Active Surveillance for Men With Newly Diagnosed Prostate Cancer: Critical Role of Pathology

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Gleason Grading System

Assign most common and 2nd most common pattern and add together resulting in Gleason Score 2-10

Gleason Scores 2-6	**Well differentiated (I/V)**
Gleason Score 3+4=7	**Moderately differentiated (II/V)**
Gleason Score 4+3=7	**Mod./poor differentiated (III/V)**
Gleason Score 8	**Poorly differentiated (IV/V)**
Gleason Score 9-10	**Undifferentiated (V/V)**

Staging

- T1 – Nonpalpable cancer on digital rectal exam
  - T1a (≤5% cancer on TURP & GS 2-6)
  - T1b (>5% cancer on TURP or GS≥7)
  - T1c (cancer detected on needle biopsy)
- T2 – Palpable cancer

In the 1980s, limited adenocarcinoma of the prostate incidentally detected on TURP was not considered as a significant disease as patients did well with short-term follow up

Patients often not even told they have cancer.

Prognosis of Untreated Stage T1a Prostatic Carcinoma: A Study of 94 cases with Extended Follow-up

Epstein JI, Paull G, Eggleston JC, Walsh PC

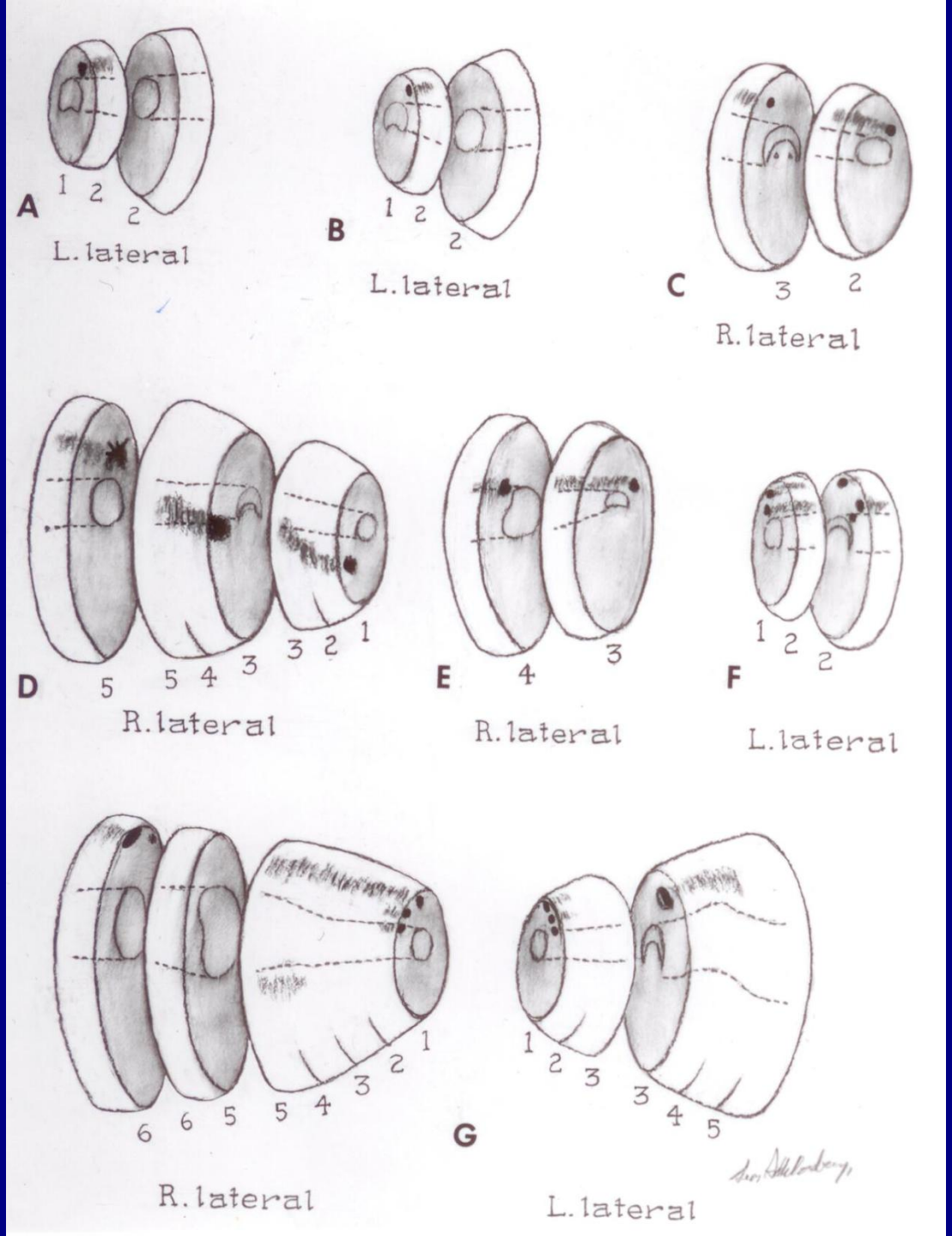
J Urol 1986

- **26/94 men died of other causes <4 years after diagnosis (mean age 75 years).**
- **Of the 50 men who remained at risk ≥8 years, 8 (16%) had progression of disease with 6 dying of prostate cancer.**

The Volume and Anatomical Location of Residual Tumor in RP Specimens Removed for Stage T1a Prostate Cancer

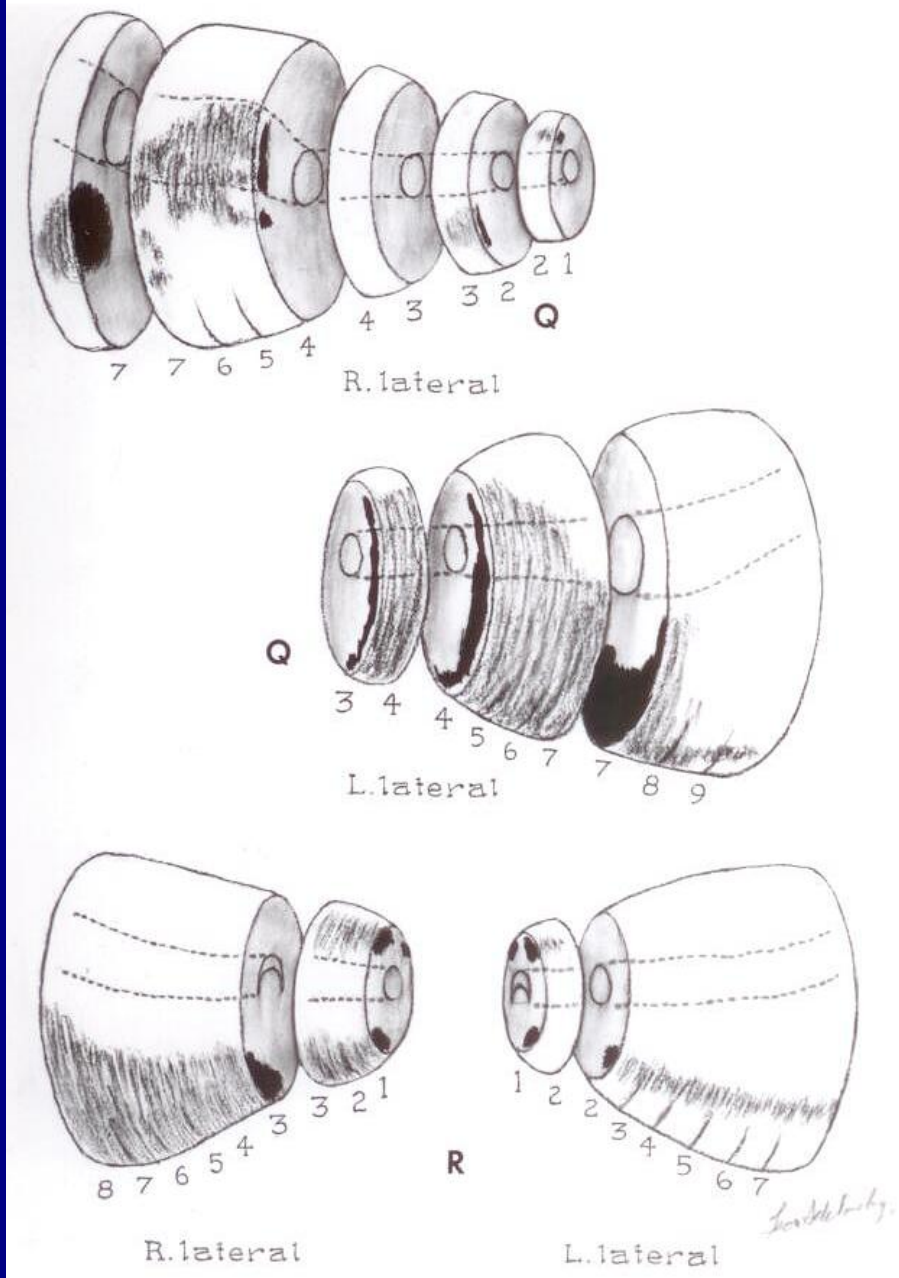
Epstein JI, Oesterling JE, Walsh PC

J Urol 1988



No Tumor
3/21 (14%)

Minimal Tumor
13/21 (62%)



Substantial Tumor
5/21 (24%)

Can Stage T1a Tumor Extent in RP be Predicted by TURP Tumor Per cent or Grade?

Larsen MP, Carter HB, Epstein JI

J Urol 1991

- 64 totally embedded RP for T1a prostate cancer.

- 6% - No residual tumor
- 74% - Minimal tumor
- 20% - Substantial tumor

- TURP cancer grade (Gleason score 2-6) and per cent (1%-5%) not predictive.

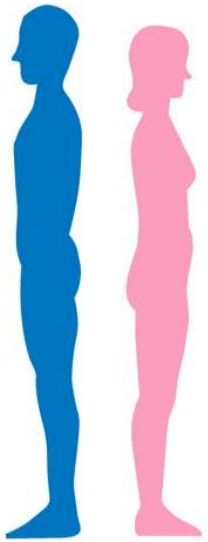
Change in Prostate Cancer Detection

- TURPs have dramatically decreased in frequency due to:
  - 1. Medical therapy for BPH
  - 2. Ablative therapy for BPH (ie. laser)
  - 3. Discovery of serum PSA test

- Currently most cancers are nonpalpable detected by needle biopsy done for elevated serum PSA levels (Stage T1c).

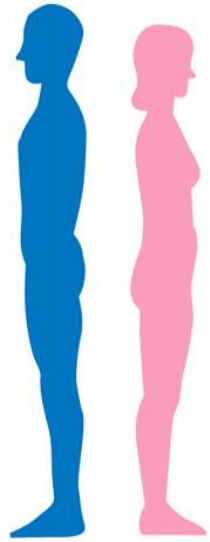
Estimated New Cases*

Males			Females		
Prostate	186,320	25%	Breast	182,460	26%
Lung & bronchus	114,690	15%	Lung & bronchus	100,330	14%
Colon & rectum	77,250	10%	Colon & rectum	71,560	10%
Urinary bladder	51,230	7%	Uterine corpus	40,100	6%
Non-Hodgkin lymphoma	35,450	5%	Non-Hodgkin lymphoma	30,670	4%
Melanoma of the skin	34,950	5%	Thyroid	28,410	4%
Kidney & renal pelvis	33,130	4%	Melanoma of the skin	27,530	4%
Oral cavity & pharynx	25,310	3%	Ovary	21,650	3%
Leukemia	25,180	3%	Kidney & renal pelvis	21,260	3%
Pancreas	18,770	3%	Leukemia	19,090	3%
All Sites	**745,180**	**100%**	**All Sites**	**692,000**	**100%**

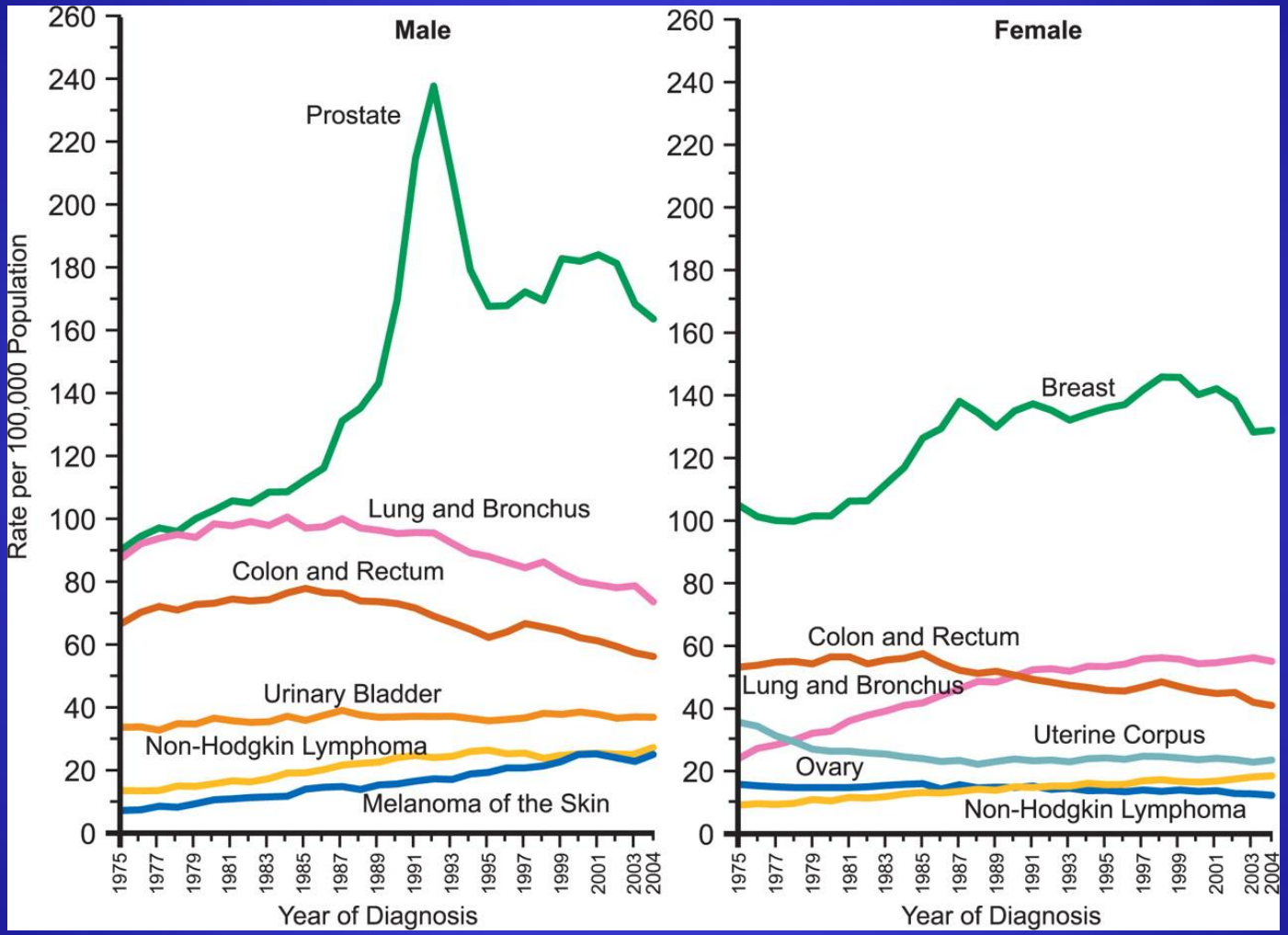


Estimated Deaths

Males			Females		
Lung & bronchus	90,810	31%	Lung & bronchus	71,030	26%
Prostate	28,660	10%	Breast	40,480	15%
Colon & rectum	24,260	8%	Colon & rectum	25,700	9%
Pancreas	17,500	6%	Pancreas	16,790	6%
Liver & intrahepatic bile duct	12,570	4%	Ovary	15,520	6%
Leukemia	12,460	4%	Non-Hodgkin lymphoma	9,370	3%
Esophagus	11,250	4%	Leukemia	9,250	3%
Urinary bladder	9,950	3%	Uterine corpus	7,470	3%
Non-Hodgkin lymphoma	9,790	3%	Liver & intrahepatic bile duct	5,840	2%
Kidney & renal pelvis	8,100	3%	Brain & other nervous system	5,650	2%
All Sites	**294,120**	**100%**	**All Sites**	**271,530**	**100%**



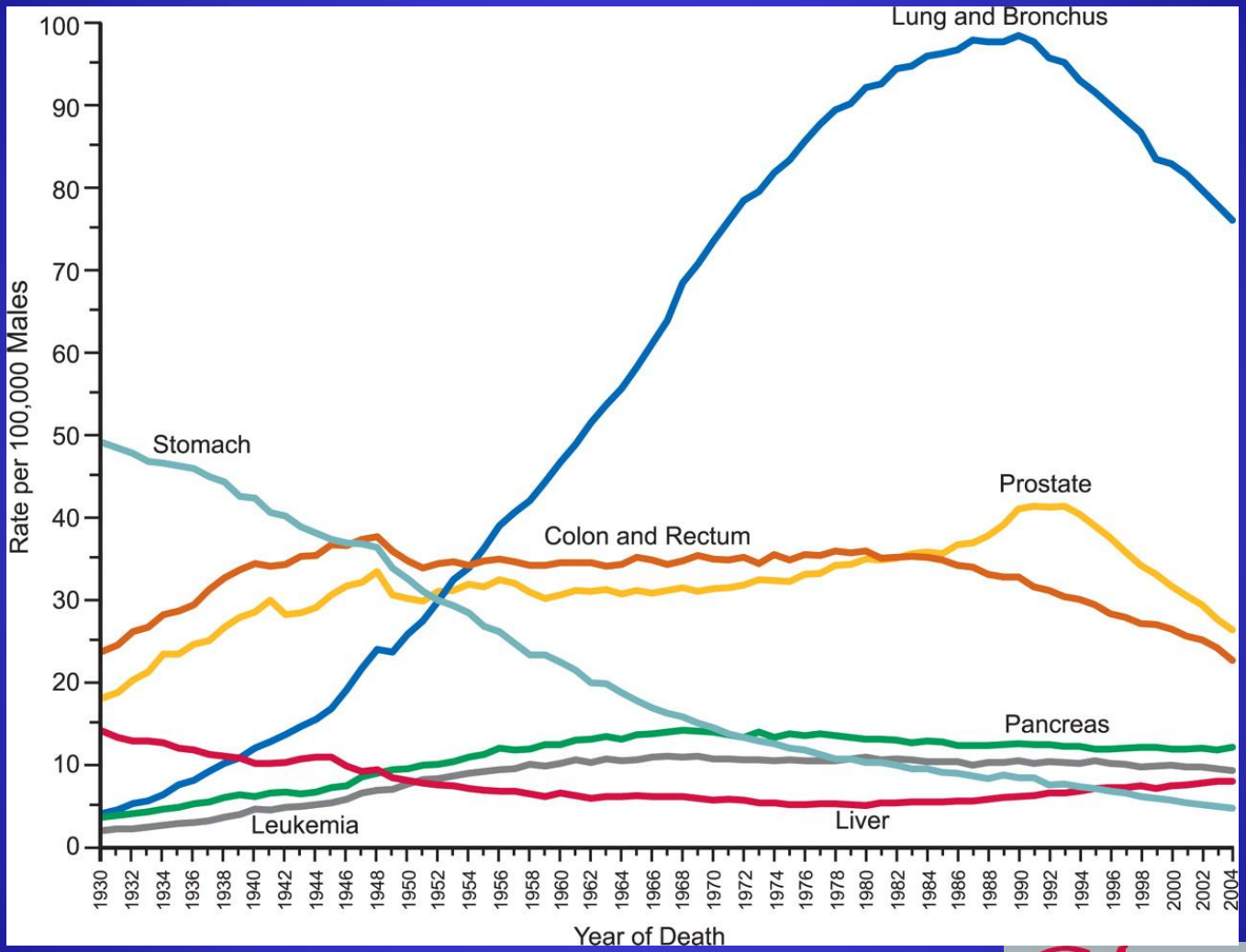
Annual Age-adjusted Cancer Incidence Rates* for Selected Cancers by Sex United States, 1975 to 2004



From Jemal, A. et al.
CA Cancer J Clin 2008;58:71-96.

CA
A Cancer Journal for Clinicians

Annual Age-adjusted Cancer Death Rates* Among Males for Selected Cancers
United States, 1930 to 2004



From Jemal, A. et al.
CA Cancer J Clin 2008;58:71-96.

CA
A Cancer Journal for Clinicians

≥50% of men with newly diagnosed prostate cancer have low risk disease (Cooperberg et al, 2003)

- **Lowering PSA trigger for biopsy**
- **More biopsy cores sampled per biopsy session**

Over Treatment of Prostate Cancer in the PSA Era

- Only 16 of every 100 patients between ages 50-70yrs with screen detected cancer will have life extended by surgery (McGregor et al, CMAJ 1998)
- 102 screen detected cancers would need to be treated per 17 lives saved at age 65yrs (Ross et al, Urology 2005)
- Treatments required to save a life double by age 75yrs and triple by age 80yrs

Most Older Men With Prostate Cancer Receive Active Treatments

Age (years)	# Men	Percentage of Men		
		Watchful Waiting	Radiation or Surgery	ADT
70-79	1263	15%	58%	27%
≥80	212	21%	21%	58%

Cooperberg et al, JNCI 2003 (data from CaPSURE)

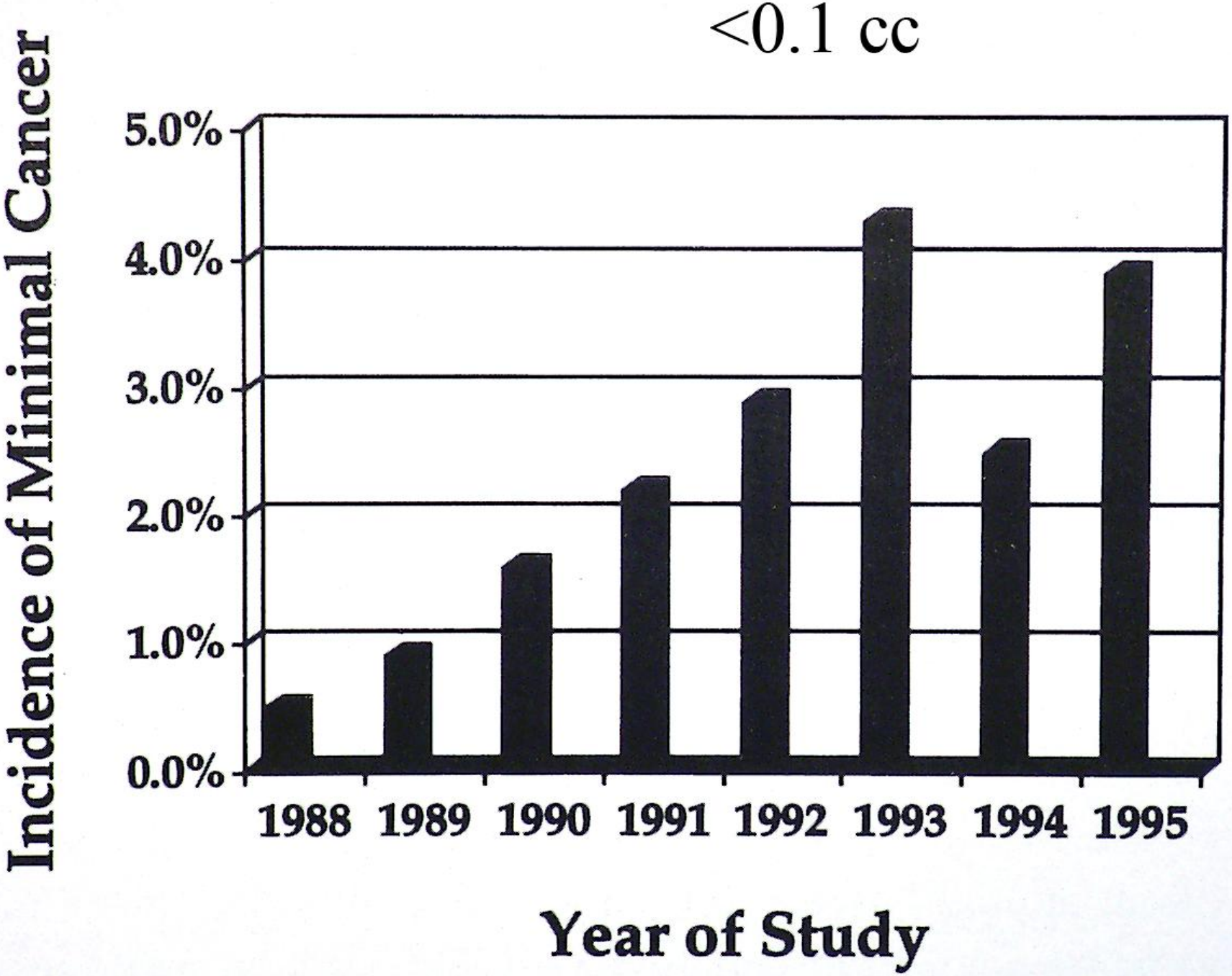
Changes in Detection and Management of Prostate Cancer Have Led to Overtreatment of Disease

- High rates of screening among the elderly
- Increasing proportion of men undergoing active treatments, regardless of grade and stage

Increasing Incidence of Minimal Residual Cancer in RP Specimens

Digiuseppe JA, Sauvageot J, Epstein JI

Am J Surg Pathol 1997


<0.1 cc
Incidence of Minimal Cancer
5.0%
4.0%
3.0%
2.0%
1.0%
0.0%
1988
1989
1990
1991
1992
1993
1994
1995
Year of Study

Little to No Residual Prostate Cancer at RP: Vanishing Cancer or Switched Specimen? A Microsatellite Analysis of Specimen Identity

Cao D, Epstein JI

Am J Surg Pathol 2005

- 31 men with minute and 10 with no residual cancer at RP
- None had prior hormonal Tx or TURP
- All 31 cases with minute cancer showed specimen identity.
- 9/10 interpretable cases with no cancer showed specimen identity.
- 1 mismatch case had GS 4+4=8 9.6 mm with PNI on biopsy

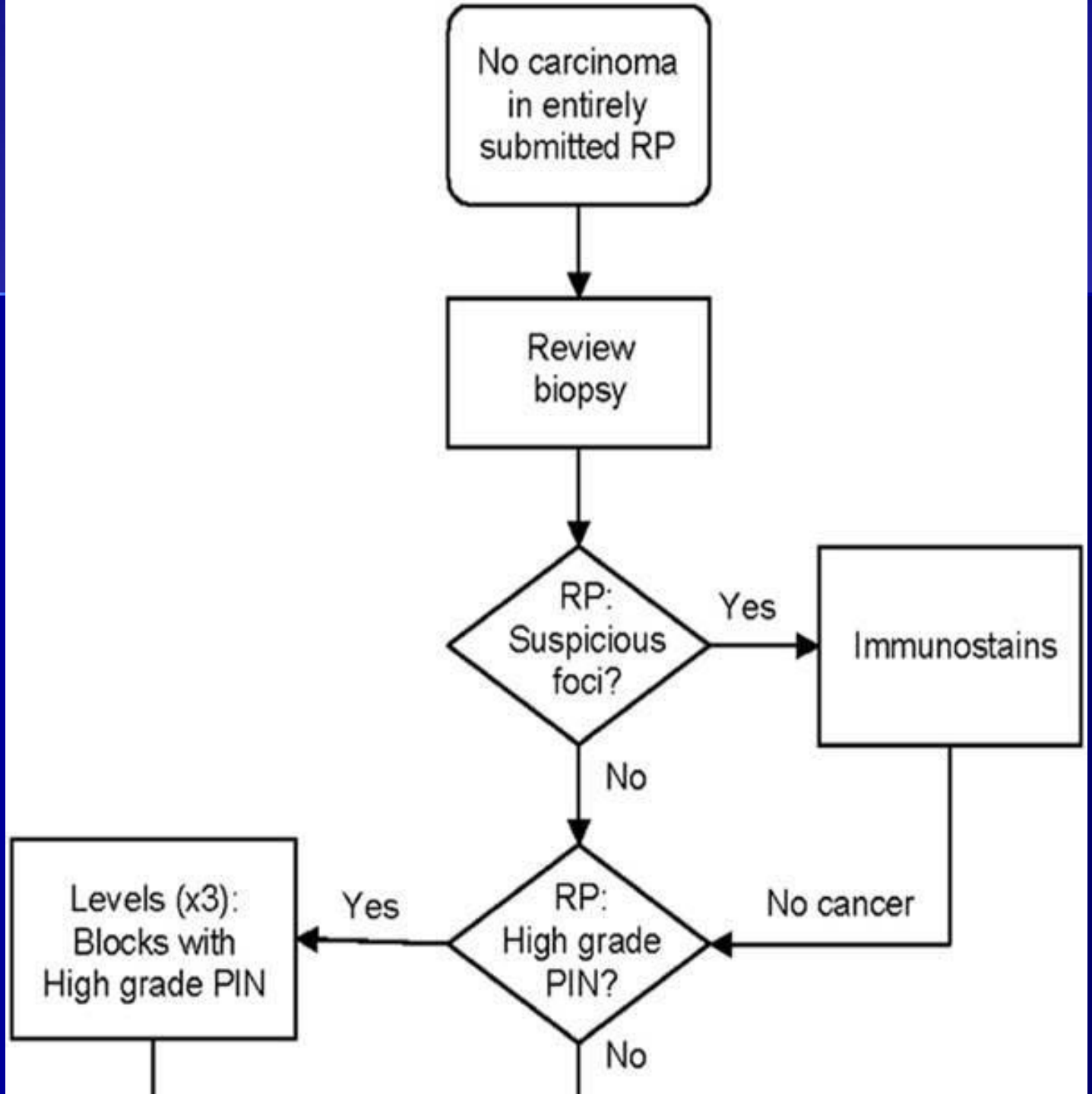
- **Specimen switch can rarely occur, and if there is high grade or a lot of cancer on the biopsy with no or very minimal cancer in the RP specimen, one should evaluate for patient identity.**

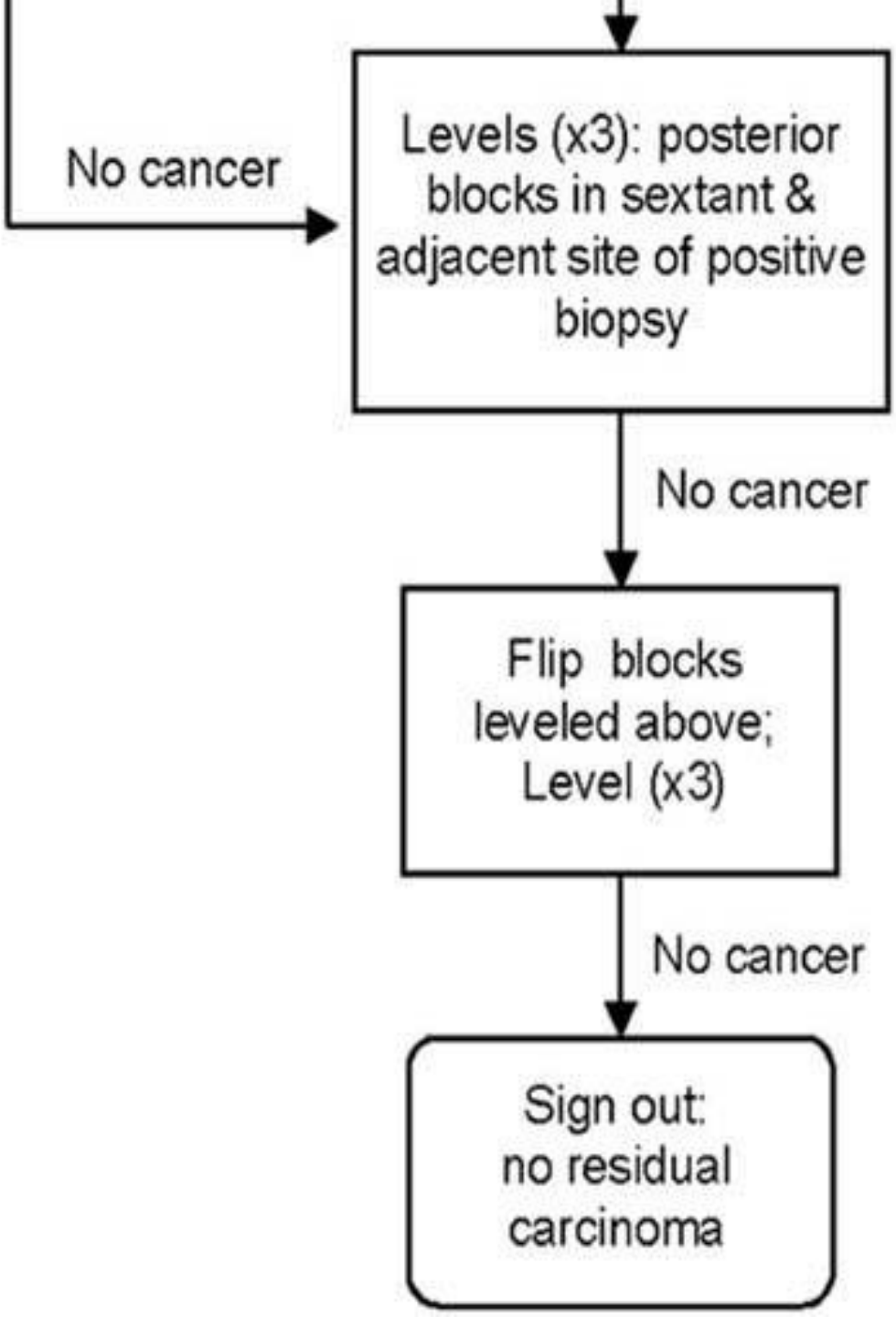
- **However, in most cases of “vanishing cancer” in RP specimens, it reflects a chance sampling of a minute cancer and not a switch in specimens.**

Detection of Cancer in RP in 34 Specimens with no Residual Cancer in the Initial Review of Slides

Duffield A, Epstein JI

Am J Surg Pathol 2009


No carcinoma in entirely submitted RP
Review biopsy
RP: Suspicious foci?
Yes
Immunostains
No
RP: High grade PIN?
Yes
Levels (x3): Blocks with High grade PIN
No cancer
No


No cancer
Levels (x3): posterior blocks in sextant & adjacent site of positive biopsy
No cancer
Flip blocks leveled above; Level (x3)
No cancer
Sign out: no residual carcinoma

Method	No. Cases.	%
IHC only	5	19
Levels x3		
-IHC	12	73
+IHC	2	
Levels x6		
-IHC	6	
+IHC	1	100

In 1.5% of RP no cancer will be found in initially submitted specimen.

A methodical limited targeted approach can identify cancer in 73% of cases, yet still 0.4% of all RPs where cancer is not identified.

Why Look for Minute Cancer?

- Patients and urologists concern when no cancer is found following major surgery
- Relatively little effort to find residual cancer in the majority of cases

Overtreatment of Prostate Cancer

- 0.4% no residual prostate cancer at RP
- 4% minute cancer at RP
- 26%-33% small volume (?insignificant) cancer

Standard Treatments for Prostate Cancer

- Radical Prostatectomy
- Radiation Therapy
- Active Surveillance
  - Watchful waiting
  - Expectant management

AUA Practice Guidelines for Localized Prostate Cancer

- As a standard, patients should be informed about surveillance
- Patients most likely to benefit from surveillance are those with a shorter life expectancy and/or low grade tumor

www.auanet.org/guidelines/

Criteria for Selection of Men for Active Surveillance

- Age (life expectancy or follow-up time)
- Patient preference
- Cancer extent (clinical stage)
- Needle biopsy findings (grade, extent)
- PSA criteria
  - PSA
  - Density

Pathologic and Clinical Findings to Predict Tumor Extent of Nonpalpable (Stage T1c) Prostate Cancer

Epstein JI, Walsh PC, Carmichael M, Brendler CN

JAMA 1994

- **Retrospectively compared 157 RP cases done for T1c disease to 64 T1a (small tumors detected on TURP) to 439 T2 (palpable tumors)**

- **26% T1c cases “potentially insignificant”**
  - **No Gleason pattern 4 (Gleason 3+3=6)**
  - **Organ confined**
  - **Tumor volume <0.5cc.**

- **T1c intermediate between T1a and T2**

Pre-Operative Model to Predict Insignificant Cancer

- Stage T1c (nonpalpable)
- Gleason score 6
- <3 cores involved by cancer
- No core with >50% involvement
- PSADensity (PSA/gland weight) <0.15

Pre Treatment Criteria Accurately Identify Men With "Significant" Cancers

Study	Study Design	# Men	Small volume (%)	NPV (%)	PPV (%)
Epstein et al, '94	Retro-spective	157	26	86	79

Active Surveillance of Prostate Cancer: The Johns Hopkins Program

- Prospective observational study
- Study initiation in 1995

Prospective Evaluation of Men with Stage T1c Adenocarcinoma of the Prostate

Carter HB, Sauvageot J, Walsh PC, Epstein JI

J Urol 1997

Pre Treatment Criteria Accurately Identify Men With "Significant" Cancers

Study	Study Design	# Men	Small volume (%)	NPV (%)	PPV (%)
Carter et al, '97	Pro-spective	240	33	81	75

National Comprehensive Cancer Network (NCCN) Practice Guidelines

RECURRENCE RISK	EXPECTED SURVIVAL	INITIAL THERAPY
Very Low: (Epstein Criteria) •T1c •Gleason score ≤6 •PSA <10ng/ml •<3 biopsy cores + •≤50% cancer in each core •PSA density <0.15	<20yr	Active Surveillance Preferred

Life Expectancy at age 65 y by Percentiles of Health

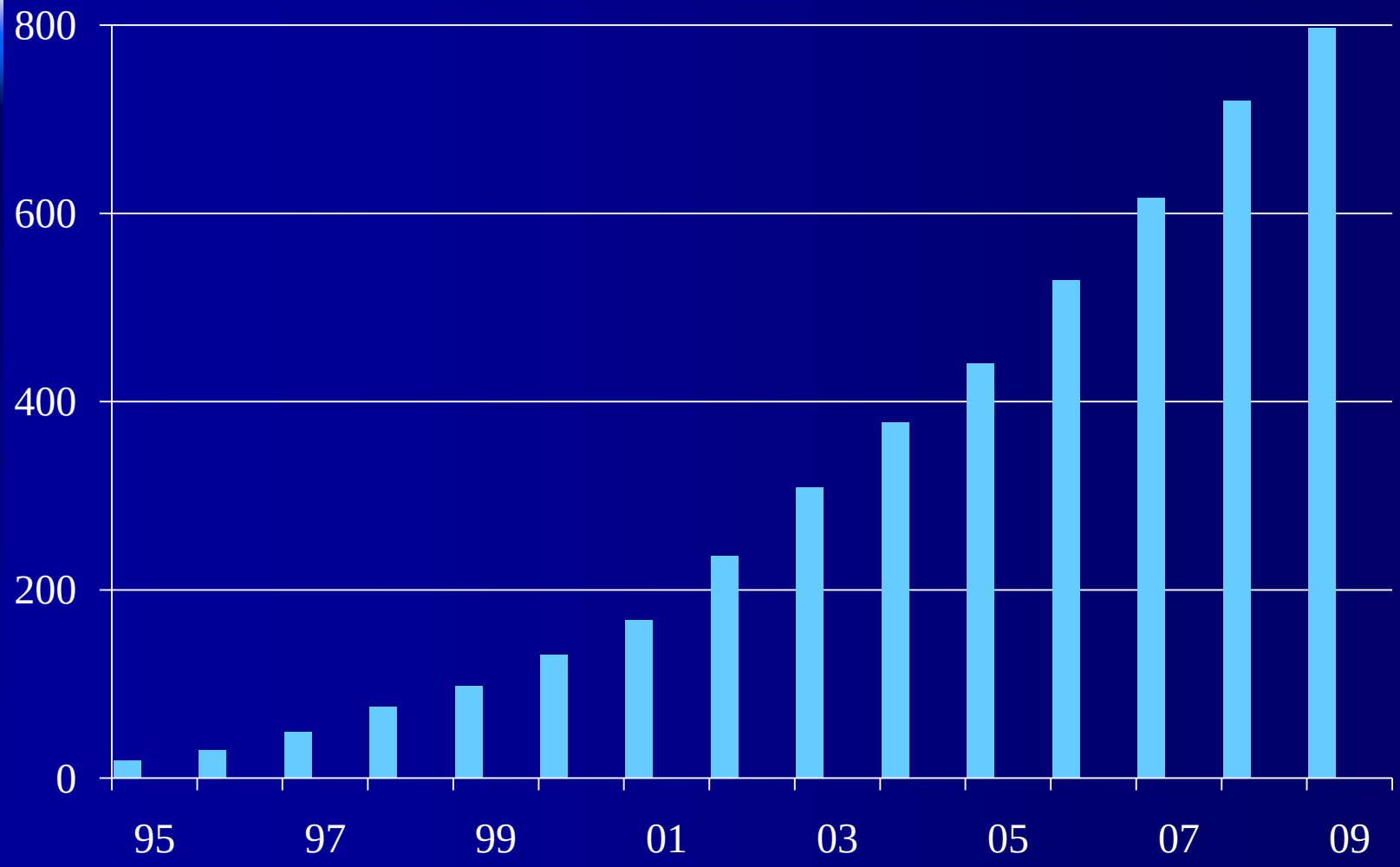
Top 25th	*Middle*	*Bottom 25th*
25.0 y	*16.7 y*	*8.3 y*

Mohler et al, J Natl Compr Canc Netw. 2010

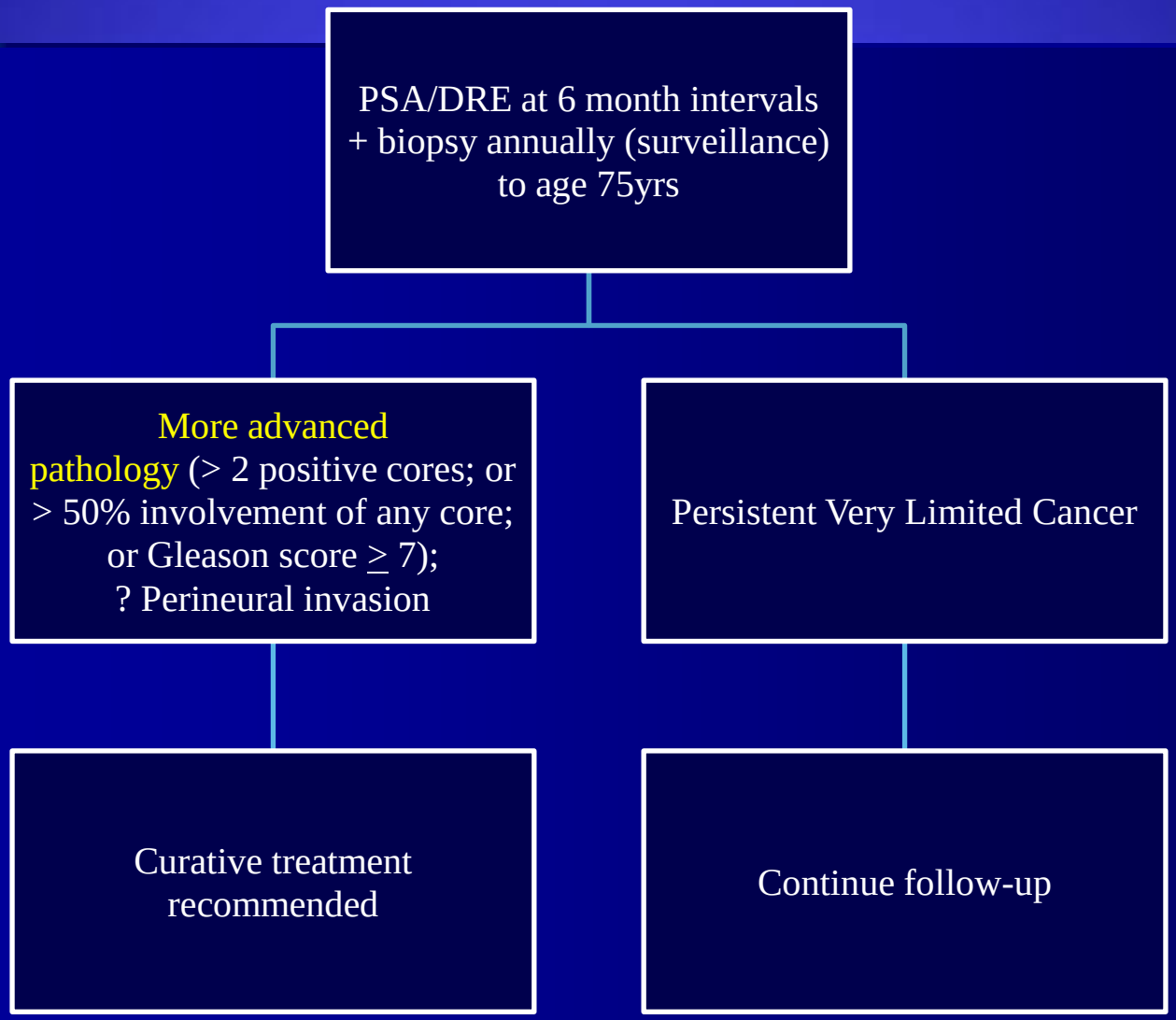
Follow-up Plan for Surveillance of Prostate Cancer

- 6-12 month monitoring with PSA and digital rectal examination at a minimum
- Surveillance (1-1.5 years) prostate biopsies

Cumulative Recruitment into Surveillance Program: Johns Hopkins



Surveillance Protocol: Johns Hopkins Program



Change in Prostate Cancer Grade Over Time in Men Followed Expectantly for Stage T1c Disease

Sheridan TB, Carter HB, Wang W, Landis PB, Epstein JI

J Urol 2008

Dedifferentiation of Cancer?

- 241 men with stage T1c prostate cancer with active surveillance with repeat yearly needle biopsy sampling to assess for more advanced cancer.

- Following the initial cancer diagnosis, all men had at least one other biopsy demonstrating cancer.

- **Average follow-up for those with persistent very limited disease was 32.3 months.**
- **45/241 cases (18.7%) showed a significant change in grade from Gleason score ≤6 to Gleason score ≥7.**
- **Gleason score 7 in 41 cases; Gleason score 8 in 4 cases).**
- **53% cases that showed higher grade did so within 24 months of diagnosis.**

GS 1st Biopsy	GS 2nd Biopsy	GS 3rd Biopsy	GS 4th Biopsy	GS 5th Biopsy	GS 6th Biopsy	GS 7th Biopsy	GS 8th Biopsy	No. of Cases
6	6							94
6	6	6						61
6	6	6	6					27
6	6	6	6	6				6
6	6	6	6	6	6			6
6	6	6	6	6	6	6	6	2
6	7							22
6	6	7						13
6	6	6	7					6
6	6	6	6	7				1
6	8							3
6	6	8						1

- **Grade progression may occur in some men with long-term follow-up who had multiple biopsies showing Gleason score 6 followed by higher grade cancer.**

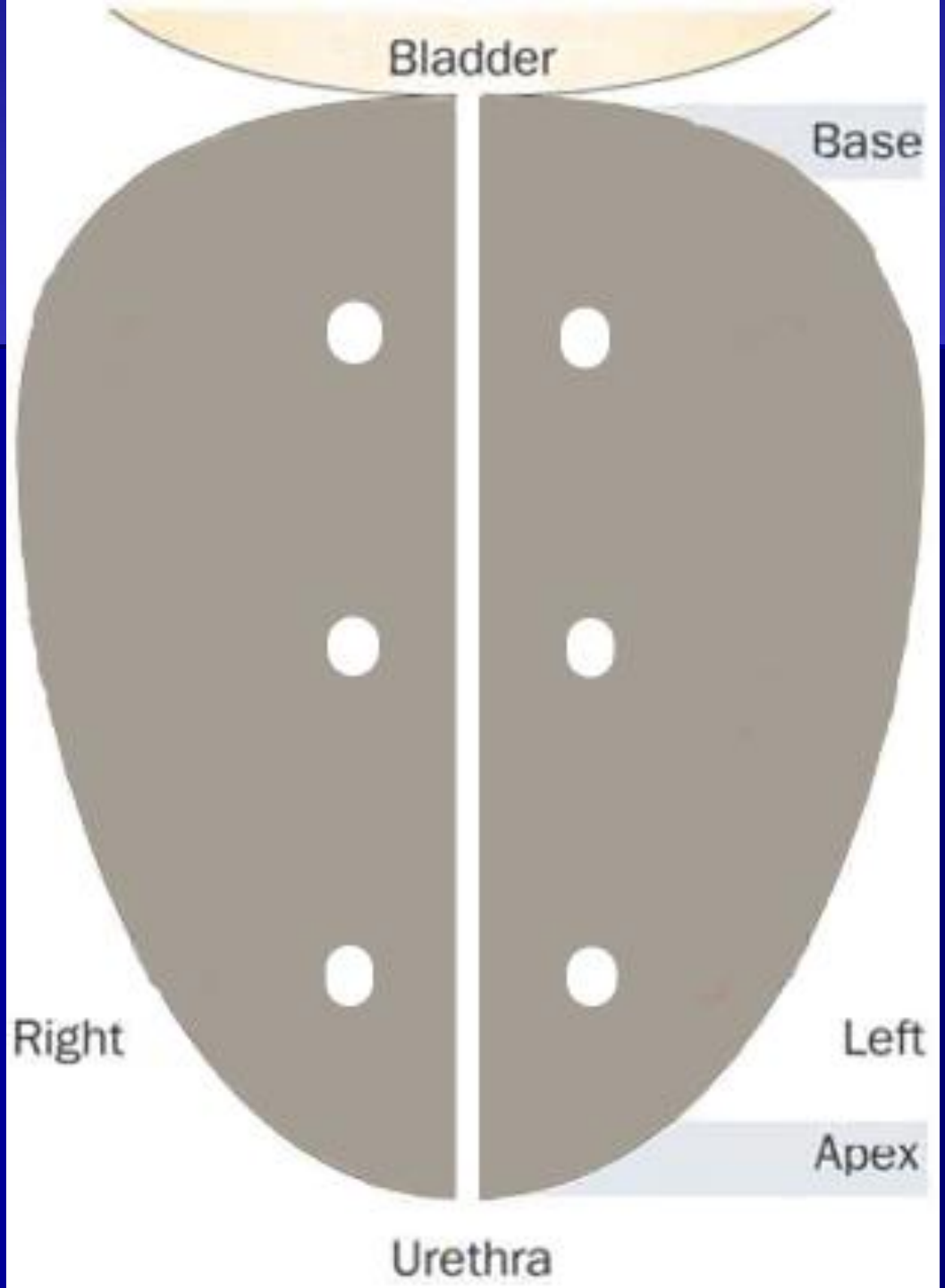
- **Within the first 3 years after diagnosis of Gleason score 6 prostate cancer, there is a relatively low risk of grade progression.**

- **Within the first 3 years, our data suggests that in most cases tumor grade did not evolve but rather that the higher grade component was not initially sampled since most grade changes occurred relatively soon after biopsy.**

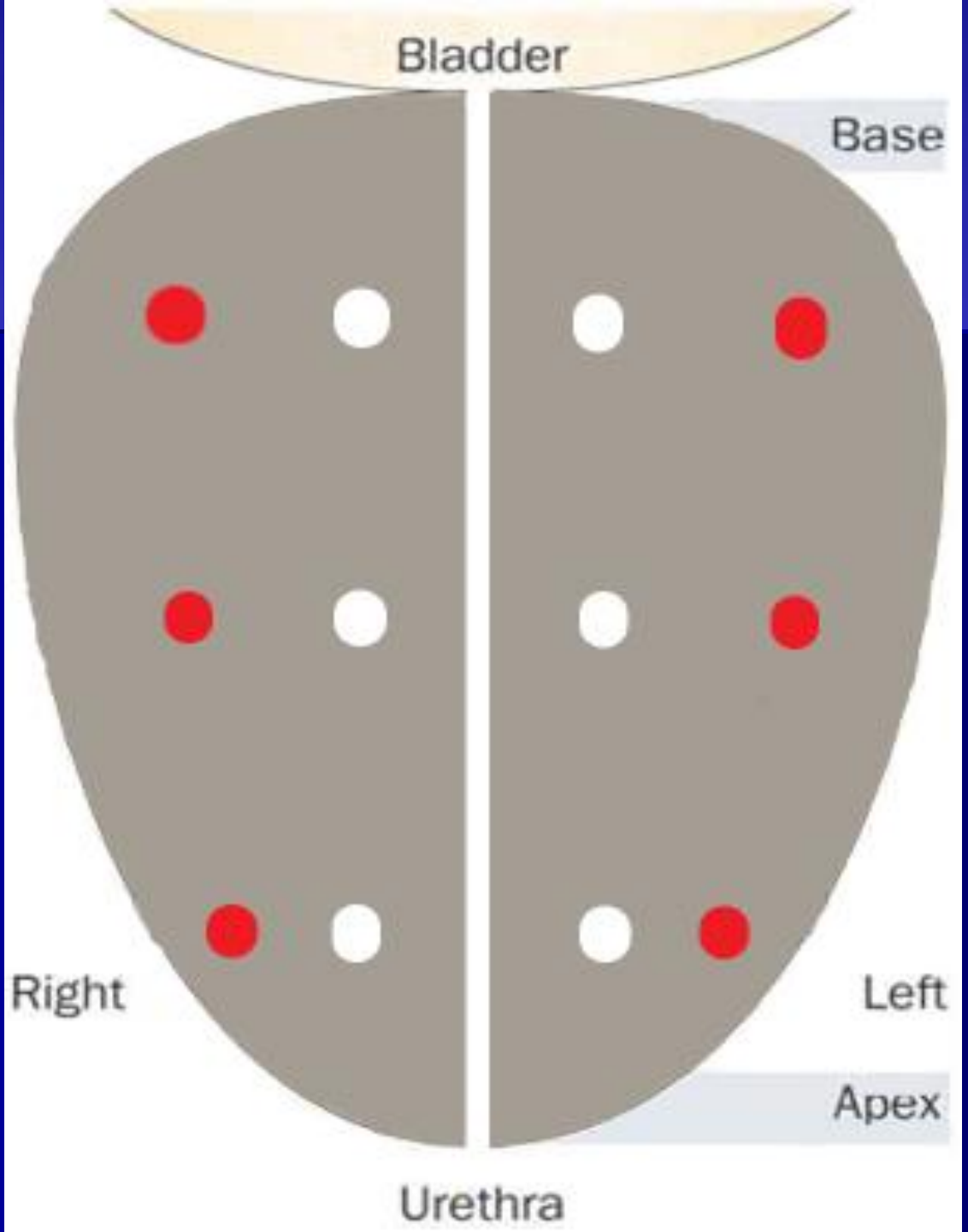
Importance of Posterolateral Needle Biopsies in the Detection of Prostate Cancer

Carter HB, Walsh PC, Epstein JI

Urol 2001


Bladder
Base
Right
Left
Apex
Urethra

- Within the Pathology Laboratory did needle biopsies on 150 RPs done for T1c disease
- Found that routine 6 core (sextant) needle biopsies often missed significant cancer
- Adding 6 posterolateral biopsies maximized detection of significant cancers
- Currently, minimum 12 core biopsy required to enter program


Bladder
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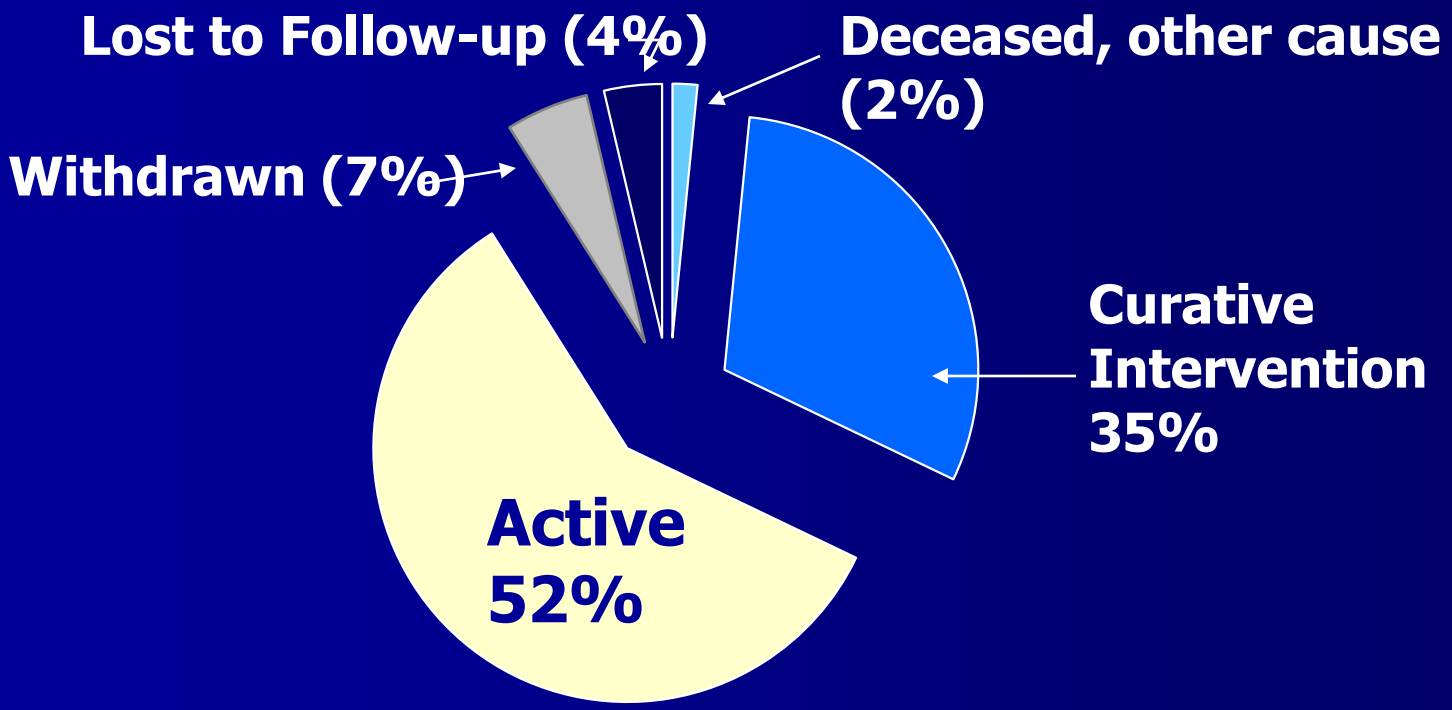
Urethra

Active Surveillance: Johns Hopkins Program



Radical Prostatectomy Findings in Patients who Fail Active Surveillance of Prostate Cancer

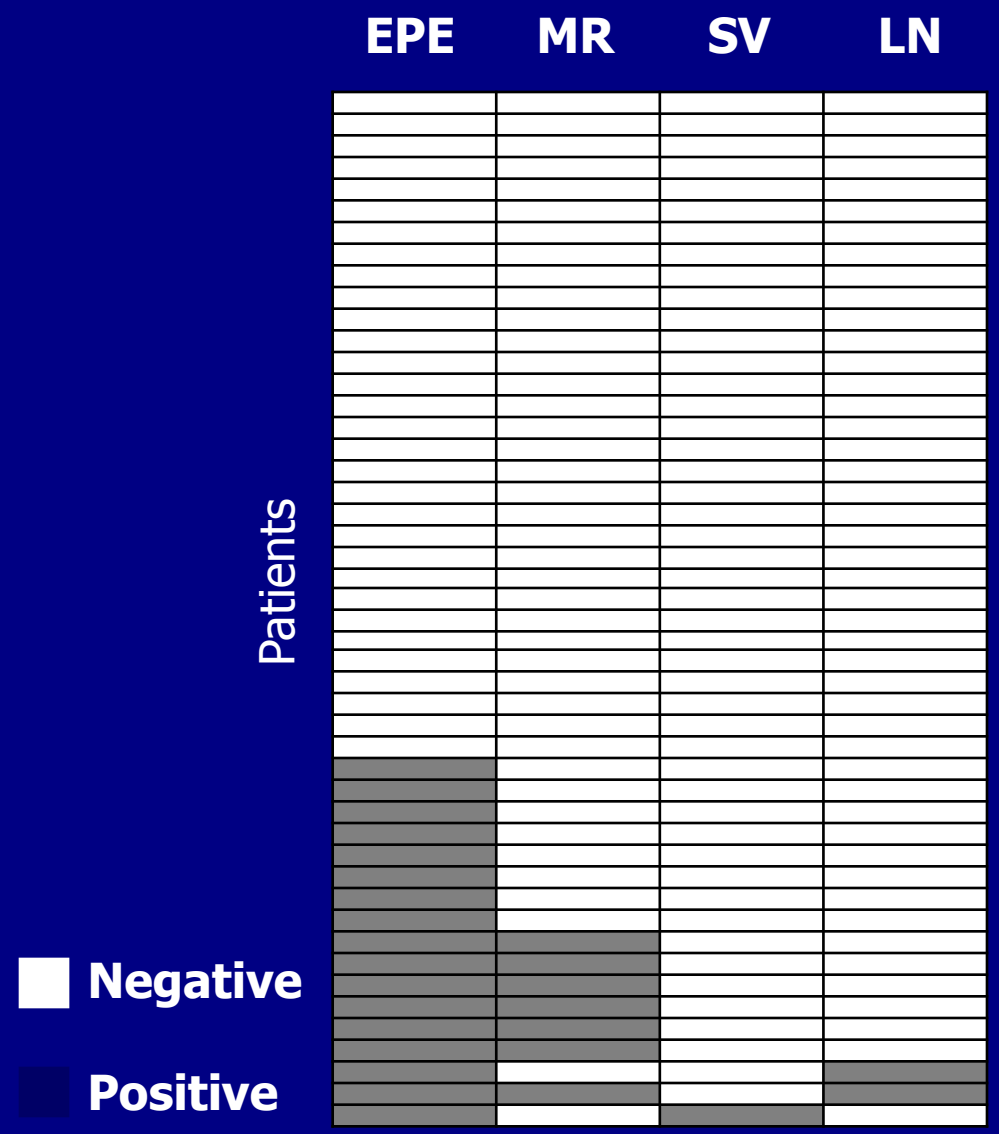
Analyzed 48 RP done because of more advanced disease on surveillance biopsies

Duffield AS, Lee TK, Miyamoto H, Carter HB, Epstein JI
J Urol (2009)

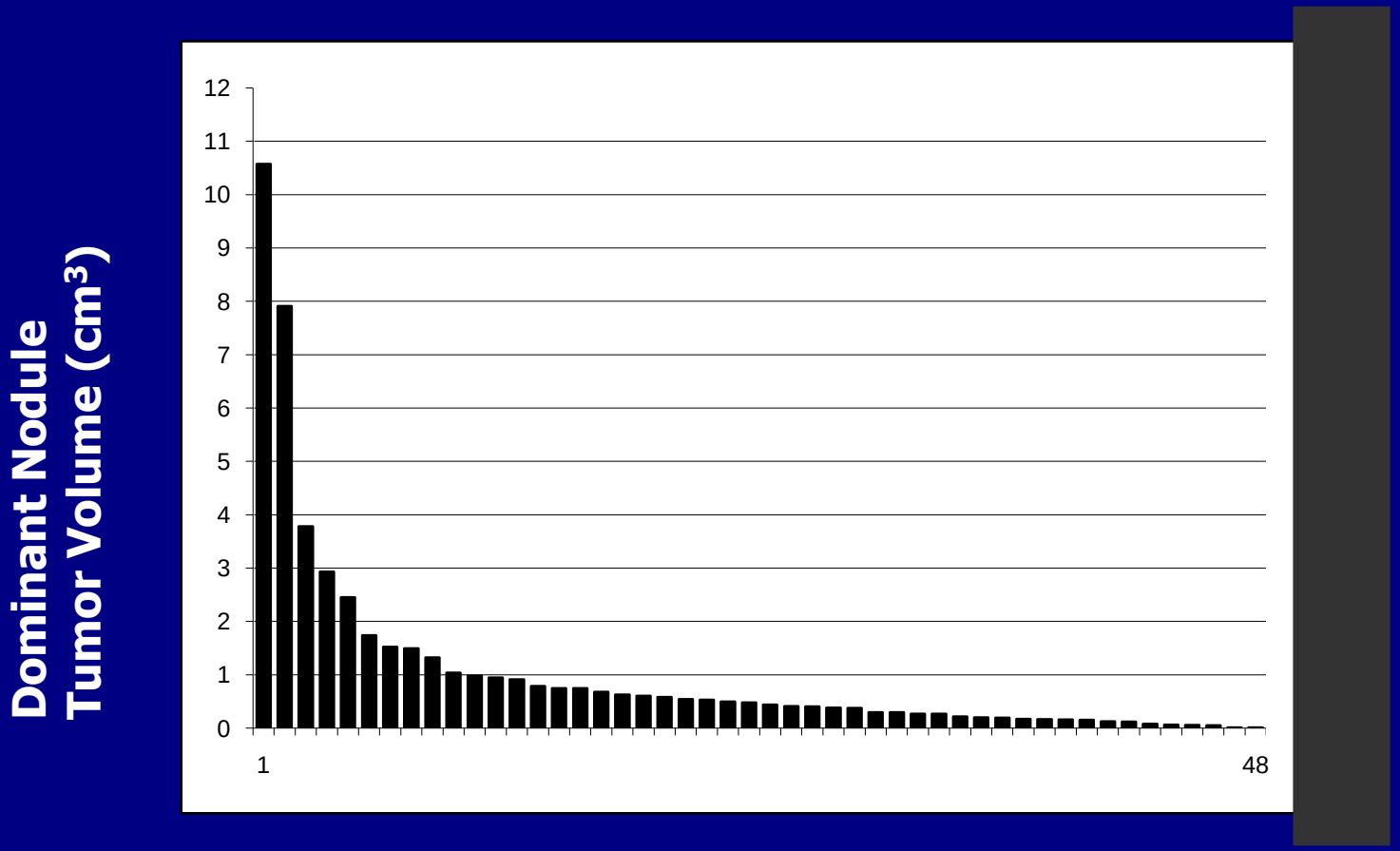
Advanced Findings on Biopsy	Percent	
>2 core involvement	29% (14/48)	**33/48 (69%)**
Gleason pattern 4/5	27% (13/48)	
>50% involvement of core	13% (6/48)	
>2 cores & >50% core	13% (6/48)	**15/48 (31%)**
GP 4/5 & >50% core	8% (4/48)	
GP 4/5 & >2 cores	6% (3/48)	
All three adverse criteria	4% (2/48)	

Radical Prostatectomy Findings: Tumor Stage

- **Extra prostatic extension (EPE): 35% (17/48)**
  - **Focal: 14.6% (7/48)**
  - **Non-focal: 20.8% (10/48)**
- **Positive surgical margins (MR): 14.6% (7/48)**
- **Seminal Vesicle (SV) involvement: 2.1% (1/48)**
- **Positive lymph node (LN): 4.2% (2/48)**



Radical Prostatectomy Findings: Tumor Volume

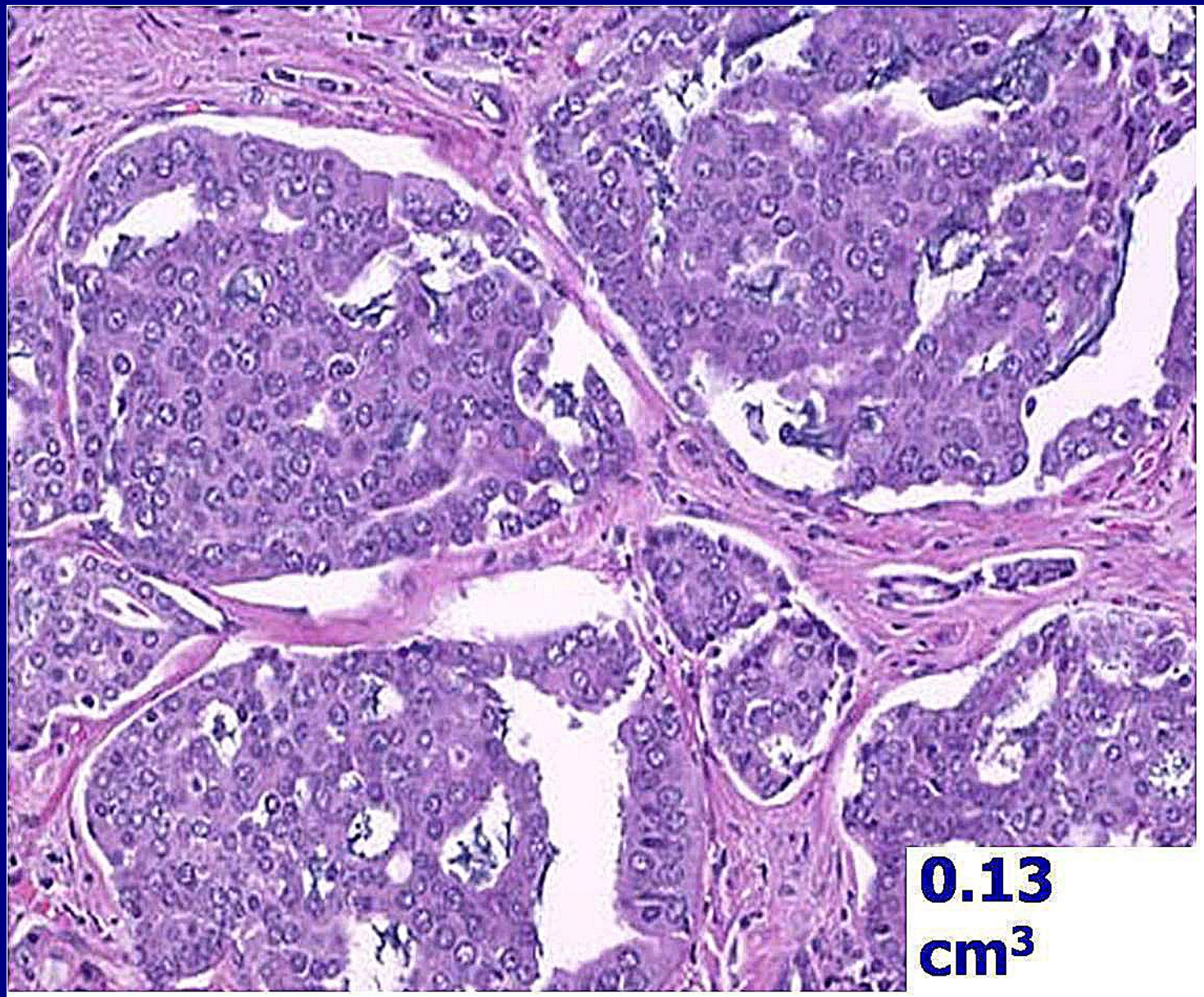


– **Dominant nodule volume > 1 cm^3: 10/48 (20.8%)**

Radical Prostatectomy Findings

- 27% (13/48) of tumors were potentially clinically insignificant
  - Organ confined
  - Dominant tumor nodule <0.5 cm^3
  - No Gleason pattern 4 or 5
- 19% (5/26) of RPs with dominant tumor nodule <0.5 cm^3 had EPE
  - Four of these cases had Gleason pattern 4

GS 4+3=7 (5)
EPE
PSA at RP: 5.4

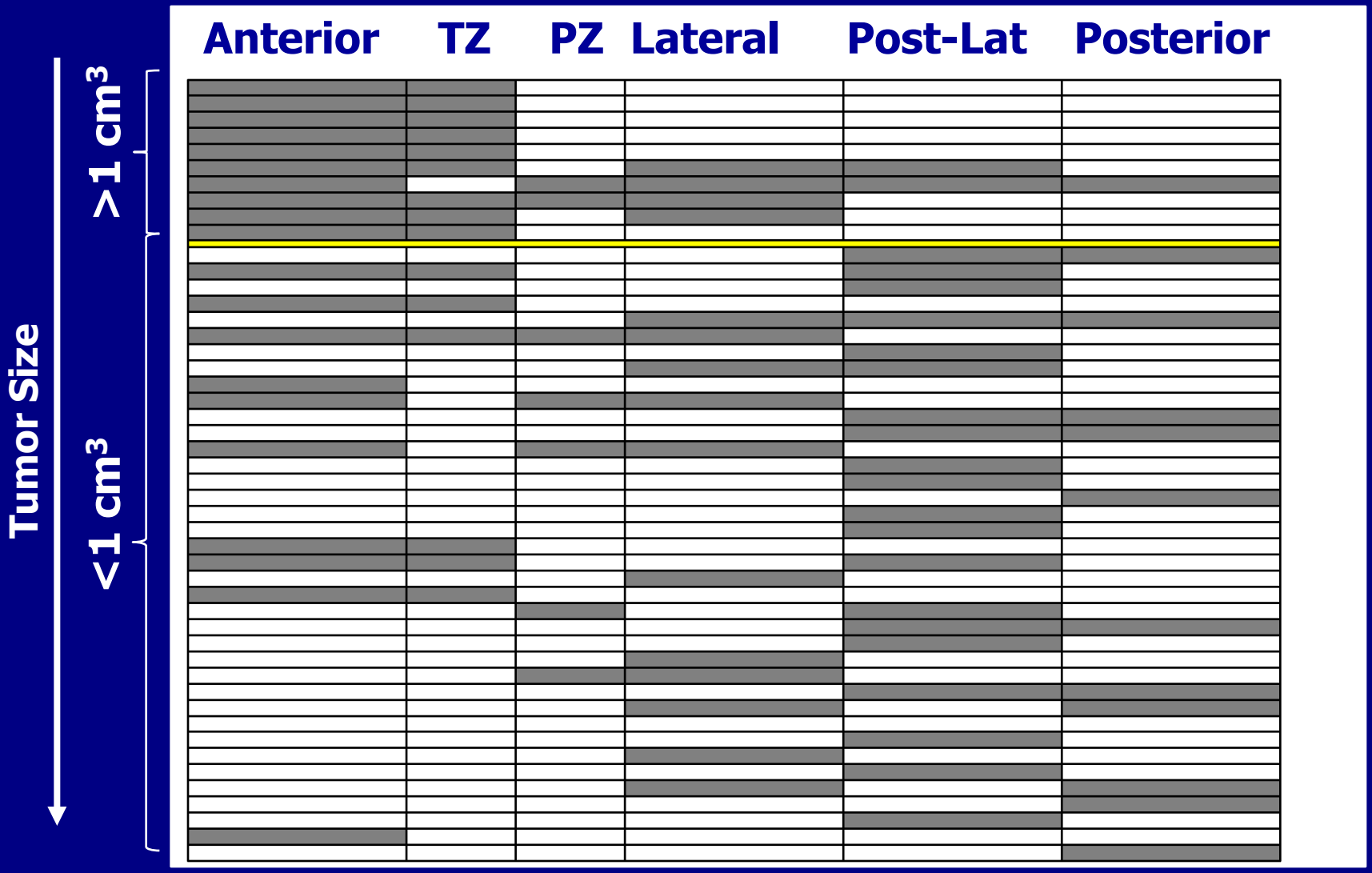


- **Even with more advanced tumor on biopsy, most RP tumors had favorable pathology**
- **A small percentage of men have advanced stage (pT3b or N1) disease**
- **Some smaller tumors in this study were fairly aggressive, but did not have alarming PSA values**
- **Repeat biopsy is the best means to find patients with small foci of high grade disease**

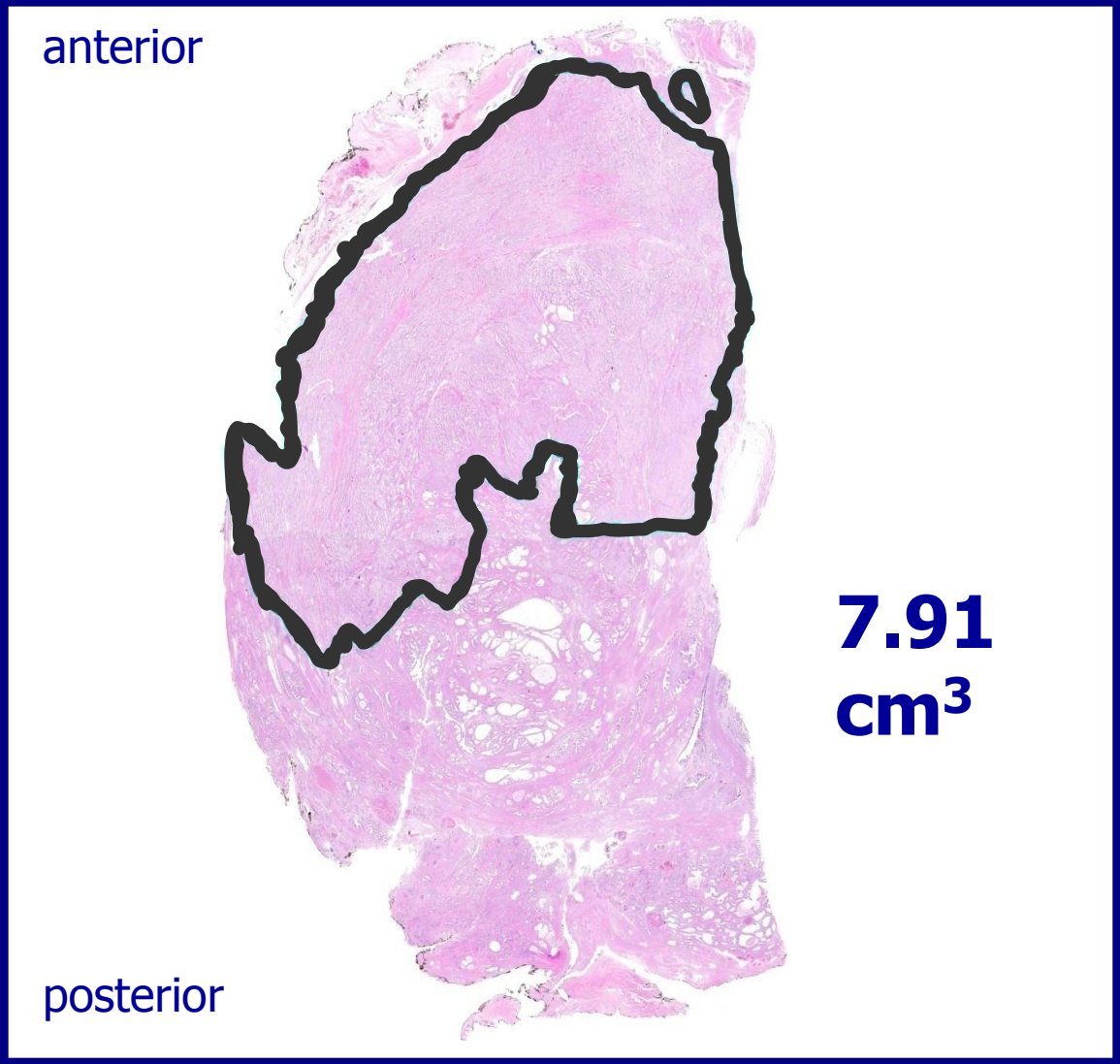
Radical Prostatectomy Findings: Dominant Nodule Tumor Location

- All 10 tumors with a dominant nodule >1 cm^3 were located predominantly in the anterior aspect of the prostate
- 9/10 of these tumors involved the transition zone

Radical Prostatectomy Findings:
Dominant Nodule Tumor Location



Radical Prostatectomy Findings: Dominant Nodule Tumor Location



4+3=7
EPE & + LN

- **Many of the larger tumors that evaded detection on biopsy were in the anterior prostate, particularly the transition zone**

- **Some of these tumors demonstrated aggressive behavior**

- **Previously, men who were enrolled in the active surveillance program did not have directed sampling of the anterior prostate**

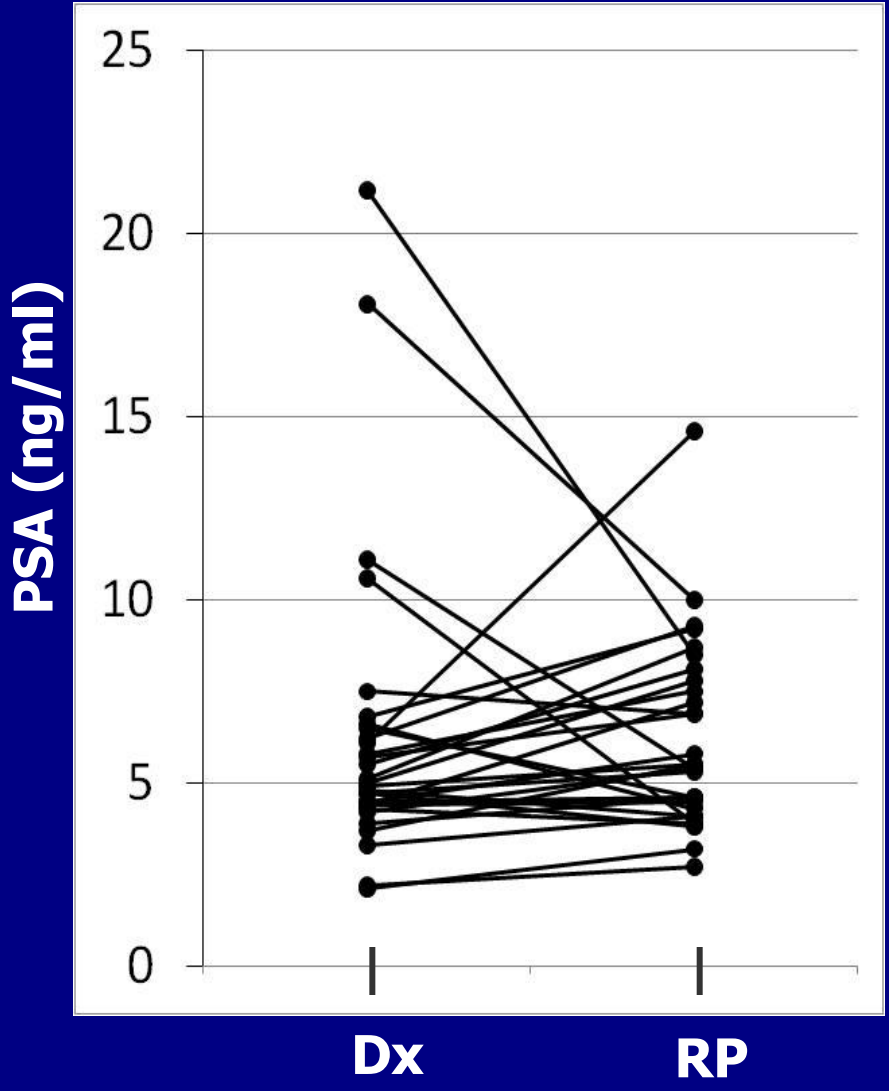
- **Based on the data of the current study, we have modified our repeat biopsy protocol to include anterior/transition zone sampling on men undergoing surveillance for minimal prostate cancer.**

Is It Possible to Predict Development of More Advanced Disease?

PSA Velocity in Men with More Advanced Disease on Biopsy

- Average PSA at diagnosis: 6.2 ng/ml (2.1 – 21.2 ng/ml)

- Average PSA at RP: 6.1 ng/ml (2.7 – 14.6 ng/ml)
  - 22 pts with increased PSA (average 1.82 ng/ml)
  - 9 pts with decreased PSA (average 4.19 ng/ml)P



Can PSA Derivatives Predict Significant Change in Expectant Management Criteria for Prostate Cancer?

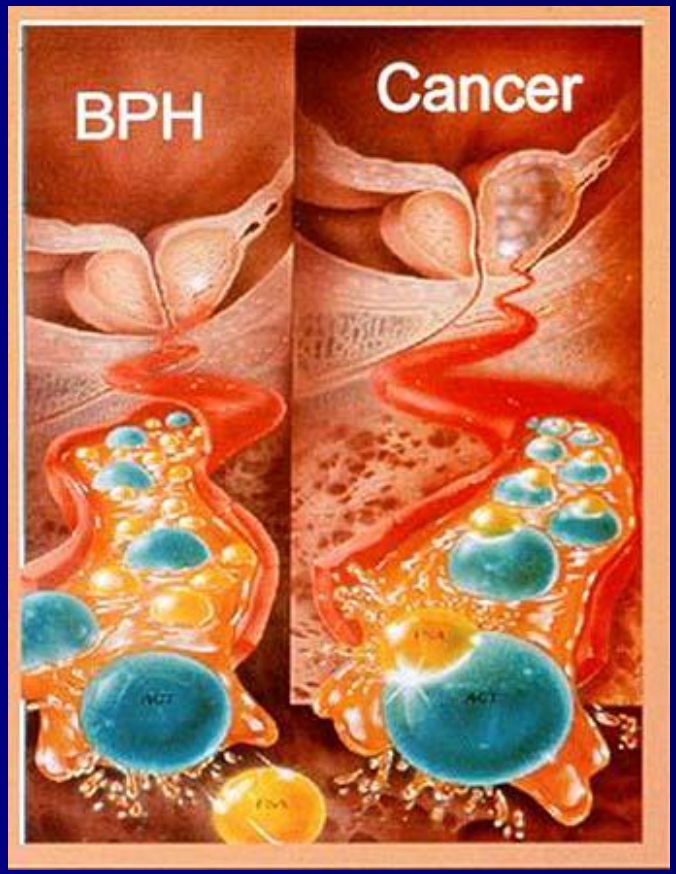
Khan MA, Carter HB, Epstein JI, Miller MC, Landis P, Walsh PC, Partin AW, Veltri Rw

J Urol 2003

Free PSA

PSA in the serum exists in free and bound forms.

Higher %free PSA in men with benign prostates compared to those with cancer.

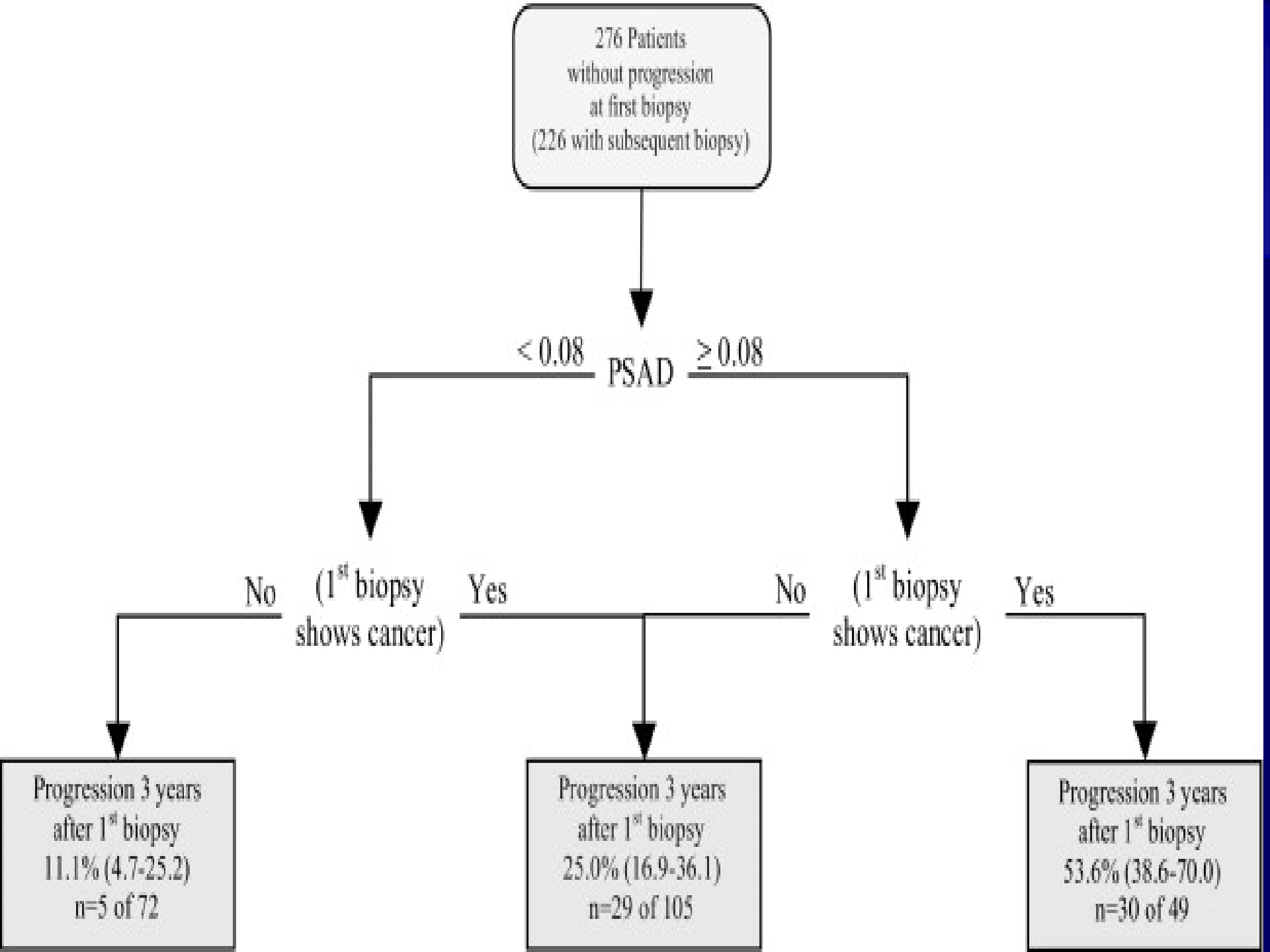


Overlap of Free PSA Levels in Men With and Without Development of More Advanced Disease on Biopsy

Risk Stratification of Men Choosing Active Surveillance for Low Risk Prostate Cancer

- **Tseng KS, Landis P, Epstein JI, Trock BJ, Carter HB**

J Urol 2010


276 Patients
without progression
at first biopsy
(226 with subsequent biopsy)
< 0.08
PSAD
≥ 0.08
No
(1st biopsy
shows cancer)
Yes
No
(1st biopsy
shows cancer)
Yes
Progression 3 years
after 1st biopsy
11.1% (4.7-25.2)
n=5 of 72
Progression 3 years
after 1st biopsy
25.0% (16.9-36.1)
n=29 of 105
Progression 3 years
after 1st biopsy
53.6% (38.6-70.0)
n=30 of 49

Relationship between the PCA3 Molecular Urine Test and Prostate Biopsy Results in an Active Surveillance Program

Tosian JJ, Loeb S, Ketterman A, Landis P, Elliot DJ, Epstein JI, Partin AW, Carter HB, Sokoll LJ

J Urol 2010

PCA3

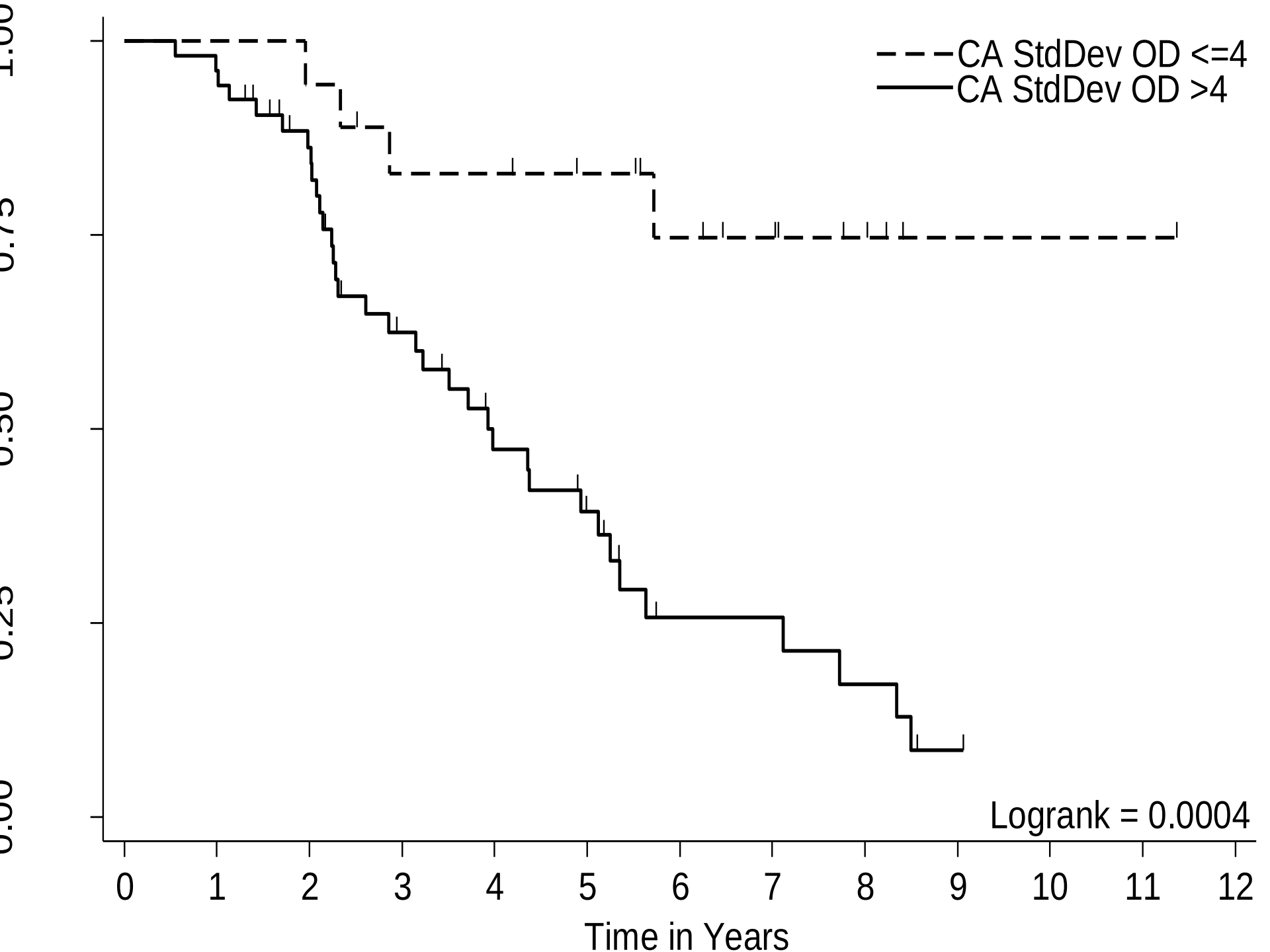
- PCA3 is a prostate specific non-coding mRNA overexpressed in prostate cancer compared to benign prostate
- Used in cases with negative biopsy despite suspicious findings to determine repeat biopsy
- Conflicting studies on predicting aggressiveness of prostate cancer
- PCA3 score not associated with predicting development of more advanced disease on biopsy.

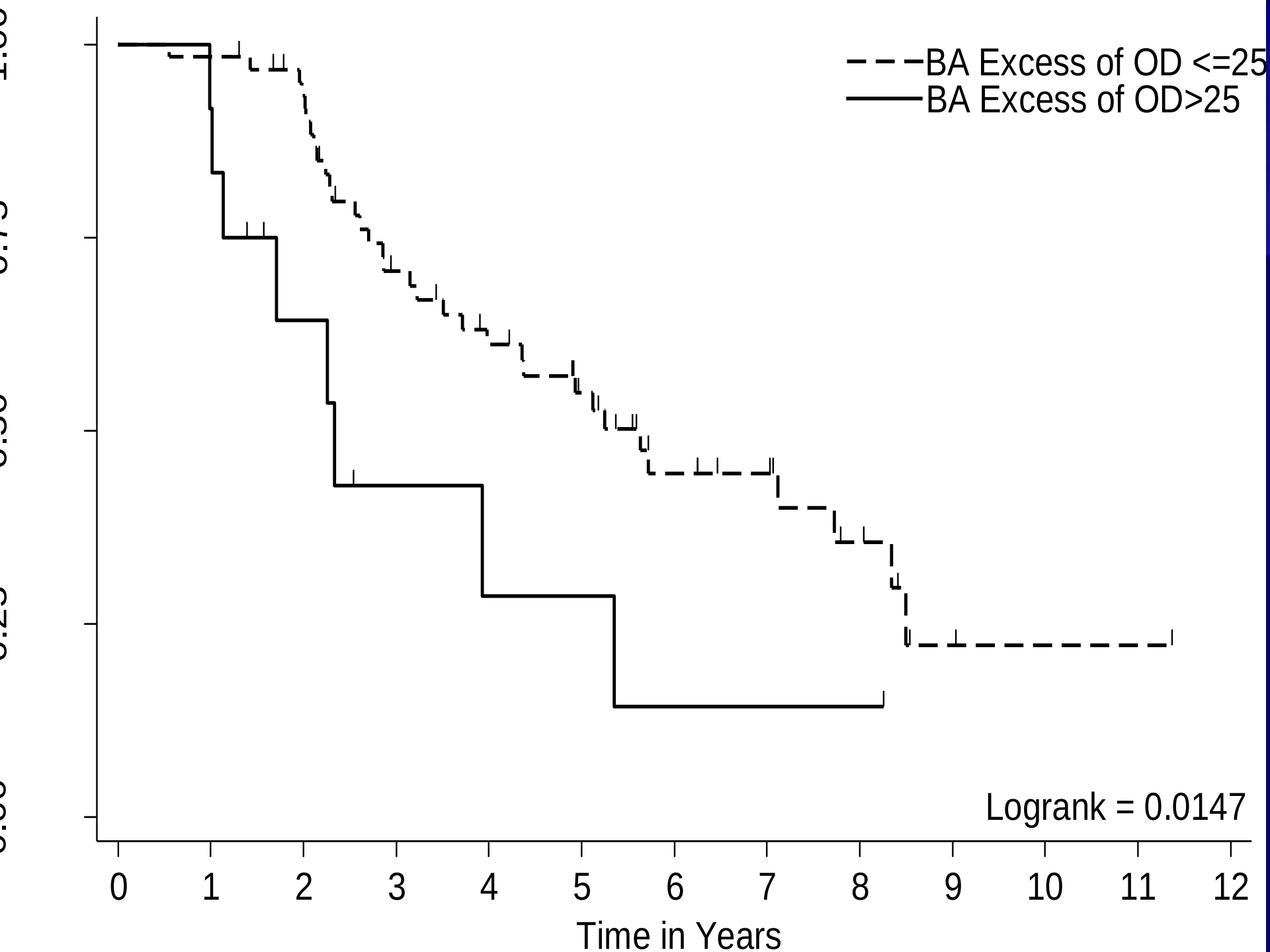
DNA Content in Biopsy Benign-Adjacent and Cancer Tissue Areas Predicts the Need for Treatment in Men with T1c Prostate Cancer in Active Surveillance Program

Isharwal S, Makarov D, Carter HB, Epstein JI, Partin AW, Landis P, Malrow C, Veltri R

BJU Int 2010

- 39 men developed more advanced biopsy findings
- 32 maintained very limited disease on biopsy
- Median follow-up: 3.7 years


CA StdDev OD <=4
CA StdDev OD >4
Logrank = 0.0004
0.00
0.25
0.50
0.75
1.00
0
1
2
3
4
5
6
7
8
9
10
11
12
Time in Years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BA Excess of OD>25
Logrank = 0.0147
0
1
2
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9
10
11
12
Time in Years

Is It Possible to Predict Less Advanced Disease in Men who Appear to Fail Biopsy Criteria of AS?

Men with Worse Findings on Follow-up Bx who Undergo RP

- **Some men on follow-up who fail biopsy criteria have insignificant prostate cancer on RP defined as:**

1) Organ confined;

2) Dominant nodule <0.5 cm^3; and

3) No Gleason pattern 4 or 5.

Findings on Radical Prostatectomy

Number of patients	67
Age at RP	66.4 years (range: 43.4-75.0)
Mean active surveillance time (initial biopsy to RP)	30.3 ± 3.23 months (mean ± SEM)
Number of biopsies performed during AS	3 times (range: 2-9)
Gleason score	
3+3=6	25 (37.3%)
3+3 with tertiary pattern 4	5 (7.5%)
3+4=7	22 (32.8%)
4+3=7	13 (19.4%)
4+5/5+4=9	2 (3%)
Extra prostatic extension	15 (22.4%)
Positive margins	2 (3.0%)
Lymph node involvement	0
Seminal vesicle involvement	1 (1.5%)
Dominant tumor nodule volume (cm3)	0.56 ±0.086
Dominant nodule volume less than 0.5cm^3	41/67 (61.2%)
Clinically insignificant cancer	19/67 (28.4%)

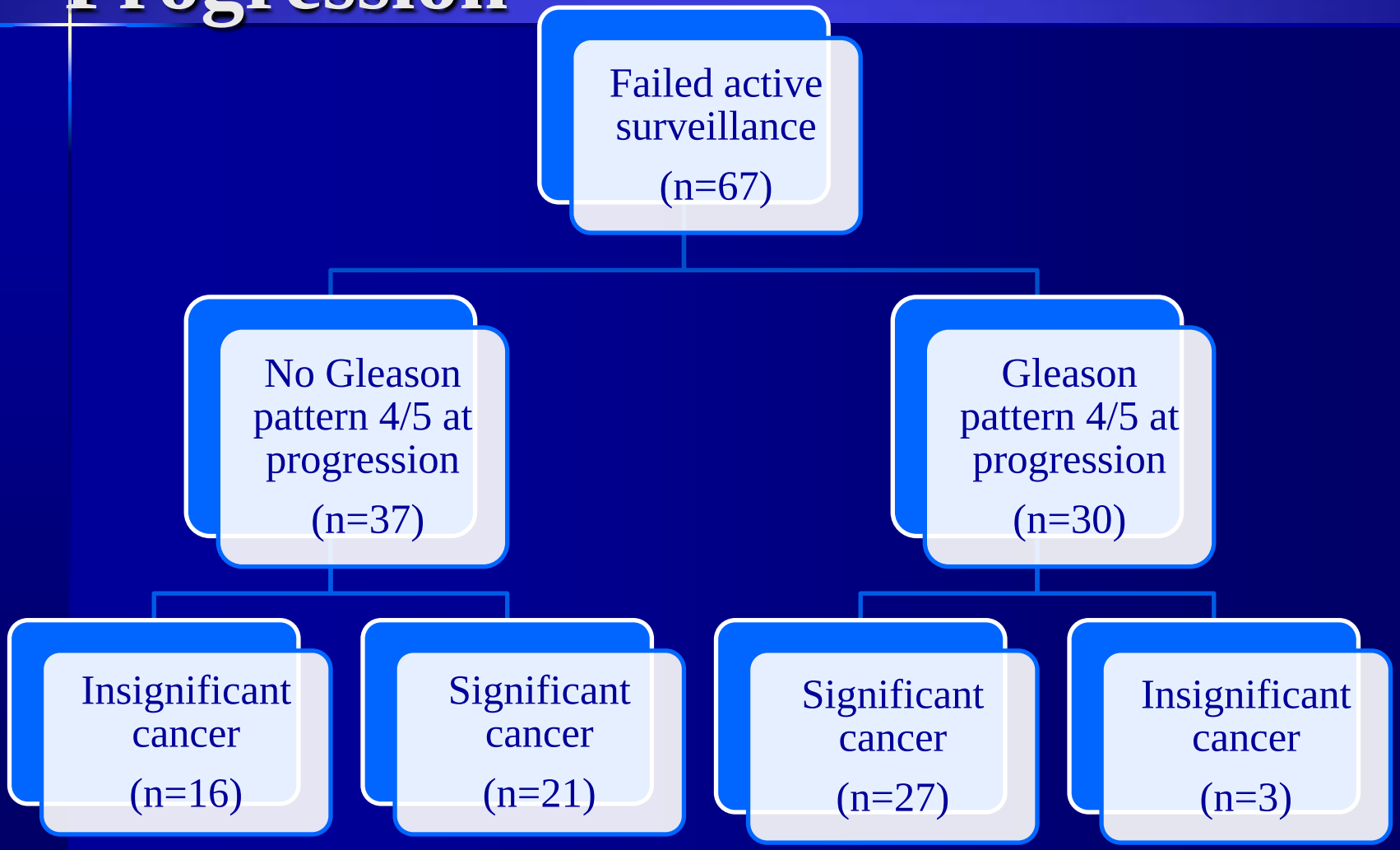
Findings at Initial Biopsy: Insignificant *vs* Significant cancer

	Insignificant (n=19)	Significant (n=48)	P value
1 core involved by cancer	16/19 (84.2%)	37/48 (77.1%)	ns
2 cores involved by cancer	3/19 (15.8%)	11/48 (22.9%)	ns
Number of cores involved by cancer	1.15 ± 0.085	1.23 ± 0.061	ns
PSA at diagnosis	4.61 ± 0.95	4.93 ± 0.23	ns
Maximum % of cancer <5%	11/19 (57.9%)	21/48 (43.8%)	ns
Maximum % of cancer	7.3 ± 1.77	10.6 ± 2.17	ns
Presence of negative interval biopsy	4/19 (21.1%)	14/48 (29.2%)	ns

Findings at Progression: Insignificant *vs* Significant Cancer

	Insignificant (n=19)	Significant (n=48)	P value
Time between progression and RP	2.8 (1.02-17.16)	2.96 (1.55-10.72)	ns
Number of cores involved by cancer	2.84 ± 0.279	2.60 ± 0.197	ns
2 or less cores involved by cancer	5/19 (26.3%)	24/48 (50%)	ns
3 or more cores involved by cancer	14/19 (73.7%)	24/48 (50%)	ns
3 or less cores involved by cancer	17/19 (89.5%)	37/48 (77.1%)	ns
4 or more cores involved by cancer	2/19 (10.5)	11/48 (22.9%)	ns
Maximum % of cancer < 5%	3/19 (15.7%)	5/48 (10.4%)	ns
Maximum % of cancer> 50%	7/19 (36.8%)	18/48 (37.5%)	ns
Maximum % of cancer	39.10 ± 4.15	41.26 ± 7.39	ns
PSA at progression	4.78 ± 0.568	5.70 ± 0.301	ns
PSA velocity	0.136 ± 0.892	0.565 ± 0.309	ns

Subgroup Analysis in Patients with No Gleason Pattern 4/5 at Progression

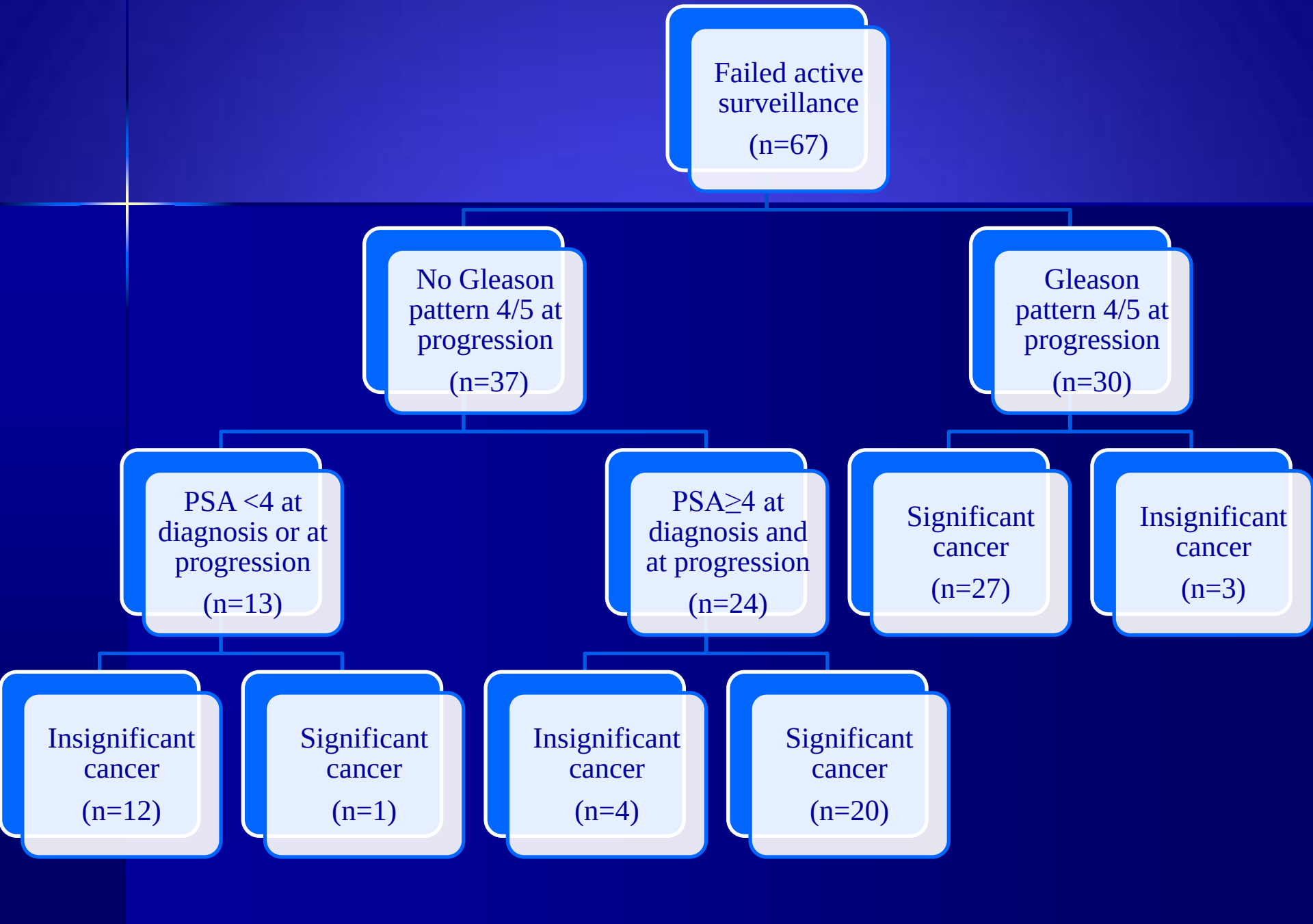


Findings at initial biopsy: Insignificant *vs* Significant cancer

	Insignificant (n=16)	Significant (n=21)	P value
1 core involved by cancer	13/16 (81.3%)	17/21 (81%)	ns
2 cores involved by cancer	3/16 (18.7%)	4/21 (19%)	ns
Number of cores involved by cancer	1.19 ± 0.101	1.19 ± 0.088	ns
PSA at diagnosis	3.68 ± 0.280	5.36 ± 0.322	0.0005***
Maximum % of cancer <5%	11/16 (68.8%)	12/21 (57.1%)	ns
Maximum % of cancer	5.81 ± 1.72	6.00 ± 1.04	ns
Presence of negative interval biopsy	4/16 (25%)	4/21 (19.5%)	ns

Findings at Progression: Insignificant *vs* Significant Cancer

	Insignificant (n=16)	Significant (n=21)	P value
Number of cores involved by cancer	2.88 ± 0.272	2.95 ± 0.297	ns
2 or less cores involved by cancer	3/16 (18.8%)	7/21 (33.3%)	ns
3 or more cores involved by cancer	13/16 (81.2%)	14/21 (66.7%)	ns
3 or less cores involved by cancer	15/16 (93.8%)	15/21 (71.4%)	ns
4 or more cores involved by cancer	1/16 (6.2%)	6/21 (28.6%)	ns
Maximum % of cancer < 5%	3/16 (18.8%)	3/21 (14.3%)	ns
Maximum % of cancer> 50%	6/19 (31.6%)	8/21 (38.1%)	ns
Maximum % of cancer	41.50 ± 7.88	39.71 ± 5.76	ns
PSA at progression	4.68 ± 0.648	6.09 ± 0.355	0.0504
PSA velocity	0.918 ± 0.584	0.248 ± 0.223	ns


Failed active surveillance
(n=67)
No Gleason pattern 4/5 at progression
(n=37)
Gleason pattern 4/5 at progression
(n=30)
PSA <4 at diagnosis or at progression
(n=13)
PSA≥4 at diagnosis and at progression
(n=24)
Significant cancer
(n=27)
Insignificant cancer
(n=3)
Insignificant cancer
(n=12)
Significant cancer
(n=1)
Insignificant cancer
(n=4)
Significant cancer
(n=20)

Conclusion

- **Most men who fail biopsy criteria while on AS have significant disease at radical prostatectomy**
- **However, about 1/4 of these men are over-treated with insignificant cancer in their RP.**

- **PSA data at the time of initial biopsy or “biopsy-progresssion” can help stratify men who are more likely to have insignificant cancer despite failing biopsy criteria.**

- **These men may be candidates to stay on active surveillance without definitive treatment.**

Summary - Problem

- PSA screening has reduced the rates of advanced prostate cancer and likely has contributed to mortality reductions
- PSA screening has led to overtreatment of some men with non lethal disease
- There is a need for improved methods to distinguish men with life threatening prostate cancer from those with indolent disease who will not benefit from treatment

Pathologists in Their Research Can Have a Critical Role in Addressing this Problem & Changing Clinical Practice

1. Identifying & quantifying the magnitude of the problem

2. Retrospectively developing criteria for AS

3. Prospectively testing the criteria

4. Identifying where detection can be improved
   - Improving how needle biopsies are performed (ie. posterolateral, anterior)

5. Reassuring patients
   - Helping to identify residual cancer
   - Low risk of grade change on AS

6. Studying newer techniques to improve prediction

7. Identify new criteria to allow men with low risk of significant cancer to stay on AS despite worrisome findings on biopsy.

Conclusion

A multidisciplinary approach with Pathology playing a key role is critical to providing the best care for men with early prostate cancer.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