JOHNS HOPKINS
MEDICINE

Prostate Cancer Grading

A Decade After the 2005 Modified System

Jonathan I. Epstein

Gleason Score 2-4 on Needle Should Not Be Made Editorial AJSP (Epstein), 2000

- 1) Poor reproducibility among experts for lower grade tumors.
- 2) Correlation with the prostatectomy score for Gleason 2-4 tumors is poor and up to 50% of the corresponding prostatectomies may have extraprostatic extension.
- 3) Gleason 2-4 may misguide clinicians and patients into believing that there is an indolent tumor.

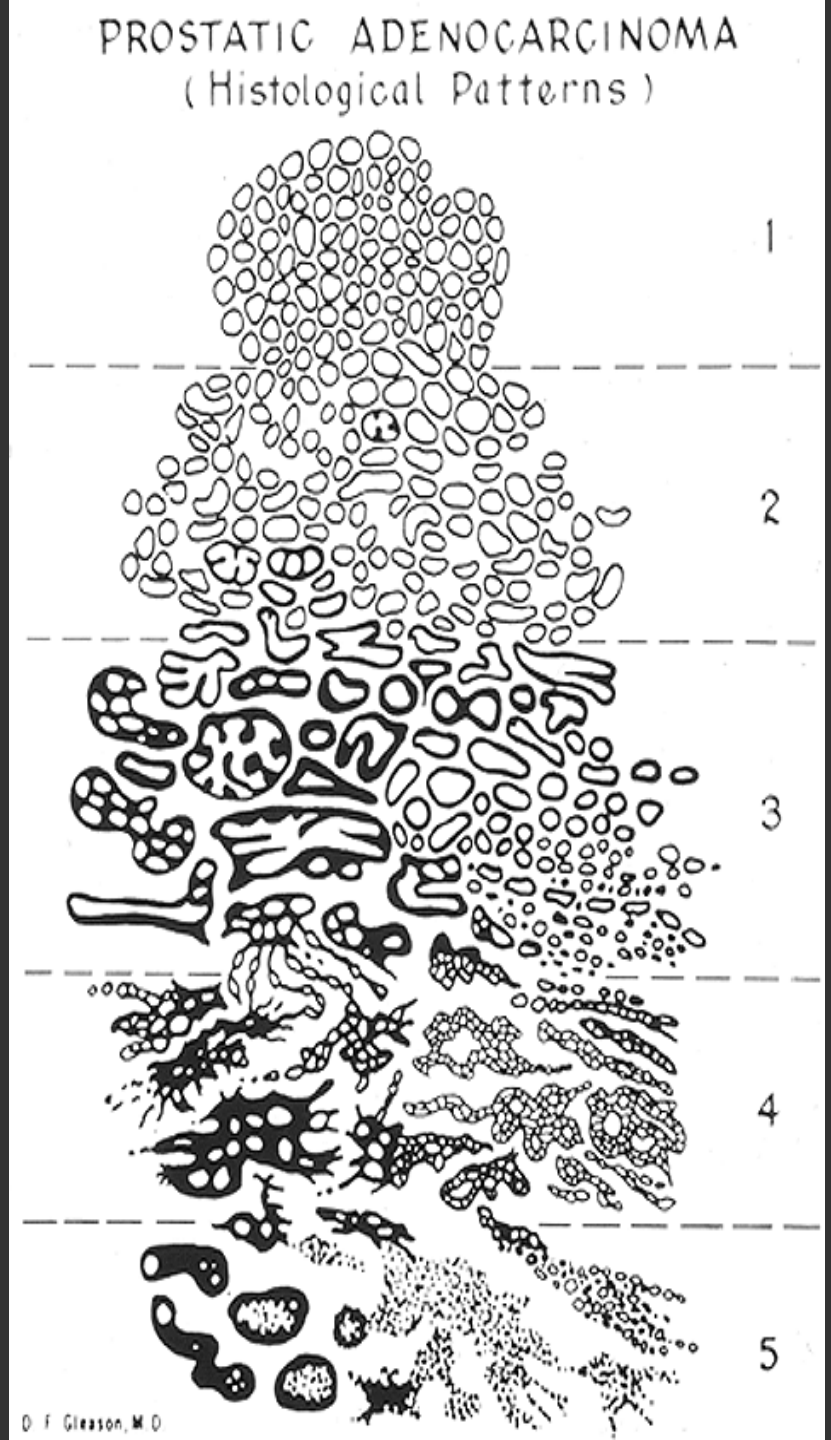
Low Grade Prostate Cancer Does Exist

- **Transition zone**
- **Small foci**
- **Seen on TURP – often indicates “insignificant” cancer**
- **Rarely sampled on needle biopsy – not indicate “indolent” tumor**

The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

The American Journal of Surgical Pathology: Volume 29. September 2005 pp 1228-1242

Epstein, Jonathan I ; Allsbrook, William C Jr; Amin, Mahul B; Egevad, Lars L and the ISUP Grading Committee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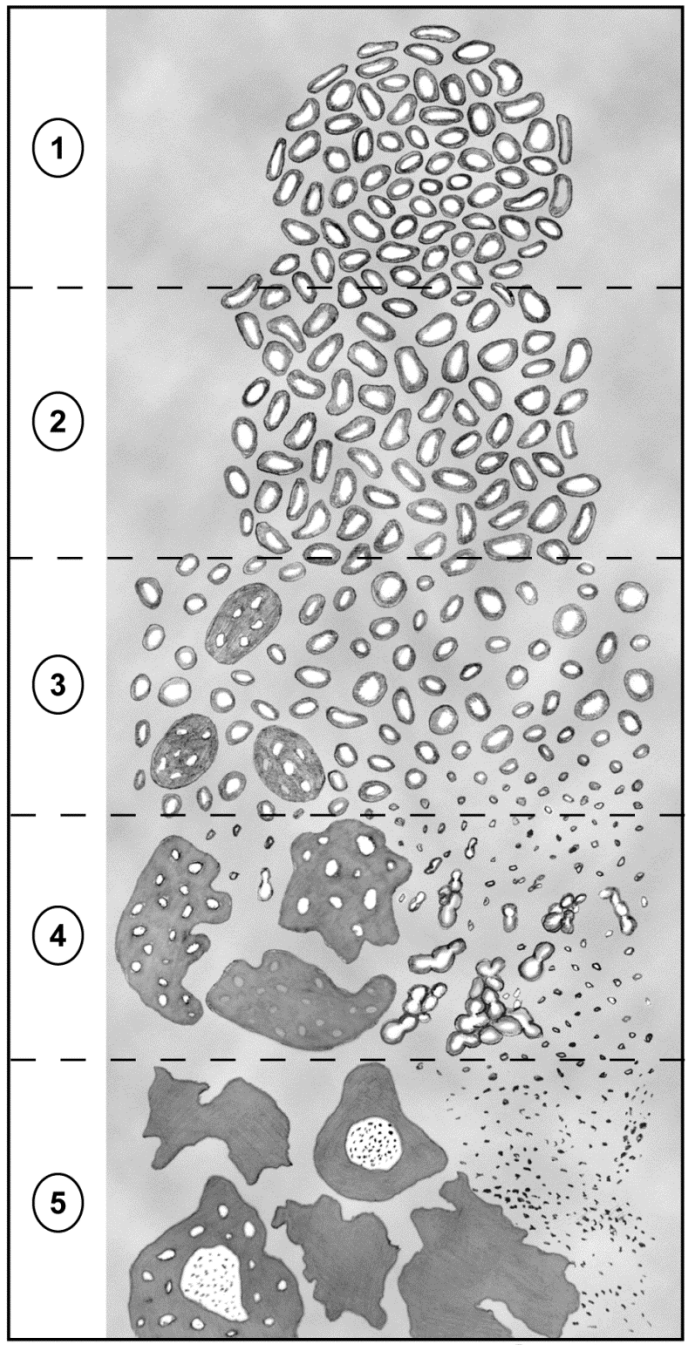
D. F. Gleason, M.D.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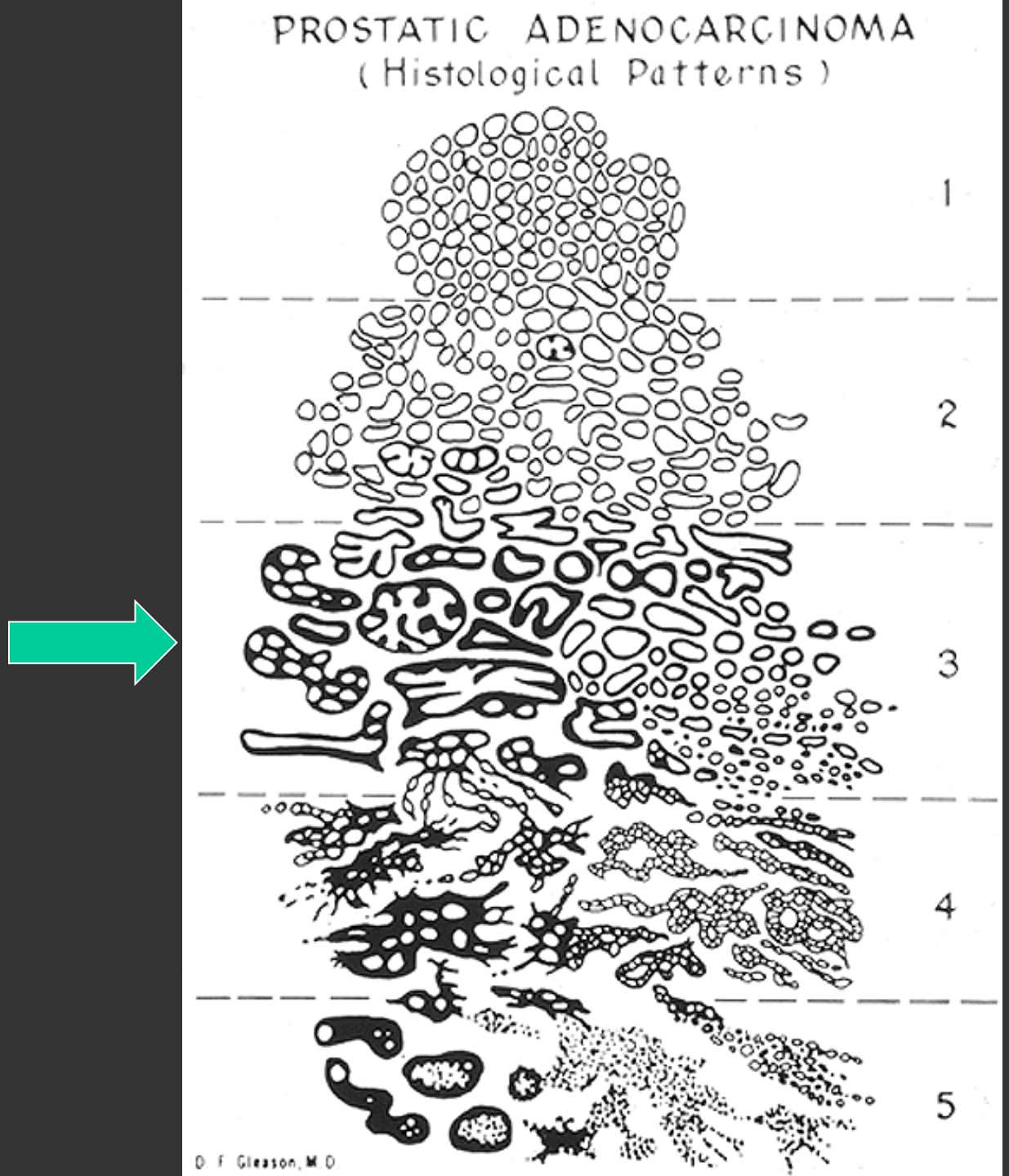
Gleason Score 2-4 on Needle Should Rarely if Ever Be Made

Consensus Conference, 2005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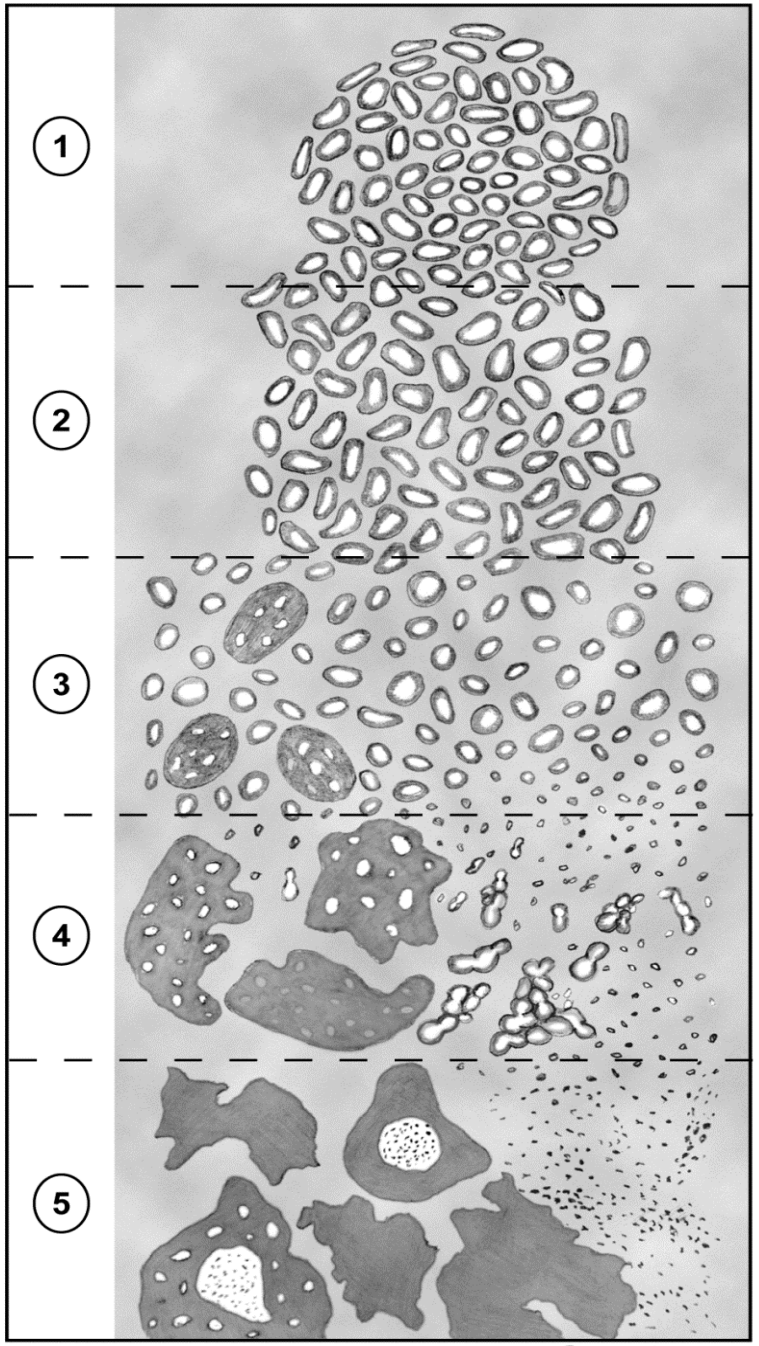
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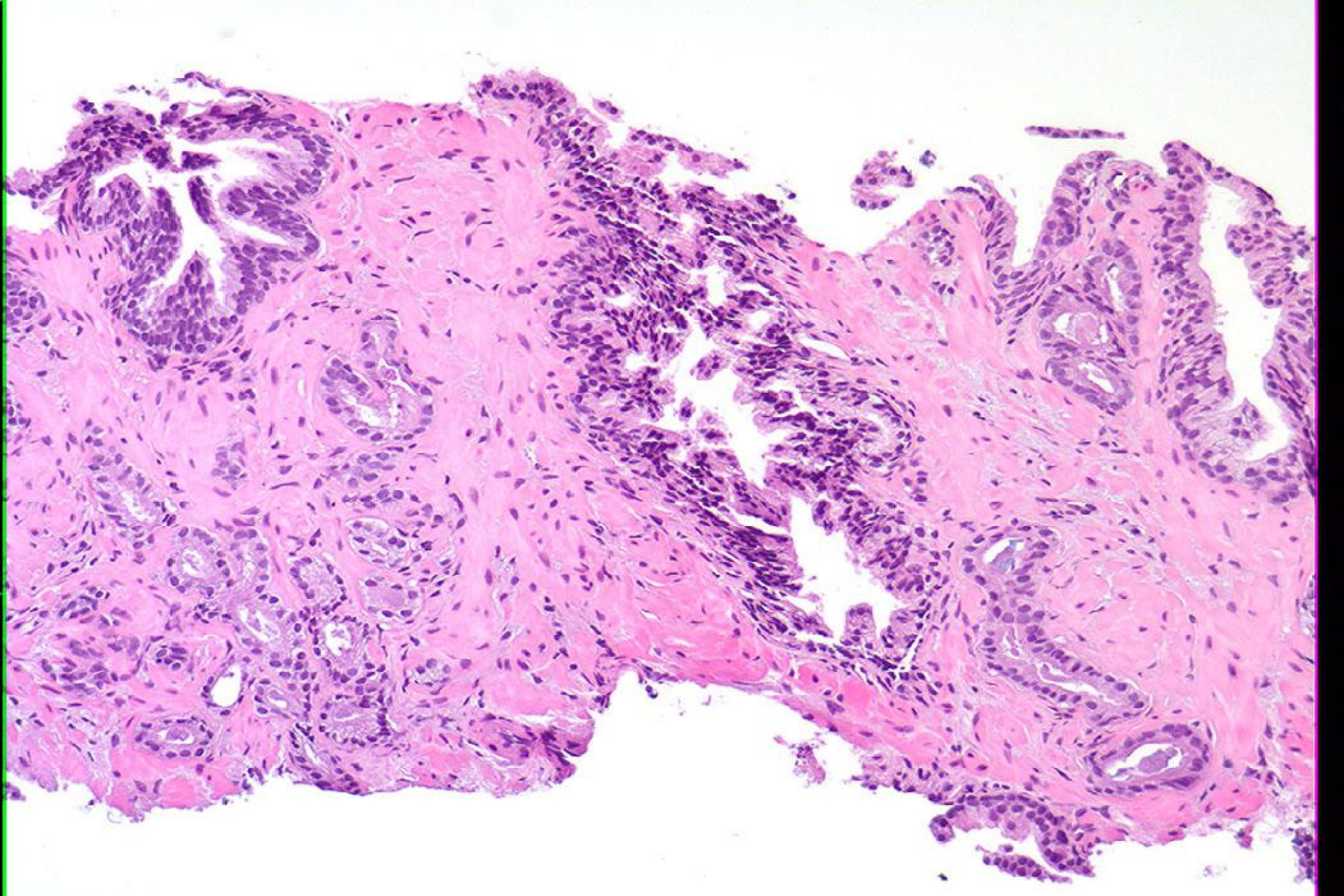

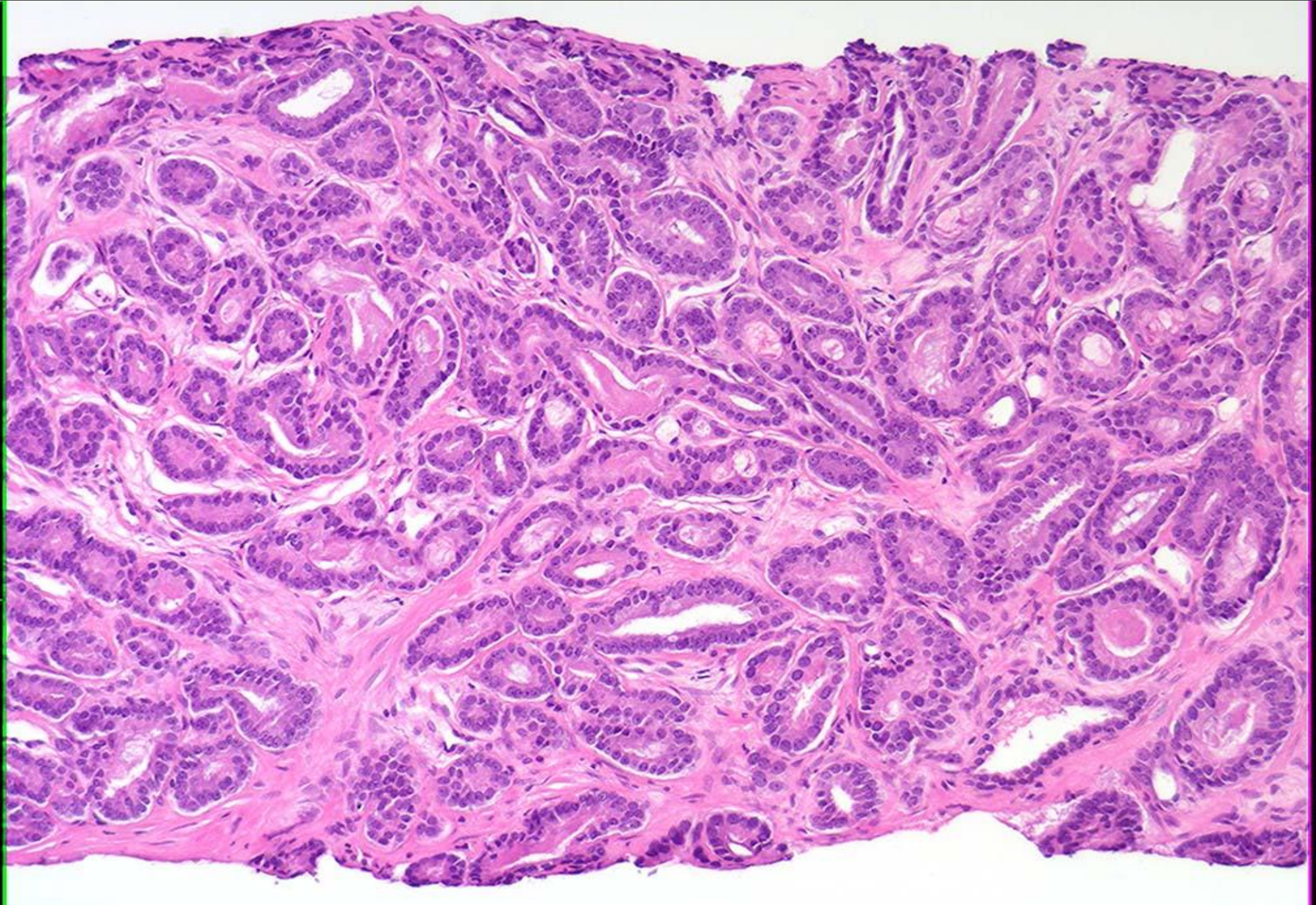

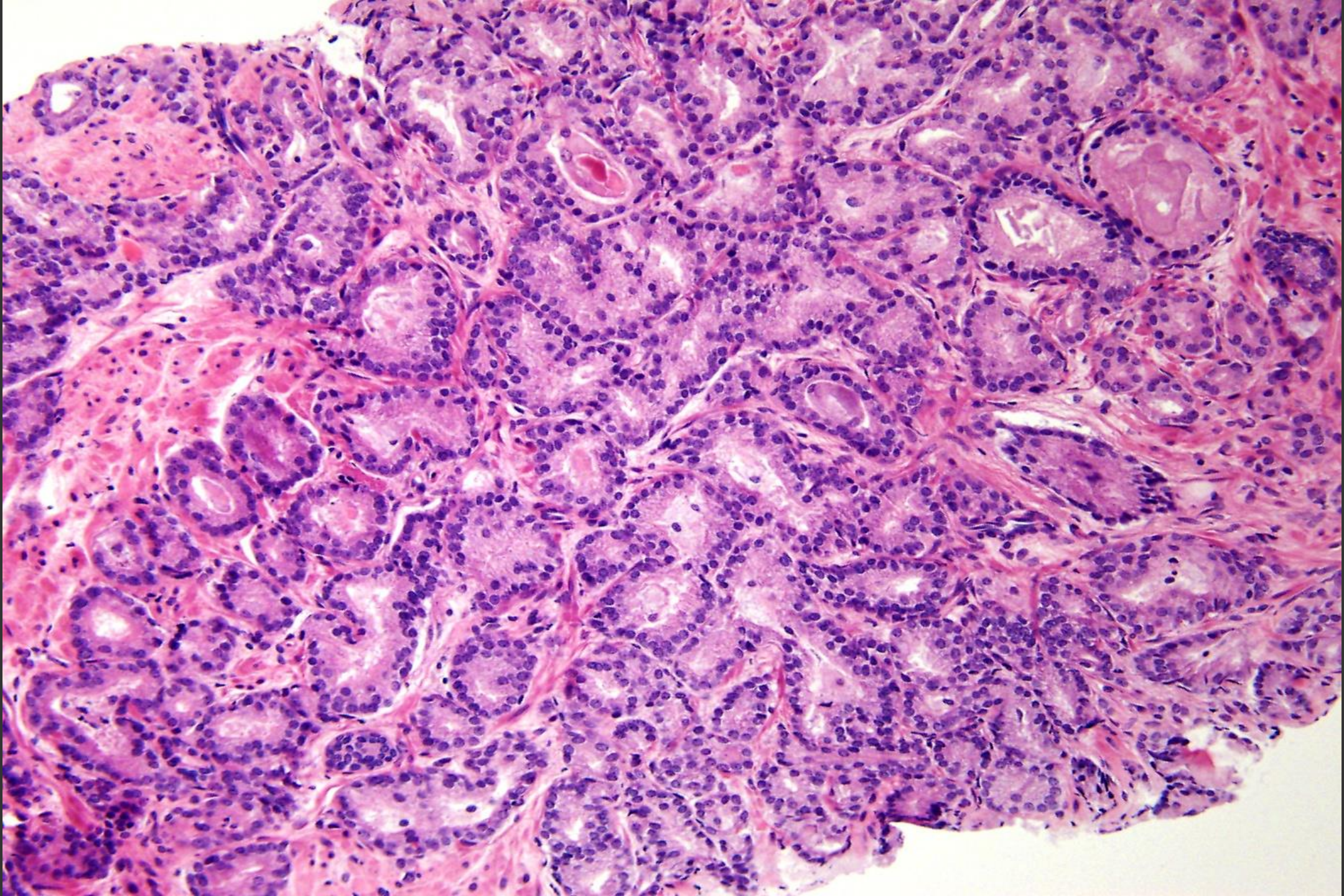

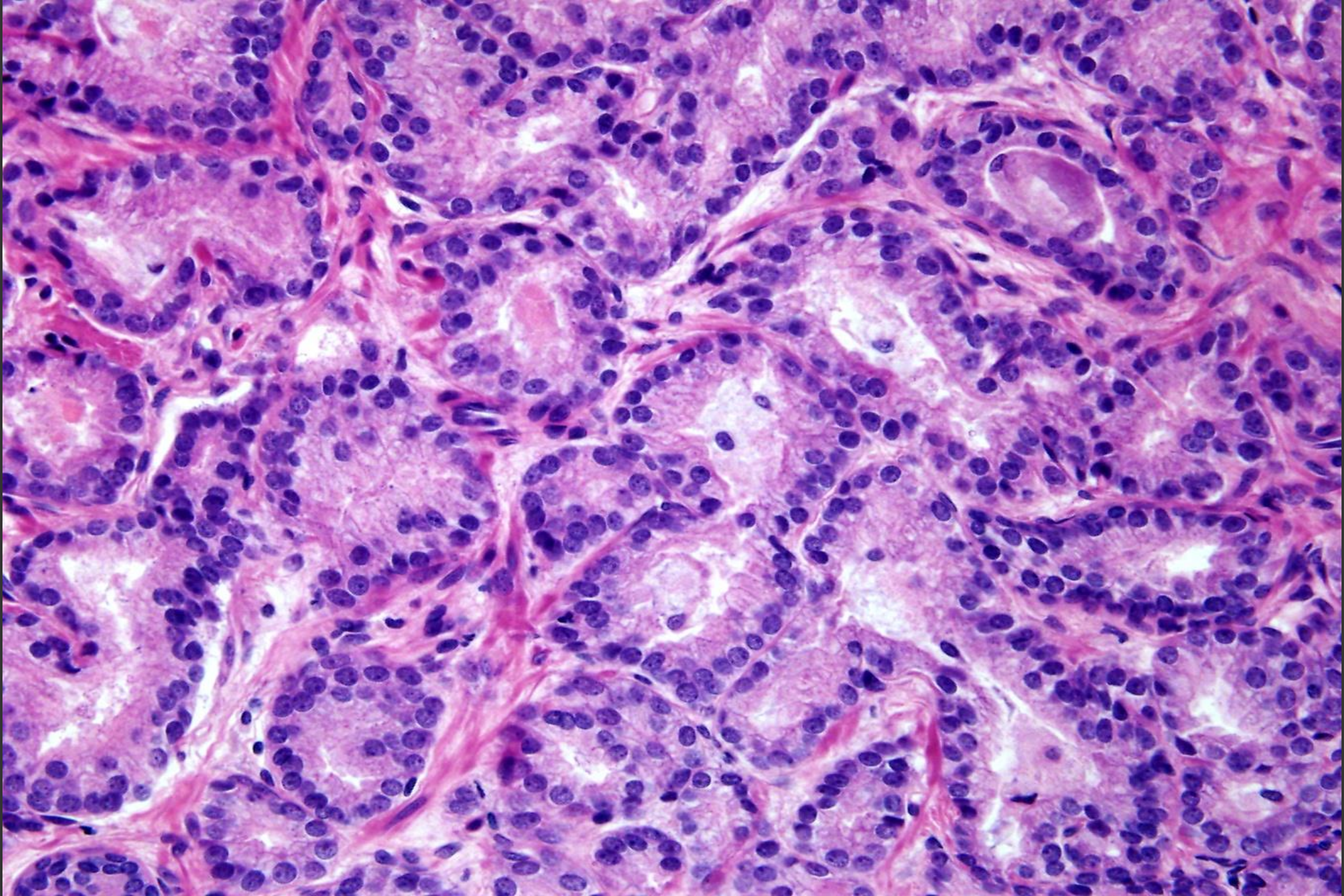

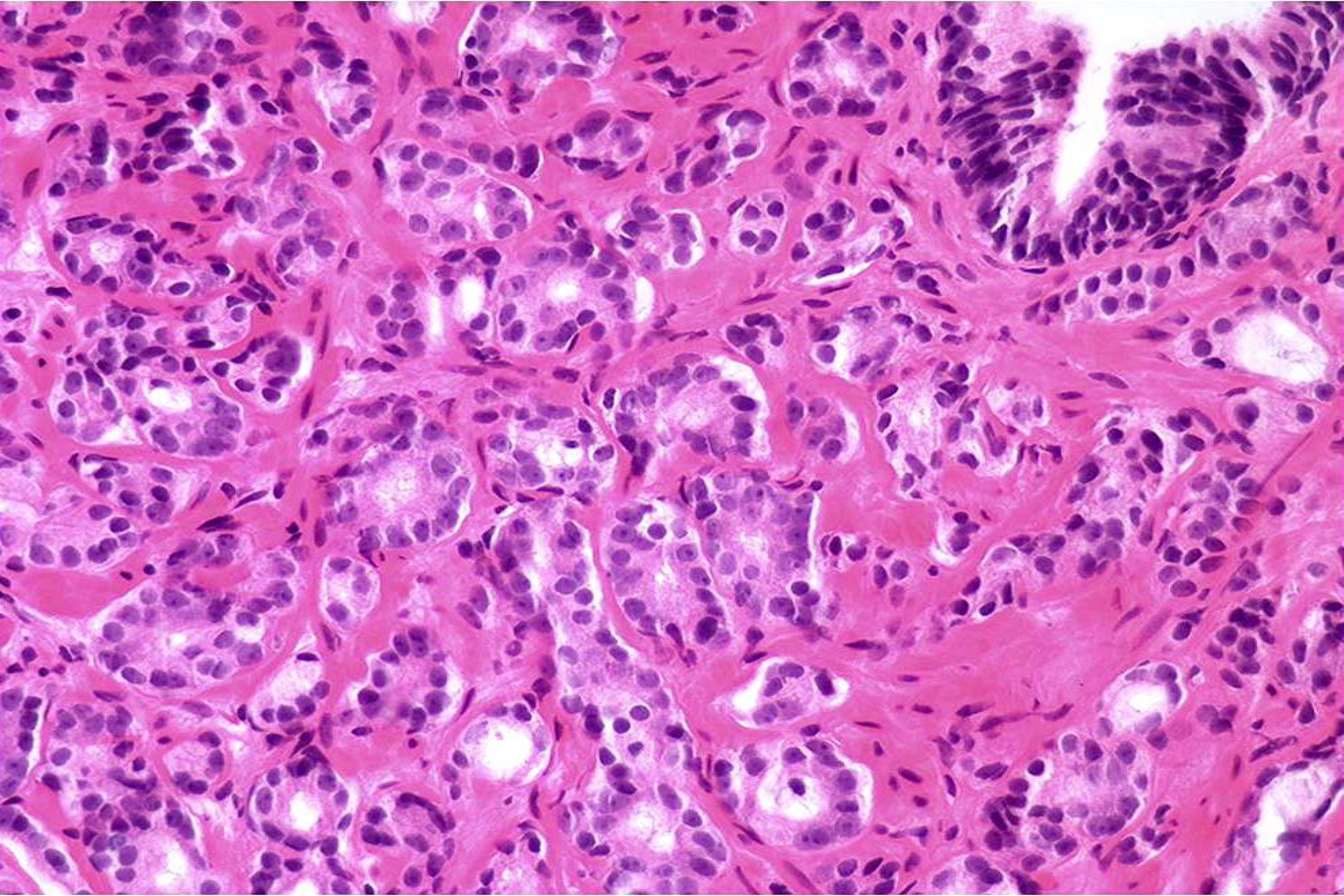

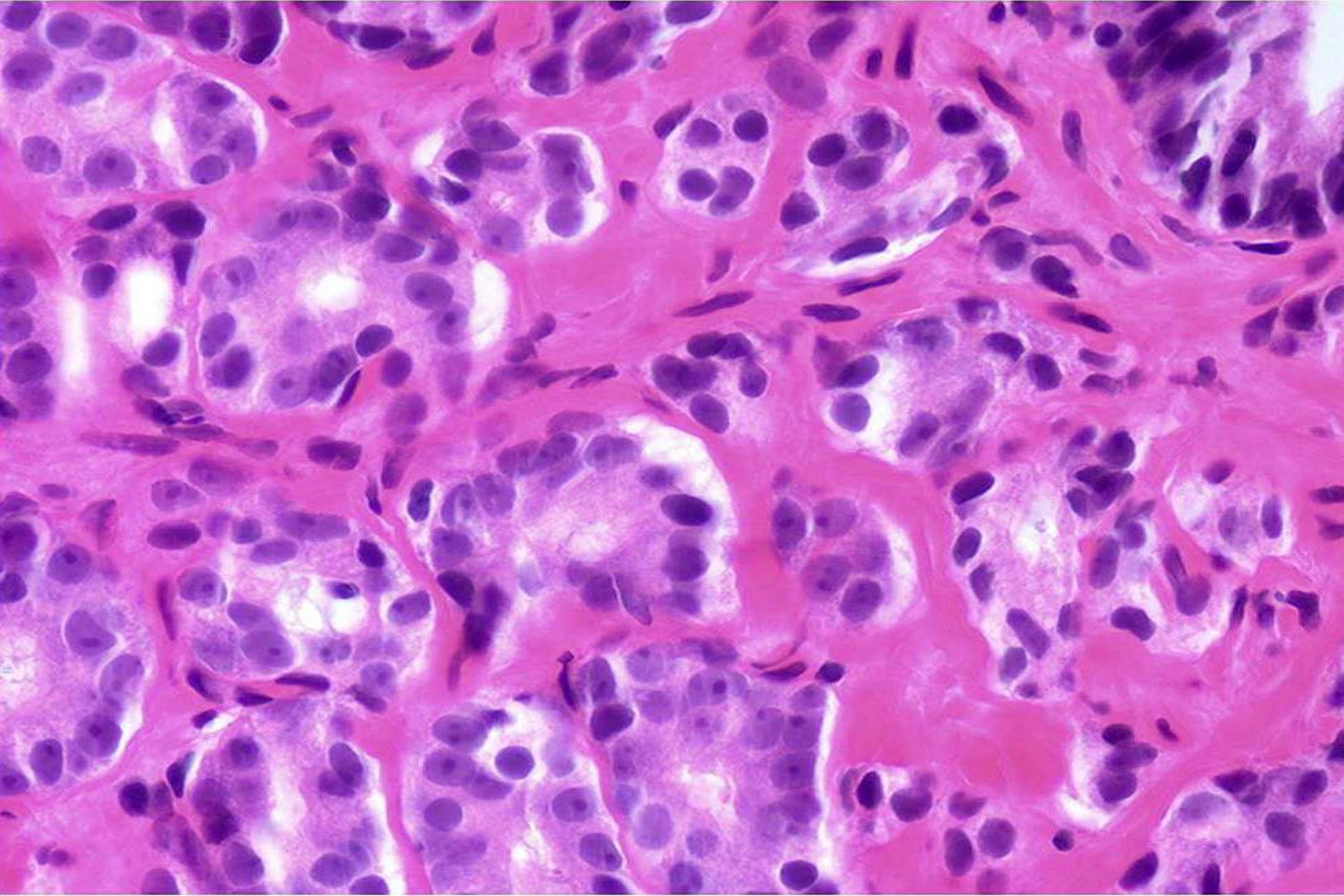

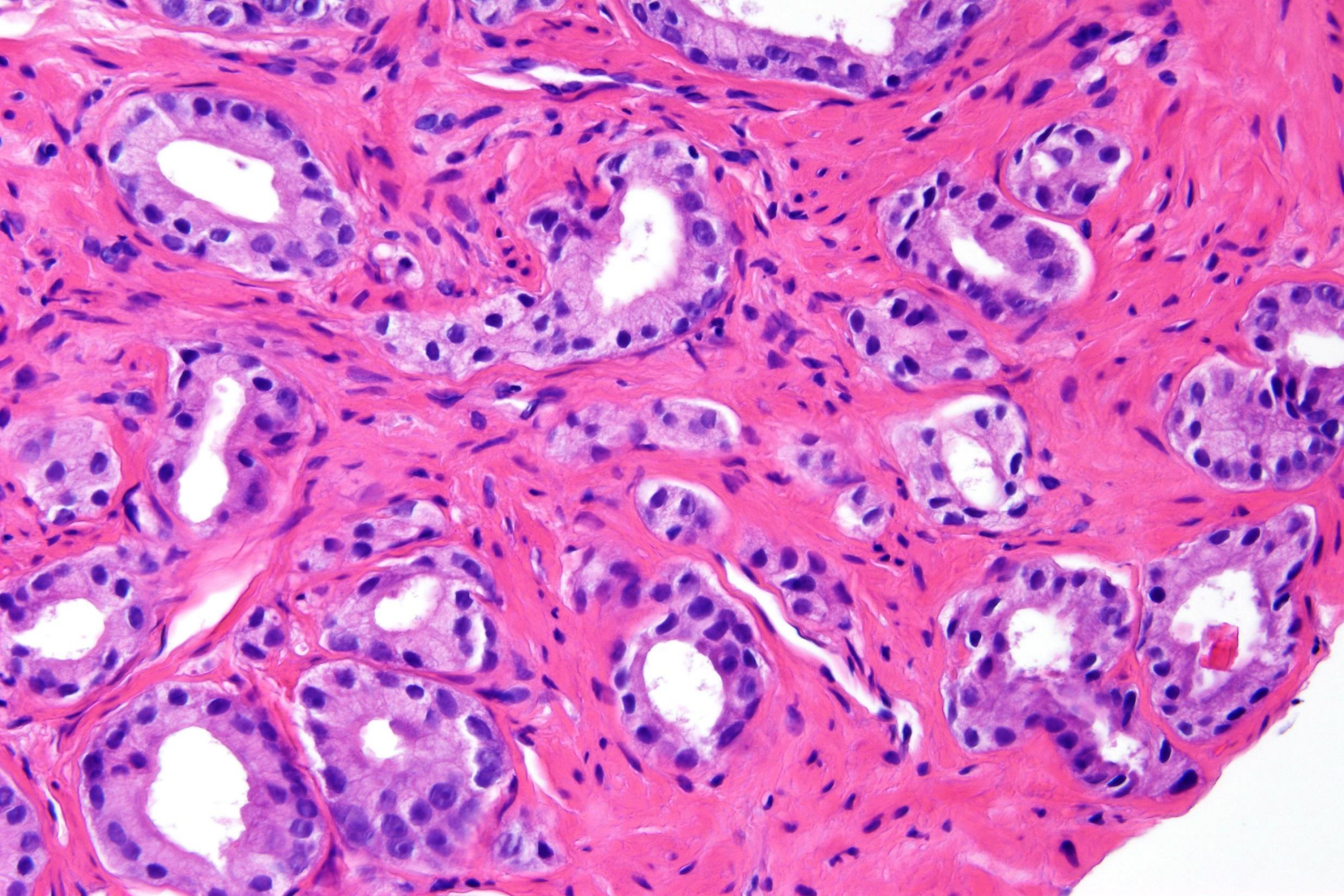

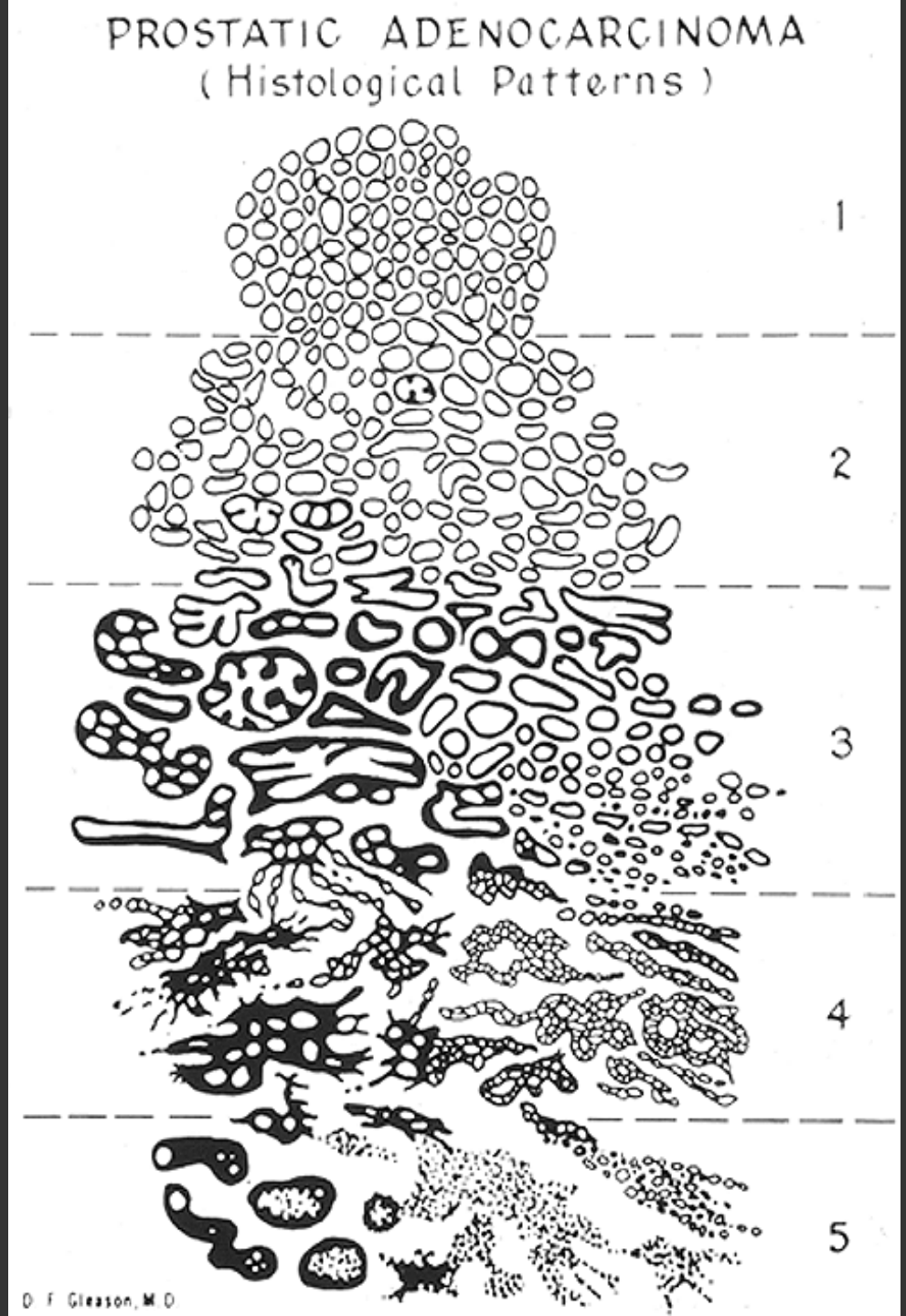
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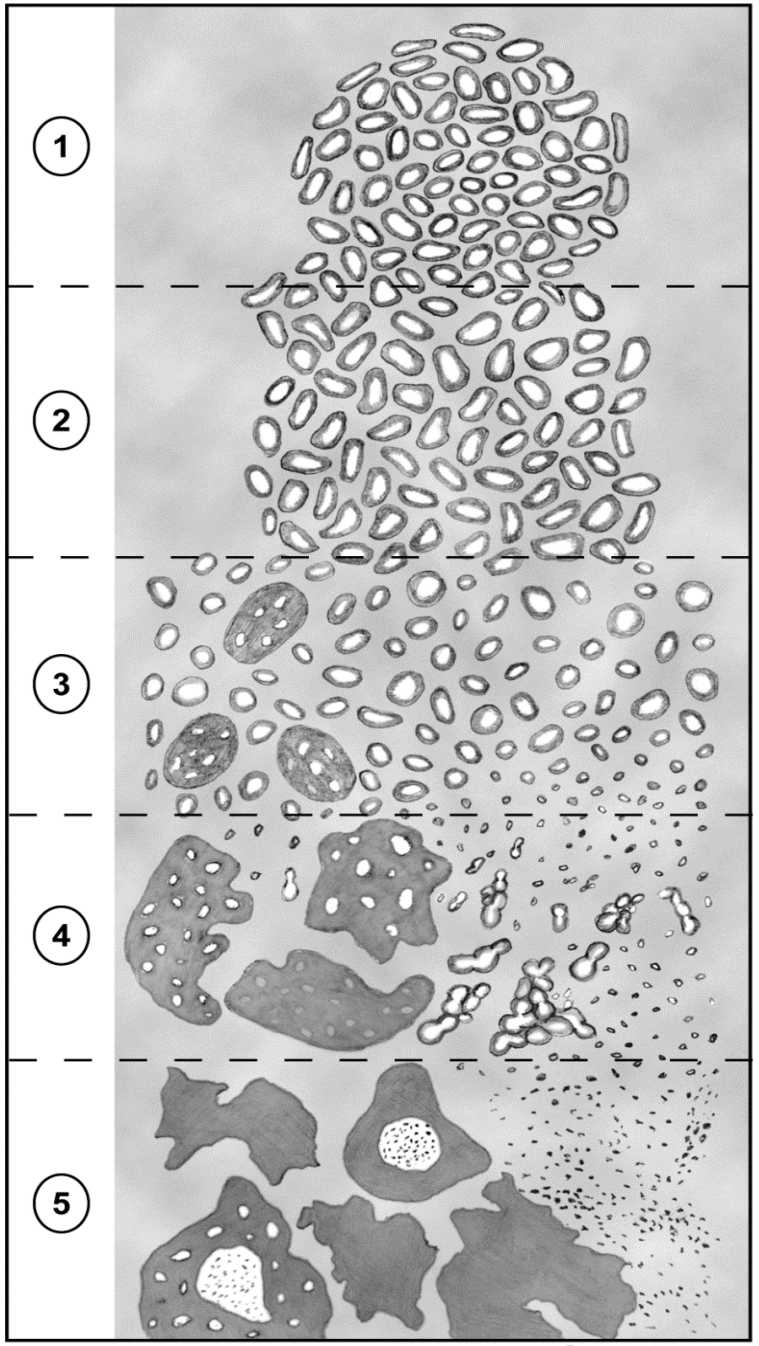
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Brumbaugh

Grading of Invasive Cribriform Carcinoma on Prostate Needle Biopsy

An Interobserver Study among Experts in Genitourinary Pathology

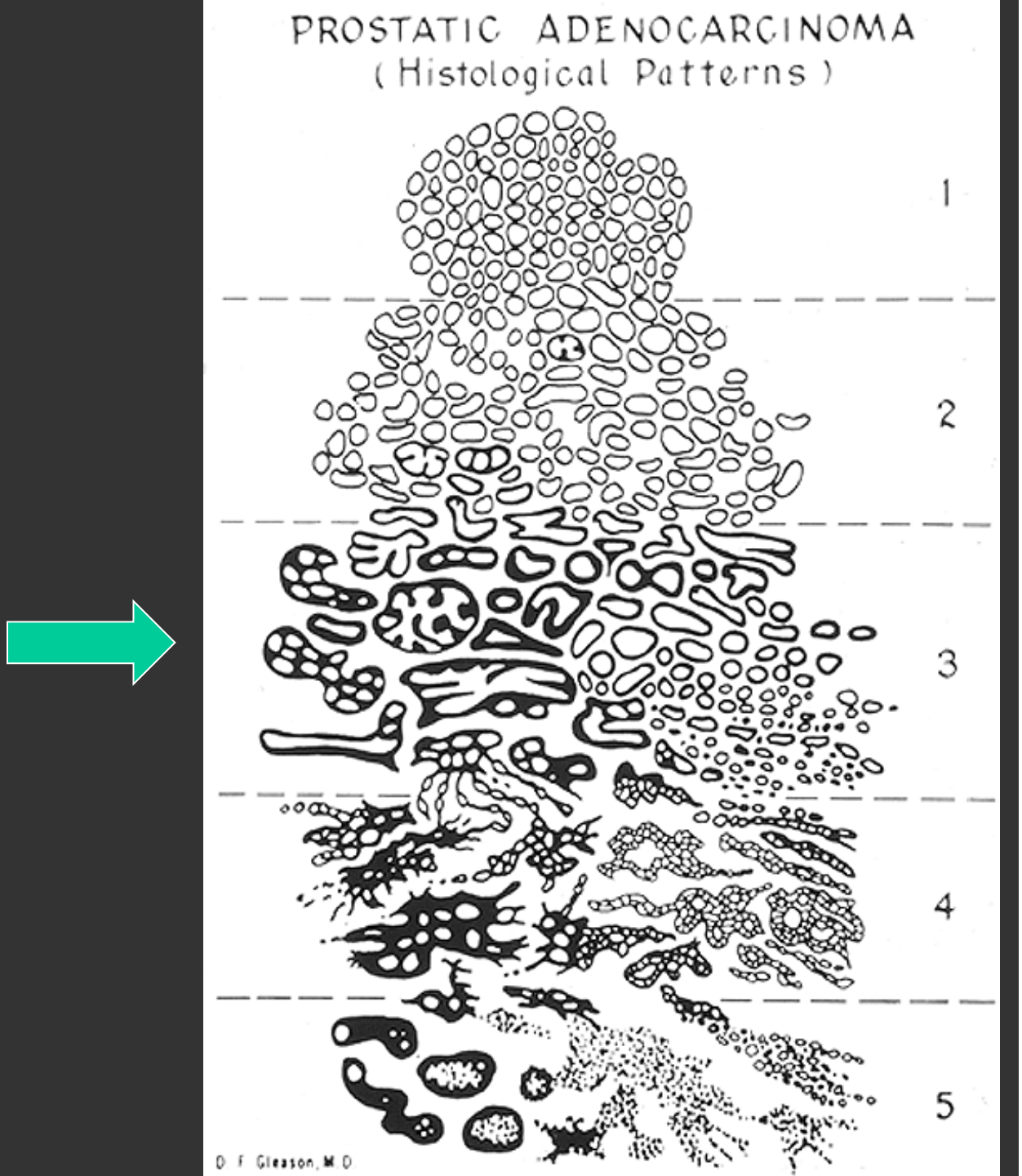
Mathieu Latour, MD, Mahul B. Amin, MD,§ Athanase Billis MD,‖ Lars Egevad MD, PhD,¶ David J. Grignon, MD,# Peter A. Humphrey, MD, PhD,** Victor E. Reuter, MD, †† Wael A. Sakr, MD, ‡‡ John R. Srigley MD, §§ Thomas M. Wheeler, MD,‖‖ Ximing J. Yang, MD, PhD,¶¶ and Jonathan I. Epstein, MD*†‡*

American Journal of Surgical Pathology - 2008

Consensus Conference on Grading of Prostatic Carcinoma

Chicago
November, 2014

Gleason Score 2-4 on Needle Should Not Be Made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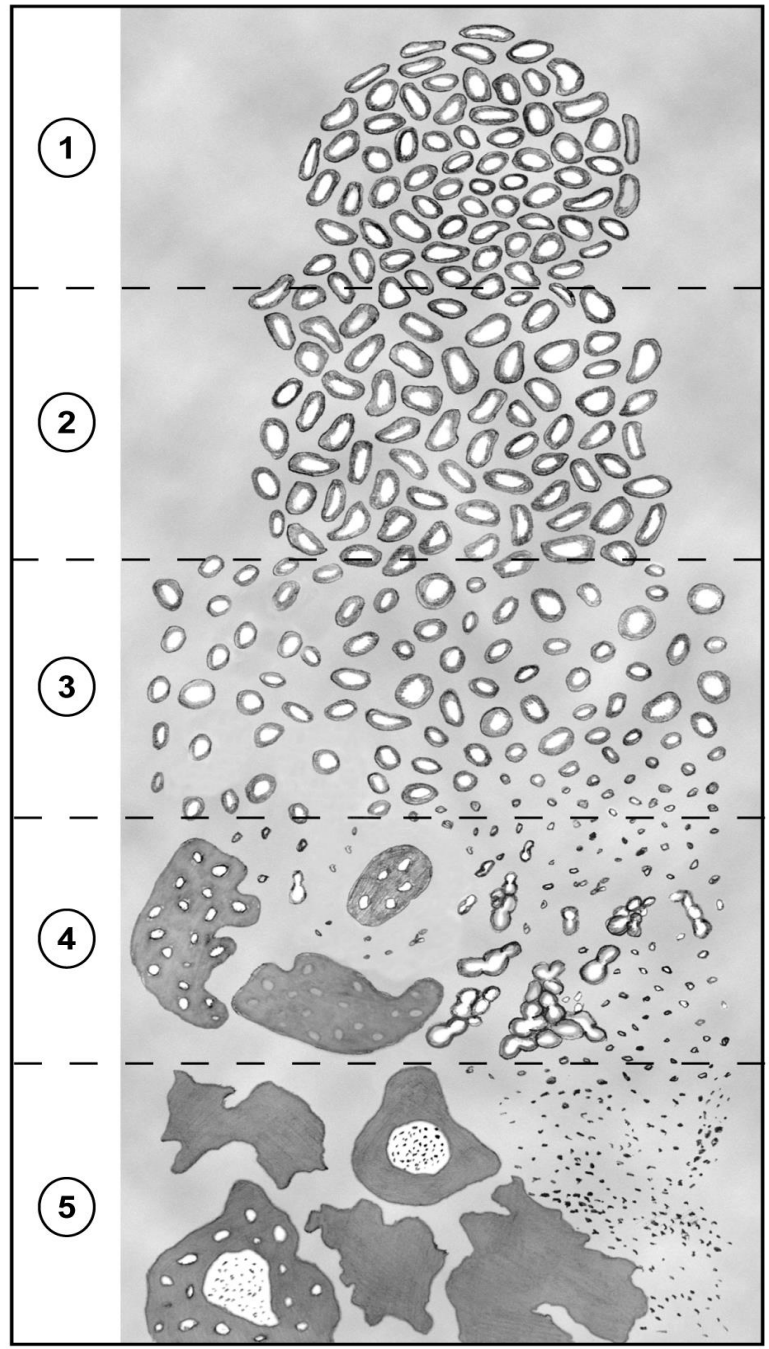
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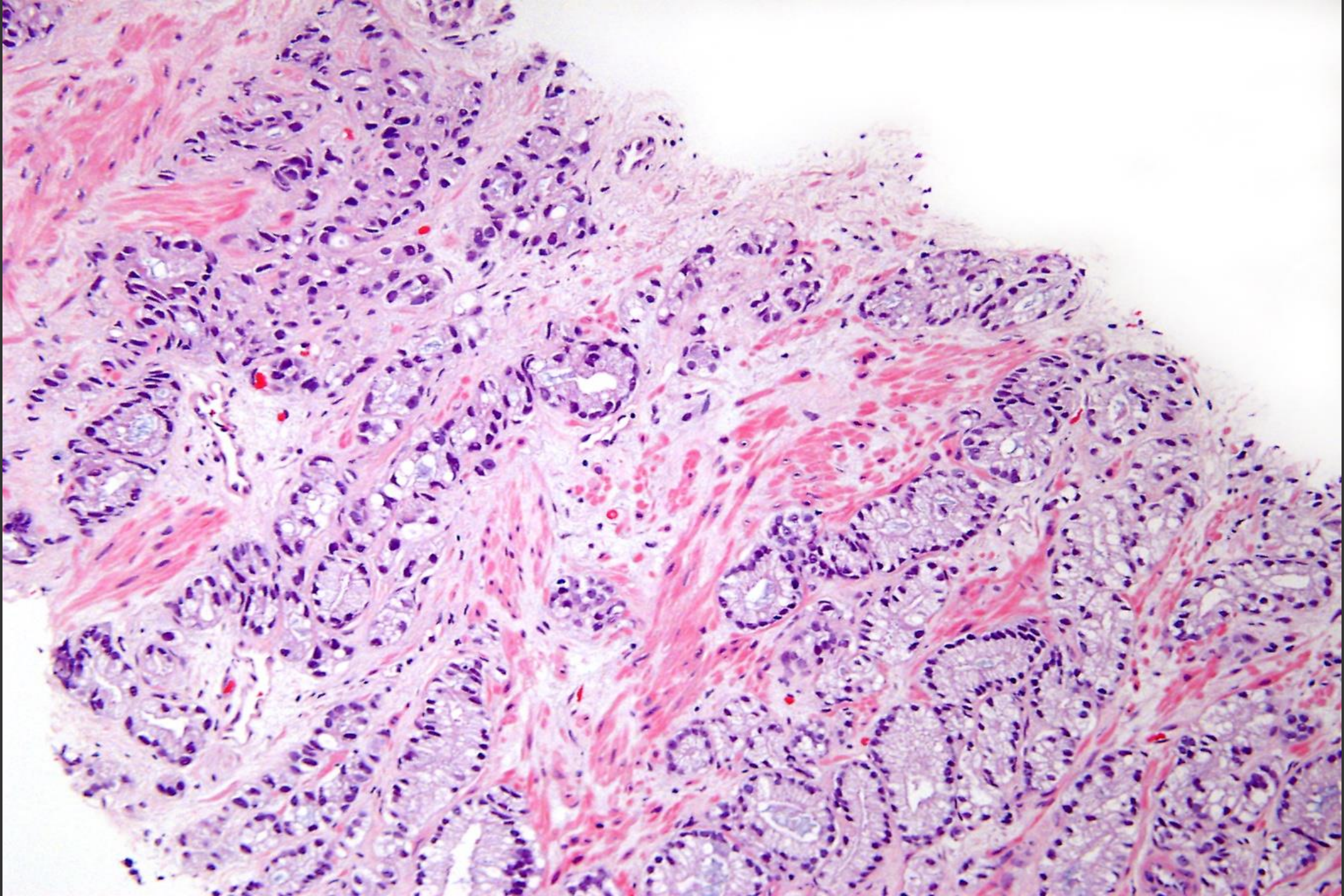
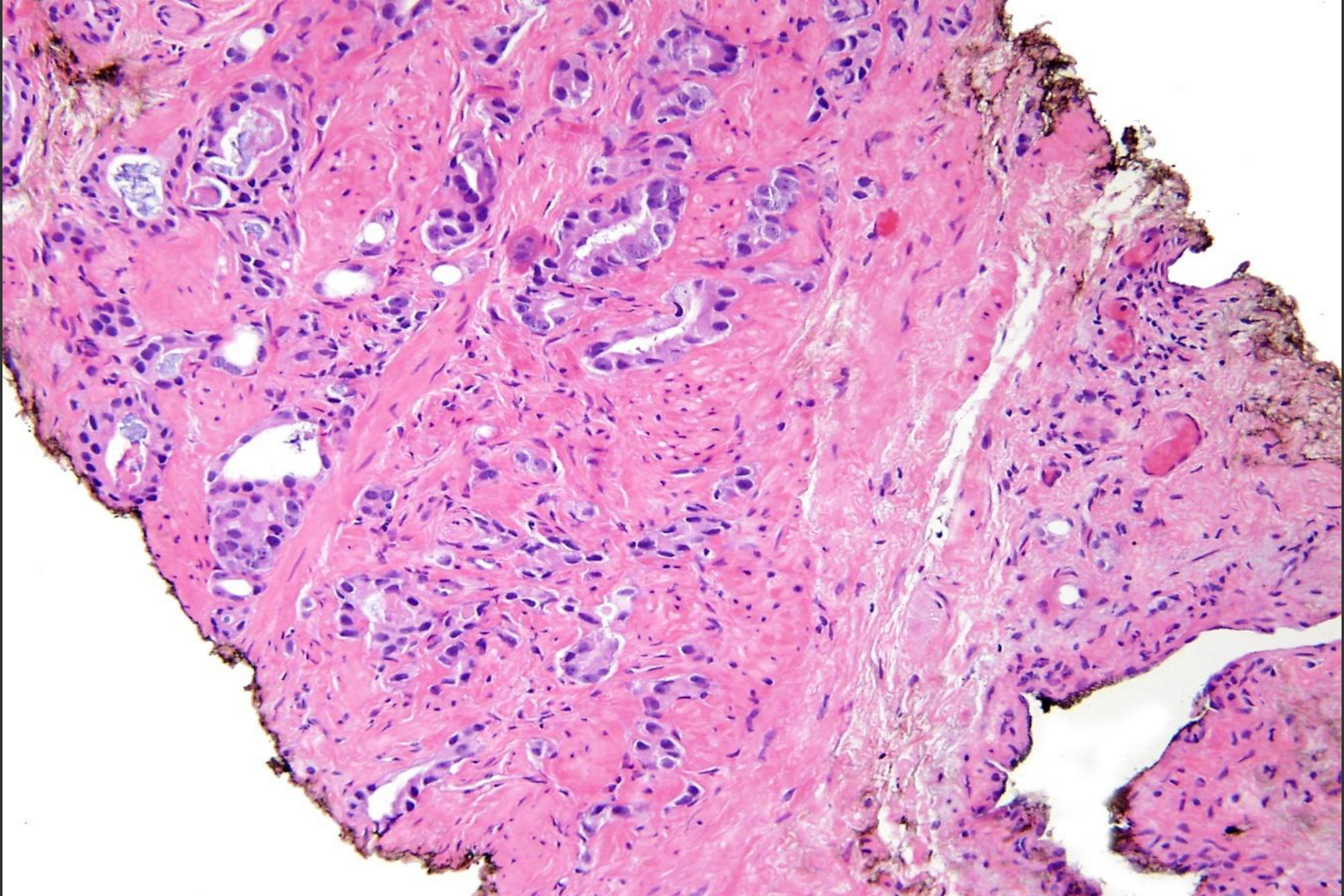
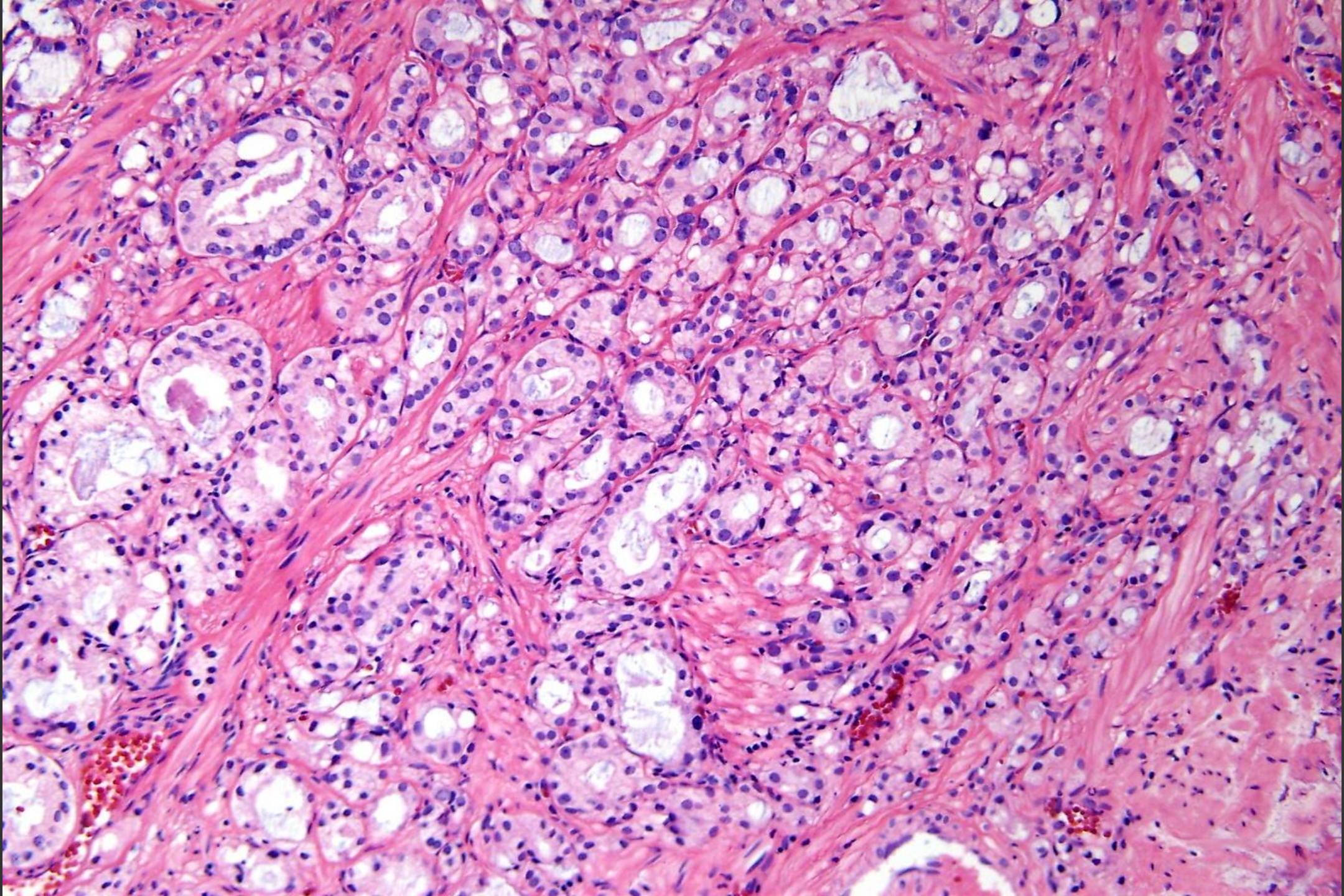
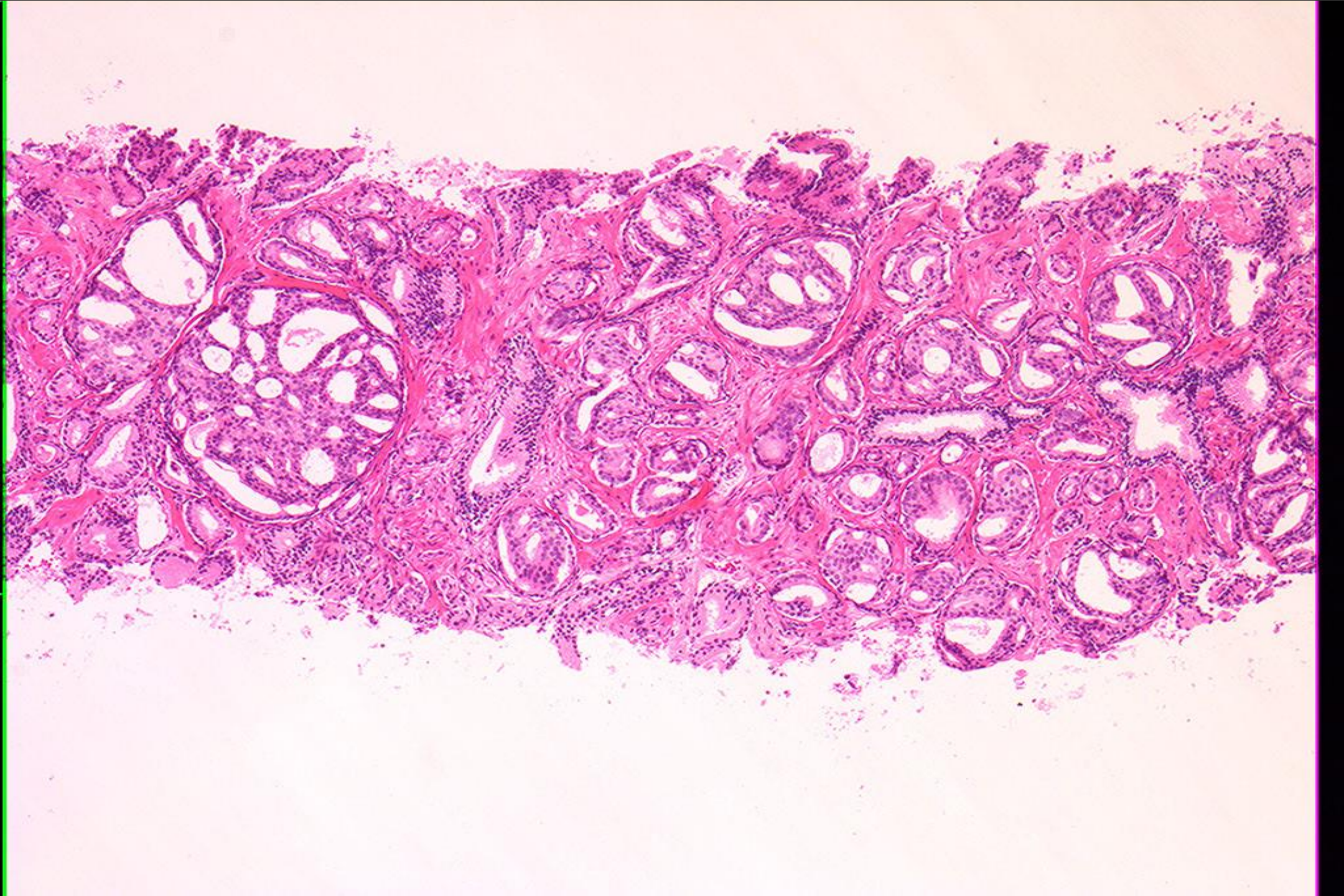
Gleason Score 3+4=7/4+3=7

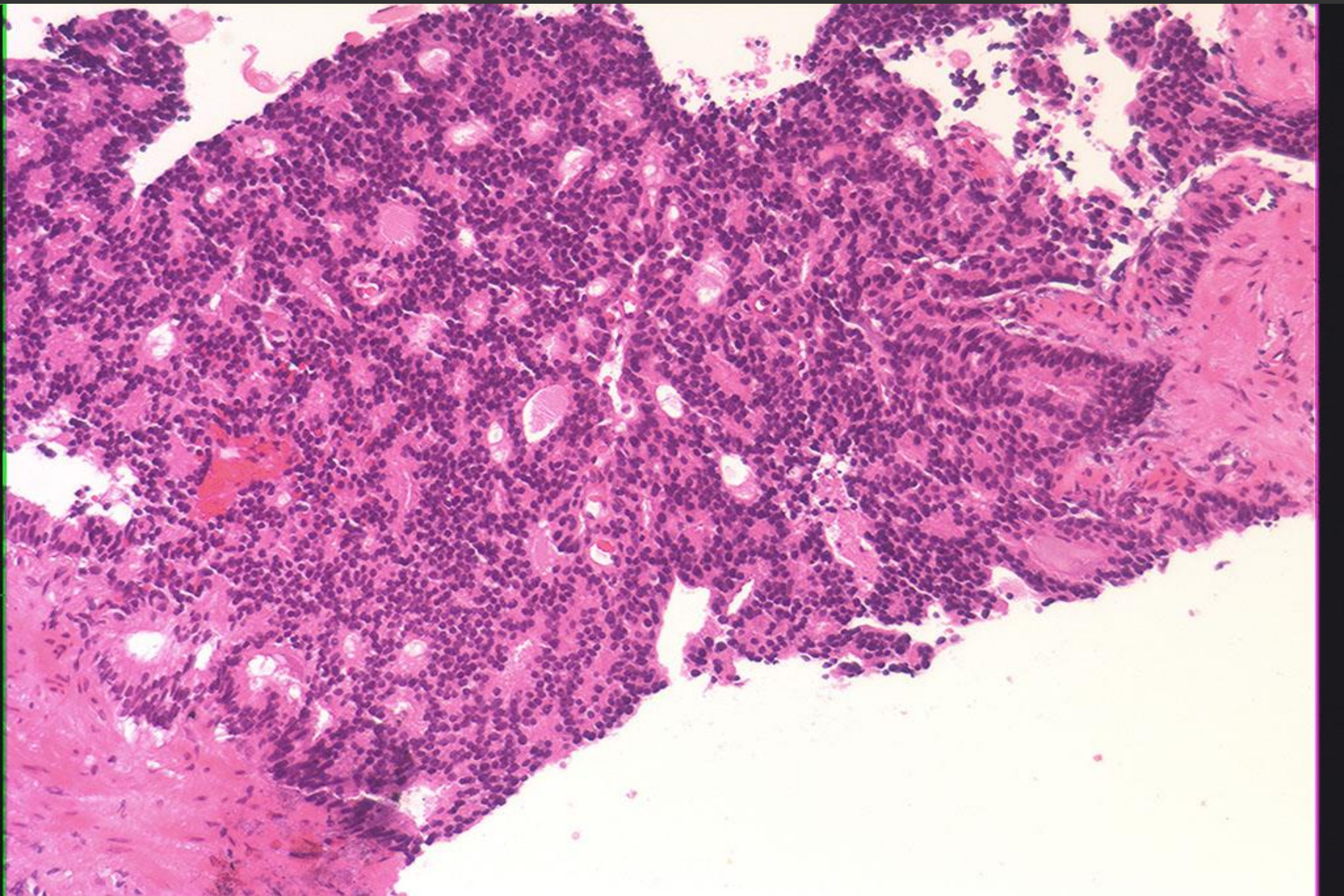


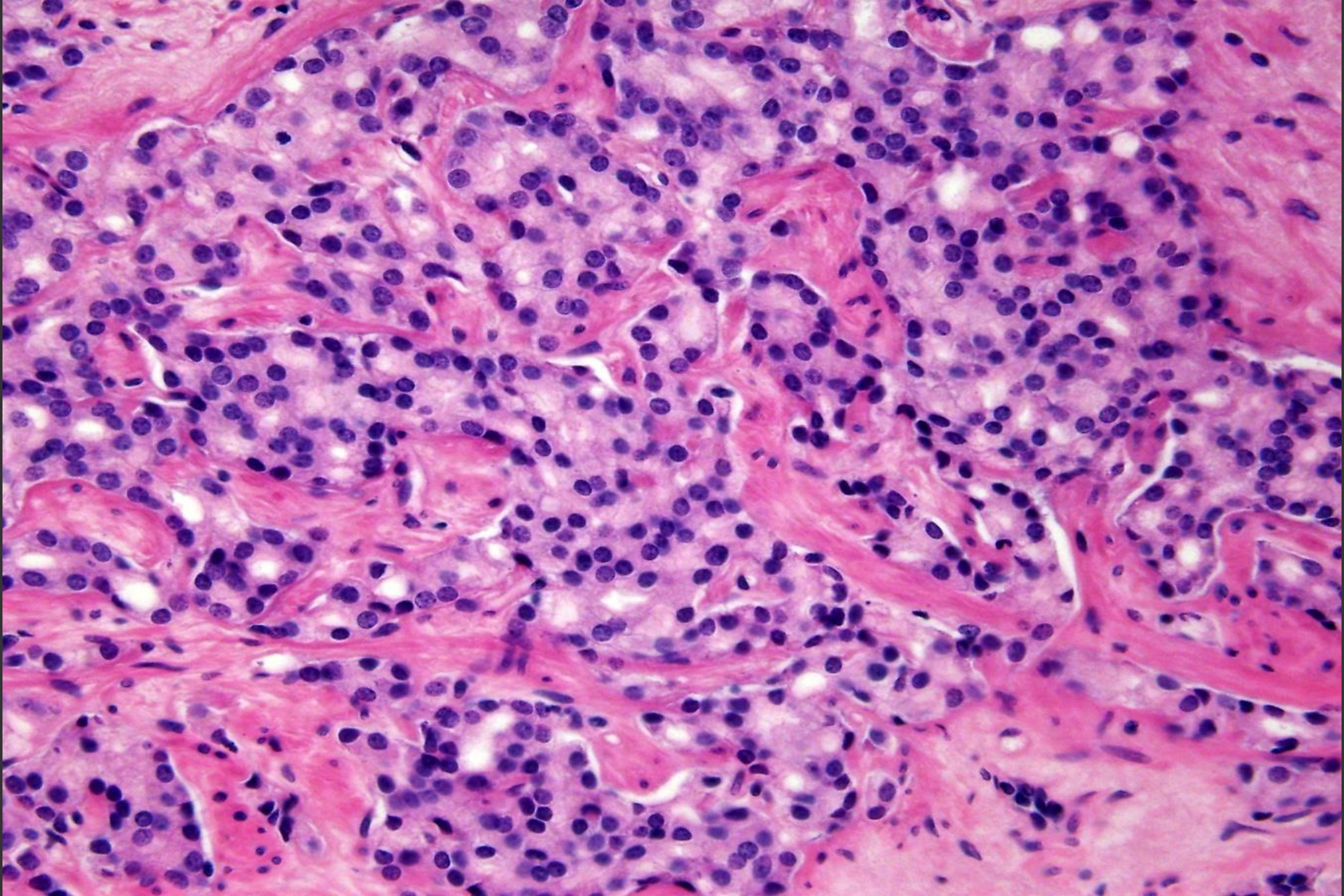




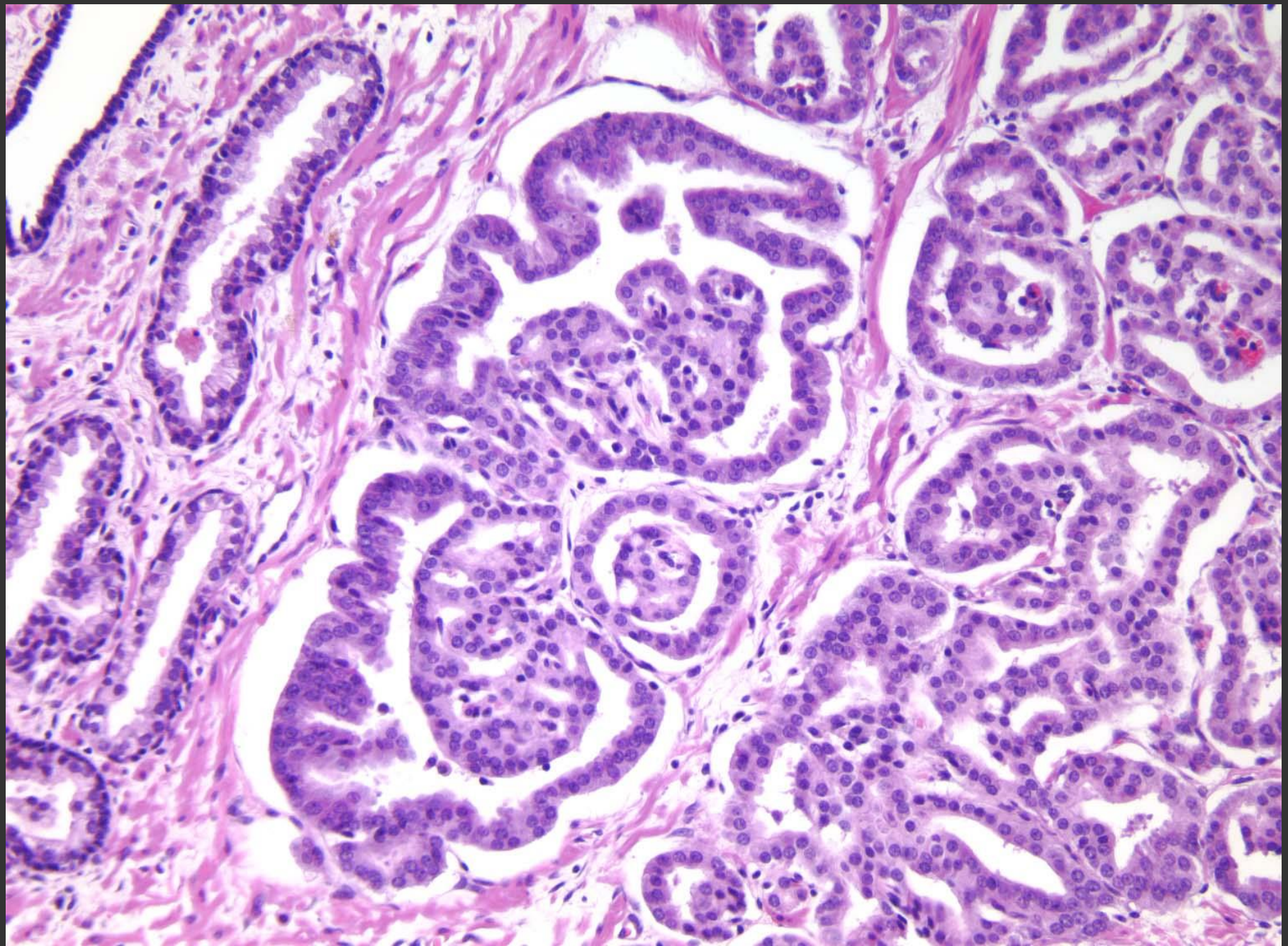
Gleason Score 4+4=8

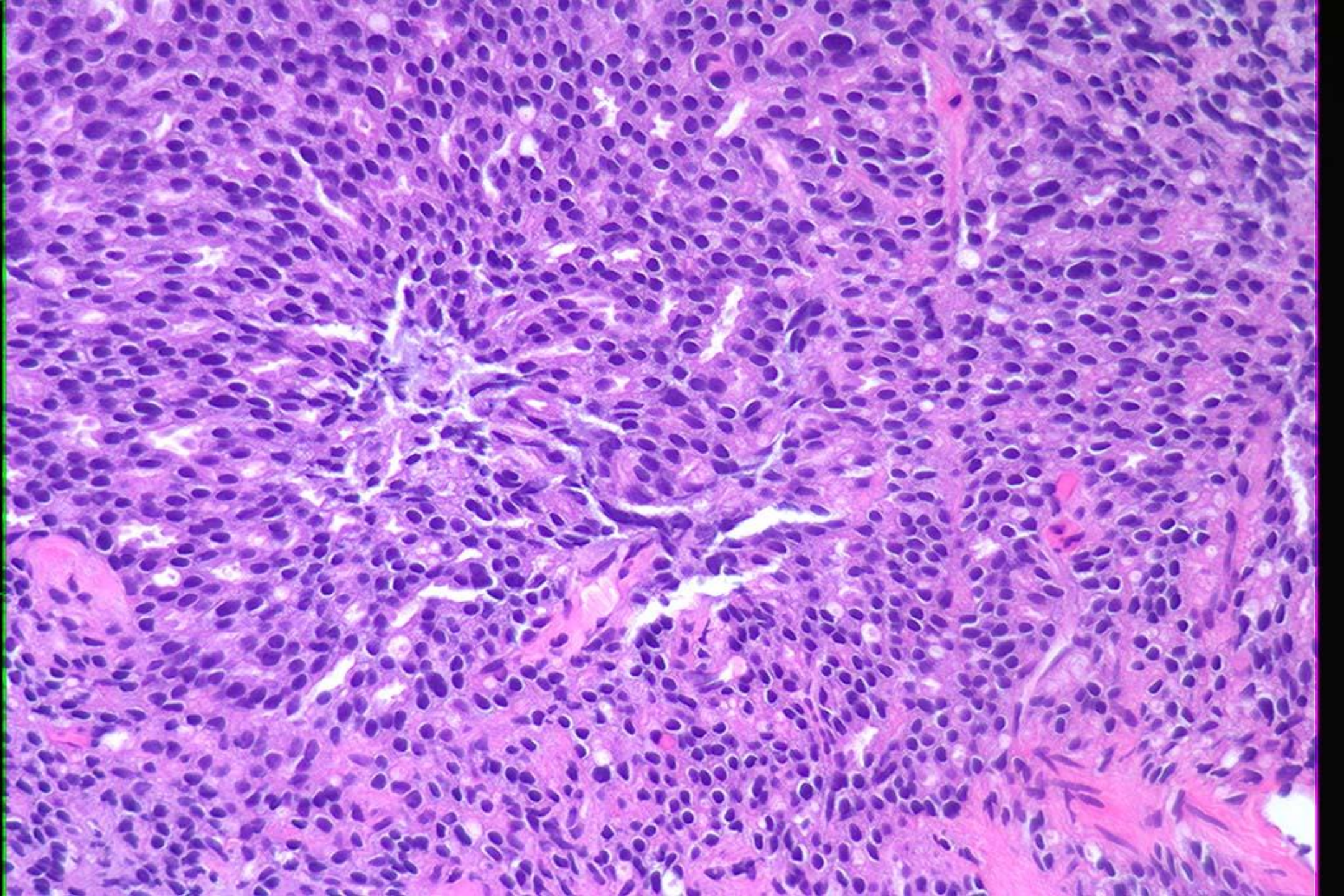


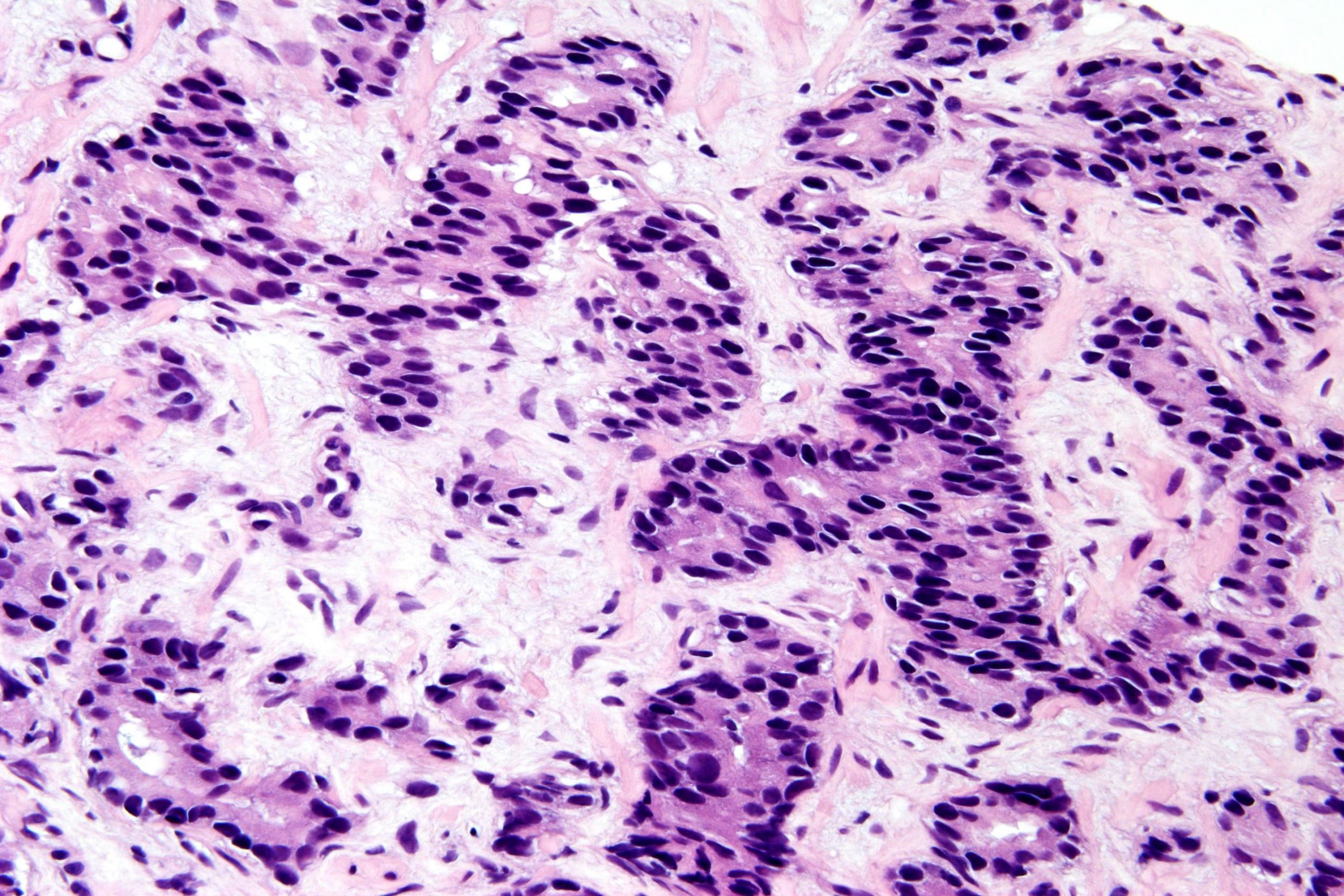


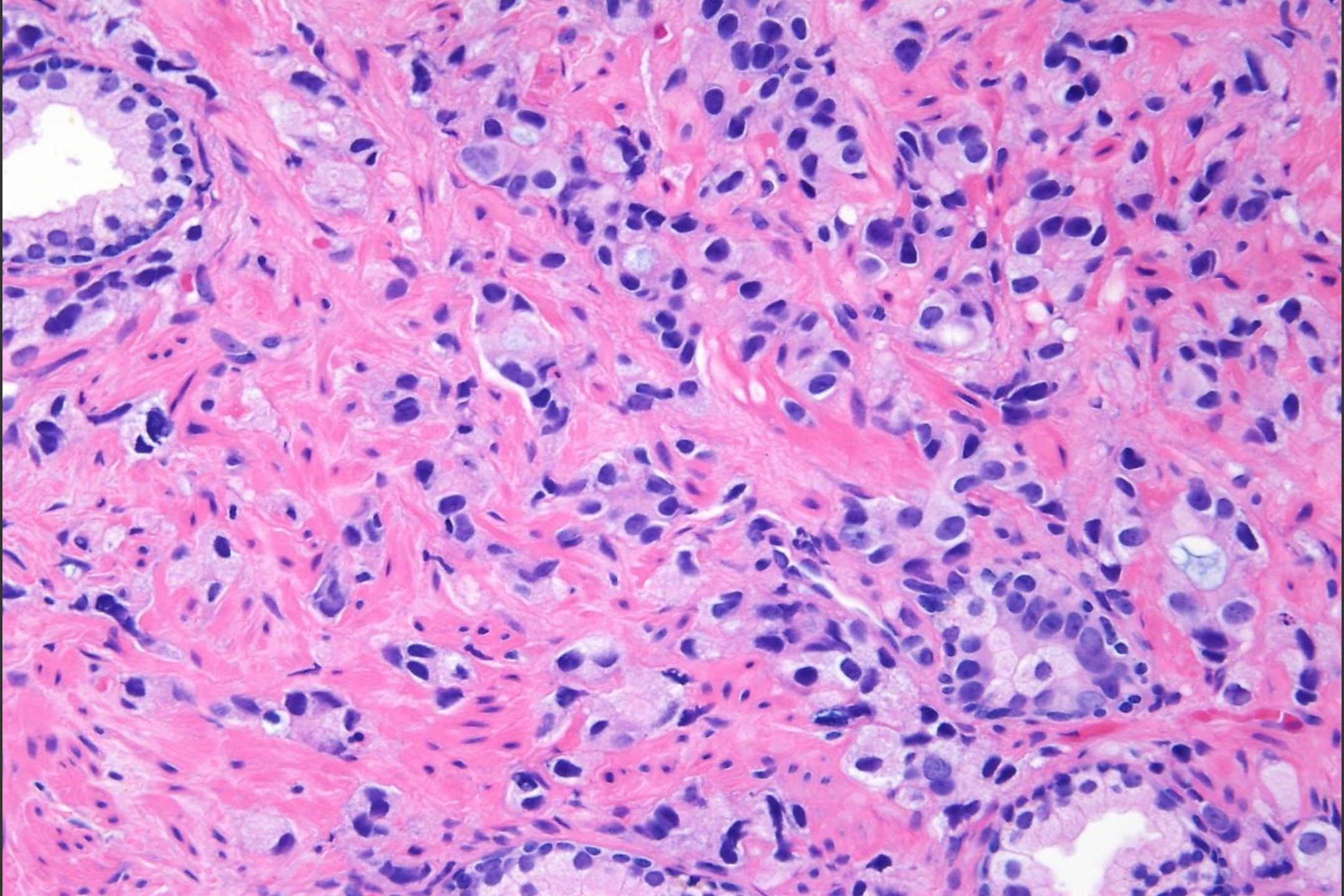


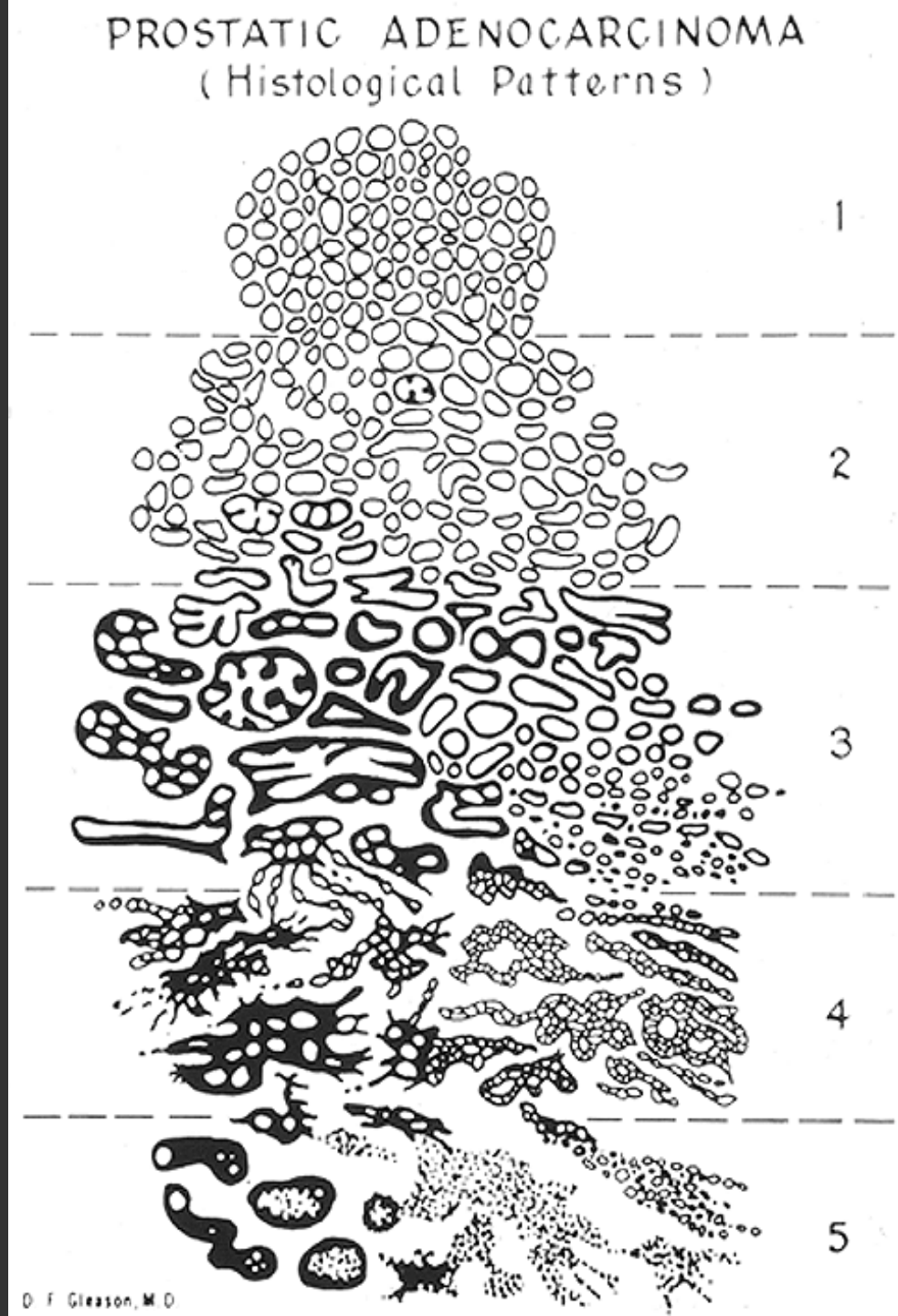
Glomeruloid Glands: Pattern 4







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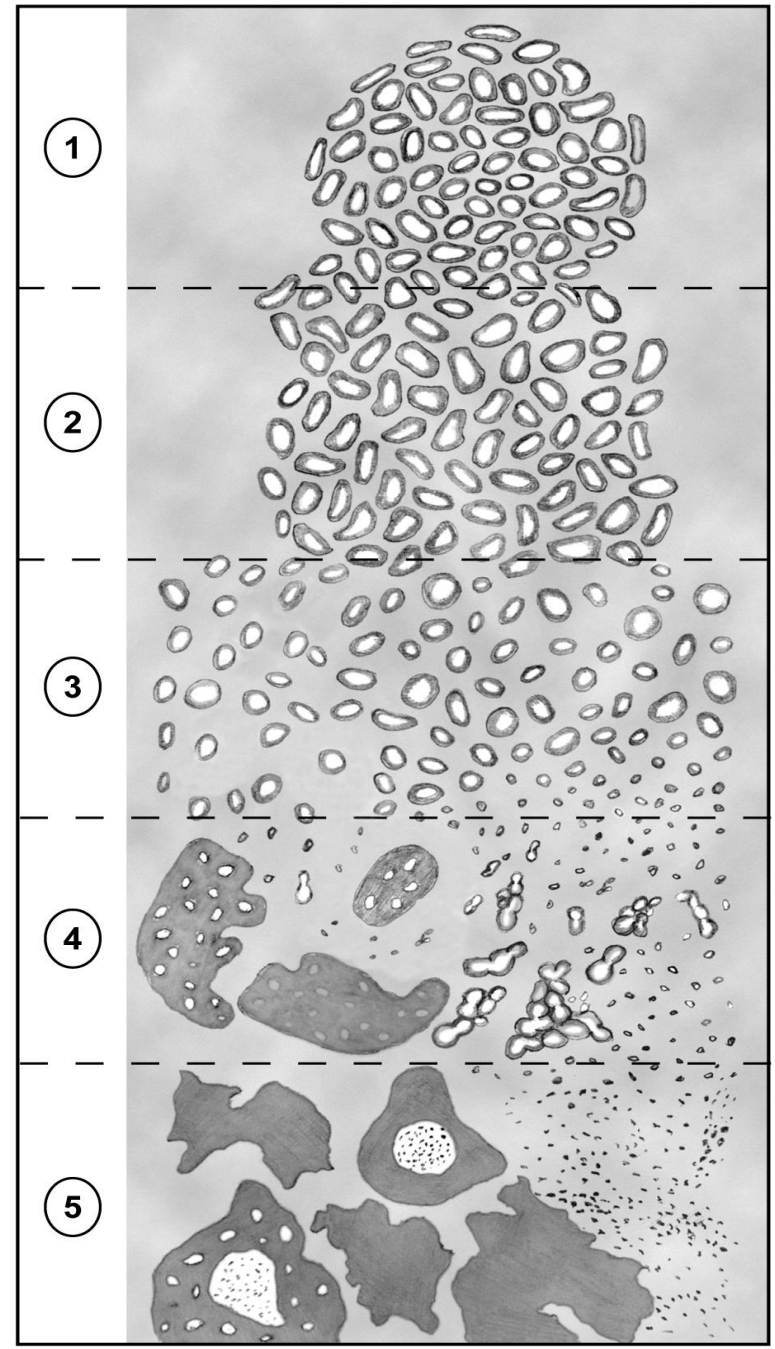
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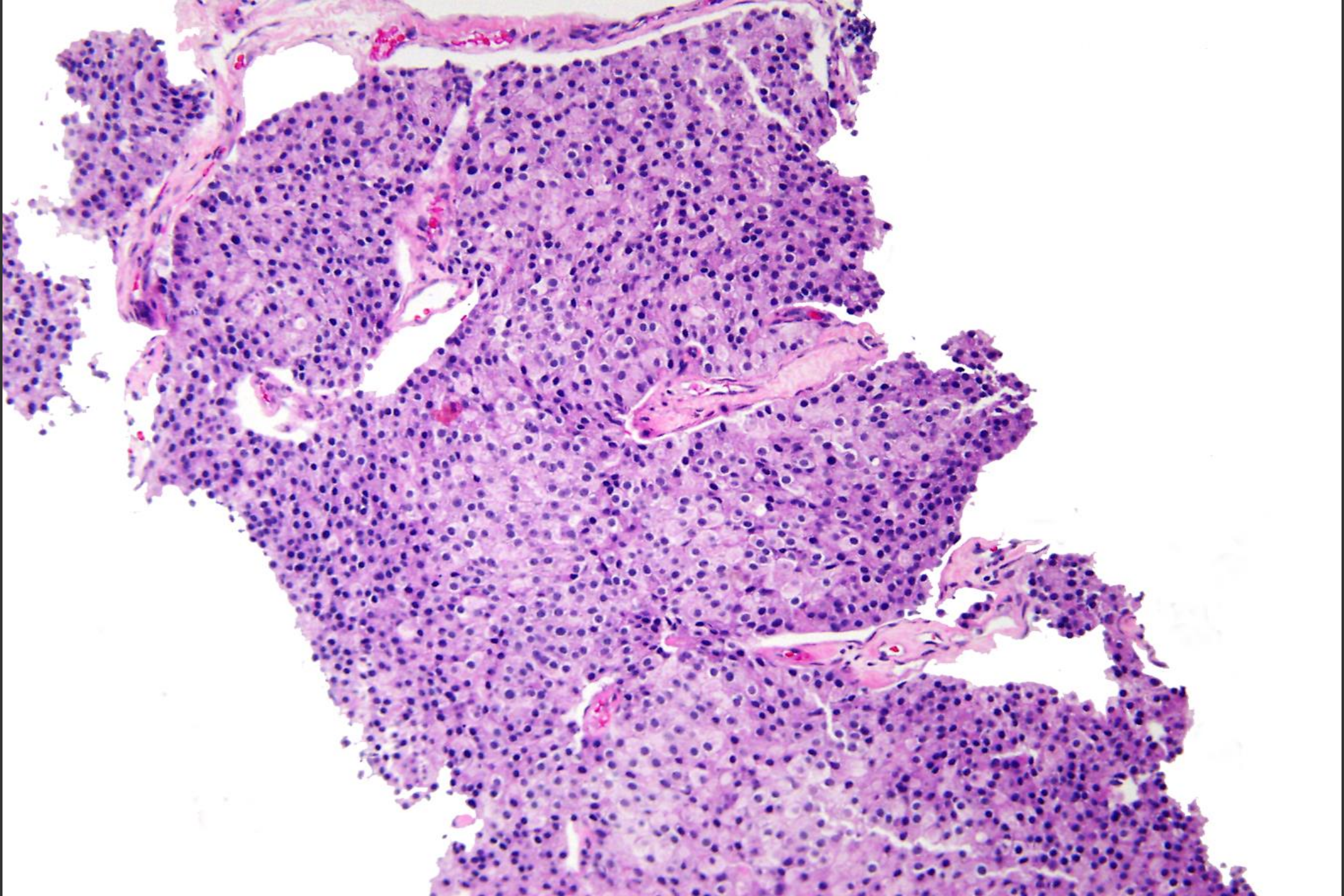

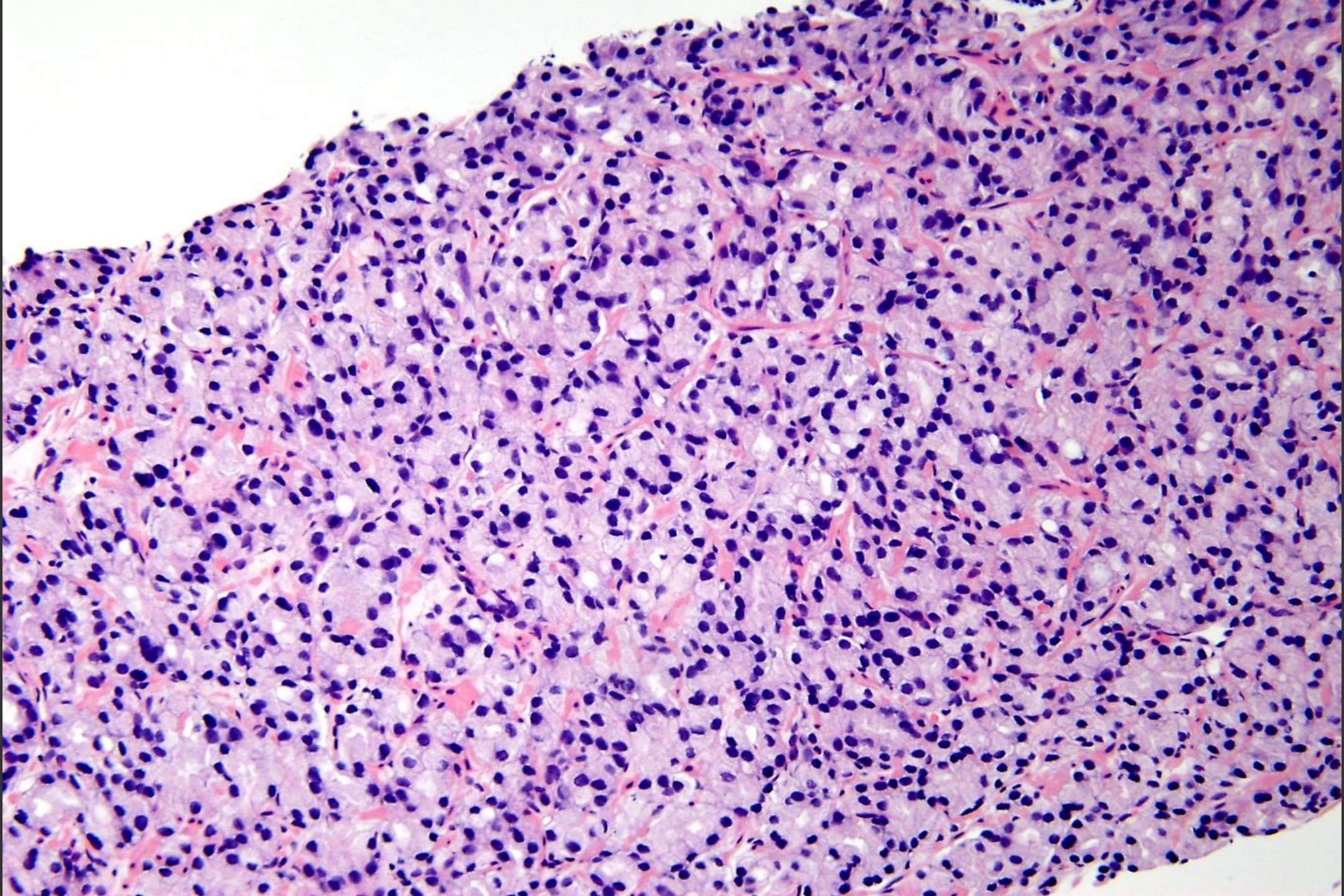

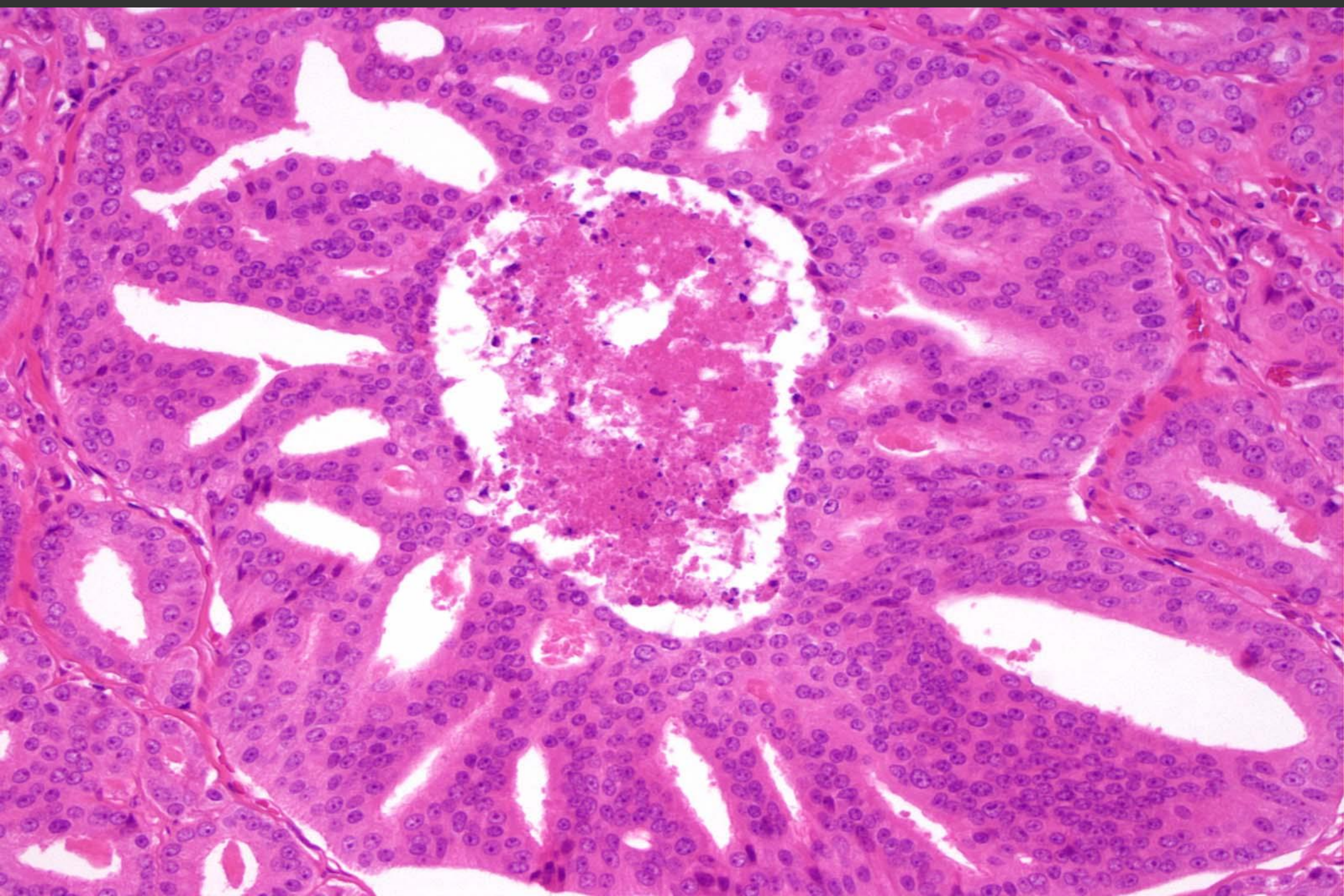

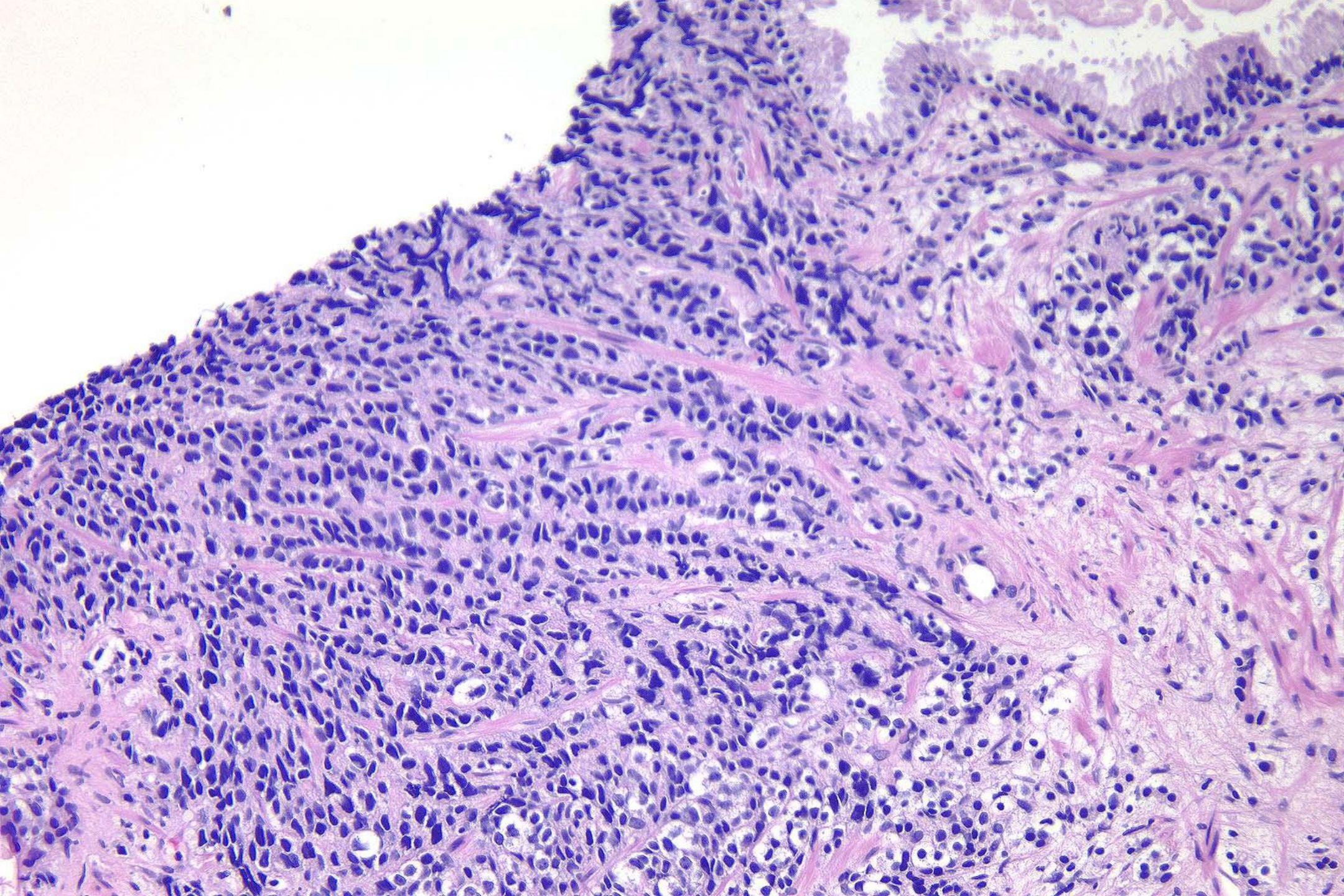

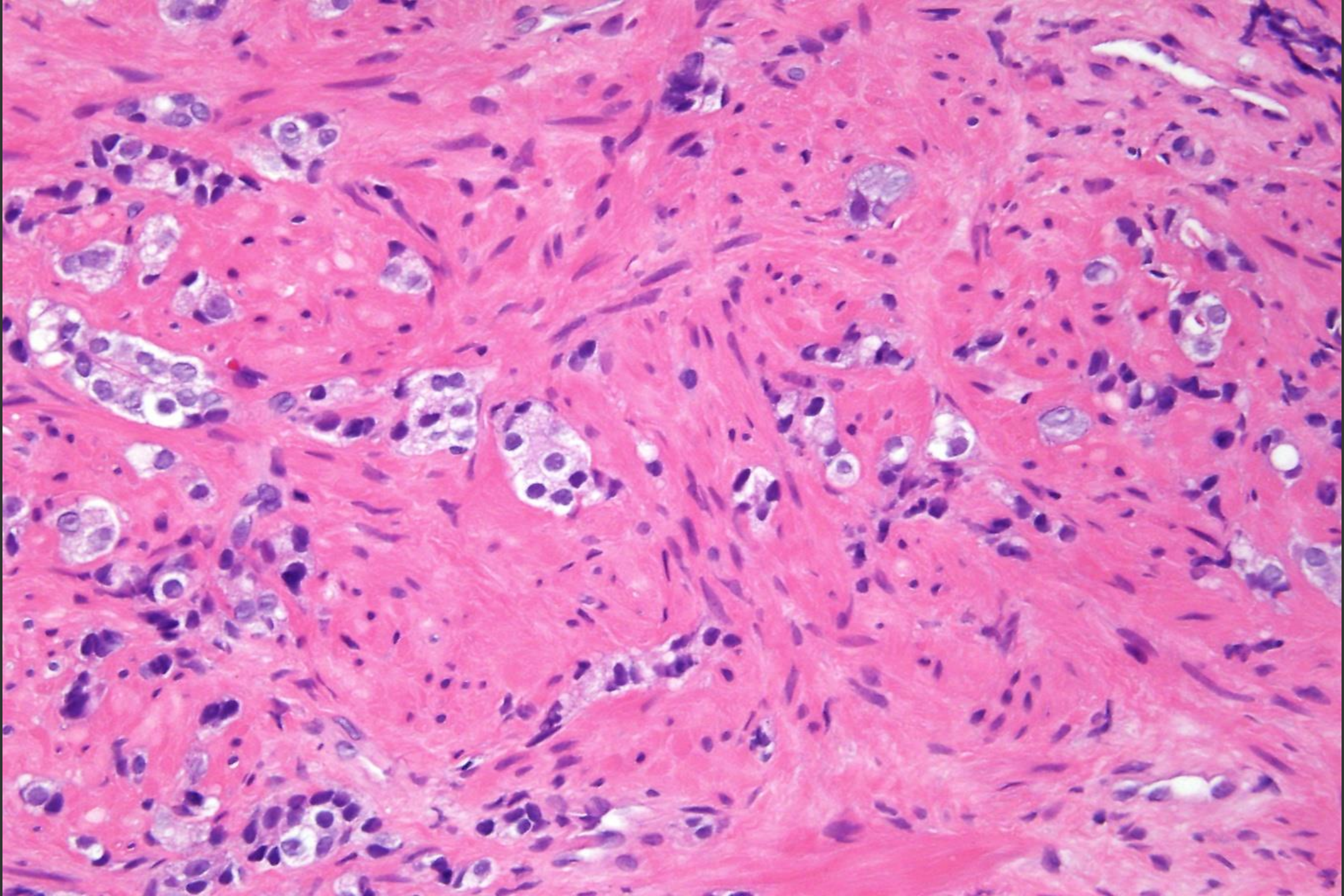

VARIANTS of ADENOCARCINOMA

Grading Variants of Prostate Adenocarcinoma

Same rule as grading usual prostate adenocarcinoma based on underlying grade pattern, except small cell carcinoma.

- **Individual well-formed glands – pattern 3**
- **Cribriform – pattern 4**
- **Individual cells or necrosis – pattern 5**

Foamy Gland Cancer

Pseudohyperplastic Cancer

Colloid Carcinoma

Signet Ring Cell-Like Adenocarcioma

Ductal Adenocarcinoma

- **Cribriform/papillary ductal adenocarcinomas should be graded as Gleason score 4+4=8**
- **PIN-Like ductal adenocarcinoma graded 3+3=6.**
- **Duct adenocarcinoma with necrosis grades as Gleason pattern 5.**

Small Cell Carcinoma

Small cell carcinoma of the prostate has unique histological, immunohistochemical, and clinical features, which differ from those associated with Gleason pattern 5 prostatic acinar carcinoma, such that small cell carcinoma should not be assigned a Gleason grade.

Post-Treatment Cancer

If histologically, ordinary prostate cancer is seen, which resembles non-treated cancer – "Cancer without significant treatment affect" and Gleason grade.

Histologically cancer is seen, yet shows treatment effect – "Cancer with significant treatment affect" and do not Gleason grade.

The International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma

Chicago
November, 2014

67 Pathology Experts in Prostate Cancer from 21 Countries

20 Urology, Oncology, and Radiation Oncology Experts

Reporting Rules for Gleason Grading

Tertiary Patterns

Two Patterns With Very Minor Component of Higher Grade

- **4+4=8 with tertiary pattern 5 behaves like 4+5=9 so now just called 4+5=9.**
- **3+3=6 with lesser amounts of pattern 4 will now be called 3+4=7 with recording the percent pattern ranging from 1%-approaching 50%.**
- **Optional how to record percent pattern 4 (per part or per case)**

Rationale for Reporting Percent Pattern 4

CONSISTENCY

1. **Currently, inconsistency with grading RPs with some pathologists reporting 3+3=6 with <5% pattern 4 as 3+3=6 with tertiary 4 and others as 3+4=7. Reporting 3+4=7 along with reporting percent pattern 4 then have uniformity amongst all pathologists.**

2. **Currently, many pathologists use 2 different grading rules for needle biopsy & RP specimens. On needle, any pattern 4 is factored into the grade (3+4=7). In RPs, if pattern 4 is <5% some call 3+3=6 with tertiary pattern 4 and if >5% then 3+4=7. If record percent pattern 4 for both specimens, a uniform grading rule with 3+4=7 and noting % pattern 4.**

IMPROVED PATIENT CARE

3. The major advantage for patient care to record the percent pattern 4 on needle for Gleason 3+4=7 would be for active surveillance (AS). For the appropriate patient, Gleason 3+3=6 is accepted for men to undergo AS. However, there may be some men, depending on age, co-morbidity, extent of cancer, MRI findings, patient desire, etc, that could be a candidate for AS with 3+4=7 if the pattern 4 is limited. Currently, this information is not apparent in pathology reports.

4. The amount of pattern 4 is not only used for active surveillance but could be used for radiation therapy as well. Currently, there is different radiation therapy for 3+4 vs 4+3. In a case with borderline 3+4 vs 4+3, one pathologist could call it 3+4 and the other 4+3. Depending on whether 3+4 or 4+3 the percent pattern 4 could range from <5% to 90% and would not be evident in a report. By reporting the case as 3+4=7 (approaching 50% pattern 4) or 4+3=7 (60% pattern 4) the borderline nature of the case would be evident and clinicians could use other factors (PSA, number of cores positive, imaging, etc.) for therapy.

PRACTICALITY

5. When a pathologist grades a specimen as 3+4 or 4+3, (s)he already has to decide what part of the tumor is pattern 4 or 3 such that to give a percent should not be that much extra effort.

6. Interobserver reproducibility of reporting percent GG4/5 on prostate biopsies is at least as good as that of reporting Gleason score." (J Urol 2004; 171:664-7)

BORDERLINE 3+3 vs 3+4

7. Having to record less than 5 percent pattern 4 in a borderline case between 3+3 and 3+4 should prompt the pathologist to verify that the pattern 4 is definitive.

Reporting Percent Pattern 4

- **Past: Adenocarcinoma of the prostate Gleason score 3+4=7 involving 20% of 1 core.**

- **Current: Adenocarcinoma of the prostate Gleason score 3+4=7 (<5% pattern 4) involving 20% of 1 core.**

- **Current: Adenocarcinoma of the prostate Gleason score 3+4=7 (approaching 50% pattern 4) involving 20% of 1 core.**

Tertiary Patterns

Three Patterns With Very Minor Component of Higher Grade

- **On RP if pattern 5 is <5% and 3rd most common pattern then report 3+4=7 with tertiary pattern 5. If >5% then is the secondary pattern (ie. 3+5=8).**

- **On needle bx. if pattern 5 is 3rd most common pattern, regardless of percentage, then include in score (ie. 3+5=8) (most common + highest grade).**

- **Only use "tertiary" for 3+4=7 with <5% (tertiary) pattern 5 or 4+3=7 with <5% (tertiary) pattern 5 on RP**

Minor Pattern of Lower Grade

- **On RP or needle do not mention if the lower grade component is <5%.**
- **Core or RP nodule with 98% pattern 4 and 2% pattern 3 is graded as 4+4=8.**

NEEDLE BIOPSY WITH DIFFERENT CORES SHOWING DIFFERENT GRADES

One should assign individual Gleason scores to separate cores as long as the cores were submitted in separate containers or the cores were in the same container yet specified by the urologist as to their location (ie. by different color inks).

Assigning a global (composite) score is optional.

Reporting of Gleason Grade in RPs

- **Each major tumor focus should be graded separately. For example: 2 tumor nodules – One left PZ 4+4=8 with larger right PZ 3+3=6. Give two scores and not call 3+4=7.**

- **Typically only the largest tumor foci are graded. Not necessary to report small multifocal lower grade cancer.**

- **Exception when there is a smaller tumor focus of higher grade, report this Gleason score.**

Impetus for a New Prostate Cancer Grading System

Movement to Rename Gleason Score 6 as not Cancer

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)**

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JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

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,*]

Urol Clinics of N Am 2014; 41:339-46

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**

Problems with Gleason System Grouping

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

- **Gleason 8-10 is often considered as one group - high grade disease**

Problems with Gleason System: Inconsistent & Inaccurate Grouping

Various combinations have been used in the literature including some of the highest impact studies:

Prostate Cancer Outcomes Study (NEJM): 2-4; 5-7; 8-10

Scandinavian Prostate Cancer Group Study (NEJM): 2-6, 7; 8-10

Prostate Cancer Intervention vs. Observation (NEJM): 2-6; 7-10

Prostate Cancer Prevention Trial (NEJM): 2-6; 7-10

D'Amico Risk Classification Stratification

- **Low Risk: T1C/T2a & PSA≤10 & Gleason ≤6**
- **Intermed. Risk: T2b or PSA 10-20 or Gleason 7**
- **High Risk: T2c or PSA>20 or Gleason 8-10**

Problems with Gleason Grading
Too Many Grades with Similar Prognoses

- 1+1; 1+2; 1+3; 1+4; 1+5; 2+1; 2+2; 2+3; 2+4; 2+5; 3+1; 3+2; 3+3; 3+4; 3+5; 4+1; 4+2; 4+3; 4+4; 4+5; 5+1; 5+2; 5+3; 5+4; 5+5

- 25 potential grades!

- What are the least number of grades with a similar prognosis?

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 (≤6)**

  Only individual discrete well-formed glands

- **Grade Group 2 (3+4)**

  Predominantly well-formed glands with a lesser component of poorly- formed/fused/cribriform glands

- **Grade Group 3 (4+3)**

  Predominantly poorly formed/fused/cribriform glands with a lesser component of well-formed glands

- **Grade Group 4 (4+4/3+5/5+3)**

  Only poorly-formed/fused/cribriform glands or

  Predominantly mix of well-formed and lack of glands

- **Grade Group 5 (4+5/5+4/5+5)**

  Lack gland formation (or with necrosis) with or w/o poorly formed/fused/cribriform glands

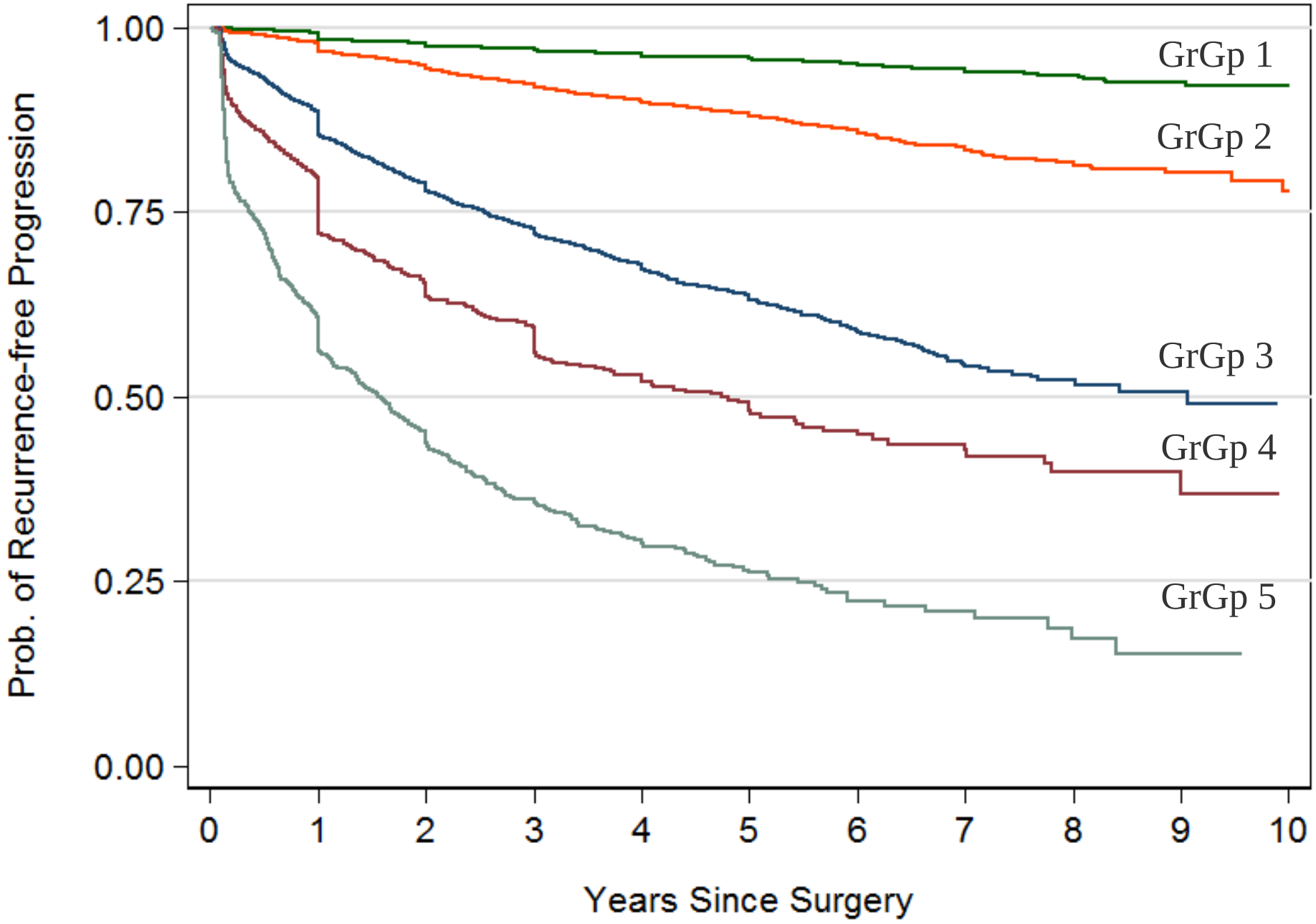
2014 - RP Data From 5 Institutions

- **Since 2005 – Modified Gleason grades**

- **University of Pittsburgh – J. Nelson, A. Parwani**
- **MSKCC – V. Reuter, S. Fine, A. Vickers, J. Eastham, D. Sjoberg**
- **CCF – C. Magi-Galluzzi, E. Klein, J. Ciezki, C. Reddy**
- **Karolinska – L. Egevad, P. Wiklund, T. Nyberg**
- **Johns Hopkins – J. Epstein, M. Han**

RP Grade Meta-Analysis

Hosp	Freq.
Pittsburgh	2,102
Karolinska	3,763
Hopkins	6,137
Memorial	6,673
CCF	2,170
Total	20,845

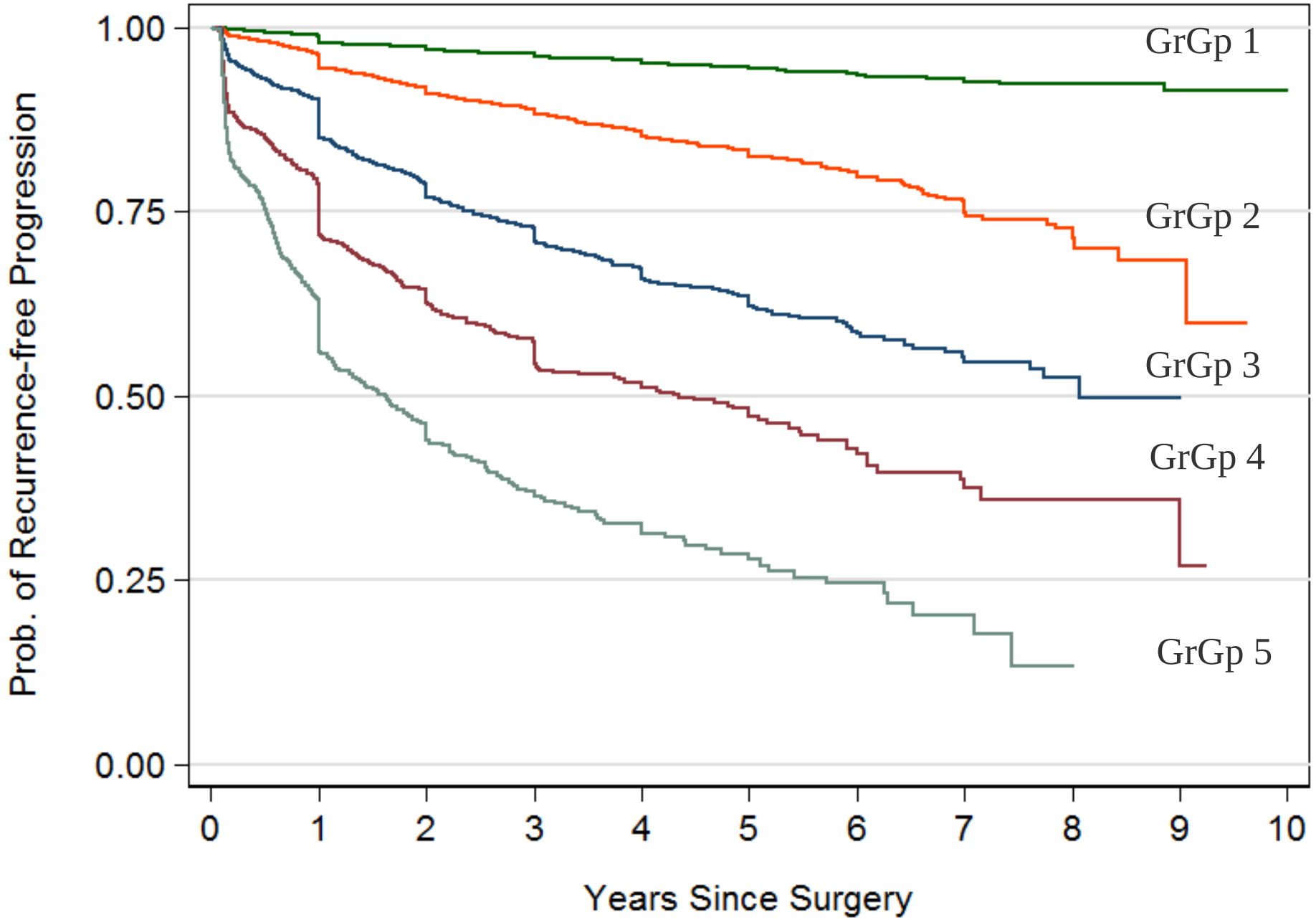

1.00
0.75
0.50
0.25
0.00
Prob. of Recurrence-free Progression
GrGp 1
GrGp 2
GrGp 3
GrGp 4
GrGp 5
0
1
2
3
4
5
6
7
8
9
10
Years Since Surgery

RP Grade
5 Year Biochemical Risk Free Survival

Grade	Gleason	BRFS	95% Confidence Intervals
1	3+3=6	96%	94%-95%
2	3+4=7	88%	87%-89%
3	4+3=7	63%	61%-65%
4	4+4=8	48%	44%-52%
5	9-10	26%	23%-30%

Biopsy Grade Meta-Analysis

Hosp	Freq.
Pittsburgh	2,102
Hopkins	6,137
Memorial	5,791
CCF	2,146
Total	16,176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0.75
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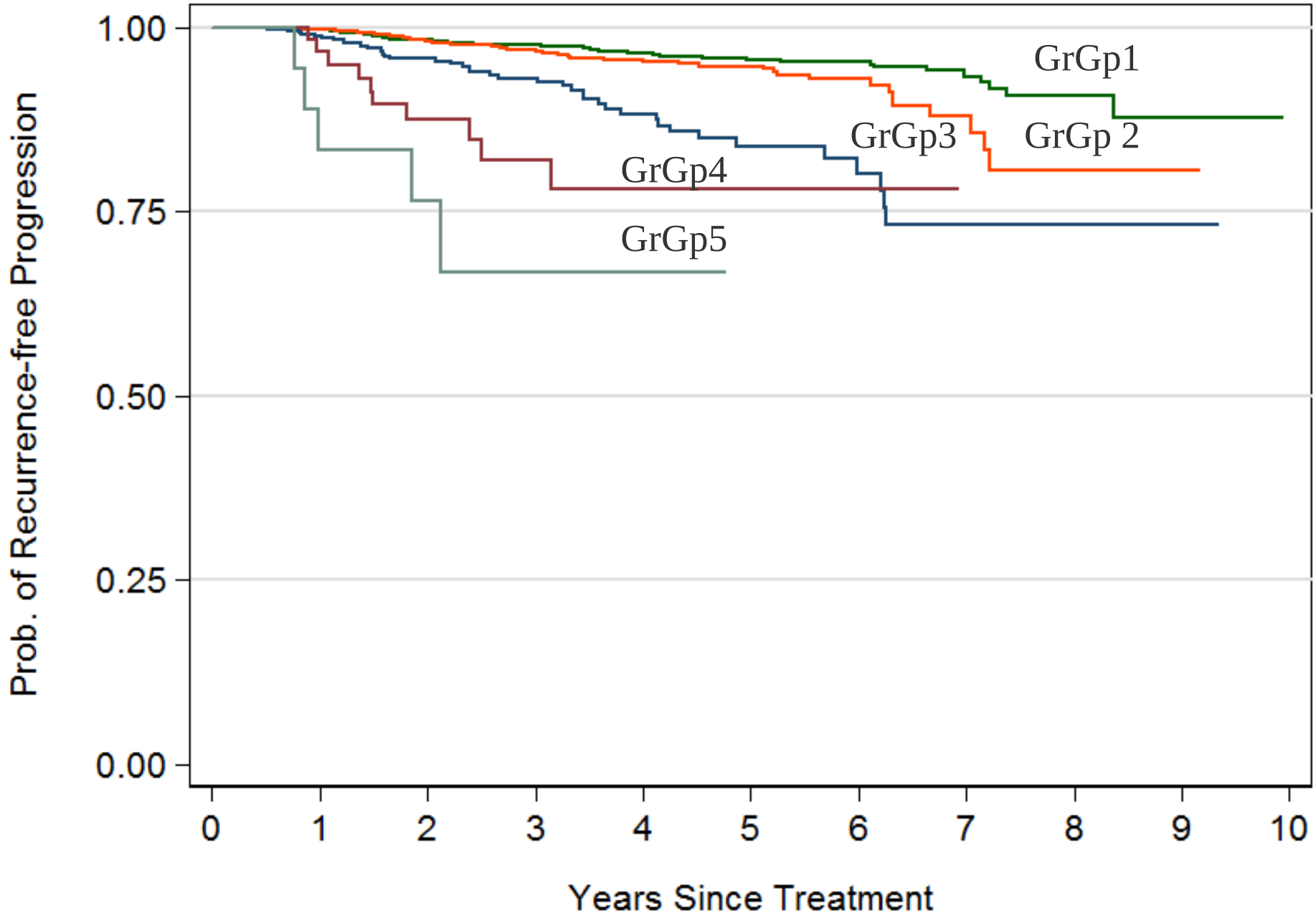
0.25
0.00
Prob. of Recurrence-free Progression
0
1
2
3
4
5
6
7
8
9
10
Years Since Surgery
GrGp 1
GrGp 2
GrGp 3
GrGp 4
GrGp 5

Radiation Therapy

CCF	**2495 (45%)**
MSKCC	**3006 (55%)**
Brachy	**3361 (61%)**
EBRT	**2140 (39%)**
Peri-RT	**1845 (34%)**
HT	


1.00
0.75
0.50
0.25
0.00
Prob. of Recurrence-free Progression
GrGp1
GrGp 2
GrGp3
GrGp4
GrGp5
0
1
2
3
4
5
6
7
8
9
10
Years Since Treatment

More Accurately Reflects Biology of Disease than Current System

Grade Group 1 (as opposed to 6/10): Excellent prognosis – no metastases. Avoids issues of GS<6

Grade Group 2 (as opposed to 7/10): Very good prognosis – rare metastases

Grade Group 3 (4+3 and 3+4 both = GS7 – D'Amico): Greater distinction from Grade Group 2

More Accurately Reflects Biology of Disease than Current System

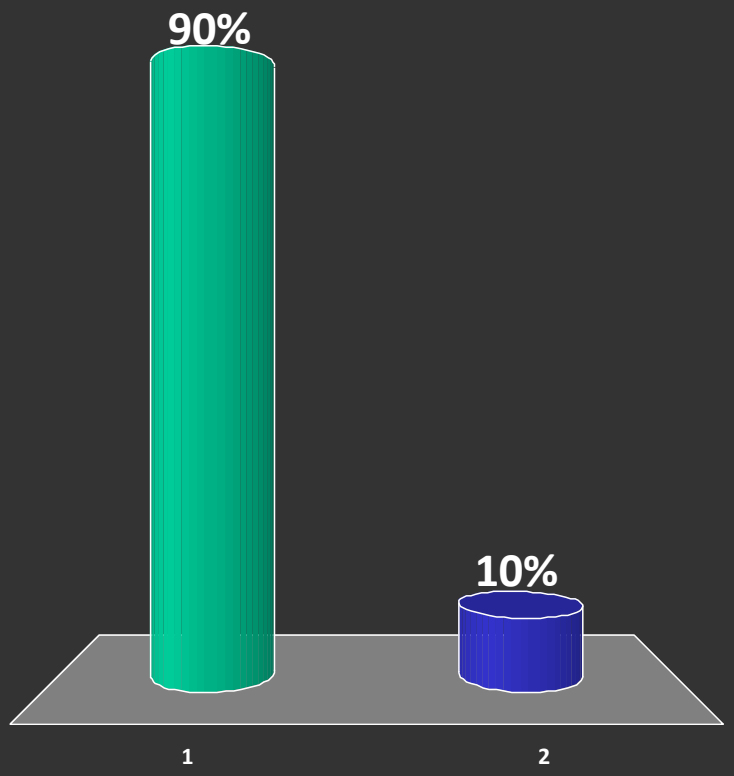
Grade Group 4 (as opposed to combined 8-10): Better prognosis than 9-10.

Grade Group 5: No need to distinguish 9 vs 10.

VOTE

A new grading system for prostate cancer should be adopted ranging from 1-5, initially used in conjunction with Gleason.

1. Yes
2. No



It is recommended to use the new grading system in parallel to the Gleason grading system

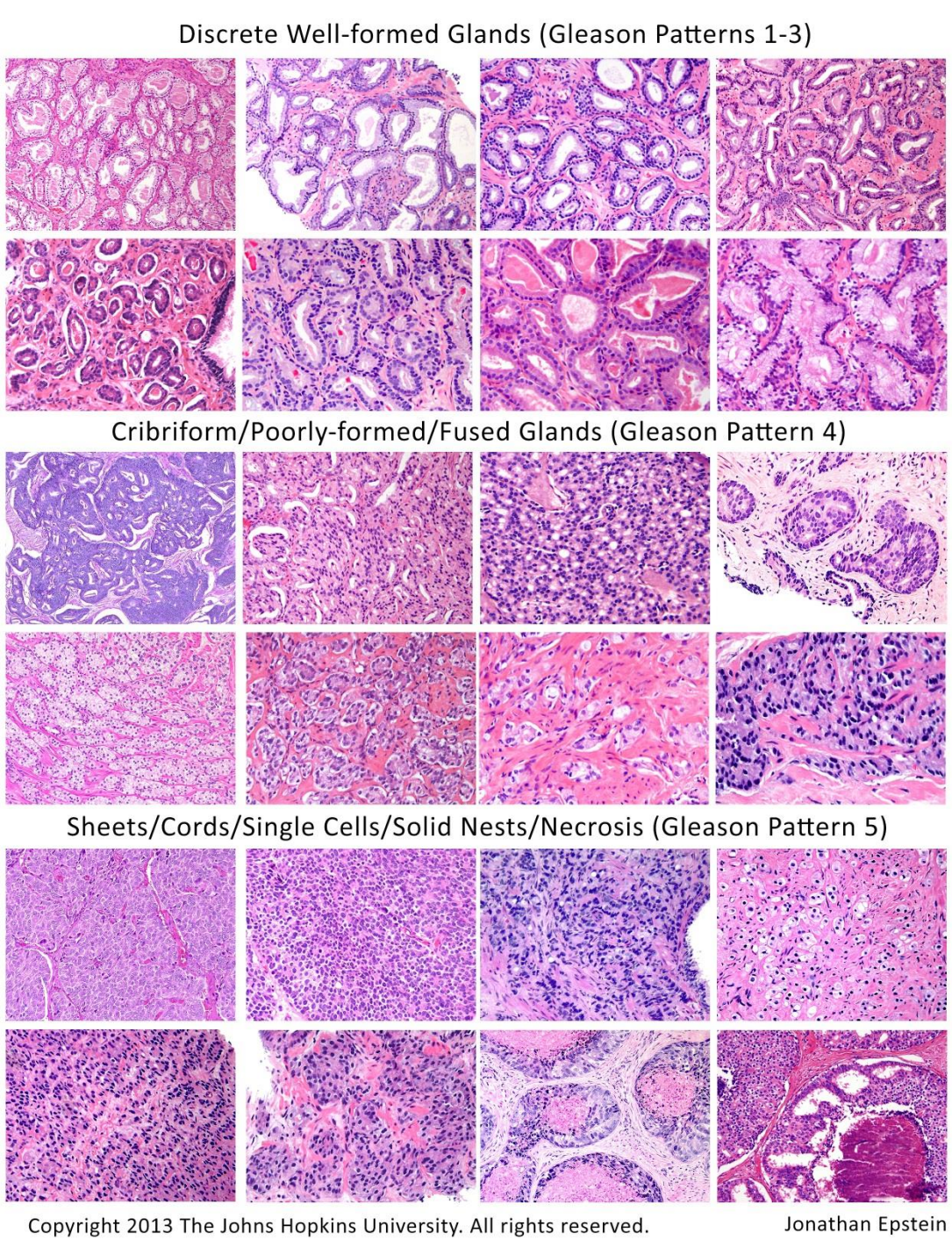
1. **Left Apex: Adenocarcinoma of the prostate Gleason score 3+3=6 (Grade Group 1) involving 20% of 1 core.**

2. **Left Mid: Adenocarcinoma of the prostate Gleason score 4+3=7 (Grade Group 3) with 60% pattern 4 involving 80% of 1 core.**

The new grading system was recently accepted by the World Health Organization (WHO) and will be included in the 2016 edition of:

Pathology & Genetics:

Tumours of the Urinary System and Male Genital System



Jonathan Epstein

CONTEMPORARY PROSTATE CANCER GRADING IMAGES

Grading diagram that uses photomicrographs instead of line drawings to show the various patterns within each grade.

Sent to Pathologists in >40 Countries

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