Update on Prostate Cancer: New Developments in Diagnosis, Grading, Staging and Reporting

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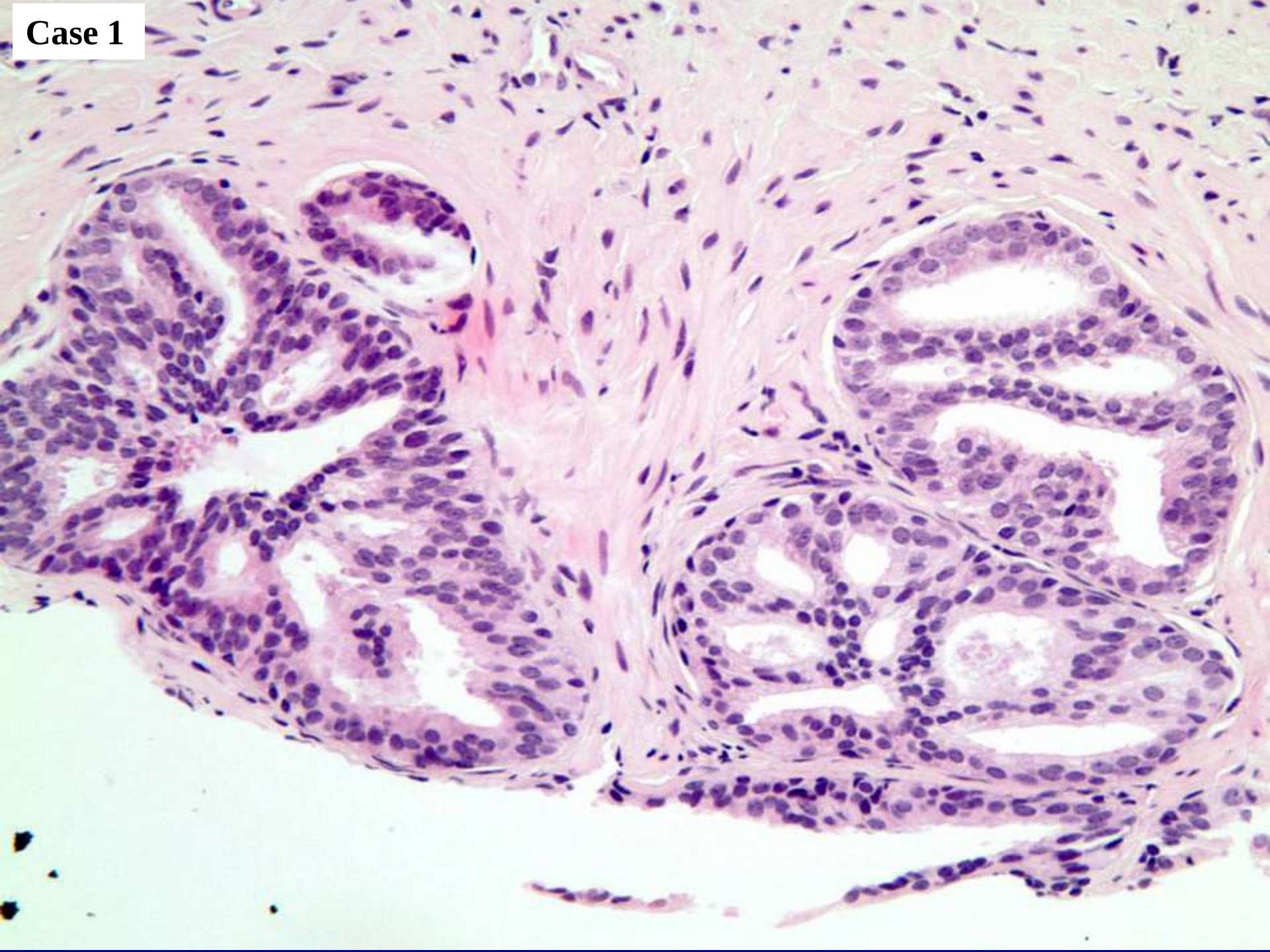
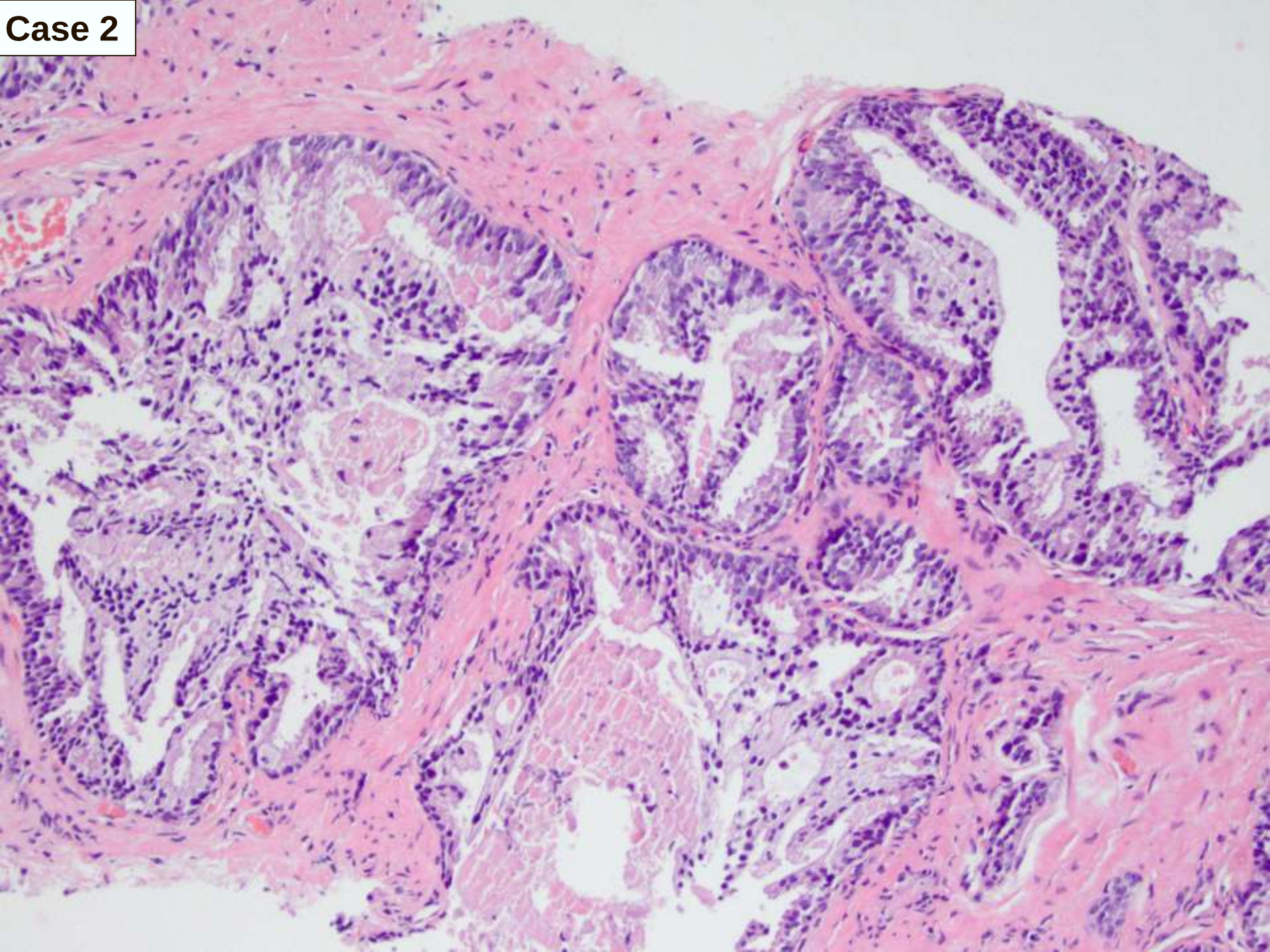

Case 1

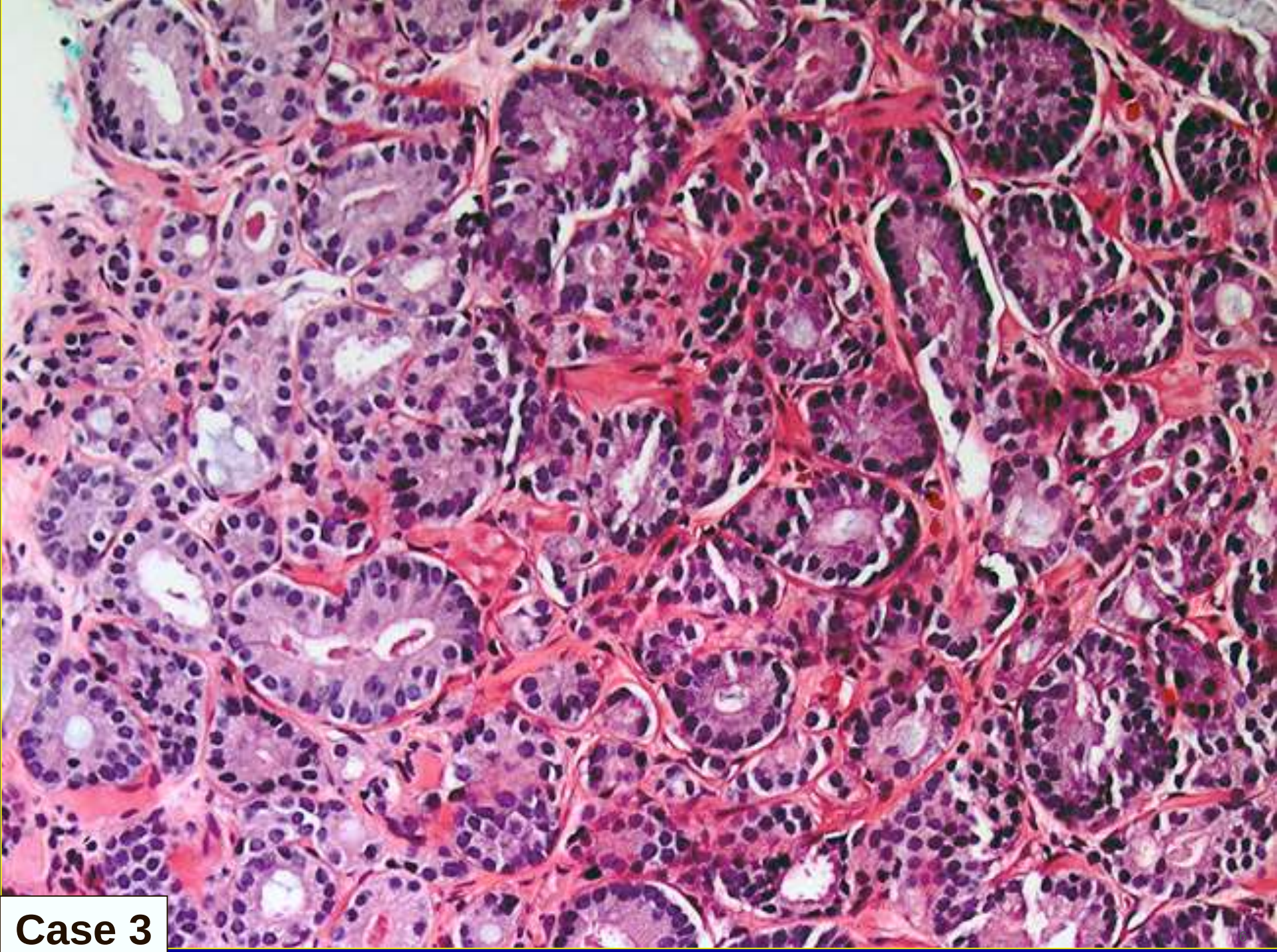
Diagnosis

- Cribriform HGPIN
- Intraductal carcinoma (IDC-P)
- Atypical intraductal proliferation (AIP)
- Prostate adenocarcinoma, Gleason score 4+4, GG 4


Case 2

Diagnosis

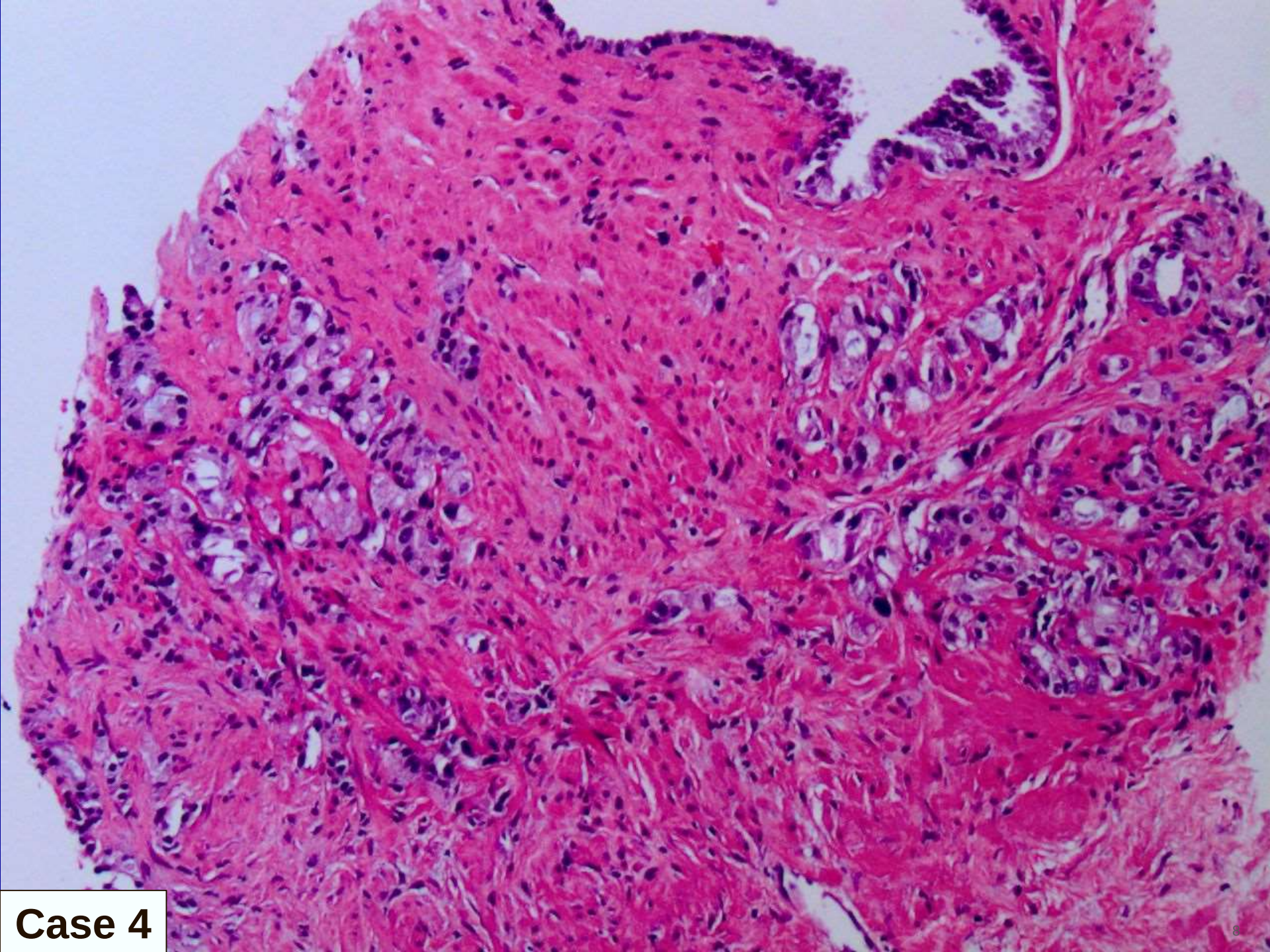
- Prostate adenocarcinoma, Gleason score 3+3=6, GG 1 with HGPIN
- Prostate adenocarcinoma, Gleason score 3+4=7, GG 2
- Prostate adenocarcinoma, Gleason score 4+3=7, GG 3
- Prostate adenocarcinoma, Gleason score 3+3, GG 1 with intraductal carcinoma (IDC-P)



Case 3

Diagnosis

- Prostate adenocarcinoma, Gleason score 3+3=6, GG 1
- Prostate adenocarcinoma, Gleason score 3+4=7, GG 2
- Prostate adenocarcinoma, Gleason score 4+3=7, GG 3
- Prostate adenocarcinoma, Gleason score 4+4=8, GG 4



Case 4

Diagnosis

- Prostate adenocarcinoma, Gleason score 3+3=6, GG 1
- Prostate adenocarcinoma, Gleason score 4+3=7, GG 3
- Prostate adenocarcinoma, Gleason score 4+5=9, GG 5
- Prostate adenocarcinoma, Gleason score 5+4=9, GG 5

Important Changes in Prostate Cancer Classification, Grading, Staging and Reporting

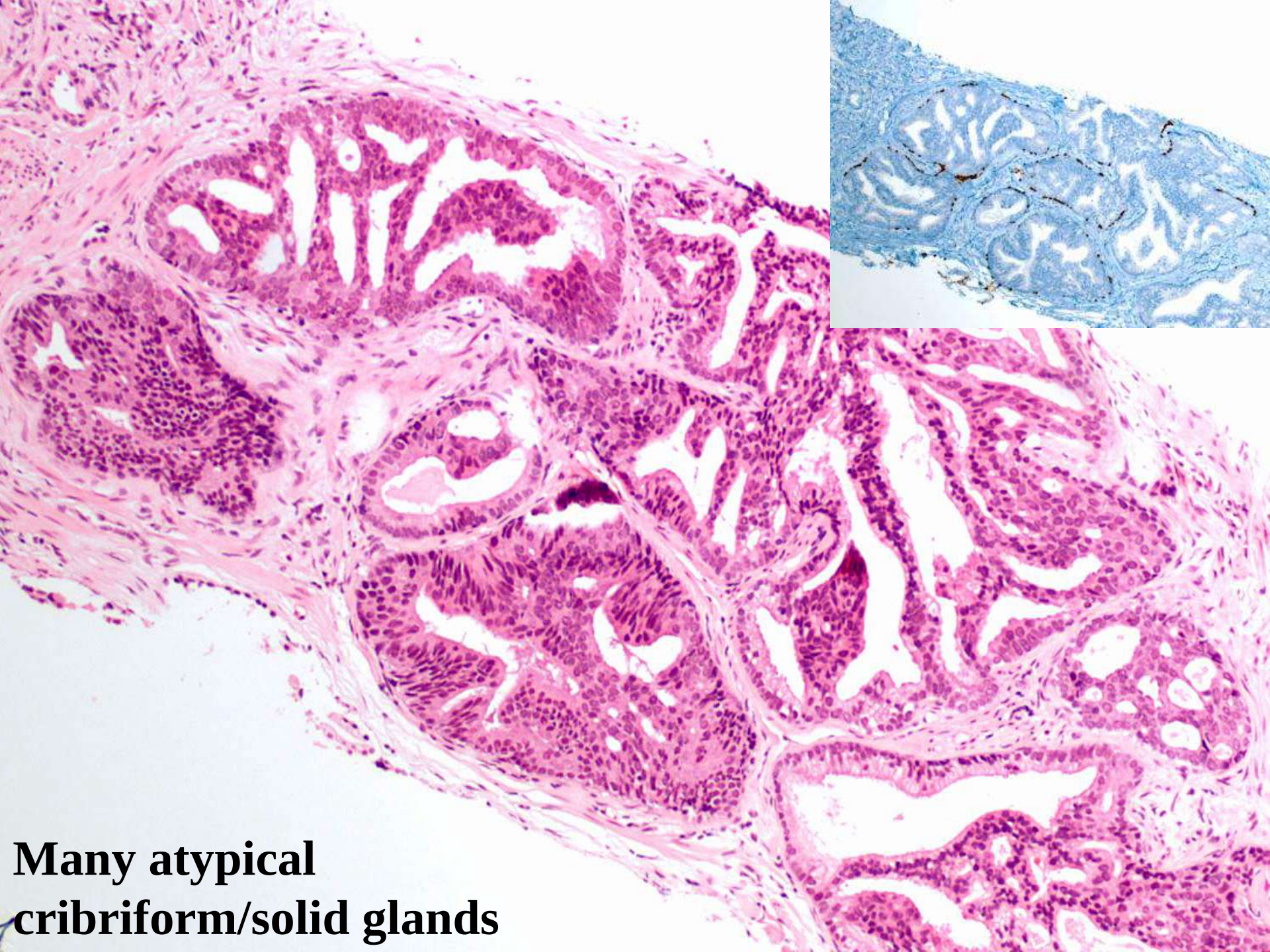
- New entities
  - Intraductal carcinoma of the prostate (IDC-P)
- Grading
  - Modifications of grading and Grade groups
  - Cribriform architecture
- Reporting
  - Tertiary pattern, % pattern 4, Multifocal tumors
- Staging
  - pT2 no longer substaged into pT2a-c

Intraductal Carcinoma of the Prostate (IDC-P)

Histological Features

Hallmarks

1. Expansile proliferation of PCa cells
   - Cribriform or solid architecture
2. Within native prostate glands
   - Basal cell layer at least partially preserved

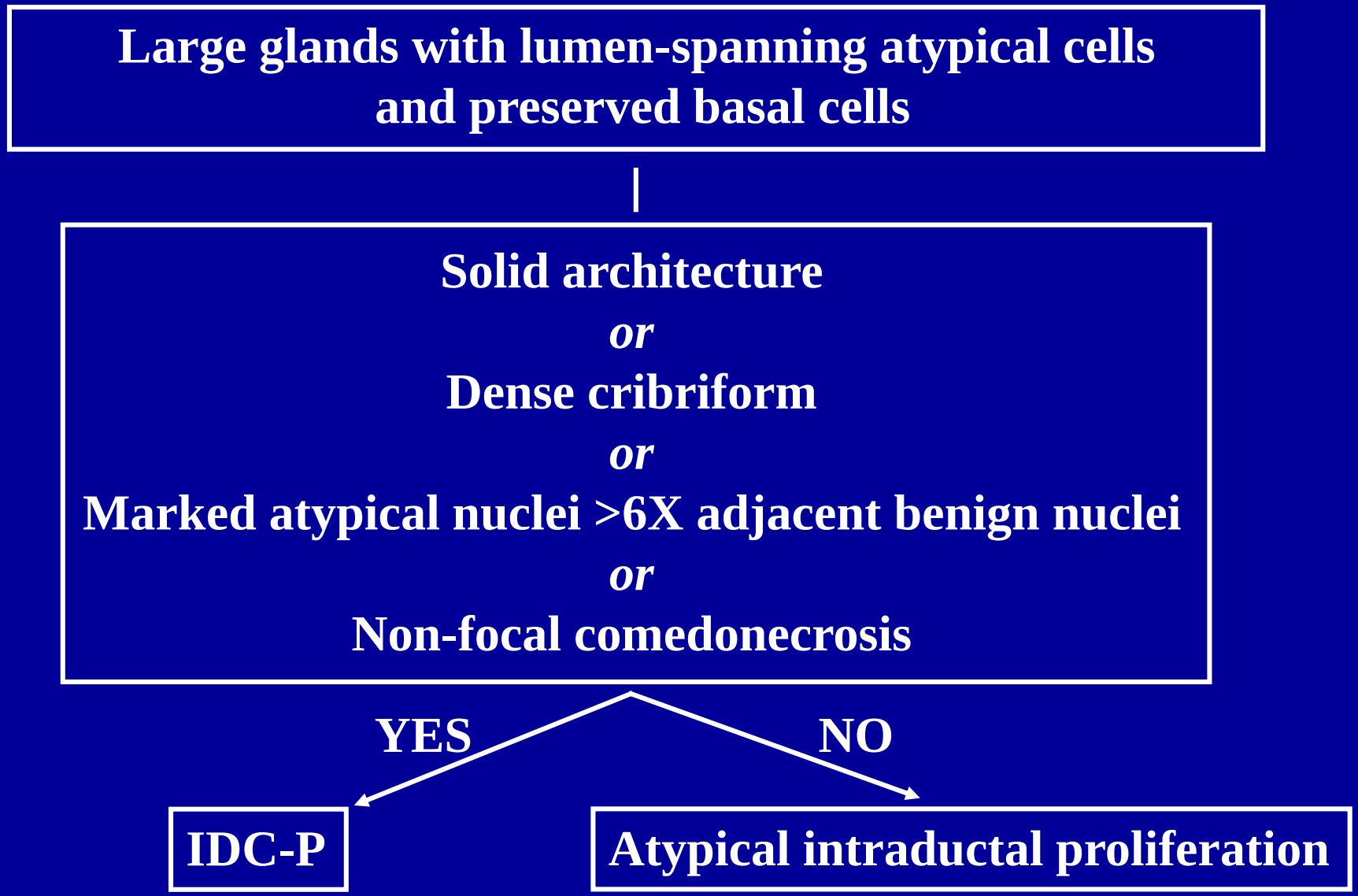


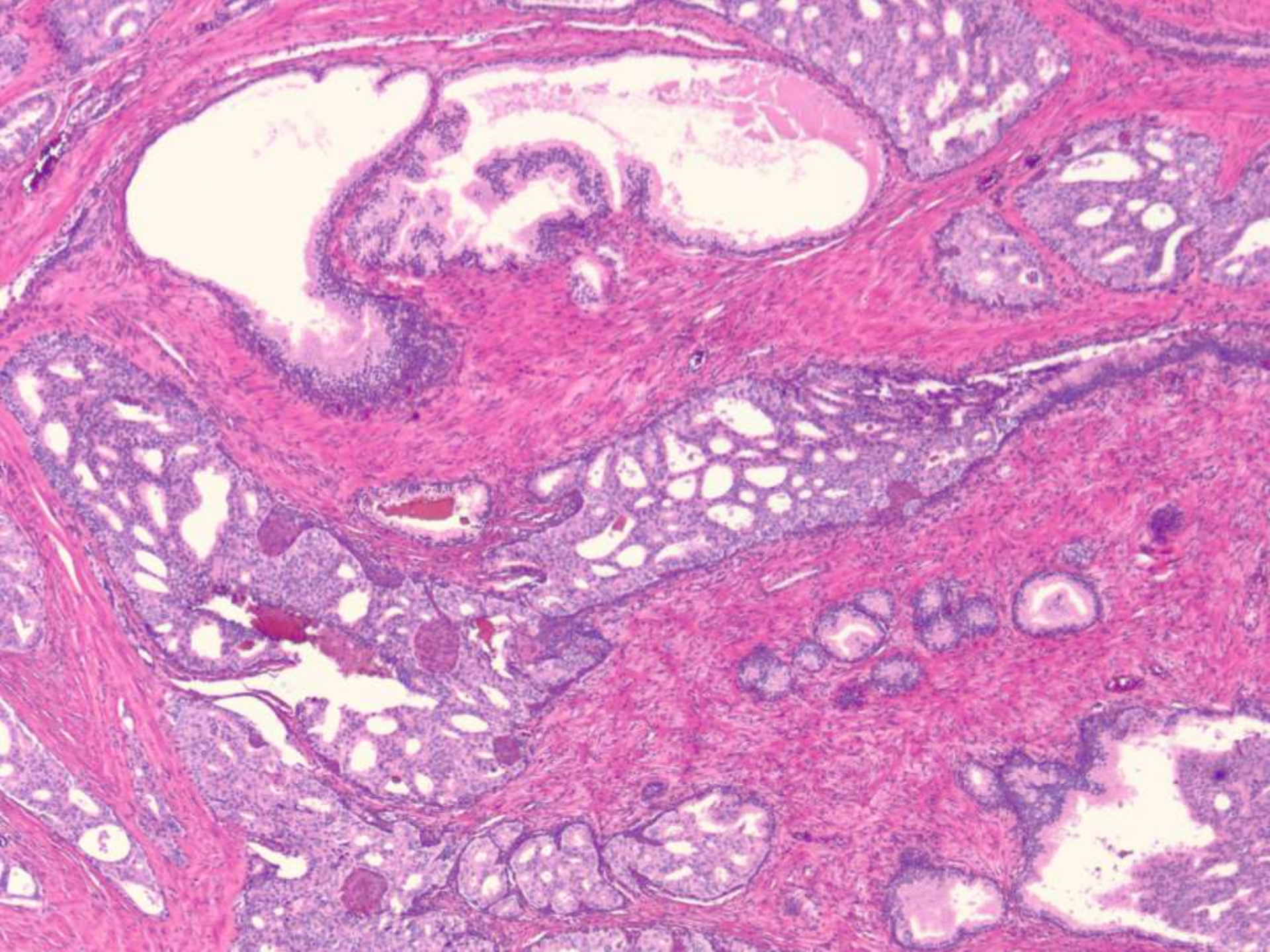
Many atypical cribriform/solid glands

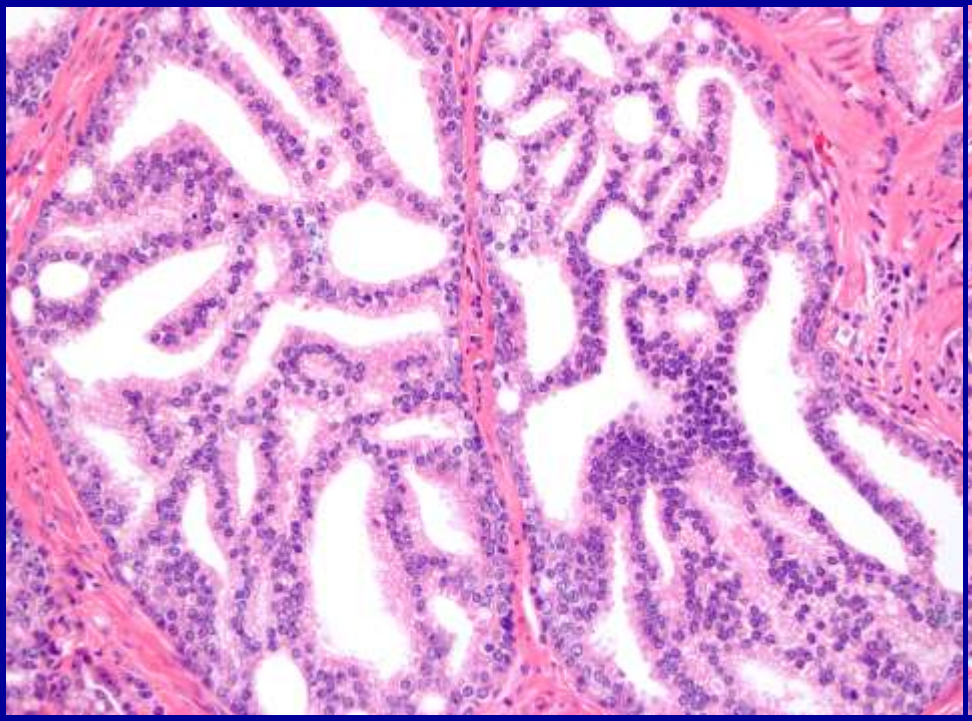
Partially involves native benign glands

Diagnostic Criteria for IDC-P

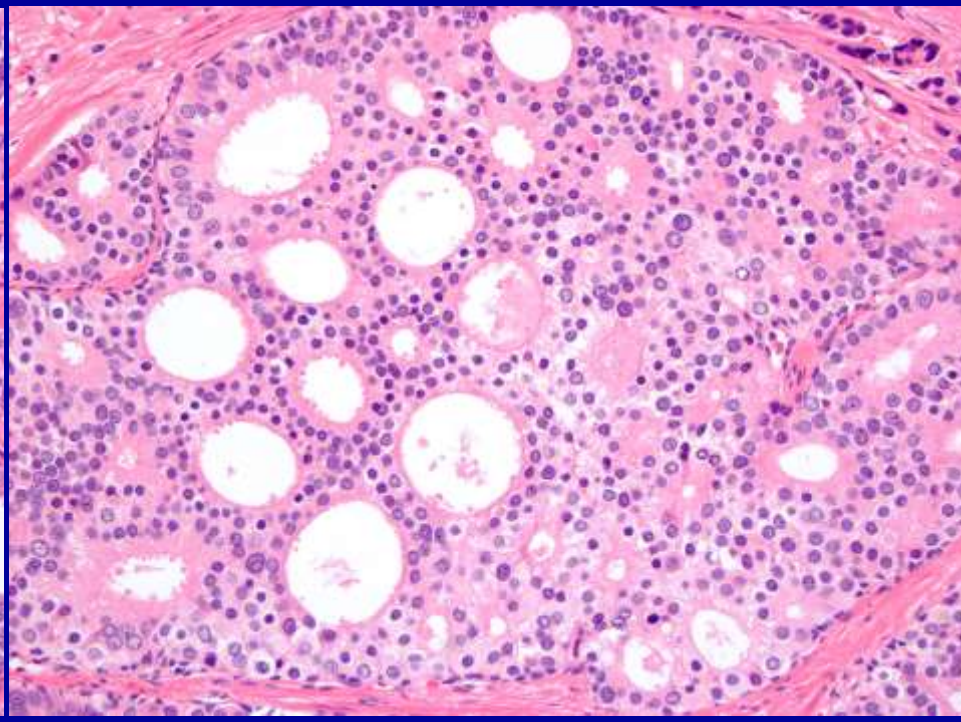
(Guo CC and Epstein JI, *Mod Pathol*. 2006)





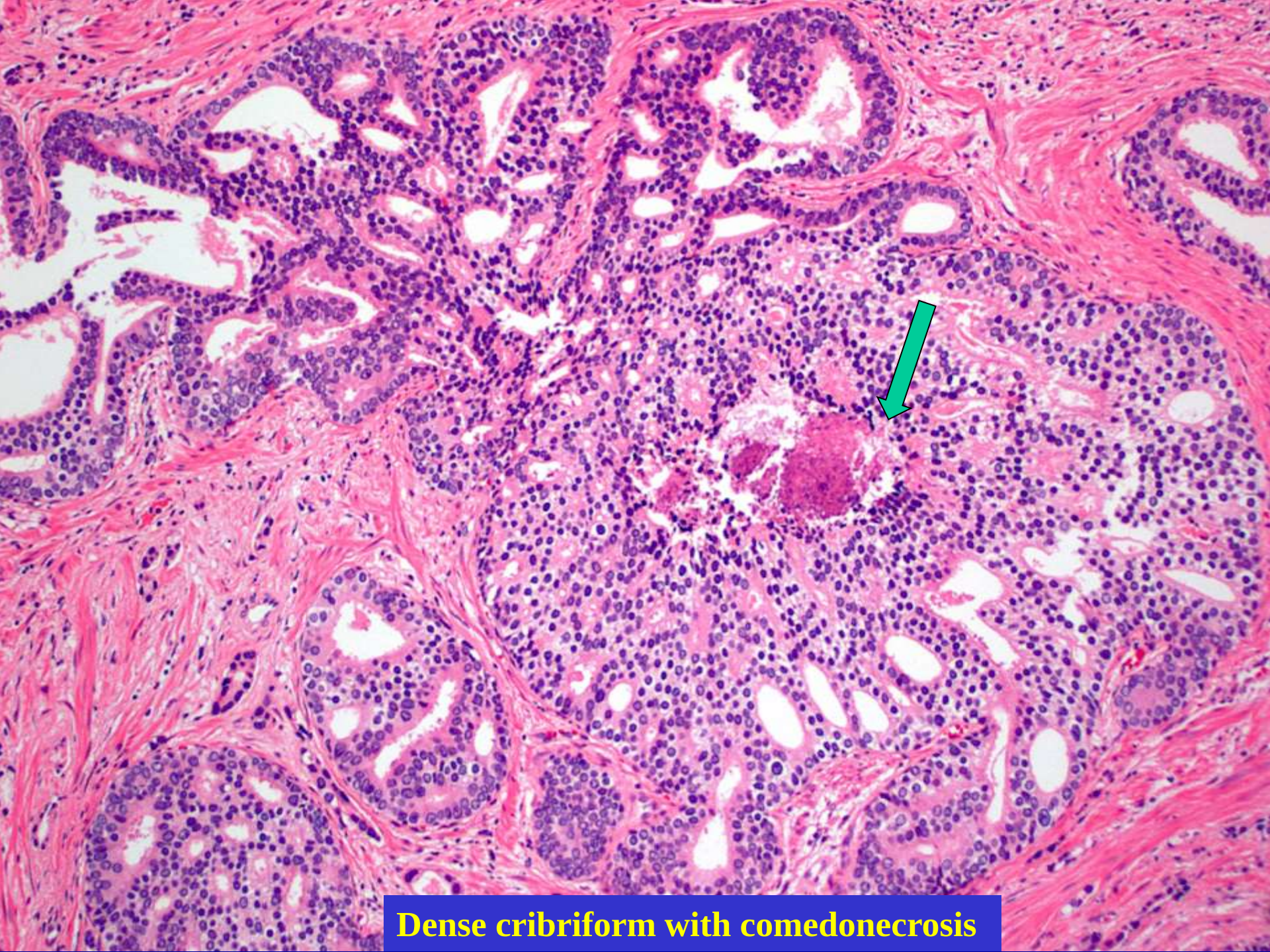


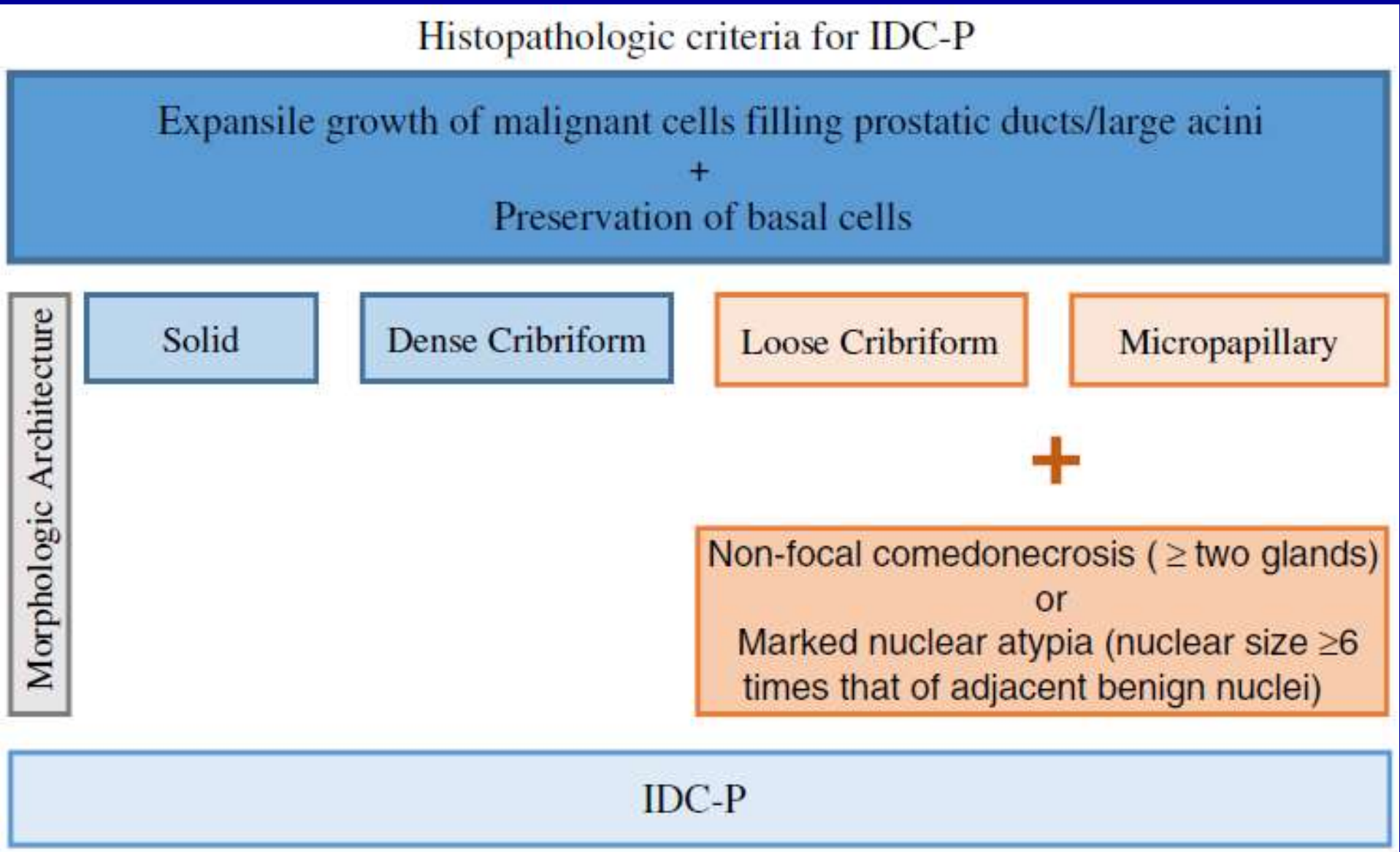
Dense cribriform:
Irregular lumina



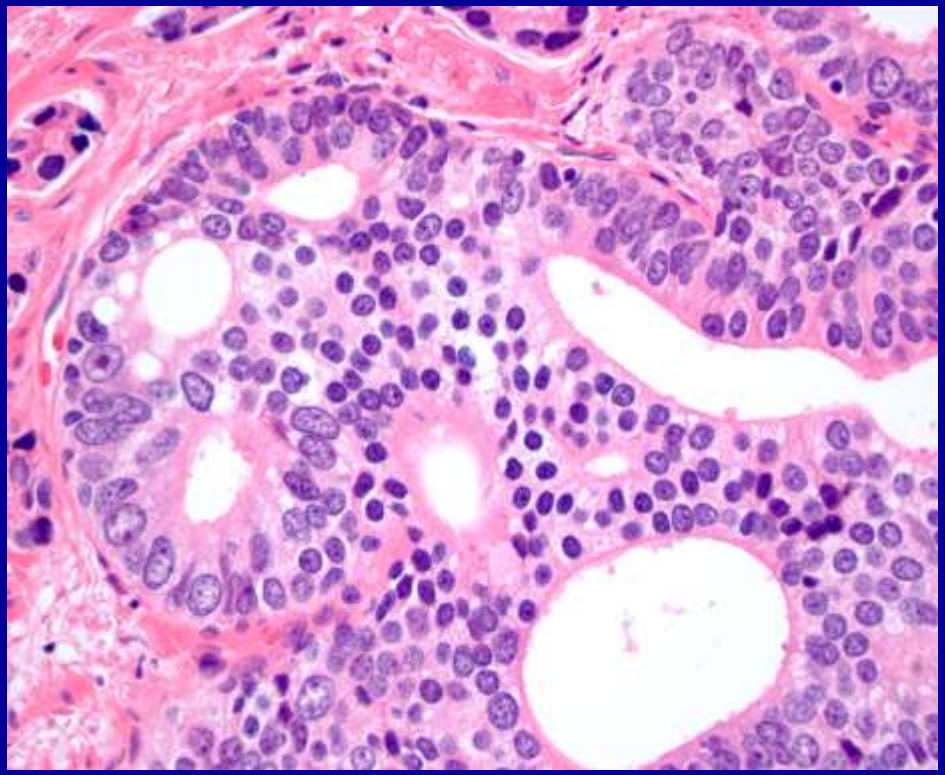
Dense cribriform:
Punched out lumina

Solid

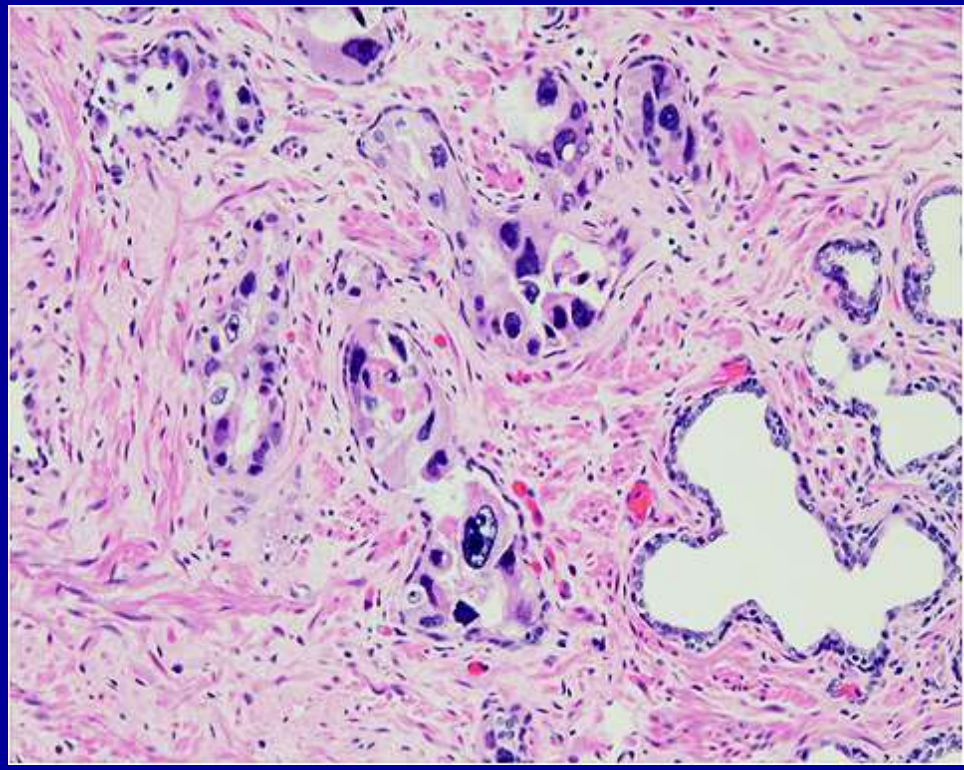

Dense cribriform with comedonecrosis


Histopathologic criteria for IDC-P
Expansile growth of malignant cells filling prostatic ducts/large acini
+
Preservation of basal cells
Morphologic Architecture
Solid
Dense Cribriform
Loose Cribriform
Micropapillary
+
Non-focal comedonecrosis (≥ two glands)
or
Marked nuclear atypia (nuclear size ≥6 times that of adjacent benign nuclei)
IDC-P

You require nuclear criteria or comedonecrosis when there is no dense or solid architecture!



Marked variation in nuclear size



Pleomorphic nuclei >6X adjacent nuclei

Intraductal Carcinoma of the Prostate (IDC-P)

Diagnostic Criteria

- Use a constellation of morphological features (architecture and cytology)
- Use stringent diagnostic criteria to ensure its unique clinical implication, ie, association with adverse outcomes
- Any atypical expansile, lumen-spanning lesion warrants further work-up

Significance of IDC-P in Prostate Biopsy

INTRADUCTAL CARCINOMA OF THE PROSTATE : OUTCOME

- Independent predictor of various adverse outcomes
- Contemporary studies focusing on outcomes lump cribriform Gleason pattern 4 and IDC-P as “cribriform architecture”
- Isolated intraductal carcinoma in prostate biopsy : Definitive therapy may be indicated although 10% of patients will have intraductal carcinoma only at radical prostatectomy, so repeat biopsy is an option

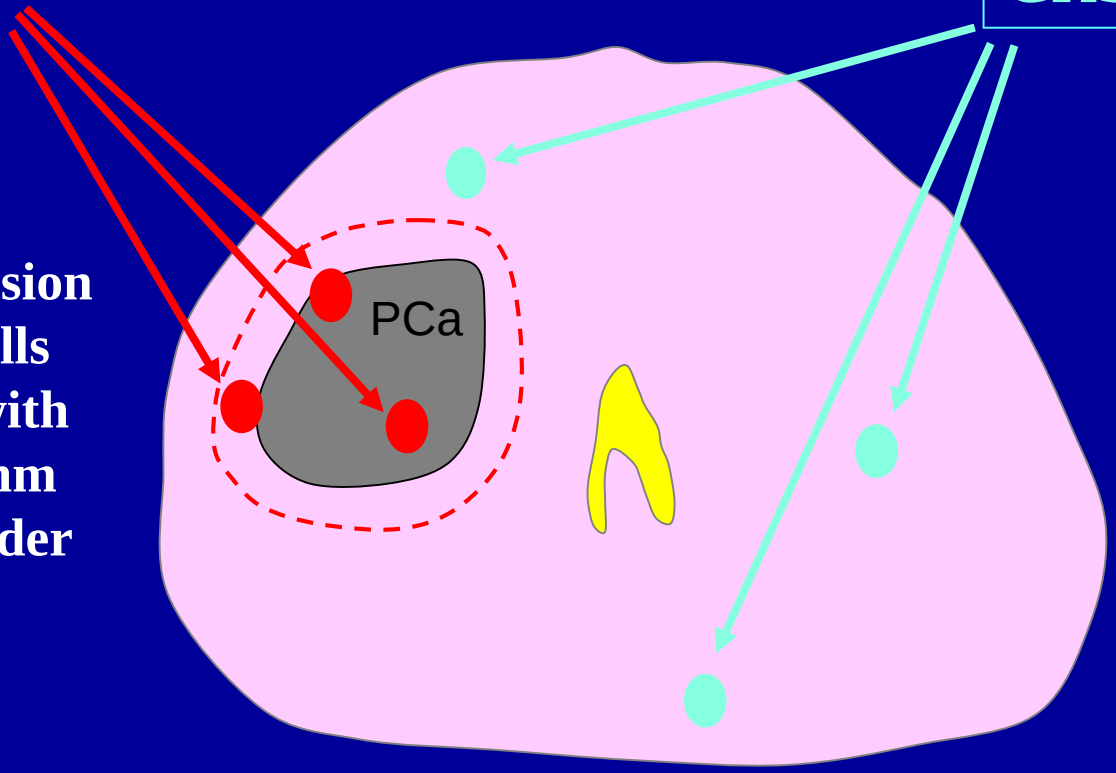
Differential Diagnosis of Intraductal Carcinoma of the Prostate
(DDX for Atypical Cribriform/Solid Lesions)

- High grade PIN
- Atypical Intraductal Proliferation (AIP)
- Invasive cribriform prostatic carcinoma
- Ductal adenocarcinoma of the prostate
- Urothelial carcinoma involving the prostate
- Metastatic (colorectal) adenocarcinoma

IDC-P *vs* Cribriform HGPIN

IDC-P

Cribriform HGPIN



✓ **Atypical cribriform lesion with basal cells intermixed with or within 3 mm from the border of PCa**

✓ **Atypical cribriform lesion with basal cells > 3 mm from the border of PCa**

Shah et al AJSP 2010; Han *et al* AJSP 2010

Morphological Difference b/w of IDC-P and Cribriform HGPIN

(*Shah, Magi-Galluzzi, Han, Zhou, AJSP 2010*)

# cases		IDC-P	Cribriform HGPIN	P value
		43	23	N.A.
# atypical cribriform lesion /prostate	Mean	23.8	2.4	0.002
	Range	1-143	1-6	
Smallest size (mm)	Mean± S.D.	0.34 ± 0.19	0.33 ± 0.13	0.848
	Range	0.2-1.1	0.2-0.6	
Largest size (mm)	Mean± S.D.	1.5 ± 1.3	0.43 ± 0.15	0.002
	Range	0.4-2.5	0.2-1.0	
Glandular contour	Regular	29 (67.4%)	19 (82.6%)	0.187
	Irregular	34 (79.1%)	12 (52.2%)	0.023
	Branching	36 (83.7%)	1 (4.3%)	< 0.001
Architecture	Irregular cribriform	41 (95.3%)	23 (100%)	0.293
	Dense cribriform or solid	10 (23.3%)	0 (0%)	0.01
Comedo necrosis		14 (32.6%)	0 (0%)	0.001
Nuclear features	Uniform	15 (34.9%)	14 (60.9%)	0.036
	Variable	22 (51.2%)	9 (29.1%)	0.35
	> 6X or pleomorphic	12 (27.9%)	0 (0%)	0.005

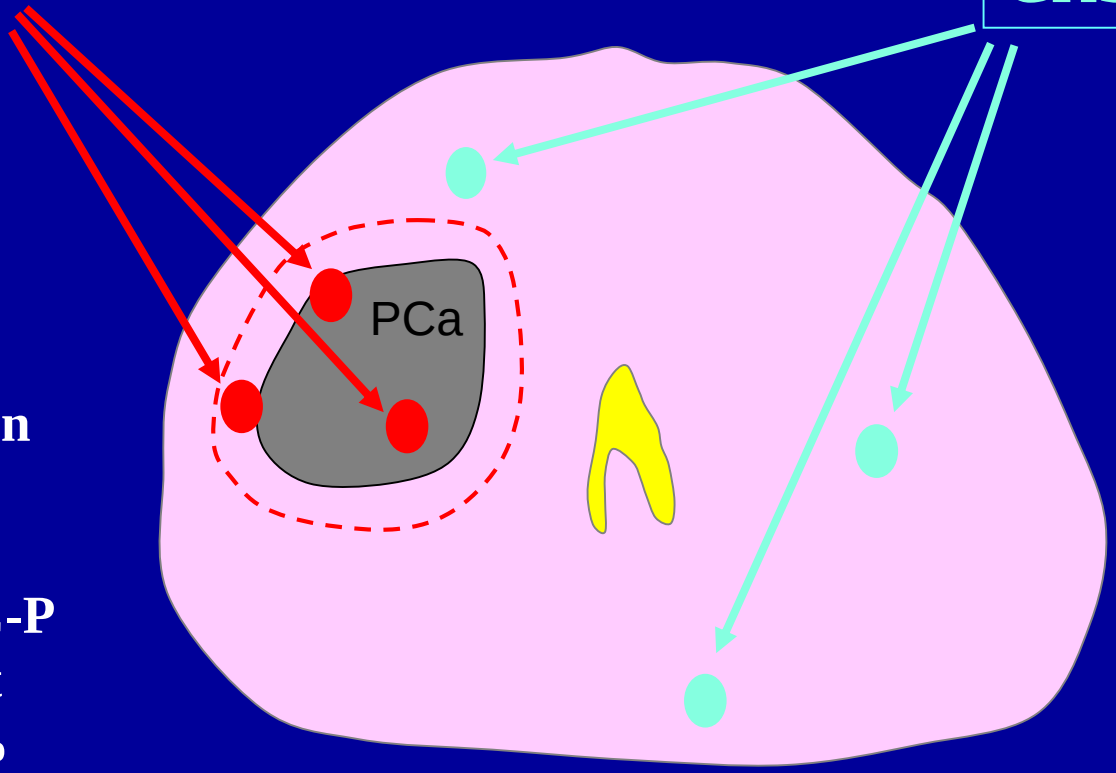
Morphological comparison between IDC-P and HGPIN

- Morphologic criteria for IDC-P has high specificity but poor sensitivity
- There is significant overlap at “lower grade” morphological spectrum (HGPIN and AIP)

IDC-P *vs* Cribriform HGPIN

IDC-P

Cribriform HGPIN



- ✓ **ERG gene fusion: 75%**
- ✓ **ERG fusion status concordant between IDC-P and adjacent PCa in 100% cases**

- ✓ **ERG gene fusion: 0%**

- ➢ **IDC-P and cribriform HGPIN are genetically distinct**
- ➢ **ERG gene status identical between IDC-P and PCa**
  - ✓ **IDC-P : resulting from intraductal spread of PCa**

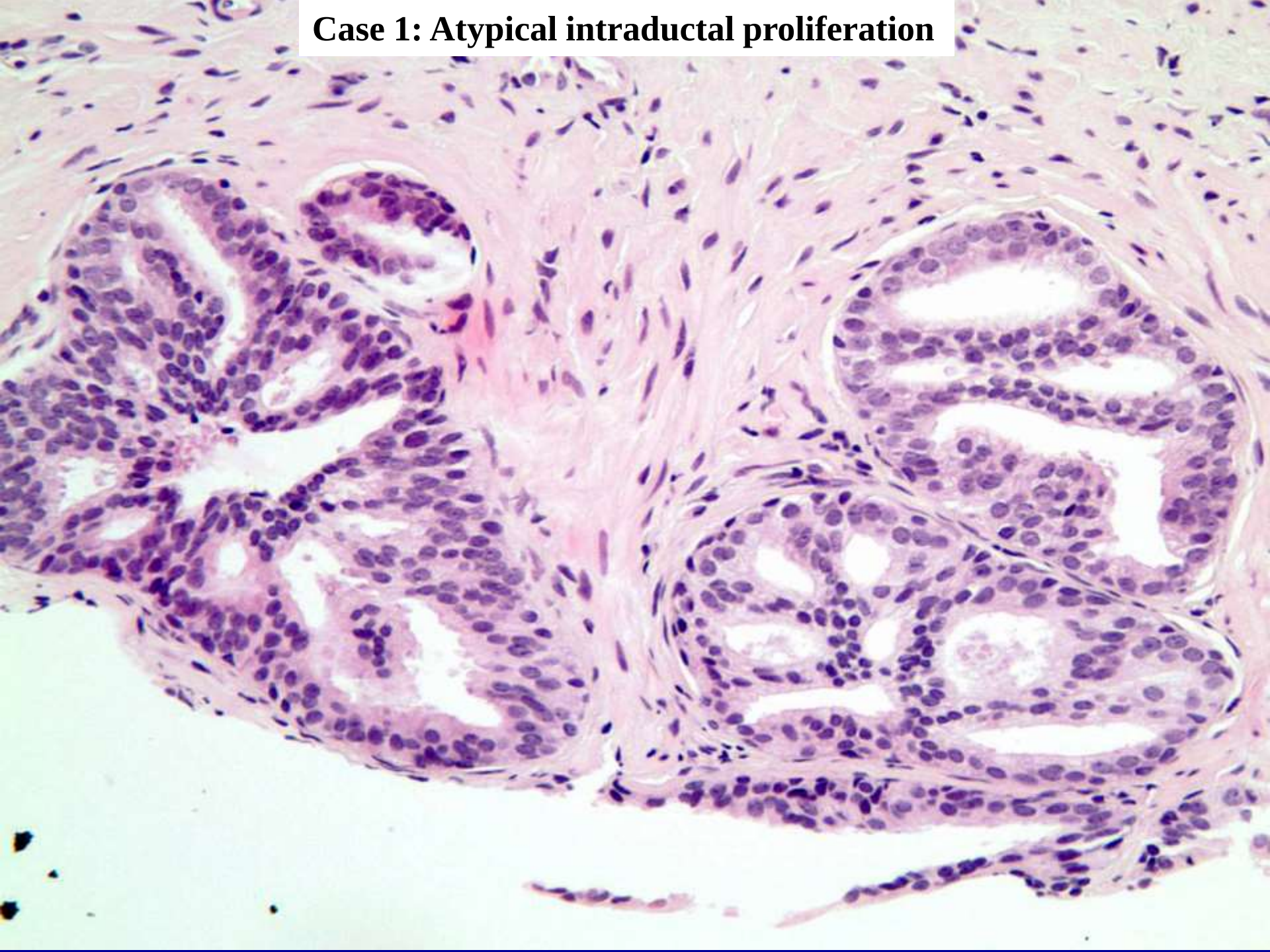
Shah et al AJSP 2010; Han *et al* AJSP 2010

MOLECULAR FEATURES OF INTRADUCTAL CARCINOMA

Study	ERG expression		PTEN loss	
	HGPIN	IDC-P	HGPIN	IDC-P
Han B et al, AJSP, 2010	0 %	75 %		
Lotan TL et al, Mod Pathol, 2013	13 %	58 %	0 %	84 %
Morais CL et al, AJSP, 2015	0 %	58 %	0 %	76 %
Morais CL et al, Hum Pathol, 2016	7 %		0 %	
Hickman RA et al, AJSP, 2017	7 %	61 %	8 % (Partial loss)	75 %
Shah RB et al, Histopathol, 2017	15 %	55 %	5 %	72 %

PTEN loss can be utilized as a surrogate marker of IDC-P

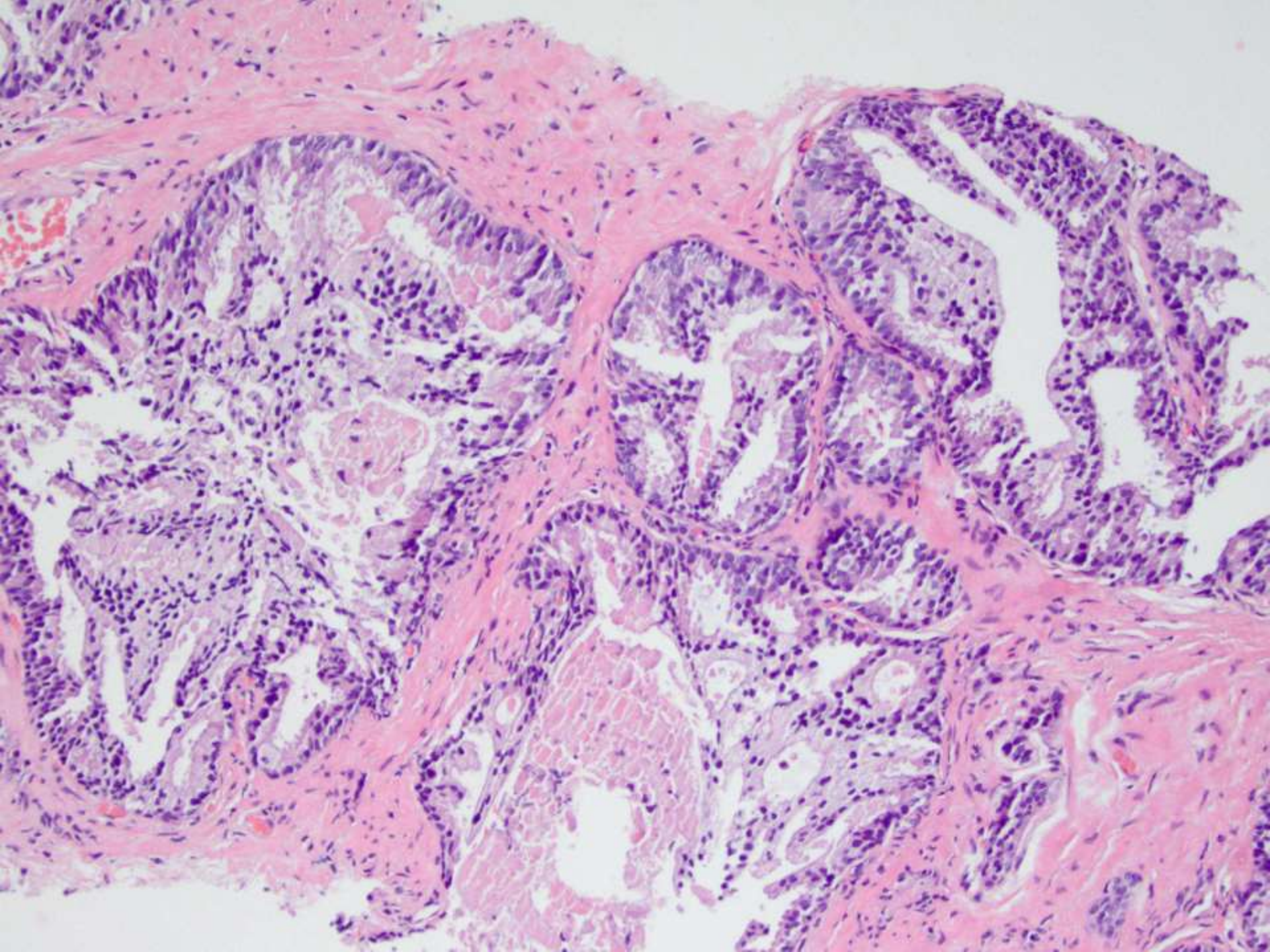
Case 1: Atypical intraductal proliferation



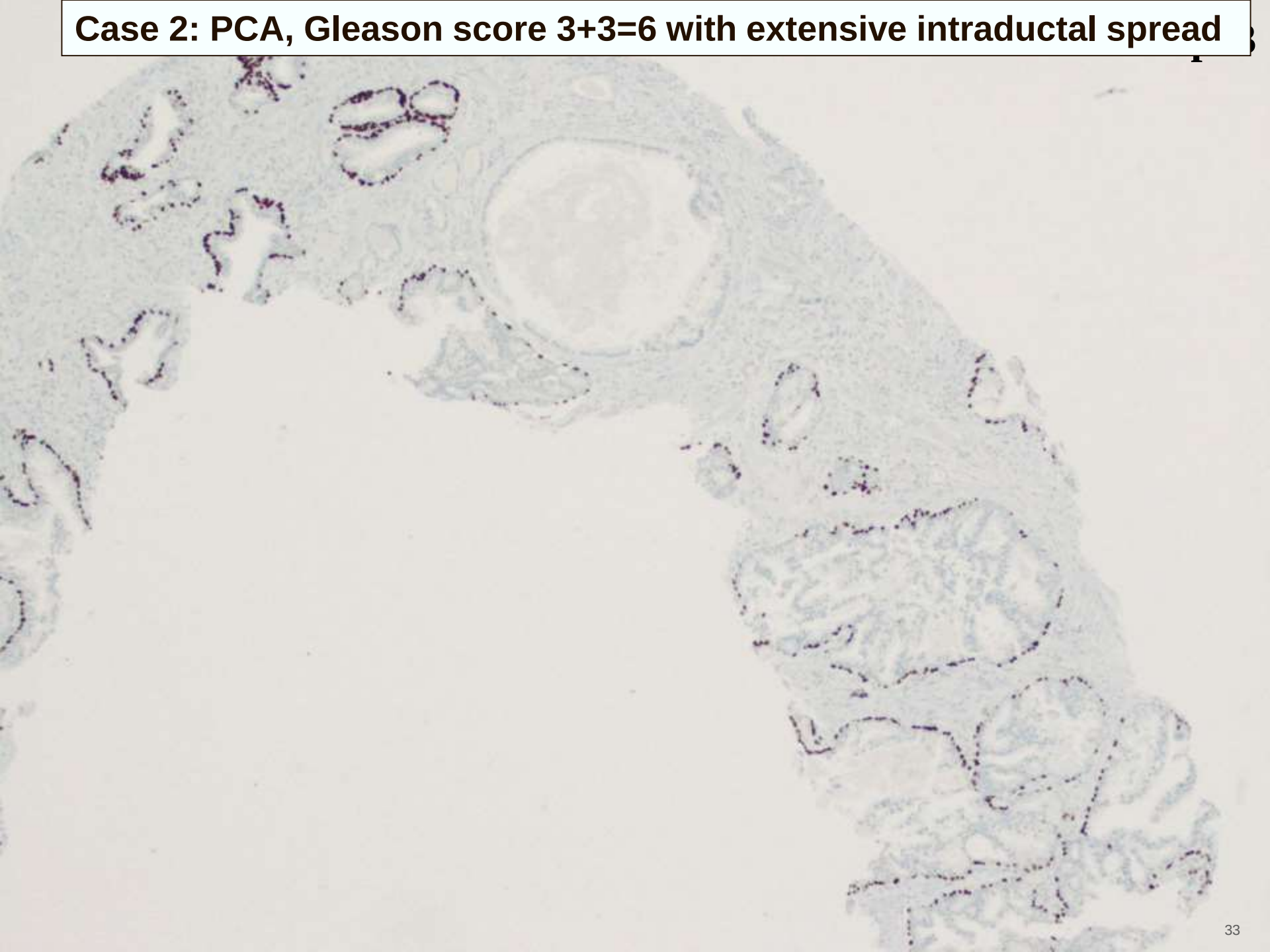
Pathology outcomes of AIP detected in prostate biopsy without an associated IDC-P and cribriform pattern 4

Table 2: Breakdown of adverse pathology at follow up in 40 patients who were potential candidates for no therapy (AIP alone) or active surveillance (AIP with Grade Group 1 or Grade Group 2 prostate cancer without cribriform Gleason pattern 4)											
Category [n (%)]	Available Follow-Up [n]	Follow-Up Biopsy [n (%)]				Radical Prostatectomy [n (%)]					
		IDC-P	IDC-P + PCa	PCa (≥ GG 3)	Total	≥ GG 3	ICD-P	EPE	SV Invasion	Cribriform GP4	Total
AIP alone 12 (30)	**6**		**1 (17)**	**2 (33)**	**3 (50)**	**NA**					
GG 1 10 (25)	**3 (1 Bx, 2 RP)**				**0 (0)**		**1 (50)**	**1 (50)**		**1 (50)**	**2 (67)**
GG 2 without cribriform pattern 18 (45)	**11 (all RP)**					**2 (18)**	**9(81)**	**9 (81)**	**1 (8)**	**8 (72)**	**11 (100)**

AIP is a marker of unsampled IDC-P and other adverse pathological features at radical prostatectomy



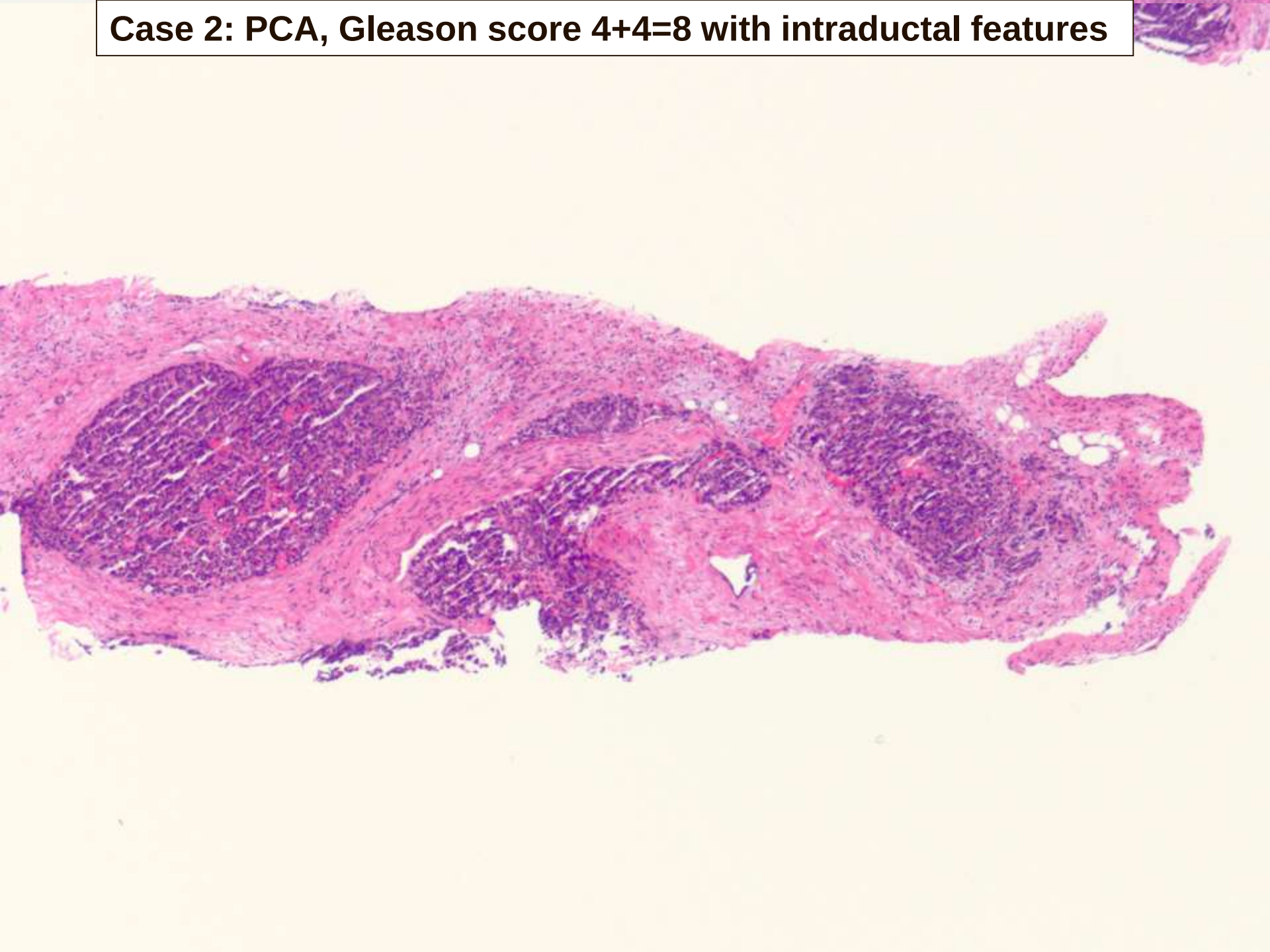
Case 2: PCA, Gleason score 3+3=6 with extensive intraductal spread



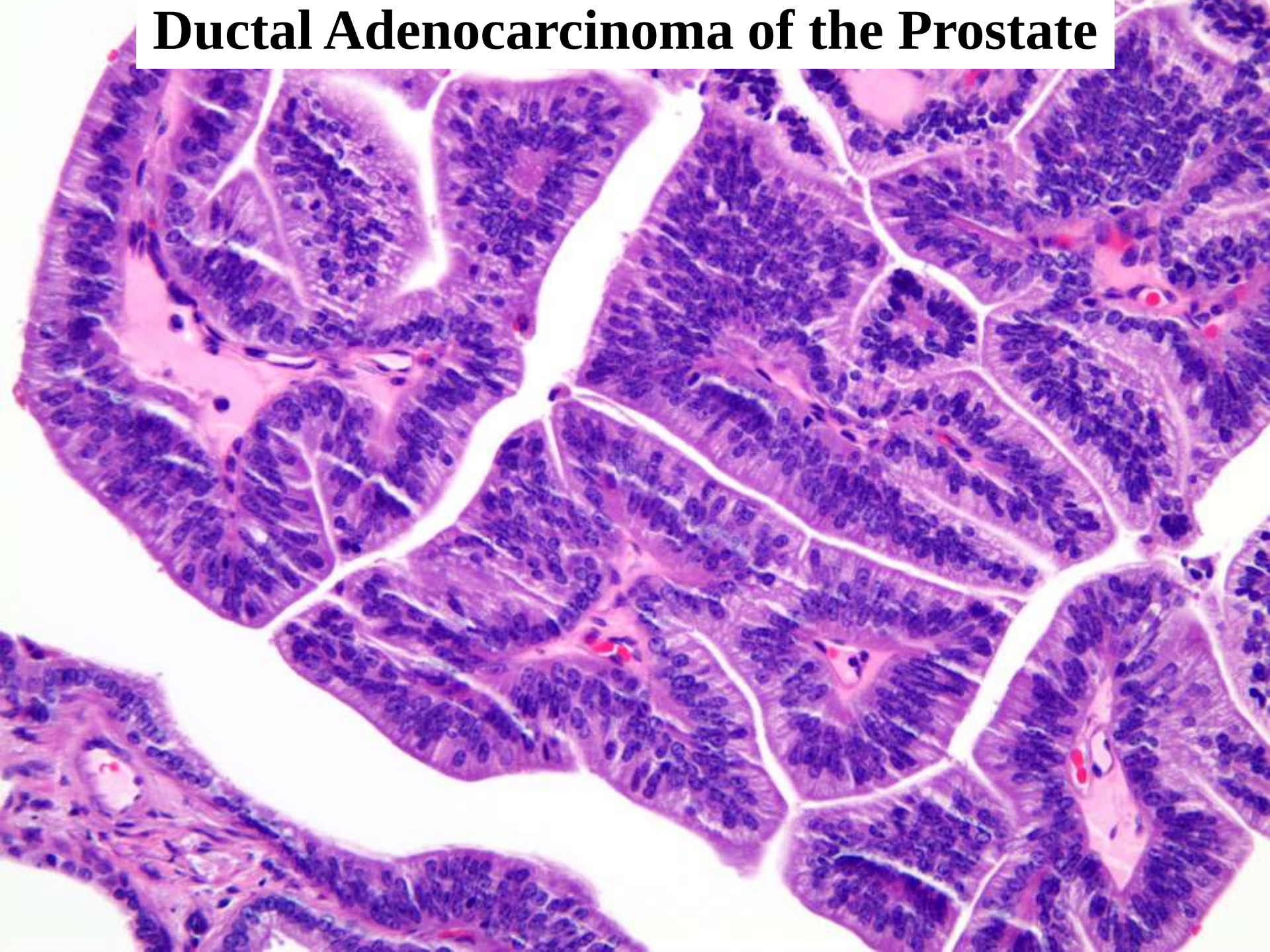
WHEN TO PERFORM BASAL CELL STAINING?

- Lack of definitive infiltrative carcinoma with a suggestion of intraductal carcinoma
- In setting of low grade infiltrative carcinoma where documentation of intraductal carcinoma is necessary to correctly assign Gleason score to case
- Not recommended in the setting of already high-grade PCa

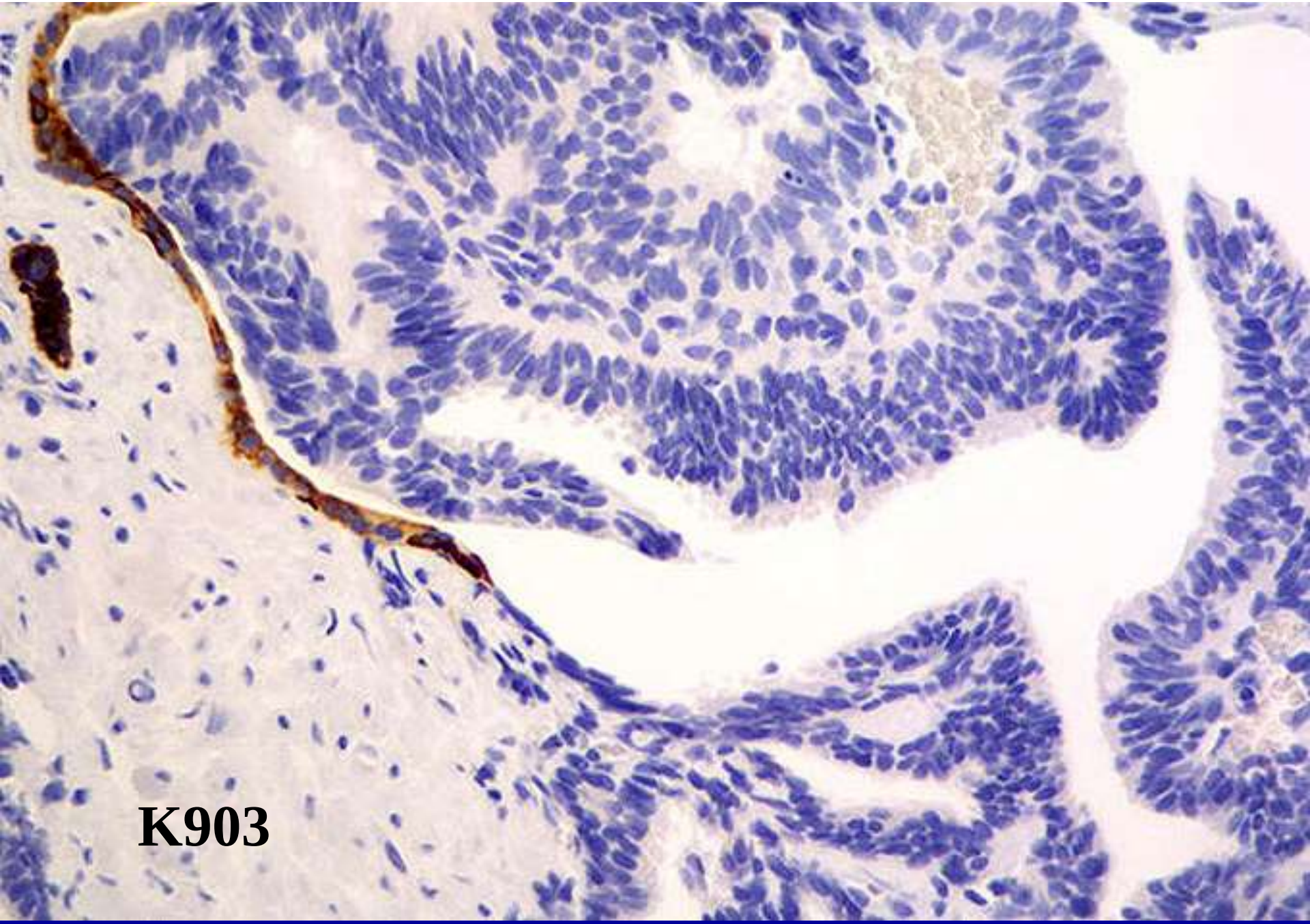
Case 2: PCA, Gleason score 4+4=8 with intraductal features



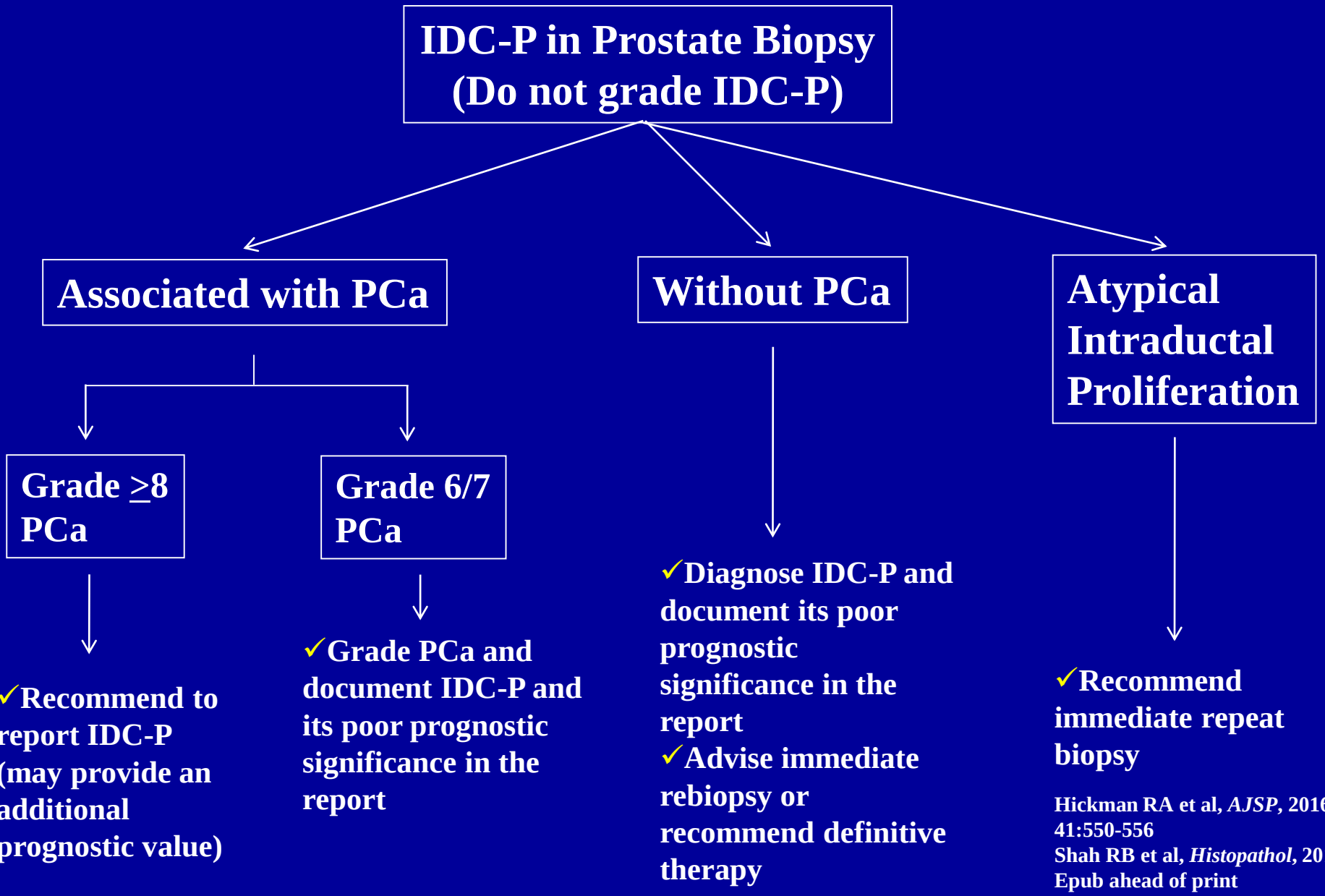
Ductal Adenocarcinoma of the Prostate



Ductal Adenocarcinoma of the Prostate with residual basal cells: Intraductal spread



Reporting Recommendations for Prostate Biopsy with IDC-P



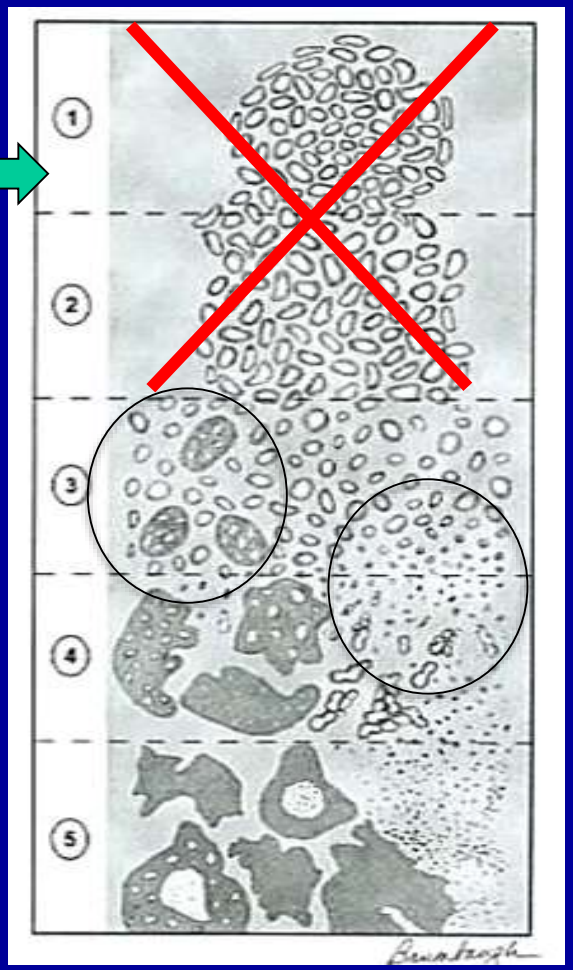
Hickman RA et al, *AJSP*, 2016; 41:550-556
Shah RB et al, *Histopathol*, 2017 Epub ahead of print

Ideal Grading System

- Prognostic ability exceeding clinical parameters
- Reproducibility among pathologists
- Grading on biopsy representative of entire cancer

EVOLUTION OF GLEASON GRADING

1967 **2005**



Key Changes: Definitional and Operational

Similarity: Gleason grading remains a mid to low power (not high power) exercise!

2005 Modifications of Gleason Grading

- Definition

✓ Gleason pattern 1 and 2 should not be assigned to needle biopsy

✓ Poorly formed glands included as pattern 4

✓ Large cribriform cancer glands separated from pattern 3 and included as pattern 4

✓ Grading new entities/variants: small glomeruloid glands included as pattern 3 while large glomeruloid glands included as pattern 4

2005 Modifications of Gleason Grading

- Operational

✓ Secondary pattern of lower grade when of limited extent

✓ Secondary pattern of higher grade when of limited extent

✓ Tertiary pattern

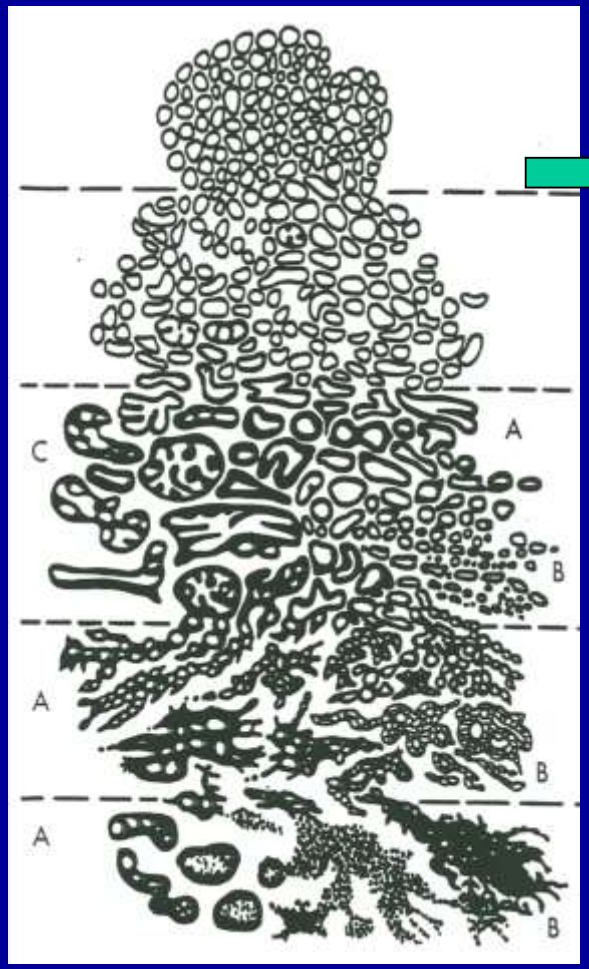
✓ Percent pattern 4/5

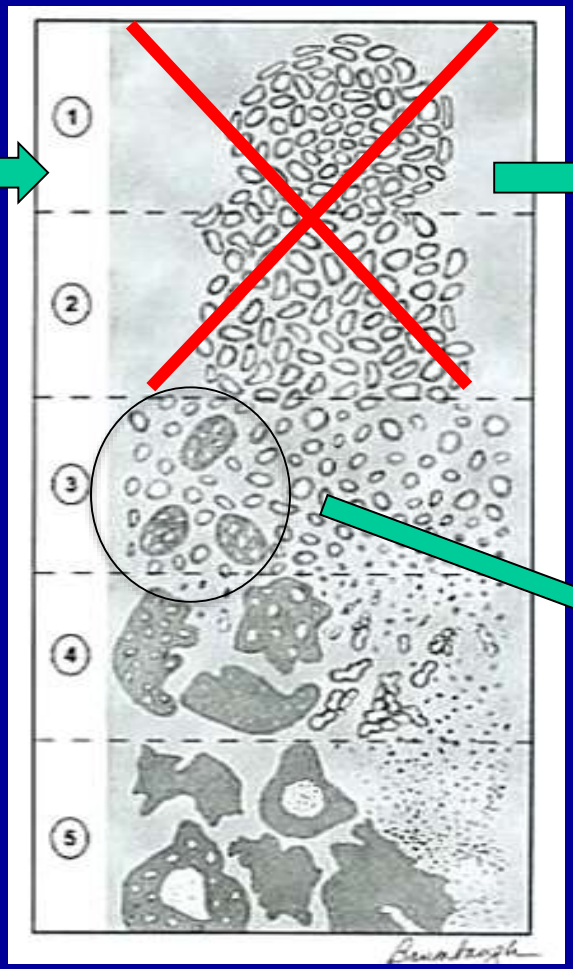
✓ Multifocal tumors

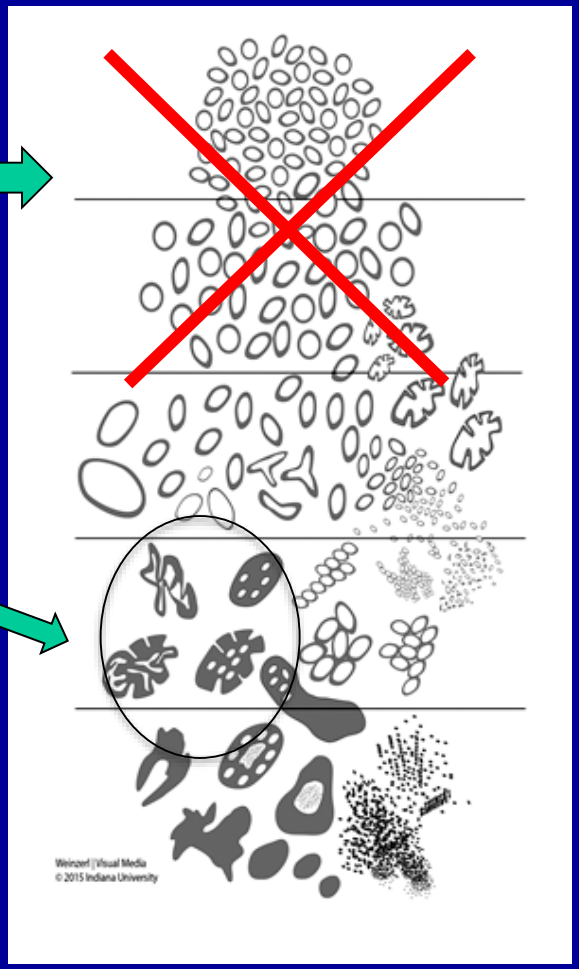
✓ Needle biopsy with different cores showing different grades

EVOLUTION OF GLEASON GRADING

1967 2005 2014







Key Changes: Definitional and Operational

Similarity: Gleason grading remains a mid to low power (not high power) exercise!

2014 Modifications of Gleason Grading

- Definition

✓ All cribriform cancer regardless of size included as Pattern 4

✓ Glomerulations regardless of size included as pattern 4

✓ Intraductal carcinoma (IDC-P) should be reported but not graded

PROBLEMS WITH CURRENT GLEASON GRADING SYSTEM

- 6 is the middle of the 2-10 numerical scale but is the lowest score reported
- Patients incorrectly may think that they have a tumor in the middle of the grade spectrum, contributing to the fear of cancer
- Gleason score often grouped into 3 tiers (6, 7, 8-10) for prognostic and therapeutic purposes despite the fact that GS 3+4 vs. 4+3 and 8 vs. 9-10 have significantly different prognosis

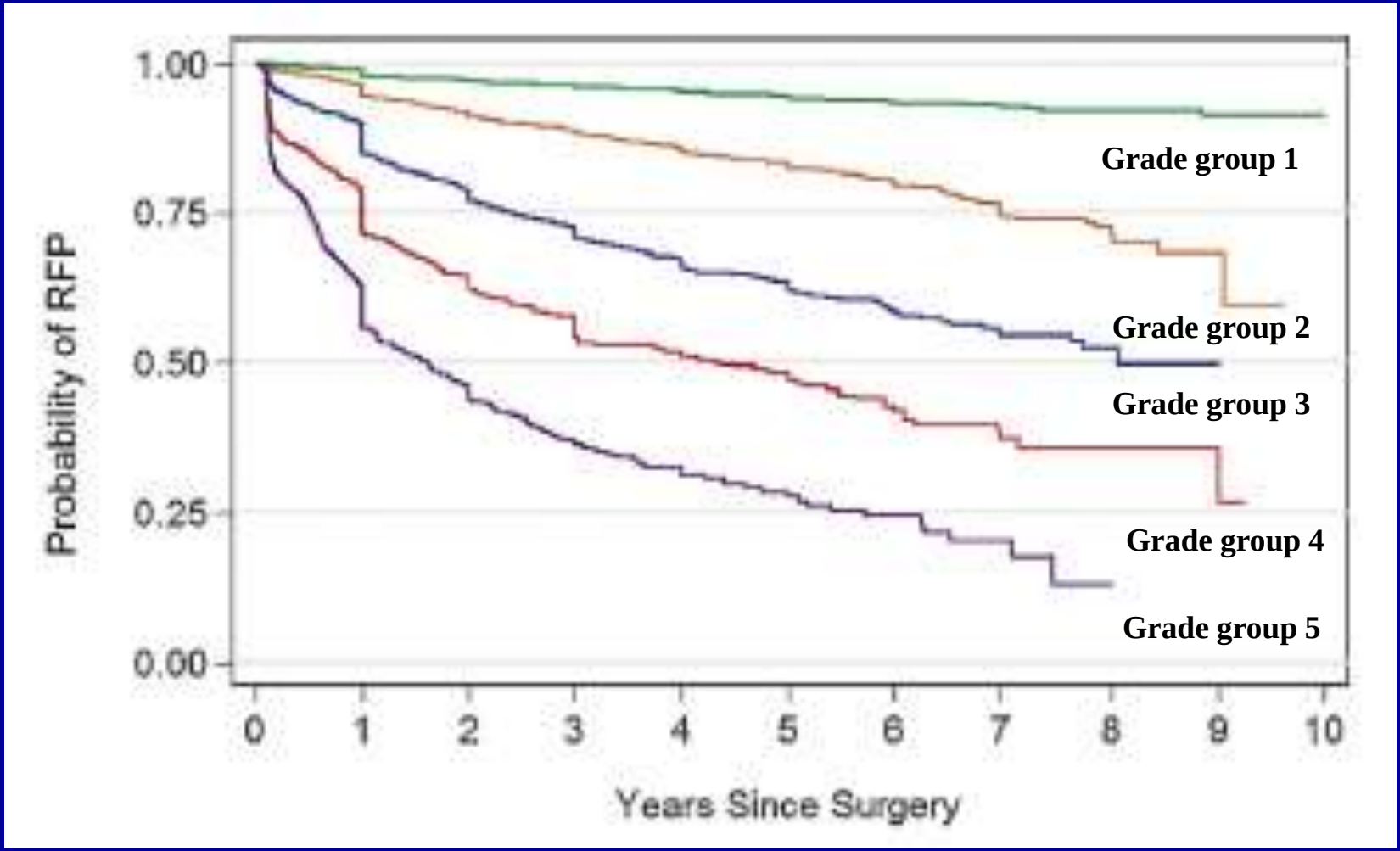
NEW GRADING SYSTEM: GRADE GROUPS

Grade group 1	GS ≤6	Only individual discrete well-formed glands
Grade group 2	GS 3+4=7	Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands
Grade group 3	GS 4+3=7	Predominantly poorly-formed/fused/cribriform glands with a lesser component of well-formed glands
Grade group 4	GS 4+4=8 GS 3+5=8 GS 5+3=8	Only poorly-formed/fused/cribriform glands Predominantly well-formed glands with a lesser component lacking glands Predominantly lacking glands or with a lesser component of well-formed glands
Grade group 5	GS 9/10	Lacks gland formation (or with necrosis) with or w/o poorly-formed/fused/cribriform glands

- Proposed by J Epstein (Johns Hopkins)

- Grade grouping NOT A NEW grading method; based on Gleason system; a novel way to group Gleason grades

OUTCOME OF 20,845 MEN BASED ON BIOPSY GRADE GROUPS



Epstein JI et al. Eur Urol 69:428, 2015

NEW GRADING SYSTEM: GRADE GROUPS

- **Advantages**

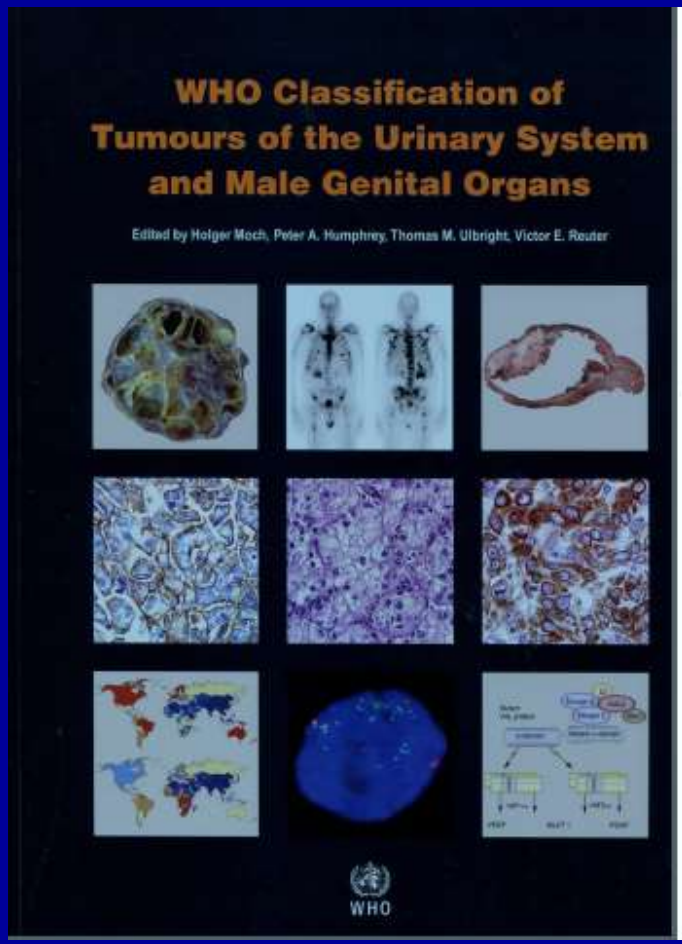
✓ More accurate stratification than the current system

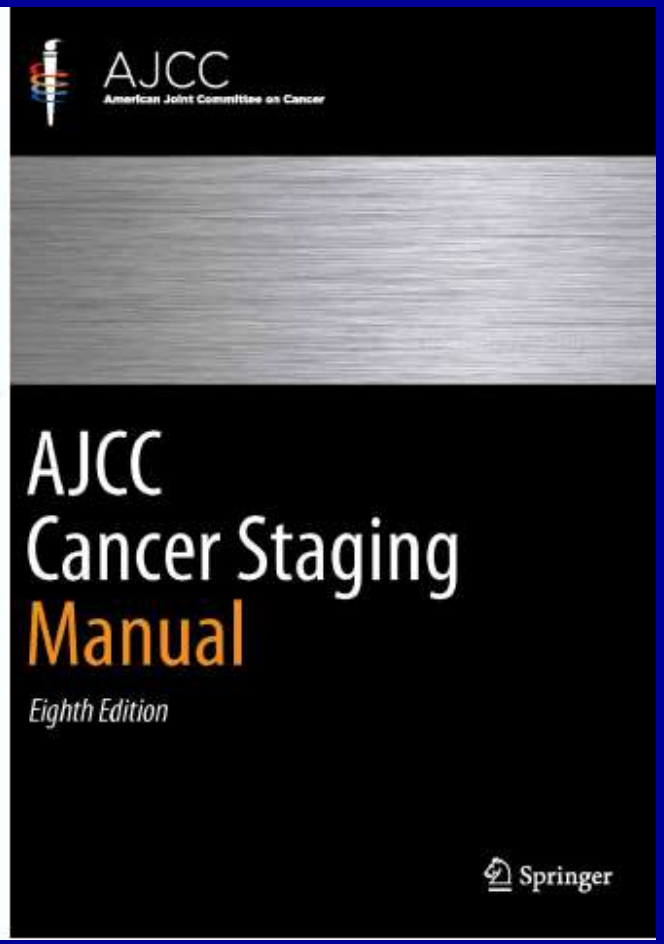
✓ Lower number of categories (5 vs 10 with Gleason)

✓ Lowest grade is 1 and not 6

- **Used in conjunction with the Gleason system**

✓ Prostate adenocarcinoma, Gleason score 3+5=8 (Grade group 4)





Accepted by 2016 WHO and AJCC…..

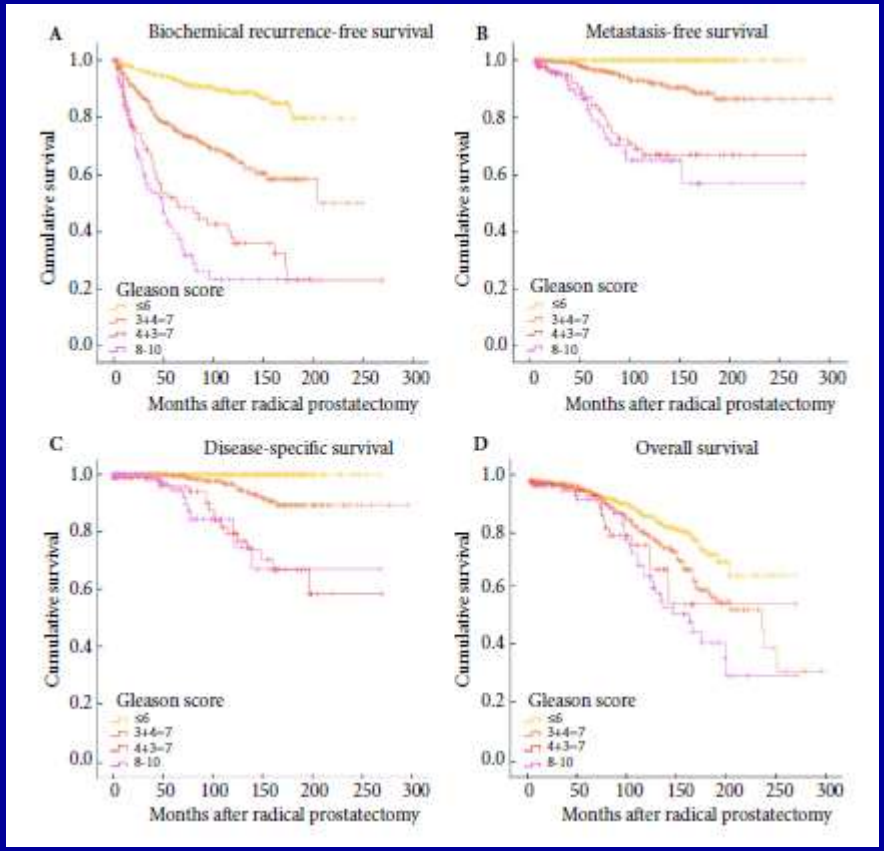
Also referred to as ISUP grade in some publications

BJUI
BJU International

Disease-specific death and metastasis do not occur in patients with Gleason score ≤6 at radical prostatectomy

Charlotte F. Kweldam, Mark F. Wildhagen*†, Chris H. Bangma* and Geert J.L.H. van Leenders

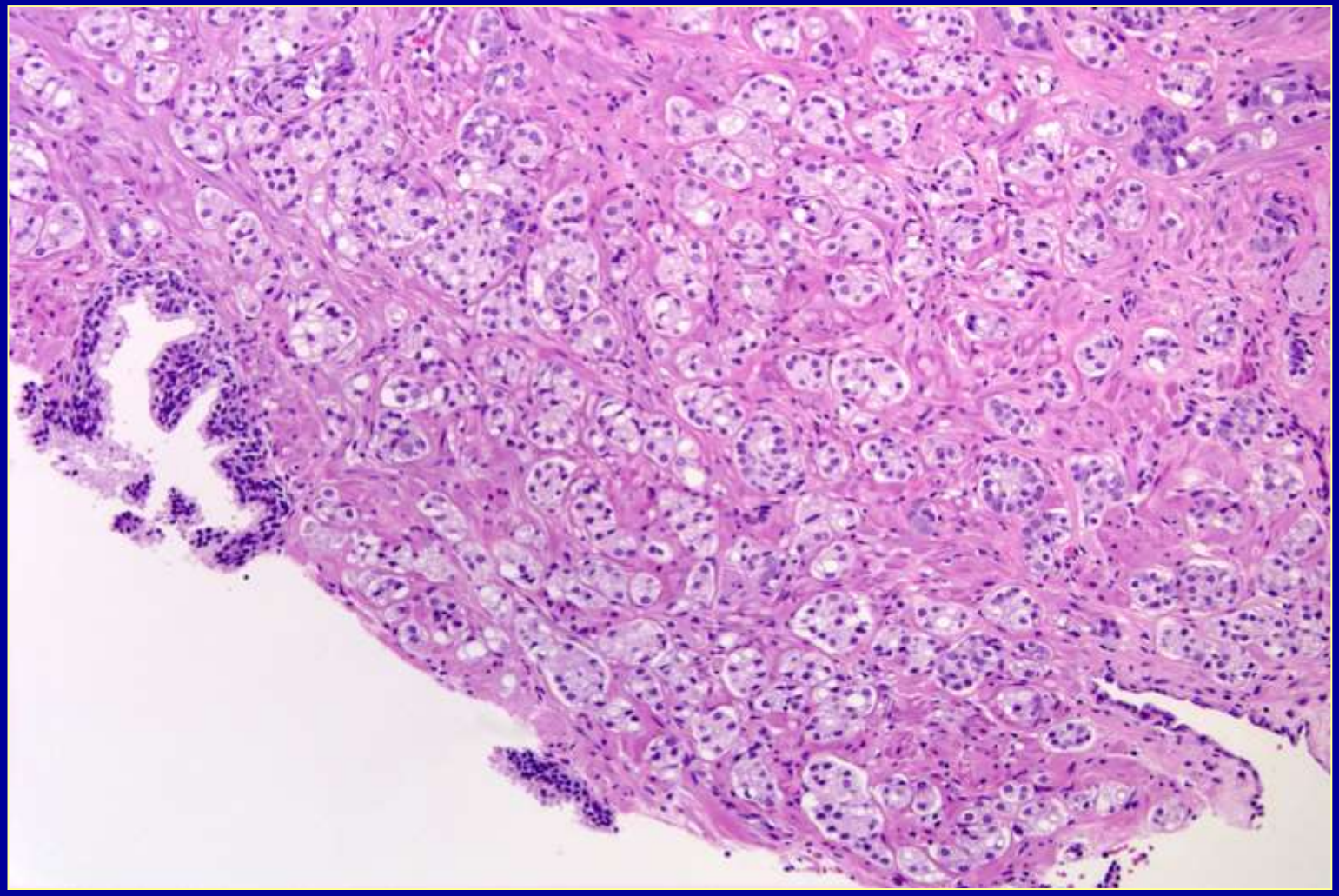
*Departments of Pathology, *Urology, and †Research Office Sophia, Erasmus Medical Center, Rotterdam, The Netherlands*



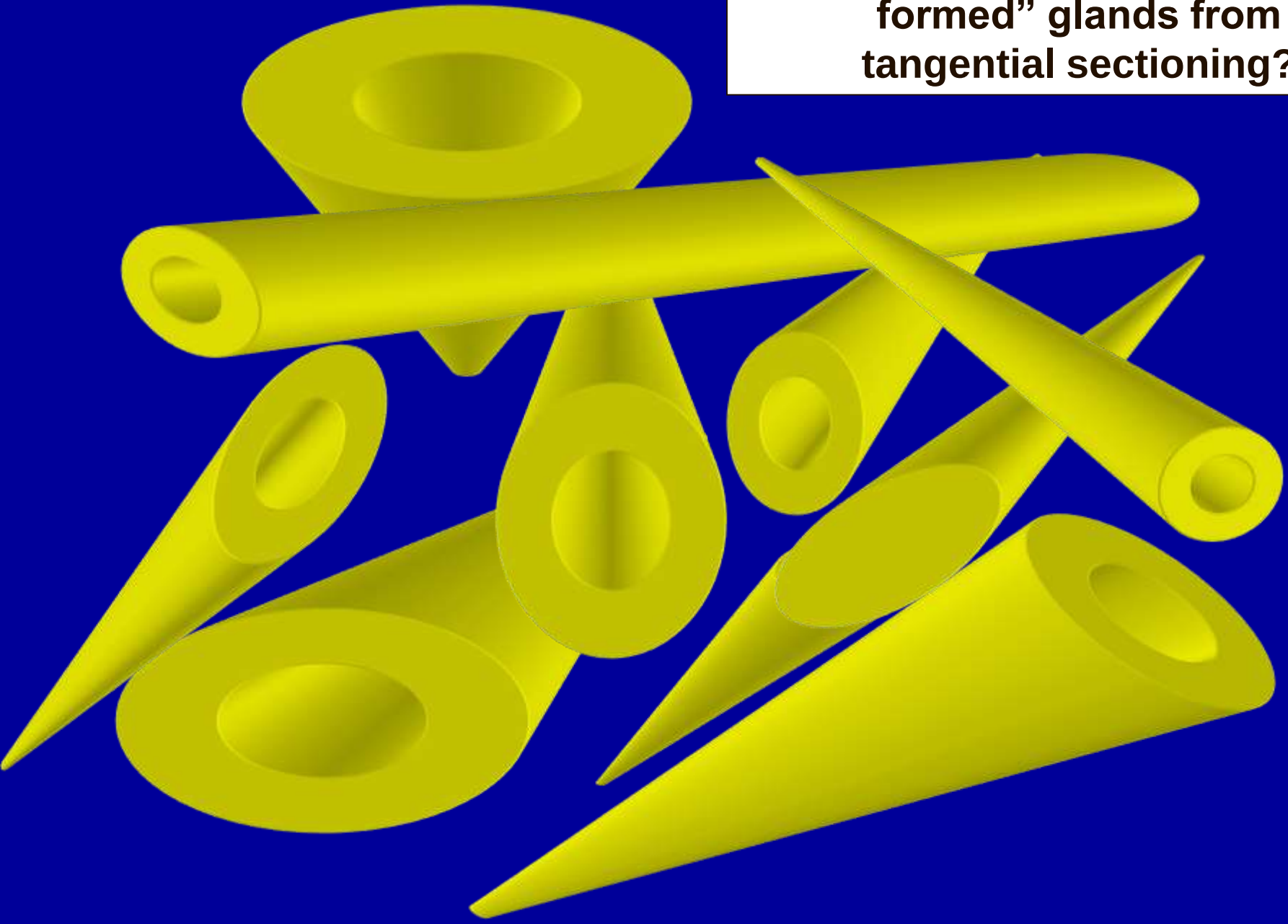
GLEASON PATTERN 4 IN CONTEMPORARY BIOPSY PRACTICE

- Morphologic subpatterns:
  - Poorly formed/Ill-formed
    Abortive glands
  - Fused glands
  - Glomeruloid (small and large)
  - Cribriform (small and large)
    Ductal
  - Papillary
    Ductal
    Non-ductal

Ill-defined glands cluster with poorly formed lumina where tangential sectioning is ruled out is Gleason pattern 4



How to differentiate “Poorly formed” glands from tangential sectioning?



ORIGINAL ARTICLE

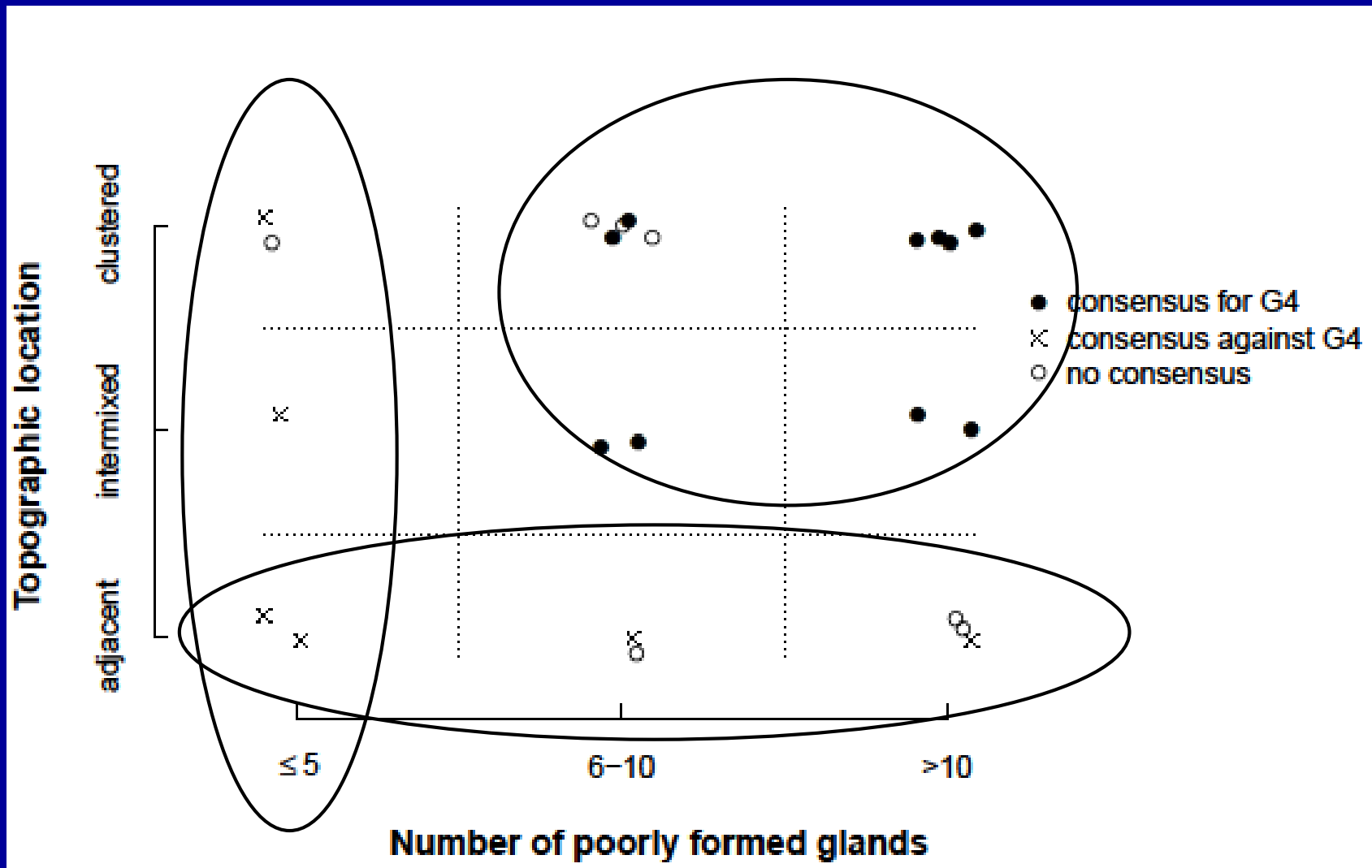
Diagnosis of "Poorly Formed Glands" Gleason Pattern 4 Prostatic Adenocarcinoma on Needle Biopsy

An Interobserver Reproducibility Study Among Urologic Pathologists With Recommendations

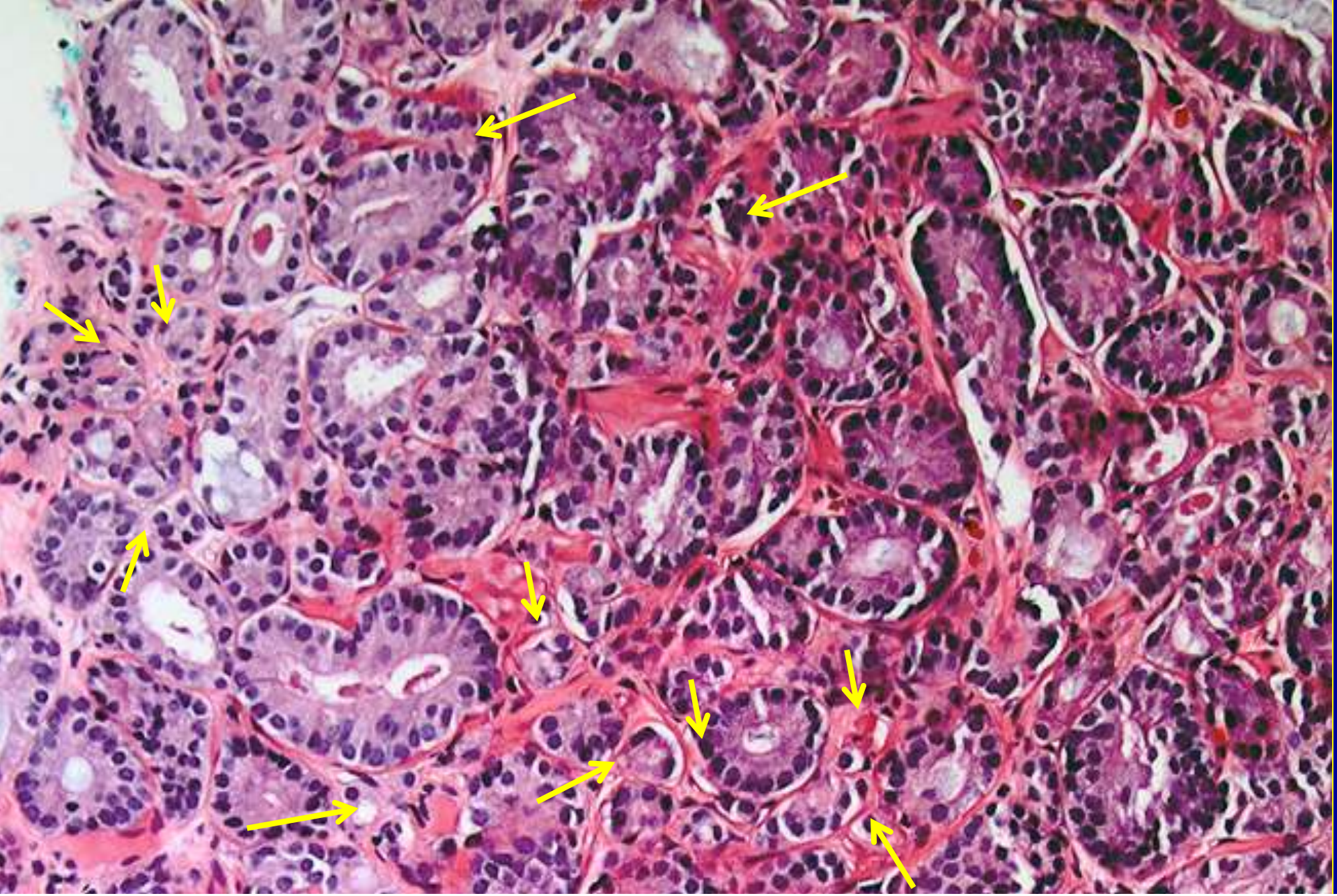
Ming Zhou, MD, PhD, Jianbo Li, PhD,† Liang Cheng, MD, PhD,‡ Lars Egevad, MD,§ Fang-Ming Deng, MD,* Lakshmi Priya Kunju, MD,‖ Cristina Magi-Galluzzi, MD, PhD,† Jonathan Melamed, MD,* Rohit Mehra, MD,‖ Savvas Mendrinos, MD,¶ Adeboye O. Osunkoya, MD,# Gladell Paner, MD,** Steve S. Shen, MD, PhD,†† Toyonori Tsuzuki, MD,‡‡ Kiril Trpkov, MD,§§ Wei Tian, MD,¶ Ximing Yang, MD, PhD,‖‖ and Rajal B. Shah, MD¶*

***Am J Surg Pathol* 2015; 39 (10):1331-9**

- Consensus definition for "poorly formed glands": Cancer glands with no or rare lumens, elongated compressed glands, and elongated nests
- Kappa=0.34
- Reproducibility improved when quantitative criteria applied



Use high threshold! Default to grade 3 if in doubt, especially dealing with small focus

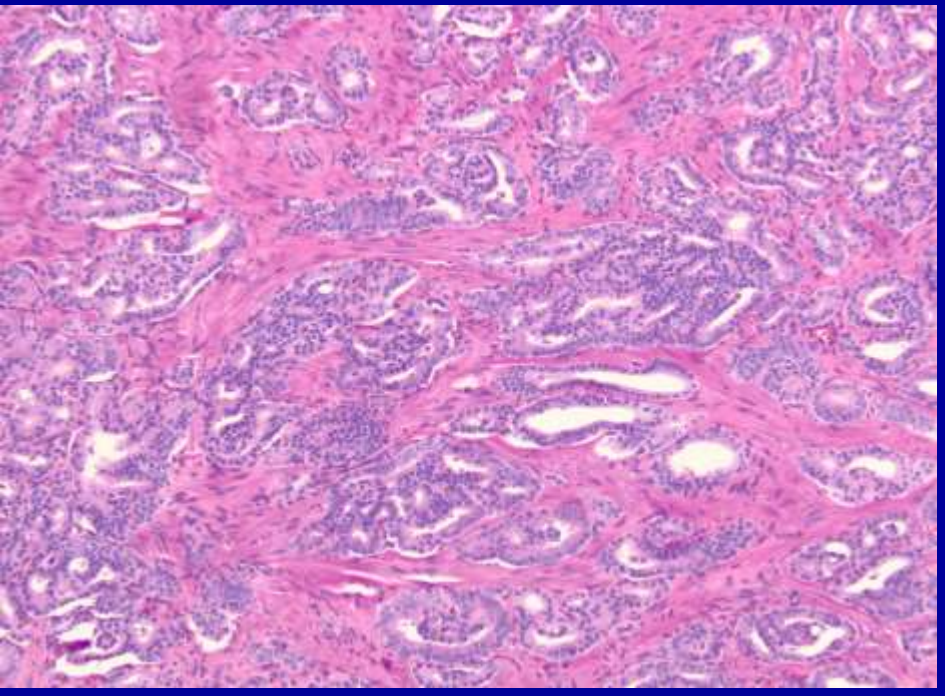
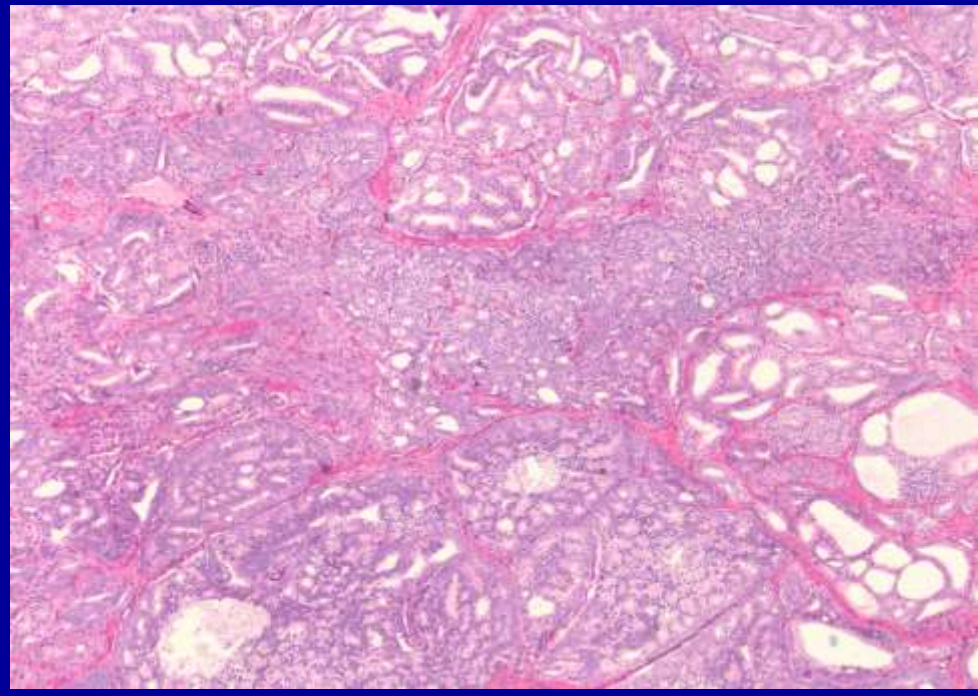
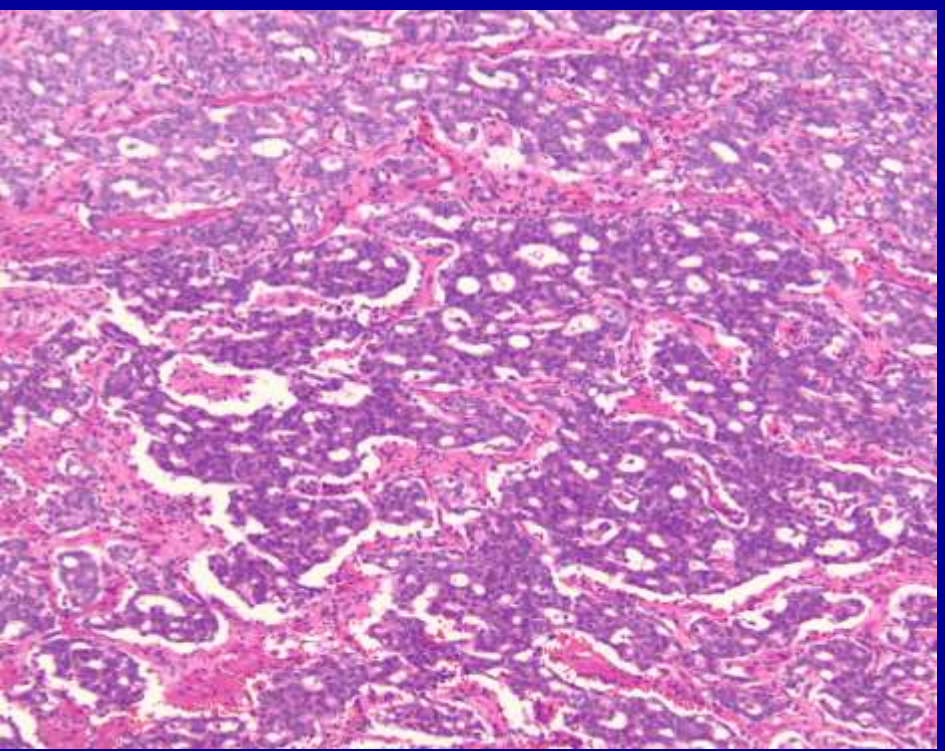
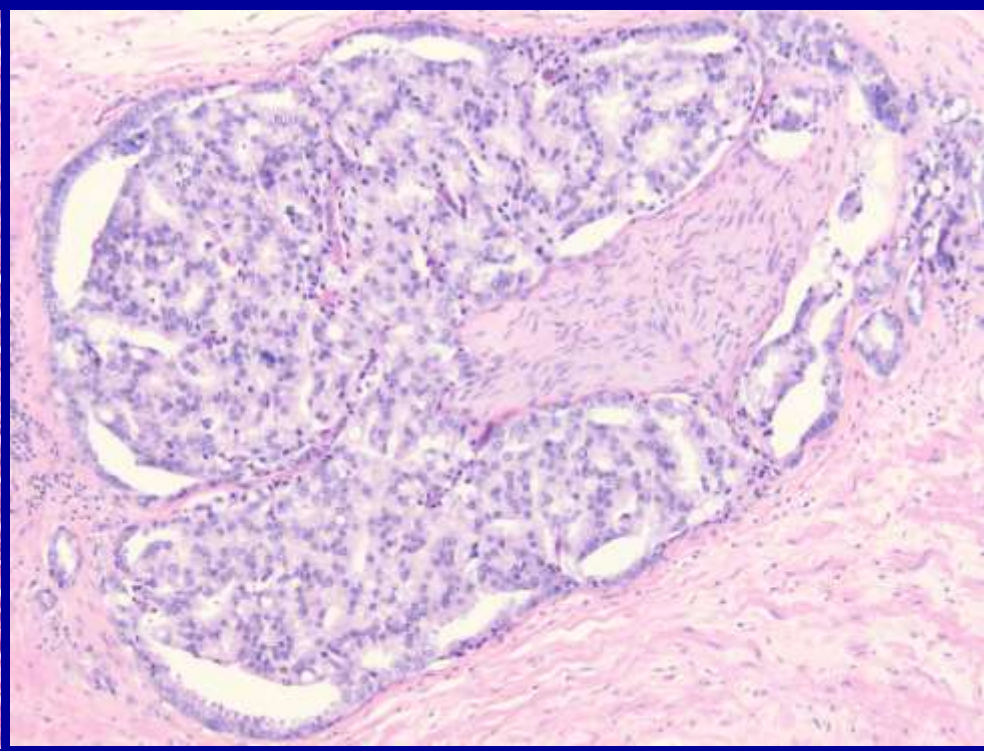


Case 3: Prostate adenocarcinoma, Gleason score 3+3=6

(Poorly formed glands adjacent to well-formed glands, >10, Consensus not pattern 4)

CRIBRIFORM GLEASON PATTERN 4

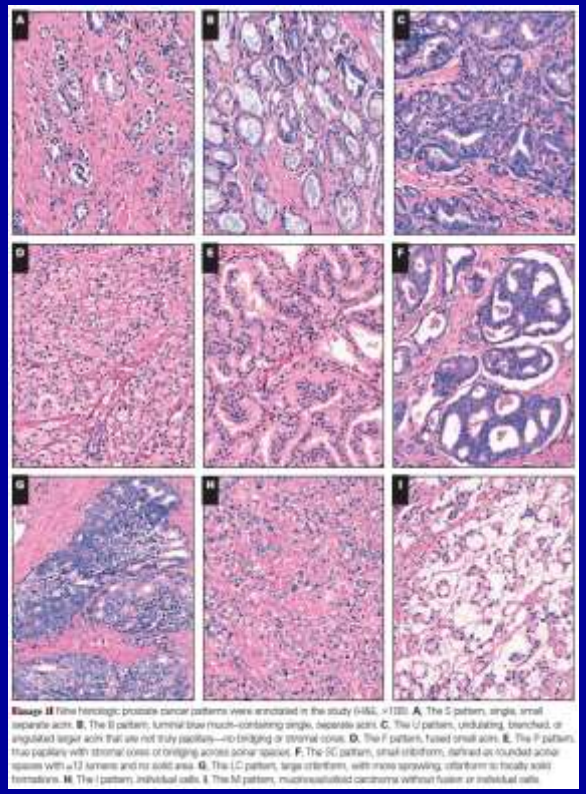
- All cribriform cancers (large and small) are pattern 4

Digital Quantification of Five High-Grade Prostate Cancer Patterns, Including the Cribriform Pattern, and Their Association With Adverse Outcome

Kenneth A. Iczkowski, MD,[1] Kathleen C. Torkko, PhD,[1] Gregory R. Kotnis, MD,[1] R. Storey Wilson, MS,[1] Wei Huang, MD,[2] Thomas M. Wheeler, MD,[3] Andrea M. Abeyta,[1] Francisco G. La Rosa, MD,[1] Shelly Cook, MD,[2] Priya N. Werahera, PhD,[1] and M. Scott Lucia, MD[1]

The presence of cribriform cancer conferred highest odds ratio for PSA failure , 5.9. among five high-grade patterns



Presence of Nine Histologic Prostate Cancer Patterns and Their Association With PSA Failure in 153 Cases*

Pattern	Present	PSA Failure (n = 76)	Non-PSA Failure (n = 77)	*P* (χ^2)	OR for PSA Failure	95% CI	*P* for OR
Low-grade (S, B, U, and M)	All, 151 (98.7) S, 151 (98.7) B, 78 (51.0) U, 122 (79.7) M, 9 (5.9)	75 (99)	76 (99)	.754†	0.314	0.018-5.464	.427
Fused small	128 (83.7)	68 (89)	60 (78)	.053	1.403	0.499-3.945	.521
Papillary	80 (52.3)	50 (66)	30 (39)	.0009	2.155	0.999-4.645	.050
Individual	35 (22.9)	25 (33)	10 (13)	.003	2.654	1.069-6.589	.035
All cribriform	58 (37.9)	46 (61)	12 (16)	<.0001	5.891	2.534-13.698	<.0001
Any large	58 (37.9)	46 (61)	12 (16)	<.0001	5.583	2.416-12.901	<.0001
Any small	26 (17.0)	21 (28)	5 (6)	.0005	6.062	1.931-19.037	.002
Large acinar‡	17 (11.1)	15 (20)	2 (3)	.0007	10.806	2.152-54.256	.004

Cribriform cancer and biochemical recurrence

TABLE 1. Biochemical Recurrence* of Prostate Cancer Containing Gleason 4

Studies	Median Follow-up (y)	BCR or Cancer-specific Survival
Prostatectomy:		
Iczkowski et al[7]	5.9	BCR: cribriform had the highest odds ratio among 5 high-grade prostate cancer patterns for PSA failure, OR = 5.89, $P < 0.0001$
Dong et al[10]	5	BCR in 32% of cribriform and 21% of noncribriform ($P = 0.009$); cribriform predicts recurrence, OR = 2.4, $P = 0.003$
Trudel et al[11]	10.8	BCR: presence of cribriform or IDC confers OR = 3.0, $P = 0.0002$. Independent predictor of BCR, along with Gleason ≥ 8 and positive margin
Kir et al[13]	3.5	96% of BCR-positive cases had cribriform pattern, vs. 57% of BCR-negative. Cribriform pattern is independent BCR predictor, OR = 11.9, $P = 0.02$
Choy et al[23]	6.3	BCR: cribriform 30%; poorly formed 22%; fused 19%
Choy et al[24]	5	In prostatectomy 3+4 cancer with low volume, BCR: If tumor volume <5%: 5% no cribriform; 18% cribriform. If tumor volume <10%: 15% no cribriform; 18% cribriform
Kweldam et al[17]	15	Cancer-specific survival, 94% in cribriform/IDC−, and 67% in cribriform/IDC+, OR = 2.8
Choy et al[25]	1.5	Cribriform or IDC associated with BCR, OR = 2.2
Biopsy:		
Harding et al[8]	2.7	Among Gleason 8 biopsy cases, cribriform pattern predicted BCR, OR = 6.1, $P = 0.018$. It is more important than 4+4 vs. 3+5
Billis et al[26]	Not given	Time to BCR was less ($P = 0.49$) in biopsy specimens with mixture of patterns than in those with exclusively a fused pattern

*Generally defined as a postoperative rise in serum PSA to ≥ 0.2 ng/mL.
BCR indicates biochemical recurrence; IDC, intraductal carcinoma; OR, odds ratio; PSA, prostate-specific antigen.

Cribriform cancer and prediction of metastasis and death

TABLE 2. Systemic Metastasis and Cancer-specific Death From Prostate Cancer

Studies	Median Follow-up (y)	Metastasis	Cancer-specific Death
Prostatectomy:			
Dong et al[10]	10	Grade 4 cribriform 13.3% vs. without cribriform 2.6%, OR = 5.6, $P = 0.02$	
Kweldam et al[16]	10	Cribriform pattern was the only independent predictor for metastasis, OR = 8.0, $P < 0.001$	Other than Gleason score, cribriform pattern was only independent predictor for metastasis, OR = 5.4, $P < 0.001$
Choy et al[25]	10	Cribriform or IDC associated with BCR, OR = 3.3, $P < 0.001$	
Biopsy:			
Kweldam et al[17]	15		If cribriform absent 94%; if present 67%. OR = 2.6, $P = 0.002$. A 3+4 = 7 cancer without cribriform was not significantly different from 3+3 = 6

Modern Pathology (2015) 28, 457–464
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Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer

Charlotte F Kweldam[1], Mark F Wildhagen[2,3], Ewout W Steyerberg[4], Chris H Bangma[3], Theodorus H van der Kwast[5] and Geert JLH van Leenders[1]

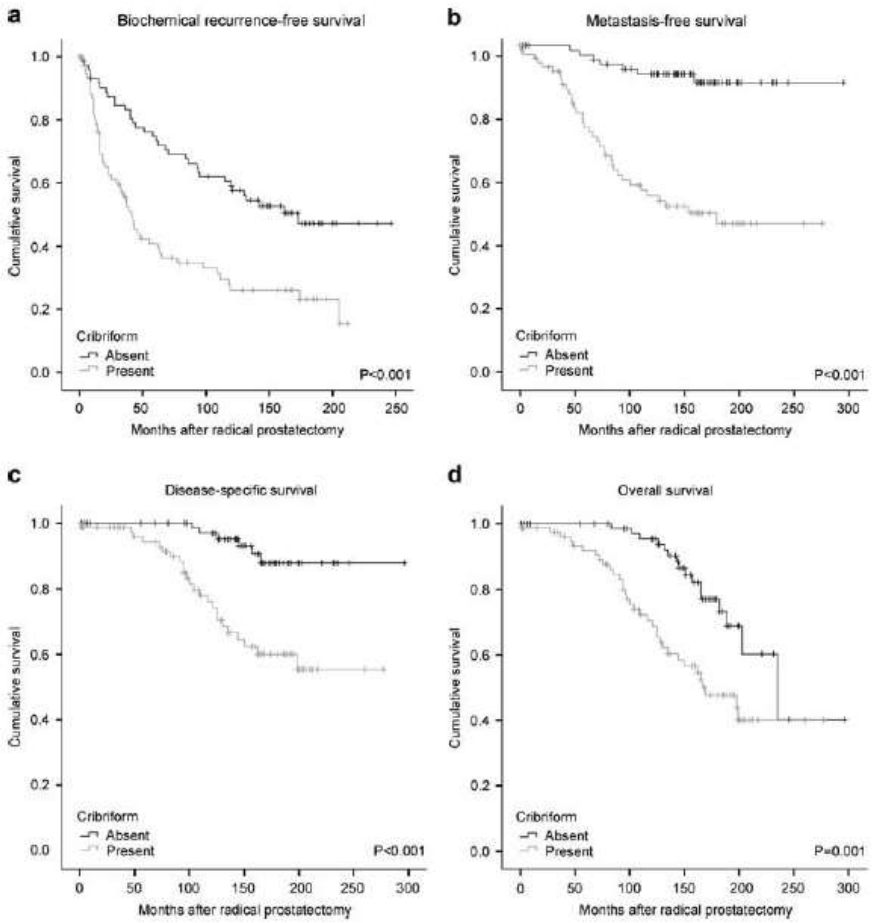

Figure 2 Kaplan–Meier estimates on impact of cribriform growth pattern in (**a**) biochemical recurrence-free survival; (**b**) distant metastasis-free survival; (**c**) disease-specific survival; and (**d**) overall survival.

Final Diagnosis **Date Signed Out:** 10/9/2018 15:45

A. Left base x 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 3+4=7, grade group 2, involving one of two cores (25%, 2.5 mm; 15% of sampled tissue).

B. Left mid x 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 3+4=7, grade group 2, involving one of two cores (60%, 7 mm, 45% of sampled tissue).

C. Left apex x 2 prostate, biopsy - Benign prostatic tissue.

D. Right base x 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 4+3=7, grade group 3, involving two cores (90%, 6 mm, 15%, 2 mm; 45% of sampled tissue).
- Gleason pattern 4 accounts for 80% of the tumor.

E. Right mid x 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 3+4=7, grade group 2, involving one of two cores (35%, 4 mm; 20% of sampled tissue).

F. Right apex x 2 prostate, biopsy - Minute focus of adenocarcinoma of prostate, Gleason score 3+3=6, grade group 1, involving one of two cores (2%, less than 0.5 mm).

G. Target 1 prostate, biopsy - Benign prostatic tissue.

H. Target 2 prostate, biopsy - Adenocarcinoma of prostate, Gleason score 4+3=7, grade group 3, involving four cores (100%, 6 mm, 100%, 5 mm, 95%, 7 mm, 75%, 6 mm; 85% of sampled tissue).
- Gleason pattern 4 accounts for 50% of the tumor.
- Perineural invasion present.

Prostate Cancer Biopsy Summary

Number of cores examined: 18
Number of cores positive: 10
Highest Grade Group: 3
Highest % of core involvement: 100%
Cribriform pattern 4: Absent
Intraductal carcinoma: Absent

Size of the cribriform glands likely matters!

Modern Pathology
https://doi.org/10.1038/s41379-018-0157-9

USCAP

ARTICLE

Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis

Eva Hollemans[1] · Esther I. Verhoef[1] · Chris H. Bangma[2] · John Rietbergen[3] · Jozien Helleman[2] · Monique J. Roobol[2] · Geert J.L.H. van Leenders[1]

Received: 29 June 2018 / Revised: 22 August 2018 / Accepted: 23 August 2018
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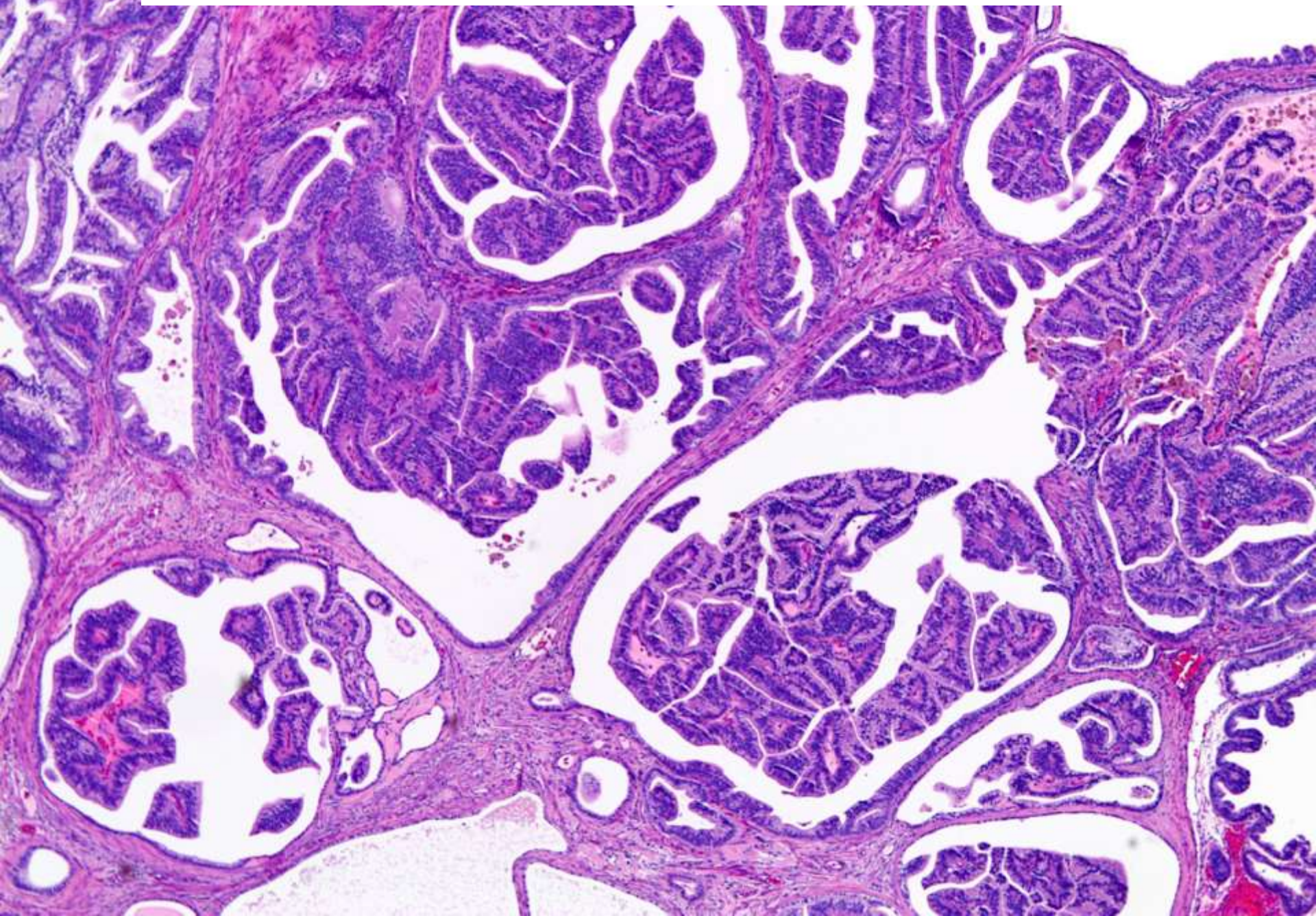
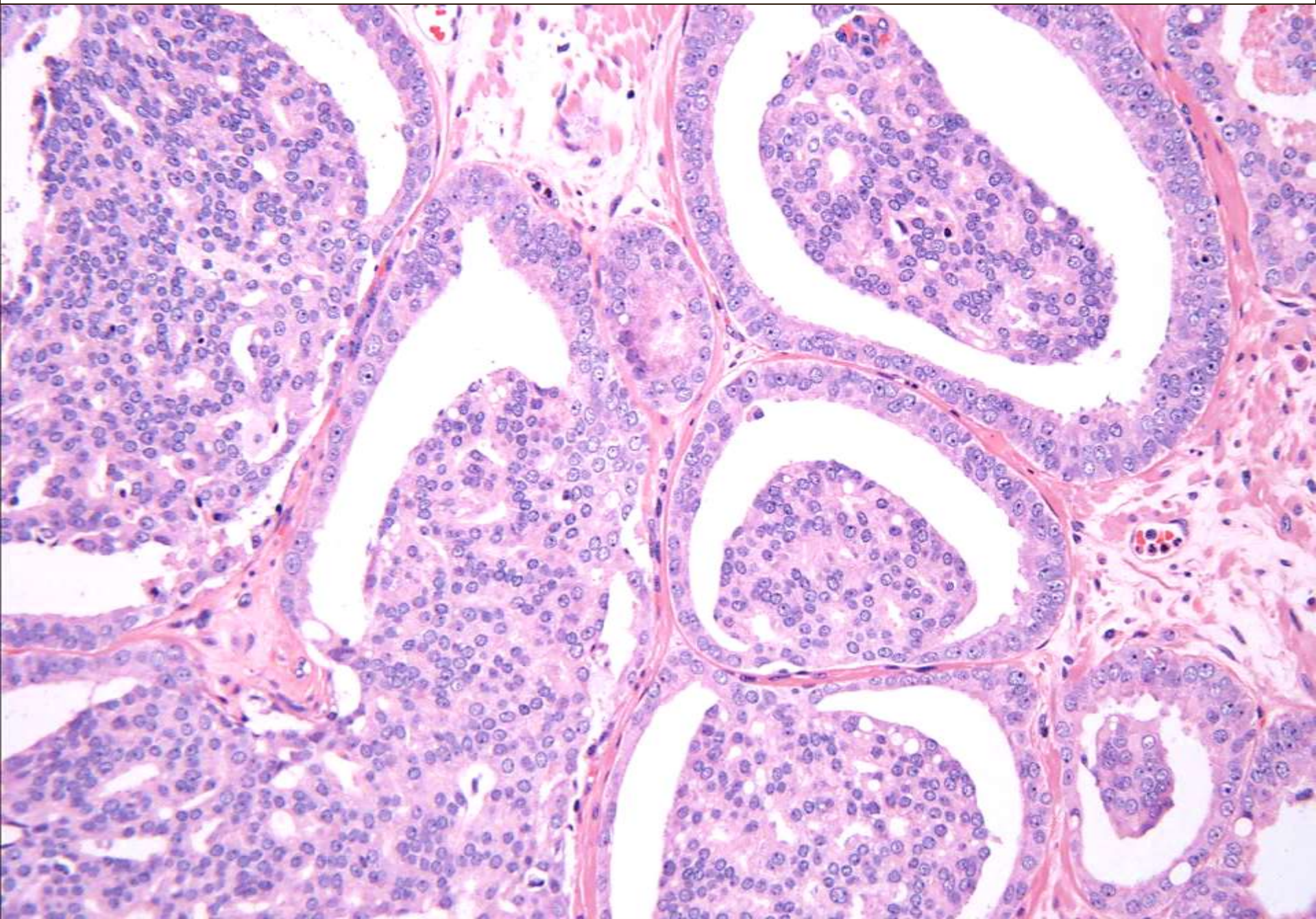
Various definition of large cribriform gland:

1) **> 12 lumens**
2) **Two times benign gland**
3) **> 0.5 mm**

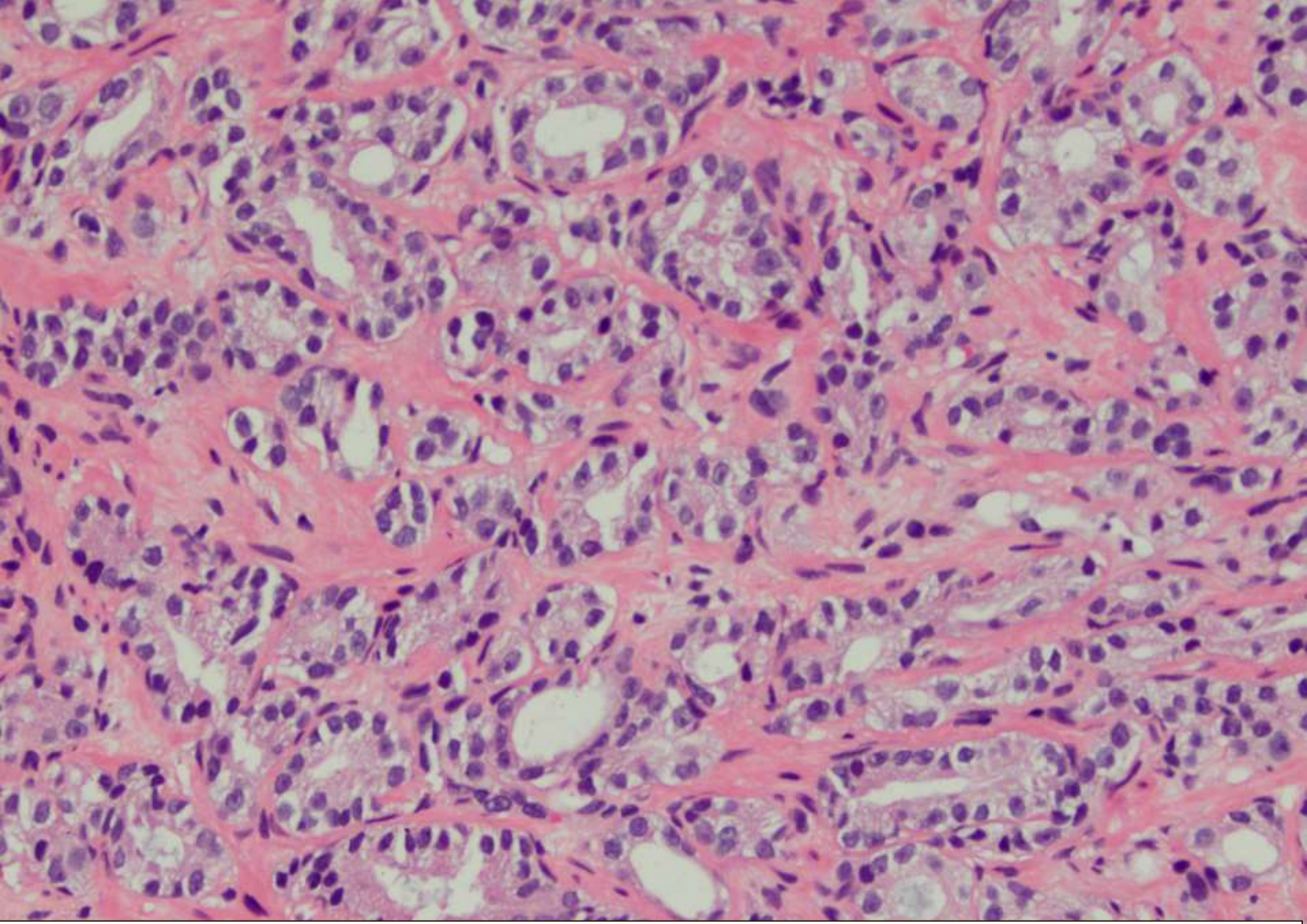
Ductal Adenocarcinoma of the Prostate



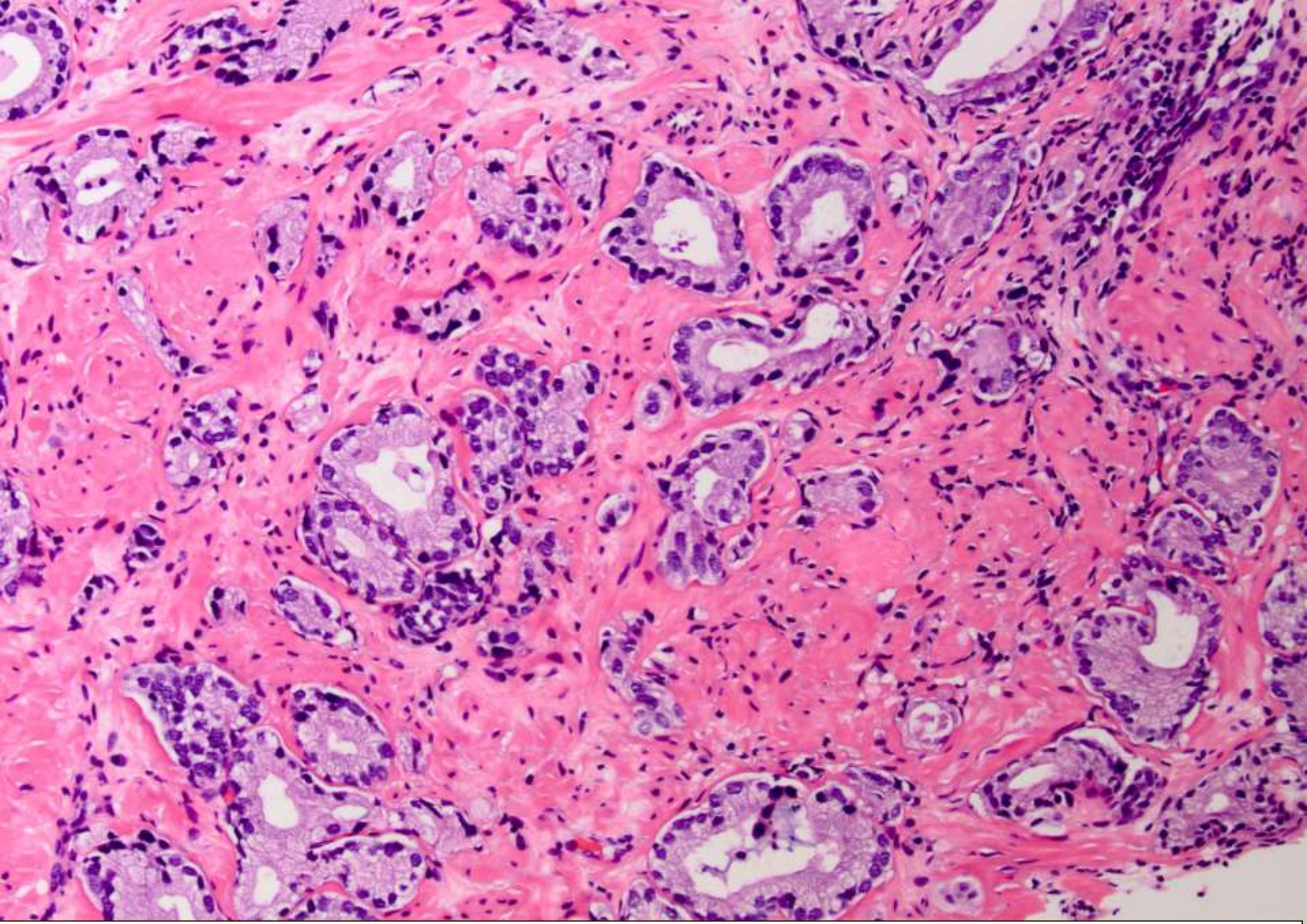
Glomeruloid structures – Now uniformly Gleason pattern 4



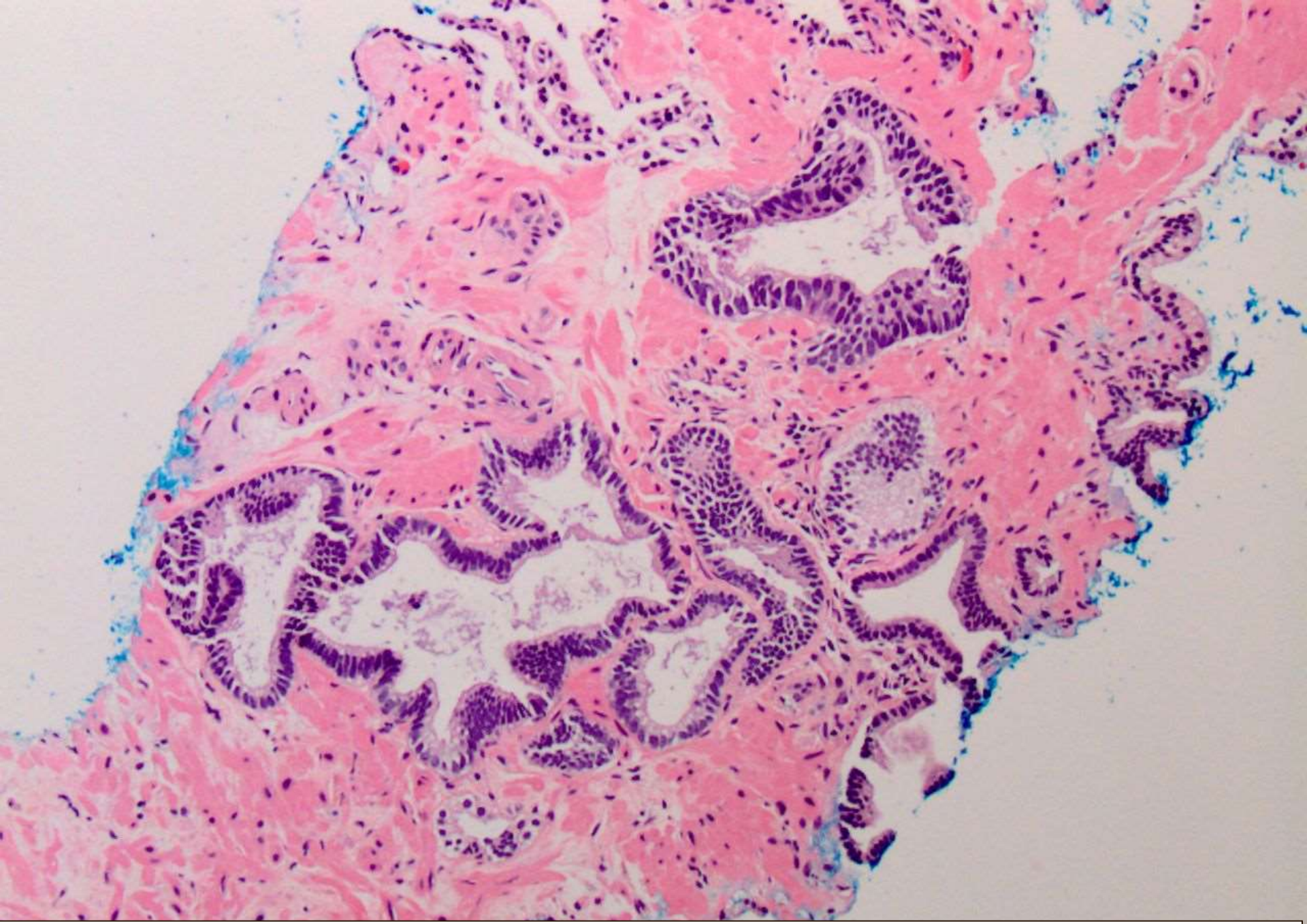
Common pitfalls that may result in over grading of Pattern 3 as 4



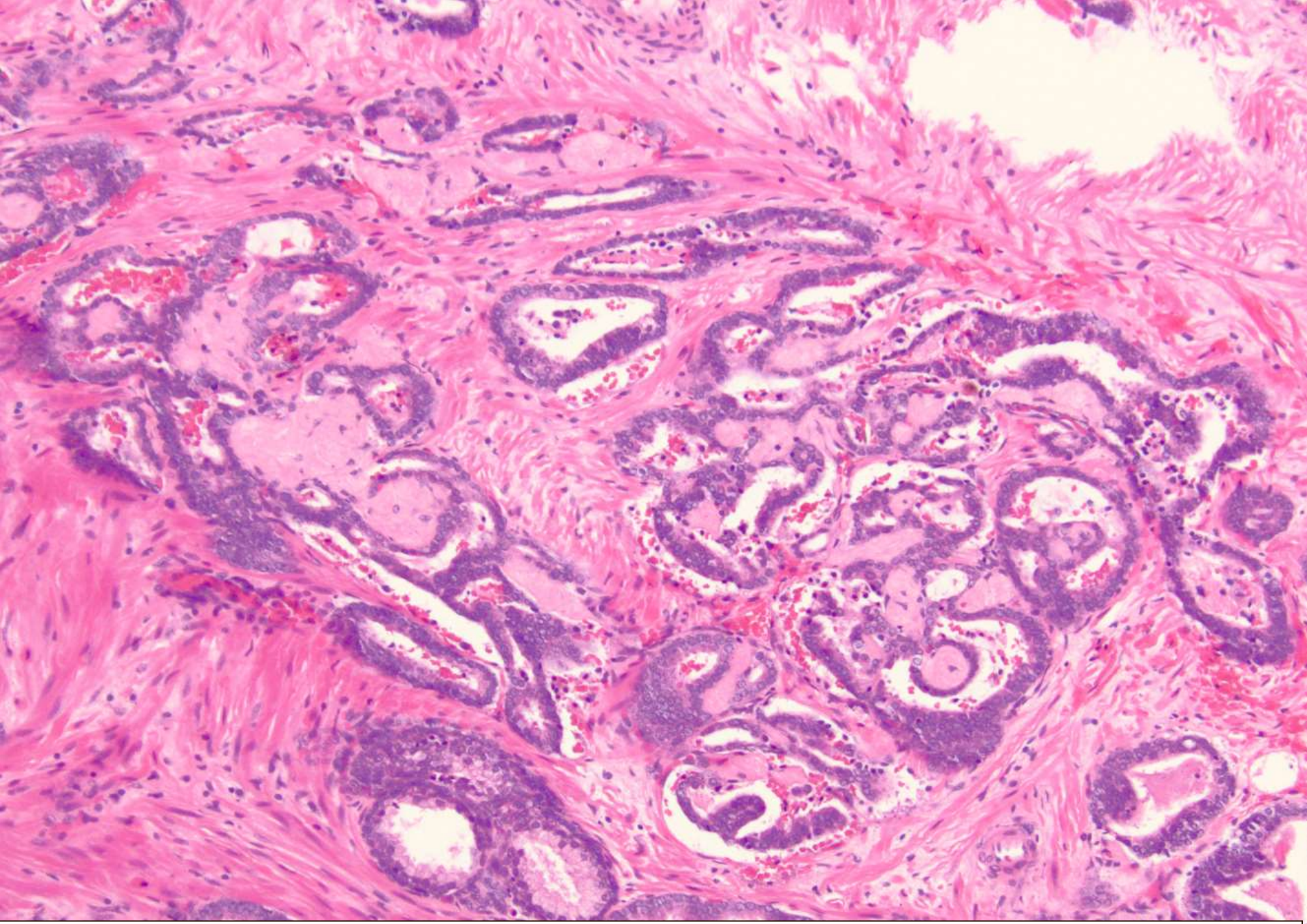
Microacinar morphology mimicking “poorly formed” pattern 4



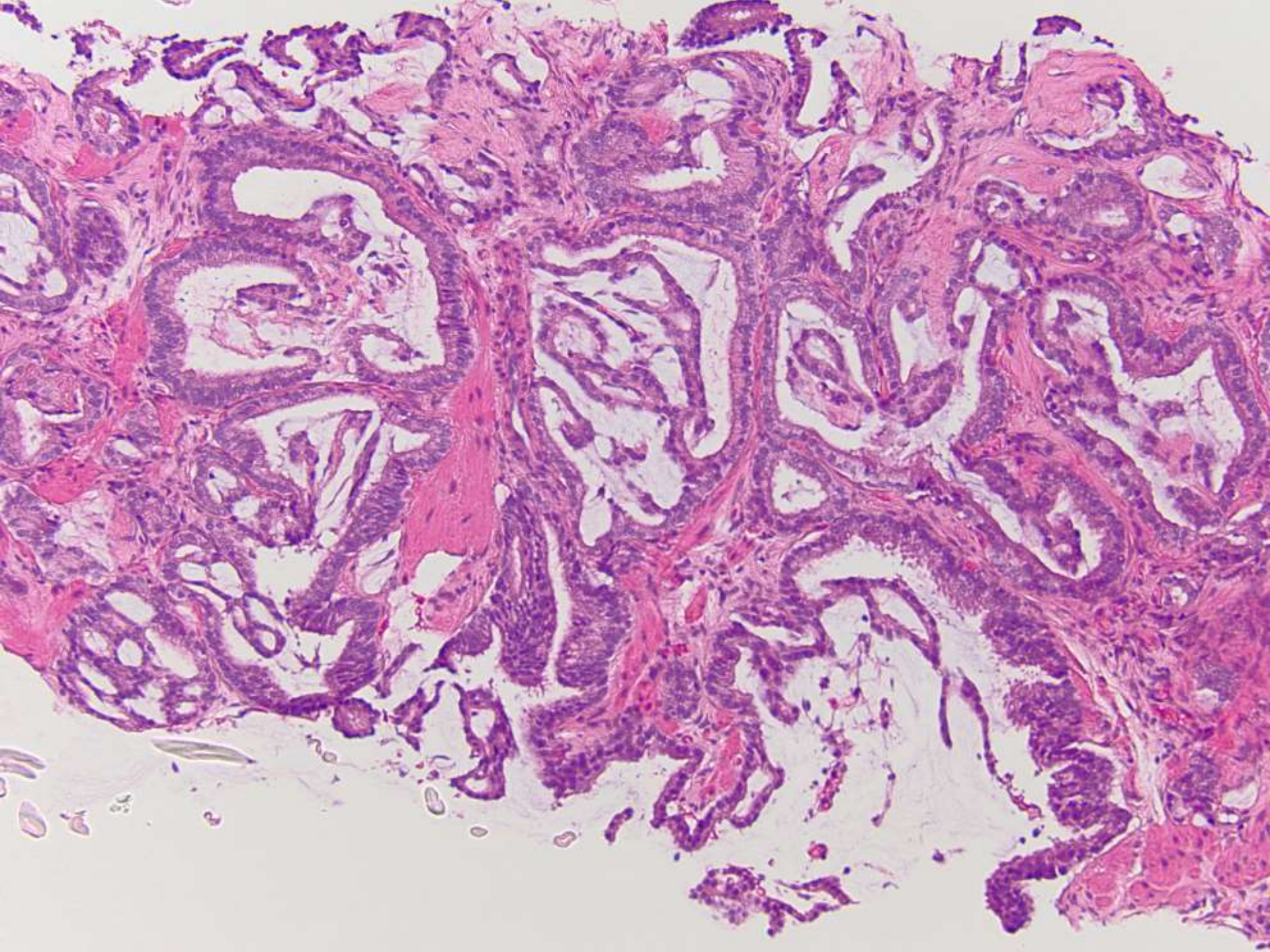
Tangentially sectioned glands mimicking “poorly formed” pattern 4

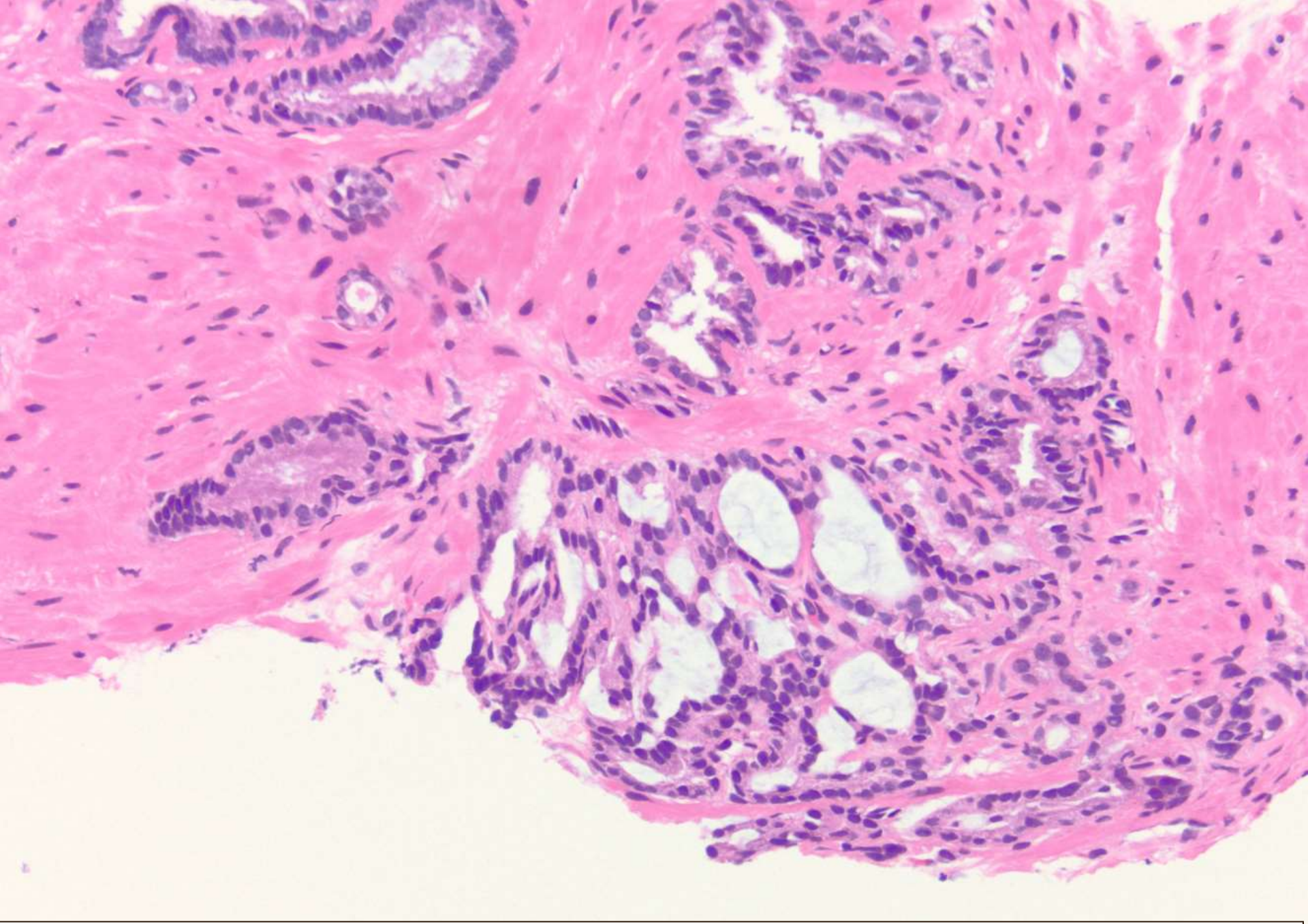


Branching of glands mimicking “fused” pattern 4

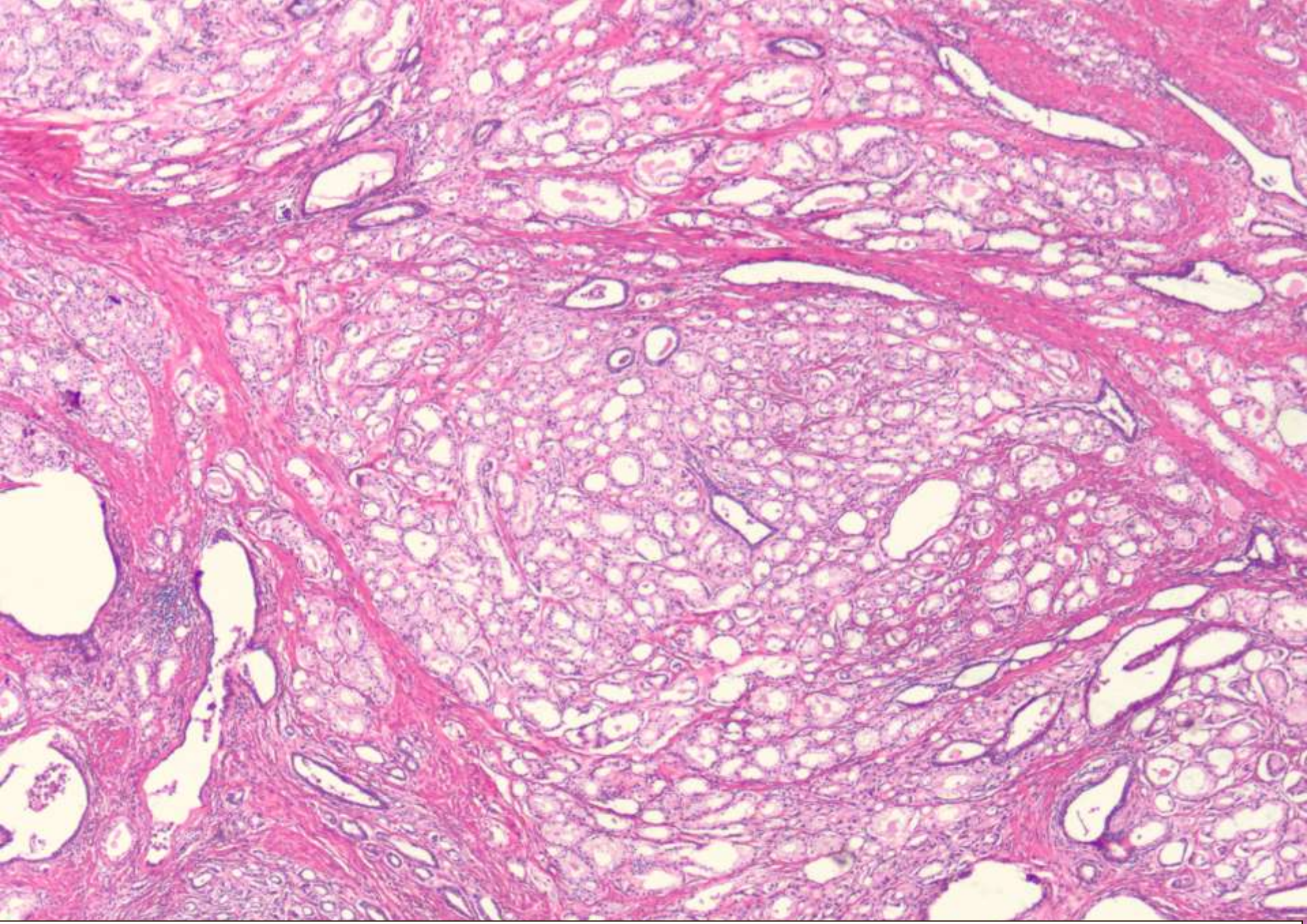


Mucinous fibroplasia mimicking cribriform pattern 4

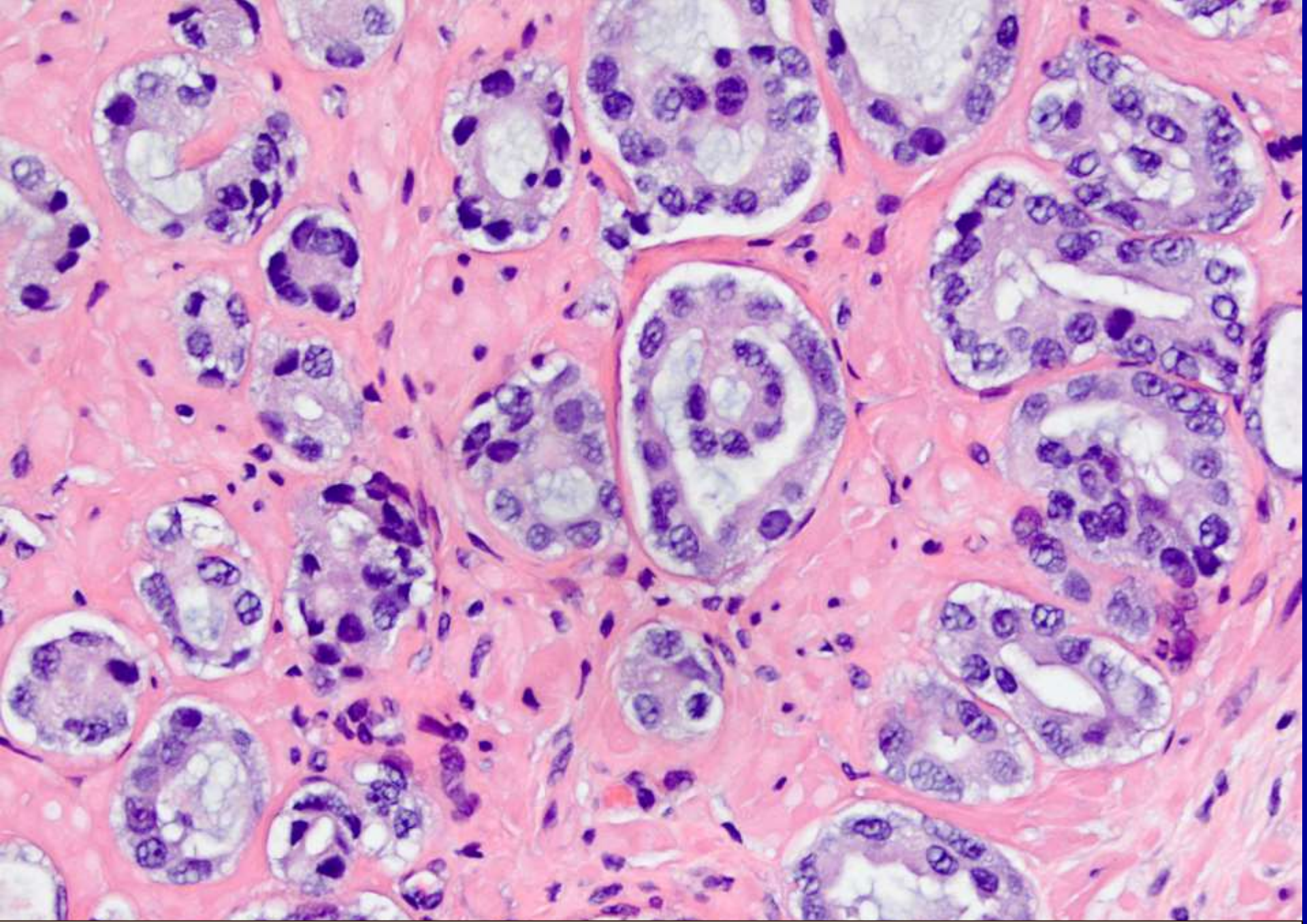




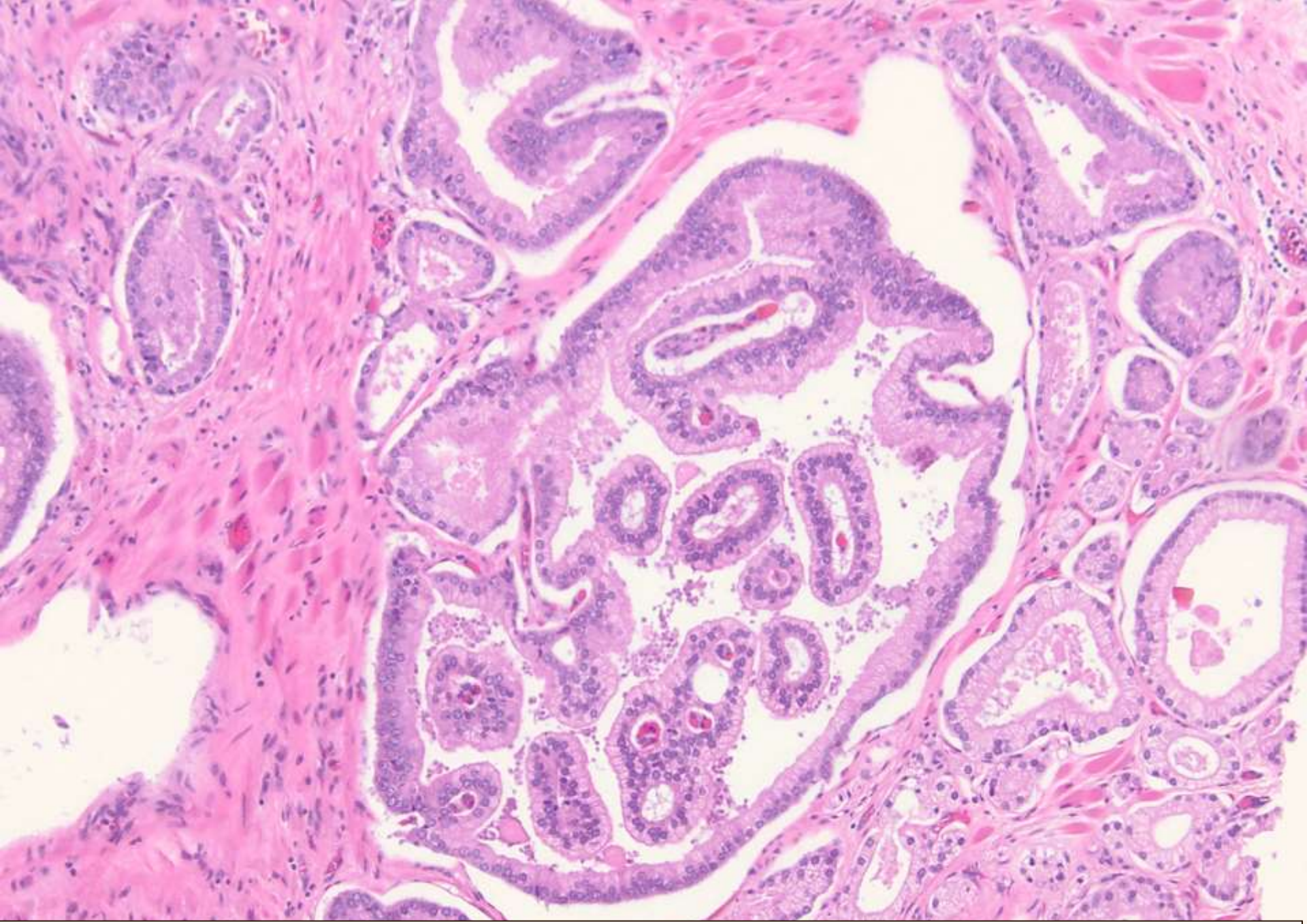
Mucinous extravasation with collapsed stroma mimicking cribriform pattern 4



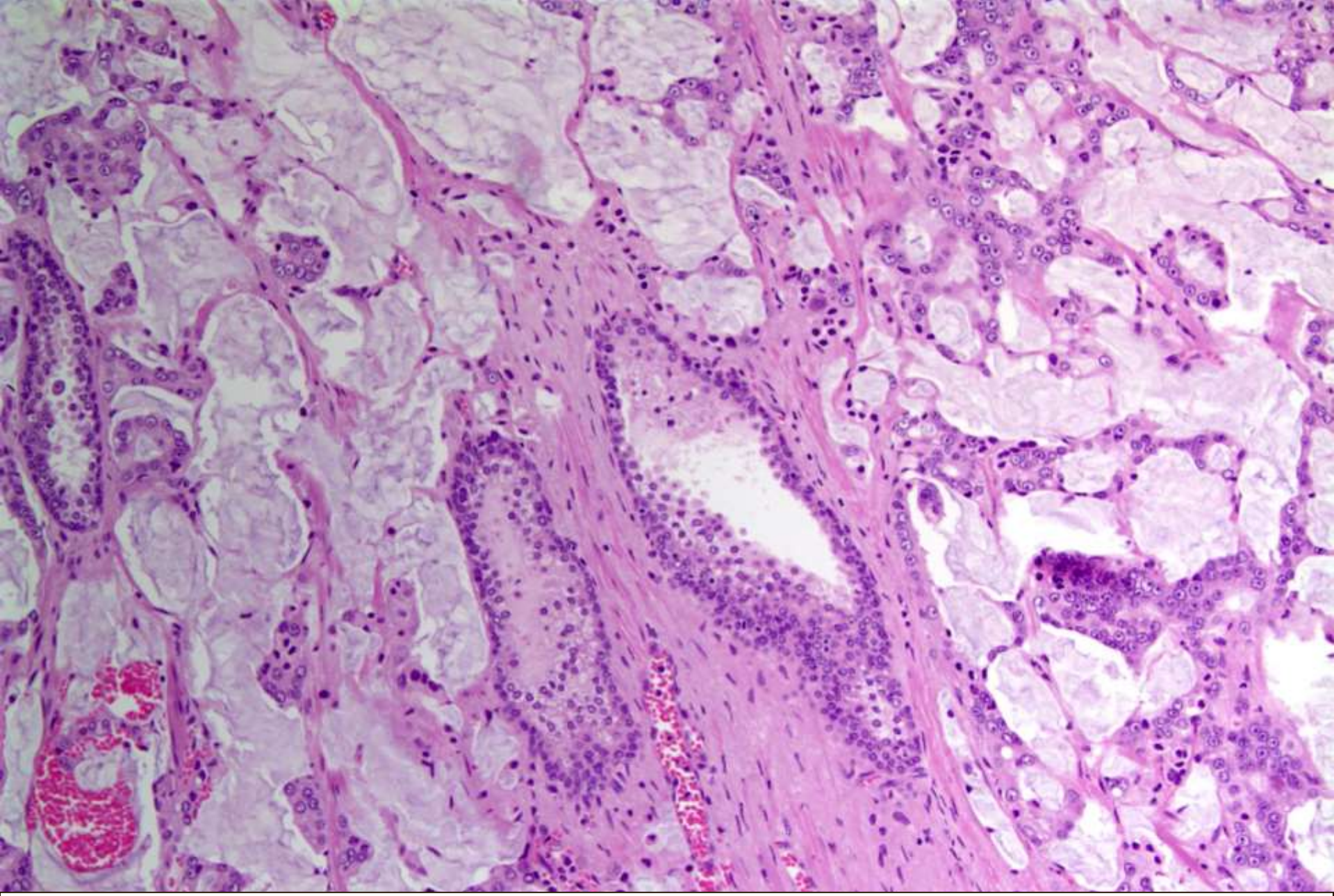
Crowded small well formed glands mimicking cribriform pattern 4



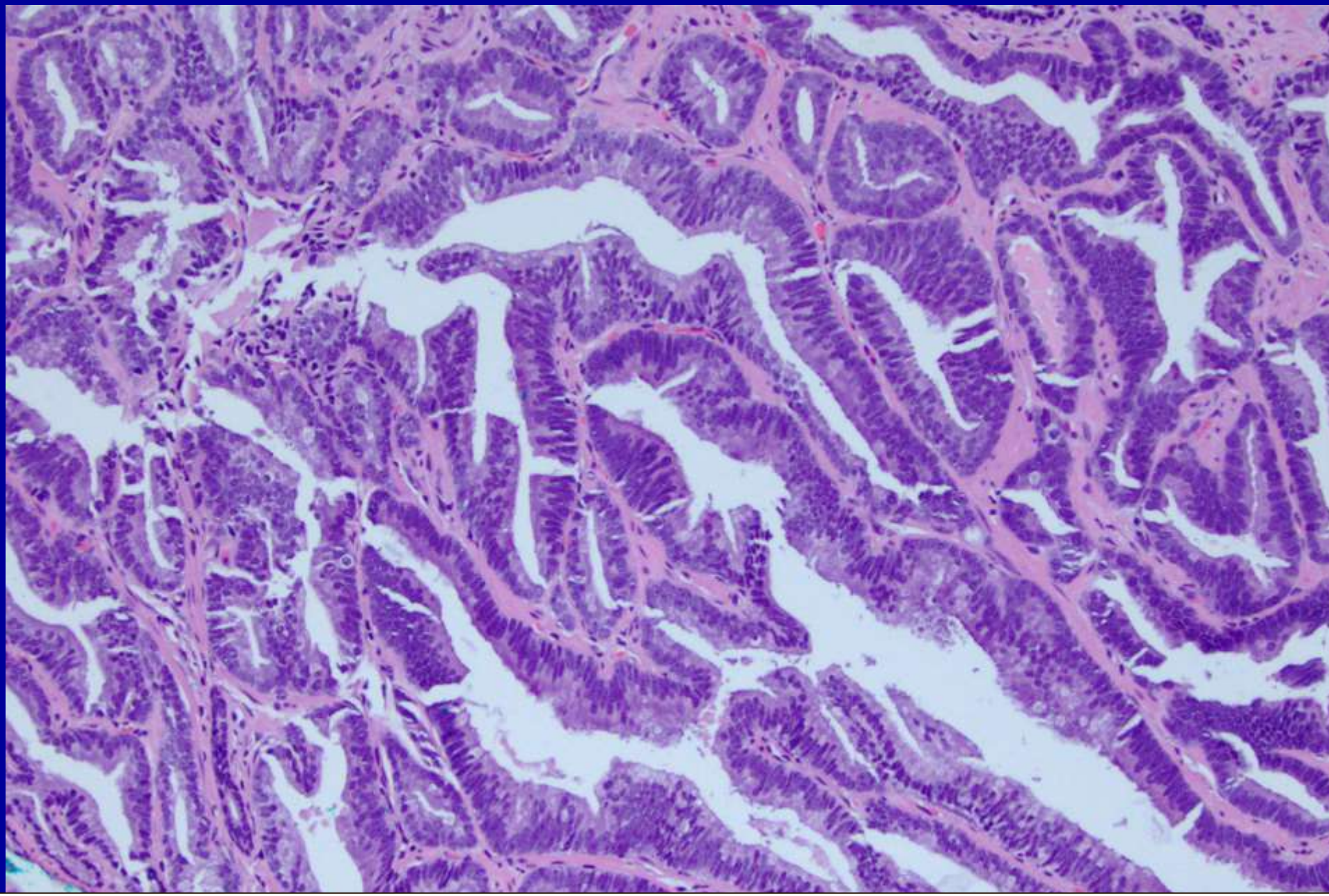
Telescoping (Gleason 3) mimicking Glomerulation pattern 4



Pseudopapillary pattern in Pseudohyperplastic PCA mimic pattern 4



Adenocarcinoma with mucinous differentiation – Grade based on architecture, Default grade is NOT Gleason pattern 4



PIN-like ductal without papillary or cribriform architecture is NOT Gleason pattern 4

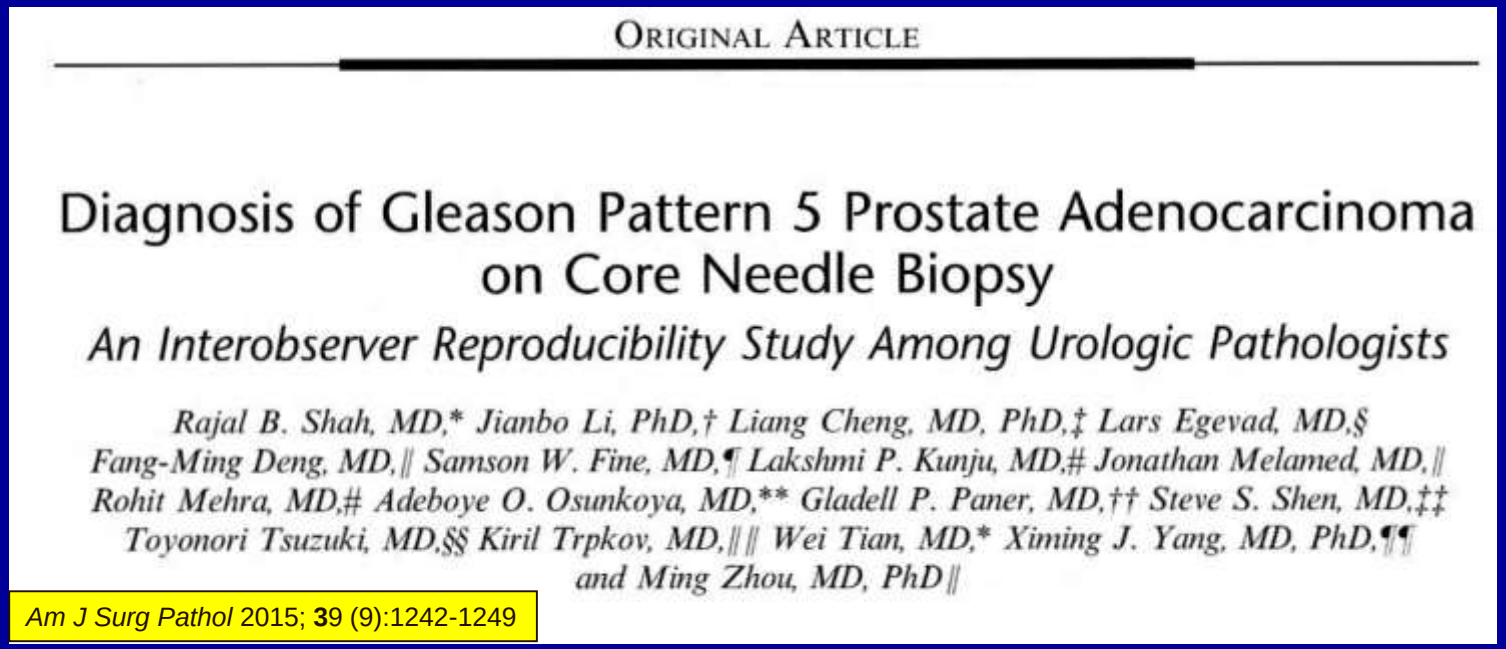
GLEASON PATTERN 5 IN CONTEMPORARY BIOPSY PRACTICE

- Morphologic subpatterns:
  - Infiltrating cords
  - Single cells
  - Solid Sheets
  - Comedocarcinoma
  - Linear arrays and solid nests
- Infiltrating cords and single cells most common; frequently co-exist
- Tertiary distribution most common presentation
- Pattern 5 under recognized in practice (Al-Hussain TO et al, Urology 2012;79:178-181)

Shah RB and Tadros Y. Hum Pathol 2014; 45:2263-2269

ISSUES WITH GLEASON PATTERN 5

- Solid nests: Size
- Single cells/cords:
  - Quantity
  - Topographic location (relationship with other pattern 4)
- Comedocarcinoma
  - True necrosis versus secretions
- Variant histology
  - Signet ring cell-like
  - Neuroendocrine differentiation



ORIGINAL ARTICLE

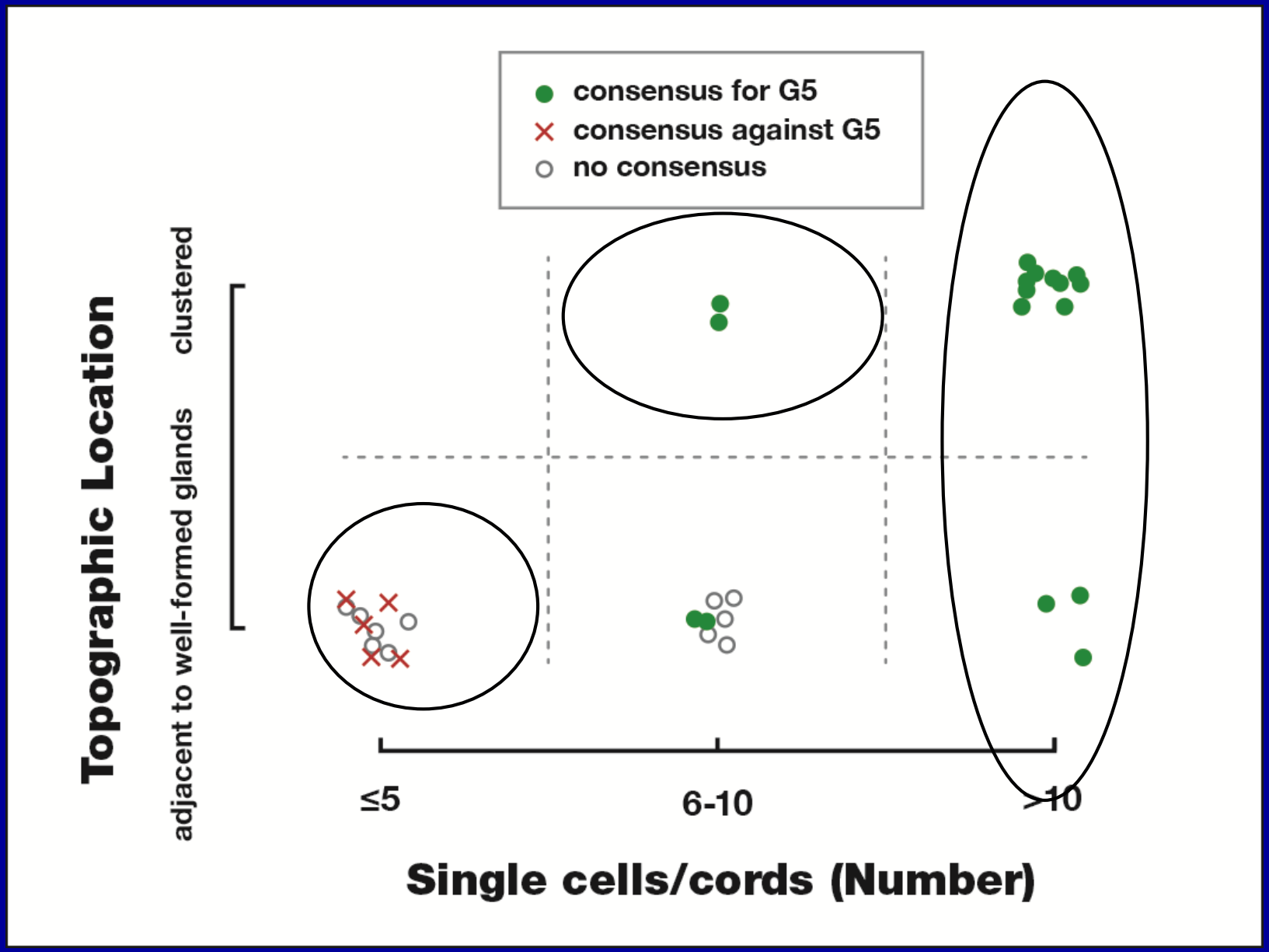
Diagnosis of Gleason Pattern 5 Prostate Adenocarcinoma on Core Needle Biopsy

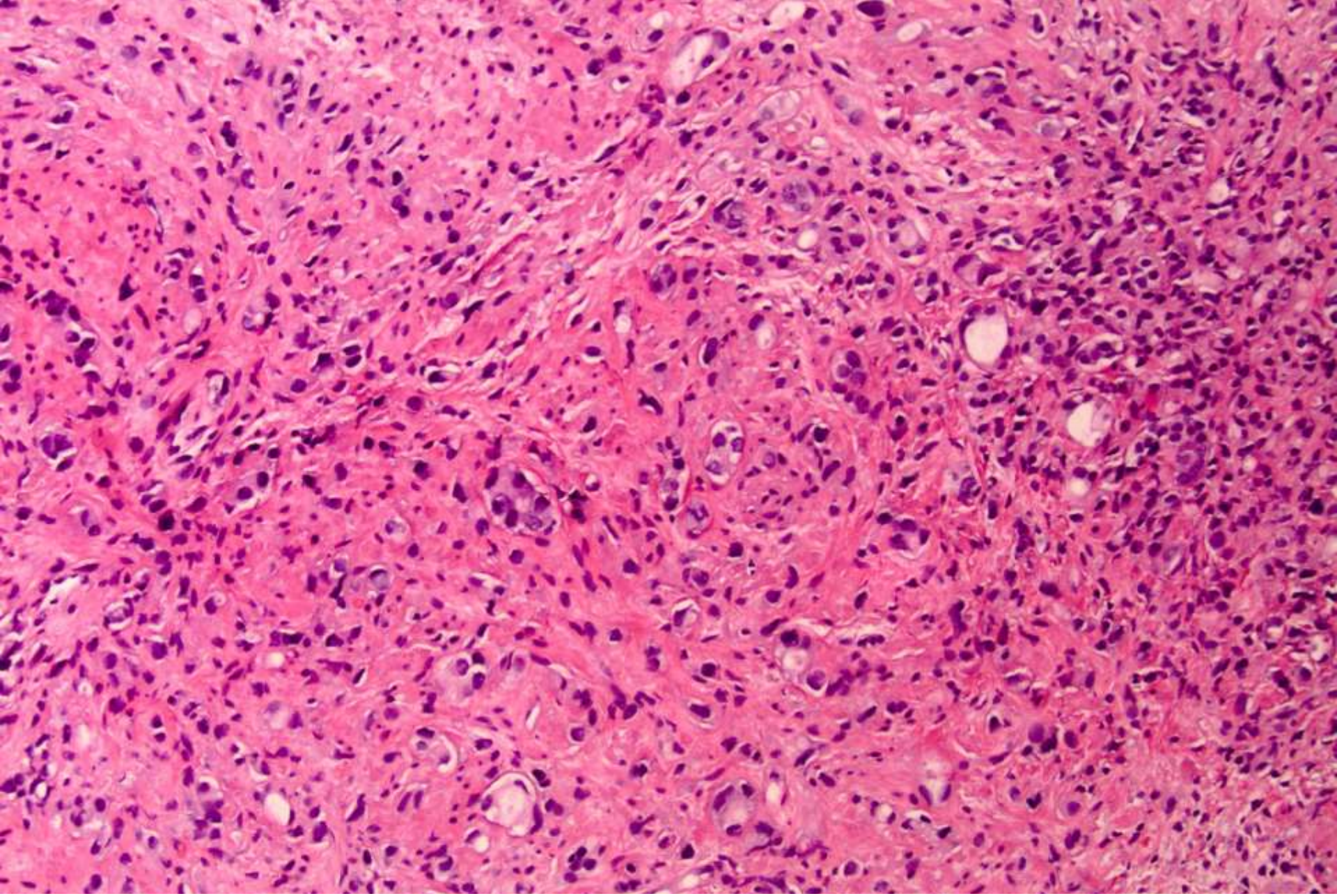
An Interobserver Reproducibility Study Among Urologic Pathologists

Rajal B. Shah, MD, Jianbo Li, PhD,† Liang Cheng, MD, PhD,‡ Lars Egevad, MD,§ Fang-Ming Deng, MD,‖ Samson W. Fine, MD,¶ Lakshmi P. Kunju, MD,# Jonathan Melamed, MD,‖ Rohit Mehra, MD,# Adeboye O. Osunkoya, MD,** Gladell P. Paner, MD,†† Steve S. Shen, MD,‡‡ Toyonori Tsuzuki, MD,§§ Kiril Trpkov, MD,‖‖ Wei Tian, MD,* Ximing J. Yang, MD, PhD,¶¶ and Ming Zhou, MD, PhD‖*

Am J Surg Pathol 2015; **3**9 (9):1242-1249

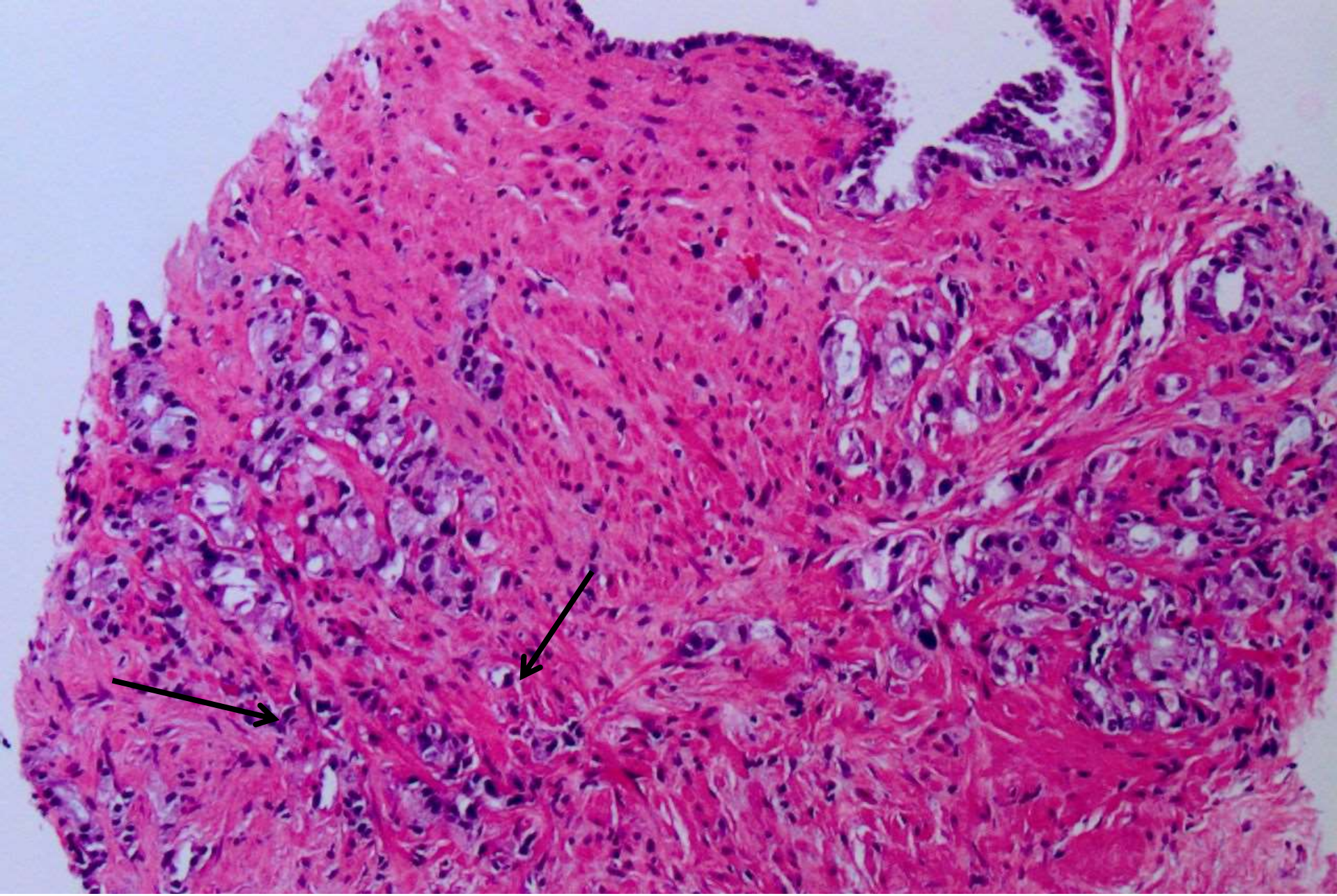
- Overall Kappa=0.376
- Among sub patterns, comedocarcinoma had highest reproducibility (k=0.499), followed by variant morphology (k=0.443), single cells/cords (k=0.369), and nests (k=0.347)
- Reproducibility improved when restrictive morphologic and quantitative criteria applied


consensus for G5
consensus against G5
no consensus
Topographic Location
adjacent to well-formed glands
clustered
≤5
6-10
>10
Single cells/cords (Number)



Prostate adenocarcinoma, Gleason score 5+4=9

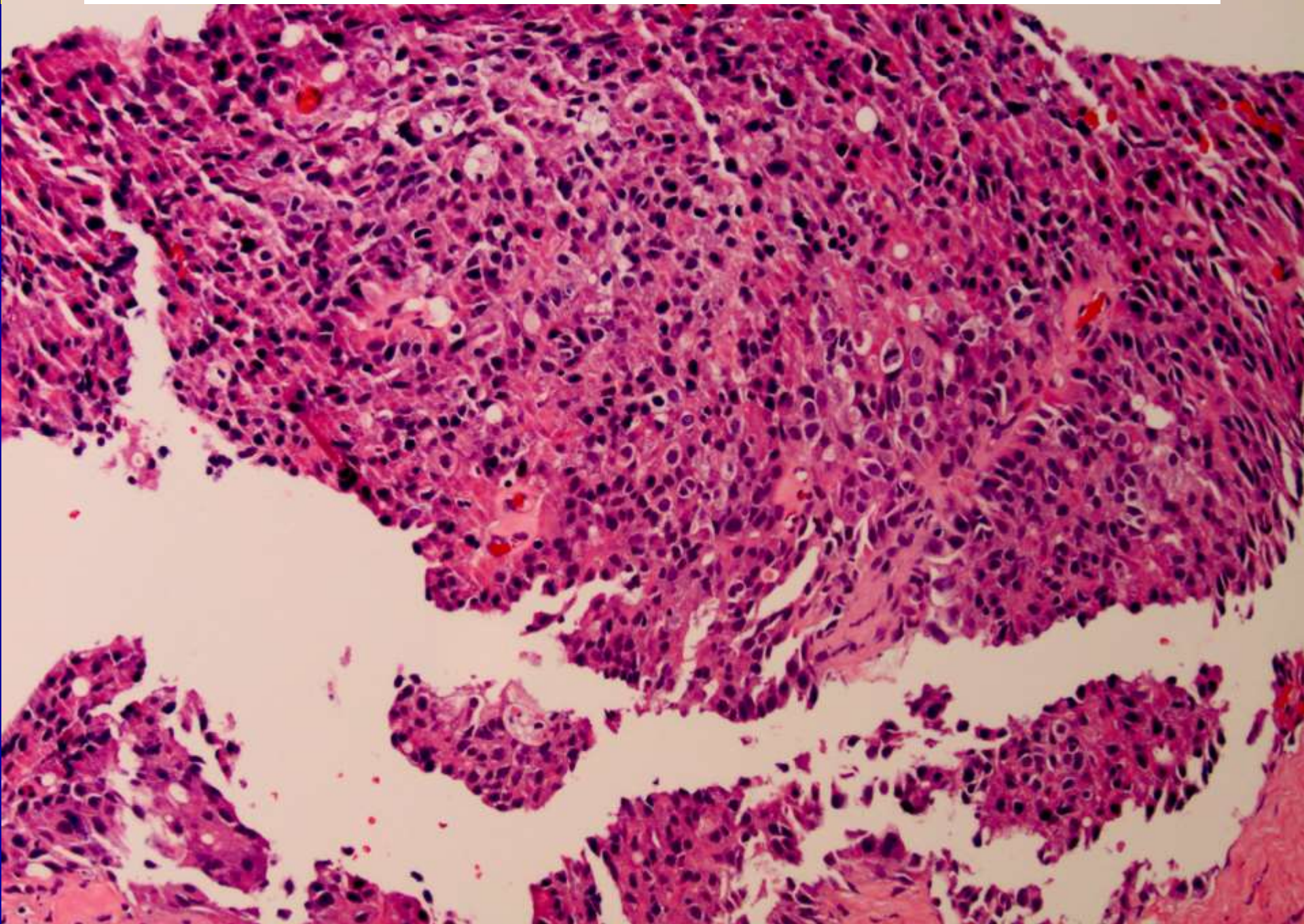
(Single cells/cords >10; clustered or intermixed with glands; Consensus for pattern 5)



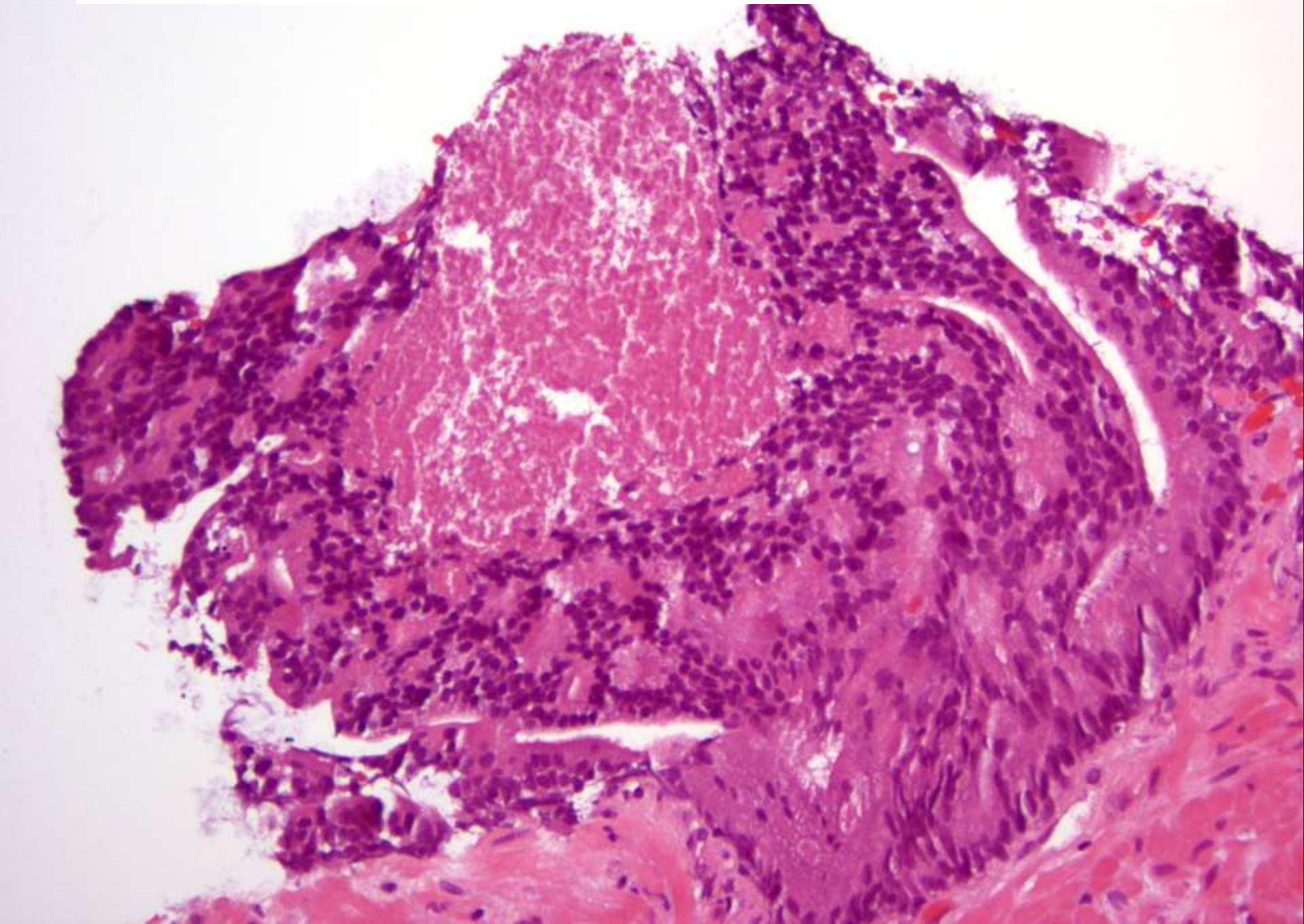
Case 4: Prostate adenocarcinoma, Gleason score 4+3=7

(Single cells/cords ≤5; Consensus against pattern 5)

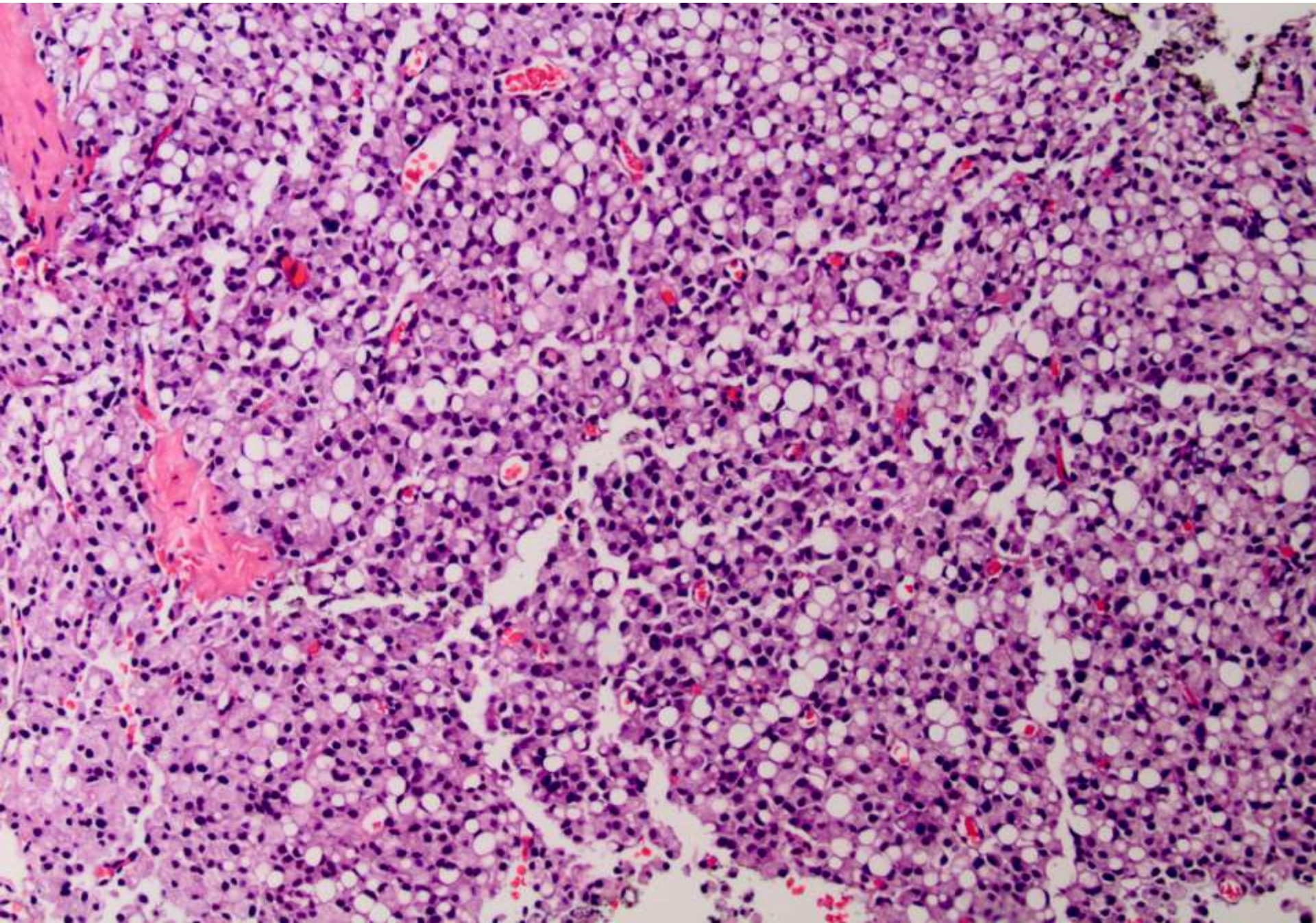
Large nests with or without glandular differentiation (Consensus for 5)



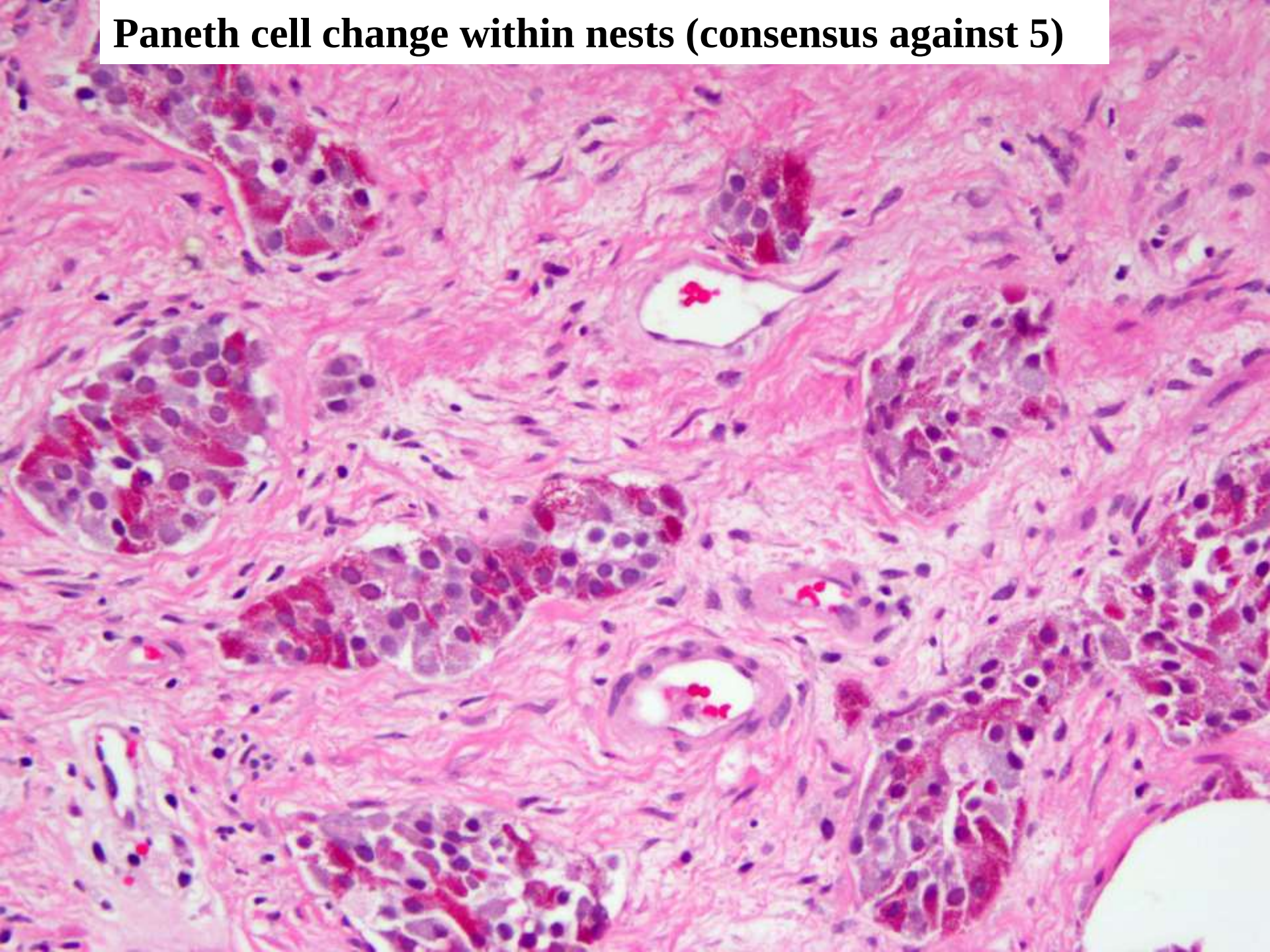
Comedonecrosis with or without karyorrhectic debris (Consensus for 5)



Signet ring cell-like cells in single cells or in nests (Consensus for 5)



Paneth cell change within nests (consensus against 5)



REPORTING

WHO 2016 RECOMMENDATION: REPORT % GLEASON PATTERN 4

- Percentage of high-grade pattern 4/5 proposed as significant prognosticator (JAMA 281;1395, 1999)
- Mainly tested in RP setting but recent studies show similar impact at biopsy
- May have implications for active surveillance and radiation therapy
- Can improve risk stratification even in 3+4 vs. 4+3 subsets of Gleason score 7
- Not established : increments to use

IMPACT OF LOW (< 10%) GLEASON 4 IN 3+4 PROSATE CANCER IN BIOPSY

- No/minimal impact of < 5% or 10% Gleason pattern 4 in 7s.
- Lack of significant risk of adverse pathology among Gleason 7 patients when G4% is 5% or 10%; however is markedly different when G4% reaches 20% (J Urol Feb 2016)
- 3+3=6 vs. 3+4=7 with ≤ 5% Gleason grade 4: No difference in pathologic findings in RP (AJSP 38:1096, 2014) and biochemical recurrence (Ann Diagn Pathol 20:48, 2016)

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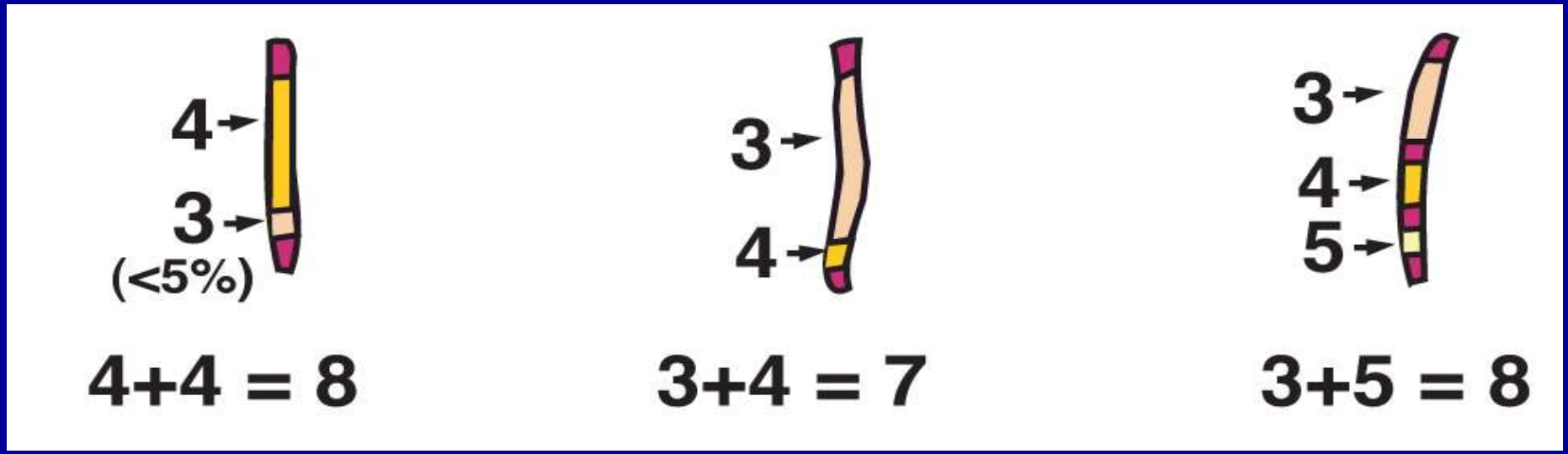
Presence of invasive cribriform or intraductal growth at biopsy outperforms percentage grade 4 in predicting outcome of Gleason score 3+4 = 7 prostate cancer

Charlotte F Kweldam[1], Intan P Kümmerlin[1], Daan Nieboer[2], Ewout W Steyerberg[2], Chris H Bangma[3], Luca Incrocci[4], Theodorus H van der Kwast[5], Monique J Roobol[3] and Geert J van Leenders[1]

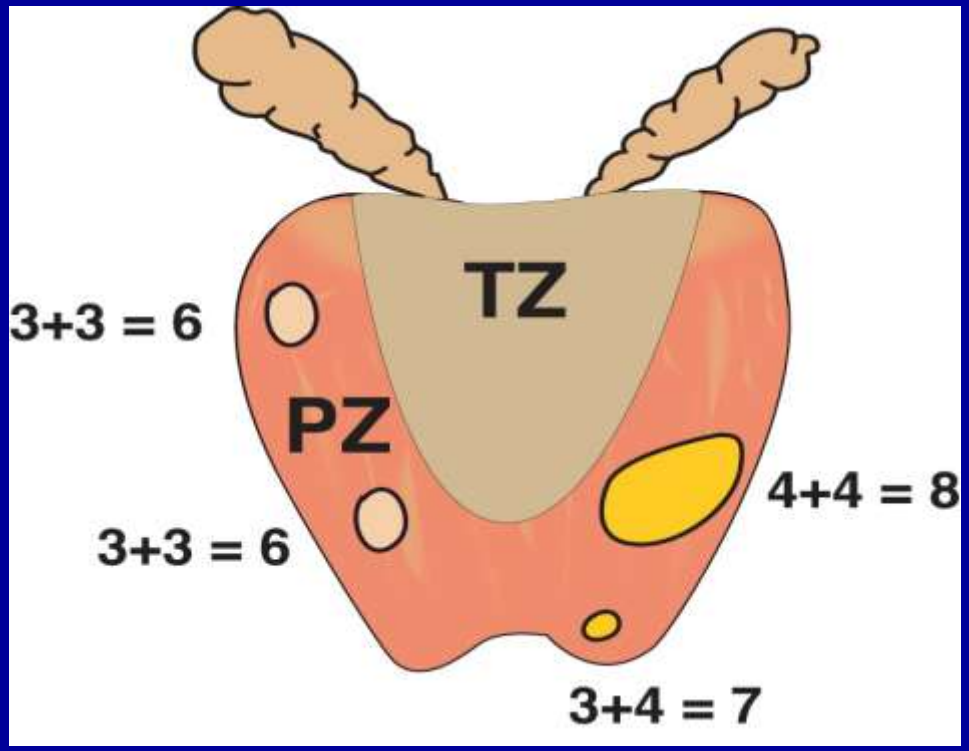
[1]Department of Pathology, Erasmus Medical Centre, Josephine Nefkens Institute, Rotterdam, The Netherlands; [2]Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands; [3]Department of Urology, Erasmus Medical Centre, Rotterdam, The Netherlands; [4]Department of Radiotherapy, Erasmus Medical Centre, Rotterdam, The Netherlands and [5]Laboratory Medicine Program, University Health Network, Toronto, ON, Canada

REPORTING IN NEEDLE BIOPSY:

1) Limited (<5%) secondary patterns of lower grade
2) Limited higher grade
3) Tertiary pattern of higher grade in needle biopsy



Multifocal cancer with different Gleason score is common

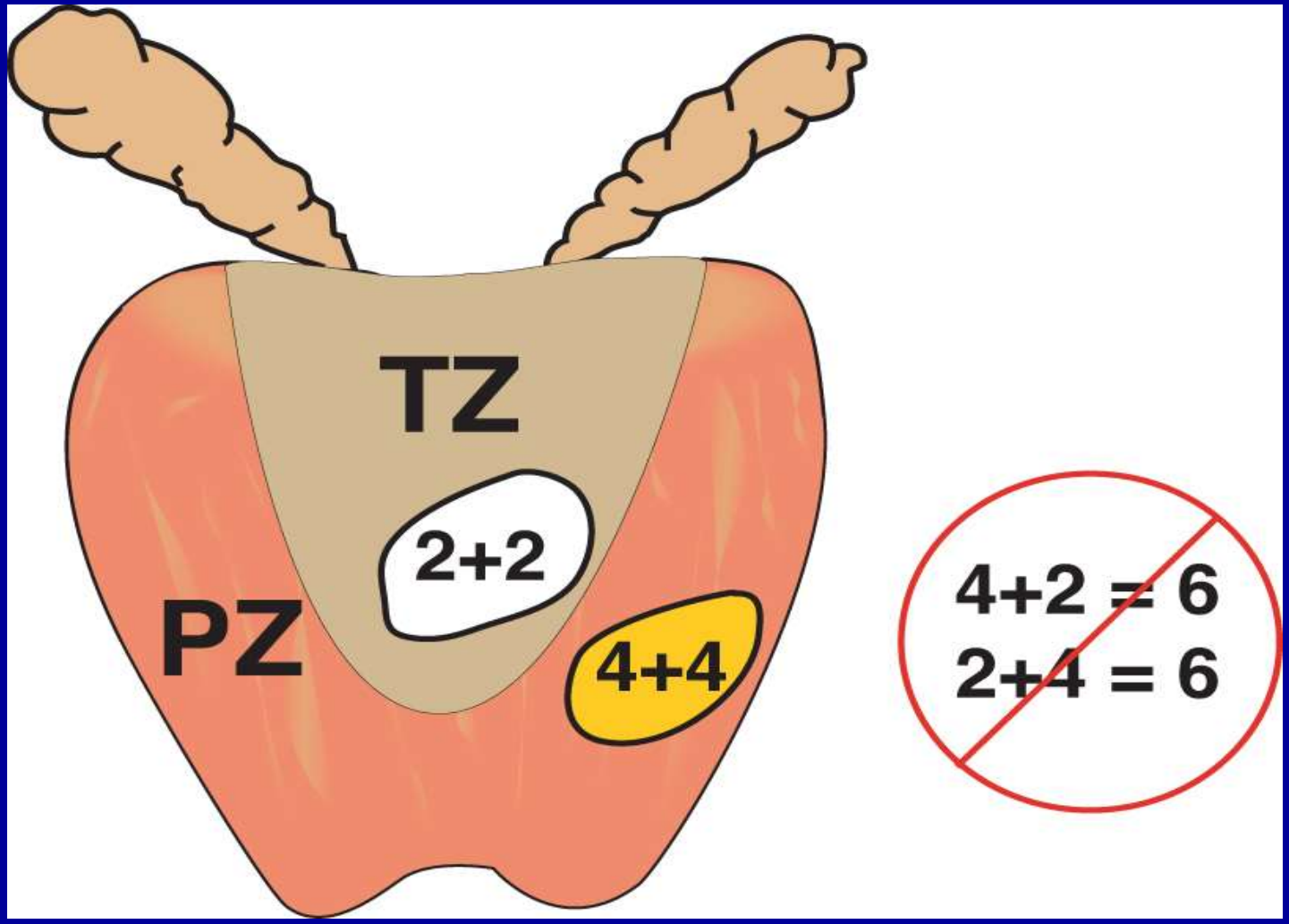


Dominant nodule (Index tumor) is reported.

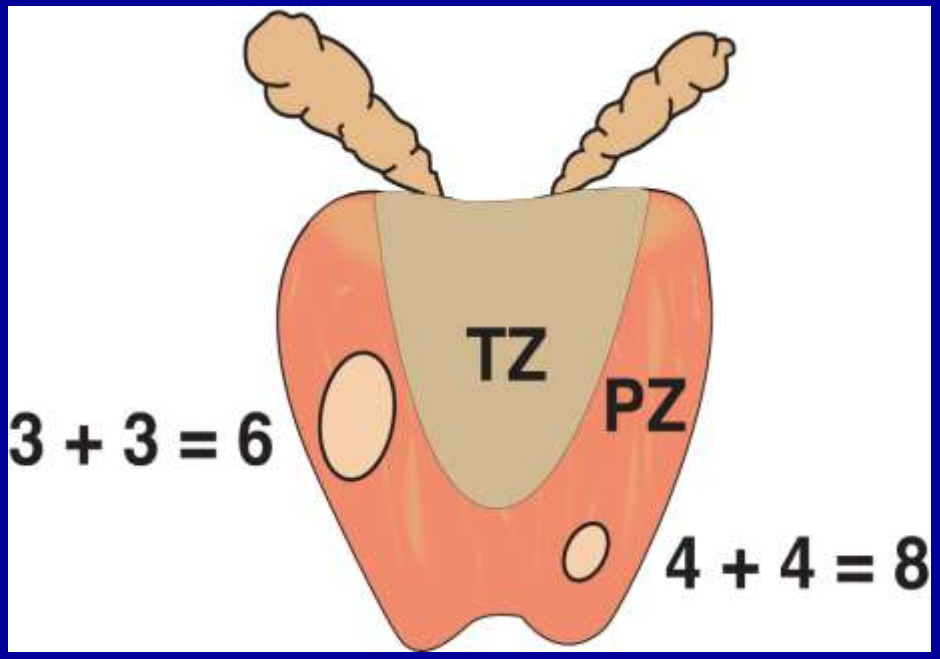
Not necessary to report small, organ-confined GS 3+3 foci

4+4=8 NOT 4+3=7

MULTIPLE DOMINANT NODULES



NON-DOMINANT NODULE OF HIGHER GRADE

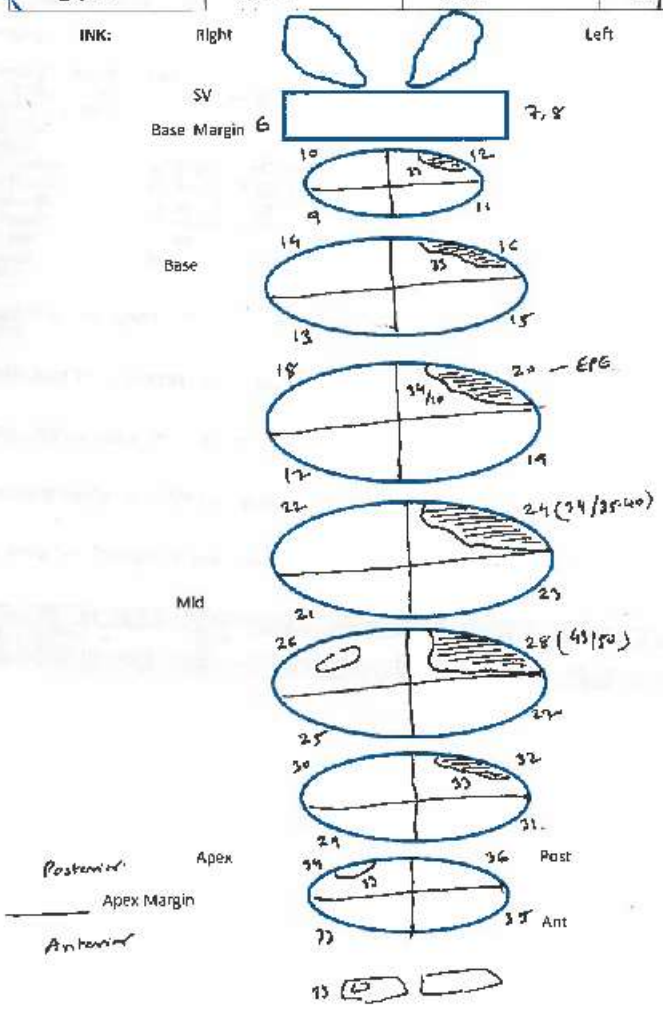


Multiple nodule with non-concurrent path parameters:

Each major tumor nodule should be graded separately

Two foci of cancer, 4+4=8 and 3+3=6. NOT 3+4=7

PROGENICS STUDY Site No	Subject No	Pathologist	Date reviewed
110	076	Shah	11/26/19

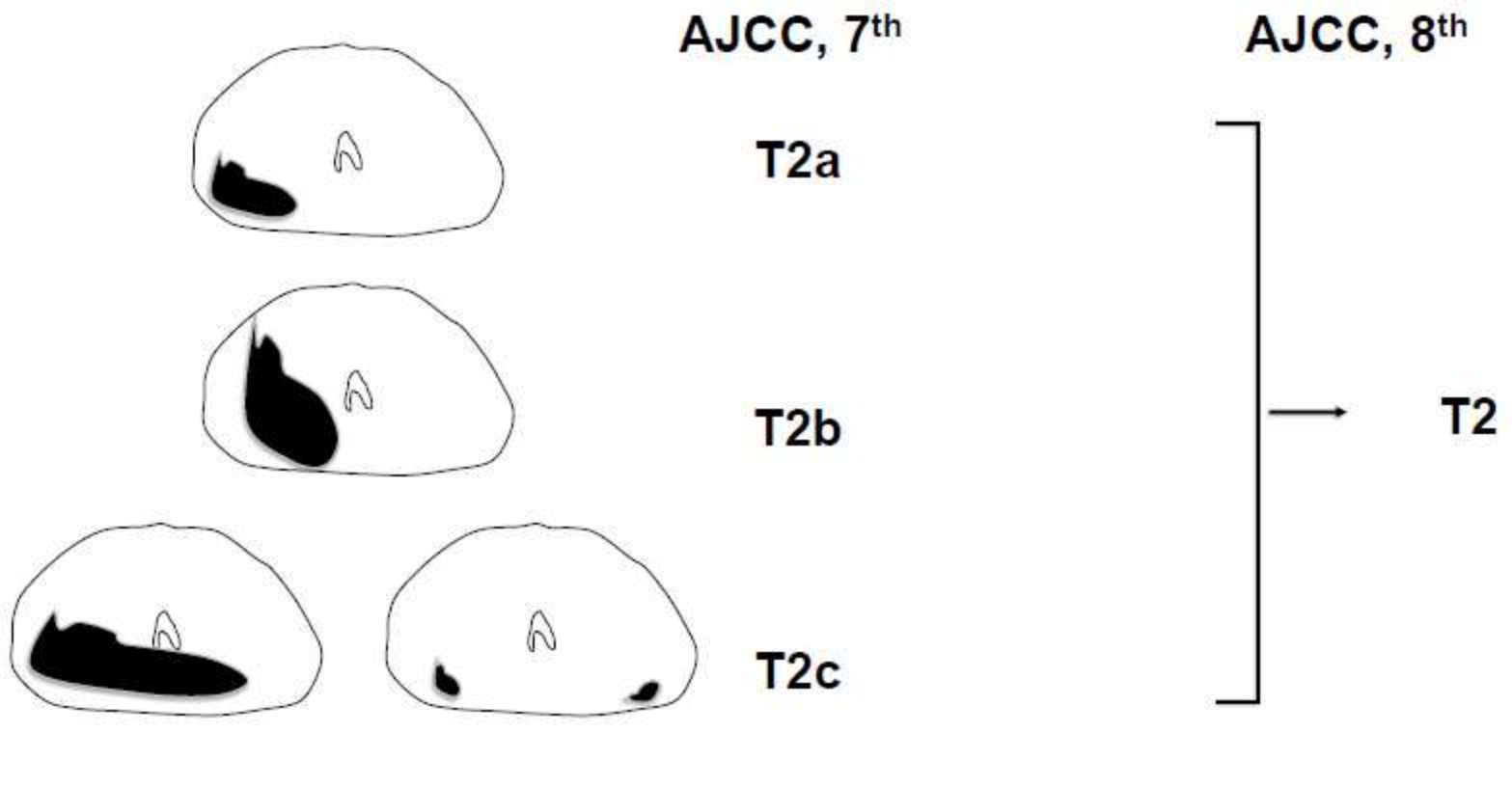


REPORTING TERTIARY GRADE/PATTERN IN RP

- Reporting approach different than biopsy
- Reported as tertiary pattern as long as higher than primary or secondary pattern
- Some experts consider tertiary pattern only <5% of tumor
- Some would assign it as tertiary pattern even it is >5% as long as the highest pattern is tertiary in quantity
- Both approaches are OK as long as understood by your urologists.

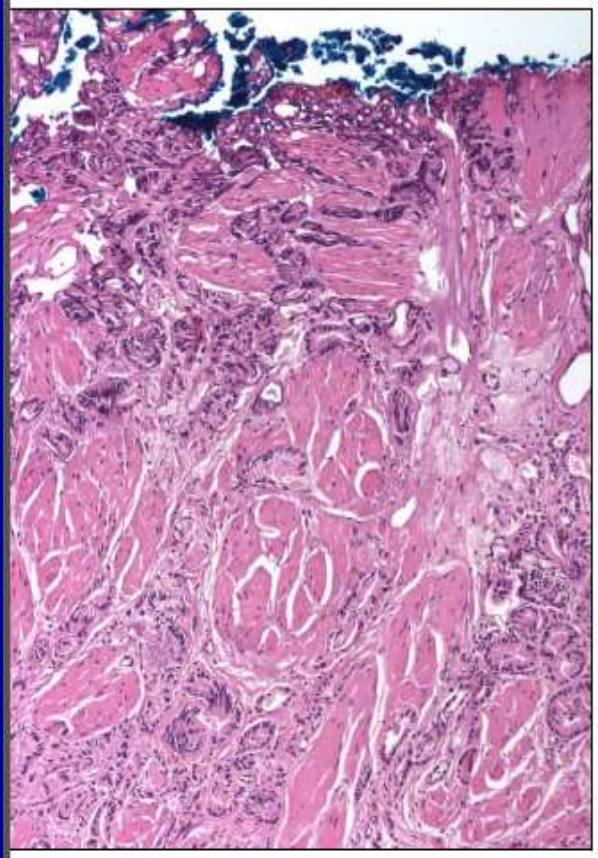
STAGING

STAGING: T2 SUBSTAGING



- Clinical stage T2 is considered as T2a-c based on DRE
- Pathological stage T2 is no longer substaged due to lack of prognostic significance

BLADDER NECK INVOLVEMENT

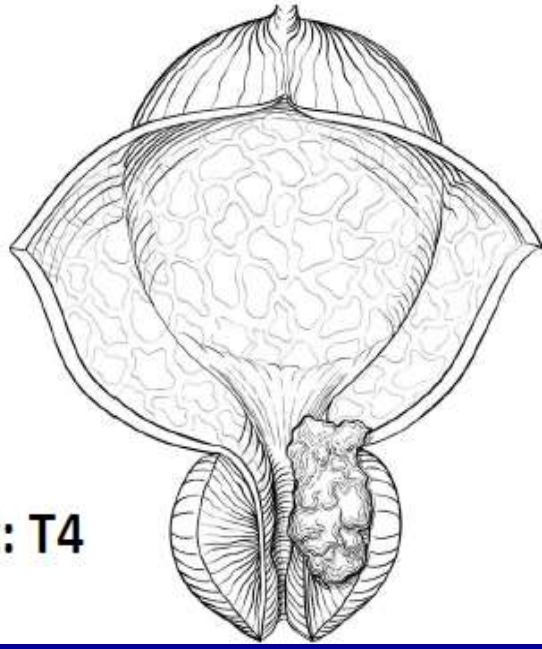


CAP

Microscopic bladder neck involvement

(Zhou M et al, Mod Pathol, 2009)

- ✓ Presence of cancer glands within smooth muscle bundles of coned bladder neck without benign prostate glands
- ✓ Staged as pT3a, not pT4



Gross bladder neck involvement: T4

GLEASON GRADE/GROUP IMPORTANT PART OF STAGING

TABLE 4. American Joint Committee on Cancer Prognostic Stage Grouping[a]

WHEN T IS...	AND N IS...	AND M IS...	AND PSA IS...	AND GRADE GROUP IS...	THEN THE STAGE GROUP IS...
cT1a-c, cT2a	N0	M0	<10 ng/mL	1	I
pT2	N0	M0	<10 ng/mL	1	I
cT1a-c, cT2a	N0	M0	≥10, <20 ng/mL	1	IIA
pT2	N0	M0	≥10, <20 ng/mL	1	IIA
cT2b-c	N0	M0	<20 ng/mL	1	IIA
T1-2	N0	M0	<20 ng/mL	2	IIB
T1-2	N0	M0	<20 ng/mL	3	IIC
T1-2	N0	M0	<20 ng/mL	4	IIC
T1-2	N0	M0	≥20 ng/mL	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any	M1	Any	Any	IVB

Abbreviation: PSA indicates prostate-specific antigen. [a]Note that, when either PSA or grade group is not available, grouping should be determined by T category and/or either PSA or grade group, as available.

TAKE HOME MESSAGES

- Report intraductal carcinoma; do not grade
- Report the presence or absence of cribriform Gleason pattern 4
- Gleason grade and Grade groups are both required for reporting
- % pattern 4 should be reported for Gleason 7 carcinoma
- Further optimization of grade groups is expected

TAKE HOME MESSAGES

- In needle biopsy when tertiary pattern is higher than primary or secondary, it should be included in final GS as secondary pattern; No specific recommendation for radical prostatectomy
- Radical prostatectomy with multiple tumors: dominant tumor is reported; for non-dominant nodule of higher grade, each major tumor graded separately
- pT2 is no longer substaged into T2a-c

Cleveland Clinic

Every life deserves world class care.