The Future of Urologic Oncology (and its Surgeon Scientists) : Promise and Peril (Guiteras Lecture-2008)

Paul Lange, MD, FACS
Nelson Chair in Urology, Professor
Department of Urology
Director: Institute for Prostate Cancer Research
University of Washington
FHCRC

Changes in Urologic Oncology from Urology Research (my career)

- **Prostate: PSA, TRUS, bx gun, ns RP, new brachytherapy**

- **Testis: AFP/hCG, ns RPLND, chemotherapy (80% cured!)**

- **Bladder: BCG, flexible cysto, PCN, ureterorenoscopy, CUR, chemotherapy**

- **Kidney: nephron sparing surgery, laparoscopy, VHL gene**

Current Senior Urology Surg/Sci Leaders in Cancer

Laboratory Training

≥ 3 Yrs.		2-3 Yrs	2 Yrs
Albertson	Lieber	Andriole	Grossman
Bander	Linehan	Brendler	Jewett
Belldegrun	Malkowitz	Flanigan	Menon
Benson	McDougall	Fradet	Sagalowski
Catalona	Messing	Lamm	
deVere White	Nelson, J	Lepor	
deWolf	Novick	Resnick	
Gomella	Partin	Scardino	
Hemstreet	Rowland	Walther	
Herr	Droller		
Klein	See		
Lange	Soloway		
	Williams		

Common Themes Surg/Sci (Cancer)

- Laboratory training (> 2 yrs)
  - lifetime into inquiry
  - alert mind
- Insights initially called serendipitous
- Insights often start at bedside or operating room
- Courage, persistence, hard work
- Not always “the expert”: collaboration
- Often did it all (busy practice/laboratory)
  - but not at the same time
- Sometimes make great advances to medicine AND science
- Mentored/inspired other Surg/Sci’s

“Of course, in retrospect so simple, right in front of our face, why didn’t we think of it sooner.”

New Simple (Radical) Ideas in Prostate Cancer

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"Of course, in retrospect so simple, right in front of our face, why didn't we think of it sooner."

- **Most men with biochemical recurrence after surgery have local-regional disease**

LANGE "STORIES" (AND FAILURES) ABOUT RADIATION THERAPY, PSA, AND LOCAL RECURRENCE (published)

- **RT after RP: IT CAN BE DONE SAFELY, MAYBE EFFECTIVE**
  - Lange, P.H. and Narayan, P.: Understaging and undergrading of prostate cancer: Argument for postoperative radiation as adjuvant therapy. Urology, XXI(2):113-118, 1983.

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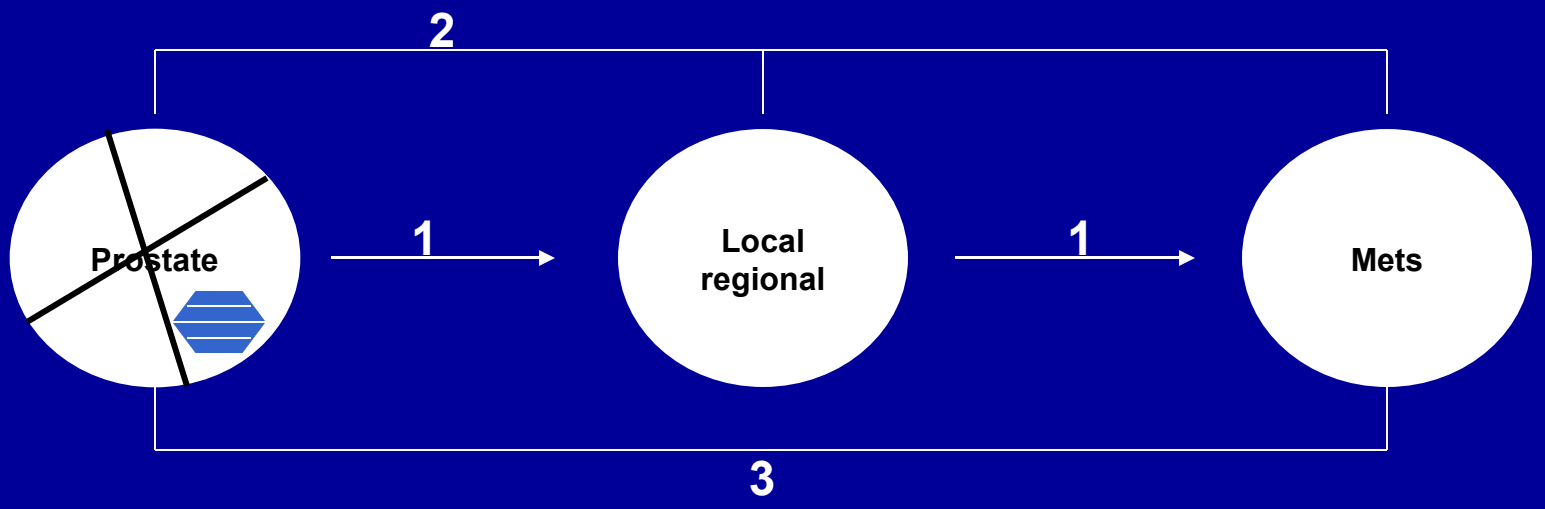
- **In biochemical recurrence (BCR) where is the disease!!!!!!**

BCR and Risk Groups (5 yr)*

Low risk:	12%
Intermediate risk:	37%
High risk:	52%

*Klein 07

Where is Disease When PSA Elevated After RT



My View: Usually its 1 or 2!

Persistent Disease After RP is Usually Local (+/- Mets)

- **Clinical local recurrence (crude)**
  - W/W vs Adj RT[2]: 3x less (15 → 5%) (7 yrs)

- **Needle biopsy prostatic fossa (better)**
  - "blind": Lightner - 1990
  - TRUS: Abi-Aba - 1992
    Foster - 1993

  } 42-49%

  - MRI: Scardino - SPORE '06: 49%
    - retrovesical (40%), anast (29%), SV (22%), SM (9%)

- **Salvage RT (best evidence)**

1. Holmberg, NEJM 2002
2. Bolla, Lancet 2005

Salvage RT (Stephenson et al)*

- PSA: - ↓ by 50% in > 80%
  - to <0.2 in >90% if initially <1.0

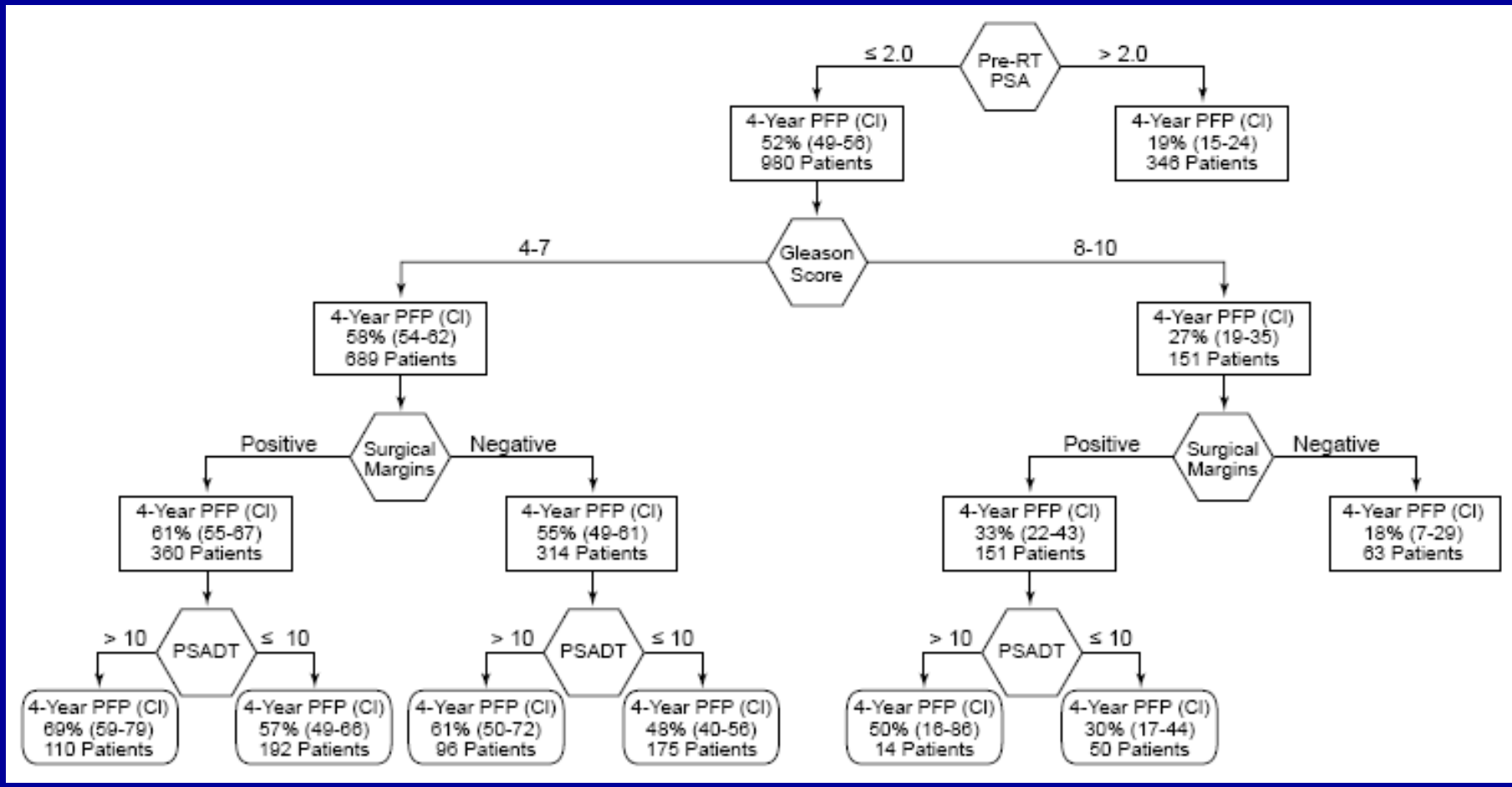
- bNED: ↓ 38% (5 yrs)
  19% (10 yrs) - old criteria and techniques

- PSA to < 0.1 ng/ml (CR): 57%
  - if CR: 50% bNED 6 yrs
  - if nadir > 0.1: only 1% FOD 6 yrs

- Risk Factors:
  - pre-RT PSA, PSADT, Grade: nomogram
  - even high risk sometimes "cured"

*Stephenson et al, AUA 2006, #1192

Outcome of 1296 Patients Treated by Salvage Radiotherapy Alone (No ADT) Stratified by Pre-Radiotherapy PSA, Gleason, Surgical Margins, and PSADT



Stephenson et al, AUA 2006, 1193

Why Does Salvage/Adj RT Fail

- Concomitant micro mets
  - **early mets in high risk**
  - **deteriorating bNED at 10 yrs**

- **RT does not sterilize local field**

- positive biopsy after salvage RT: 28% (4/14)*

- older dosimetry studies

- traditional fields missed (Russell, Lange, et al-I press-8 years!!!)

*Lange, JU, 1990

Prostatic Fossa Fields for Adjuvant or Salvage Radiotherapy

- 26 post-radical prostatectomy patients
- Comparison of AP & LAT radiation field margins to location of prostatic fossa surgical clips
- 77% (20/26) of LAT portals had rectal margin ≤ 1 cm
- 54% (14/26) of AP portals had lateral edge margin ≤ 1 cm

Ellis, Miller, Russell et al. Abstract #1005. IJROBP 1999; 45(3) Suppl.

New Simple Ideas in Prostate Cancer

"Of course, in retrospect so simple, right in front of our face, why didn't we think of it sooner."

- **Most men with biochemical recurrence after surgery have local-regional disease**
  - PSA declines in most after salvage RT if PSA ≤ 1 ng/ml
- **We often have not been getting the first echelon of lymph nodes in prostate cancer**
  - With sentinel node detection and extended lymphadenectomy, 60% of N+ are outside traditional lymphadenectomy field (e.g. internal iliac artery)

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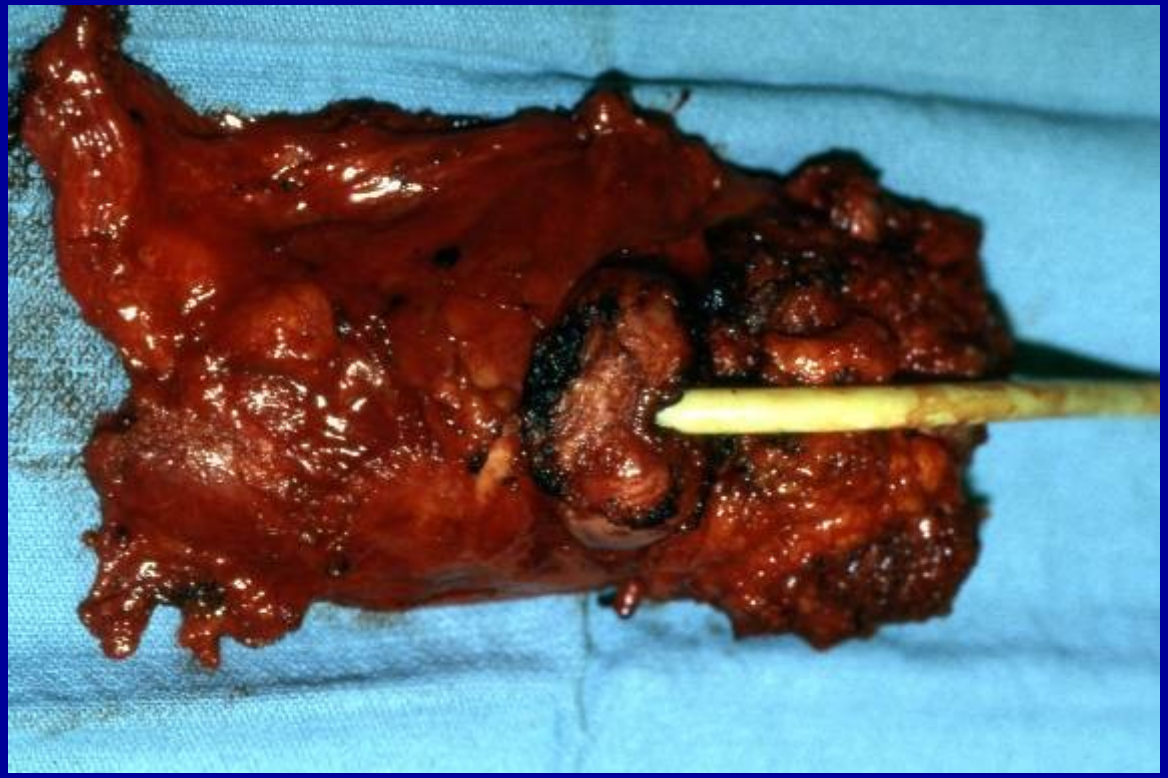
- **WE'RE DOING THE WRONG LND, ALMOST ALL BIOCHEMICAL RECURRENCE (BCR) HAS LOCO-REGIONAL DISEASE**
  - -LN drainage in monkeys and in cystoprostaqtectomy (unpublished)
  - -cystoprostatectomy and CUR in high risk prostate cancer-n=18 (unpublished)
  - -"if we could cut people in half, we would cure much more prostate cancer" JU, 06

- **In BCR where is the disease!!!!!!!**



Exenterative Salvage Surgery for locally advanced prostate cancer

Hong Gee Sim, Daniel W. Lin, Celestia Higano, William J. Ellis and Paul H. Lange

Introduction & objective

Surgical management of locally advanced prostate cancer remains a challenging problem because of the poor functional and oncological results associated with contemporary series of salvage radical prostatectomy and treatment of hormone refractory disease. We present a series of locally advanced prostate cancer managed with cystoprostatectomy and reviewed the results.

Method

Retrospective data collection and analysis of 62 men with advanced prostate cancer who underwent cystoprostatectomy between 1 September 1989 to 1 September 2005 was performed. The pre-operative demographic profile, peri-operative parameters and functional and oncological outcome were reviewed and analyzed.

Results

Demographic profile:

The mean age at diagnosis of prostate cancer was 57.8 ± 8.1 years and the mean age at cystoprostatectomy was 63.7 ± 8.4 years. The mean time from primary treatment to cystoprostatectomy was 81 ± 145 months. PatientsÕ presenting symptoms mainly relate to the lower urinary tract (bladder and outlet obstruction 27/62, urinary retention 6/62, ureteric obstruction 4/62, hematuria 4/62) and lower gastrointestinal tract (rectal/pelvic pain 4.62, hematochezia 2/62, bowel obstruction 2/62). Surgery was indicated for radiation failure in 26/62 patients, hormone refractory disease in21/62, as primary surgical therapy in 14 patients and as treatment for recurrence after primary radical prostatectomy in 1 patient.

Standard lymphadenectomy(SLND) vs. Extended LND(ELND)

- Heidenreich et al (Marberg) - JU: 2002
  - ELND(103) vs SLND(100)
  - 28 vs 11 nodes, 26% vs 12% N+, 42% O/S SPLND
  - L. Risk: 2.8% vs HR-26%
- Bader et al: (Berne) - JU: 2002
  - Organ confined disease (clinical): EPLND
  - 24% N+
  - 2/3's O/S SLND
  - Internal iliac artery (+/-) - 58%
    - IIA alone - 19%
- Wanroschek et al (Augsberg) - Euro Urol & Urol Int: 1999, 2003
  - SLN detection and ELND: N = 200
  - in intermediate and advanced: 35%
  - in good risk: 12% (??)

SLN (sentinal node) DETECTIOIN IN 1000 CASES(AUGSBURG)*

- SLN and ELND only if SLN+
  - SLN+/ELND+ = 96% (1% false negative)
  - HR: SLN and ELND in all
- N+: 20%
- LR-0, IR- 7%, HR-22%
- LOCATION:
  - 63% o/s of SLND
  - IIA ALONE - 22%
  - IIA (+/-) - 53%
  - IIA (+/-) & OTHER (MEDIAL) - 63%
-

*Wachermann et al
JU 177: 916, 2007

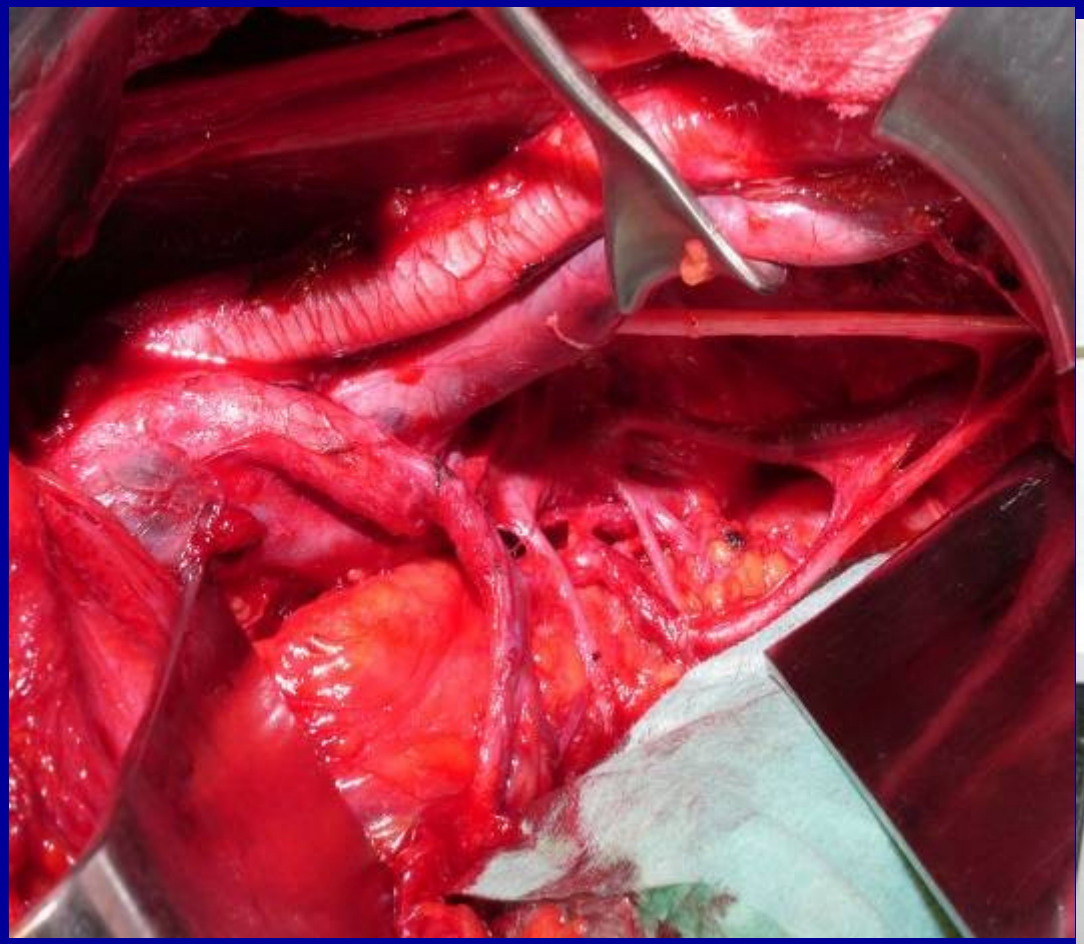
LN Micro-mets and Survival

- **% N0/PCR- IHC IN N0 AND BCR(1):**
  - **IHC+ = CTK+ & PSA**
  - **N = 180 N0**
  - **13 % IHC+ in N0**
  - **MVA: at 10 yrs, IHC+ significant for BCR**
  - **IHC+ = N= for BCR (61% vs 69%)**

- **PSA +/or PSMA RT-PCR IN NO AND BCR(2)**
  - **N = 109 No**
  - **30% PCR+ in No**
  - **IHC+/PCR+ = 56% pts, 44% nodes**
  - **BCR: 72% N+, 53% No/PCR+, 9**

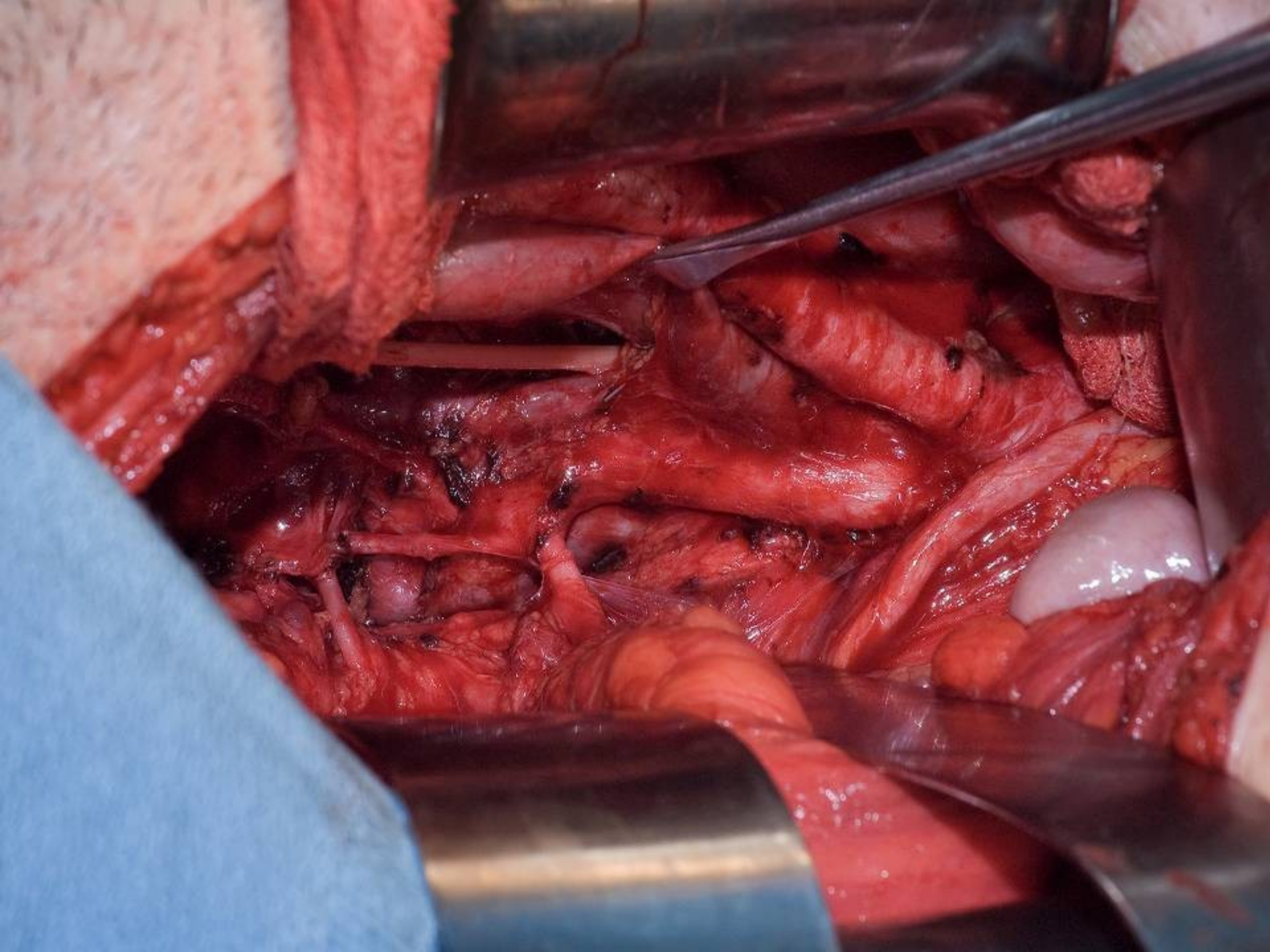
1)PAGLIARULO ET AL(USC)
JCO. 18: 2735,2006
2) MIYAKE (JAPAN)
CLIN. CAN RES 15: 1192,2007

Intraoperative Localization of Primary Lymphatic Landing Sites*



Gamma-probe guided search

*Studer, 2008



New Simple Ideas in Prostate Cancer

"Of course, in retrospect so simple, right in front of our face, why didn't we think of it sooner."

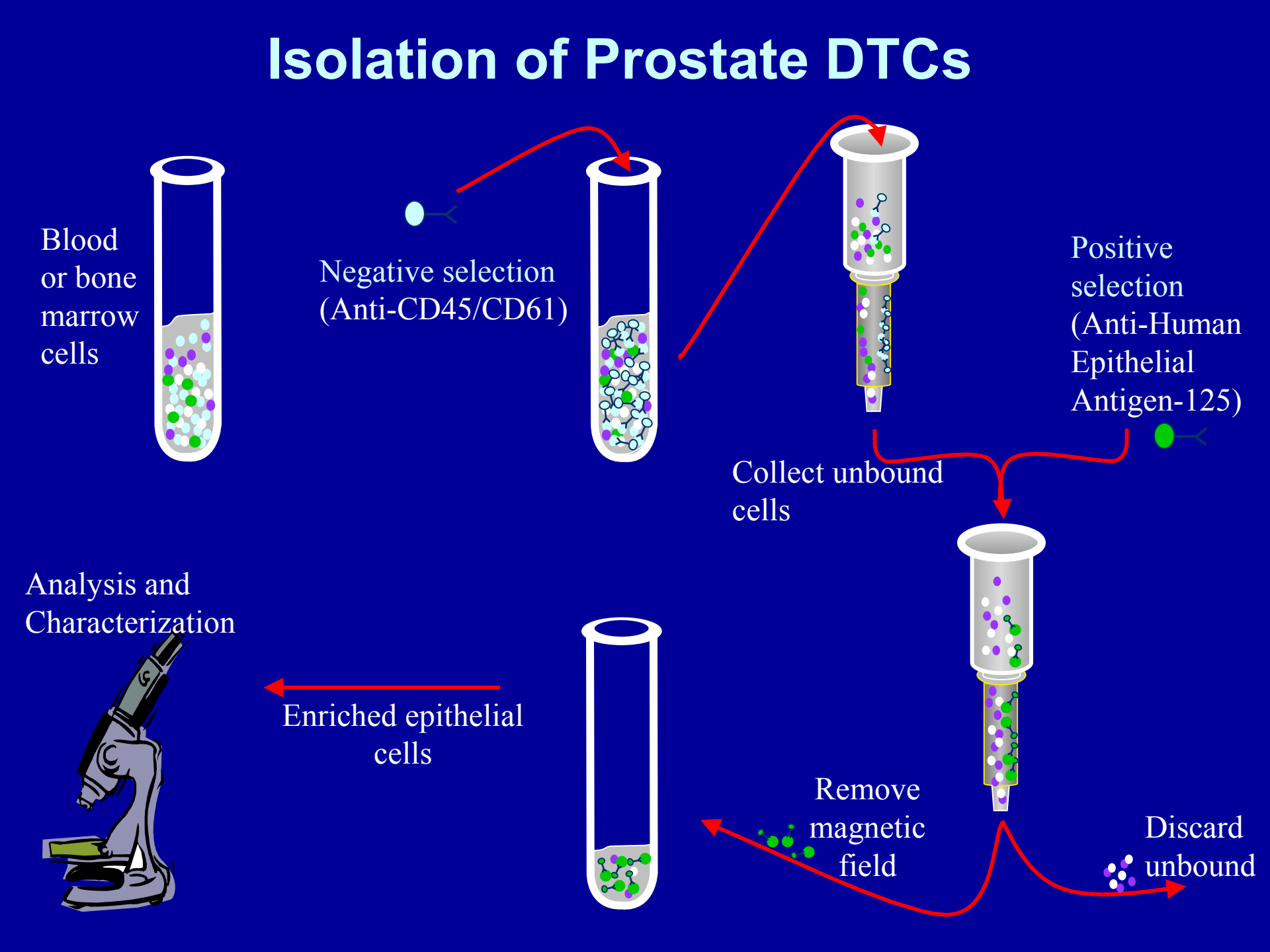
- **Circulating prostate cancer cells present in bone marrow**
  - in most before RP
  - in many after RP
  - necessary but not sufficient condition for biochemical recurrence

Disseminated Tumor Cells

- CTC = "circulating" → **blood**
  - Half-life ~1-3 hours[2]
  - Prognostic in metastatic breast cancer
- DTC = "disseminated" → **bone marrow**
  - Unknown half-life
  - No clear prognostic significance

[2]Meng, S. et al. Clin Cancer Res, 2004

Isolation of Prostate DTCs



Spectrum of Patients who Possess DTC

	Percent of patients
Normal >50 yo	**1/15 7%**
Normal <50 yo	**2/15 13%**
Before RP	395/537 74%
Post-RP NED < 1yr	14/28 50%
Post-RP NED 1-5 yrs	19/27 70%
Post-RP NED > 5 yrs	25/49 51%
Untreated recurrence after RP	19/24 79%
Metastatic - Hormone sensitive	7/15 47%
Metastatic - Hormone refractory	21/30 70%

Few
+ normals

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The majority of patients +

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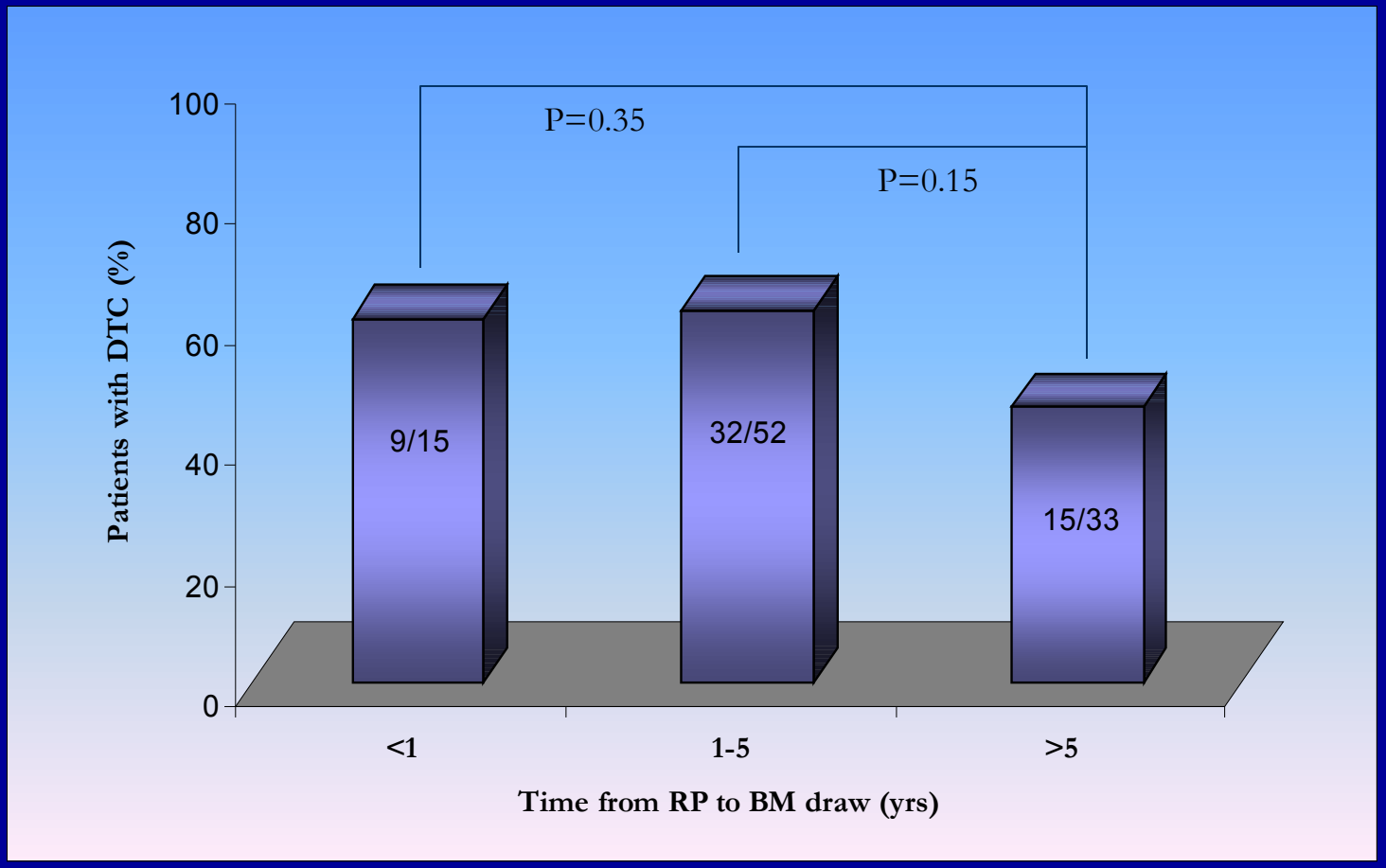
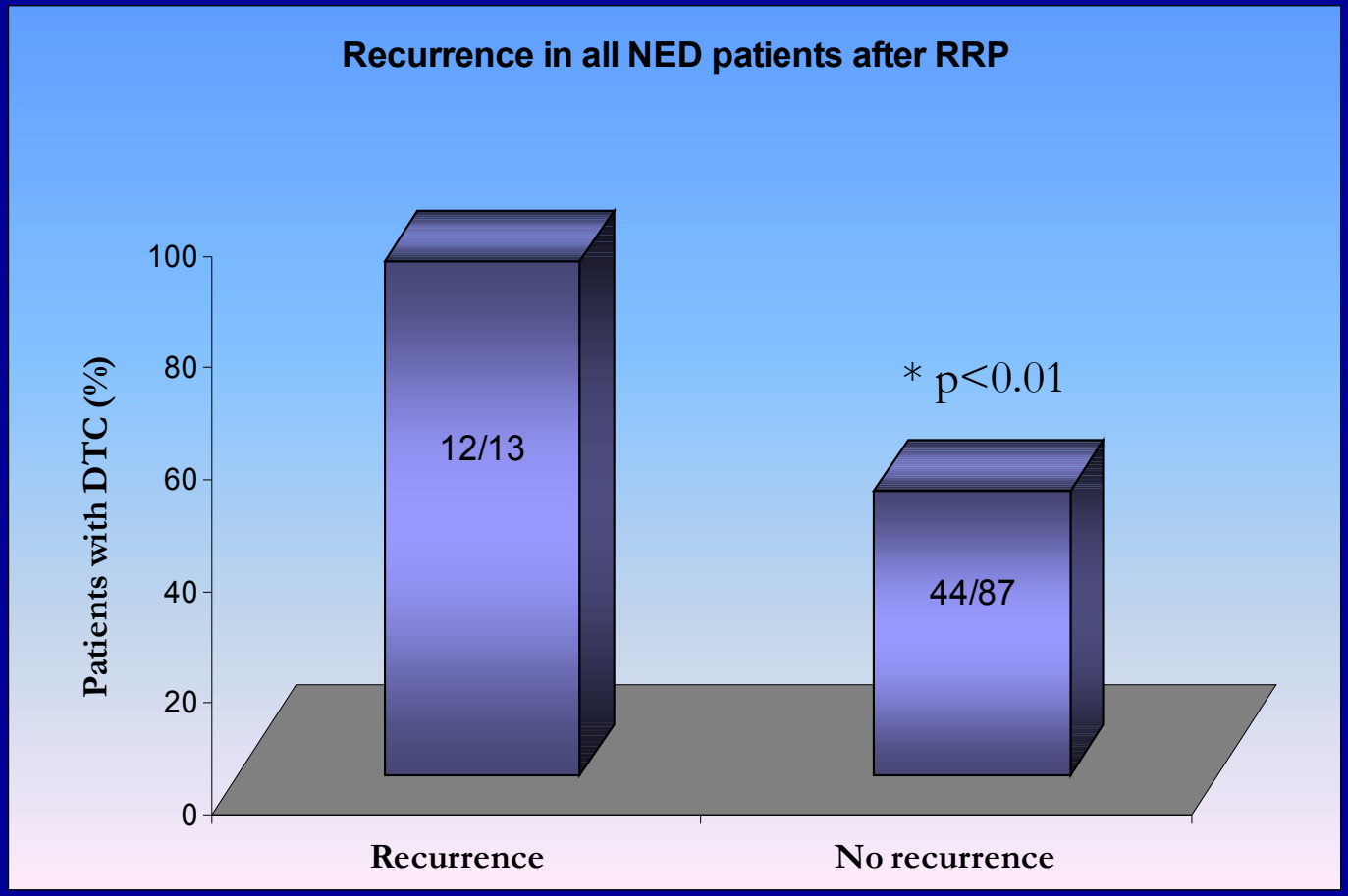
Presence implies dormancy, especially at 5+ years.

DTC and Patients NED after RP



- 46-62% (mean 56%) DTC detection in patients NED after radical prostatectomy

Recurrence in NED Patients



- Recurrence: PSA ≥ 0.4 ng/ml or salvage radiation Rx
- Only 1 patient without DTC at NED draw has recurred to

Cox Proportional Hazards Model- Time from BM

Variable	Hazard ratio	95% CI
DTC	**13.48**	**1.15-158.02**
PSA		
<10	Referrent	
>10	1.21	0.18-7.95
Grade		
5-6	Referrent	
7	5.57	1.26-24.68
8-10	4.83	0.28-82.72
Stage		
T2	Referrent	
T3-4, any N	1.38	0.30-6.36
Margin (+)	2.27	0.64-8.08
Age		
40-57	Referrent	
58-65	0.97	0.15-6.32
>65	1.63	0.32-8.31
Race	1.01	0.11-8.6

Abbreviations: DTC, disseminated tumor cells; PSA, prostate specific antigen

Early Conclusions

- DTC present in 70% before RP
  - -no correlation with standard pre-RP variables
- 56% of men NED post -RP have DTC
- Presence of DTC in men NED post RP is significant risk factor for biochemical recurrence
  - - “necessary but not sufficient” (HR 4.5)
  - - tumor dormancy
  - - are they really tumor cells (<8% in “normals”), and if so, can they be differentiated to provide clinical value
- Molecular characterization : FISH(chrom. 8 abn’s) telomerase activity, cDNA microarray, aCGH

Genomic Results*

- DTC in patients with local disease pre-RP (LDC)
  - Statistically distinct from normal cells
  - On average, 14 sites of genomic change
  - In comparison to primary tumor, several similarities
  - Alterations in LDC often detected in ADC but not visa versa

- DTC in patients with advanced disease (ATC)
  - On average, 32 sites of genomic change
  - Perturbations include those frequently altered in metastatic prostate cancer (8q,10q,13q,16q)
  - Include a deviation only seen in hormone refractory prostate cancer (Xq gain about AR)
  - Profile is much more chaotic

$\Rightarrow$ Suggests an evolution of changes over time

* Can. Res. (in press)

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- **Circulating prostate cancer cells present in bone marrow**

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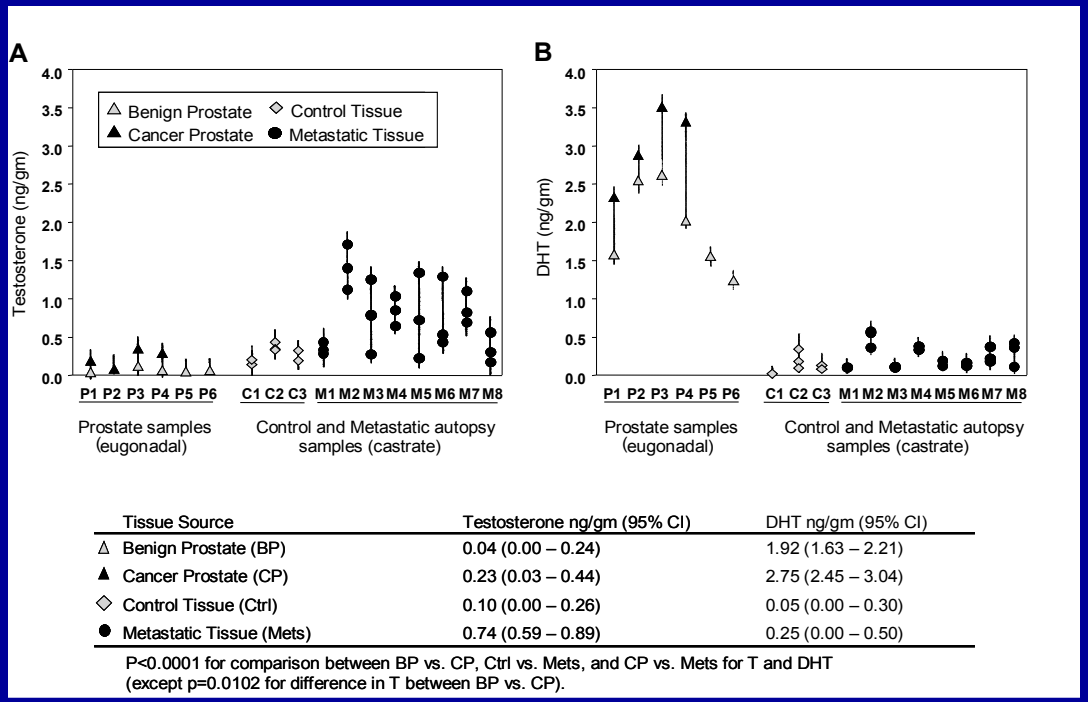
In castrate resistant prostate cancer, the tissue can still make androgens

- tissue androgen and AR levels sufficient for androgen stimulation
- enzymes converting cholesterol to androgen upregulated

Prostate Androgen Activity with Biochemical Castration (Normals)

- Androgen levels after castration
  - serum levels clearly decreased
  - prostate levels decreased about 75%, but detectable
- Heterogeneity in tissue androgen levels after castration, despite uniform decrement in serum levels
- Heterogeneous changes in androgen regulated genes observed in untreated vs. castrate subjects
- Several known androgen regulated genes were strongly down-regulated after castration (e.g. NDRG1, FKBP51, TMPRSS2) . However, many genes described as androgen-regulated (AR, PSA, ACPP, NKX3.1, ANKH, KLK2, TMEPAI) were ***not altered*** in the castrate subjects

Tissue androgens in primary and metastatic human prostate cancer



Tissue Source	Testosterone ng/gm (95% CI)	DHT ng/gm (95% CI)
△ Benign Prostate (BP)	0.04 (0.00 – 0.24)	1.92 (1.63 – 2.21)
▲ Cancer Prostate (CP)	0.23 (0.03 – 0.44)	2.75 (2.45 – 3.04)
◇ Control Tissue (Ctrl)	0.10 (0.00 – 0.26)	0.05 (0.00 – 0.30)
● Metastatic Tissue (Mets)	0.74 (0.59 – 0.89)	0.25 (0.00 – 0.50)

P<0.0001 for comparison between BP vs. CP, Ctrl vs. Mets, and CP vs. Mets for T and DHT (except p=0.0102 for difference in T between BP vs. CP).

- Primary and metastatic prostate cancer maintains tissue androgen levels adequate to support survival
- Transcripts for enzymes of steroidogenesis are upregulated in resistant prostate cancer
- Castrated CaP xenografts maintain tumor androgens in the absence of measurable DHEA
- Targeting tumoral androgen metabolism provides a new means of improving efficacy of androgen ablation

Targeted Androgen Pathway Suppression TAPS

Clinically localized prostate cancer

- **T1-T3**
- **Gleason ≥ 7**
- **PSA < 40**

→

- **LHRH agonist + dutasteride**
- **LHRH agonist + dutasteride + casodex**
- **LHRH agonist dutasteride, casodex, ketoconazole**

(3 months) →

PROSTATECTOMY

Endpoint: Tissue androgens at RP

Conclusions

- Most men after RP (?RT) with BCR have logo-regional disease

- More N+ at RP then heretofore realized
  - have not been getting first echalon

- Most men before RP and many after RP have tumor cells in their bone marrow

- In castrate condiditons (normals, Cap-hormone responsive and hormone resistant), the prostate tissue can make and response better to androgens

WHAT'S GOING ON!!!!

Insuring the Future of GU Oncology and the Surg/Sci

- Articulate and celebrate Surg/Sci
- Provide emotional and resource support
- Codify training
- Alter the specialty/subspecialty
  - Society of Urologic Oncology (SUO) leadership retreats
    - 7/05
    - 12/05
    - 2/06

Urologic Oncology not Viewed (Inside and Outside) as Distinct Robust Discipline Either Organizationally, Cognitively, or Technically

- **Uro Onc is really not "special"**
  - **Training now mostly technical**
- **Clinical trials participation meager and/or fragmented (in USA)**

We are Increasingly "Challenged" by Other Disciplines

- Interventional Radiology
  - "Interventional Oncology"
- Medical Oncology

SUO Retreat Resolutions

- Cancer should be multi-disciplinary but ideally a knowledgeable urological oncologist should be the quarterback

  - knowledge of the organ, it's diseases and perturbations vital

  - best for optimal care and progress

SUO Retreat Resolutions

- **Promote/support surgeon scientists**
- **Encourage and embellish SUO Fellowships**
  - **Increase participation in systemic therapy and clinical trials**
  - **Develop qualifying test**
  - **Accreditation**
  - **Think about certification**

SUO Retreat Resolutions

- **Promote/support surgeon scientists**
- **Enlarge and embellish SUO Fellowships**
- **Facilitate practicing urologist's activity in IR procedures and systemic therapy**

  - **SUO clinical trials program**

  - **Systemic therapy CME courses**
    - **IR courses later**

EUA: "Open Form"

- "One or two operations seem to so bedazzle the trainees and indeed younger consultants that they seem hell bent on ending up like cardio thoracic surgeons"*

- "Urological disease will always be there and urologists are best placed and adapted to treat it, be it by surgery or some other medical therapy. If we persist in a luddite belief that we are only surgeons then there will be very few urololgists left"*

* Peter Whelan (Leeds), 06

Does ELND or SLND Affect Survivals

NO:

- Capsure: 5 yr bNED same with and without LND[1]

- Mayo: 10 yr. bNED (TxNo) same b/t SLND & "ELND" [2]

(1) Bergland JU, 2007
(2) Dimarco, JU, 2005

Does ELND or SLND Affect Survivals

YES:

- Berne: 39% bNED in N+ with ELND at 4 yrs[1]
- JHH (SLND vs "ELND")[2]
  - : N+=1% vs 3%
  - : BCR-90% vs 56%
- SEER (n=13020)[3]
  - : CCS with >10 nodes > in No
- SKMCC (# nodes removed & BCR) [4]
  - : increasing nodes, increasing N+
  - : in No, ↑ nodes , ↓BCR (HR 0.9)
- 15-20% N+ (1-2 nodes) bNED long term[5]

(1) Bader, JU, 2003, (2) Allaf, JU, 2004,
(3) Joslyn Urol, 2006, (4) Masterson, JU 2006
(5) multiple referances