

# Clinical and Pathologic Characteristics of Prostate Cancer (including new markers such as PCA3)

~ M. Scott Lucia, MD

## Prostate Cancer: Clinical and Pathological Characteristics



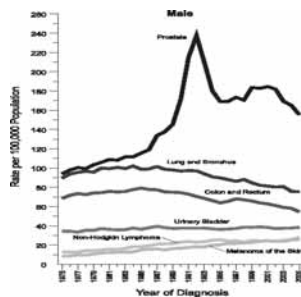
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 Dept. of Pathology  
 University of Colorado Denver SOM

## Prostatic Carcinoma - 2009<sup>1</sup>

- >192,000 new cases expected
- 27,360 deaths expected
- Lifetime risk of prostate cancer in U.S.:
  - Diagnosis: ~17%
  - Death: ~3%
- More men die *with* prostate cancer than *of* it

1. Jemal A. et al. Cancer Statistics 2009. *CA Cancer J Clin* 2009;59:225-48.

Annual Age-adjusted Cancer Incidence Rates among Males and Females for Selected Cancers, United States, 1975- 2005



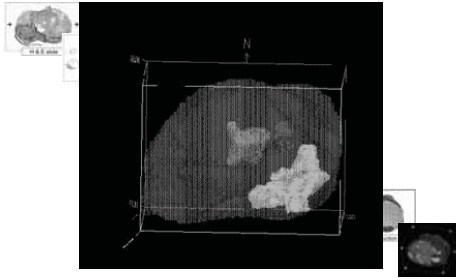
From Jemal, A. et al.  
*CA Cancer J Clin* 2009;59:225-249.



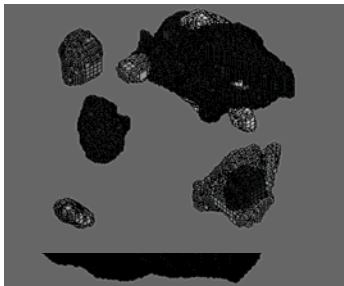
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3-Dimensional Reconstruction of Whole-Mounted Prostatectomy Specimens



3-Dimensional Reconstruction of Prostatectomy: Tumor Multifocality and Heterogeneity



**Multifocality of 293 carcinomas from 151 prostates (< 1994)**

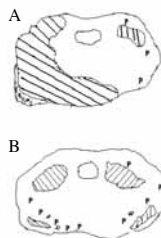
Miller GJ, J Urol 152:1709, 1994

Tumors/Pt.	No. Pts. (%)	No. Tumors	Mean Tumor Vol. (cc)
1	66 (43.7)	66	6.52
2	47 (31.1)	94	1.48
3	25 (16.6)	75	1.01
4	8 (5.3)	32	0.59
5	4 (2.6)	20	0.40
6	1 (0.7)	6	0.22
Totals	151 (100)	293	

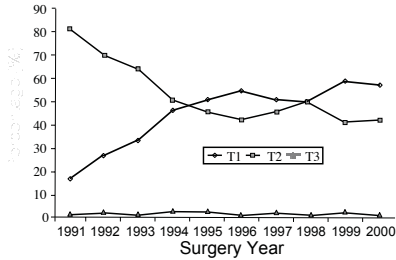
- Prostatectomies 1997-2006:
    - Solitary = 20 % (Mean vol = 2.14 cc)
    - Multifocal = 80% (range 2- 17 tumors)
- Lucia MS, Unpub

Representative Diagrams of Prostate Cancer and HGPIN in Early 1990s (A) and Present (B)

- A. Tumors were larger, more confluent and more advanced
- B. Tumors now smaller, more multifocal and more localized

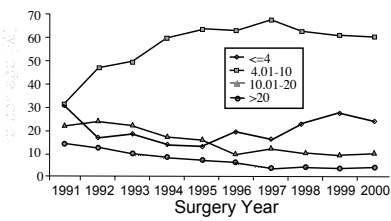


DoD CPDR National Database: Clinical T stage at diagnosis for patients who underwent prostatectomy



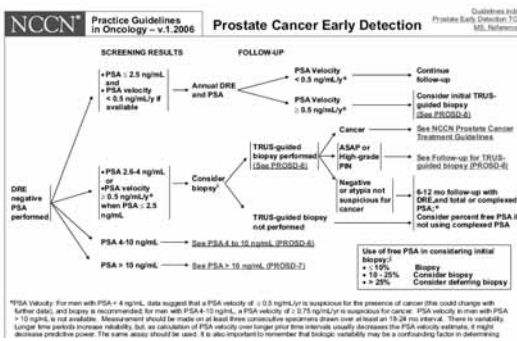
DoD = Department of Defense  
CPDR = Center for Prostate Disease Research  
Moul JW, et al. Surgery 2002;132:213-9  
© 2002, Mosby, Inc.

DoD CPDR National Database: PSA level at diagnosis for patients who underwent prostatectomy



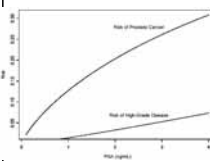
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NCCN Guideline For Prostate Cancer Screening



Prostate Cancer in "Normal" PSA  
(PCPT Placebo Arm)

PSA, overall & high-grade (Gleason 7+) prostate cancer			
PSA ng/ml	No. of men	No. (%) with prostate cancer	No. (%) of cancer with high-grade
≤ 0.5	486	32 (6.6)	4 (12.5)
0.6 - 1.0	791	80 (10.1)	8 (10.0)
1.1 - 2.0	998	170 (17.0)	20 (11.8)
2.1 - 3.0	482	115 (23.9)	22 (19.1)
3.1 - 4.0	193	52 (26.9)	13 (25.0)
Total	2950	449 (15.2)	67 (14.9)



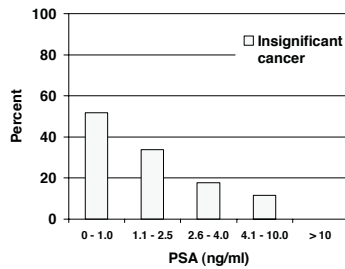
Thompson et al. JAMA 2005; 294: 66-70

PSA as a Marker for Prostate Cancer

PSA	Sensitivity	False positive rate
1.1	82.0	59.4
1.6	67.4	41.2
2.1	54.4	29.2
2.6	43.6	20.4
3.1	35.8	14.9
4.1	24.5	7.7
6.1	5.4	2.0
8.1	2.0	0.9
10.1	1.0	0.5

Thompson et al. JAMA 2005; 294: 66-70

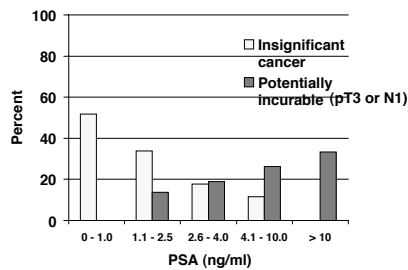
PCPT: PSA and Insignificant Cancer\*



\* GS≤6, <3 cores with cancer, no core with >50% tumor

Lucia MS, et al. Cancer Prev Res 2008;1:167-73.

PCPT: PSA and Insignificant Cancer\*



\* GS≤6, <3 cores with cancer, no core with >50% tumor

Lucia MS, et al. Cancer Prev Res 2008;1:167-73.

Prostatic Carcinoma: Issues for Screening and Detection

- Serum prostate specific antigen (PSA)
  - A continuum of risk over all values
- Digital rectal exam
  - Poor sensitivity
- Random biopsy schema
  - Sampling issues
  - Significant vs "Insignificant" tumors



### Ideal Biomarker for Prostate Cancer

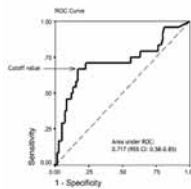
- Sensitive and specific for aggressive cancer
- When modulated, correlates with disease outcome
- Reproducible
- Quick and easy to assay
- Low cost
- Minimal invasiveness

### New Biomarkers for Prostate Cancer Detection: PCA3

- First described in 1999 as DD3\*
- Non-coding RNA
- Unknown function
- Prostate specific, highly overexpressed in more than 95% of prostate cancers
- Not detected in any other tissue or cancer

\*Bussemakers *et al.*, Cancer Res 1999;59:5975-5979

### RNA Analysis of PCA3 Gene in Urinary Sediments



- Ratio PCA3:PSA is used as a quantitative measure
- Ratio PCA3:PSA is consistently higher in samples from cancer patients

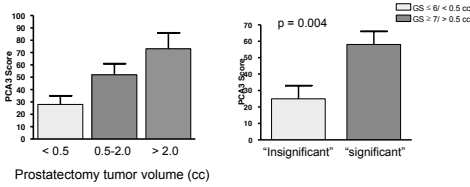
Hessels *et al.*, Eur Urol 2003;44:8-16

### Validation Studies - PCA3

	Patients	Sensitivity	Specificity	Negative predictive value
Hessels <i>et al.</i> , 2003	108	67%	83%	90%
Tinzi <i>et al.</i> , 2004	158	82%	76%	87%
Fradet <i>et al.</i> , 2004	443	66%	89%	84%
Groskopf <i>et al.</i> 2006	122	69%	79%	

Hessels *et al.*, Eur Urol 2003;44:8-16  
Tinzi *et al.*, Eur Urol 2004;46:182-186  
Fradet *et al.*, Urology 2004;64:311-315  
Groskopf *et al.* Clin Chem 2006;52: 1089-1095

PCA3 score as a function of tumor volume and Gleason score

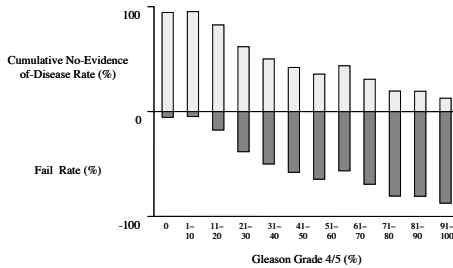


Nakanishi, H et al. J Urol 2008;179:1804-9. Used with permission

Pathology of Prostate Cancer:  
Assessing Aggressiveness

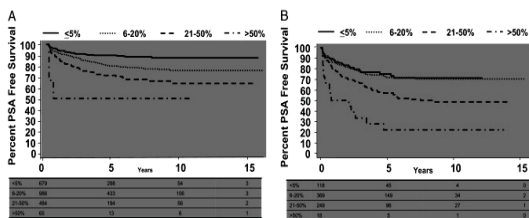
- Histologic type and grade
- Pathologic stage
- Margin status
- Tumor volume
- Biomarkers/molecular determinants?
  - Systems pathology – can we improve on traditional pathology?

Failure Rates as a Function  
of Percent GS 4/5 Cancer



Stamey TA, et al. JAMA. 1999;281:1395-400. Copyrighted 1999, American Medical Association.

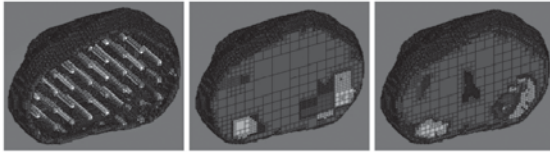
Actuarial 15-year Estimates of Biochemical  
Progression Rates Segregated by Percent  
Tumor Involvement



Rampersaud EN, et al. J Urol 2008;180:571-76  
© 2008 American Urological Association



Improved tumor sampling with saturation biopsies leads to improved detection and grading – implications for targeted therapy

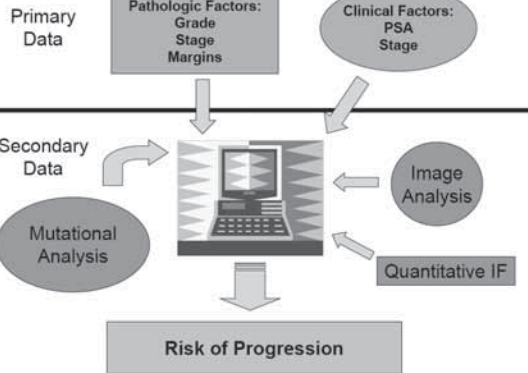
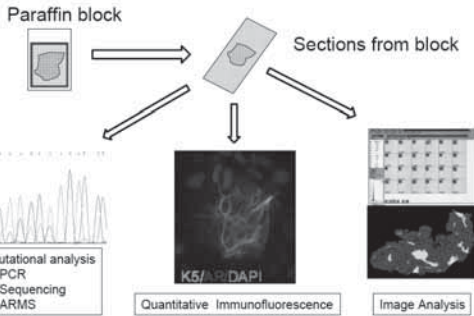


- Saturation grid-biopsy data (left)
- Reverse-reconstruction model (center)
- Actual RRP specimen (right)
- Model error: -15% for Gleason 3+4 tumor (right, 5.1cc)  
+15% for Gleason 3+3 tumor (left, 0.093cc)

Crawford et al, *BJU Int* 96:999-1004, 2005

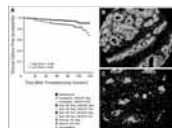
**Systems Pathology**

Definition: Analyzing the interrelationships of multiple elements (molecular and pathological) in a system rather than each one at a time



**Systems Analysis Approach for the Prediction of Prostate Cancer Progression After Radical Prostatectomy\***

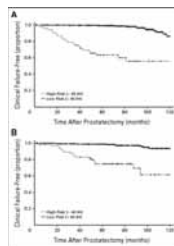
- Clinicopathologic: Grade, LN mets
- Image analysis: Pca gland lumen architecture, cytoplasm color/texture
- IF: AR, AMACR



CI=0.84

↑ Analysis of AR and AMACR

Kaplan-Meier curve demonstrating the classification of patients from the (A) training cohort and (B) validation cohort as being at low risk (blue line) or high risk (yellow line) for experiencing clinical failure (CF)



\* Donovan, M. J. et al. *J Clin Oncol*; 26:3923-3929 2008

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