



**Critical Role of Pathology
for Active Surveillance
Criteria and Definition of
“Progression”**

Jonathan I. Epstein



- No relevant disclosures

Outline

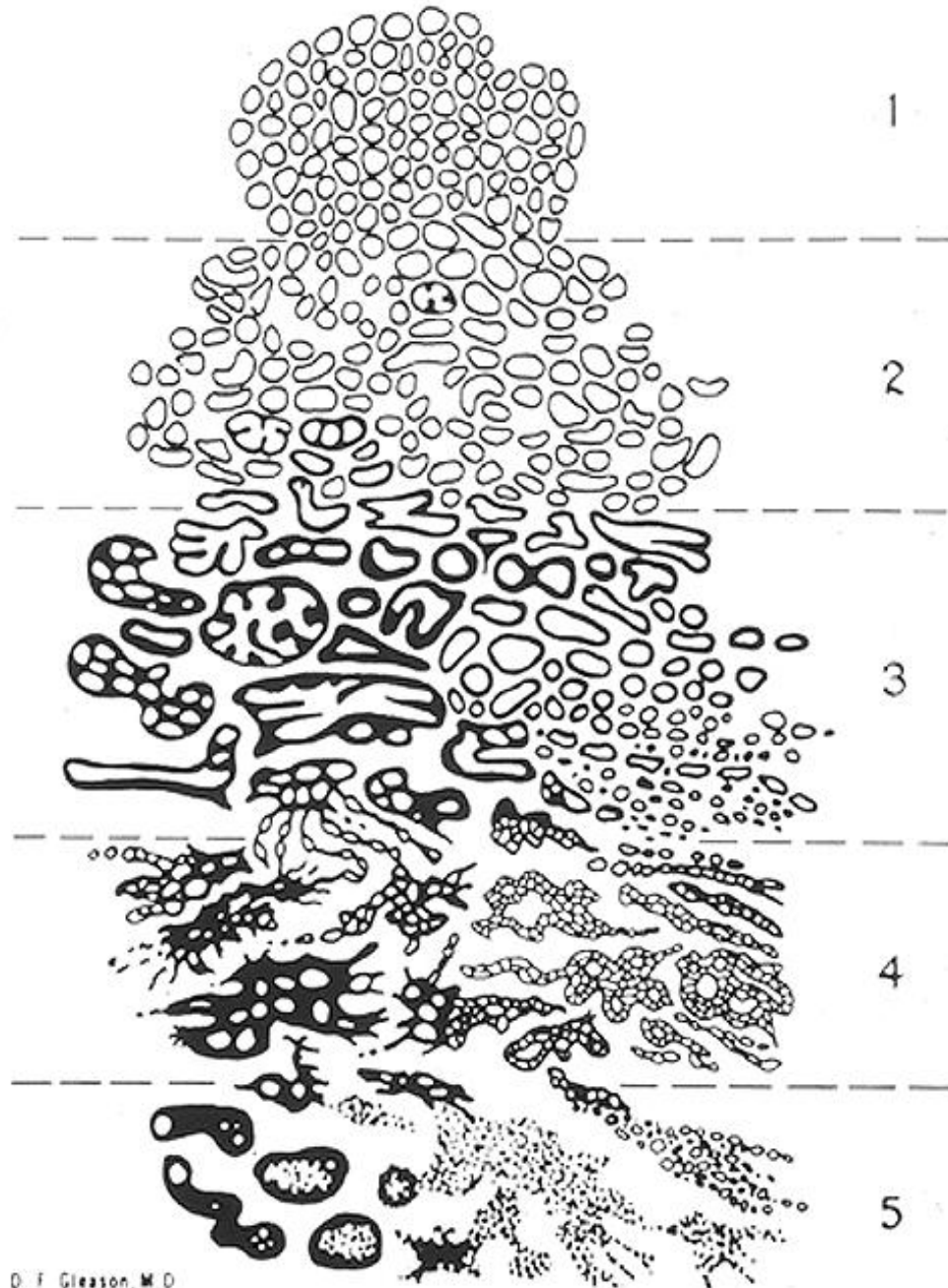
- **Brief introduction to Gleason system**
- **Criteria for selection for AS**
- **Trigger for intervention on AS**
- **Changes in reporting grade for AS**

Pioneers of the Gleason System

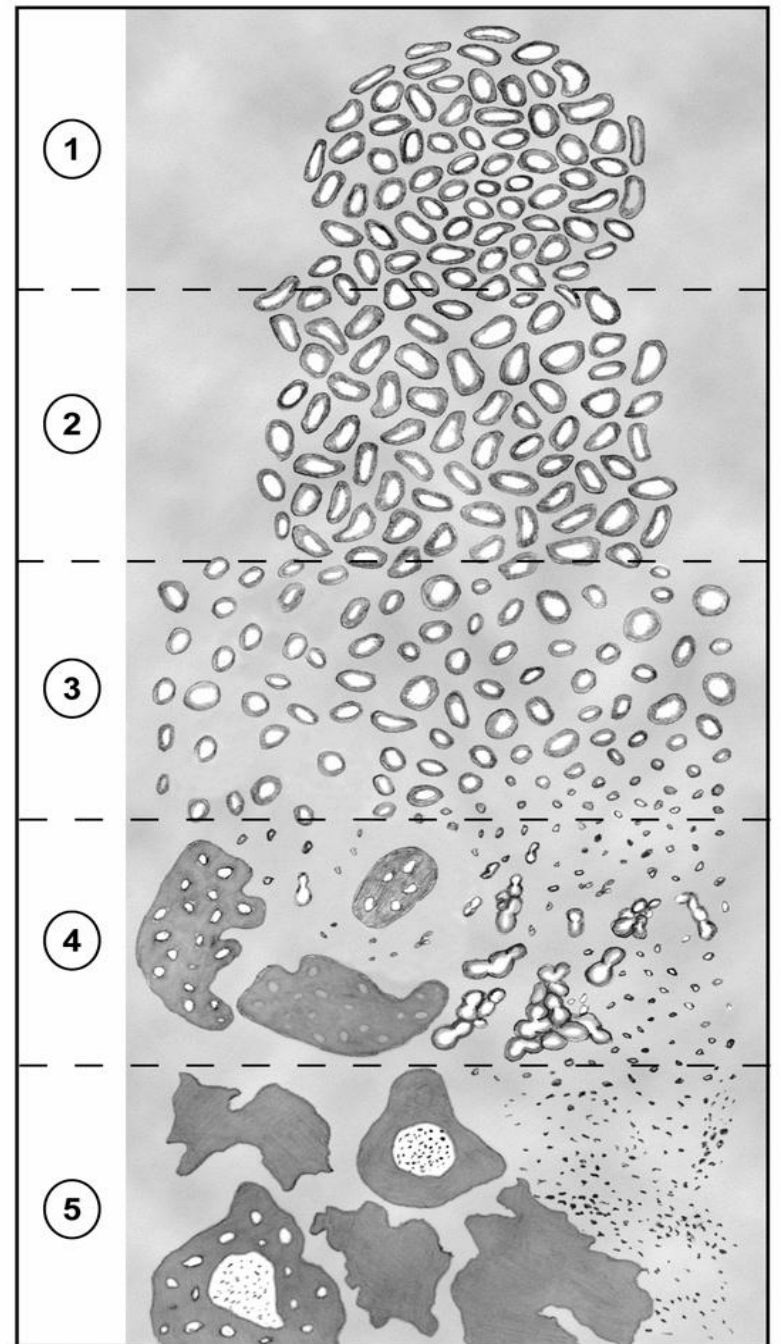
- **Donald Gleason - Chief of the Department of Pathology at the Veteran's Hospital in Minnesota**
- **George T. Mellinger - head of Department of Urology at the Minneapolis Veteran's Hospital established the Veteran's Affairs Cooperative Research Group (VACURG)**
- **John C. Bailar III - statistician**



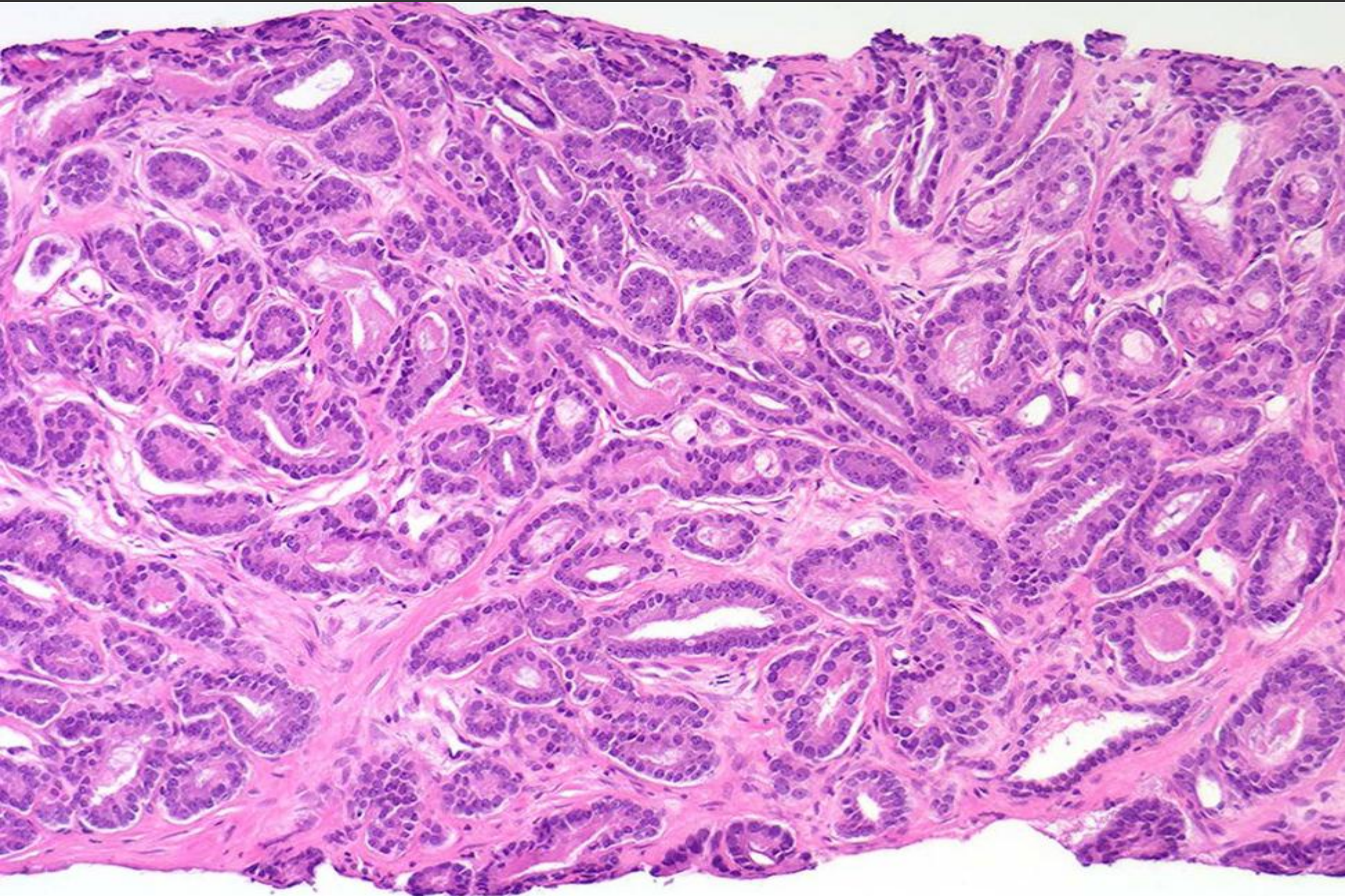
PROSTATIC ADENOCARCINOMA (Histological Patterns)



D. F. Gleason, M.D.



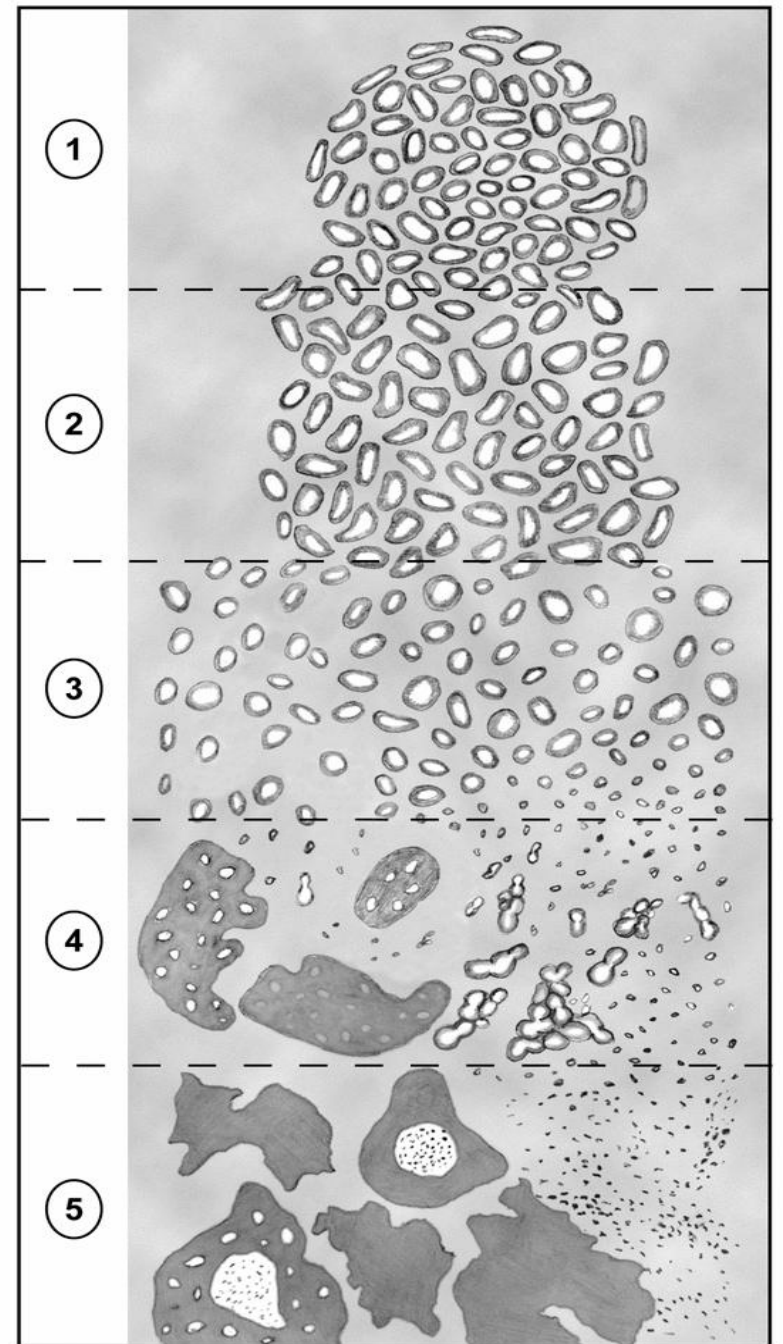
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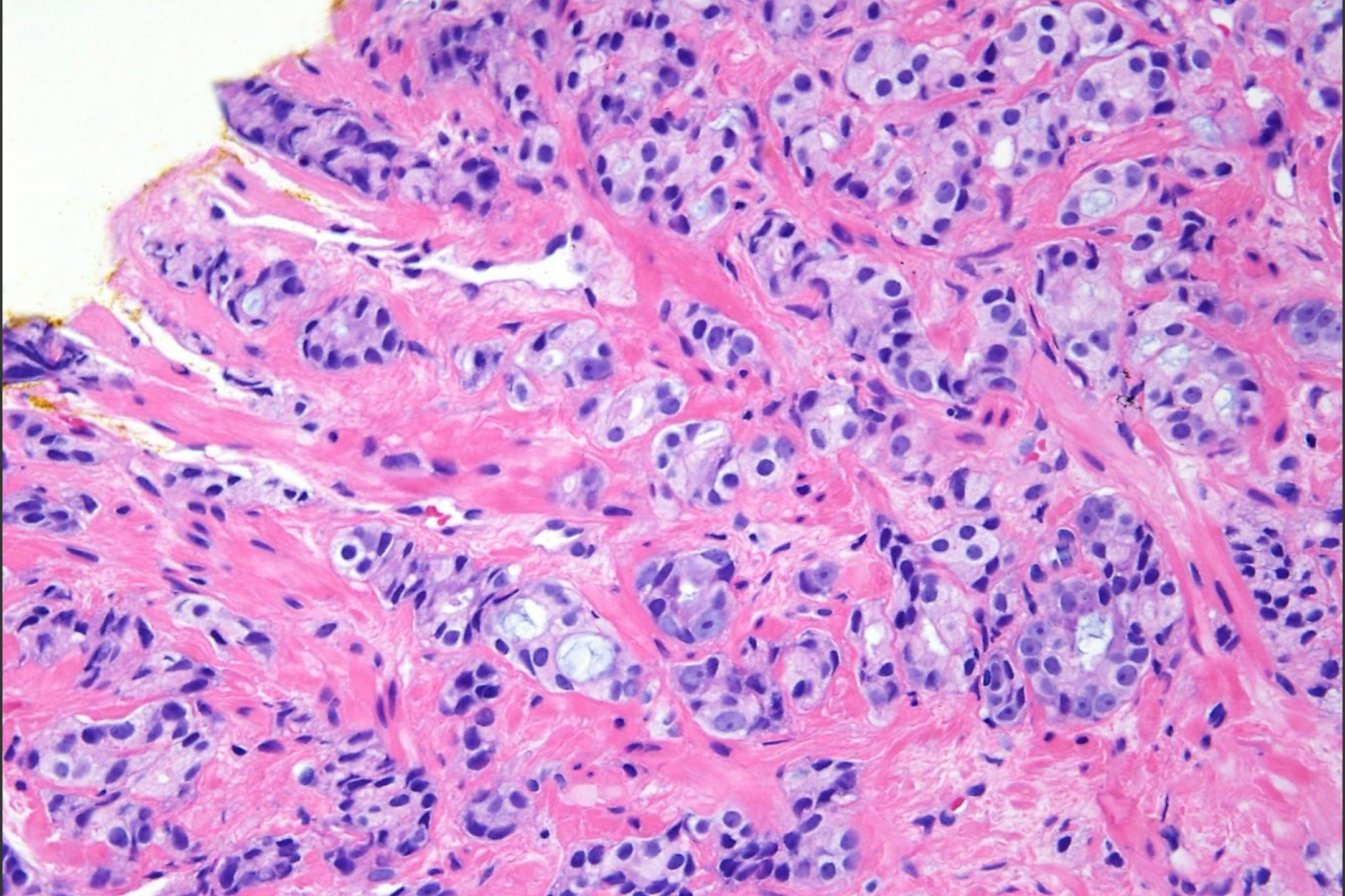
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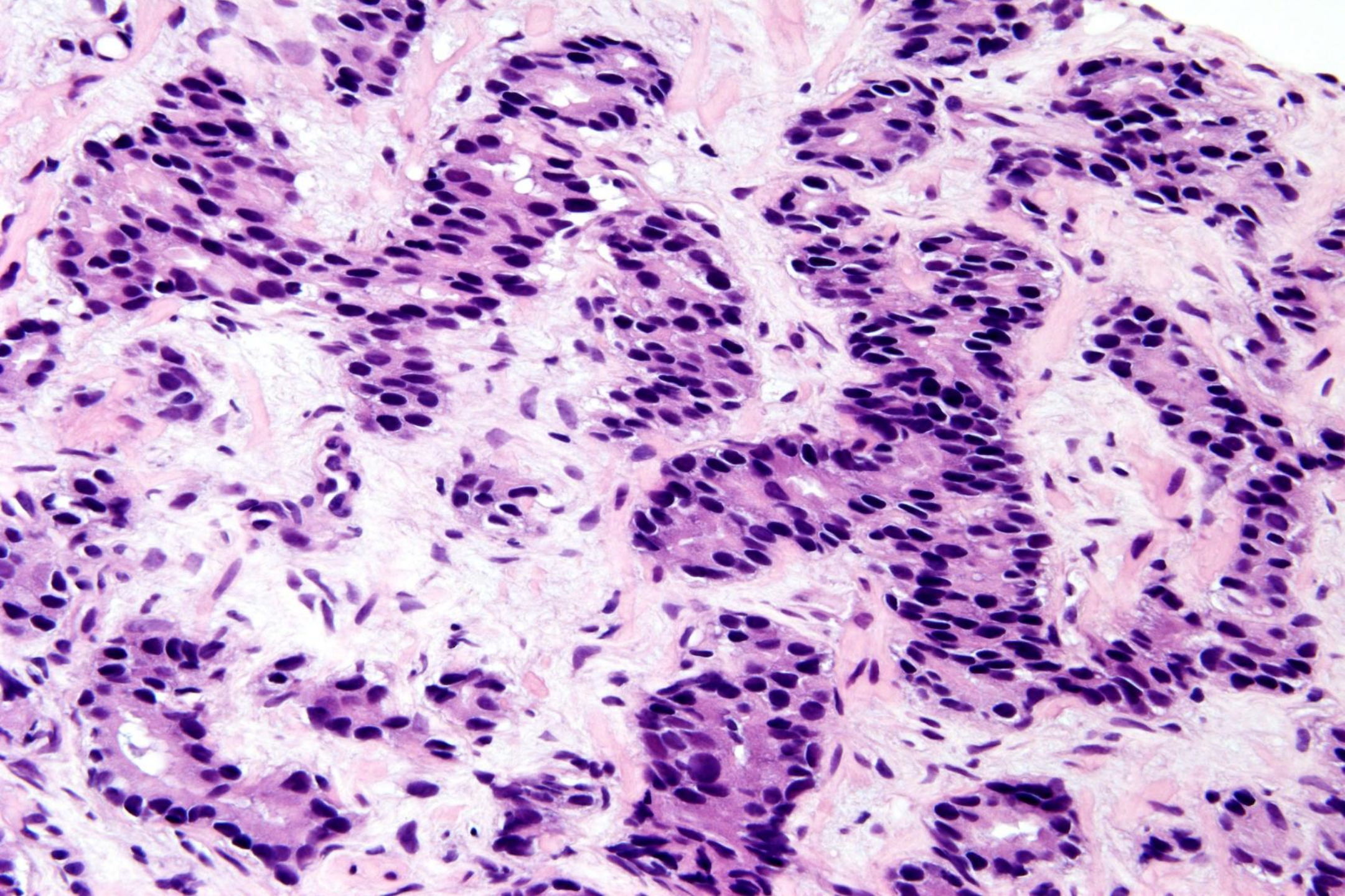


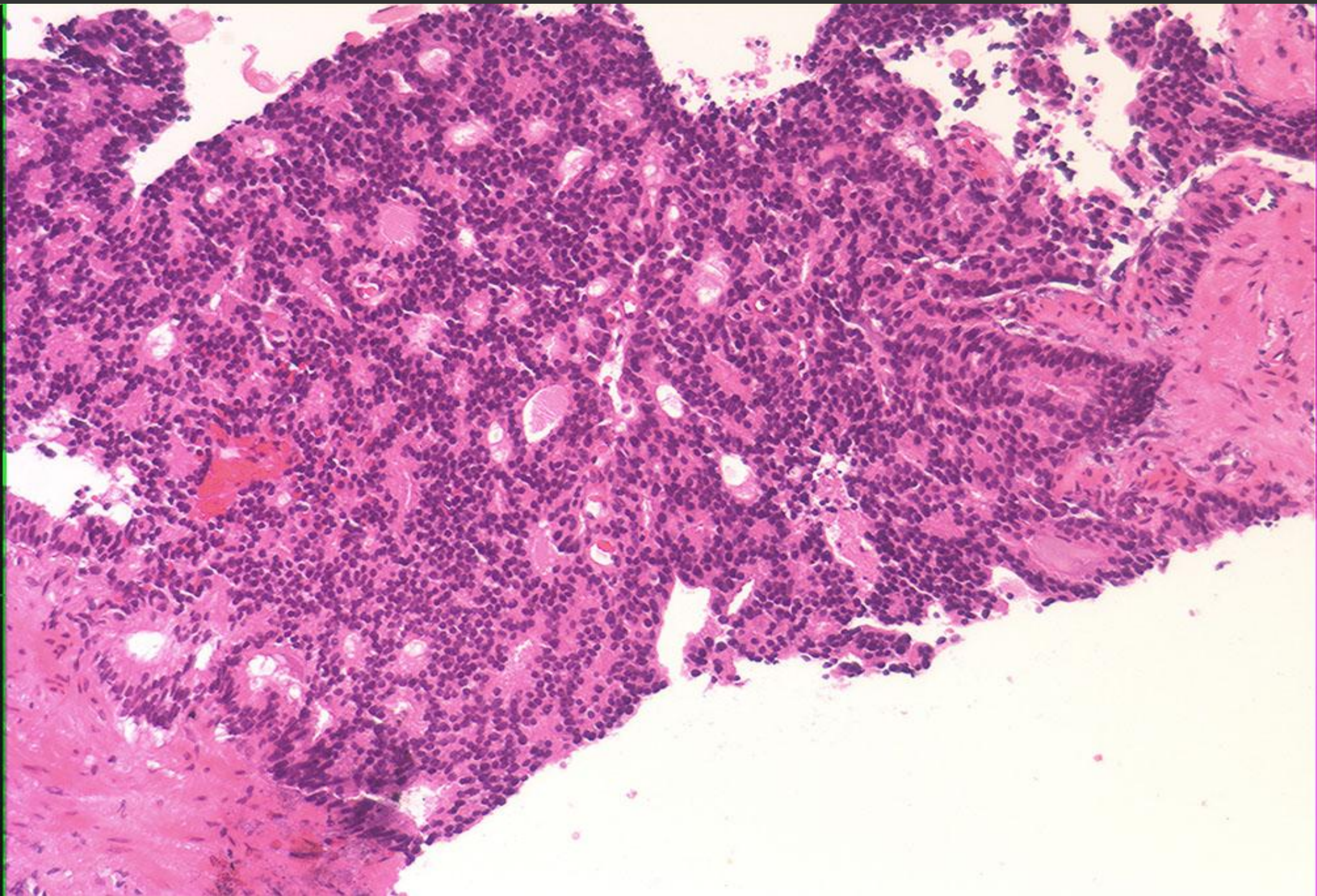
Brumbaugh

Different Types of Pattern 4

- **Poorly-Formed Glands**
- **Fused Glands**
- **Cribriform Glands (From the Latin word for sieve)**







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, other findings)**
- PSA criteria
 - PSA
 - Density

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

Jonathan I. Epstein, MD; Patrick C. Walsh, MD; Marné Carmichael; Charles B. Brendler, MD

JAMA 1994

Pre-Operative Model to Predict Insignificant Cancer

- Stage T1c (nonpalpable)
- Gleason score 6
- <3 cores involved by cancer
- No core with >50% involvement
- » PSA Density (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

Problems with Prostate Cancer Grading

- Regularly, review prostate cancer biopsies sent in by patients or clinicians where either change to a high grade (Gleason 6 to 7) or to a lower grade (Gleason 7 to 6).
- Unrelated to AS, frequently change other grades, as well.
- Correct grade is critical and the foundation for the optimal treatment for prostate cancer.

www.hopkinsconsults.org

Why Discrepant Grading?

- **Most pathologists are good diagnostically and grade accurately**
- **Some either due to inexperience or lack of skill can grade blatantly in error**
- **However, in some cases, the grading can be subjective and should rely on pathologists with extensive experience.**

Measuring Discontinuous Foci



- Cancer involving 5% of the area of the core or
- Small foci of cancer discontinuously involving 80% of the length of the core
- Studies have shown that in the vast majority of cases this represent a single larger tumor going in and out of plane of section of needle biopsy so should be considered 80% core involvement.

The NCCN definition of favorable risk prostate cancer?

Low (D'Amico)

- T1-T2a
- Gleason score 6
- PSA <10ng/ml

Very low (Epstein)

- T1c
- Gleason score 6
- PSA <10ng/ml
- PSA density <0.15ng/ml/cc
- <3 *biopsy cores with cancer*
- ≤50% *of core with cancer*

■

Why Distinguish Between *Very Low* (factors in extent of cancer on bx) and *Low Risk Disease*?

1) Cancer *extent* on biopsy AND PSA *density* at diagnosis are directly associated with grade reclassification during surveillance

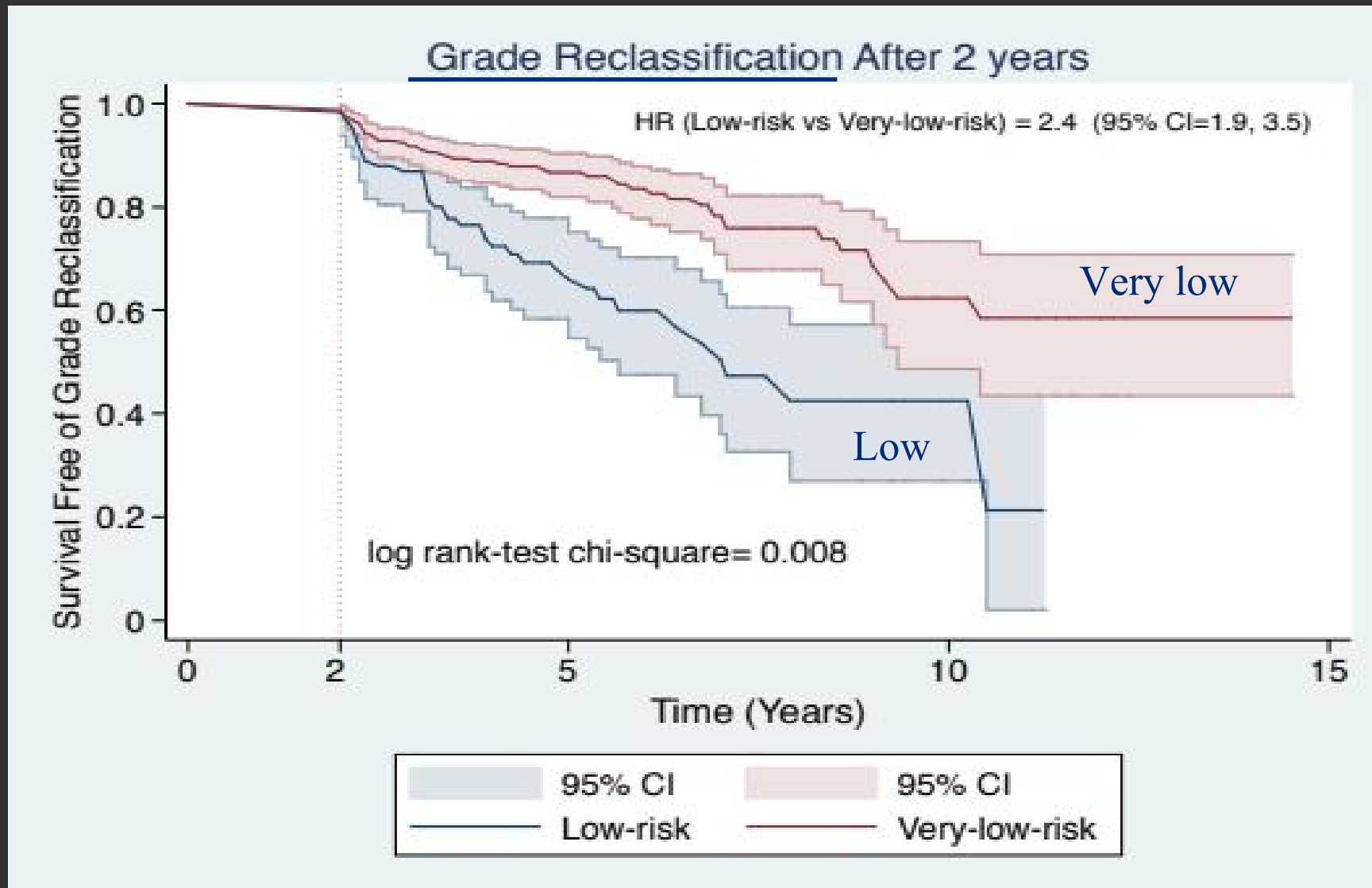
(Loeb et al, Eur Urol 2015)

2) 2 fold higher risk of surgically confirmed non organ confined cancer and Gleason pattern 4 in men with *low risk* versus *very low risk* disease (Tosoian et al, J Urol 2013)

3) 2 fold higher risk of metastatic disease, prostate cancer death, and treatment failure with surveillance for low risk vs very low risk disease

(Godtman et al, Eur Urol 2016)

Low risk (D'Amico) and *very low risk* represent 2 distinct subsets if untreated



Variable Inclusion Criteria

- T1c (minority) vs T1c-T2a vs. T1c-T2
- PSA \leq 10 (most) vs. PSA \leq 15 vs. PSA \leq 20
- PSAD \leq 0.15 vs. PSAD \leq 0.2 vs. not criteria (most)
- Gleason score \leq 6 (almost all) vs. \leq 3+4=7 (older men)
- \leq 2 positive cores (most) vs. \leq 3 cores vs. \leq 33% vs. \leq 50%
- \leq 50% max per core (most) vs. \leq 20% vs. not criteria
- Unilateral vs. Bilateral

Variable Criteria for Reclassification

- **Most based on subsequent worse biopsy (grade, no. cores, max. % cancer per core) criteria than original inclusion criteria**
- **JHH has never used PSA based criteria to determine reclassification as never been shown to be accurate**
- **Recent dropping of PSA based criteria in other AS centers, yet some use PSA doubling times or use to trigger MRI or more frequent biopsies**

Risk prediction tool for grade re-classification in men with favourable-risk prostate cancer on active surveillance

Mufaddal M. Mamawala, Karthik Rao, Patricia Landis, Jonathan I. Epstein, Bruce J. Trock, Jeffrey J. Tosoian, Kenneth J. Pienta and H. Ballentine Carter

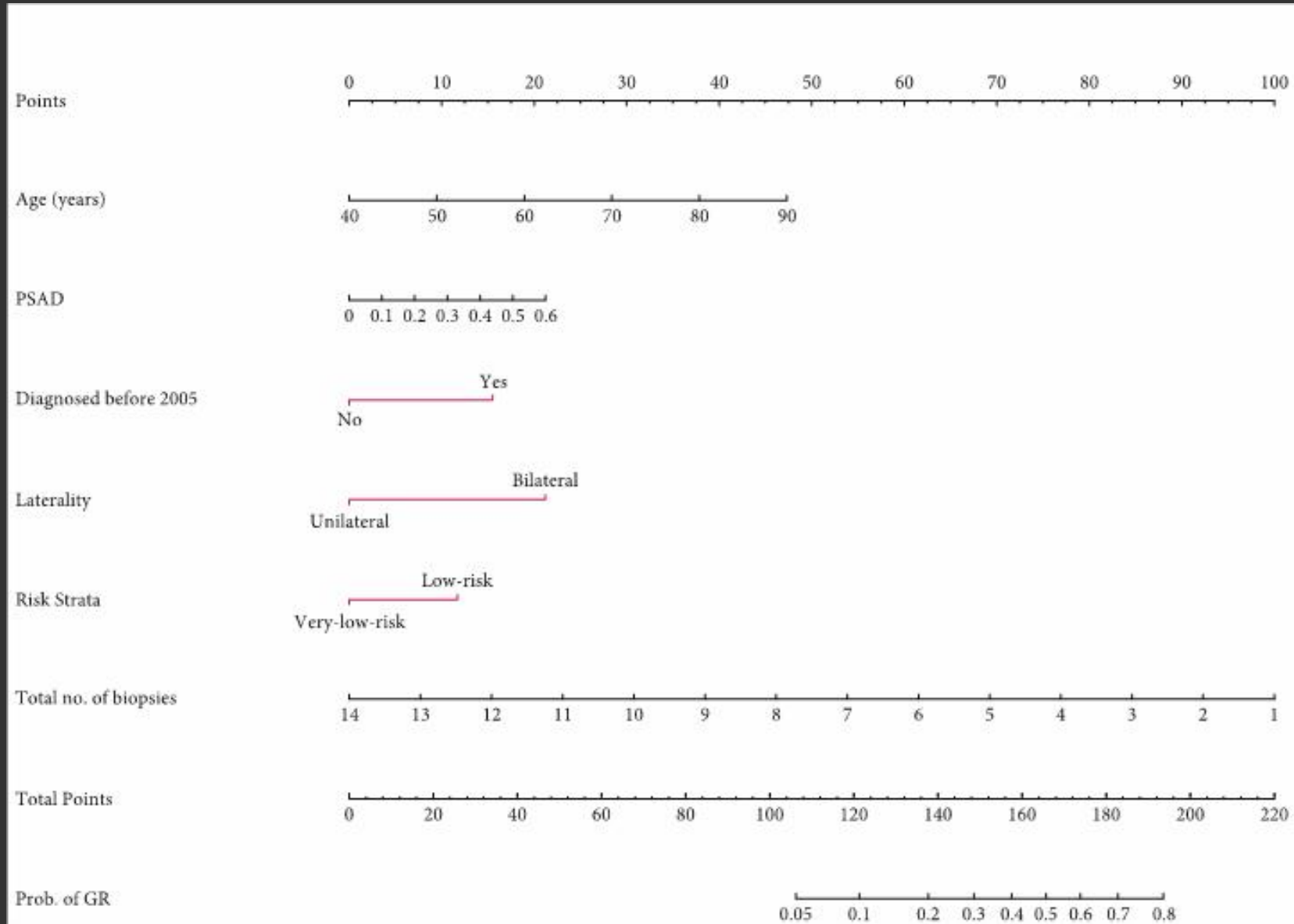
The James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD, USA

BJU Int 120:25-31, 2017

Multivariable Model Results

Covariates	B Coefficient	OR	P- value
Diagnosed before 2005	0.385	2.16	< .0001
Age, y	0.047	1.05	0.0004
PSA Density at last biopsy (per 0.1 unit increase)	0.076	1.19	0.04
Laterality as of last biopsy (Bilateral vs. Unilateral)	0.525	2.86	< .0001
Risk status as of last biopsy (Low-risk vs. Very-low-risk)	0.290	1.79	0.0009
Total number of biopsies (Biopsies not showing Gleason \geq 7)	-0.381	0.68	< .0001

Grade Reclassification Nomogram



Practical Utility of Calculator

- **60% of our cohort had a predicted probability of grade reclassification of $\leq 20\%$ with a false negative rate of $\leq 10\%$.**
- **Reassure patients that they have a high probability of successfully staying on AS and can space out the repeat biopsies.**

**AS for Men with Gleason Score 3+4=7
(Grade Group 2)**

Is it safe?

Surveillance Outcomes Differ Depending on *Selection Criteria* and *Triggers* for Intervention

Program	Gleason score 7 (%)	Biopsy frequency, yrs	10yr treated (%)	Metastases (%)	PCSM (%), 10yr	Overall mortality (%)
<i>Johns Hopkins</i> n=1298	0	1-2	50	0.4	0.1	4
<i>Sunnybrook</i> n=993	13	3-4	36	2.8	1.9	15

Tosoian JJ et al, J Clin Oncol 2015

Klotz L et al, J Clin Oncol 2015

Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience

Hima Bindu Musunuru, Toshihiro Yamamoto, Laurence Klotz, Gabriella Ghanem, Alexandre Mamedov, Peraka Sethukavalan, Vibhuti Jethava, Suneil Jain, Liying Zhang, Danny Vesprini and Andrew Loblaw*

J Urol 2016

Gleason ≤ 6 – 15 year metastases-free survival 94%

Gleason 3+4=7 with PSA ≤ 20 - 15 year metastases-free survival 84%

“AS for Gleason 7 disease should be offered only in the setting of a clinical trial.”

Are There Subgroups of Favorable Gleason Score 3+4=7 (Grade Group 2) Who Would be Candidates for Active Surveillance

- **Extent**
- **Percent Pattern 4**
- **Cribriform vs. non-cribriform**

JAMA Oncology | **Brief Report**

Adverse Pathologic Findings for Men Electing Immediate Radical Prostatectomy Defining a Favorable Intermediate-Risk Group

Hiten D. Patel, MD, MPH; Jeffrey J. Tosoian, MD, MPH; H. Ballentine Carter, MD; Jonathan I. Epstein, MD

JAMA Oncology 2018

Cohorts

- **A prospective cohort of men (2005-July 2016) undergoing radical prostatectomy.**
- **VLR – 1,264 men**
- **LR – 4,849 men**
- **FIR (1-2 cores of Gleason 3+4=7, PSA<20ng/ml) – 608 men**

Rates of Adverse Pathology at RP

- VLR - 4.7%
- LR - 5.8%
- FIR - 24.7%

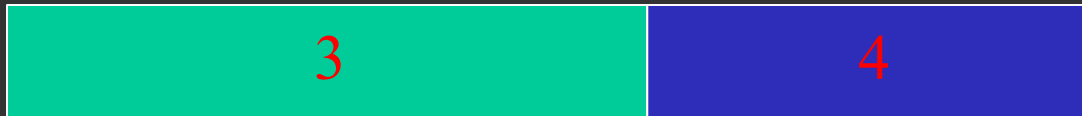
Men with FIR and 1-2 positive cores with no core >50%

- 18.5% had adverse pathology at RP

Percent Gleason Pattern 4 In Gleason Score 7



3+4=7 with <10% pattern 4 **May be candidate AS**



3+4=7 with close to 50% pattern 4 **Not a candidate AS**


Percent Pattern 4

Major GU Pathology societies recommend reporting percent Gleason pattern 4 on needle biopsy with Gleason scores $3+4=7$ and $4+3=7$.

Currently, not being performed by many pathologists.



The percentage of high-grade prostatic adenocarcinoma in prostate biopsies significantly improves on Grade Groups in the prediction of prostate cancer death

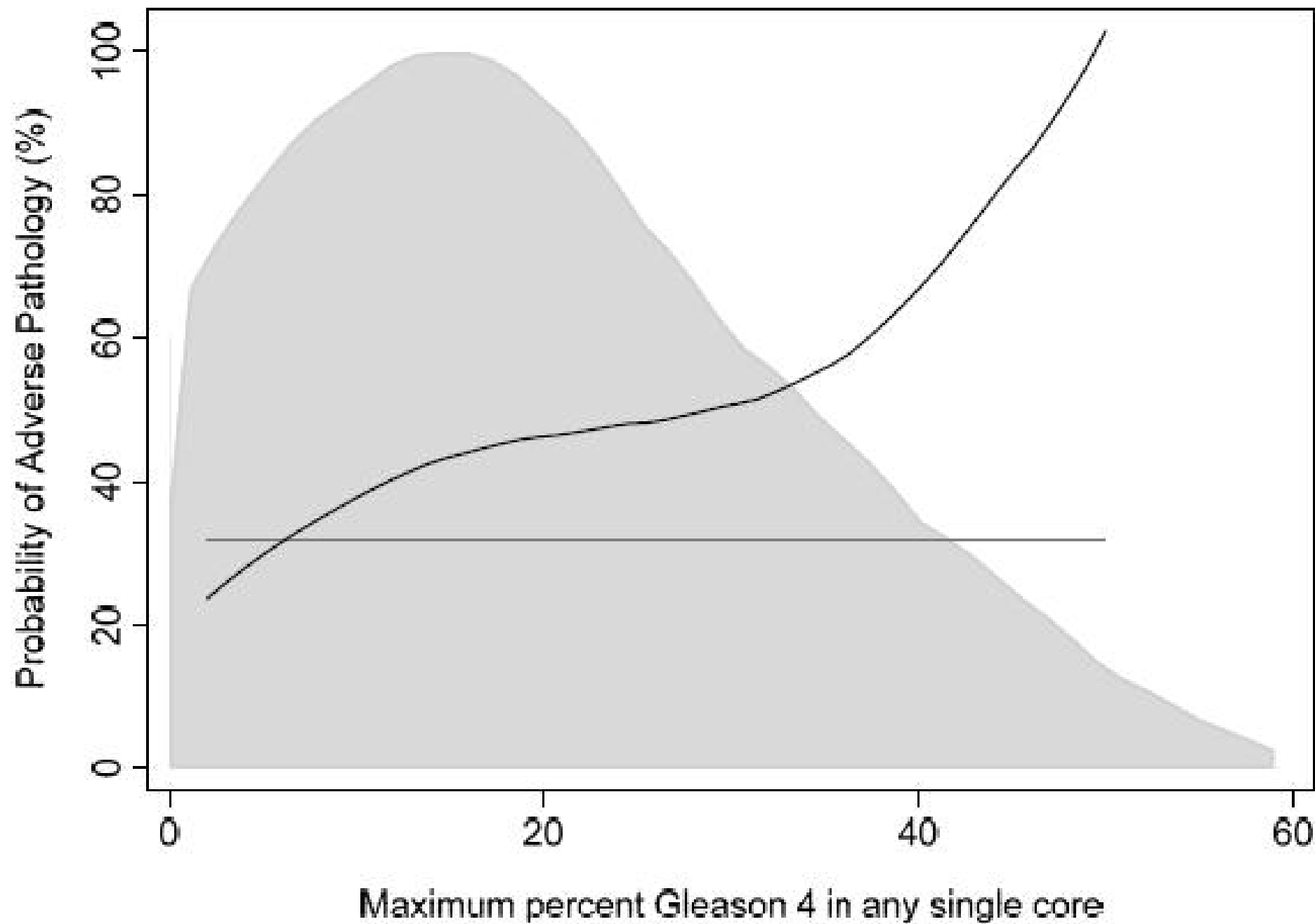
Daniel M Berney,¹  Luis Beltran,¹ Holly Sandu,² Geraldine Soosay,³ Henrik Møller,^{1,4} Peter Scardino,⁵ Jacqueline Murphy,² Amar Ahmad,² Jack Cuzick² & on behalf of the Transatlantic Prostate Group

- **Followed patients with AS.**
- **<5% pattern 4 same risk of cancer death as Gleason score 6.**
- **Weakness - Different treatment as older study population and sextant biopsies.**

Clinical Usefulness of Total Length of Gleason Pattern 4 on Biopsy in Men with Grade Group 2 Prostate Cancer

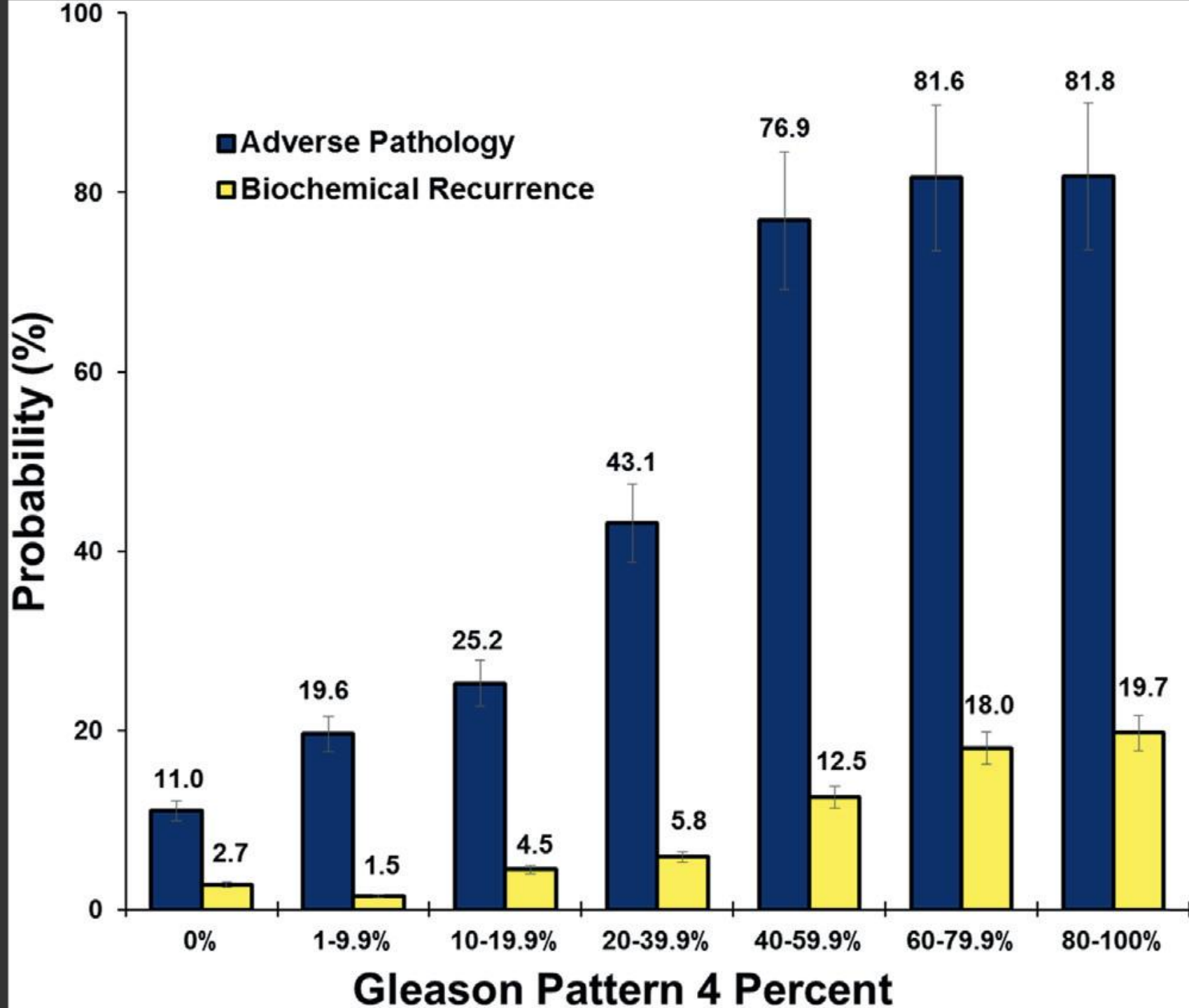
Lucas W. Dean, Melissa Assel, Daniel D. Sjoberg, Andrew J. Vickers,*
Hikmat A. Al-Ahmadie, Ying-Bei Chen, Anuradha Gopalan,
S. Joseph Sirintrapun, Satish K. Tickoo, James A. Eastham,
Peter T. Scardino, Victor E. Reuter, Behfar Ehdai and Samson W. Finet

J Urol 2019



Prognostic Value of Percent Gleason Grade 4 at Prostate Biopsy in Predicting Prostatectomy Pathology and Recurrence

Adam I. Cole, Todd M. Morgan,* Daniel E. Spratt, Ganesh S. Palapattu, Chang He, Scott A. Tomlins, Alon Z. Weizer, Felix Y. Feng, Angela Wu, Javed Siddiqui, Arul M. Chinnaiyan, Jeffrey S. Montgomery, Lakshmi P. Kunju, David C. Miller,† Brent K. Hollenbeck,‡ John T. Wei and Rohit Mehra§



Need for Additional Studies on Percent Pattern 4

- **Is there a cut-off for percent pattern 4 that is helpful to identify which men with $3+4=7$ can undergo AS and how to measure (max per core or average between all cores)?**
- **Need long term follow-up studies of men on AS.**

Cribriform Glands

Vast majority of studies on prostate cancer with cribriform architecture demonstrate associations with both adverse clinical outcomes and molecular features typically seen in advanced disease.

Cribriform glands in 3+4=7 – should it rule out AS?

Need long term follow-up studies of men on AS.

Other Findings on Biopsy

Relation to AS

Findings That Do Not Affect AS

- Atypical (ASAP) foci
- High grade prostatic intraepithelial neoplasia (HGPIN)
- Perineural invasion

Finding that Does Affect AS

Intraductal Carcinoma (IDC-P)

- Typically associated with high grade invasive carcinoma.
- Rarely, a precursor (in-situ cancer) lesion that can go on to invasive **high grade** cancer.
- If IDC-P present with tumor that is otherwise good for AS, then should **not** under go AS.

Finding That Possibly Affects AS

Atypical Intraductal Proliferation (AIP)

- In some cases atypical glands have some but not all the features of IDC-P.
- Termed *Atypical Intraductal Proliferation (AIP)*.
- If present on biopsy that otherwise would be good for AS, would recommend repeat biopsy before going on AS.

Impetus for a New Prostate Cancer Grading System

The Word “Cancer” Drives Overtreatment

- **Fear of death from cancer likely plays some role, and removing the label “cancer” could reduce unnecessary treatment of low grade disease.**
- **Proposed name: IDLE (indolent lesion of epithelial origin) (Esserman, Lancet Oncol et al., 2013)**

Gleason Score 6 Adenocarcinoma: Should It Be Labeled As Cancer?

H. Ballentine Carter, Alan W. Partin, Patrick C. Walsh, Bruce J. Trock, Robert W. Veltri, William G. Nelson, and Donald S. Coffey, *The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD*
Eric A. Singer, *National Cancer Institute, National Institutes of Health, Bethesda, MD*
Jonathan I. Epstein, *The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, MD*

When is Prostate Cancer Really Cancer?

David M. Berman, MD, PhD^a, Jonathan I. Epstein, MD^{b,*}

Do Adenocarcinomas of the Prostate With Gleason Score (GS) ≤ 6 Have the Potential to Metastasize to Lymph Nodes?

Hillary M. Ross, Oleksandr N. Kryvenko,† Janet E. Cowan,‡ Jeffry P. Simko,‡§
Thomas M. Wheeler,|| and Jonathan I. Epstein, MD*¶##*

American Journal of Surgical Pathology 2012

Arguments in Favor of Retention of Gleason Score 6 Cancer

- **Morphological**
- **Molecular**
- **20% undersampling of higher grade cancer with Gleason 6 on biopsy**
- **Patients will be lost to follow-up if called IDLE tumor**

Gleason Score 6 Prostatic Adenocarcinoma Should Still be Called “Cancer”

- **Rather there is a need to change what patients think when they hear they have Gleason score 6 cancer.**
- **Urologists need to reassure and educate patients.**
- **Modify how we report prostate cancer grade to more accurately reflect their behavior.**

Problems with Gleason System: Scale

- **6 is the lowest grade reported although the scale goes from 2-10**
- **Patients are told they have a Gleason score of 6 out of 10 and logically but incorrectly think that they have a tumor in the middle of the grade spectrum, contributing to the fear of cancer**

- **Urologists need to reassure and educate patients when told they have Gleason score 6 cancer.**
- **Modify how pathologists report prostate cancer grade to more accurately reflect their behavior.**

Qualitative Study About Grading

- Majority of patients (84%) agreed that it would be clearer if grades were reported on a scale of 1-5 instead of 6-10
- 88% would prefer to hear they have “Group 1” rather than “Gleason 6”
- 80% would feel more comfortable choosing active surveillance with “Group 1” versus “Gleason 6”

Problems with Gleason System Grouping

- Gleason 7 is not homogeneous: $4+3=7$ has a much worse prognosis than $3+4=7$

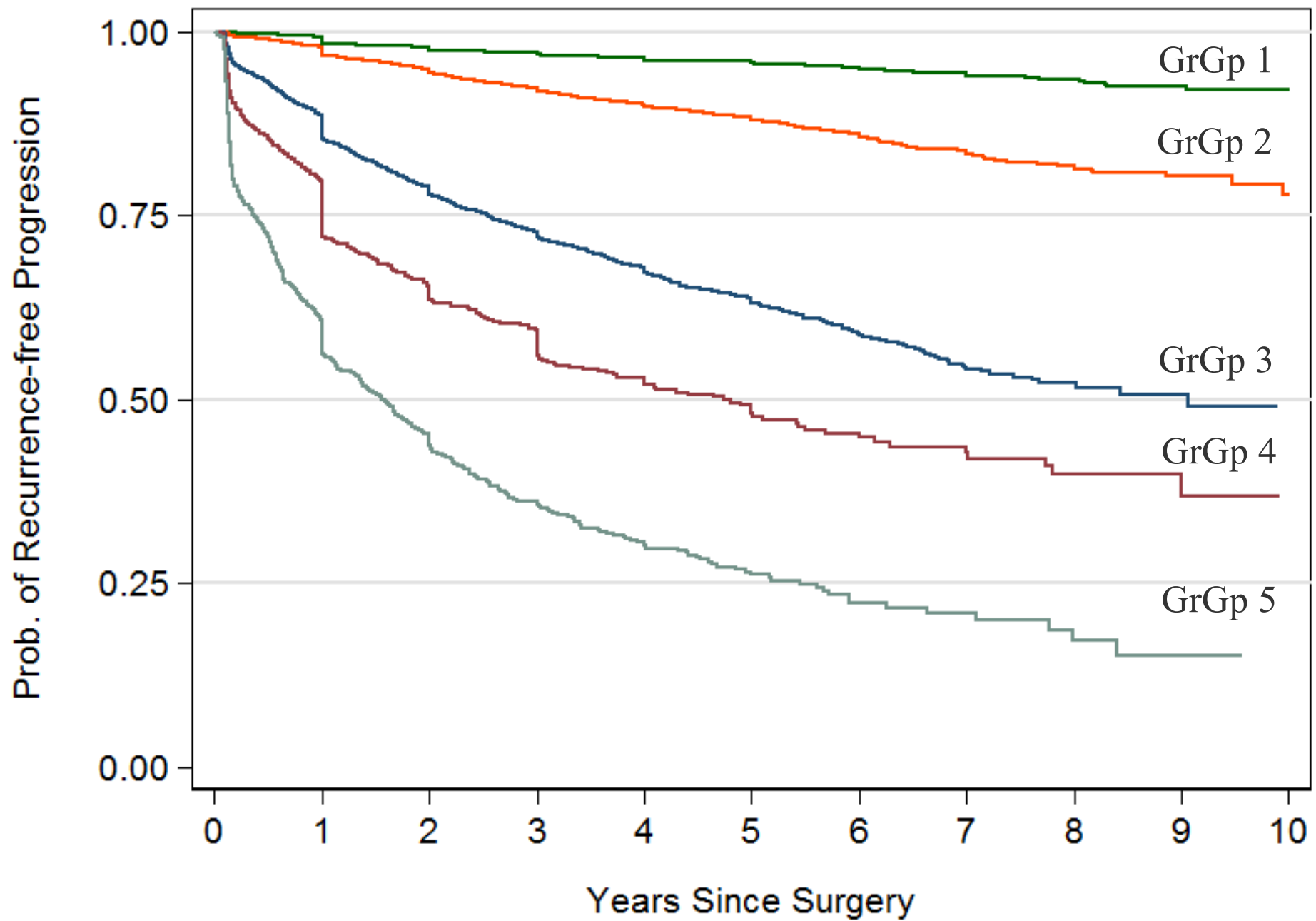
Prognostic Gleason grade grouping: data based on the modified Gleason scoring system

Phillip M. Pierorazio*, Patrick C. Walsh*, Alan W. Partin* and Jonathan I. Epstein*†‡

BJU International 2013; 111:753-60

New 5 Grade System

- **Grade Group 1 (Gleason score ≤ 6)**
- **Grade Group 2 (3+4=7)**
- **Grade Group 3 (4+3=7)**
- **Grade Group 4 (Gleason score 8)**
- **Grade Group 5 (Gleason score 9-10)**



The new grading system is accepted

2016 World Health Organization (WHO)

Pathology & Genetics:

Tumours of the Urinary System and Male Genital System

College of American Pathologists (CAP)

AJCC Cancer Staging Manual –TNM System (8th Edition)

Summary

- **Pathology plays a critical role in:**
- **Criteria for selection for AS**
- **Criteria for intervention on AS**
- **Reporting prostate cancer to more accurately reflect extent and grade for both urologists and patients**



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