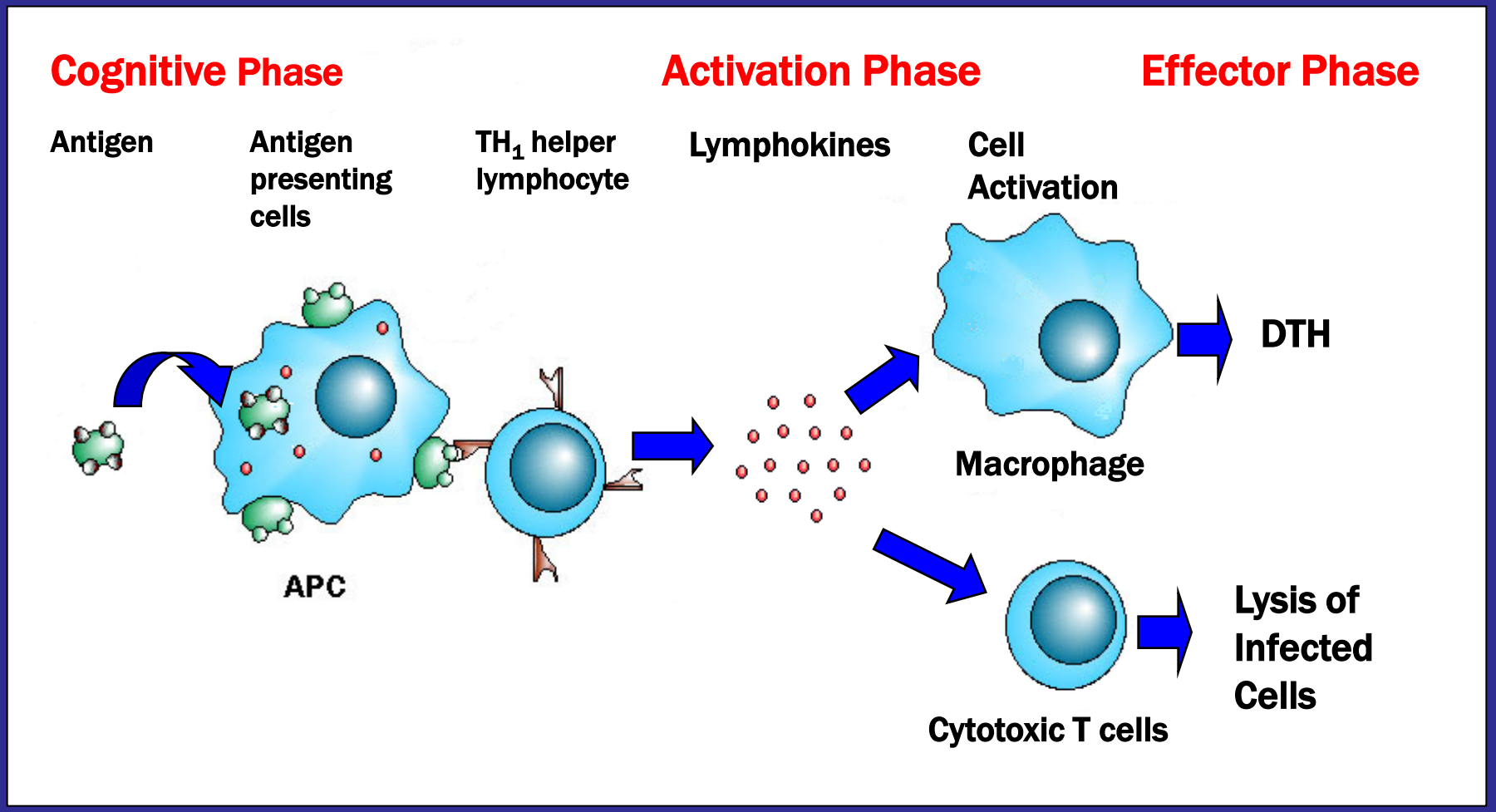
- Assesses cell-mediated immune function

- 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

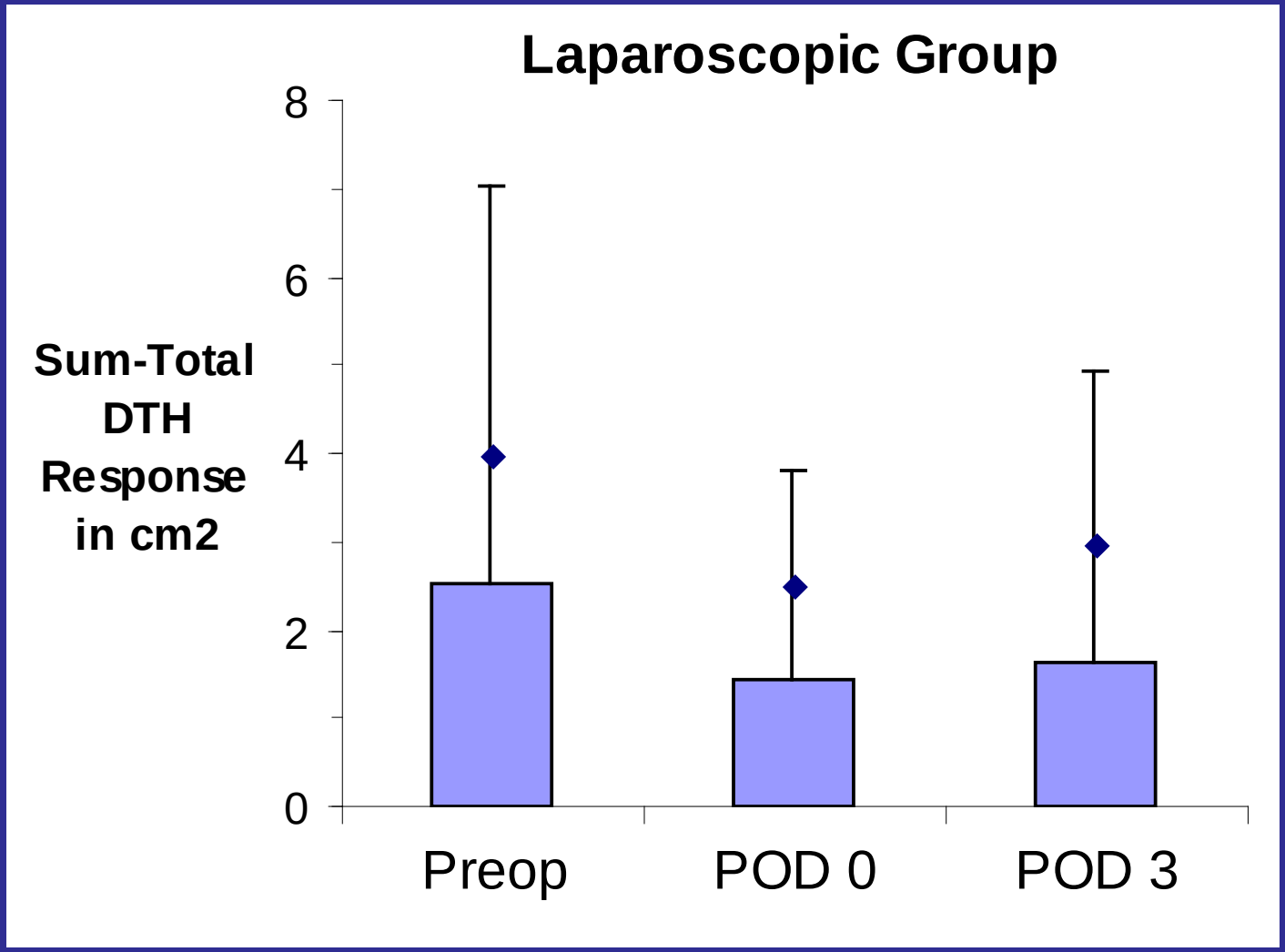
DTH Response



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



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

Where the Same Genes Effected ? *

Group	# Genes 12 hours	# Genes 24 hours
Altered expression in both groups	60 (13%)	77 (39%)
Increased expression in ***Open Group*** only	338	80
Increased expression in ***CO2 Group*** only	59	41

* 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

Trial	No. pts.	Oncologic Results
COST	863	No Difference
COLOR	1248	No Difference
Meta-Analysis		No Difference
Lacy et al	***208***	***Lap. Benefit***

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 ?

* Tjandra JJ et al. Colorectal Dis 2006;8:375-388.

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 immunopsuppression
- May lead to novel pharmocologic 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)

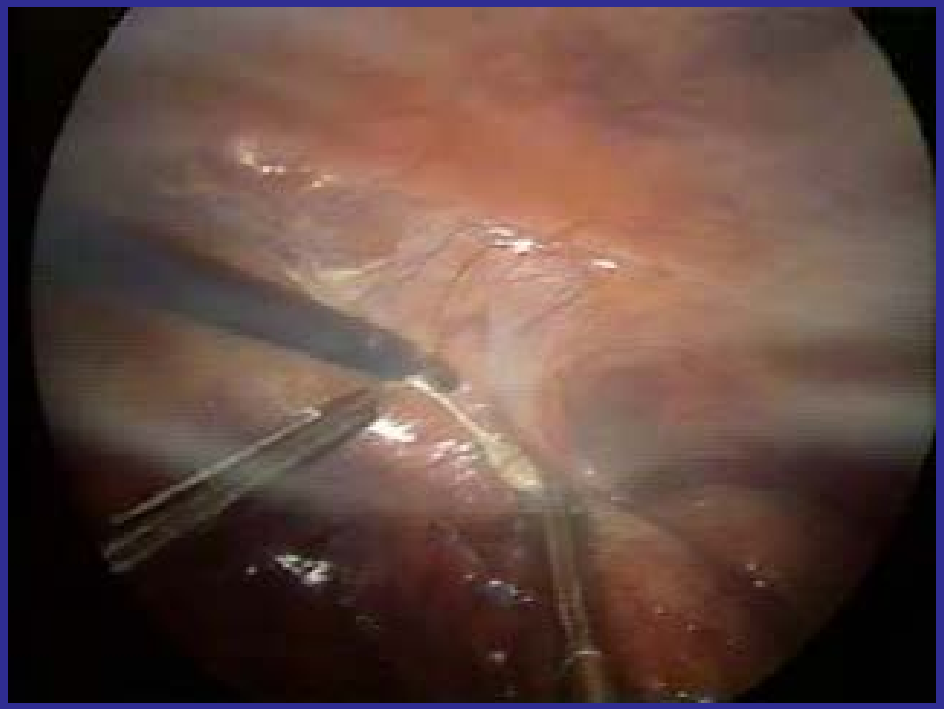
Problems with Murine Studies vs Human Setting

- 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

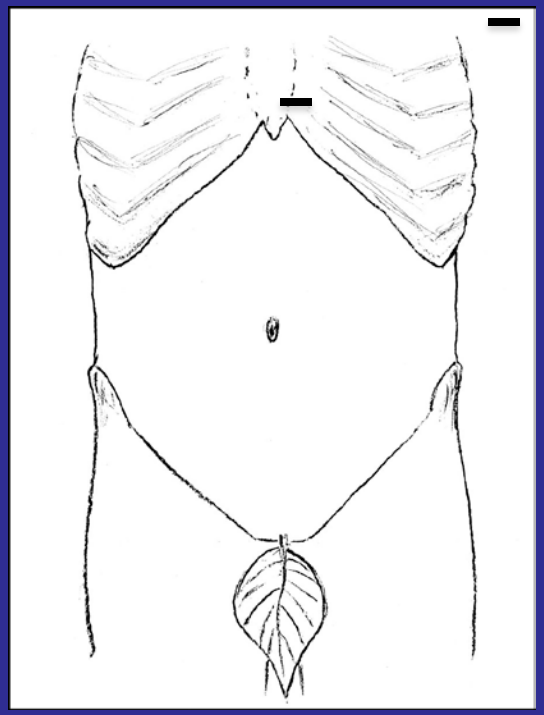
- Open and Closed methods are more alike than they are different in regards to cancer
- Intrabdominal trauma is similar
- Both methods are associated with increased rates of tumor growth after resection
- Will not cure cancer by using MIS methods alone

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

* Cranshaw et al. JAMA Surg 2015;150(5):410-5.

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