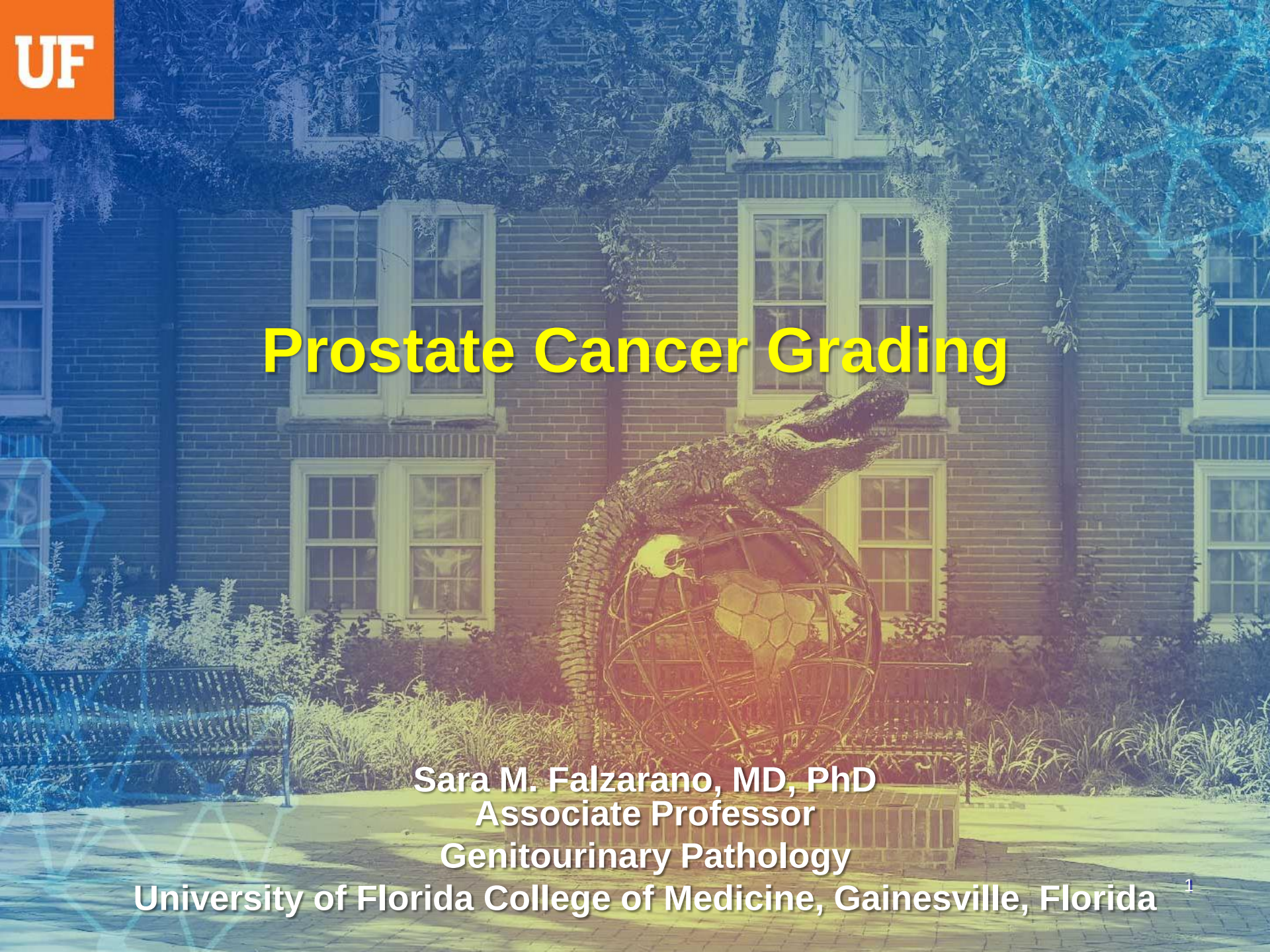


Prostate Cancer Grading

Sara M. Falzarano, MD, PhD
Associate Professor
Genitourinary Pathology
University of Florida College of Medicine, Gainesville, Florida

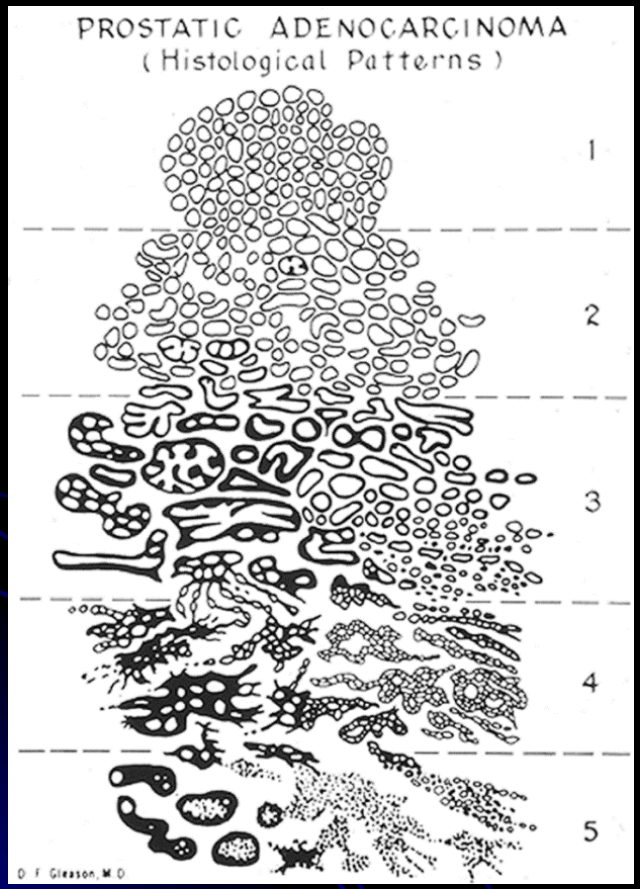
Objectives

- Provide an overview of the histologic grading system for prostatic adenocarcinoma (PCA)
- Review architectural patterns of PCA
- Discuss relevant reporting elements in PCA diagnosis with respect to grading
- Touch upon the development of ancillary tools in optimizing PCA grading

“The wide-ranging biologic malignancy of prostate cancer is strongly correlated with its extensive and diverse morphologic appearances”

Gleason DF. Hum Pathol. 1992 Mar;23(3):273-9

Prostate Cancer Histologic Grading
The Gleason Score System

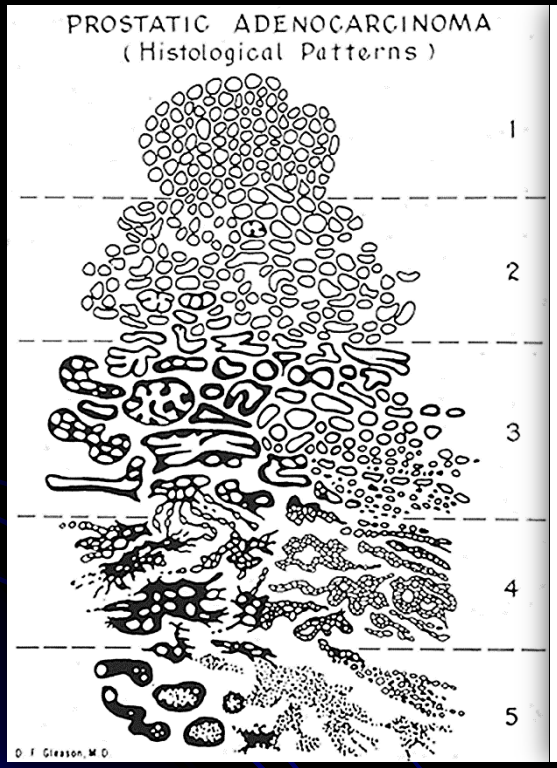


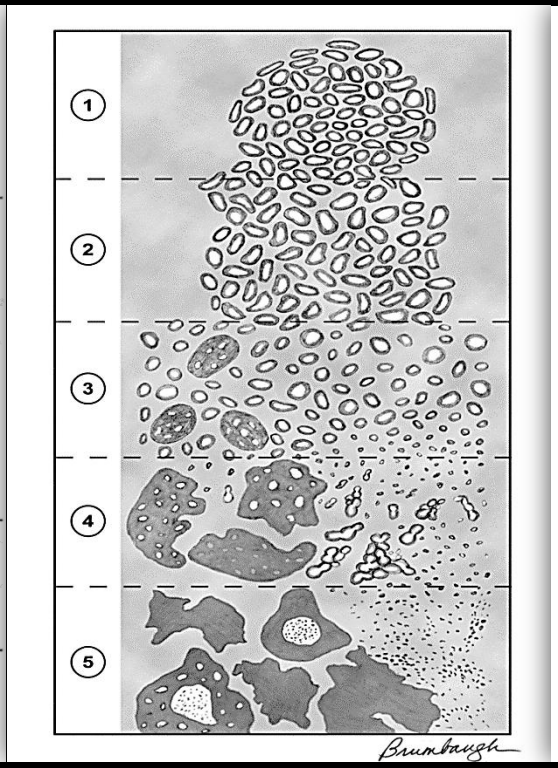
- Assigned on microscopic appearance of tissue
- Architectural patterns arranged into 5 grades (in order of increasing biologic malignancy as determined by mortality data)
- Reported as a combined sum (score) of the two most common grades, with scores ranging from 2 to 10

Epstein JI et al. Am J Surg Pathol 2016;40:244–252
Gleason DF, Mellinger GT. J Urol. 1974;111:58–64

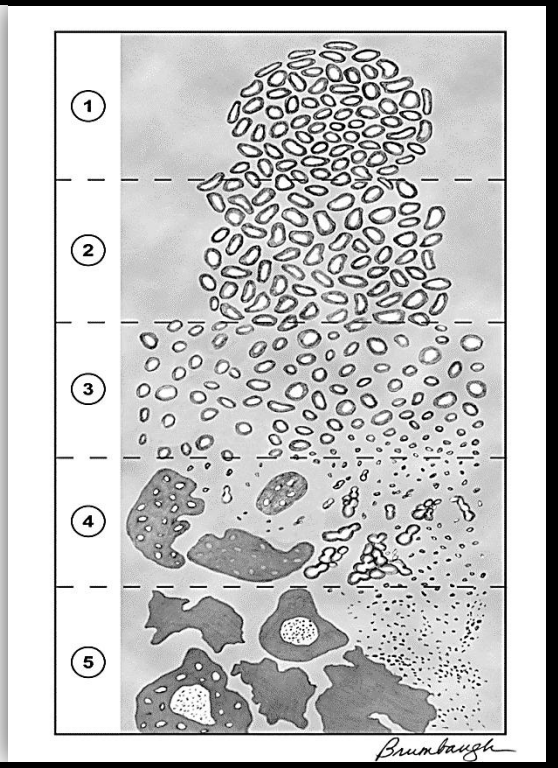
Evolution of the Gleason Score System
The *Modified* Gleason Score System

Original Gleason | **2005 ISUP*** | **Current Scheme**





- Inclusion of poorly formed glands in Pattern 4
- MOST cribriform pattern should be graded as 4



- All cribriform glands = pattern 4

*ISUP: International Society of Urological Pathology

Brimo F. et al. Eur Urol 2016;63:892

Rationale for a New Reporting System: the Grade Group Proposal

1. Grade (Pattern) 1 and 2 are not assigned at biopsy (and rarely if ever in resection specimens)

2. Gleason score 3+3=6 is the lowest (best) score at biopsy (NOT an "intermediate" score between 2 and 10)

Epstein JI et al. Am J Surg Pathol 2016;40:244–252

Five Grade Groups(GG) = the Least Number of Score Groups with Distinct Prognosis

3. Optimal grouping of the different Gleason scores (GS) by prognosis
   - ✓ Splitting GS 7 (3+4/4+3) cancers (now GG2/3)
   - ✓ Lumping GS 9 and 10 cancers (GG5)

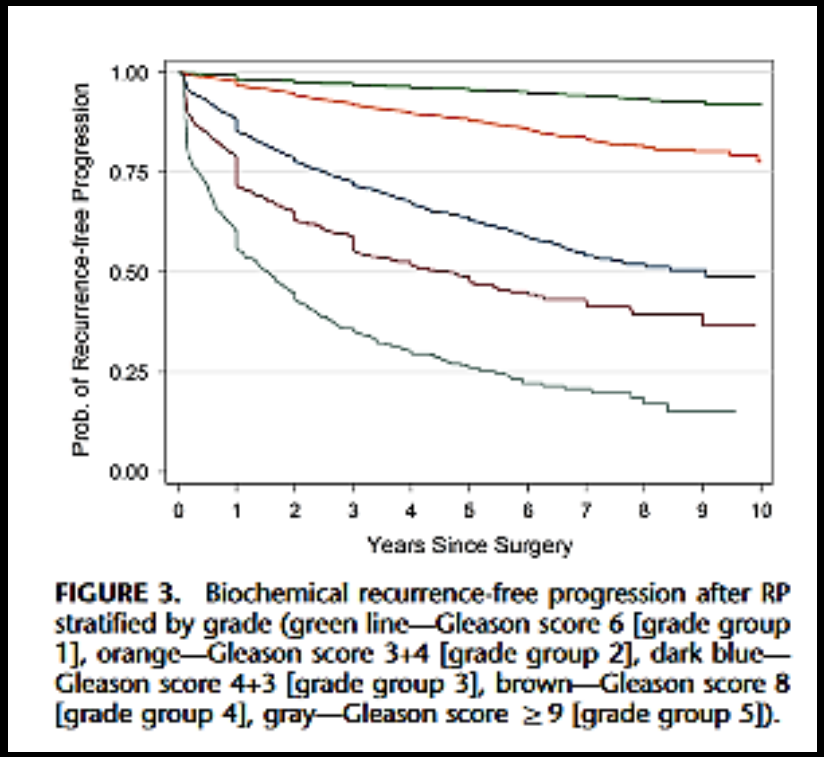


FIGURE 3. Biochemical recurrence-free progression after RP stratified by grade (green line—Gleason score 6 [grade group 1], orange—Gleason score 3+4 [grade group 2], dark blue—Gleason score 4+3 [grade group 3], brown—Gleason score 8 [grade group 4], gray—Gleason score ≥9 [grade group 5]).

Adapted from Epstein JI et al. Eur Urol 2016;69:428

The Grade Group System

Group	Gleason Score	Histologic Criteria	Advantages
1	3 + 3	Only individual, discrete, well-formed glands	Excellent prognosis; helps avoid overtreatment
2	3 + 4	Predominantly well-formed glands with lesser component of poorly-formed/fused/glomeruloid/cribriform glands	Improved prognostic discrimination amongst Gleason “7”
3	4 + 3	Predominantly poorly-formed/fused/glomeruloid/cribriform glands with lesser component of well-formed glands	
4	8	Only poorly formed/fused/cribriform glands or - Predominantly well-formed glands with a lesser component lacking glands - Predominantly lacking glands with a lesser (>5%) component of well-formed	Distinct prognosis
5	9 or 10	Lack gland formation or show comedonecrosis with or without poorly-formed/fused/glomeruloid/cribriform glands	Similar prognosis

Adapted from Kryvenko ON and Epstein JI. Arch Pathol Lab Med 2016;140:1140

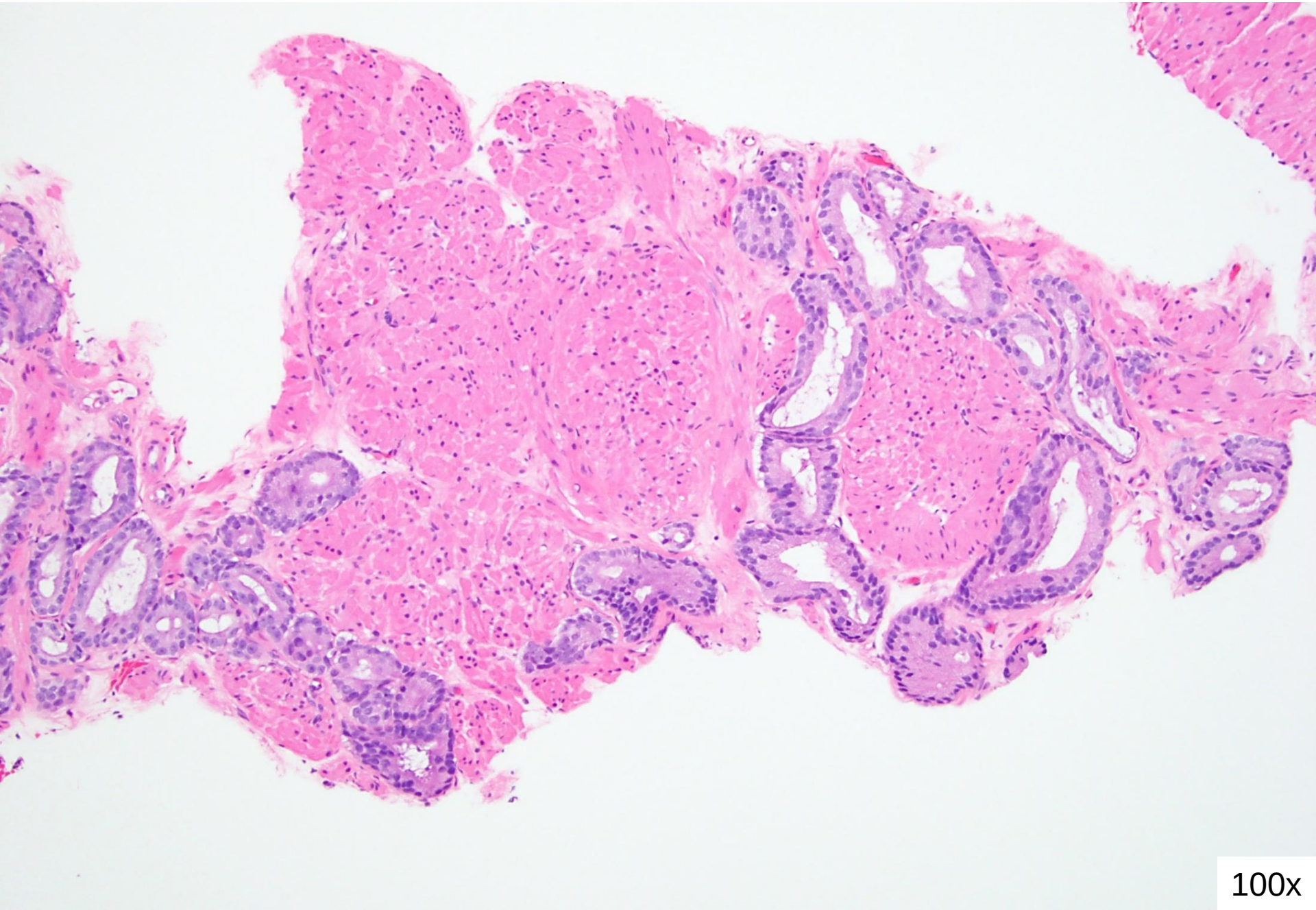
Objectives

- ✓ Provide an overview of the histologic grading system for prostatic adenocarcinoma (PCA)
- Review architectural patterns of PCA
- Discuss relevant reporting elements in PCA diagnosis with respect to grading
- Touch upon the development of ancillary tools in optimizing PCA grading

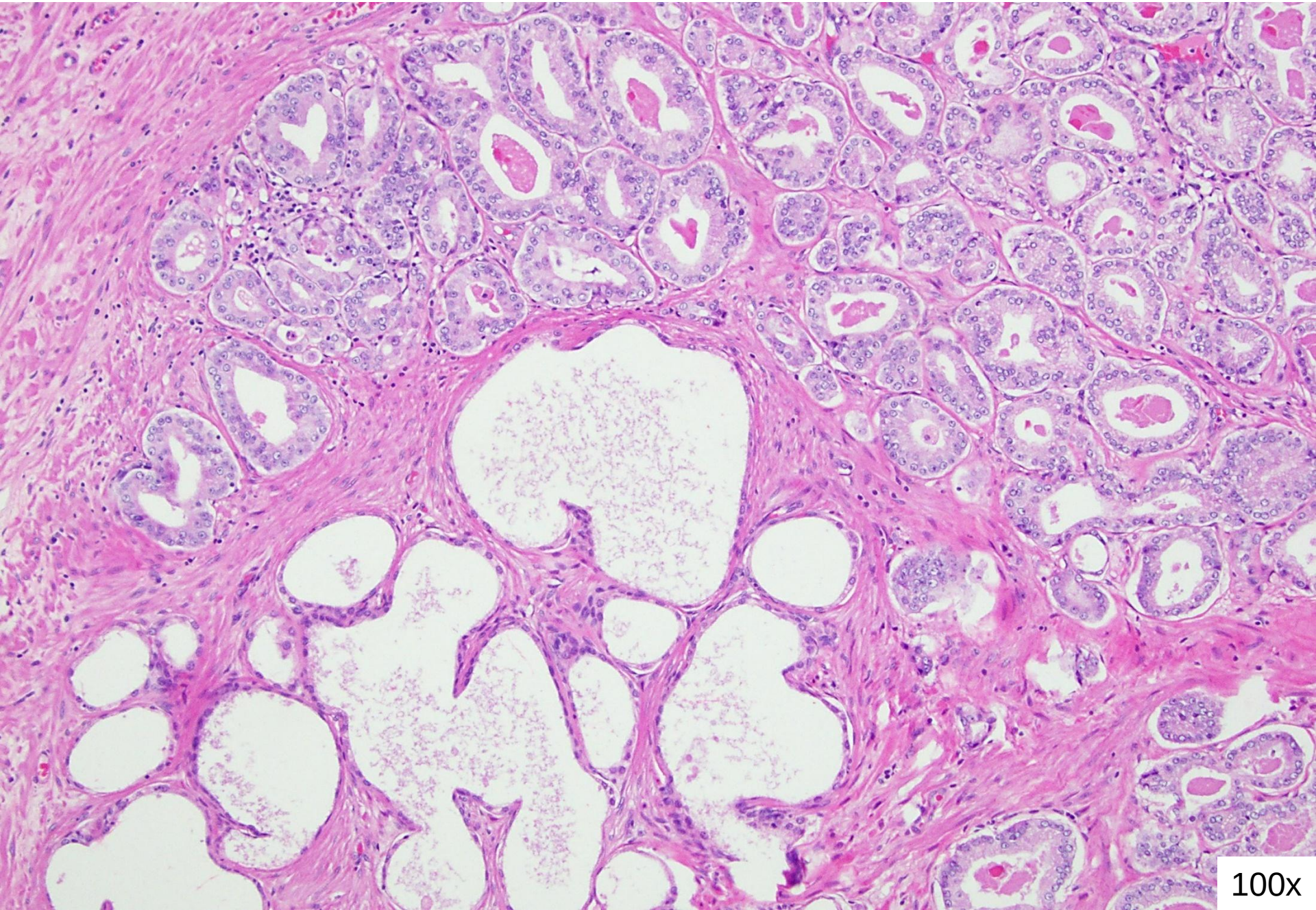
Gleason pattern 3

- Individual, discrete, well-formed glands

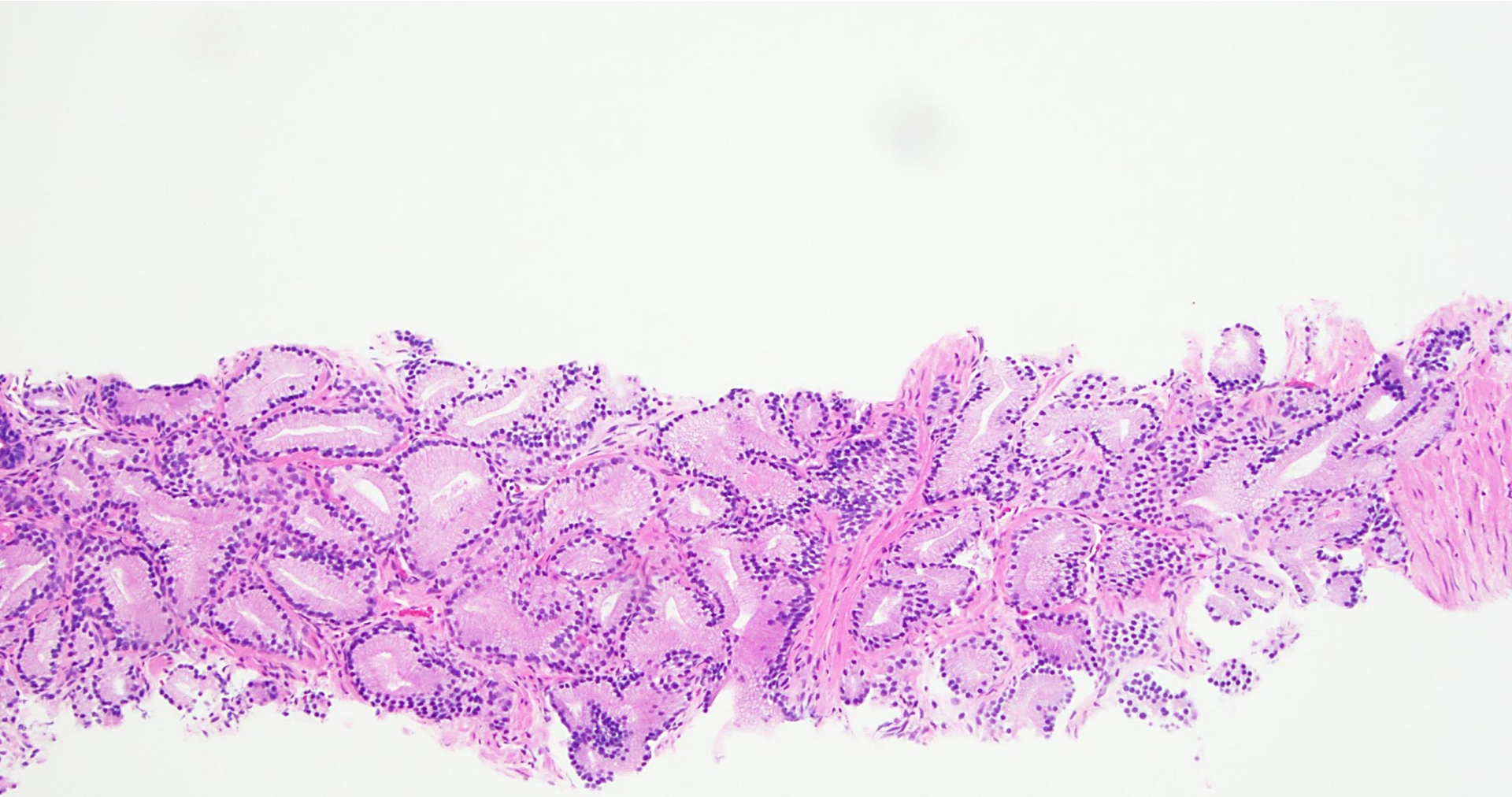
Gleason pattern 3/GG1



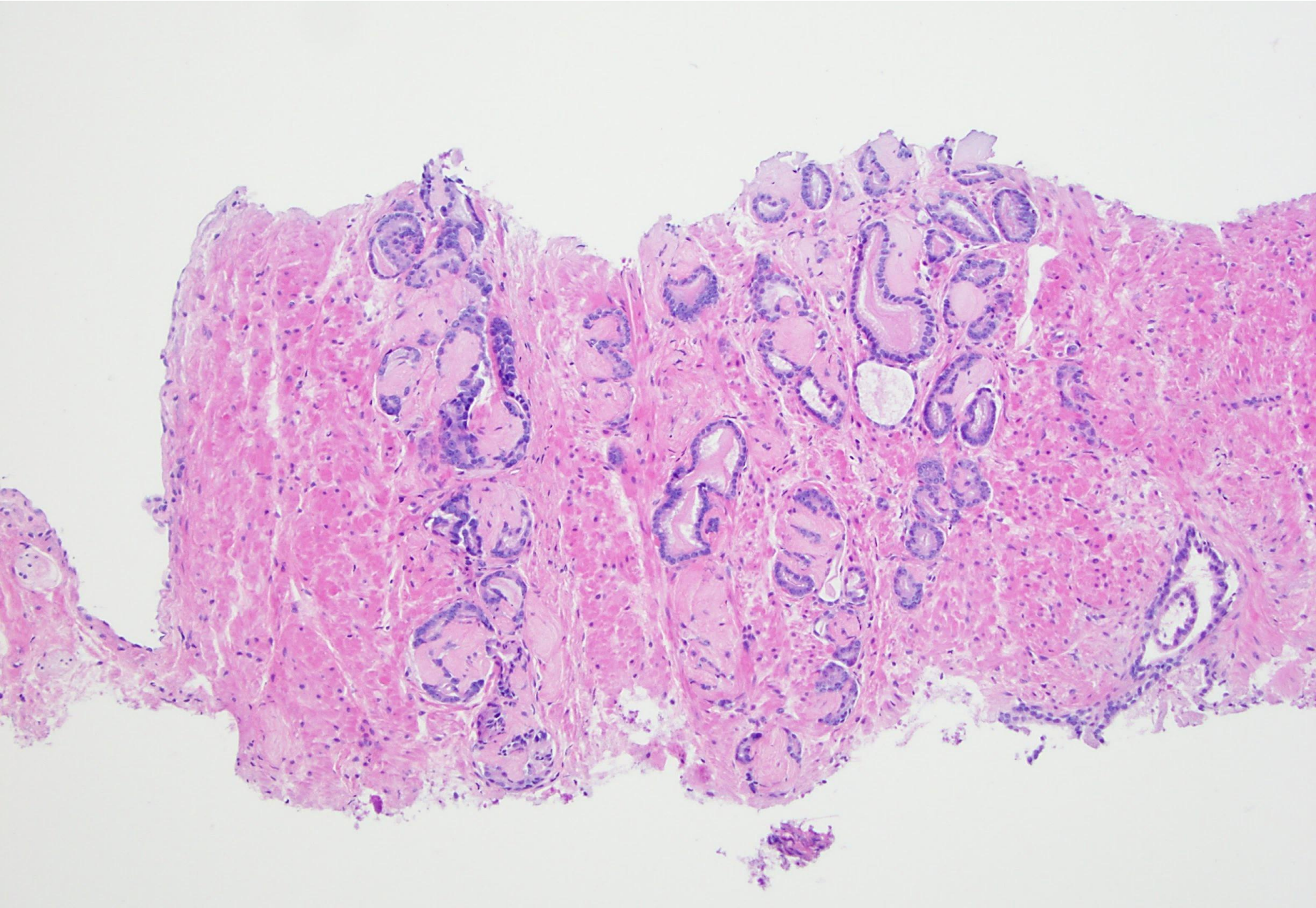
Gleason pattern 3/GG1



Gleason pattern 3/GG1: Pseudohyperplastic



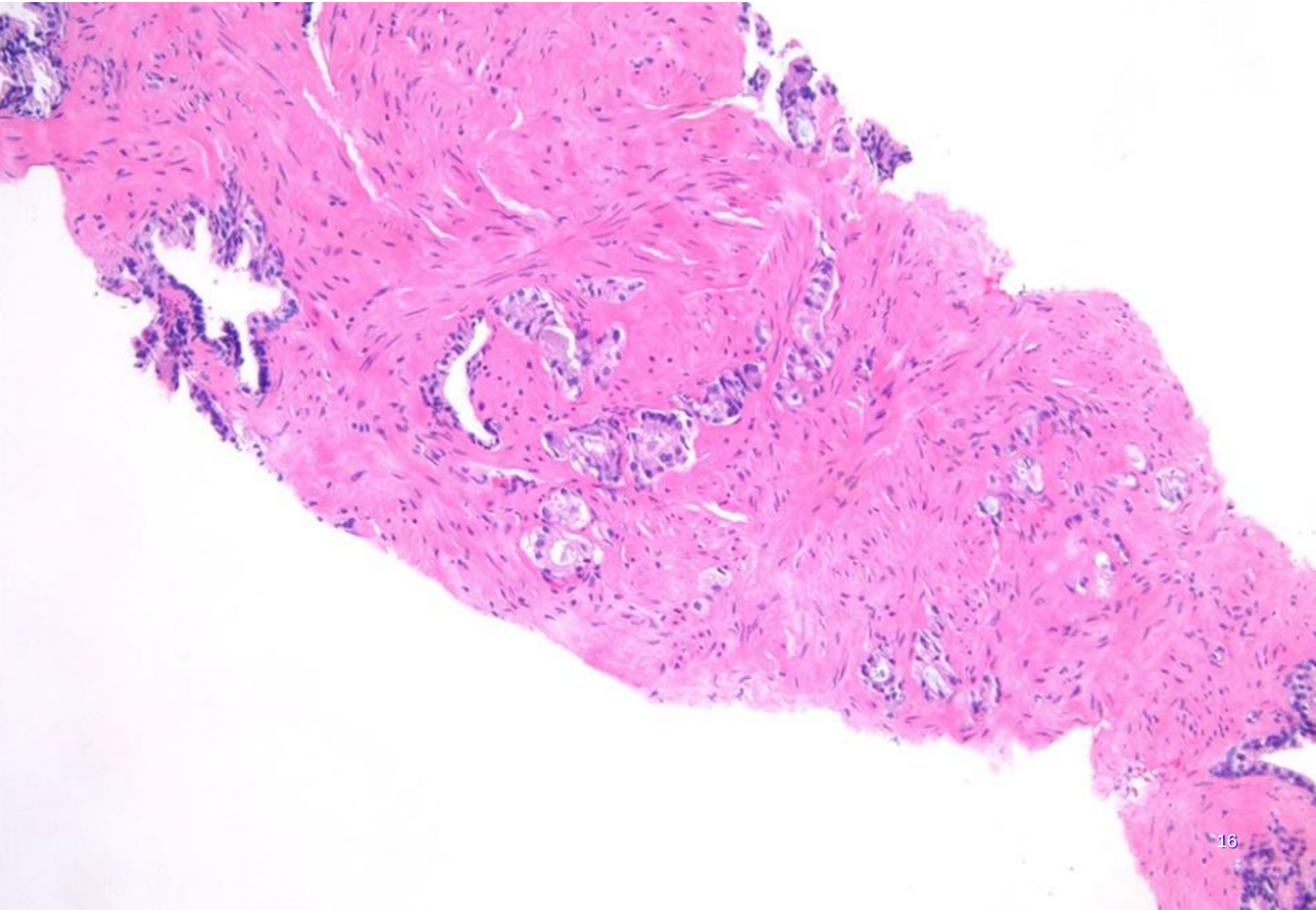
Gleason pattern 3/GG1: Mucinous Fibroplasia



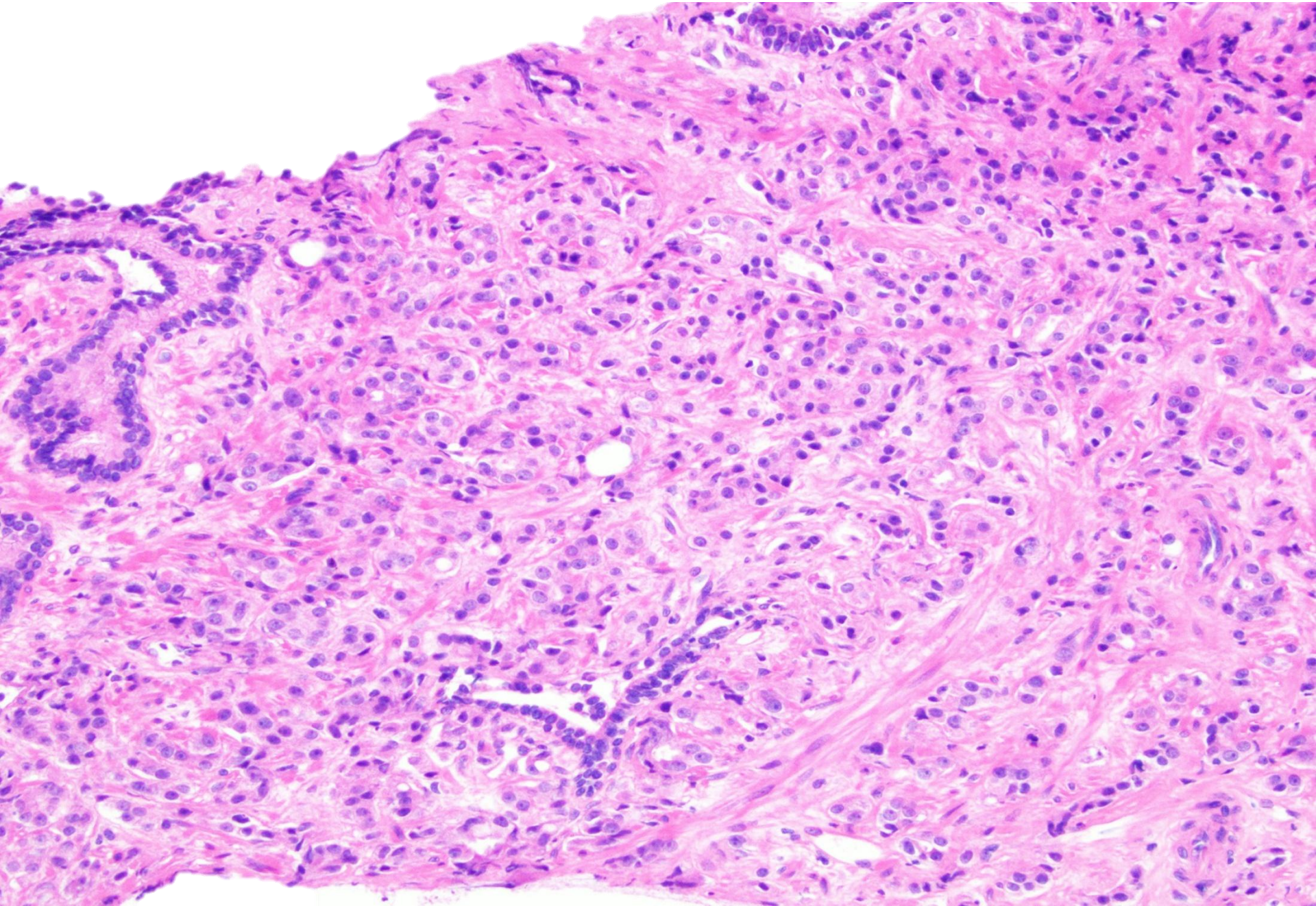
Gleason pattern 4 PCA

- Poorly-formed glands
- Fused glands
- Glomeruloid structures
- Cribriform architecture

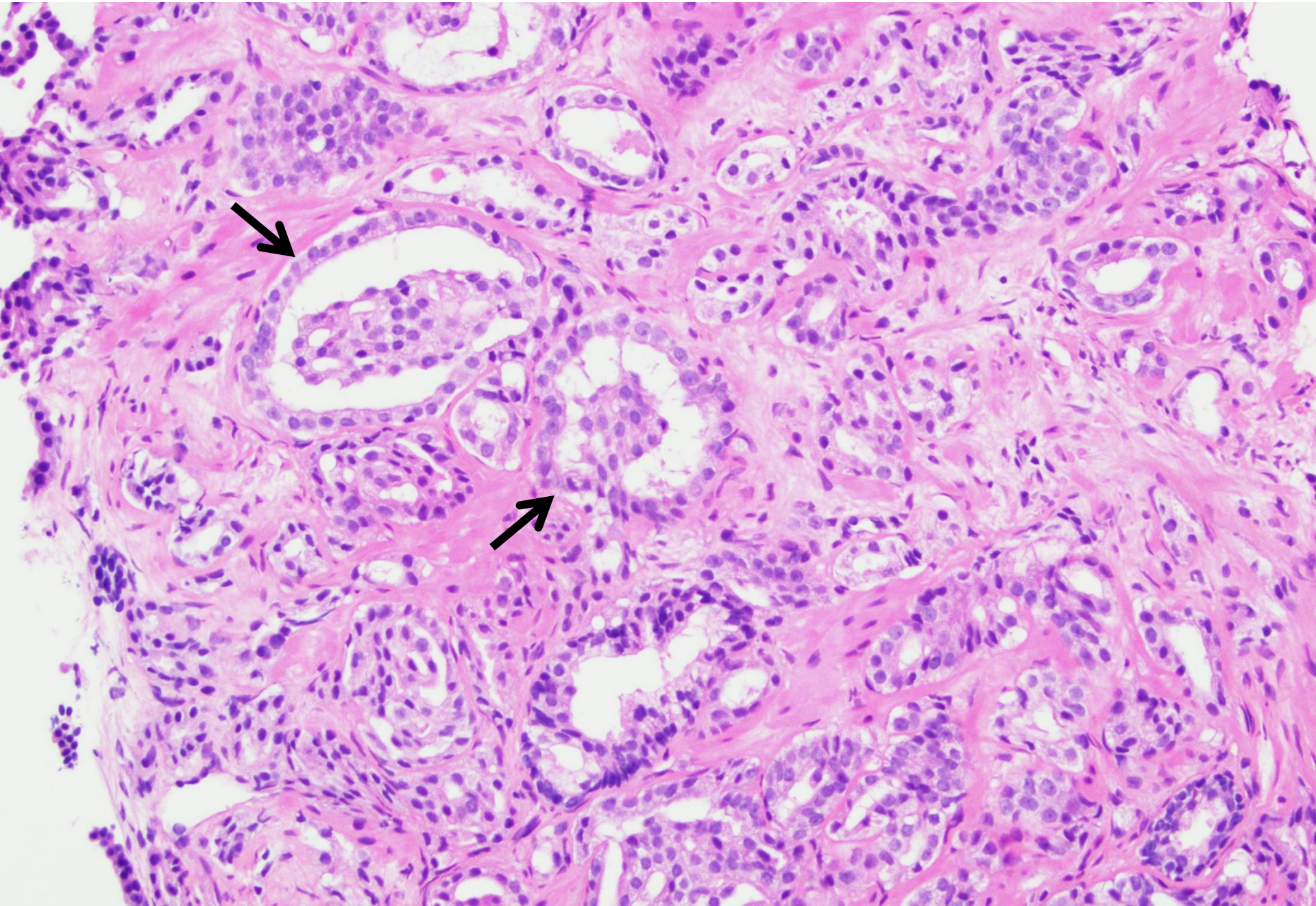
Pattern 4: Poorly-Formed Glands



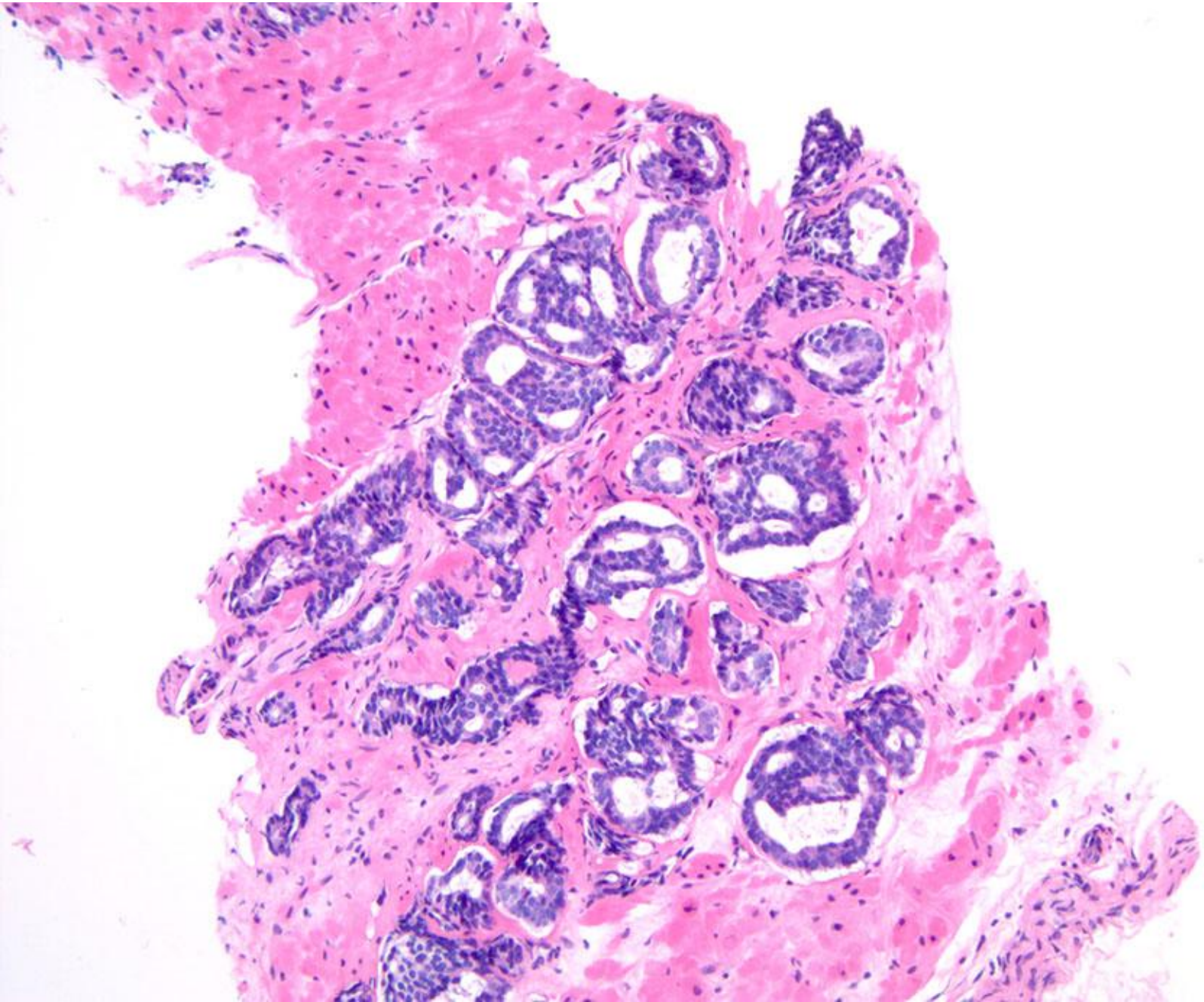
Pattern 4: Poorly-Formed/Fused Glands



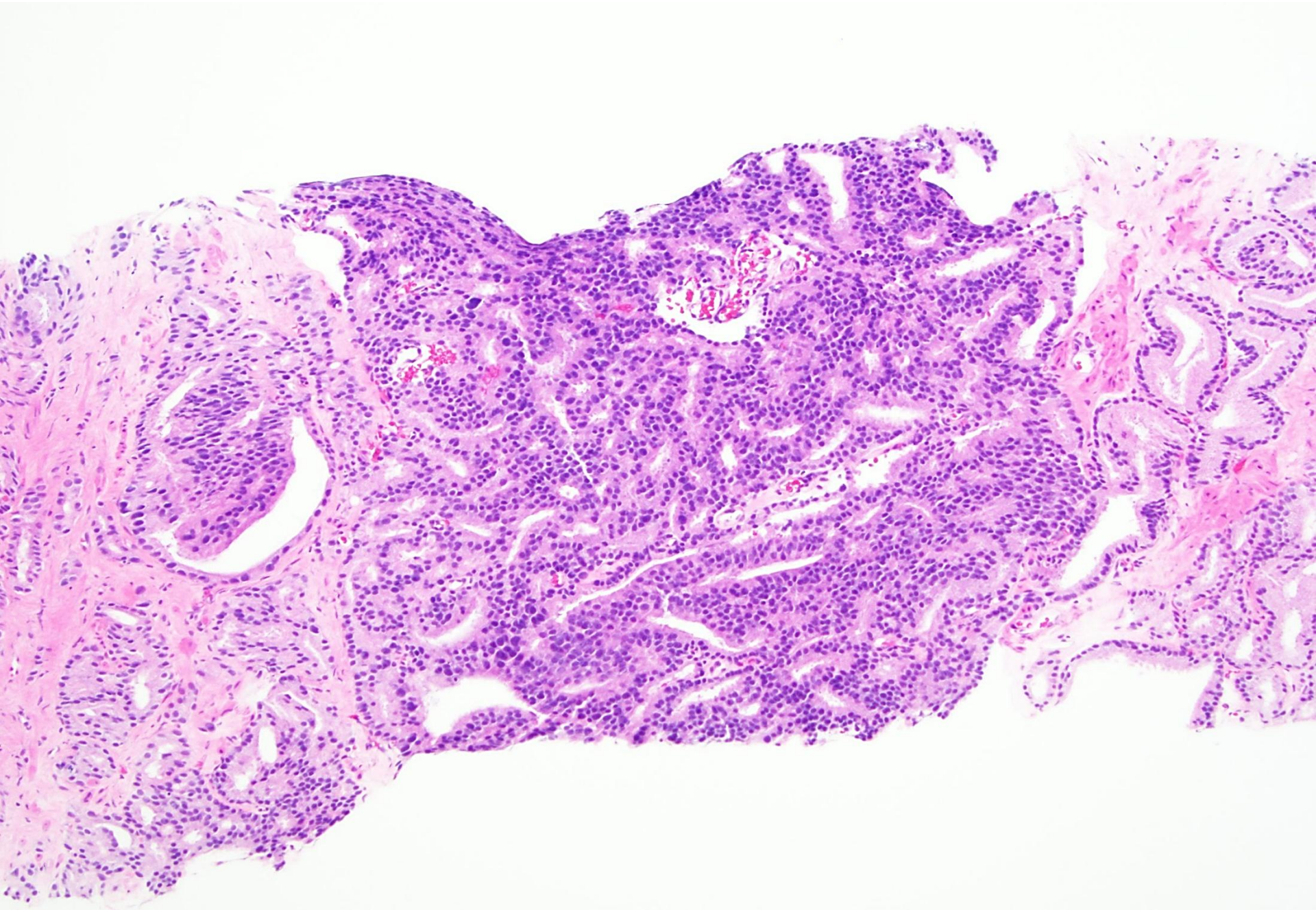
Pattern 4: Glomeruloid Glands



Pattern 4: Cribriform Architecture



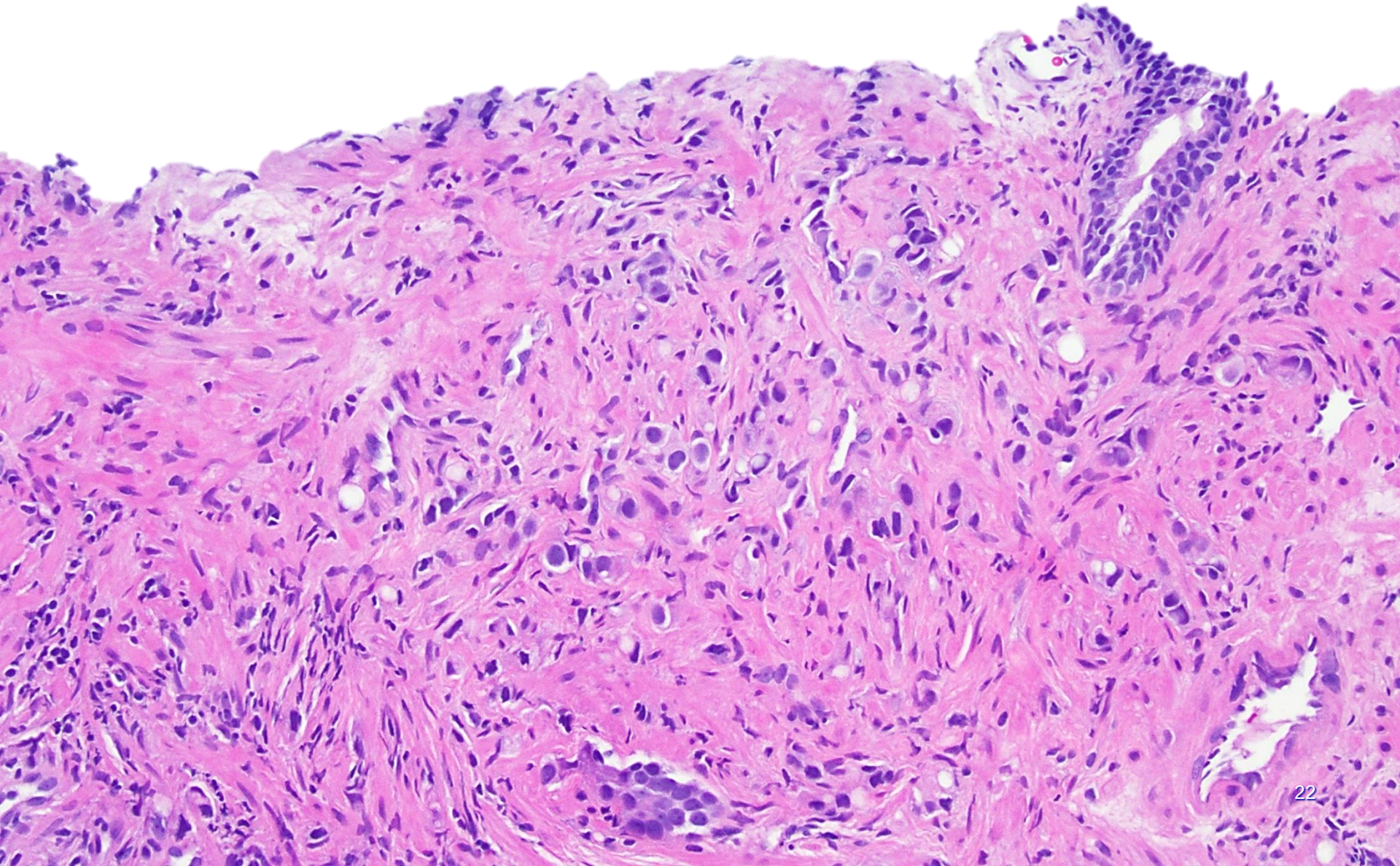
Pattern 4: Cribriform Architecture



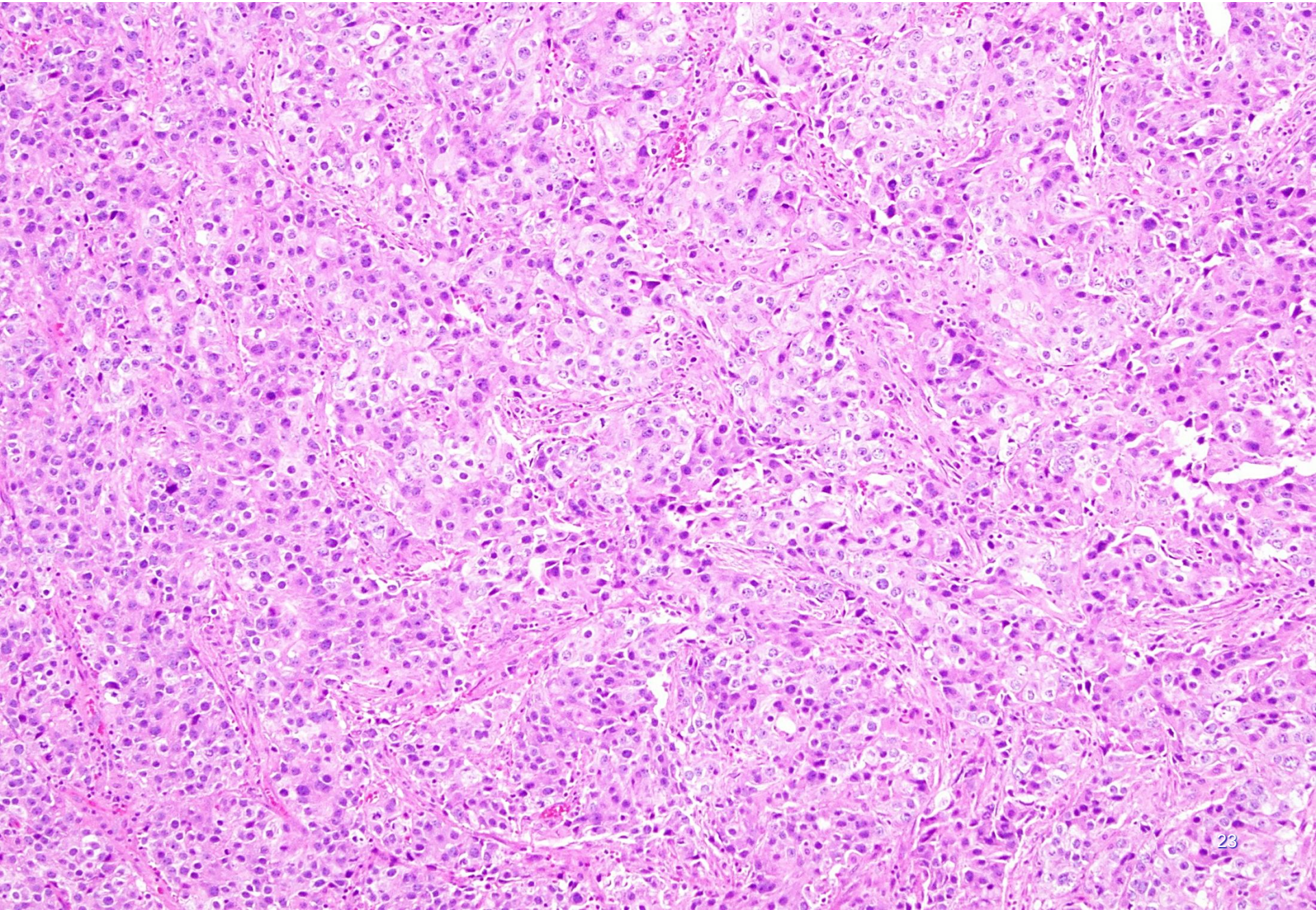
Gleason pattern 5 PCA

- Single cells/cords
- Solid growth
- Comedonecrosis

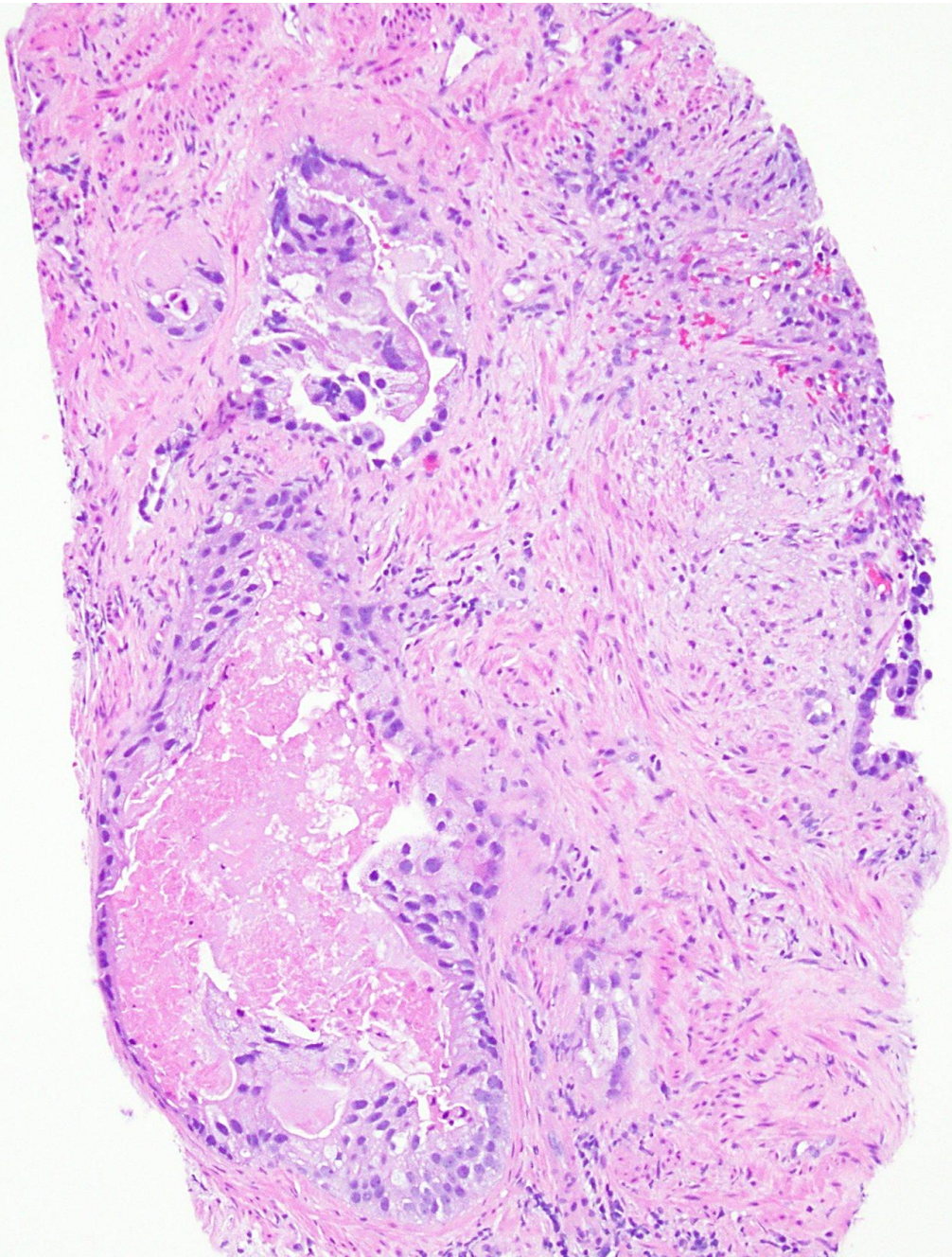
Pattern 5: Single cells



Pattern 5: Solid growth



Pattern 5: Comedonecrosis



Objectives

- ✓ Provide an overview of the histologic grading system for prostatic adenocarcinoma (PCA)
- ✓ Review architectural patterns of PCA
- ▪ Discuss relevant reporting elements in PCA diagnosis with respect to grading
- ▪ Touch upon the development of ancillary tools in optimizing PCA grading

Grade-complementing Reporting Elements

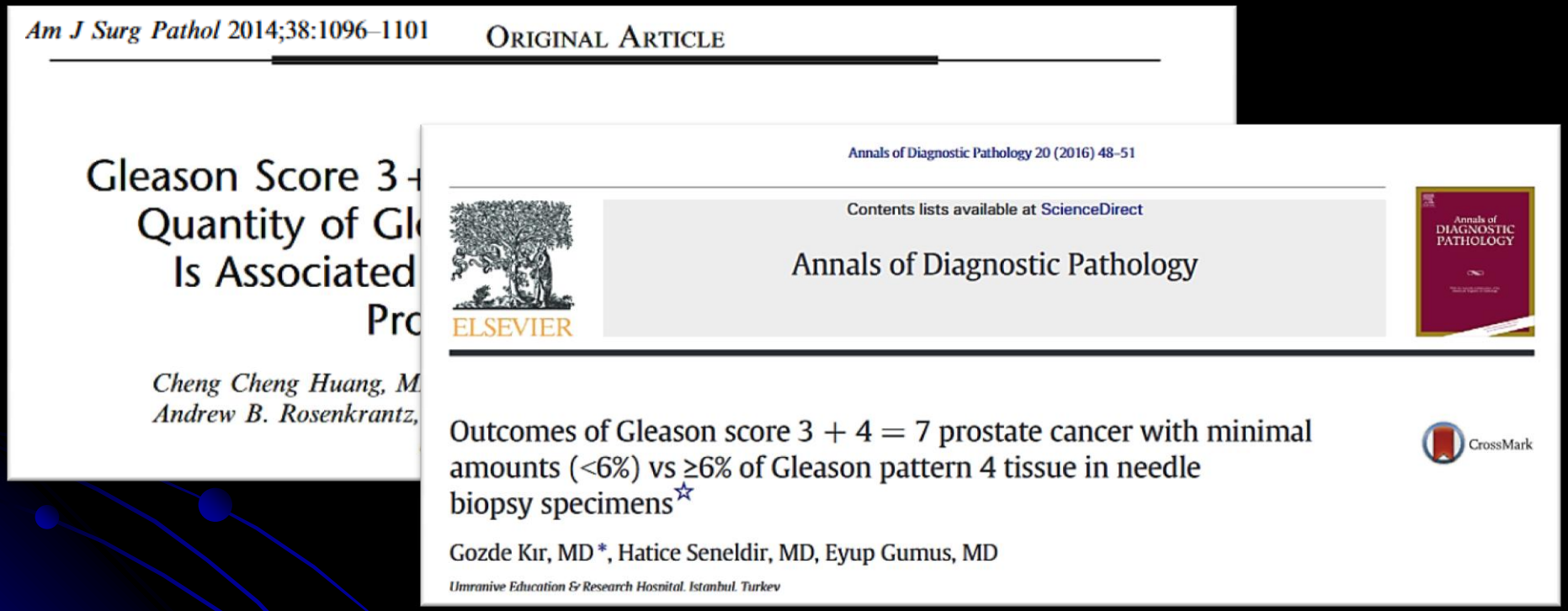
- Percentage pattern 4
- Minor component of higher (“tertiary”) grade
  - ✓ Biopsy
  - ✓ Radical prostatectomy
- Case-level biopsy score (global versus highest)
- Cribriform pattern 4/Intraductal carcinoma of the prostate

Percent pattern 4

- Pattern 4 amount*/whole tumor amount x 100

*In biopsies = length of core occupied by pattern 4

Percent pattern 4 in needle biopsy rationale



Am J Surg Pathol 2014;38:1096–1101 ORIGINAL ARTICLE

Gleason Score 3 +
Quantity of Gl
Is Associated
Pro

Cheng Cheng Huang, M
Andrew B. Rosenkrantz,

Annals of Diagnostic Pathology 20 (2016) 48–51

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

ELSEVIER

Outcomes of Gleason score 3 + 4 = 7 prostate cancer with minimal amounts (<6%) vs ≥6% of Gleason pattern 4 tissue in needle biopsy specimens☆

Gozde Kır, MD *, Hatice Seneldir, MD, Eyup Gumus, MD

Umranive Education & Research Hosnital. Istanbul. Turkev

- Similar rates of radical prostatectomy adverse pathology and outcome for patients with biopsy GG1 versus GG2 with ≤5% pattern 4

Epstein JI et al. Arch Pathol Lab Med 2021;145:461–493

Percent pattern 4 in needle biopsy rationale

J Urol. 2016 August; 196(2):405-11

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

Adam I. Cole, Tod
Chang He, Scott A
Angela Wu, Javed
Lakshmi P. Kunju,
John T. Wei and F

From the Department of Urol
Oncology (DES, FYF), Departr
Pathology (SAT, AMC, LPK, R
University of Michigan Medica

J Urol. 2019 January ; 201(1): 77–82

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 Ehdaie, Samson W. Fine†
Urology Service, Department of Surgery (LWD, JAE, PTS, BE) and Departments of Epidemiology-Biostatistics (MA, DDS, AJV) and Pathology (HAAA, YBC, AG, SJS, SKT, VER, SWF), Memorial Sloan Kettering Cancer Center, New York, New York

- Increasing percent pattern 4 on biopsy correlates with increasing rate of radical prostatectomy adverse pathology

Epstein JI et al. Arch Pathol Lab Med 2021;145:461–493

Percent pattern 4 in needle biopsy rationale

- In low-volume Grade Group (GG)2 disease at biopsy (favorable intermediate risk)
  - Active surveillance eligibility
- In cases with highest GG3 +/- [limited] GG4 at biopsy
  - ?Identification of borderline cases (GG2/3) for adjuvant ADT after radiation
    - >>>limited GG3
    - Multiple positive cores with mix of grades

Percent pattern 4 recommendations

Table 3. Summary of Recommendations on Percent Pattern 4

1	Record percent Gleason pattern 4 in needle biopsy specimens with Grade Groups 2 and 3
2	**Preferred method of reporting percent Gleason pattern 4: either ≤5% or ≤10% and 10% increments thereafter for Grade Groups 2–3**
3	**Report percent Gleason pattern 4 in needle biopsies in other parts (jars) of lower grade in cases with at least one part showing Gleason score 4 + 4 = 8 (Grade Group 4)**

Require more data and/or lack compelling clinical rationale(s)/prevailing practice patterns

1	Whether to record percent Gleason pattern 4 in radical prostatectomy specimens with Grade Groups 2 and 3
2	Whether to report percent Gleason pattern 4 for needle biopsy Grade Groups 2 and 3 with limited cancer volume
3	Whether to report percent Gleason pattern 4 in needle biopsy on other parts (jars) of lower grade in cases with at least one part showing Gleason scores 9-10 (Grade Group 5)

Bold items reflect first time recommendations by the Genitourinary Pathology Society.

TABLE 2. Summary of ISUP 2019 Modifications to Prostate Cancer Grading

Report in biopsies the percentage Gleason pattern 4 for all GS 7 (ISUP GG 2 and 3)

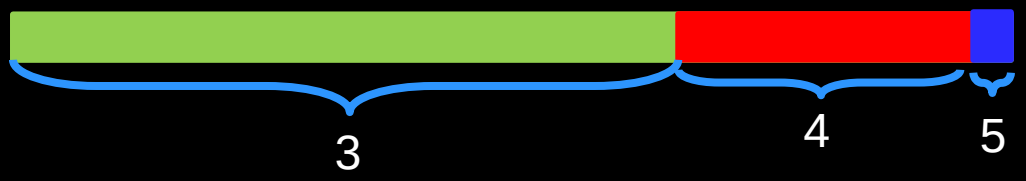
Epstein JI et al. Arch Pathol Lab Med 2021;145:461–493
Van Leedders GJLH et al. Am J Surg Pathol. 2020;44(8):e87-e99

"…roughly half of the tumors contained more than one histologic grade, *a troublesome phenomenon* observed by all those who have attempted to grade prostate cancers"

Gleason DF. Hum Pathol. 1992 Mar;23(3):273-9

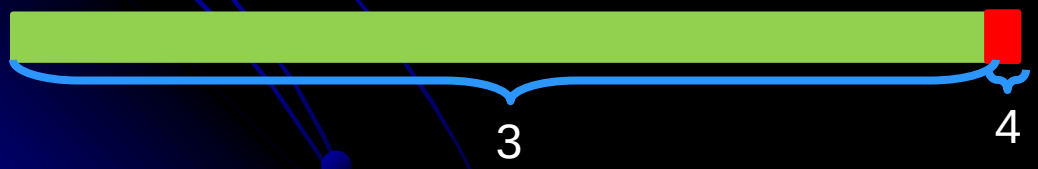
Minor (tertiary) pattern reporting in biopsy

- Any quantity of high-grade tumor on needle biopsy should be included in the Gleason score



3+5=8 (GG4) (<5% p5)

4+5=9 (GG5)

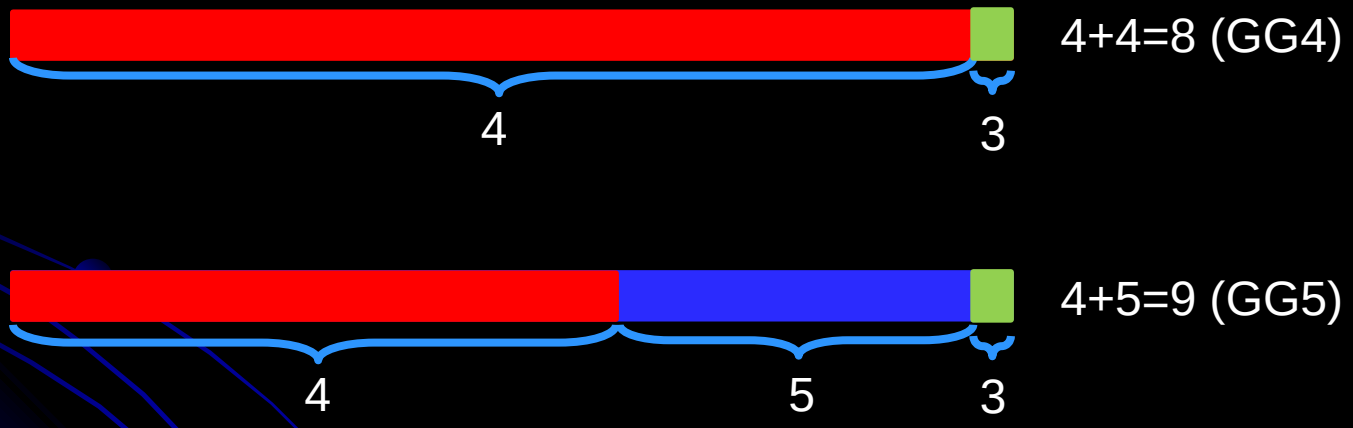


3+4=7 (GG2) (<5% p4)

Epstein JI et al. Am J Surg Pathol. 2005;29(9):1228-42

Minor (tertiary) pattern reporting in biopsy

- Small (<5%) amount of lower-grade pattern in an otherwise high-grade cancer should be ignored



Epstein JI et al. Am J Surg Pathol. 2005;29(9):1228-42

Minor (tertiary) pattern reporting: Radical prostatectomy specimens

- Significant variations in definition and cutoff in the literature
- Currently limited to ≤5% highest grade component
  - ✓ If more than 5%, the higher grade should be incorporated in the final Gleason score/Grade Group
- Noted along the Gleason score and Grade Group (i.e., “Grade Group 2 with minor component of pattern 5, Gleason score 3+4=7 with minor tertiary pattern 5”)

“Tertiary” Grade Patterns recommendations

	Table 4. Summary of Recommendations on Tertiary Grade Patterns
1	When a minor tertiary (3rd most common) Gleason pattern 5 is found on biopsy or TURP, it should be combined with the primary pattern to derive the overall Gleason score
2	**Replace “tertiary grade pattern” in radical prostatectomy specimens with the term “minor tertiary pattern 5”**
3	**Only use “minor tertiary pattern 5” in radical prostatectomy specimens with Grade Groups 2 or 3 (Gleason score 3 + 4 = 7 or 4 + 3 = 7)**
4	**Use 5% as the cutoff for what is allowed as minor tertiary pattern 5. If >5% Gleason pattern 5, then Gleason pattern 5 is considered the secondary Gleason pattern in the Gleason score**
5	**Minor tertiary pattern 5 is noted along with the Gleason score, with the Grade Group based on the Gleason score**

Abbreviation: TURP, transurethral resection of the prostate.

Bold items reflect first time recommendations by the Genitourinary Pathology Society.

TABLE 2. Summary of ISUP 2019 Modifications to Prostate Cancer Grading

Report in biopsies the percentage Gleason pattern 4 for all GS 7 (ISUP GG 2 and 3)
For radical prostatectomies, include the presence of tertiary/minor Gleason patterns 4 and 5 in the GS, if constituting > 5% of the tumor volume
Report in radical prostatectomies presence of tertiary/minor Gleason patterns 4 and 5

Epstein JI et al. Arch Pathol Lab Med 2021;145:461–493
Van Leedders GJLH et al. Am J Surg Pathol. 2020;44(8):e87-e99

“Another problem is reported as “under-grading” of the original biopsy compared with the grade of the resected specimen”

Gleason DF. Hum Pathol. 1992 Mar;23(3):273-9

Case-level biopsy score
Global versus Highest

- When multiple cores are positive from different sites with grade heterogeneity
  - ✓ Highest score = the part(jar) with the highest Gleason score
  - ✓ Global score = Gleason scores from different jars combined into one

Case-level biopsy score
Correlation with outcome

Am J Surg Pathol 2018;42:1522–1529

ORIGINAL ARTICLE

Concordance of "Case Level" Global, Highest, and Largest Volume Cancer Grade Group on Needle Biopsy Versus Grade Group on Radical Prostatectomy

Kiril Trpkov, MD, FRCPC, Sakkarn Sangkhamanon, MD,* Asli Yilmaz, MD, FRCPC,* Shaun A.C. Medlicott, MD, FRCPC,* Bryan Donnelly, MD, FRCPC,† Geoffrey Gotto, MD, FRCPC,† and Melissa Shea-Budgell, MSc‡*

- In systematic biopsies, no significant difference in predicting final score at radical prostatectomy between global and highest score

Case-level biopsy score: Issues

- Geographic differences in practice patterns
  - ✓ Highest score per part used by most US clinicians
    - Predictive tools validated using highest GS
  - ✓ Global score widely used in other countries (e.g., Europe, Canada, Australia, South Korea)

Case-level biopsy score: Issues

- Multifocality of prostate cancer contraindication to global score
- Lack of consensus as to the optimal method to derive global score
  - The most common pattern in the case and the highest pattern in any part
  - The average of grades of all parts together (as if it was 1 positive core)
  - The average of the grades from certain parts together based on the location of the tumor (right versus left side)

Epstein JI et al. Arch Pathol Lab Med 2021;145:461–493

“Targeted” biopsies: Let’s be PRECISE and START using a checklist

- International consensus on separate reporting of histologic results of standard and targeted cores (Gleason score/Grade Group and maximum cancer core length)
- Cores from each targeted lesion should be graded as a one part (jar)

Moore CM et al. Eur Urol. 2013;64(4):544-552
Moore CM et al. Eur Urol. 2017;71(4):648-655

Specimen and Case-level score recommendations

- Report in systematic biopsies a separate Gleason score (GS)/Grade Group(GG) for each individual biopsy site as indicated by clinician
- Report in mpMRI-targeted biopsies a global (aggregate) GS/GG for each targeted lesion
- Providing a case-level score is optional

Epstein JI et al. Arch Pathol Lab Med 2021;145:461–493
Van Leedders GJLH et al. Am J Surg Pathol. 2020;44(8):e87-e99

Objectives

- ✓ Provide an overview of the histologic grading system for prostatic adenocarcinoma (PCA)
- ✓ Review architectural patterns of PCA
- ✓ Discuss relevant reporting elements in PCA diagnosis with respect to grading
- ▪ Touch upon the development of ancillary tools in optimizing PCA grading

“On re-examining routine clinical material […] I have duplicated exactly my previous histologic scores approximately 50% of the time…”

Gleason DF. Hum Pathol. 1992 Mar;23(3):273-9

The Ongoing Quest for Precision Medicine

- Molecular assays
  - ✓ to help further stratification in low- and favorable intermediate-risk disease
  - ✓ to help treatment selection in high-risk and castration-resistant disease
- Digital pathology (machine-learning-based grading)
  - ✓ to improve accuracy and reproducibility
  - ✓ to help identify and incorporate prognostic factors such as novel growth patterns or stromal features

Summary

- Prognosis of prostate cancer is tied to its morphologic appearance
- The 5-tiered Grade Group system better stratifies patient risk and guides clinical care
- Standardization of reporting is essential for multidisciplinary management
- Novel tools are emerging to augment the histologic diagnosis of prostate cancer and help create more “automated” approach to grading

in the past decade. Histologic grading can provide part of the answer to these clinical management problems but one hears the old criticism, "grading is fine for predicting the experience of groups of patients but has little predictive value for the individual patient." This is a petulant criticism expressing a yearning for the simple yes-or-no answers that evade us so frequently in many difficult areas of medical practice. There is no test and never will be a test that can predict, for a chronic disease like cancer, that the patient will die of the disease on a certain date or will always be cured by treatment "X." The complexities of the tumor/host conflict preclude such accurate predictions. We are fortunate that our predictions work as well as they do. We have to work with variable and only partially known probabilities, such as those provided by histologic grading, and do our best with them to provide the optimal therapy as we do in other difficult areas of clinical medicine. For prostate

Gleason DF. Hum Pathol. 1992 Mar;23(3):273-9