Intraductal Lesions of the Prostate

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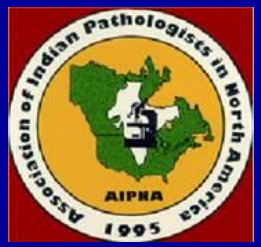
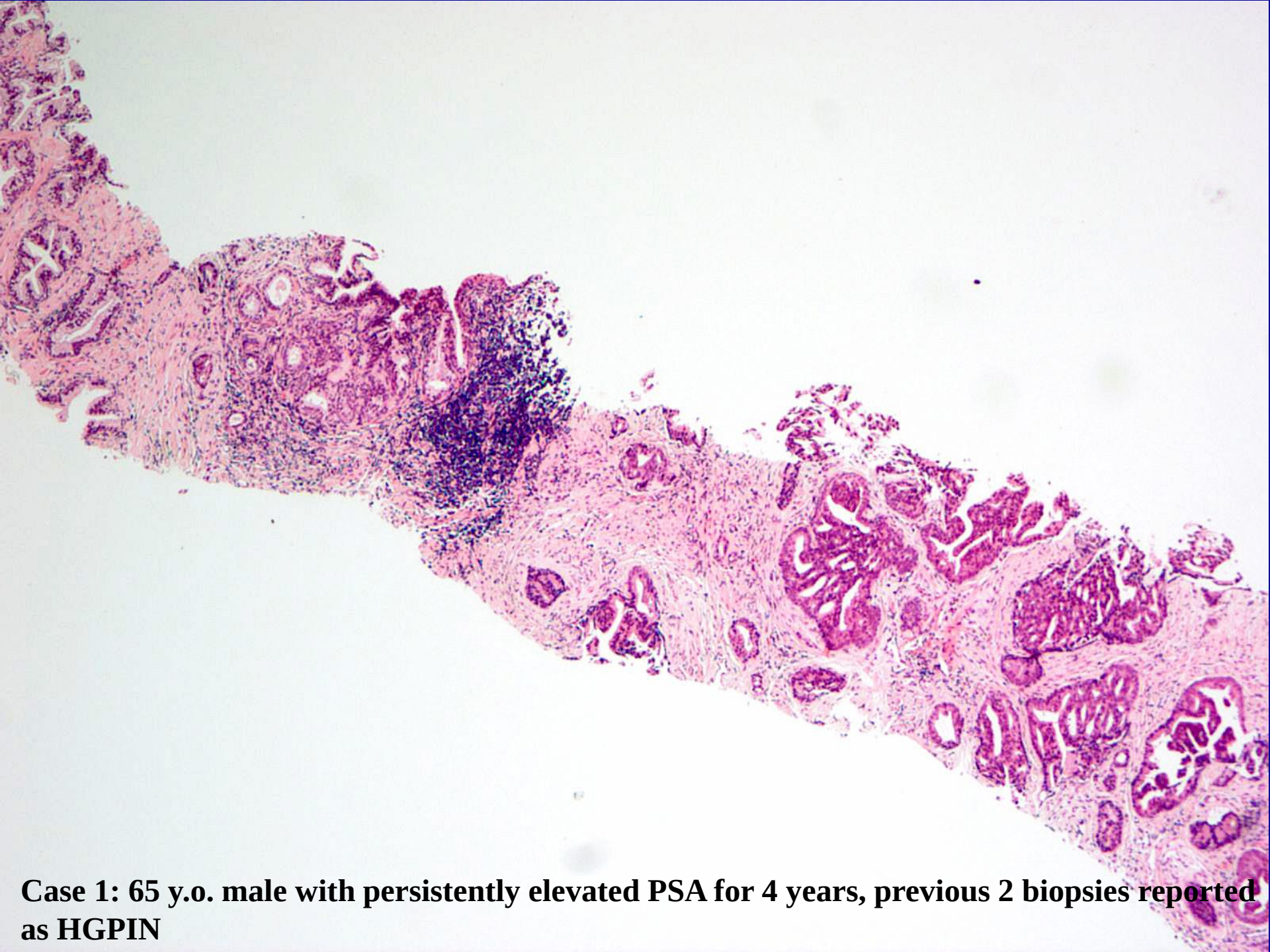
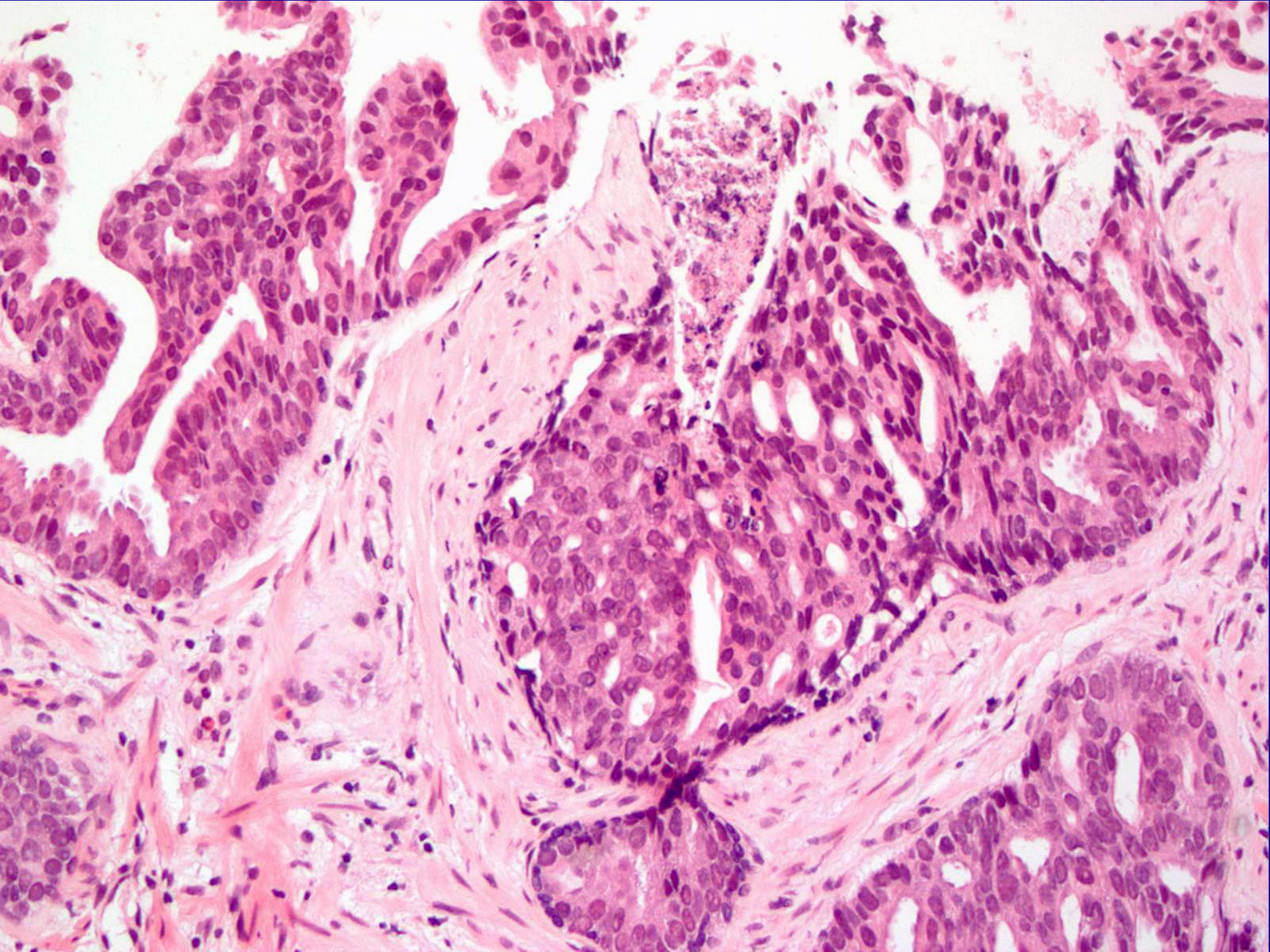


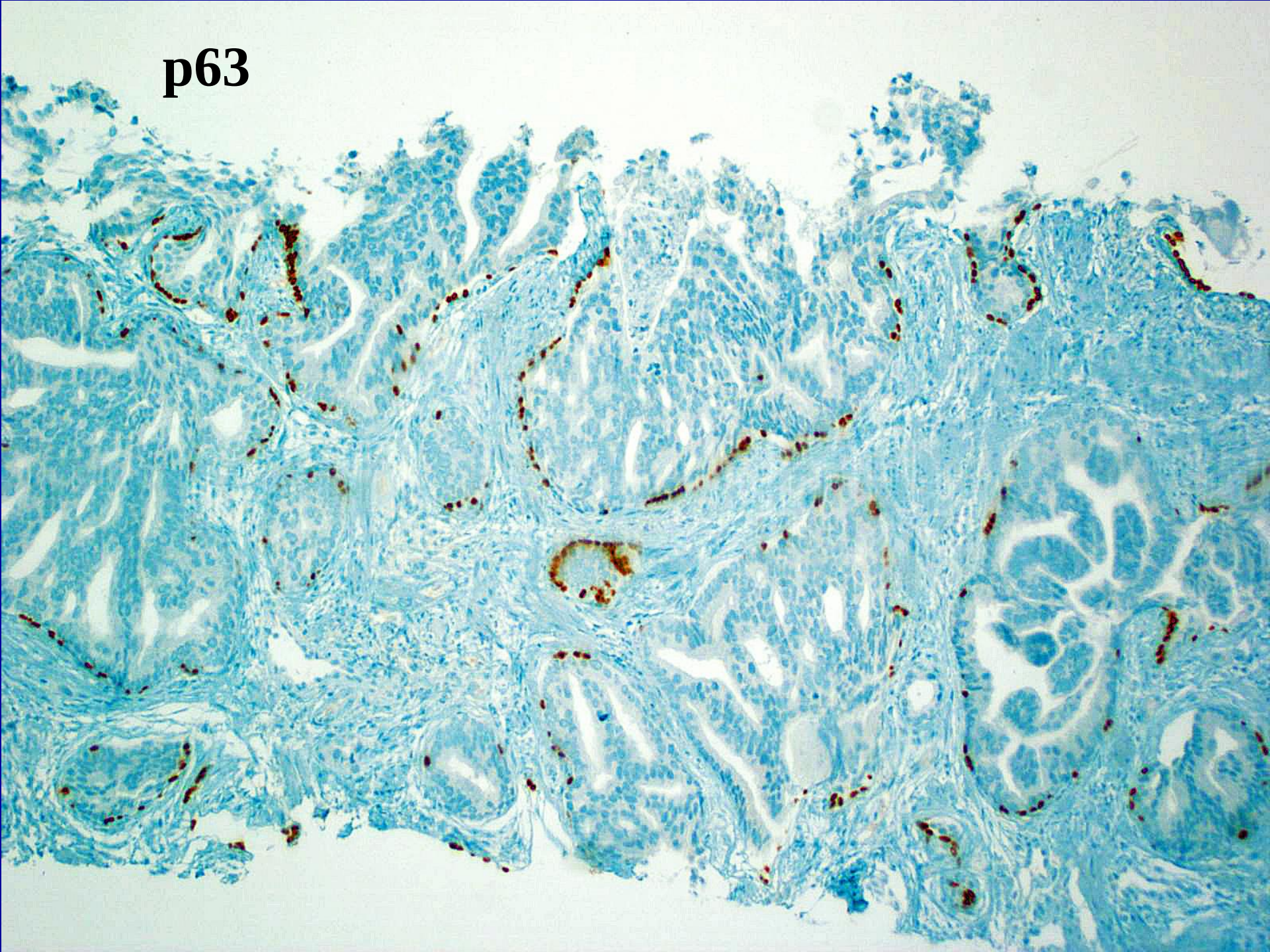


Case 1: 65 y.o. male with persistently elevated PSA for 4 years, previous 2 biopsies reported as HGPIN



Diagnosis

- Invasive cribriform prostatic carcinoma
- Ductal adenocarcinoma of the prostate
- Cribriform high grade PIN
- Atypical intraductal proliferation
- Intraductal carcinoma of the prostate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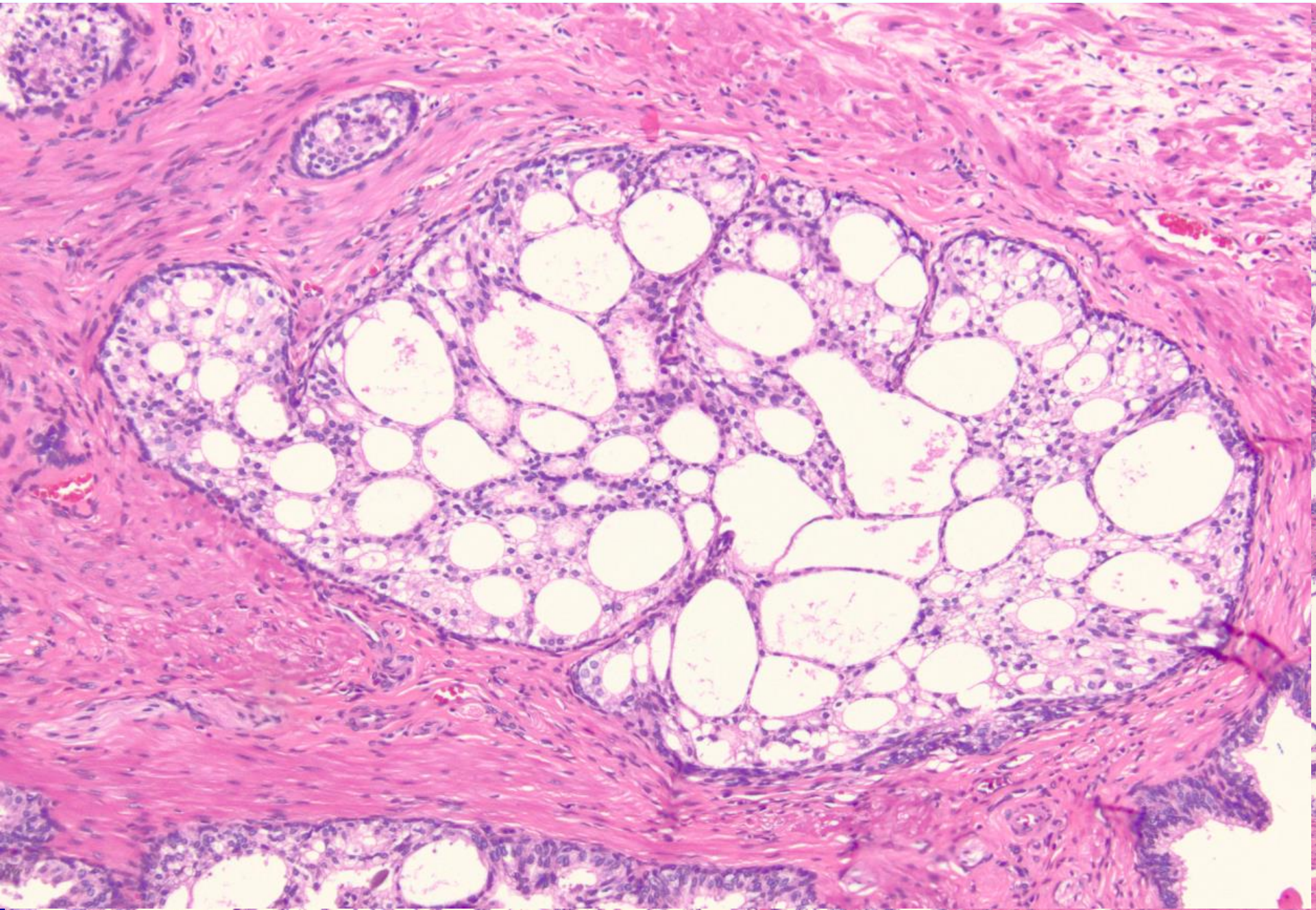
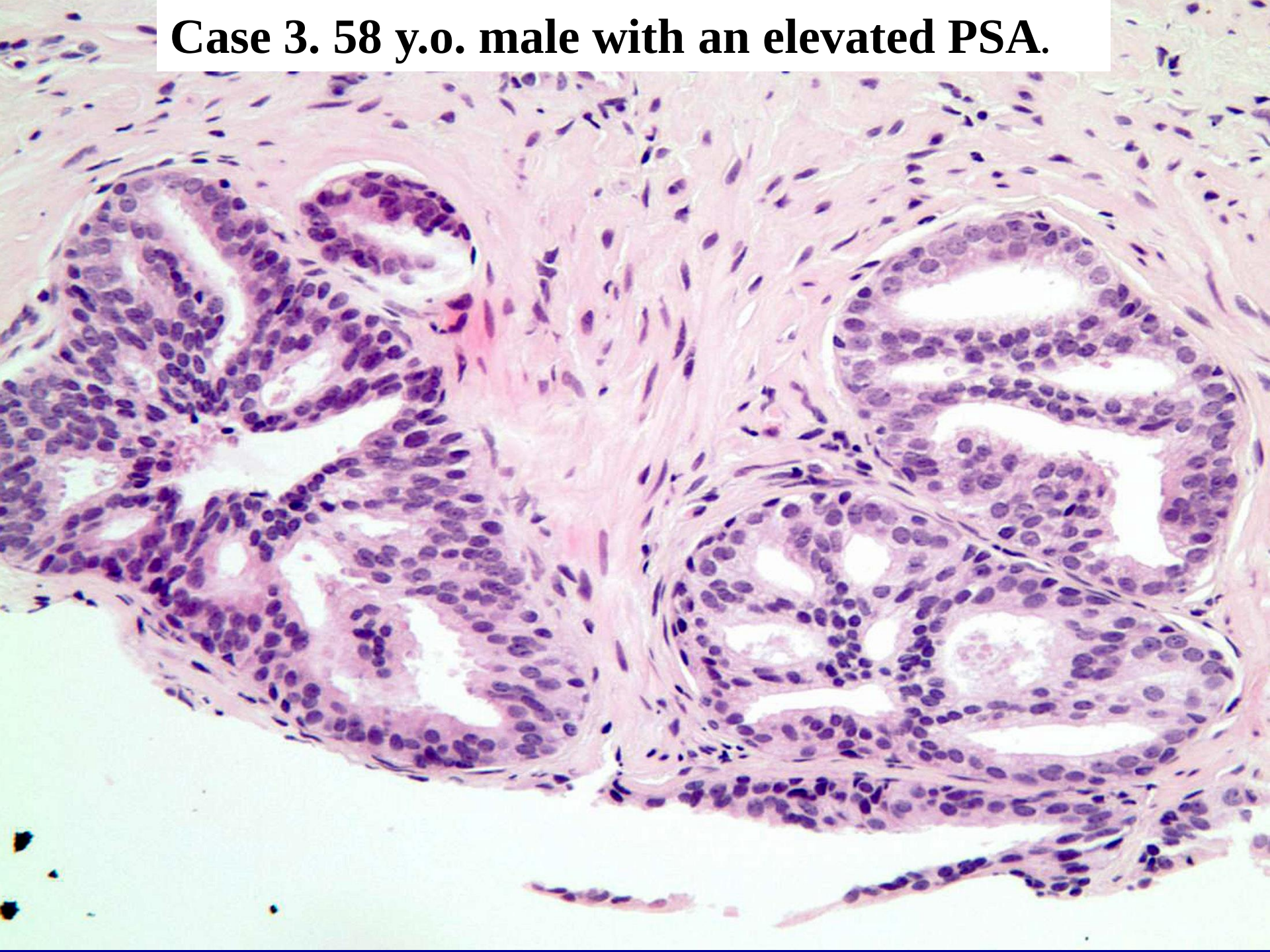
Case 2: 60 y.o. male with urinary obstruction. He underwent TURP



Diagnosis

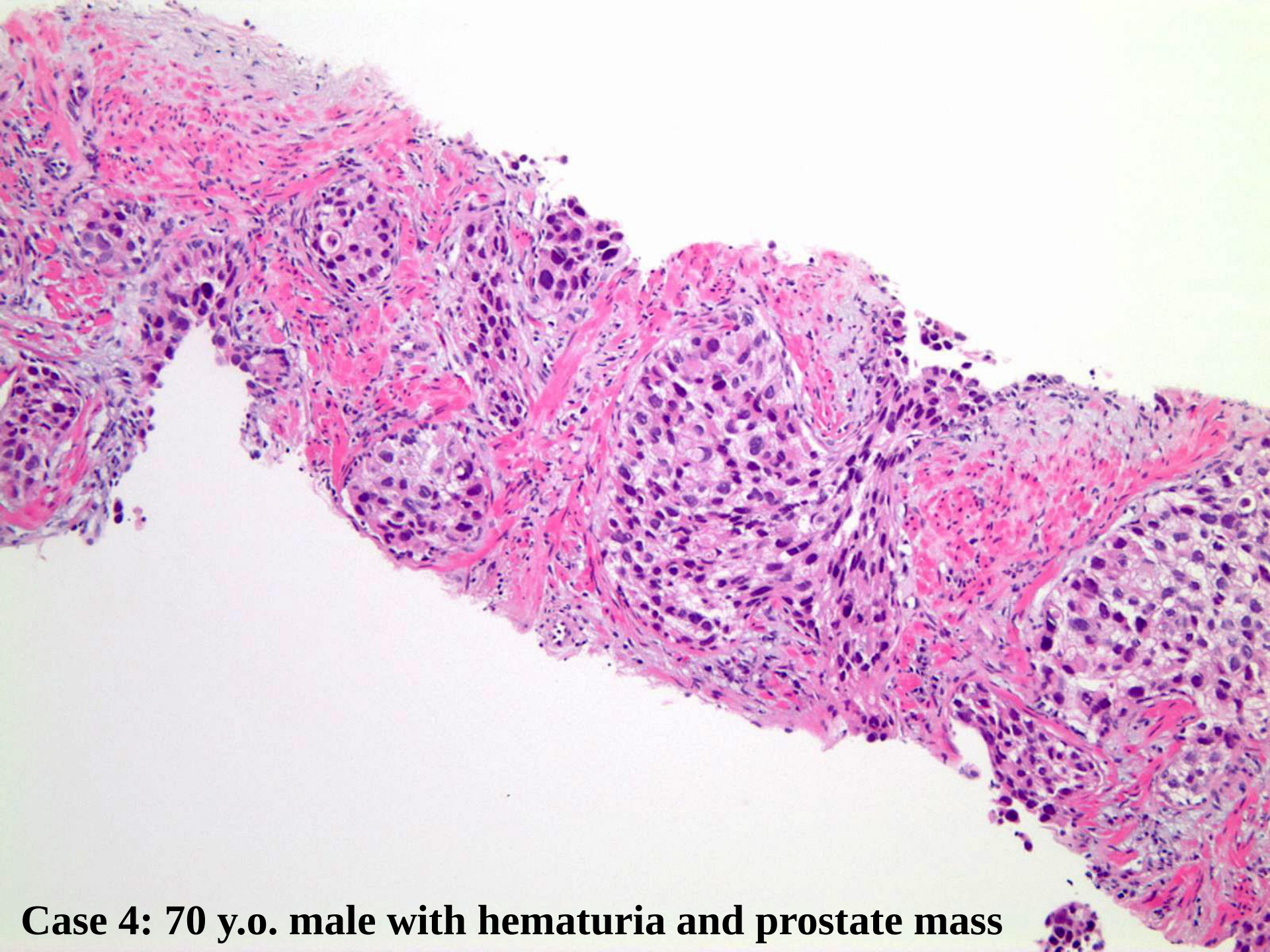
- Cribriform HGPIN
- Intraductal carcinoma (IDC-P)
- Clear cell cribriform hyperplasia
- Prostate adenocarcinoma, Gleason score 4+4, GG 4

Case 3. 58 y.o. male with an elevated PSA.

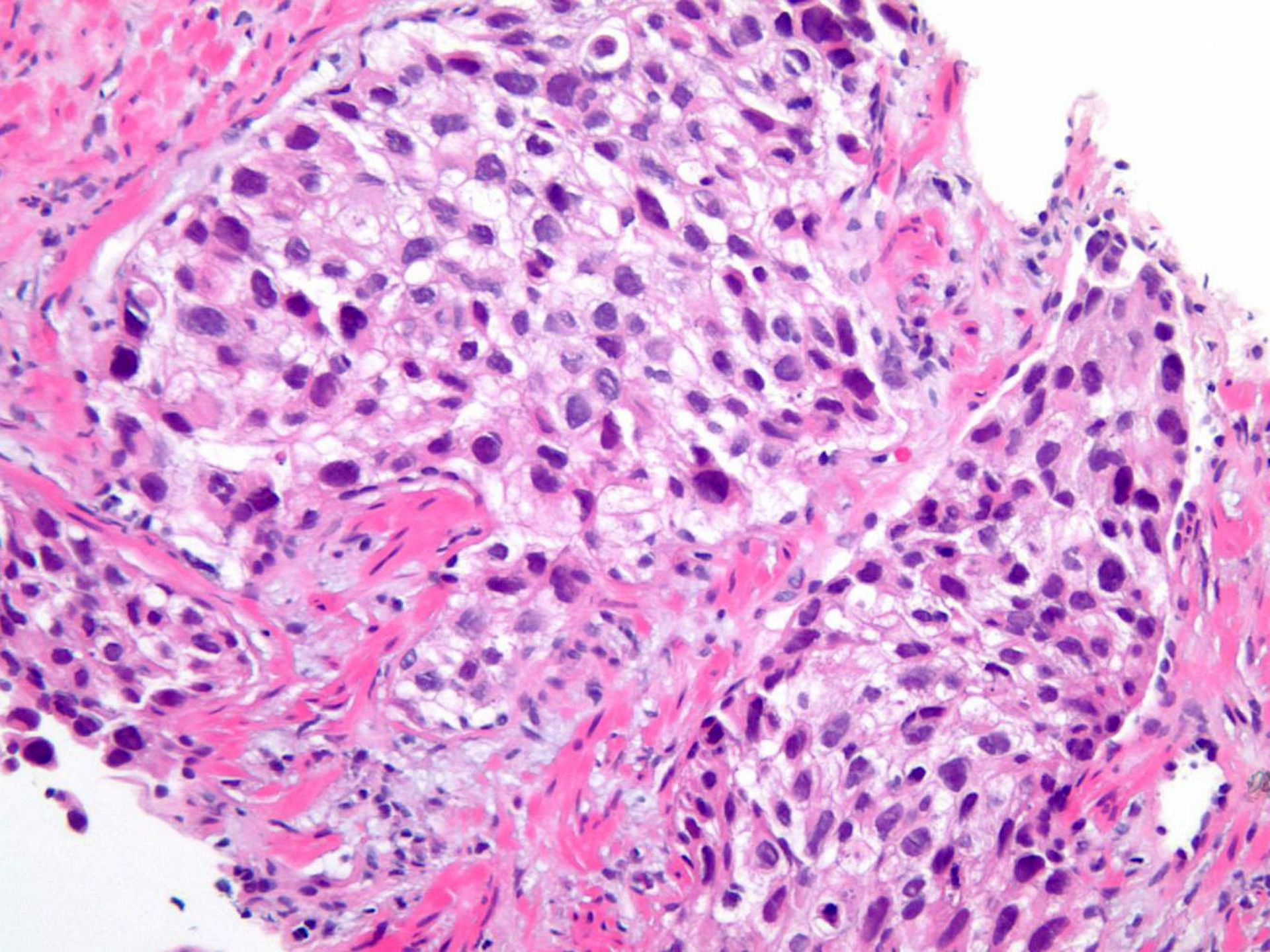


Diagnosis

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



Case 4: 70 y.o. male with hematuria and prostate mass



Diagnosis

- Prostate adenocarcinoma, Gleason score 5+5=10, Grade group 5
- Intraductal carcinoma (IDC-P)
- High grade urothelial carcinoma with intraductal spread
- Basal cell hyperplasia

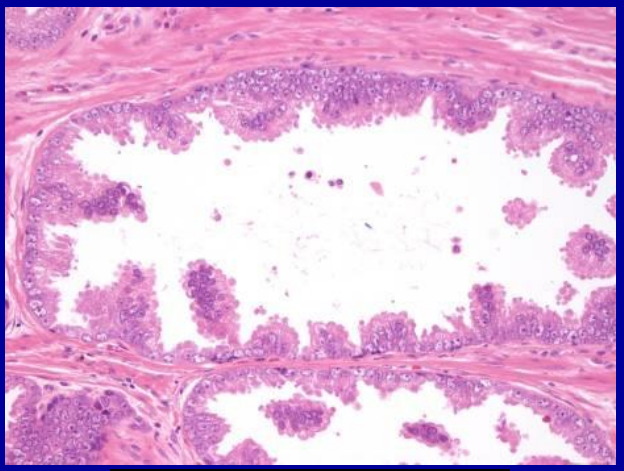
Intraductal Lesions of the Prostate: Definition

- Cellular proliferation limited to the gland
- Basal cells are at least partially preserved
- Cytology of proliferating cells may range from benign, atypical to frankly malignant

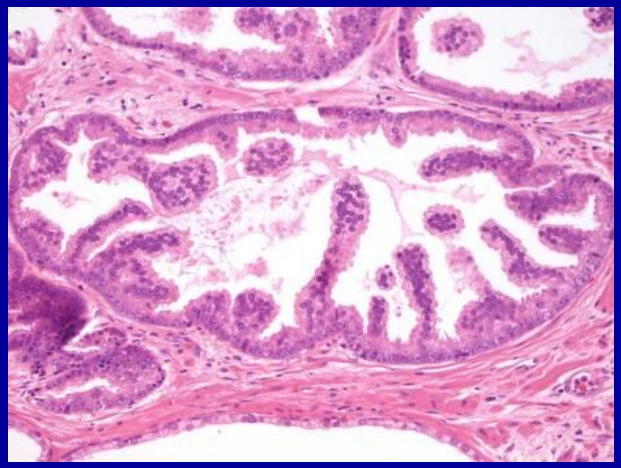
Intraductal Lesions of the Prostate: Spectrum

Benign	Premalignant	Suspicious	Malignant
• Central zone glands • Clear cell cribriform hyperplasia	• HGPIN	• Atypical intraductal proliferation	• Intraductal carcinoma • Ductal adenocarcinoma • Urothelial carcinoma

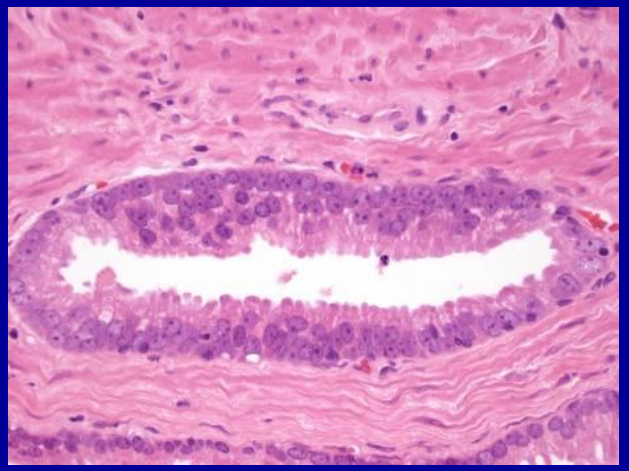
Intraductal Lesions: Major Architectural Patterns



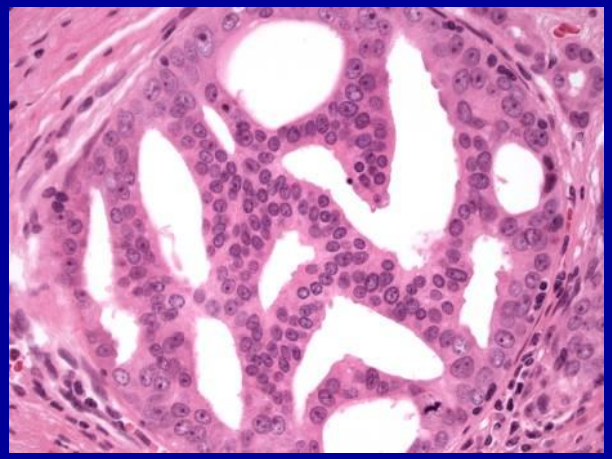
Tufting



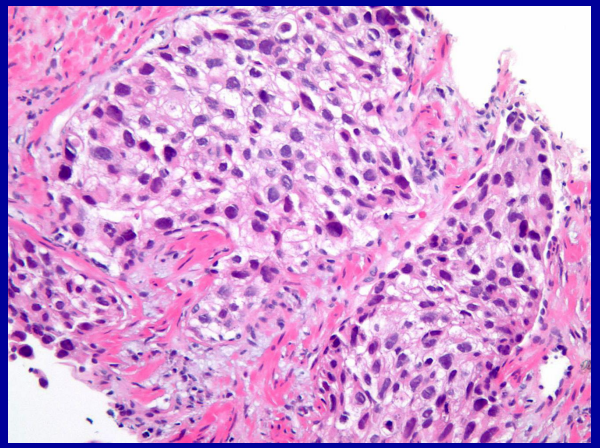
Micropapillary



Flat



Cribriform



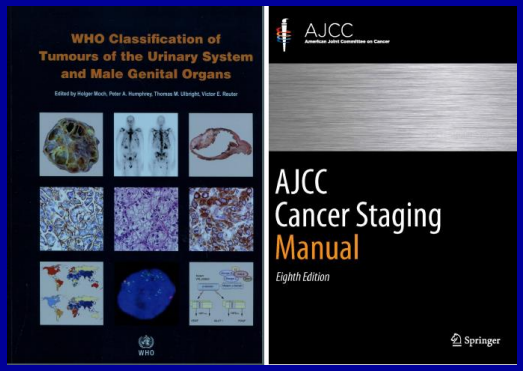
Solid

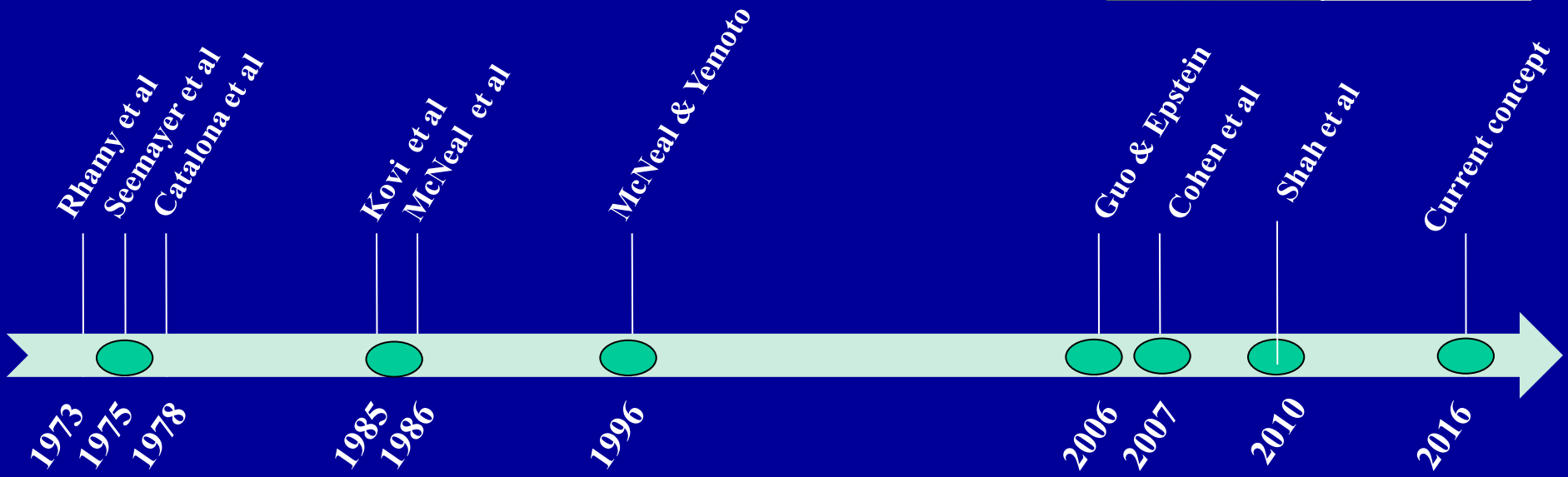
Intraductal Carcinoma of the Prostate (IDC-P)

Current Perspective

-IDC-P refers to expansile, lumen- spanning proliferation of prostate cancer cells within prostatic ducts and acini caused by the retrograde spread of high-grade PCa cells

- A distinct entity in the 2016 WHO blue book



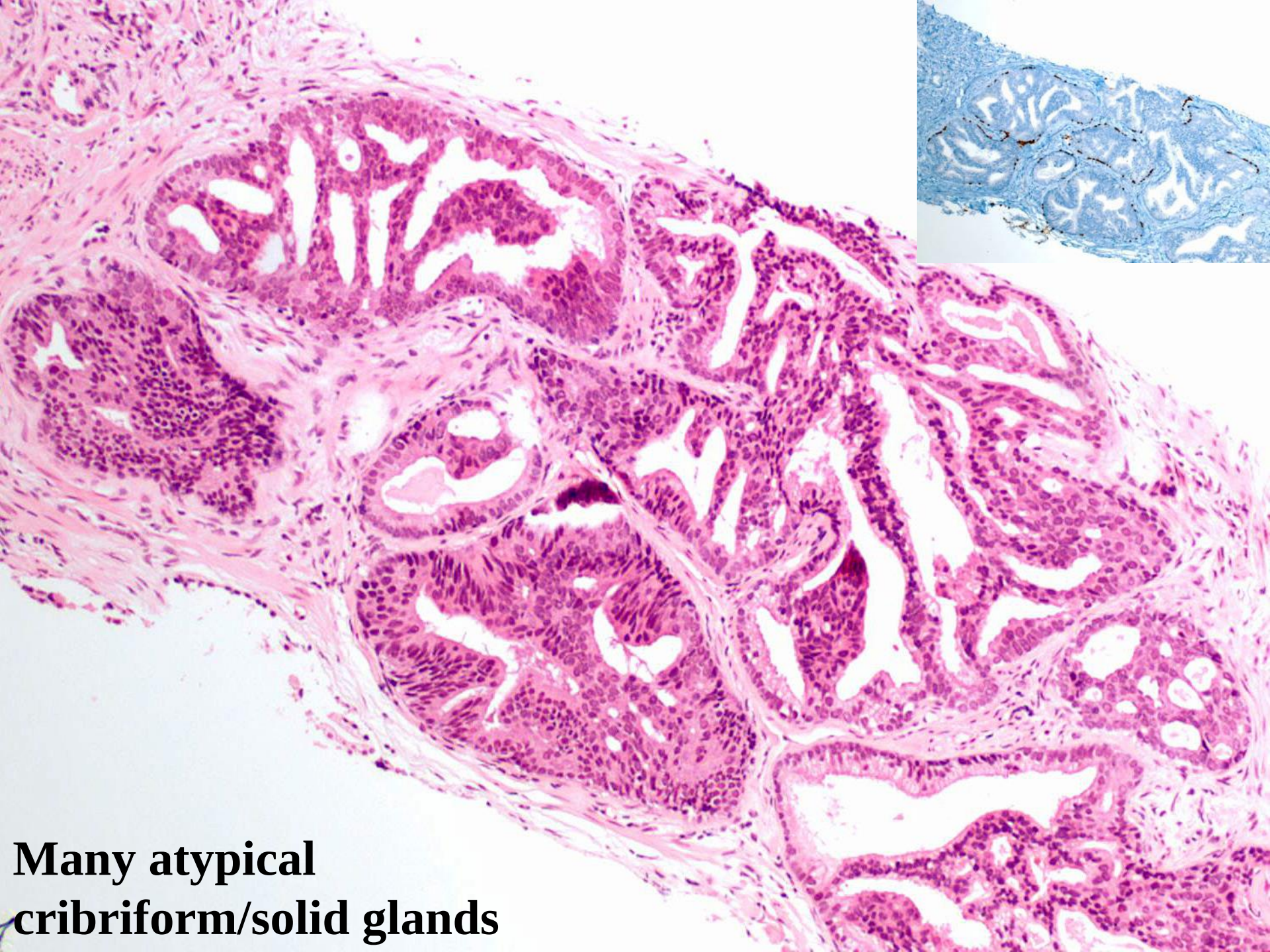


Intraductal Carcinoma of the Prostate (IDC-P)

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

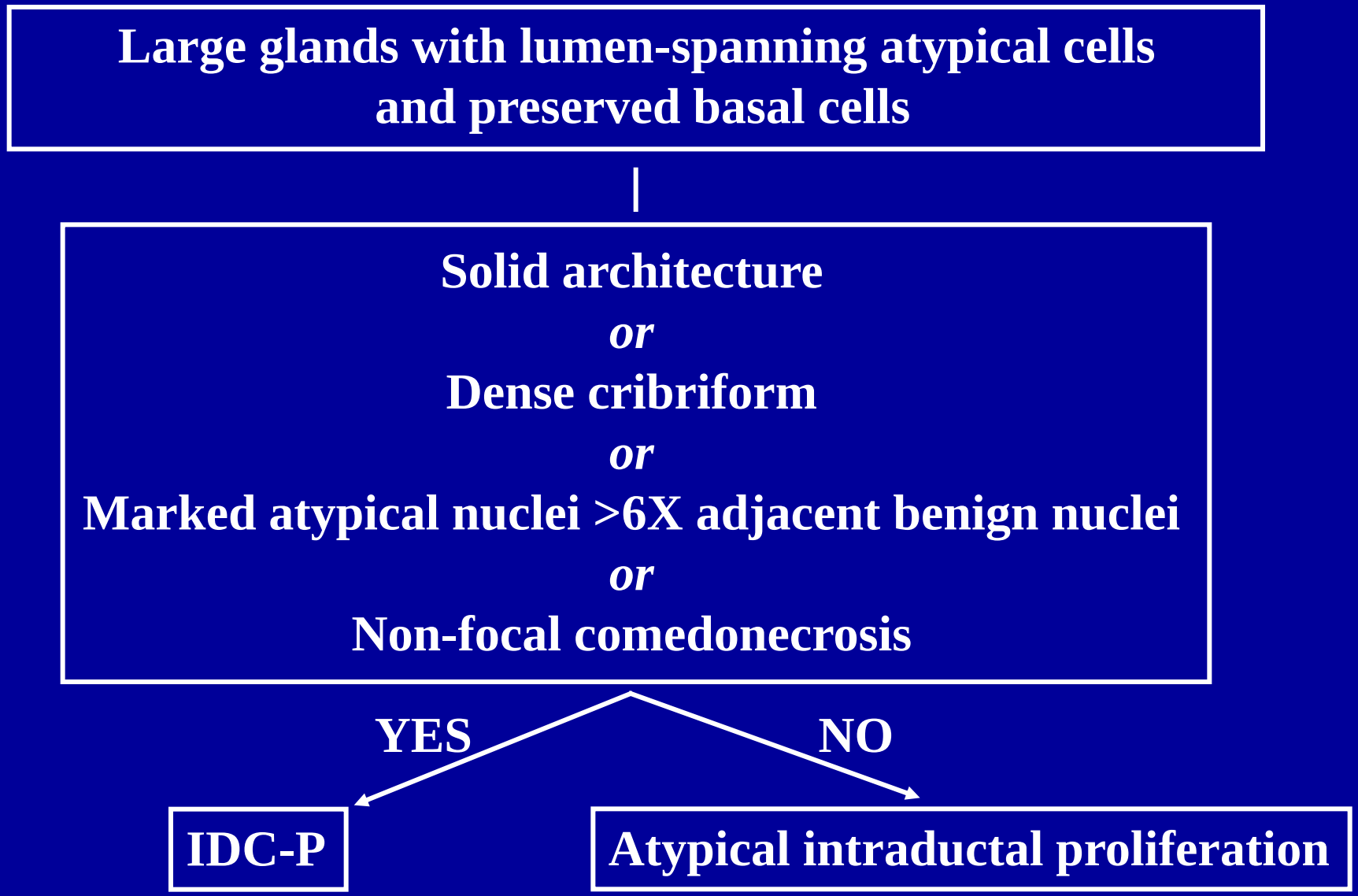


Many atypical cribriform/solid glands

Partially involves native benign glands

Diagnostic Criteria for IDC-P

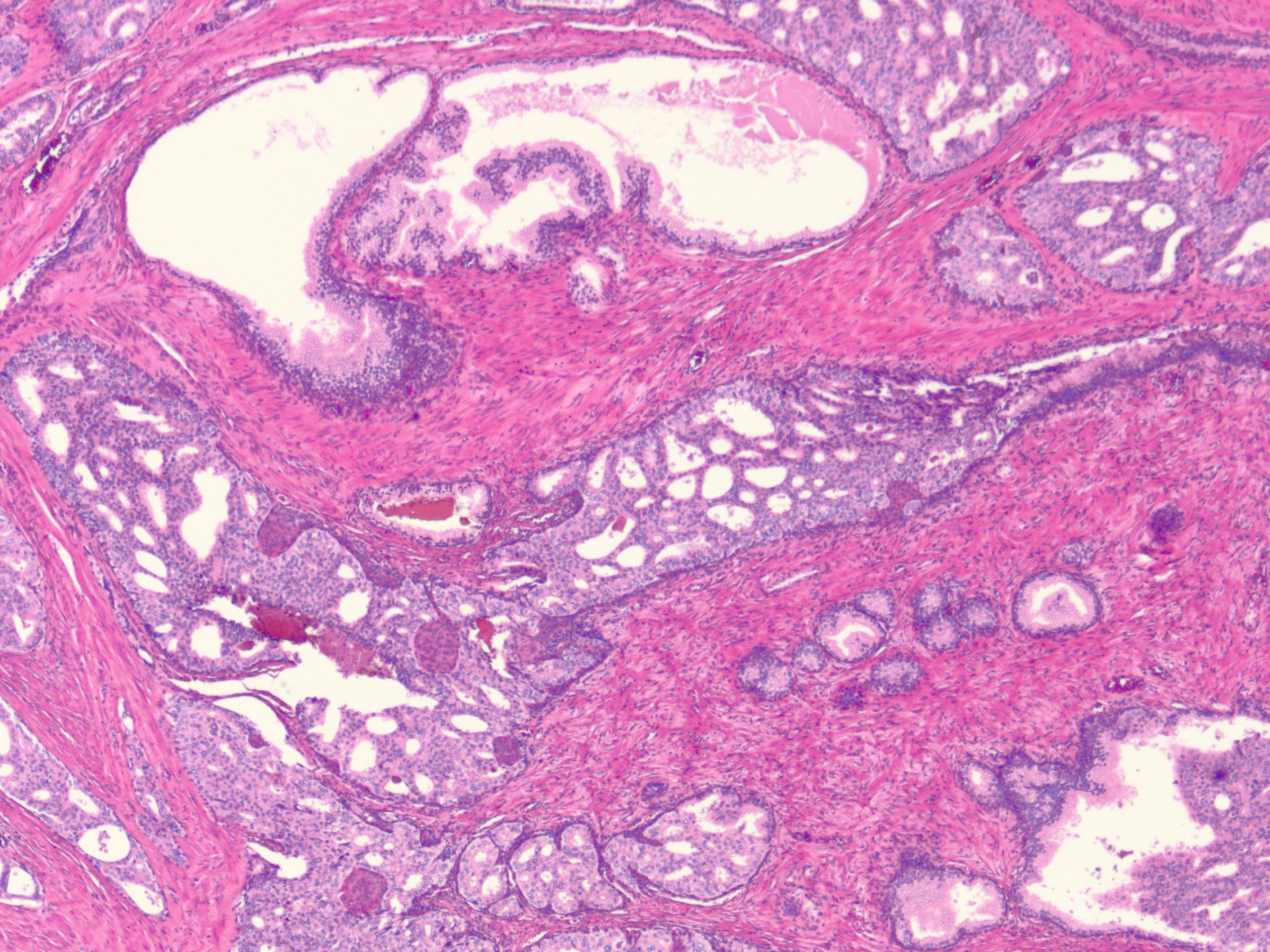
(Guo CC and Epstein JI, *Mod Pathol*. 2006)



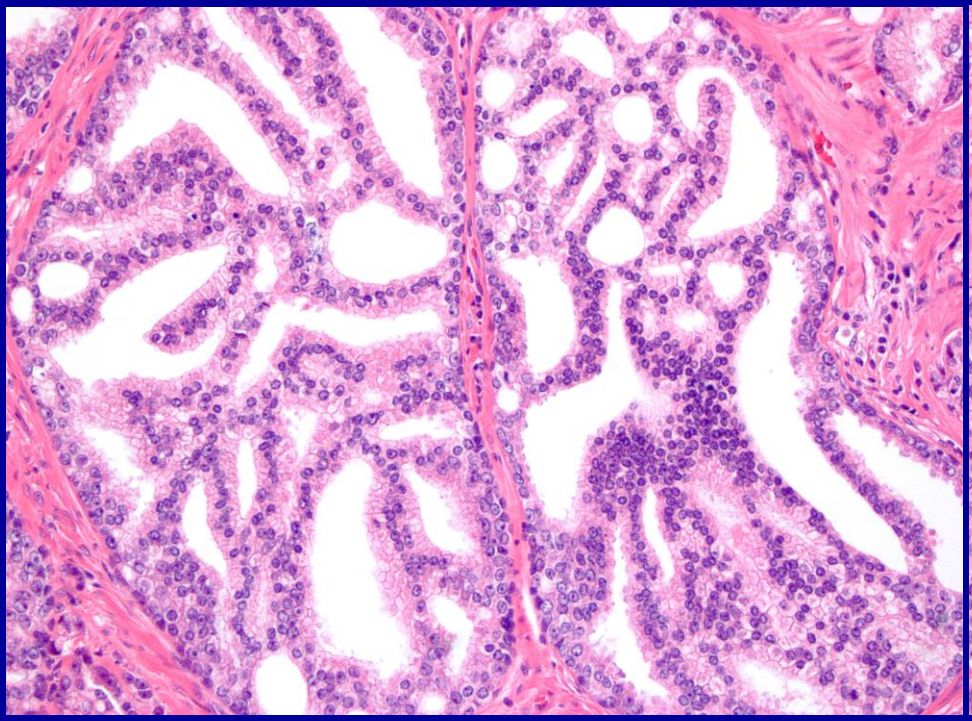
Minor Diagnostic Criteria for IDC-P

(Cohen RJ et al, *Arch Pathol Lab Med*; 2007
Shah RB et al, *Am J Surg Pathol*; 2010)

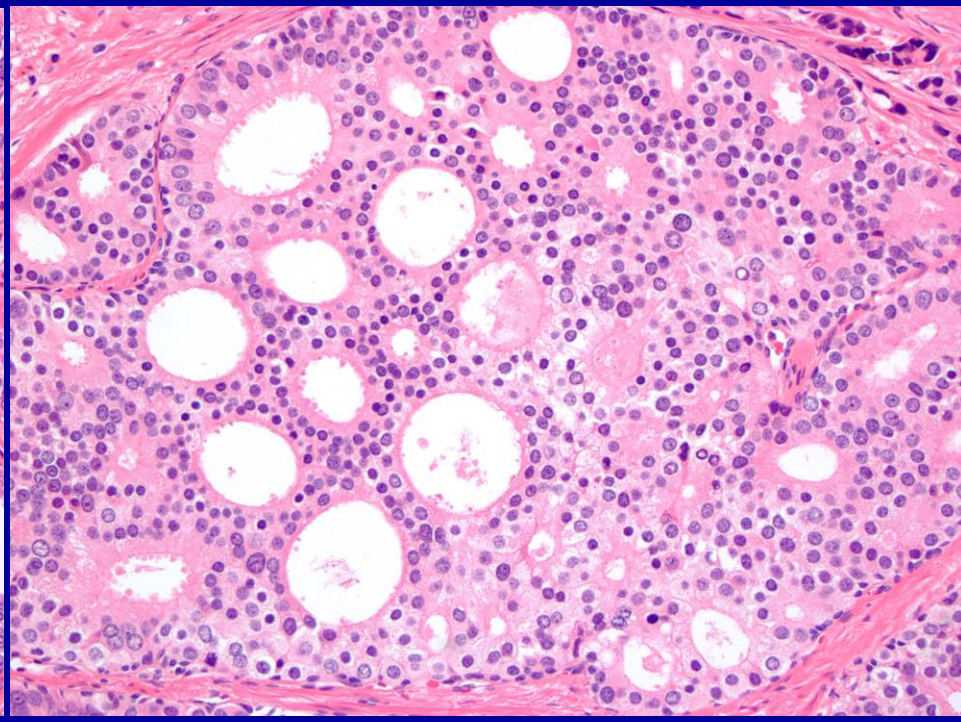
- ✓ Involvement of many glands (> 6)
- ✓ Irregular glands or branching at right angles
- ✓ Easily identifiable/frequent mitoses
- ✓ Two cell populations with an outer pleomorphic cells and a central cuboidal monomorphic cells



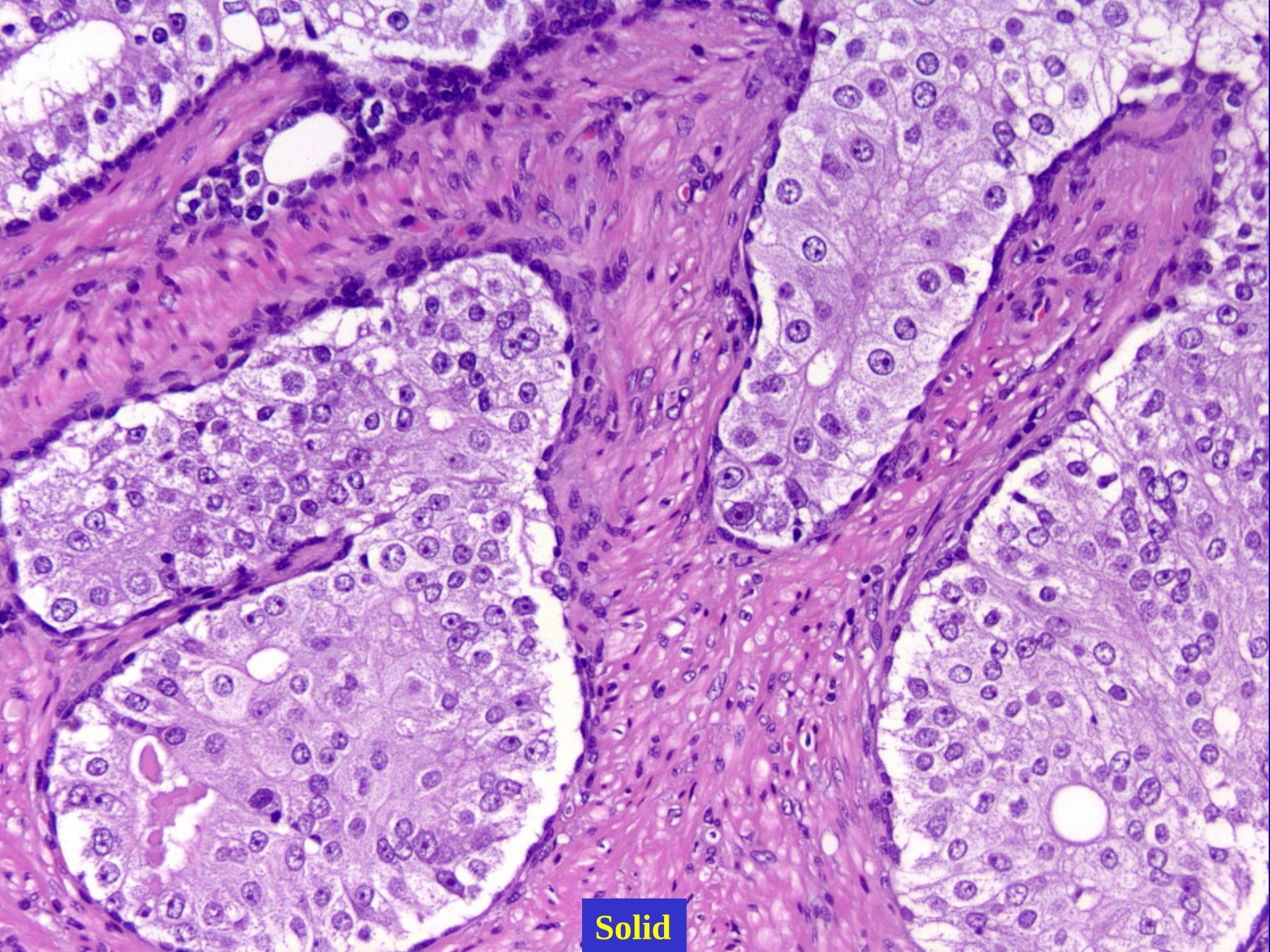
Dense cribriform = cellular mass > 50% of luminal spaces

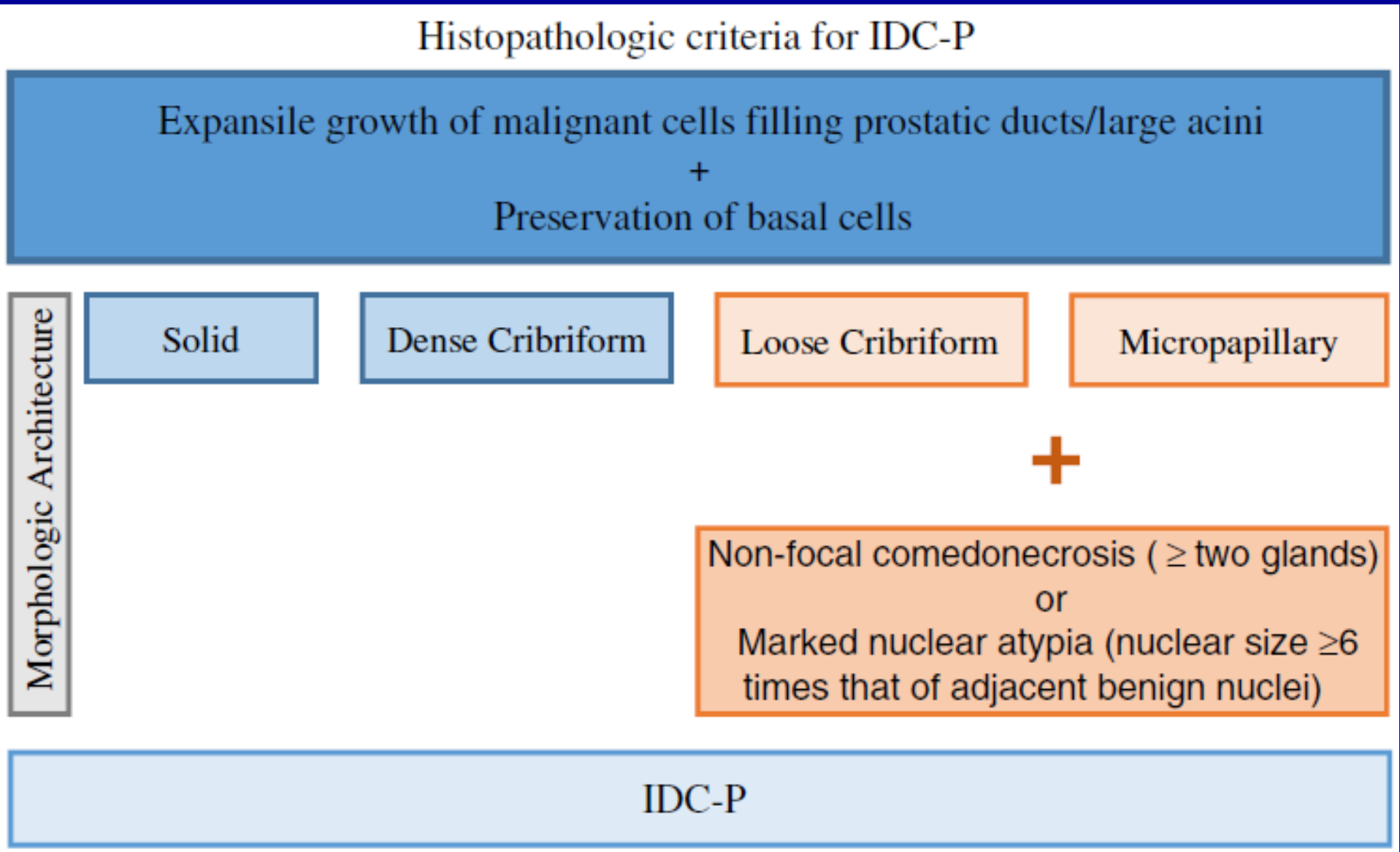


Dense cribriform:
Irregular lumina

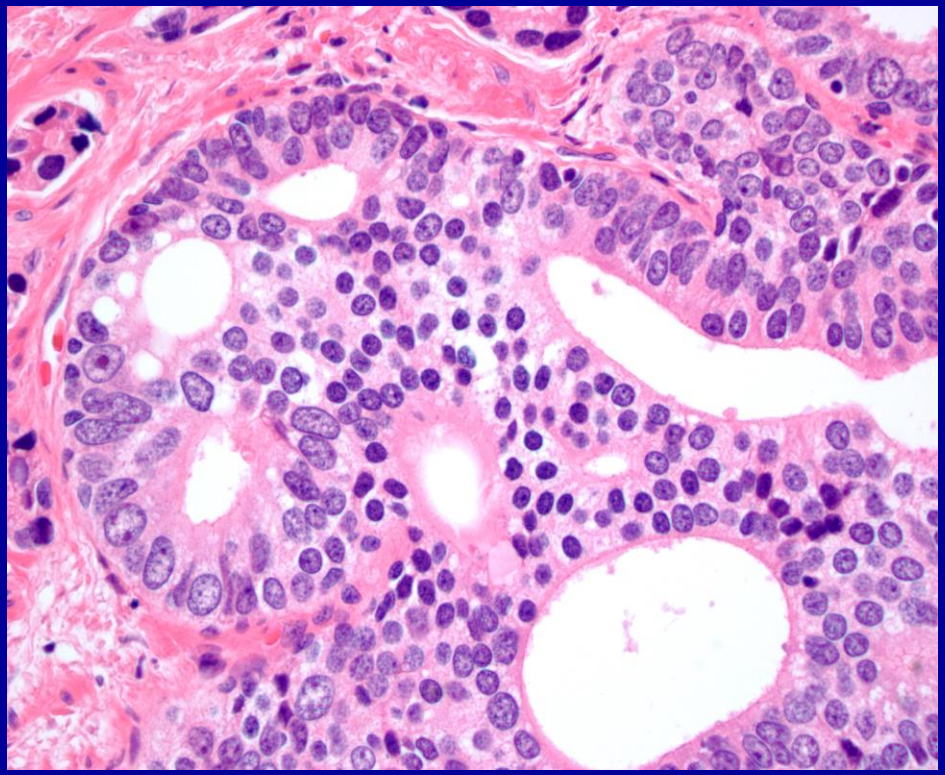


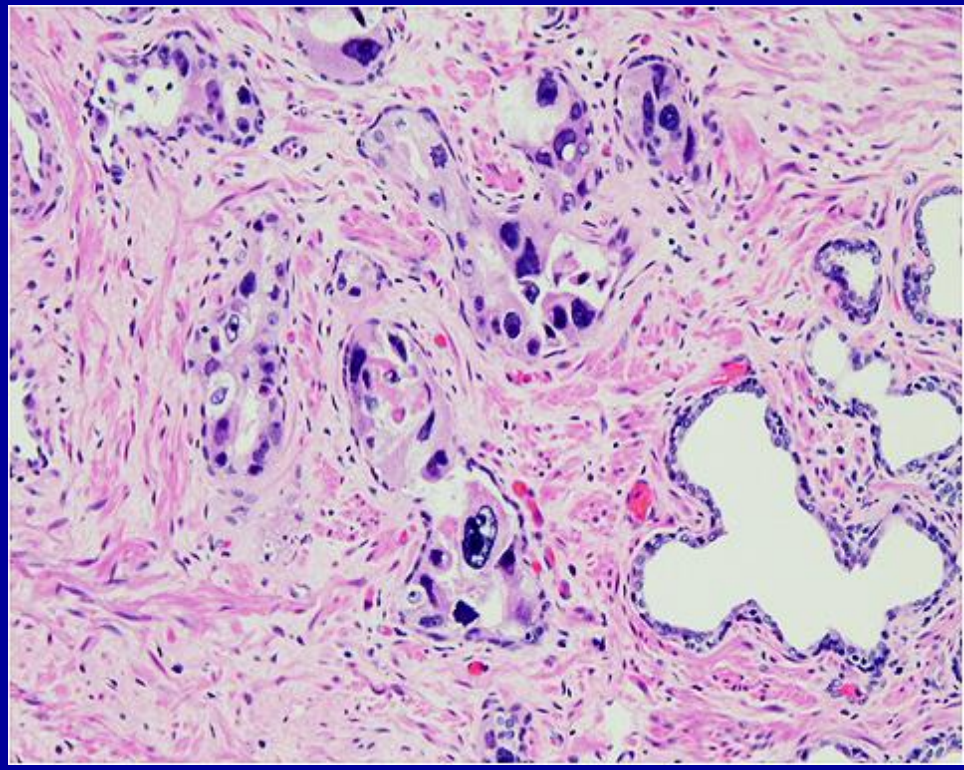
Dense cribriform:
Punched out lumina


Solid



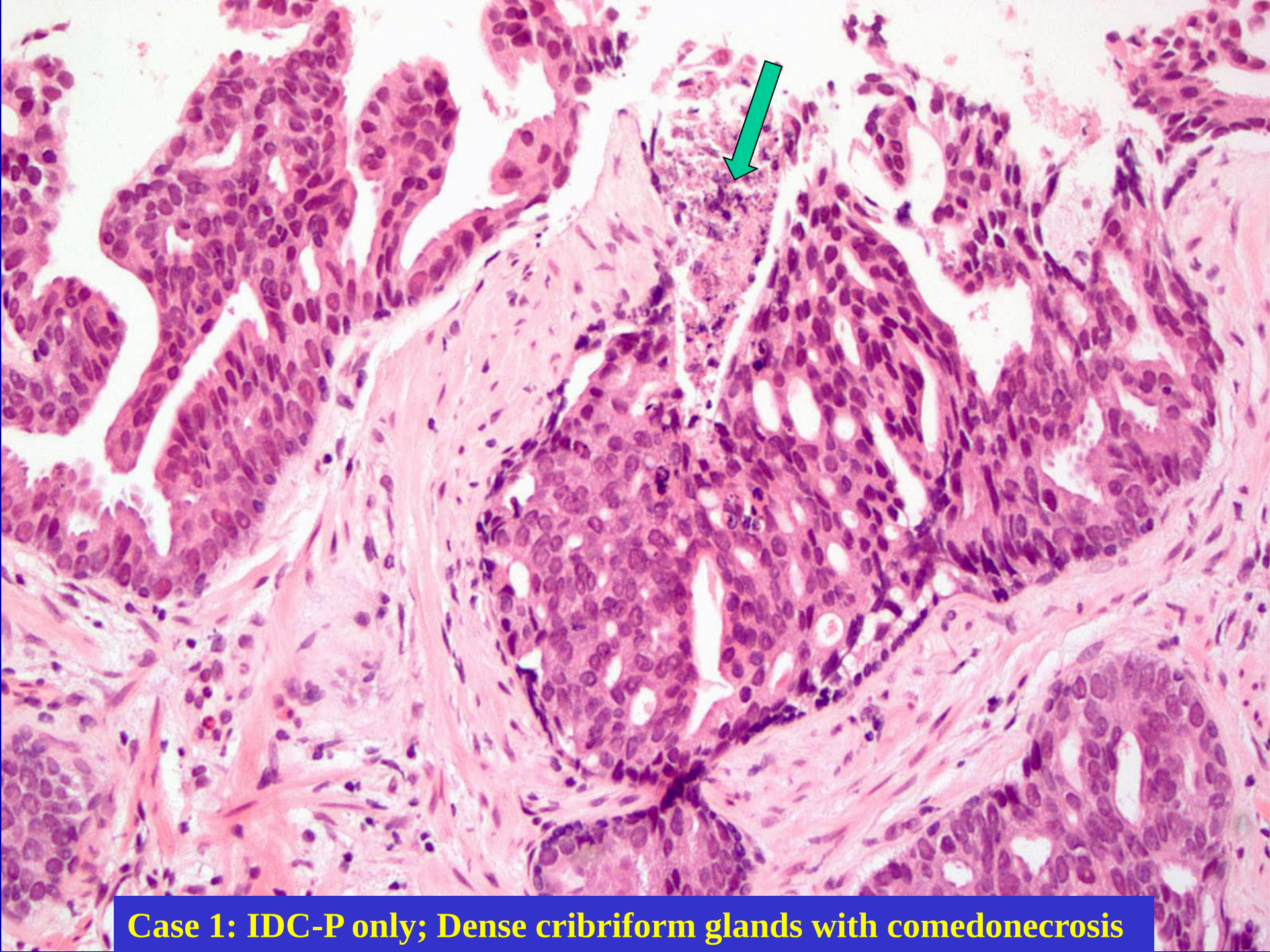
Nguyen J, Magi-Galluzzi C. ***Adv Anat Pathol*****, 2018**





Marked variation in nuclear size

Pleomorphic nuclei >6X adjacent nuclei

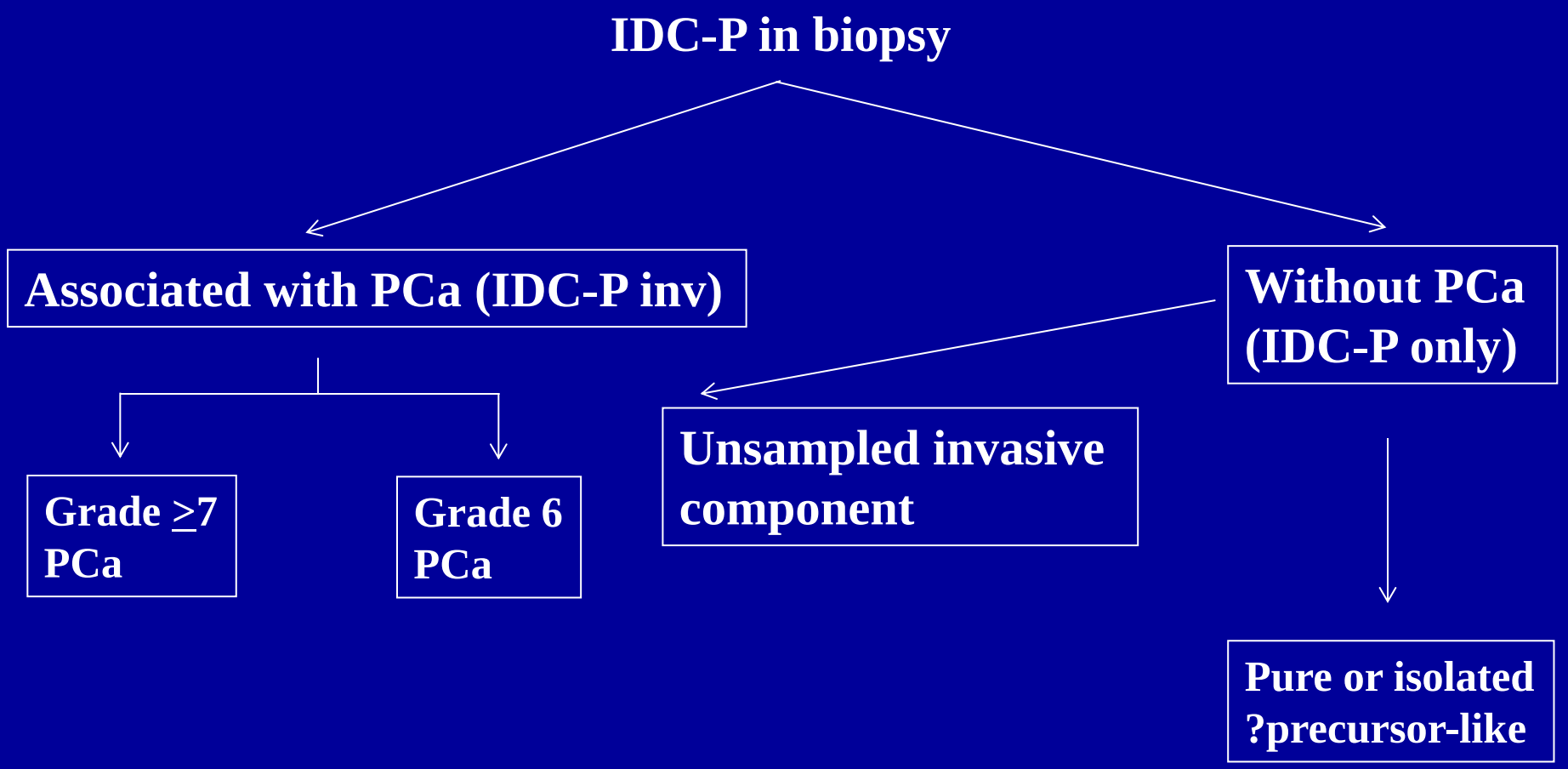


Case 1: IDC-P only; Dense cribriform glands with comedonecrosis

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 and potential treatment implications, ie, definitive therapy for IDC-P only


IDC-P in biopsy
Associated with PCa (IDC-P inv)
Without PCa (IDC-P only)
Grade ≥7 PCa
Grade 6 PCa
Unsampled invasive component
Pure or isolated ?precursor-like

INTRADUCTAL CARCINOMA OF THE PROSTATE : OUTCOME

- Independent predictor of various adverse outcomes in both biopsy and RP: biochemical recurrence, metastasis and disease specific death
- Contemporary studies focusing on outcomes lump cribriform Gleason pattern 4 and IDC-P as “cribriform architecture”; distinction between two is of little clinical significance
- Isolated intraductal carcinoma in prostate biopsy : Definitive therapy may be indicated although some of patients will have intraductal carcinoma only or Grade Group 1 PCa (Precursor-like) at radical prostatectomy, so repeat biopsy is an option

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 %

TABLE 3 Best model for morphological features associated with PTEN loss prostate cancer (PCa)

Morphological feature	Relative risk	95% CI lower	95% CI upper	*P* value
IDC-P	4.993	3.451	7.223	<0.001
Cribriform Gleason pattern 4	2.459	1.814	3.333	<0.001
Stromogenic PCa	2.255	1.634	3.112	<0.001

Abbreviation: CI, confidence interval.

Shah RB et al, *Prostate*,;2019

Loss of PTEN is a surrogate marker of IDC-P

MOLECULAR FEATURES OF INTRADUCTAL CARCINOMA

TABLE 3. Tissue Biomarkers in Predicting Upgrading and/or Significant Disease in Prostate Cancer

Biomarkers	Description	Key Data
SChLAP1	*SChLAP1* (a long noncoding RNA) expressed over 3-fold higher levels in cribriform architecture/IDC-P positive tumors	Genomic instability in *SChLAP1* underpins clinical aggression in association with cribriform and IDC-P architecture[39]
PTEN	Genomic *PTEN* loss is associated with tumor progression and poor prognosis; IDC-P demonstrates loss of *PTEN*, similar to adjacent invasive prostate cancer	*PTEN* loss in IDC-P and adjacent invasive carcinoma suggests a clonal relationship and could predict unfavorable pathology[40]
	PTEN loss with MYC/8q gain or LPL/8p loss is associated with more aggressive Gleason pattern 3 tumors	*PTEN* loss in association with MYC/8q gain and LPL/8p loss suggests tumor clonality and predicts upgrading at RP[41]
APC, *RASSF1*, and *TBX15* methylation	*APC*, *RASSF1*, and *TBX15* methylation is associated with cribriform architecture/IDC-P	First evidence for association between cribriform architecture/IDC-P and methylation biomarkers[42]
BRCA2	*BRCA2* germline mutations exhibit clinically aggressive prostate cancer and overall poor prognosis with associated IDC-P	Presence of IDC-P in *BRCA2* germline mutation carriers is associated with poorer outcomes[43]

IDC-P indicates intraductal carcinoma of the prostate.

Nguyen J, Magi-Galluzzi C. *Adv Anat Pathol*, 2018

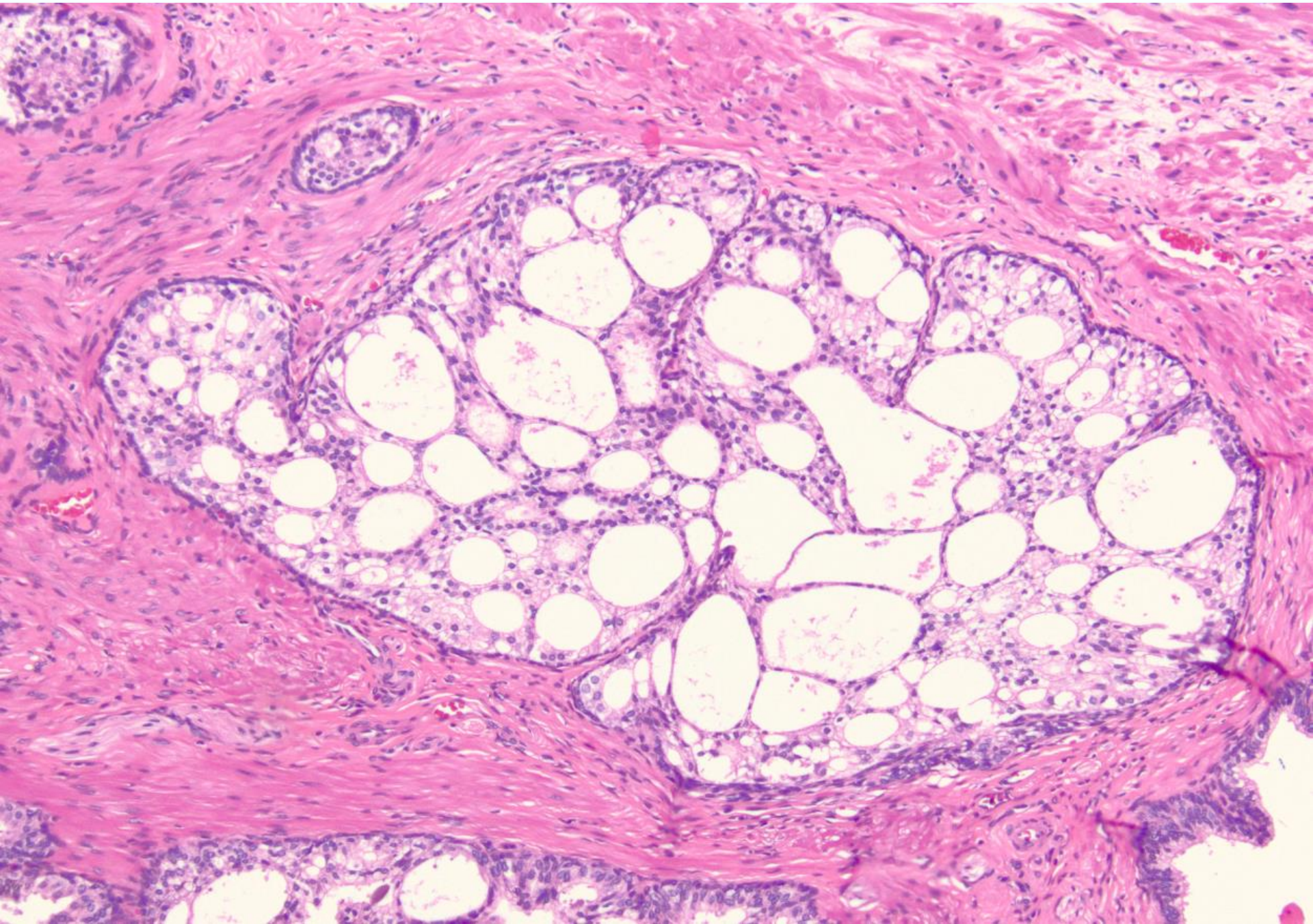
Patients with IDC-P may be offered germline mutational study
Reporting of IDC-P is clinically important parameter

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

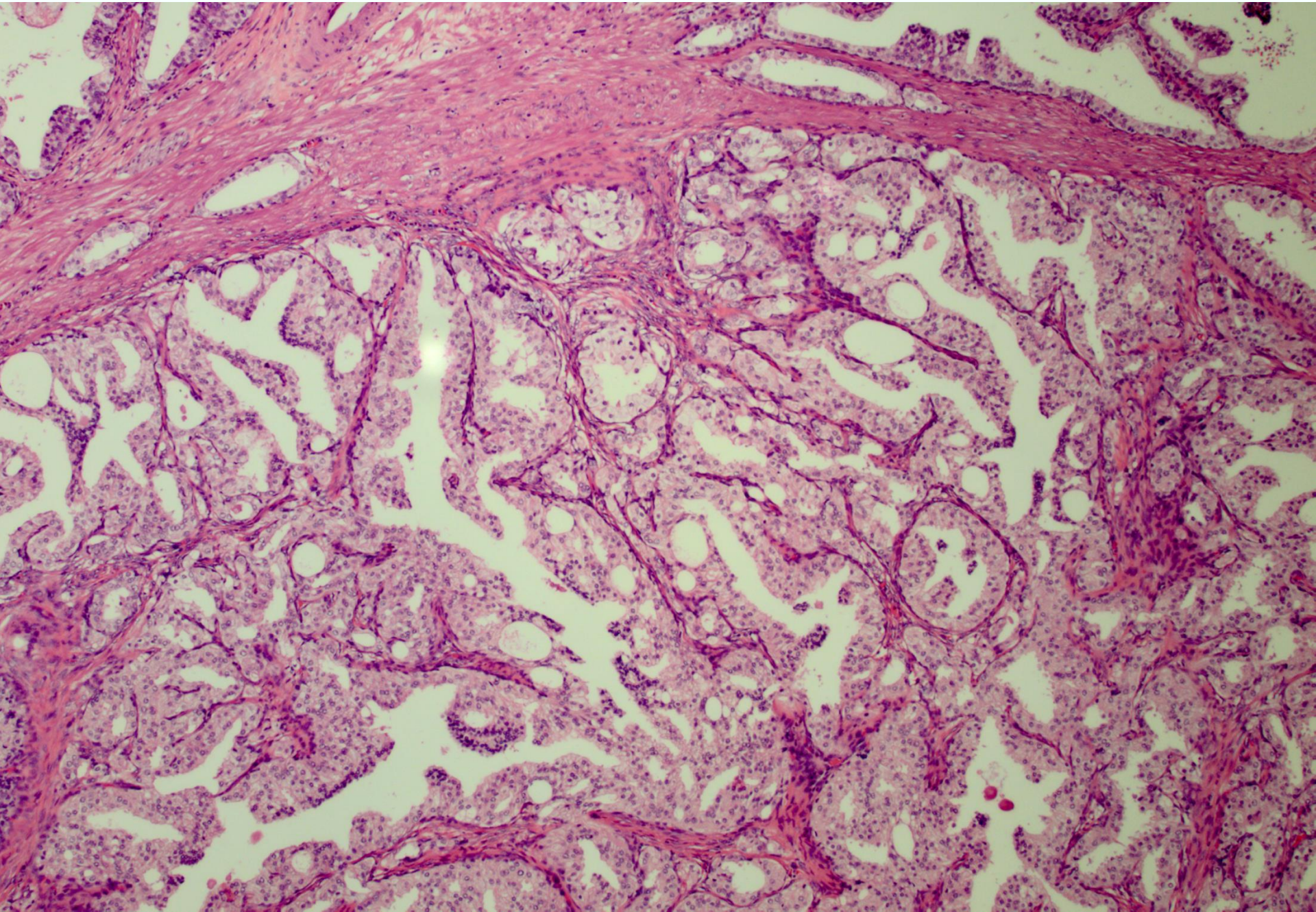
- Clear cell cribriform hyperplasia
- High grade PIN
- Atypical Intraductal Proliferation (AIP)
- Invasive cribriform prostatic carcinoma
- Ductal adenocarcinoma of the prostate
- Urothelial carcinoma involving the prostate

Disease Spectrum	Clinical significance
Clear cell cribriform hyperplasia	Benign
HGPIN	Putative precursor lesion, Risk of associated cancer <25%
Intraductal carcinoma (IDC-P)	Almost always associated with high grade and high volume PCa
Ductal adenocarcinoma	High grade (4 or 5) and high stage disease
Cribriform carcinoma	High grade (4 or 5) and high stage disease
Urothelial carcinoma	High grade, high stage, distinction from PCa critical

Case 2: Clear cell cribriform hyperplasia, Bland cytology; Prominent basal cells



Case 2: Nodular proliferation of cribriform glands, pale cytoplasm



Clear cell cribriform hyperplasia

Architecture of glands (large and branching) may mimic IDC-P

Clear cytoplasm, benign cytology and prominent basal cells

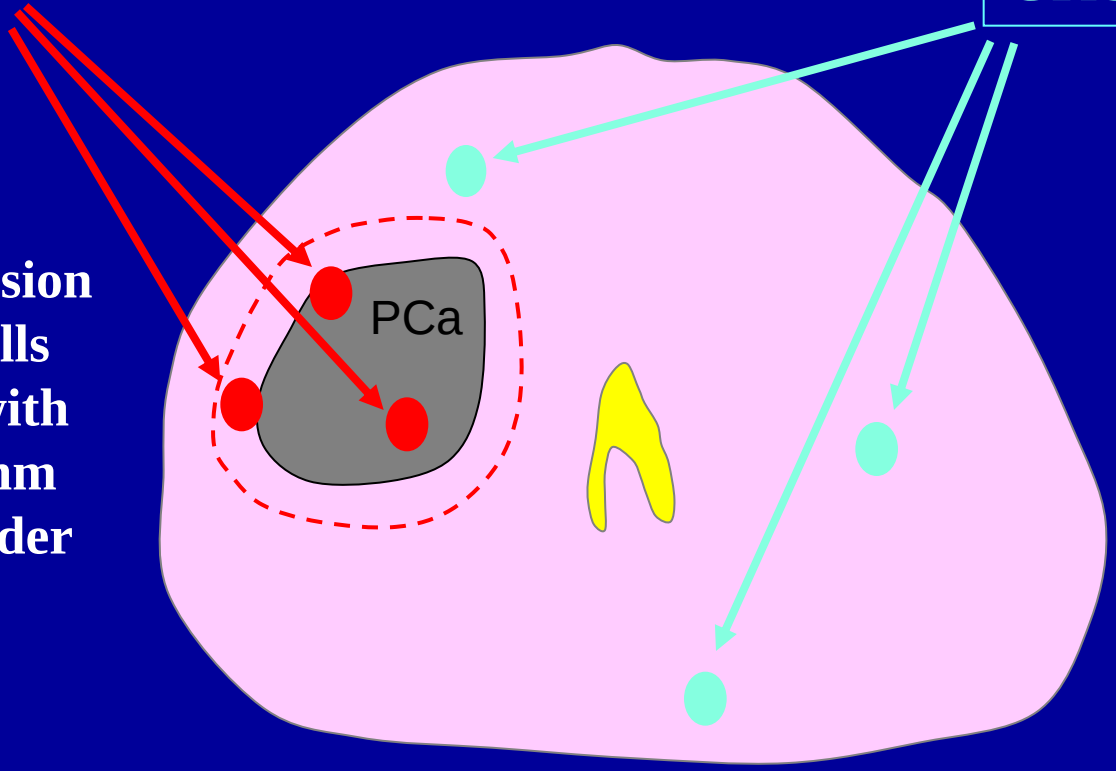
Represents a spectrum of BPH

Limited to the transition zone, TURP>>>NBX

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 RB et al AJSP 2010; Han B *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

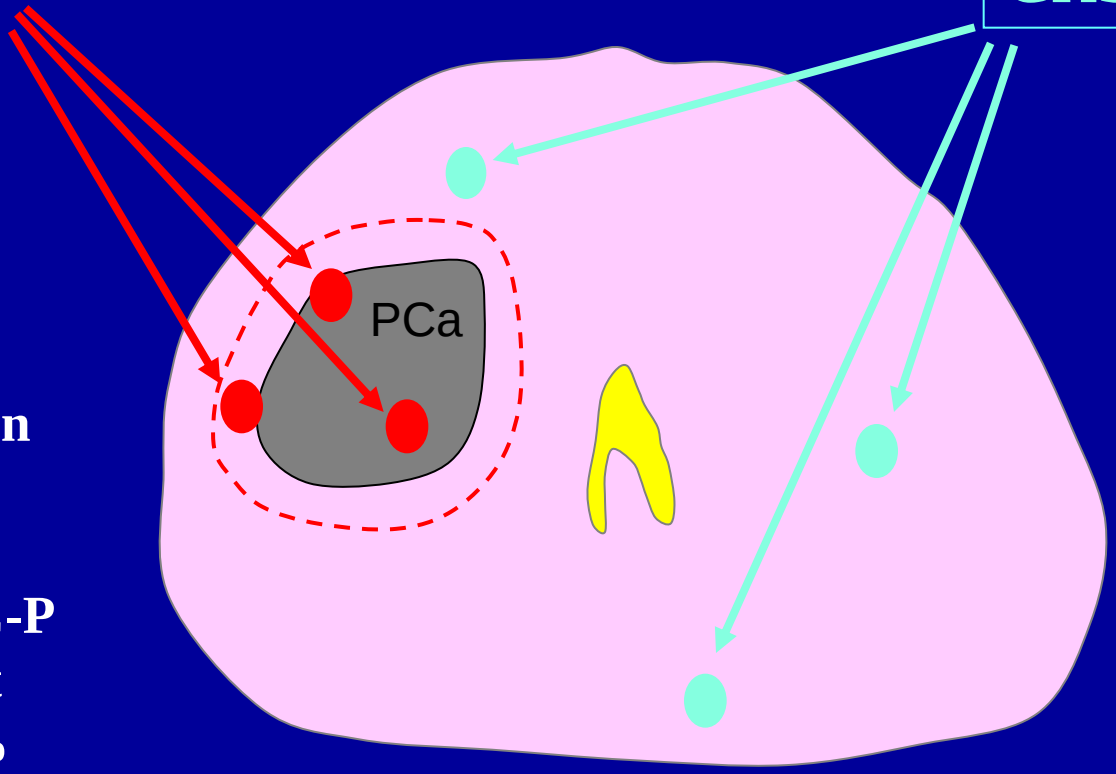
Morphological comparison between IDC-P and HGPIN

- Morphologic criteria for IDC-P has high specificity but poor sensitivity
- There is significant overlap at “lower grade” morphological spectrum creating diagnostic difficulties with HGPIN
- Diagnosis of “cribriform HGPIN” should not be made in needle biopsy
- Such lesions referred to as AIP, suspicious for IDC-P

IDC-P *vs* Cribriform HGPIN

IDC-P

Cribriform HGPIN



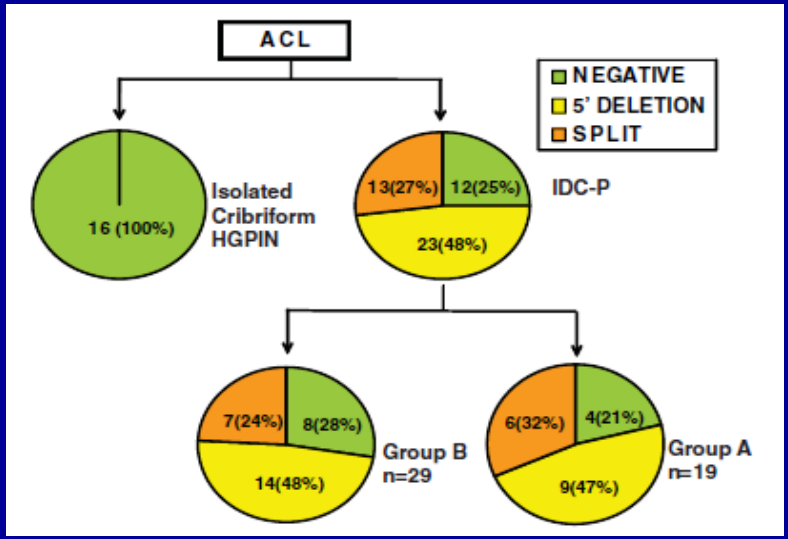
✓ **ERG gene fusion: 75%**

✓ **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**
- **IDC-P : resulting from intraductal spread of PCa**

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



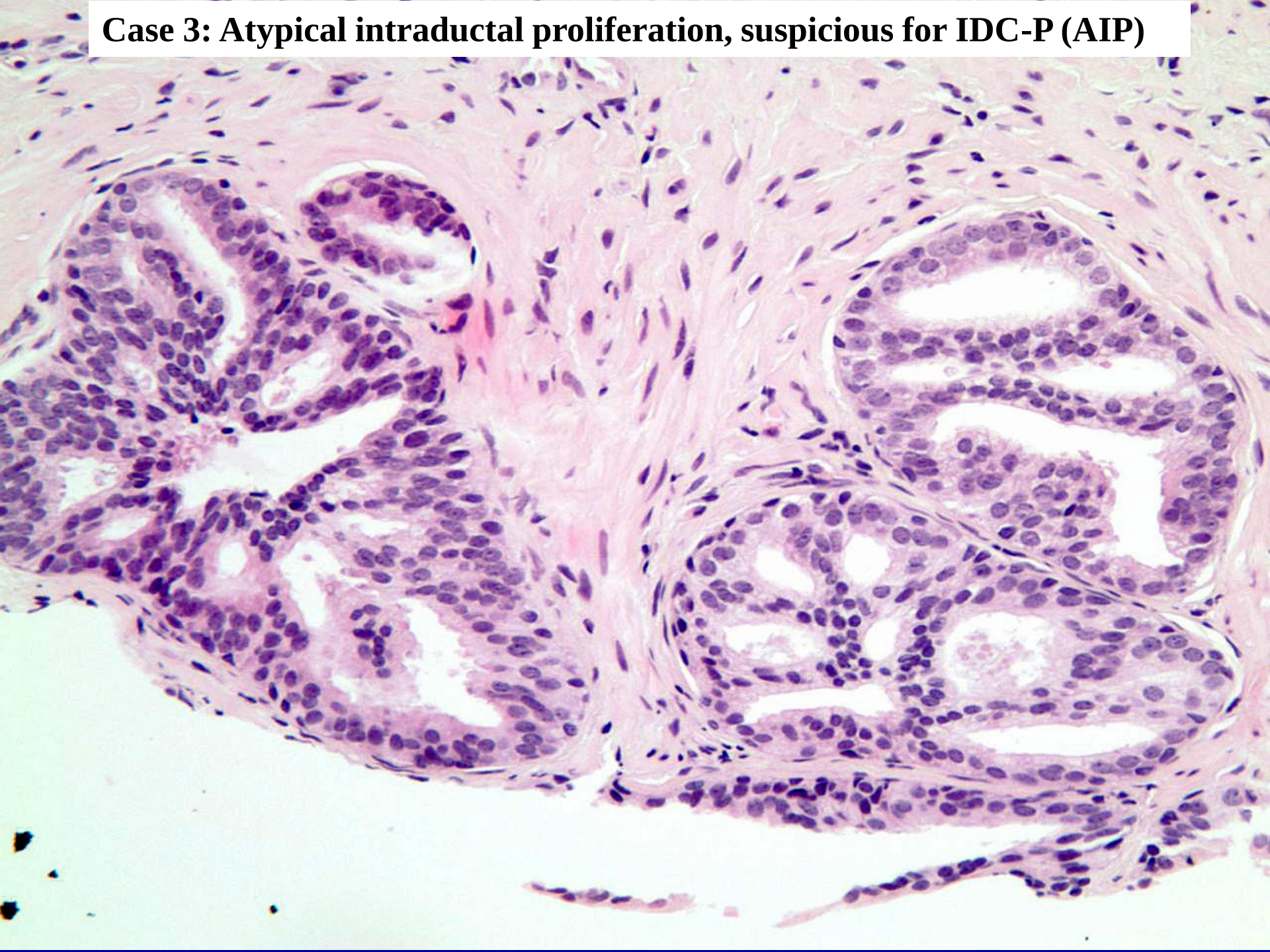
Atypical cribriform lesion with nearby invasive PCa (ACL-PCa/IDC-P) :

Group A (Meeting Guo and Epstein criteria): ERG rearrangement in 47% cases

Group B (Not meeting Guo and Epstein criteria): ERG rearrangement in 48% cases

IDC-P with "low-grade" features share similar molecular profile like classic IDC-P!

Case 3: Atypical intraductal proliferation, suspicious for IDC-P (AIP)



Histopathology

Histopathology 2019 DOI: 10.1111/his.13878

Atypical intraductal proliferation detected in prostate needle biopsy is a marker of unsampled intraductal carcinoma and other adverse pathological features: a prospective clinicopathological study of 62 cases with emphasis on pathological outcomes

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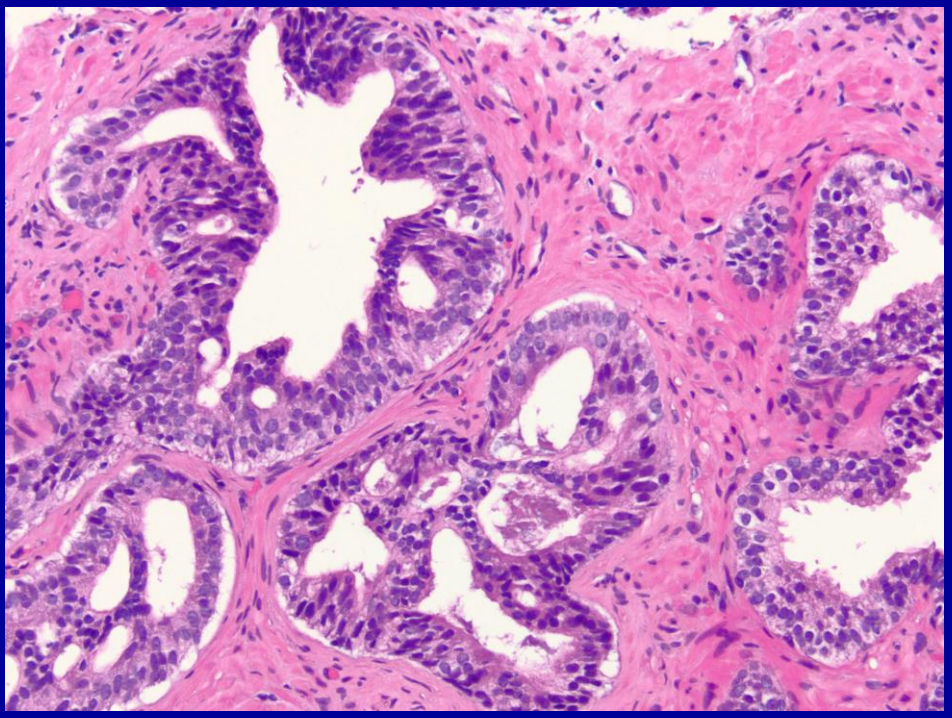
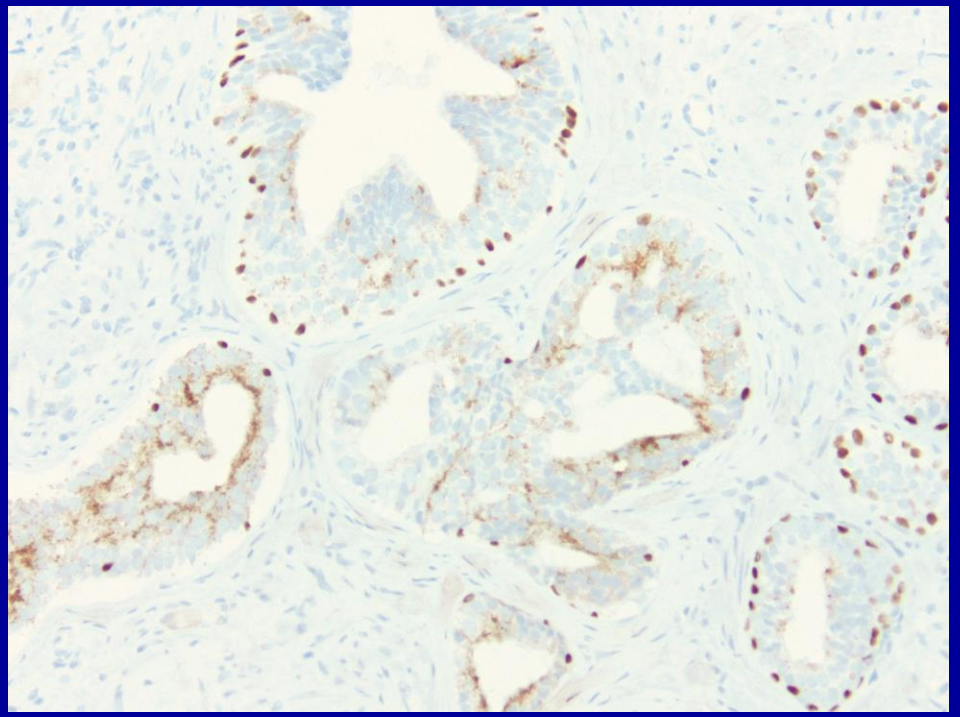
[1]*Robert J. Tomsich Pathology and Laboratory Medicine Institute, and* [2]*Glickman Urological and Kidney Institute, The Cleveland Clinic, Cleveland, OH, USA*

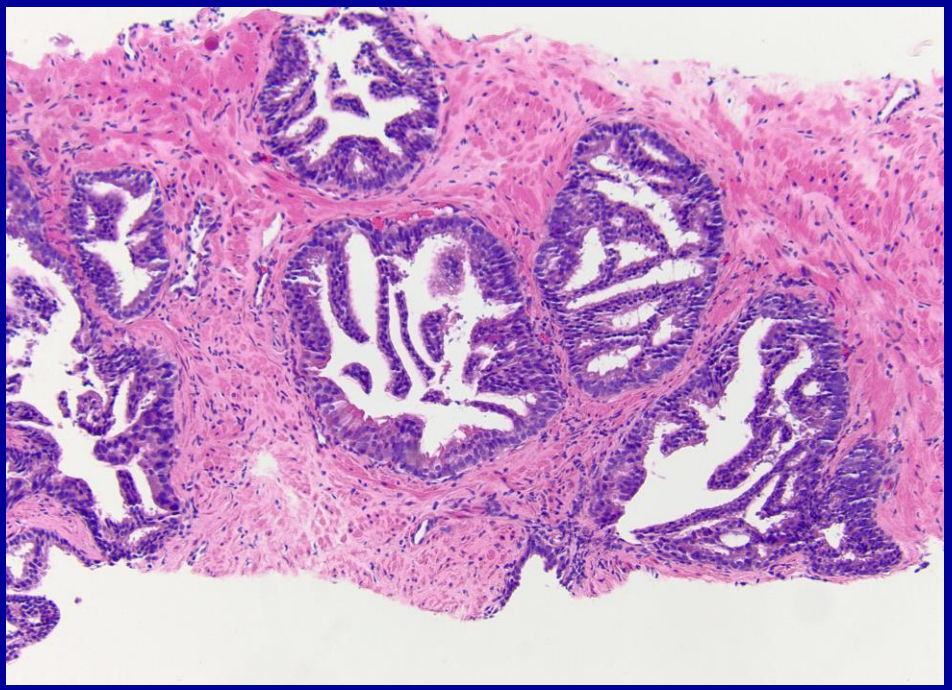
Table 2. Breakdown of adverse pathology at follow-up in 40 patients who were potential candidates for no therapy (AIP alone) or active surveillance (AIP with grade group 1 or 2 prostate cancer without cribriform Gleason pattern 4)

		Follow-up biopsy [*n* (%)]				Radical prostatectomy (RP) [*n* (%)]					
Category [*n* (%)]	Available follow-up (*n*)	IDC-P	IDC-P + PCa	PCa (> GG 3)	Total	> GG 3	ICD-P	EPE	SV invasion	Cribriform GP4	Total
AIP alone12 (30)	6		1 (17)	2 (33)	3 (50)	NA					
GG 110 (25)	3(1 Bx, 2 RP)				No tumour		1 (50)	1 (50)		1 (50)	2 (67)
GG 2 without cribriform pattern18 (45)	11 (all RP)					2 (18)	9 (81)	9 (81)	1 (8)	8 (72)	11 (100)

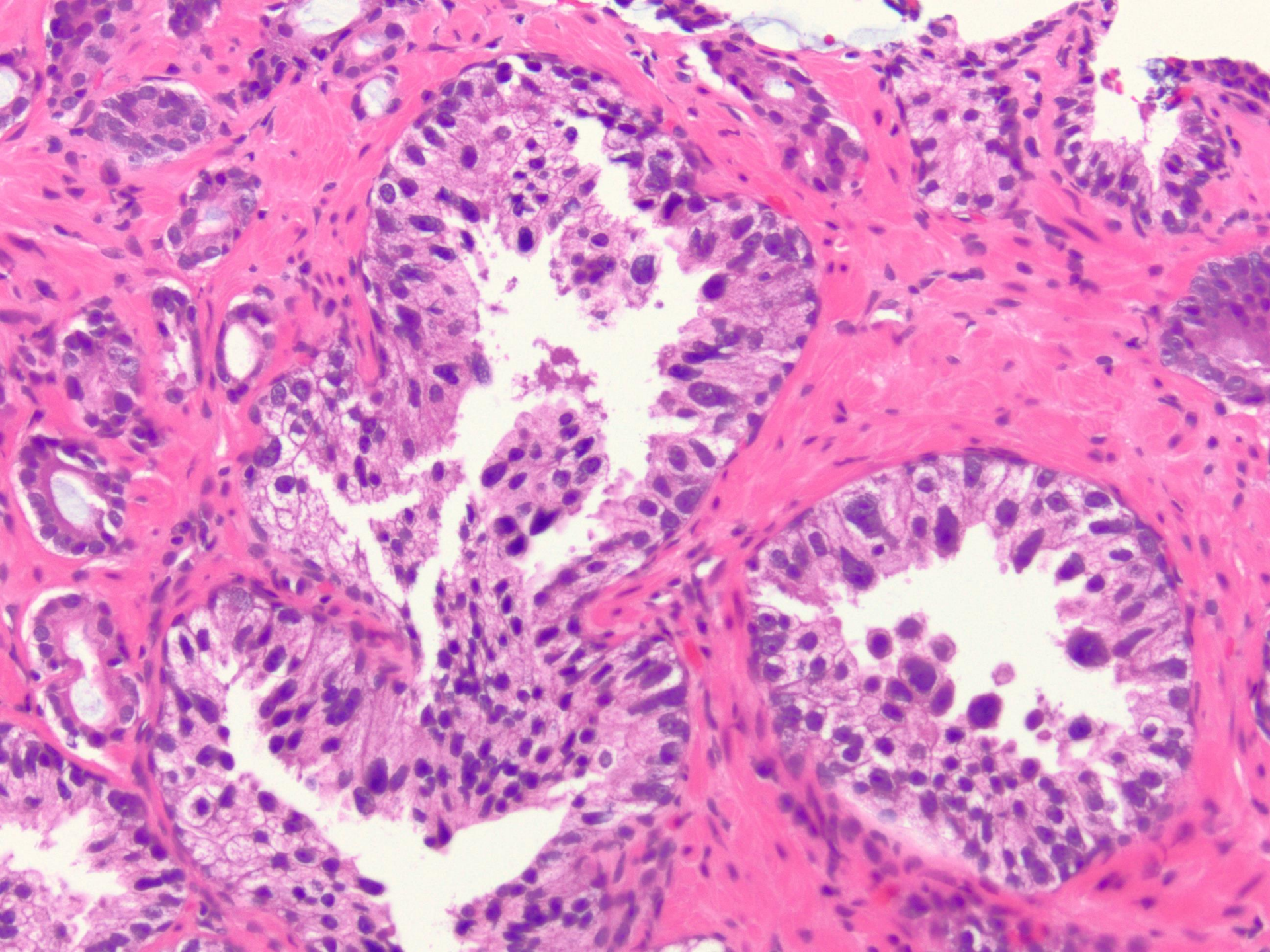
AIP, atypical intraductal proliferation; GG, grade group; IDC-P, intraductal carcinoma; EPE, extraprostatic extension; SV, seminal vesicle; NA, not applicable.





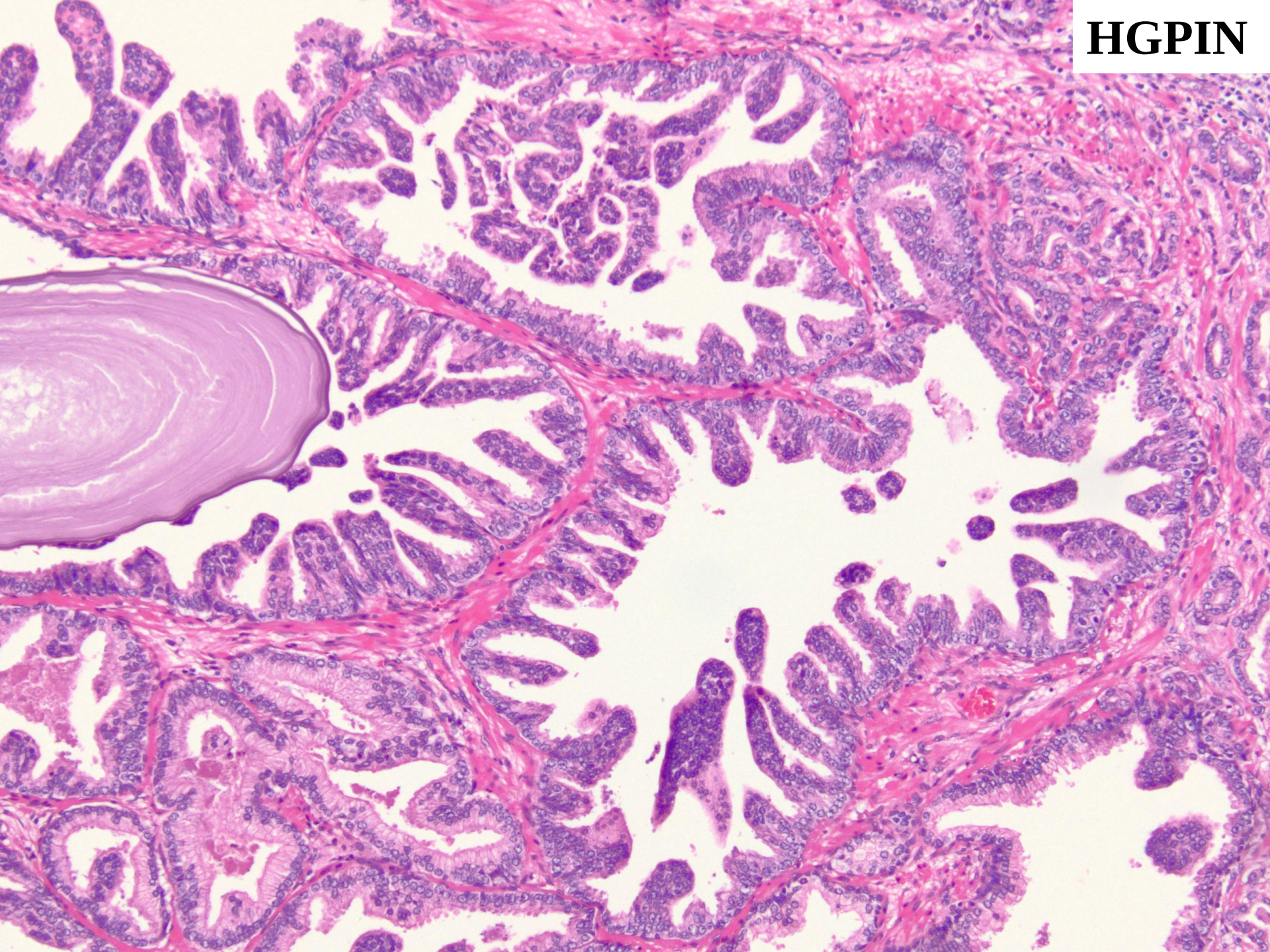


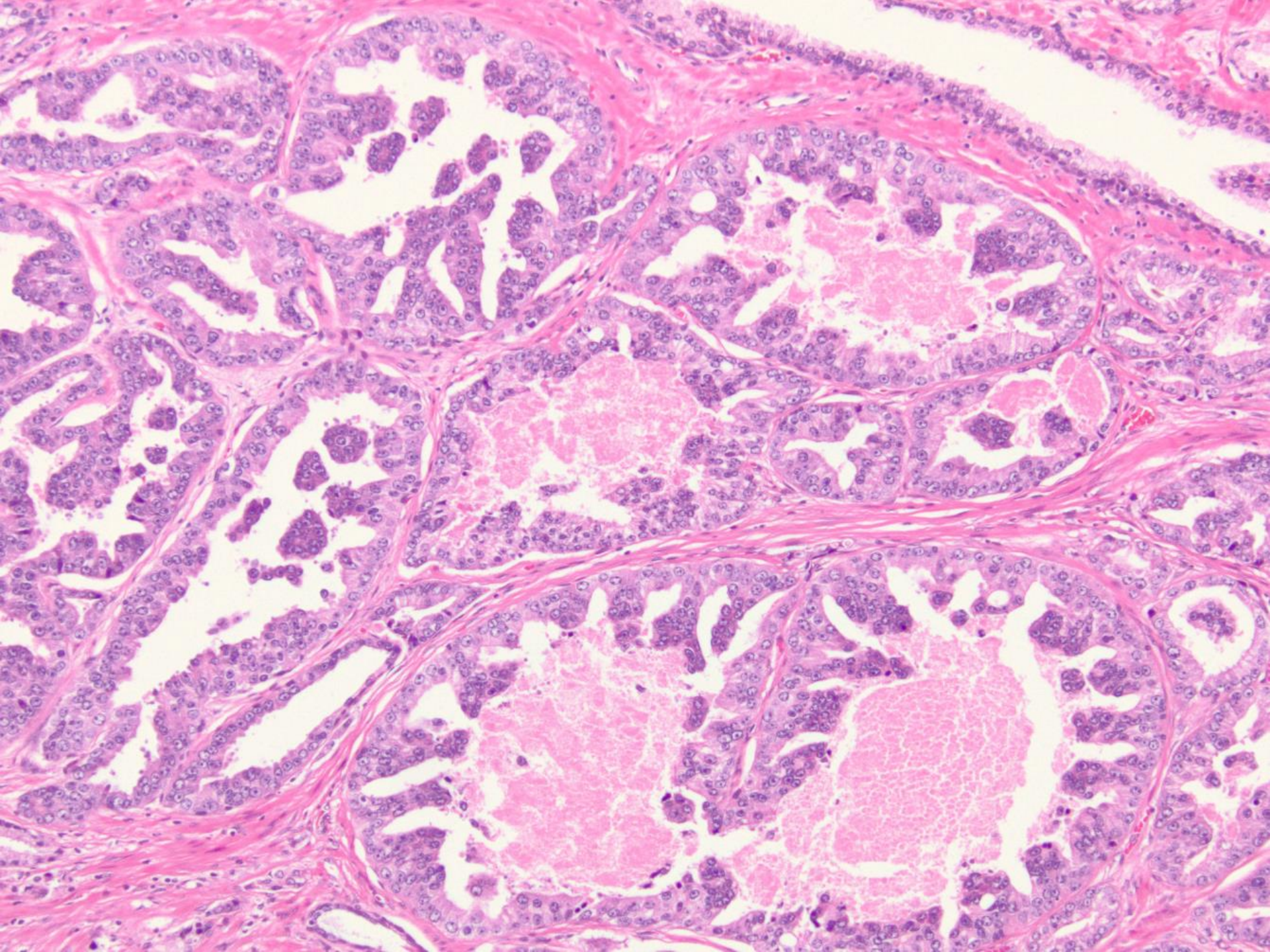
Expansile loose cribriform (luminal spaces account for > 50% of cellular proliferation) morphology



AIP: Morphological Spectrum

- Expansile loose cribriform proliferation (90%)
- Non-cribriform proliferations with marked cytological atypia exceeding HGPIN but falls short of x6 nuclear criteria (10%)


HGPIN



Histopathology

Histopathology 2017, 71, 693–702. DOI: 10.1111/his.13273

Atypical intraductal proliferation and intraductal carcinoma of the prostate on core needle biopsy: a comparative clinicopathological and molecular study with a proposal to expand the morphological spectrum of intraductal carcinoma

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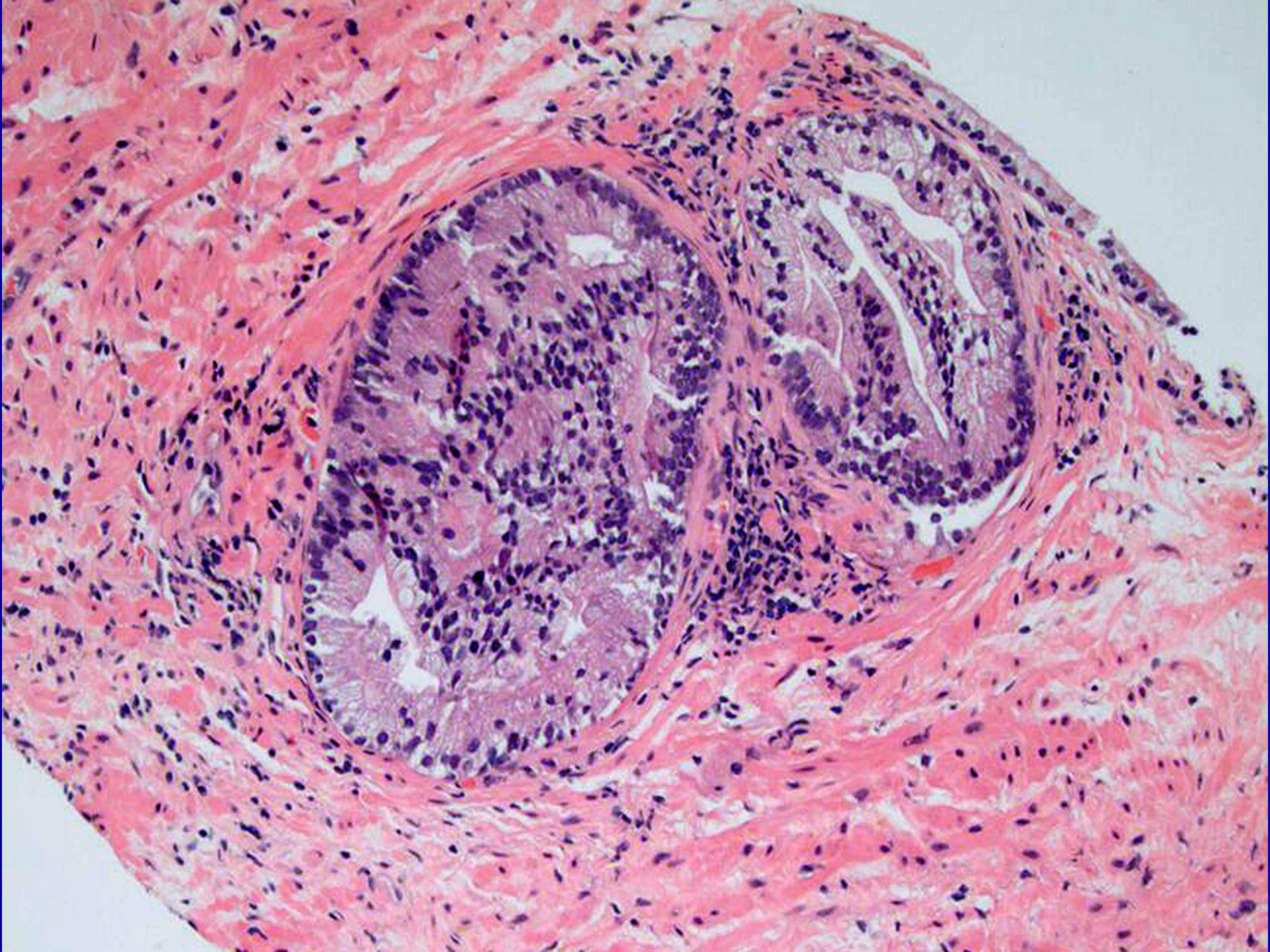
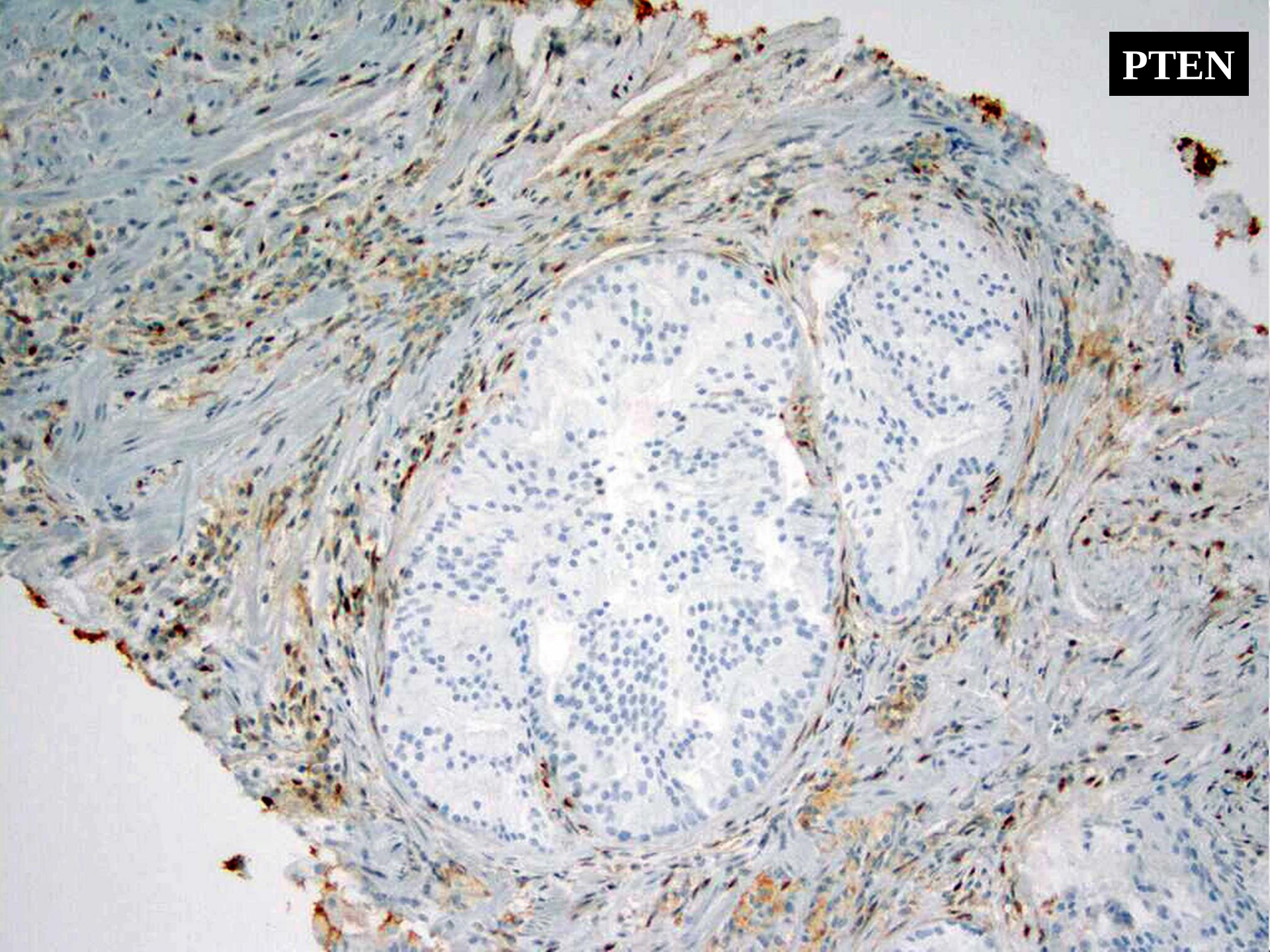
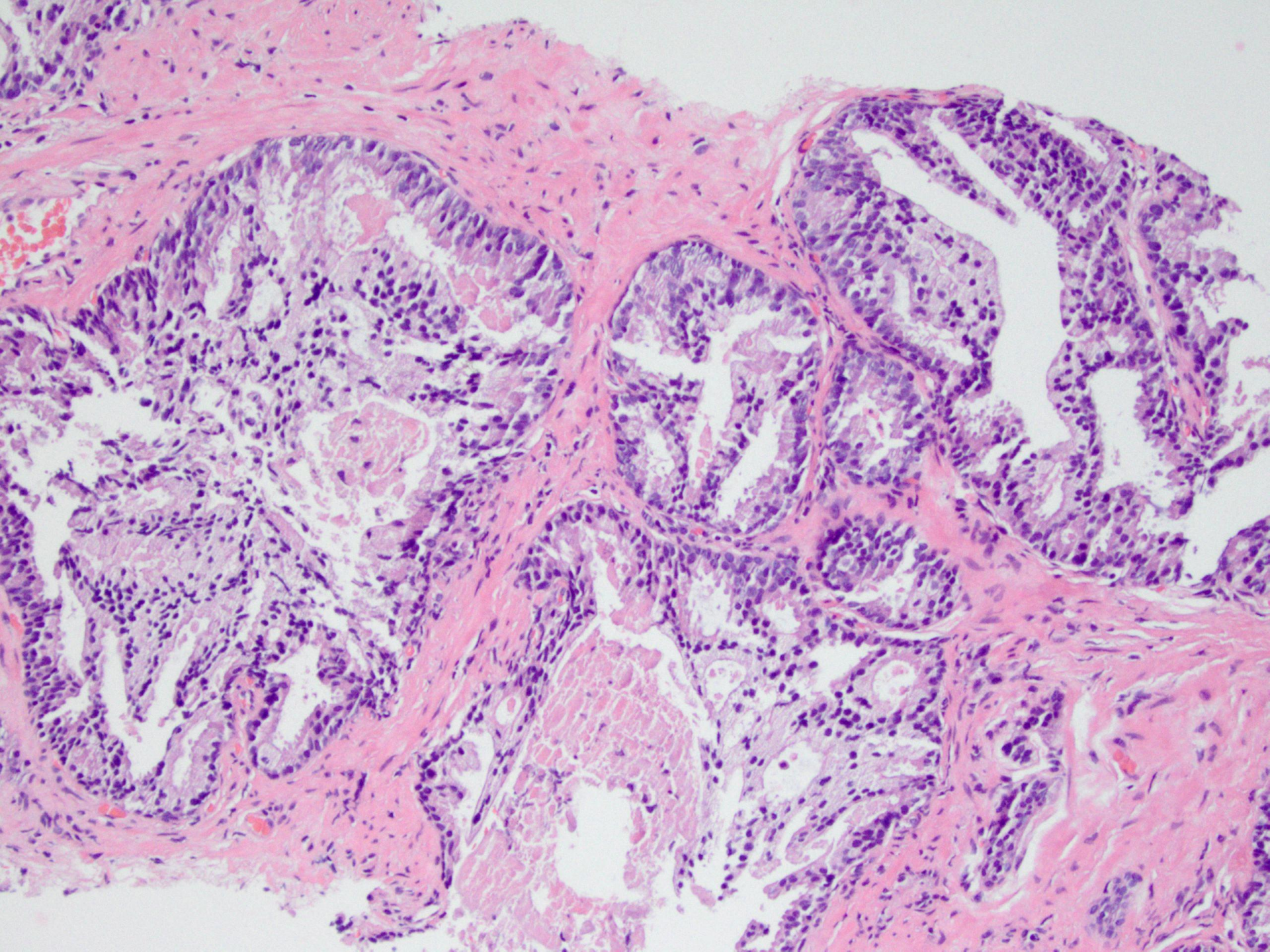
	Concordance of molecular markers expression pattern in AIP, IDC-P and Invasive PCa	
	ERG	PTEN
Hickman et al, AJSP, 2017	100%	95%
Shah RB et al, Histopathol, 2017	96%	89%




PTEN

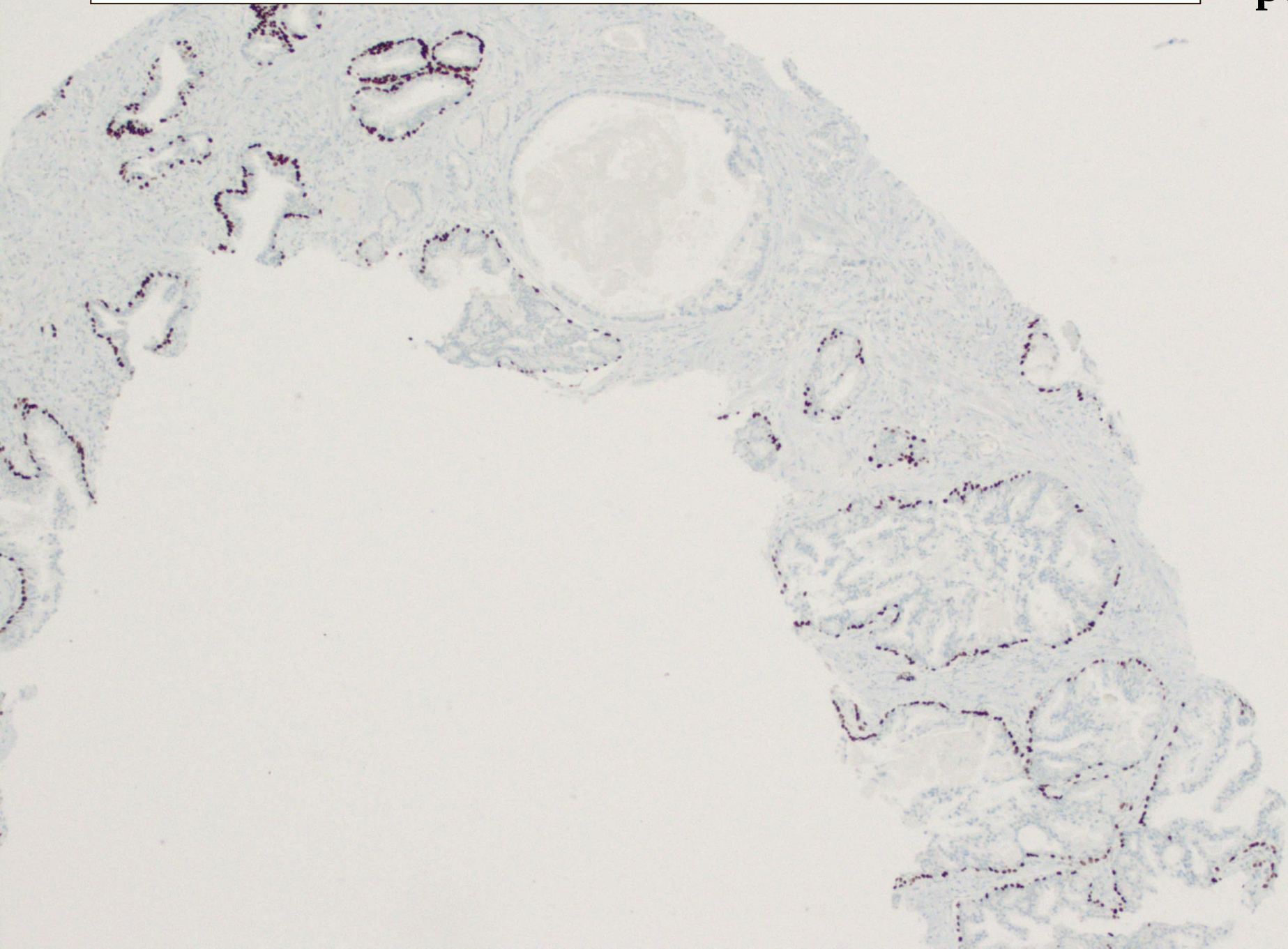
Atypical Intraductal Proliferation: Summary

- Topographic, clinical and molecular similarities between AIP and IDC-P suggest they are related lesions
- Due to specific treatment implications for the diagnosis of IDC-P, the term “low-grade IDC-P” is not recommended instead use “AIP, suspicious for IDC-P”
- Any expansile atypical loose cribriform glands in biopsy warrant a repeat biopsy
- Be conservative but high index of suspicion is necessary to avoid misdiagnosis as HGPIN



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

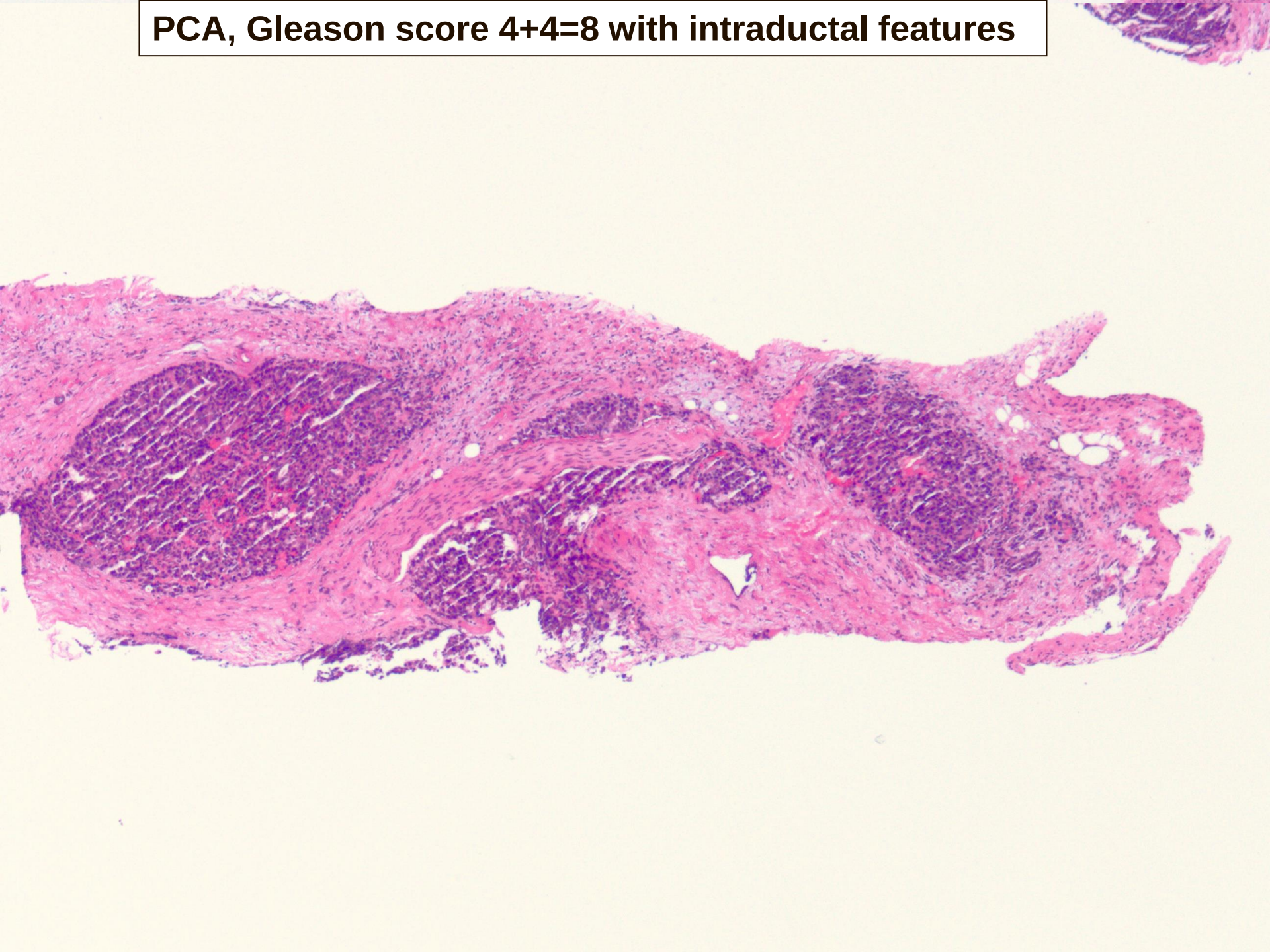
p63



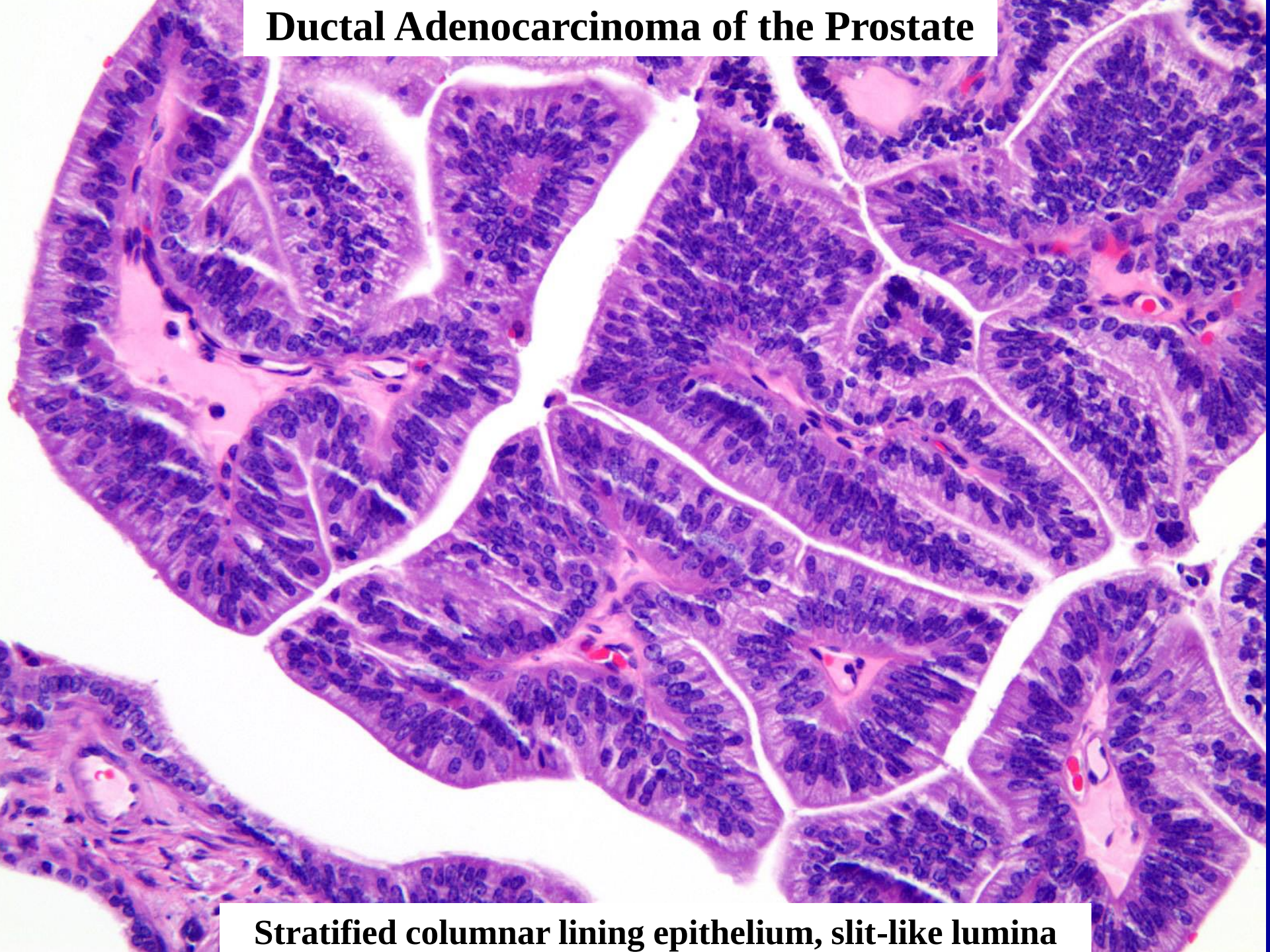
WHEN TO PERFORM BASAL CELL STAINING?

- 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; refer such cases as “PCa with intraductal features”

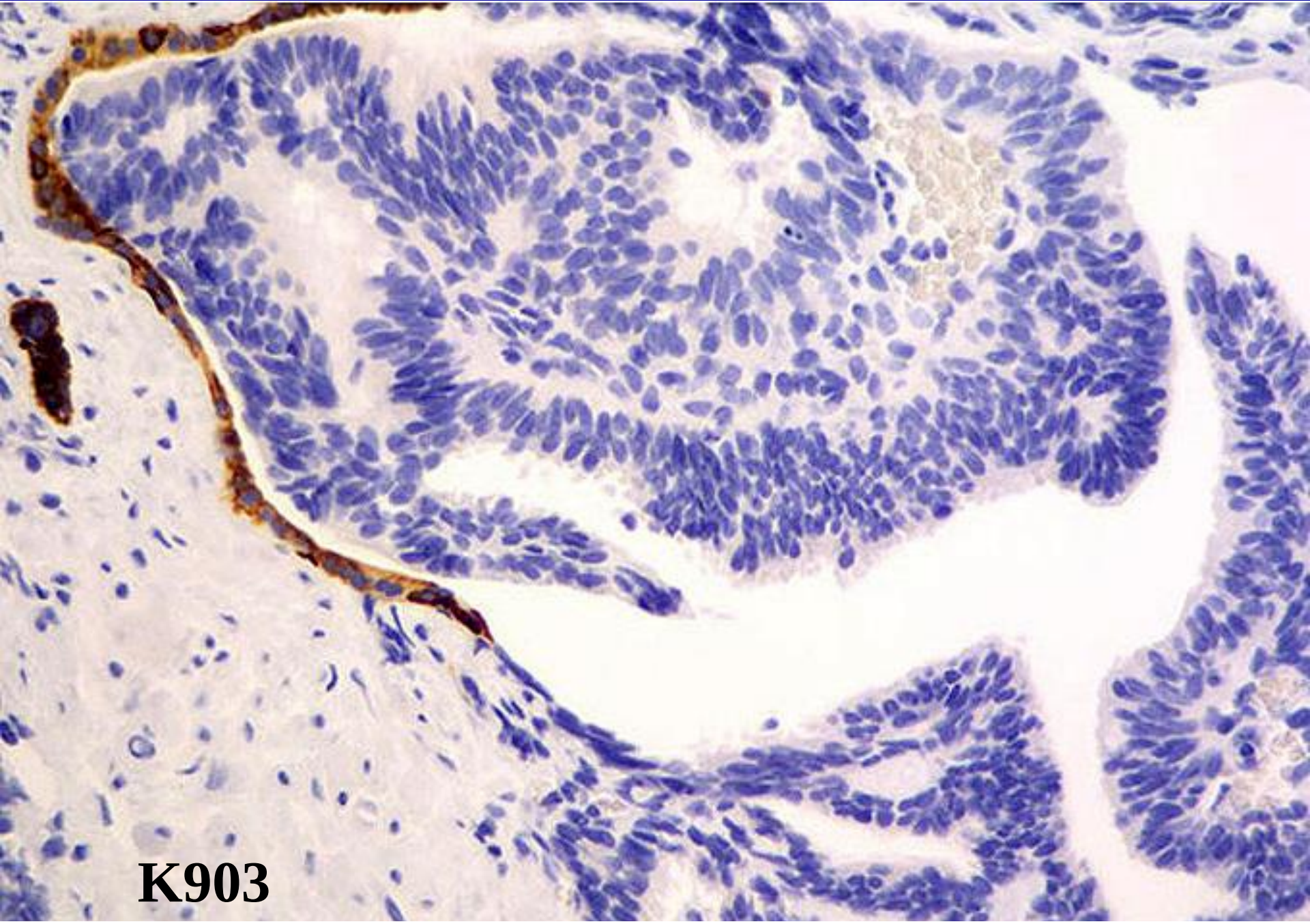
PCA, Gleason score 4+4=8 with intraductal features



Ductal Adenocarcinoma of the Prostate



Stratified columnar lining epithelium, slit-like lumina

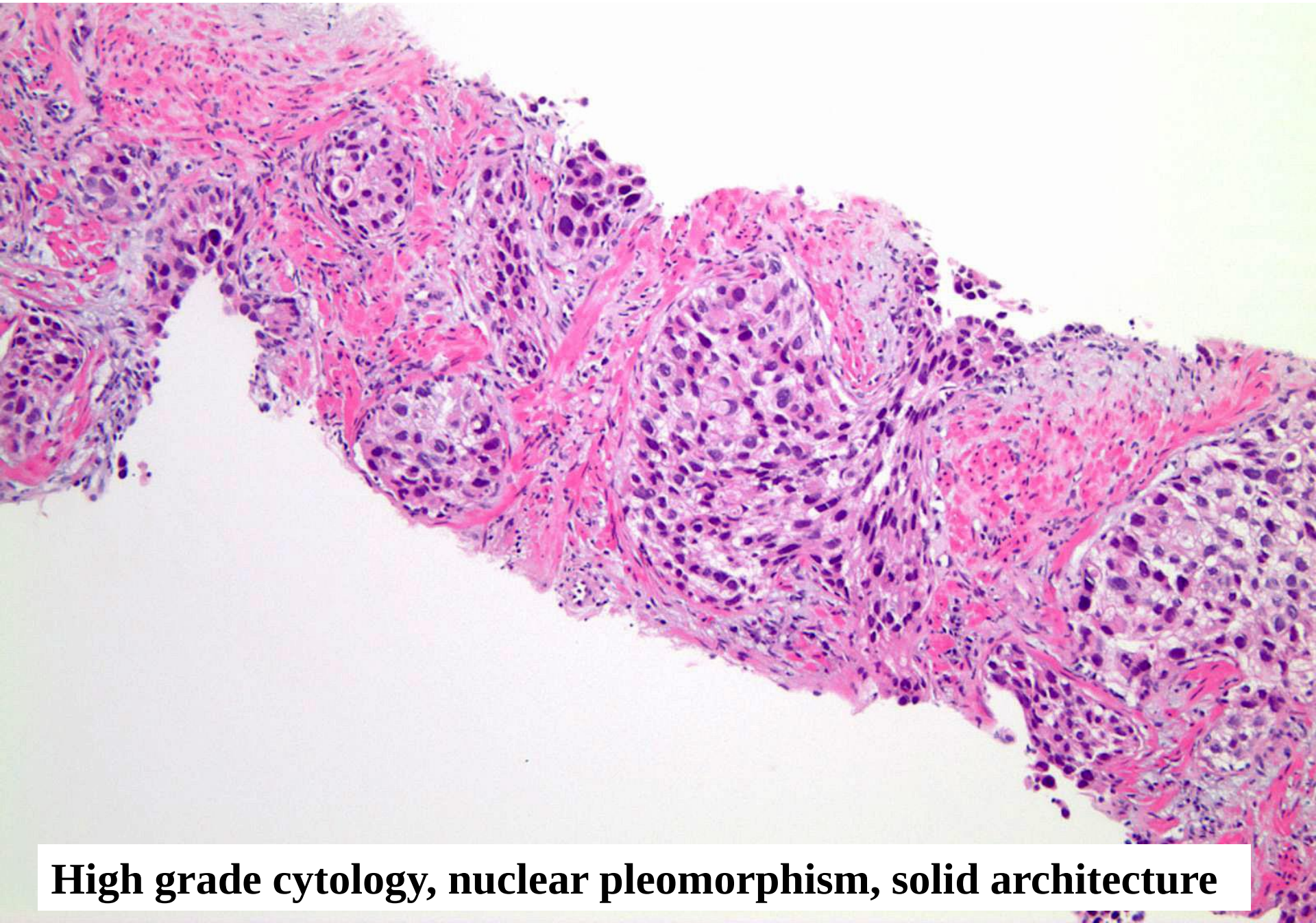


Ductal Adenocarcinoma of the Prostate with residual basal cells: Intraductal spread

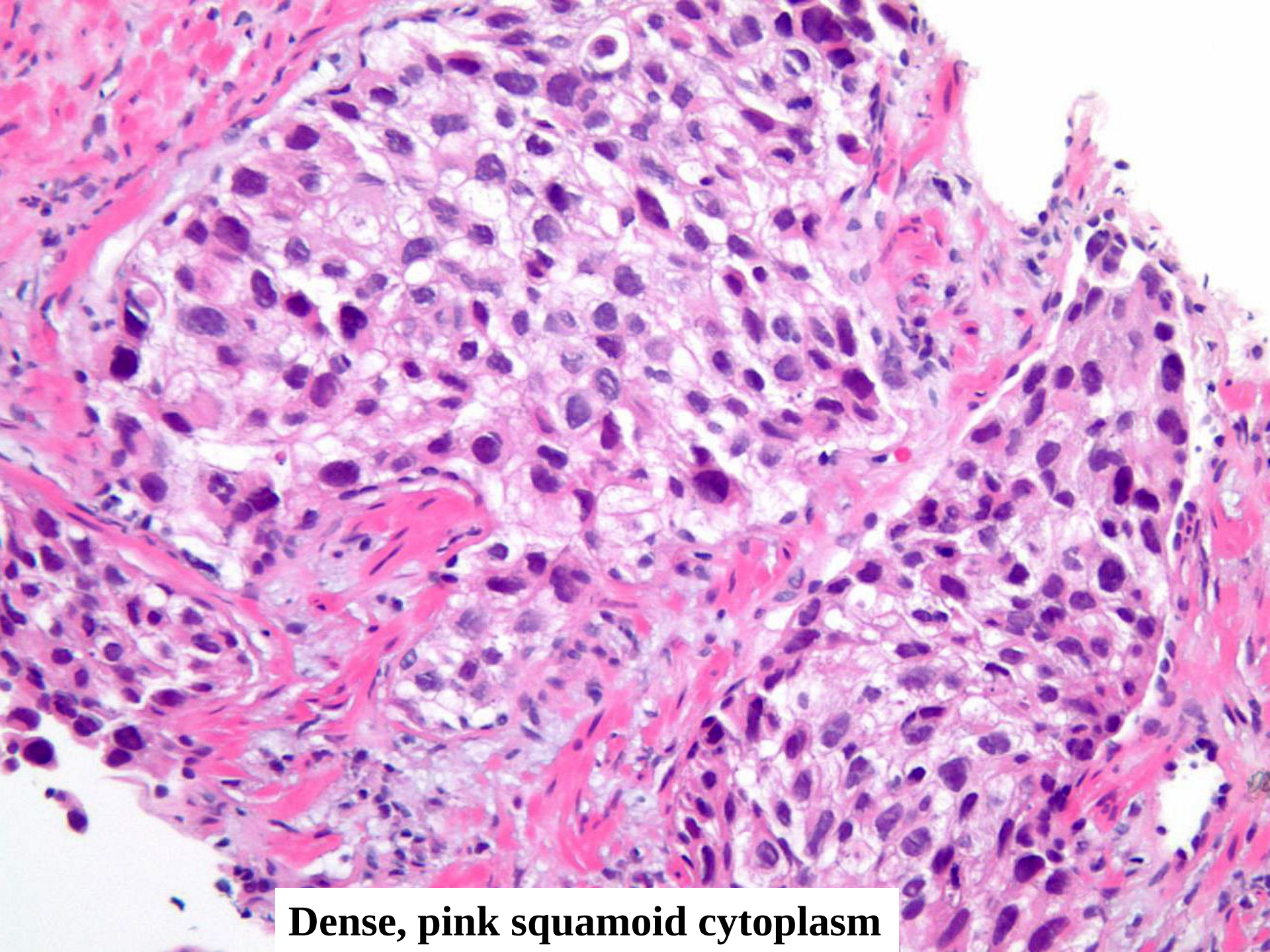
Ductal Adenocarcinoma

- Variant of non-acinar adenocarcinoma
- Accounts for <1% in pure form and ~5% in mixed ductal-acinar form
- Arise and spread within preexisting large primary periurethral ducts or in peripheral ducts
- Basal cells may be preserved

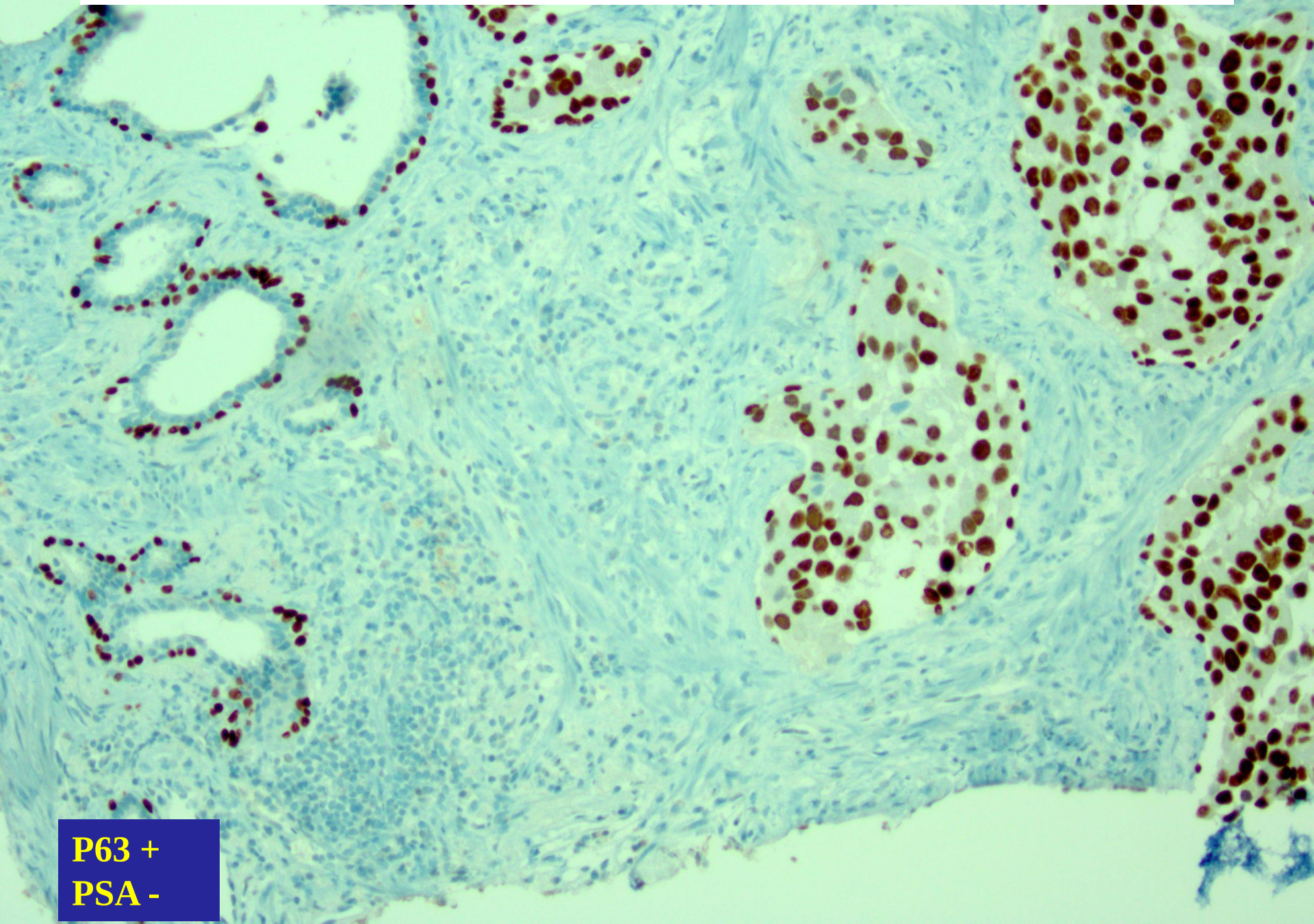
Case 4: High Grade Urothelial Carcinoma Involving Prostatic Acini



High grade cytology, nuclear pleomorphism, solid architecture

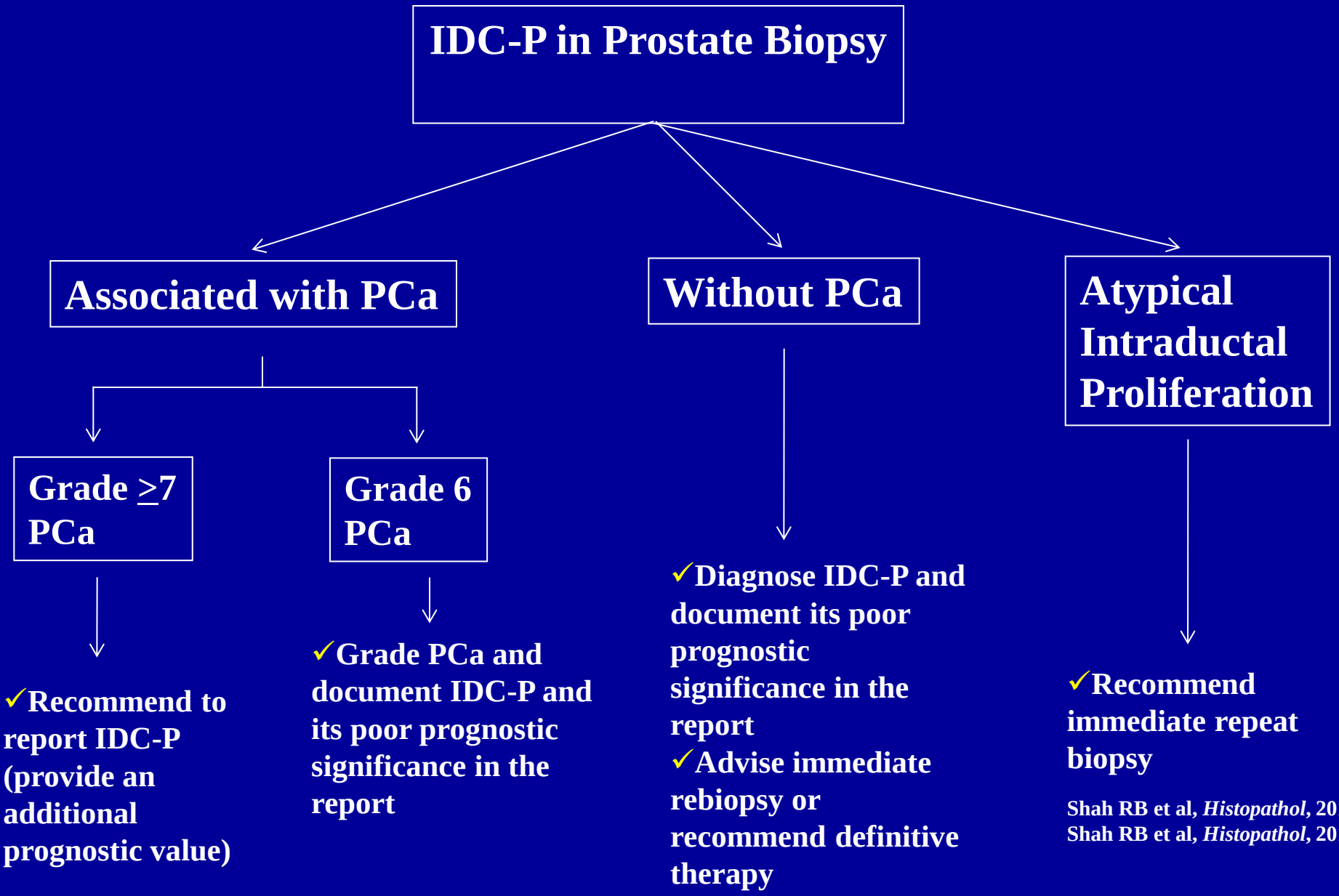

Dense, pink squamoid cytoplasm

High Grade Urothelial Carcinoma Involving Prostatic Acini

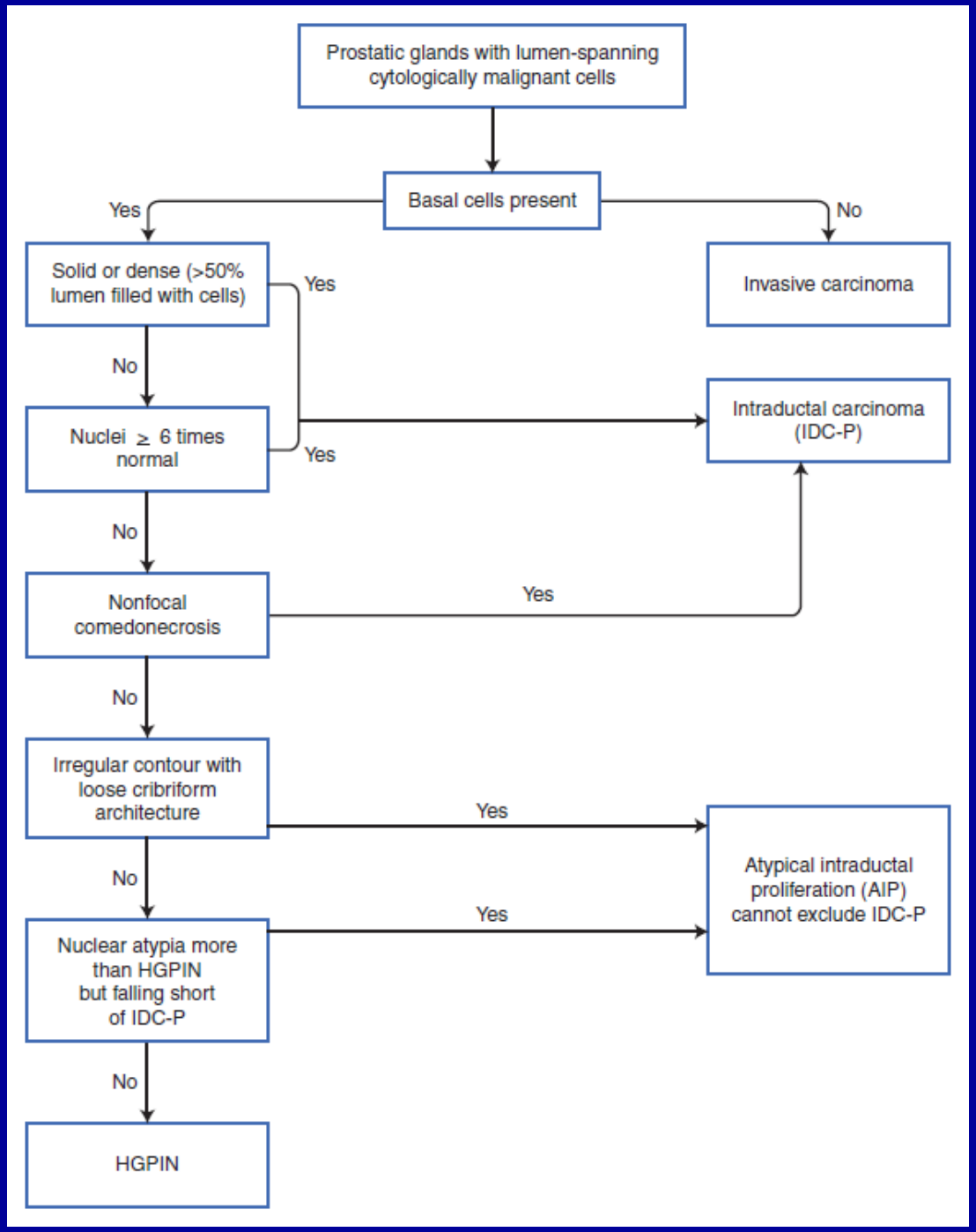


P63 +
PSA -

Reporting Recommendations for Prostate Biopsy with IDC-P



Shah RB et al, *Histopathol*, 2017
Shah RB et al, *Histopathol*, 2019



Shah RB, Zhou M
Prostate Biopsy Interpretation: An Illustrated Guide
2nd edition, Springer, 2019

Thank you!