VIRTUAL

UT SOUTHWESTERN MEDICAL CENTER

ASCP 2020 VIRTUAL

SEPTEMBER 9-11, 2020

Outline

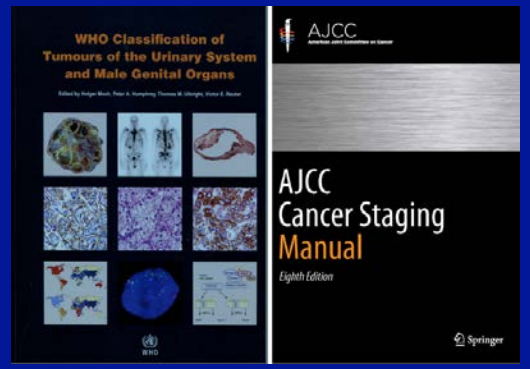
- Historical perspective
  - Intraductal carcinoma
  - Invasive cribriform cancer
- Modern day definition
  - Problem areas
- Clinical significance
- Incorporating into patient management

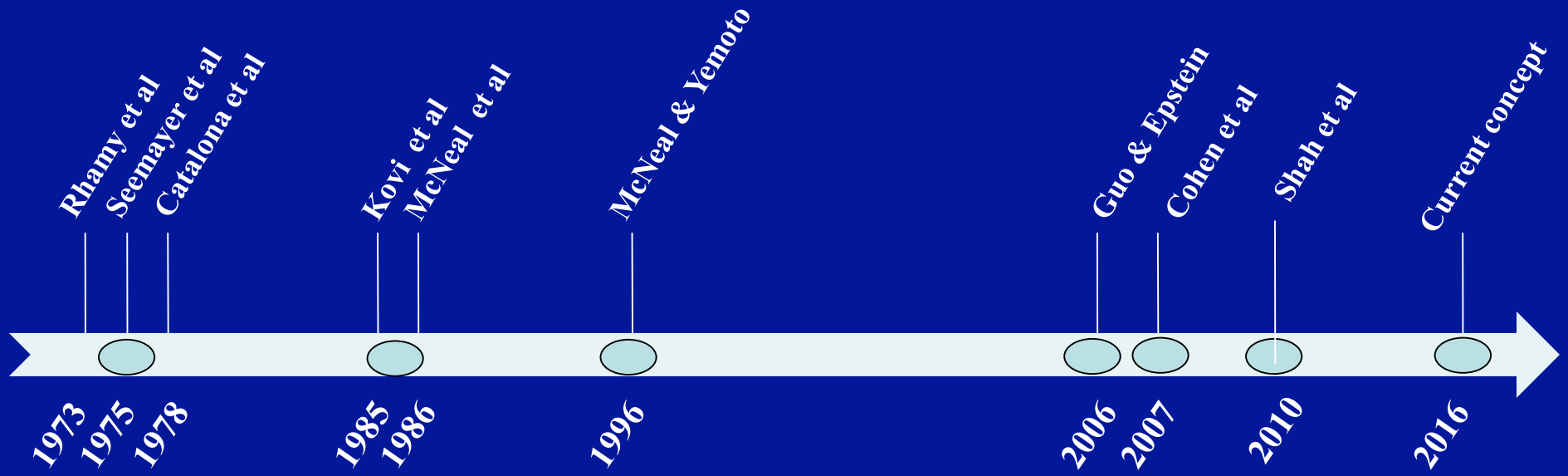
Intraductal Carcinoma of the Prostate (IDC-P)

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)

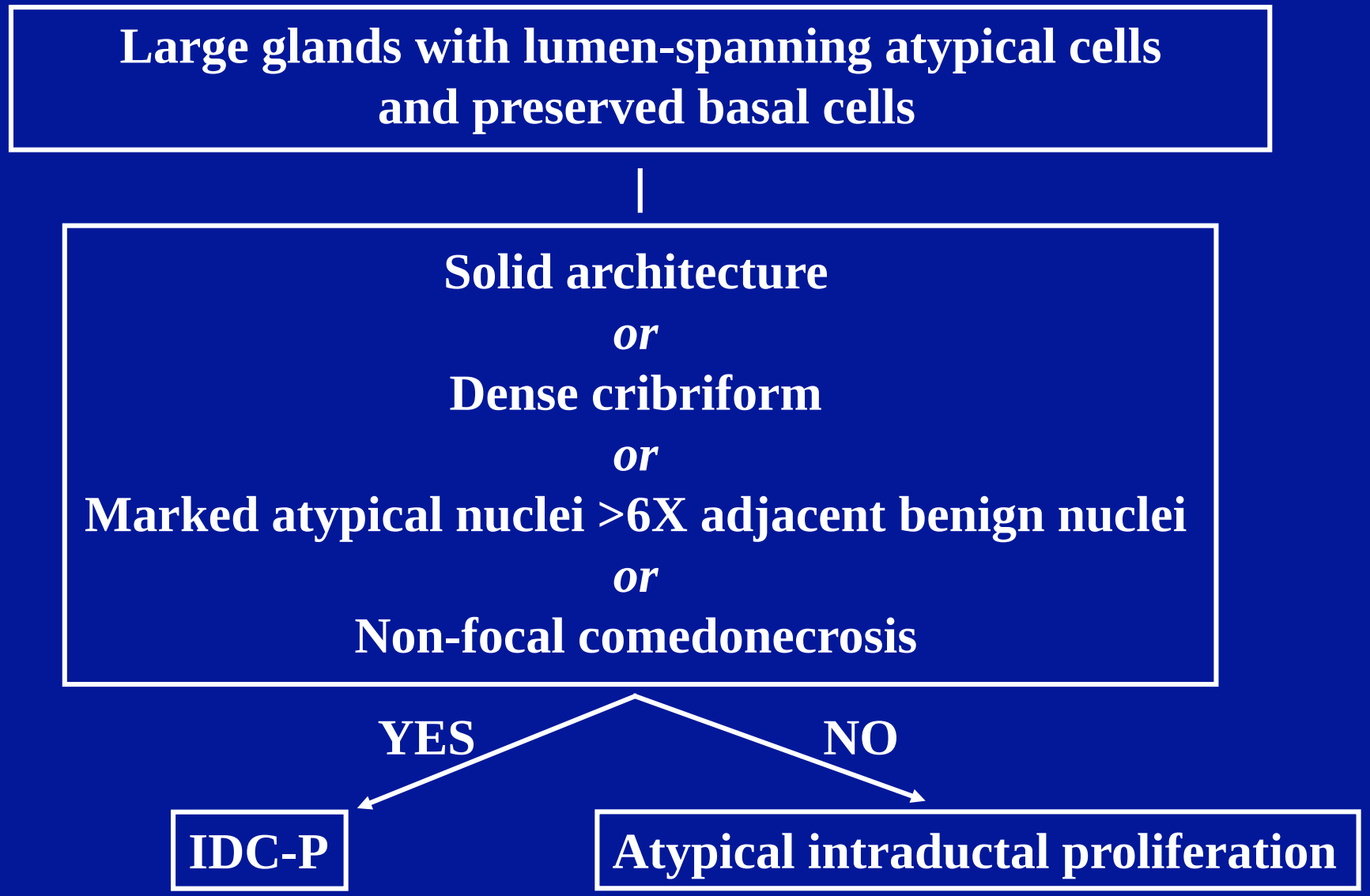
Histological Features

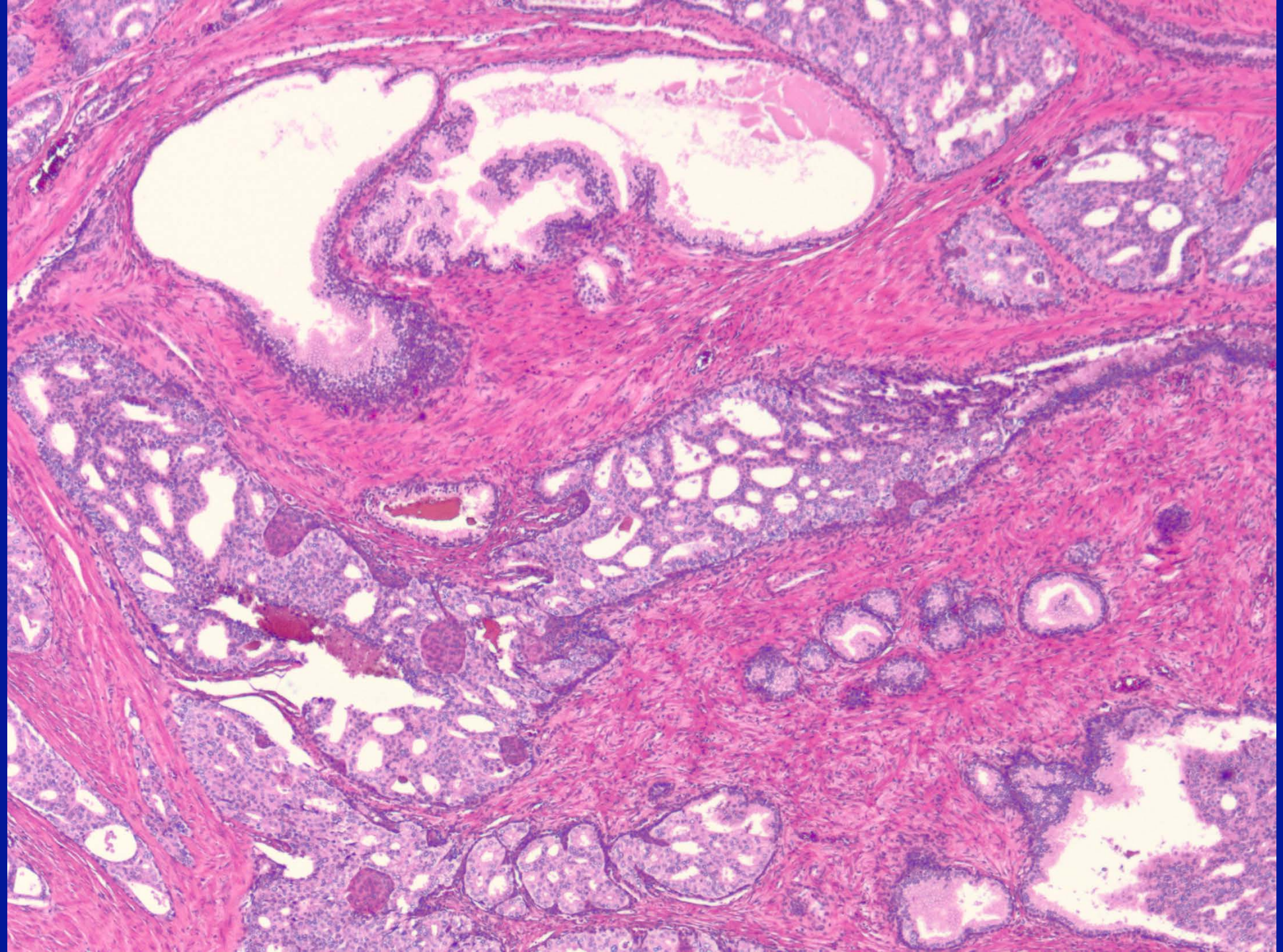
Hallmarks

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

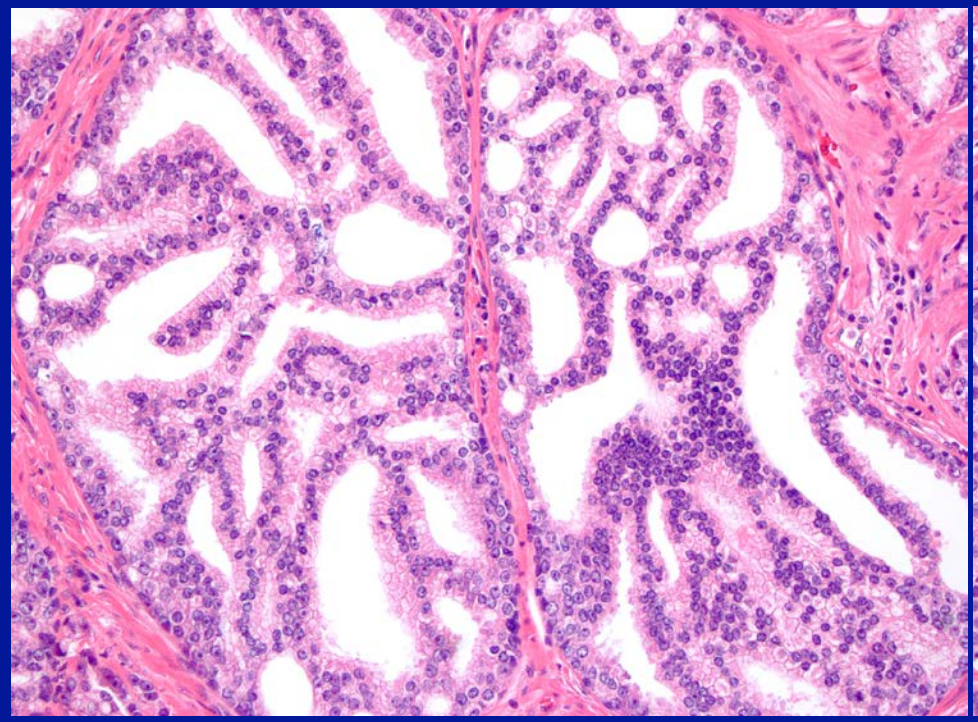
Diagnostic Criteria for IDC-P

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

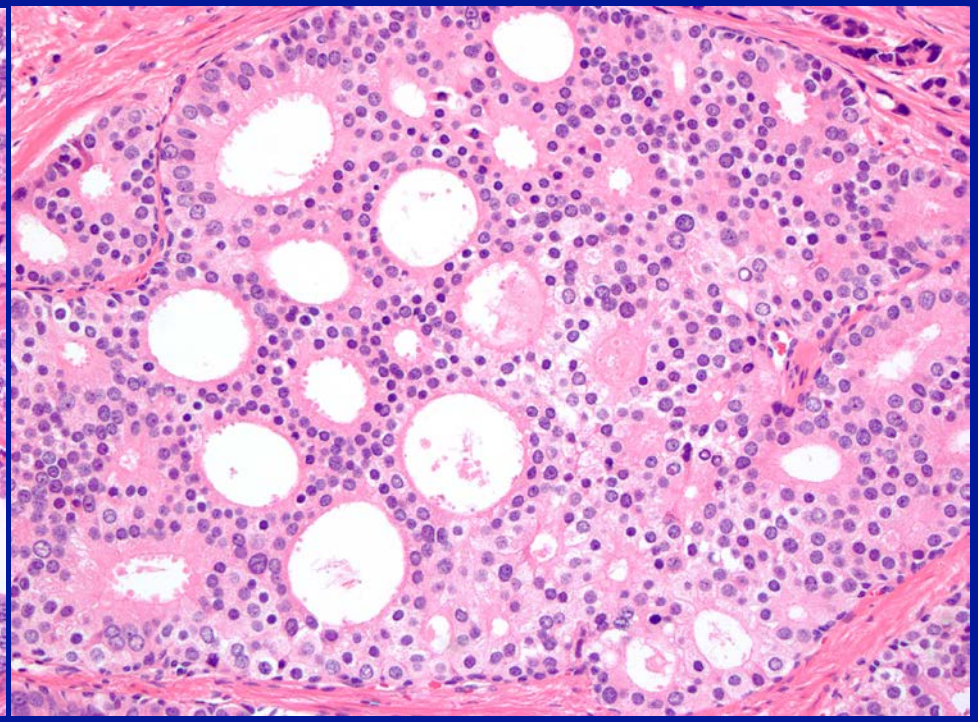




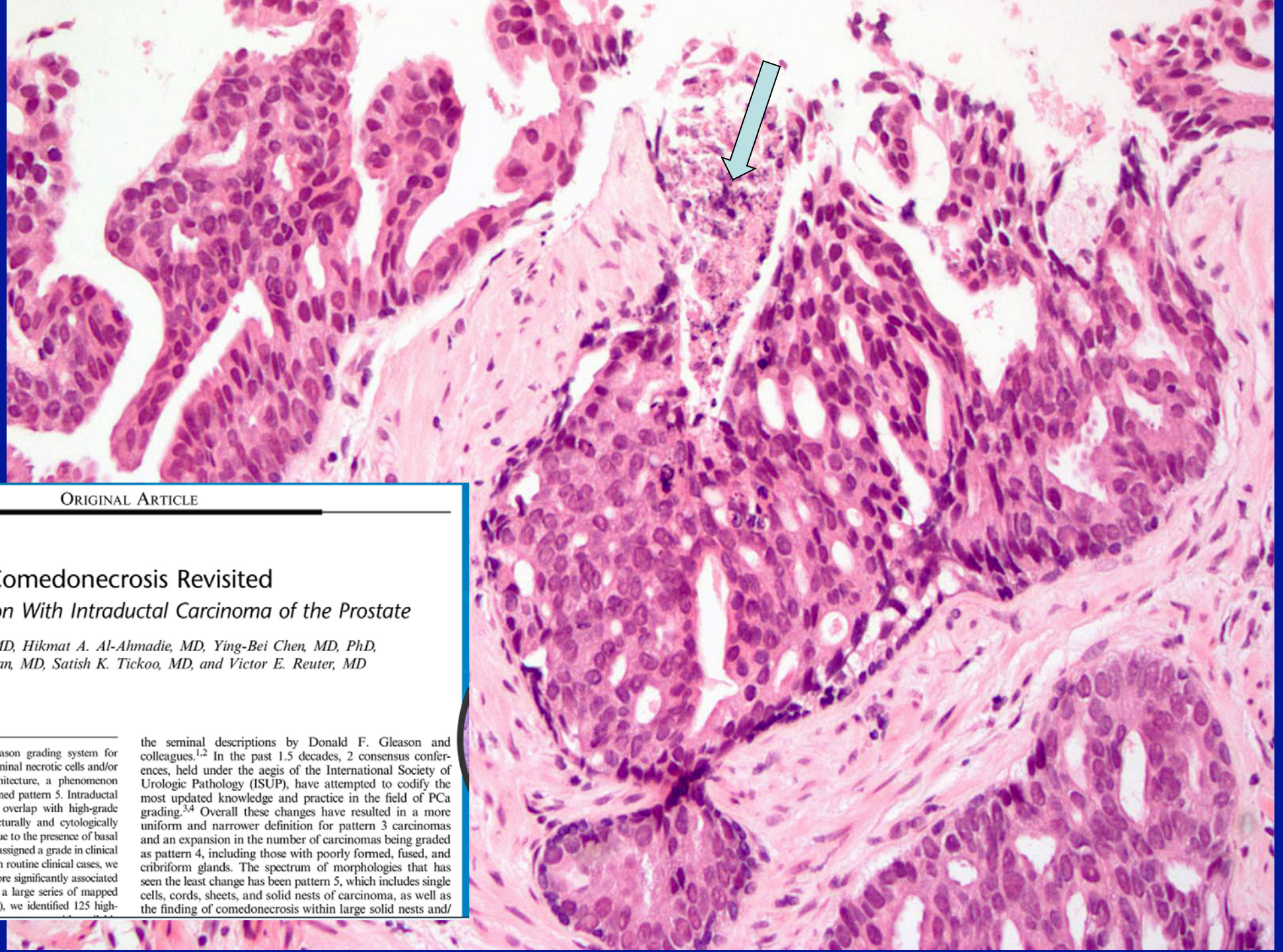
Dense cribriform = cellular mass > 50% of luminal spaces



Dense cribriform:
Irregular lumina



Dense cribriform:
Punched out lumina



ORIGINAL ARTICLE

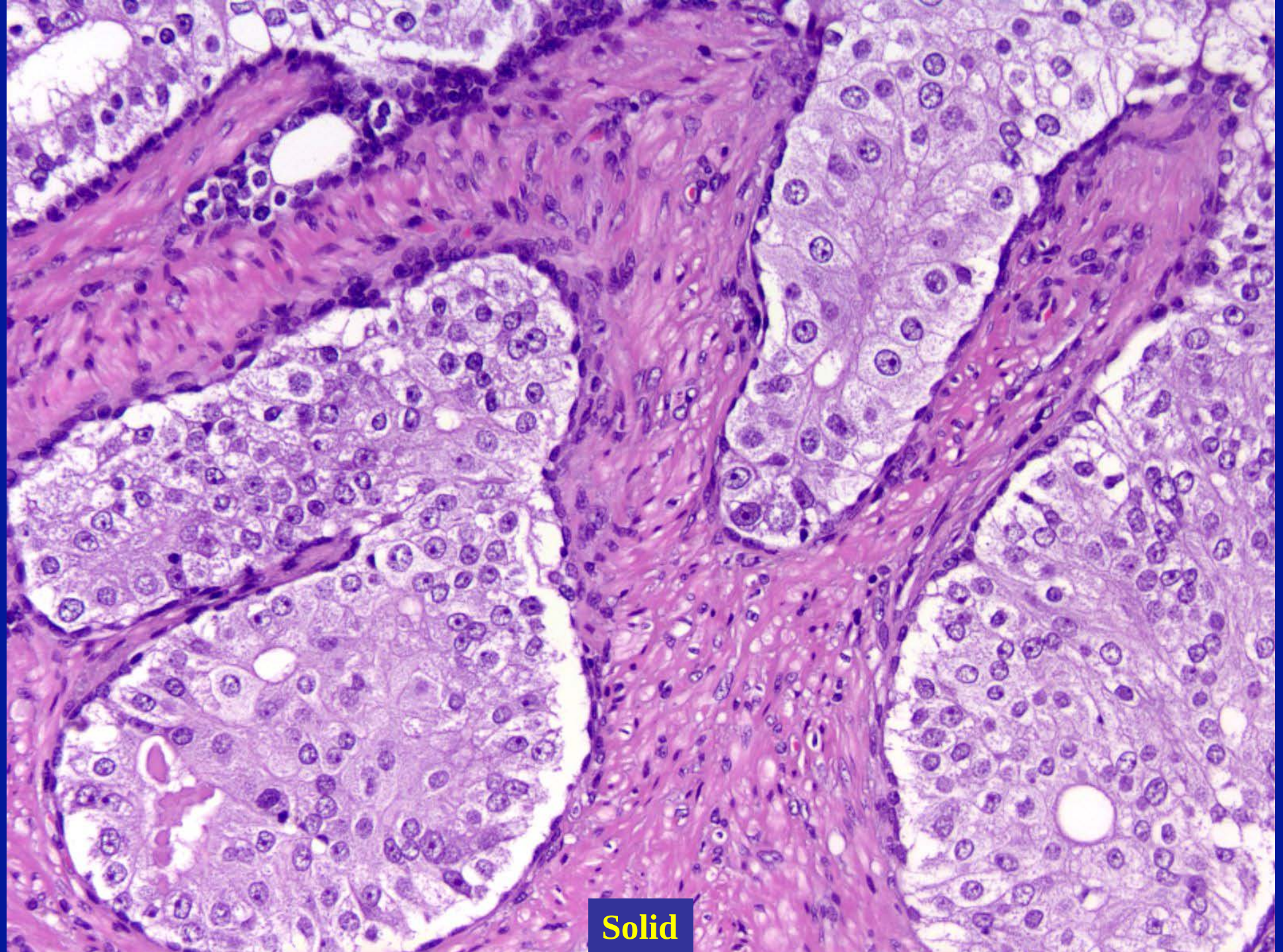
Comedonecrosis Revisited

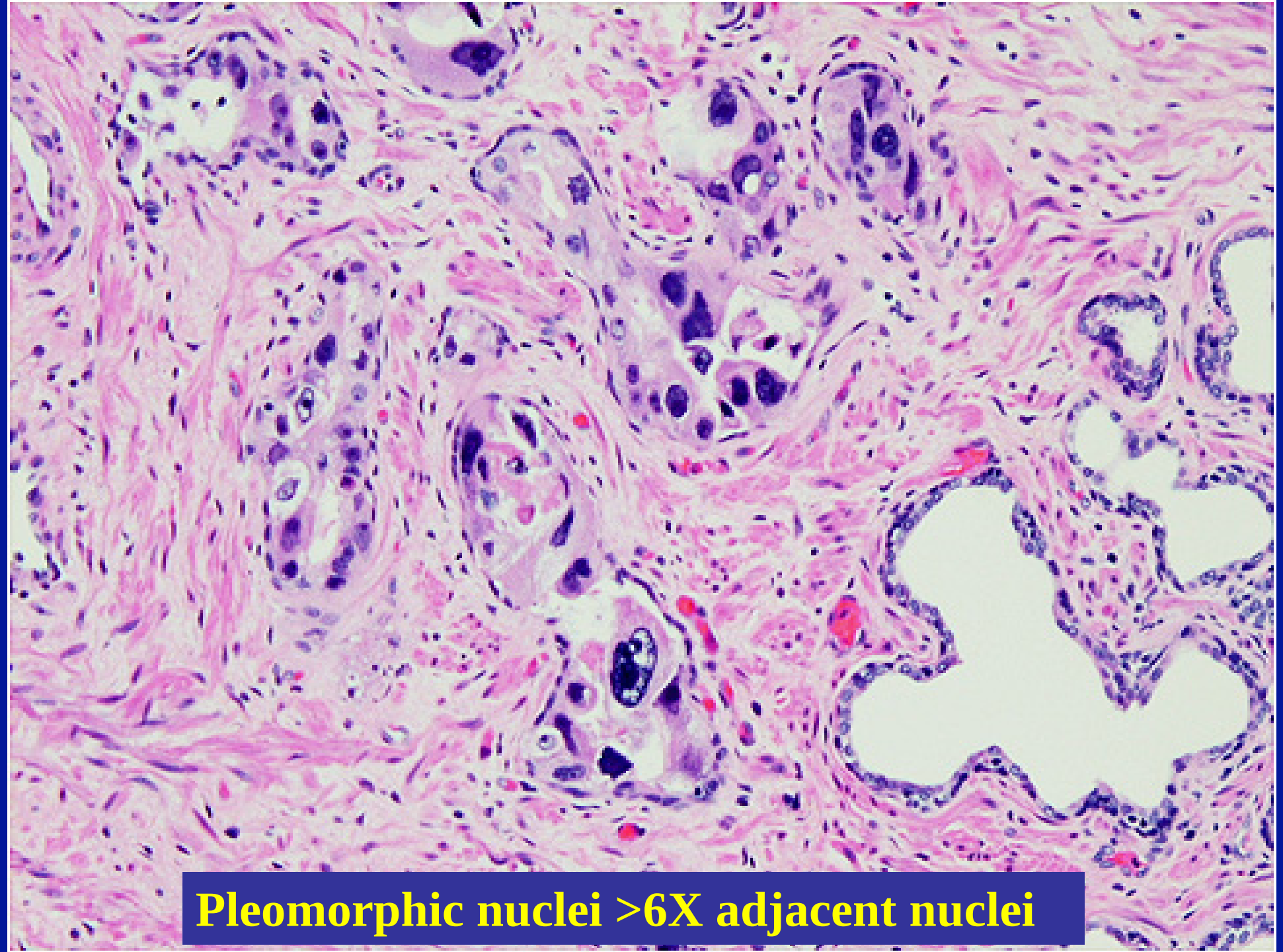
Strong Association With Intraductal Carcinoma of the Prostate

Samson W. Fine, MD, Hikmat A. Al-Ahmadie, MD, Ying-Bei Chen, MD, PhD, Anuradha Gopalan, MD, Satish K. Tickoo, MD, and Victor E. Reuter, MD

Abstract: From the advent of the Gleason grading system for prostate cancer, cancer displaying intraluminal necrotic cells and/or karyorrhexis within cribriform/solid architecture, a phenomenon termed "comedonecrosis," has been assigned pattern 5. Intraductal carcinoma (IDC-P) shows morphologic overlap with high-grade cribriform/solid adenocarcinoma architecturally and cytologically and may also show central necrosis, yet due to the presence of basal cells at the duct periphery is not currently assigned a grade in clinical practice. On the basis of observations from routine clinical cases, we hypothesized that comedonecrosis was more significantly associated with IDC-P than invasive disease. From a large series of mapped radical prostatectomy specimens (n = 933), we identified 125 high-

the seminal descriptions by Donald F. Gleason and colleagues.[1,2] In the past 1.5 decades, 2 consensus conferences, held under the aegis of the International Society of Urologic Pathology (ISUP), have attempted to codify the most updated knowledge and practice in the field of PCa grading.[3,4] Overall these changes have resulted in a more uniform and narrower definition for pattern 3 carcinomas and an expansion in the number of carcinomas being graded as pattern 4, including those with poorly formed, fused, and cribriform glands. The spectrum of morphologies that has seen the least change has been pattern 5, which includes single cells, cords, sheets, and solid nests of carcinoma, as well as the finding of comedonecrosis within large solid nests and/

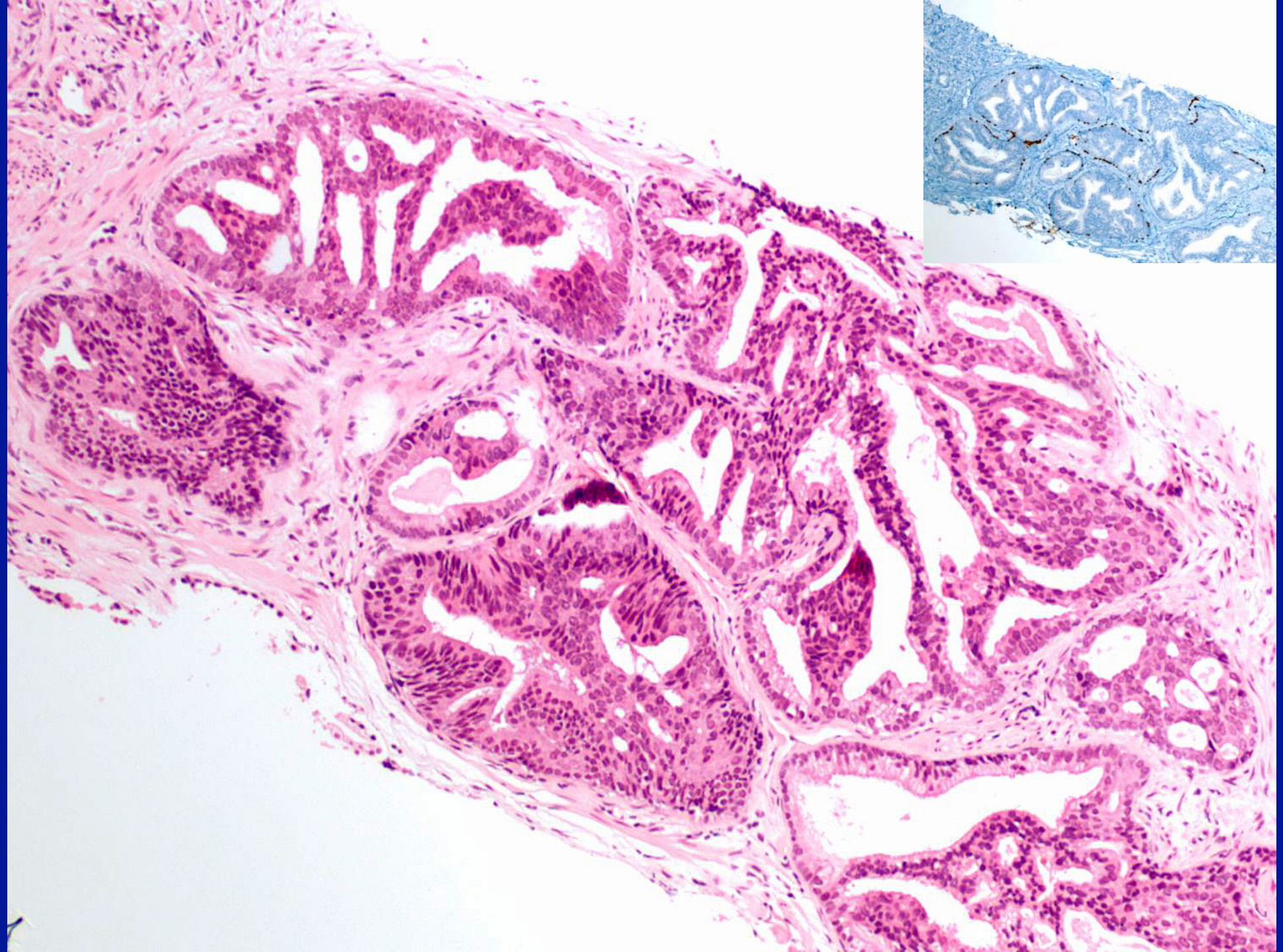

Solid

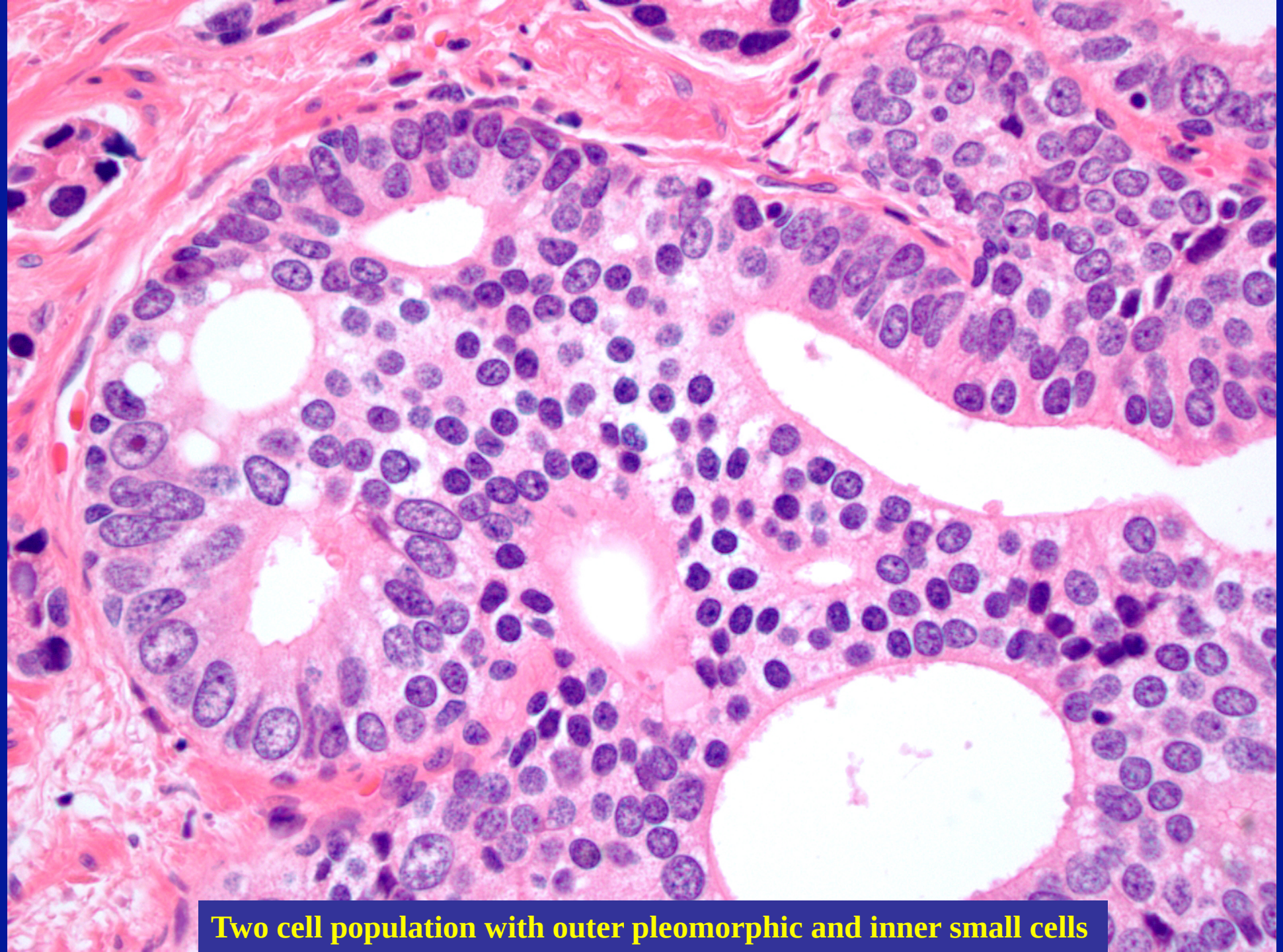

Pleomorphic nuclei >6X adjacent nuclei

Minor Diagnostic Criteria for IDC-P

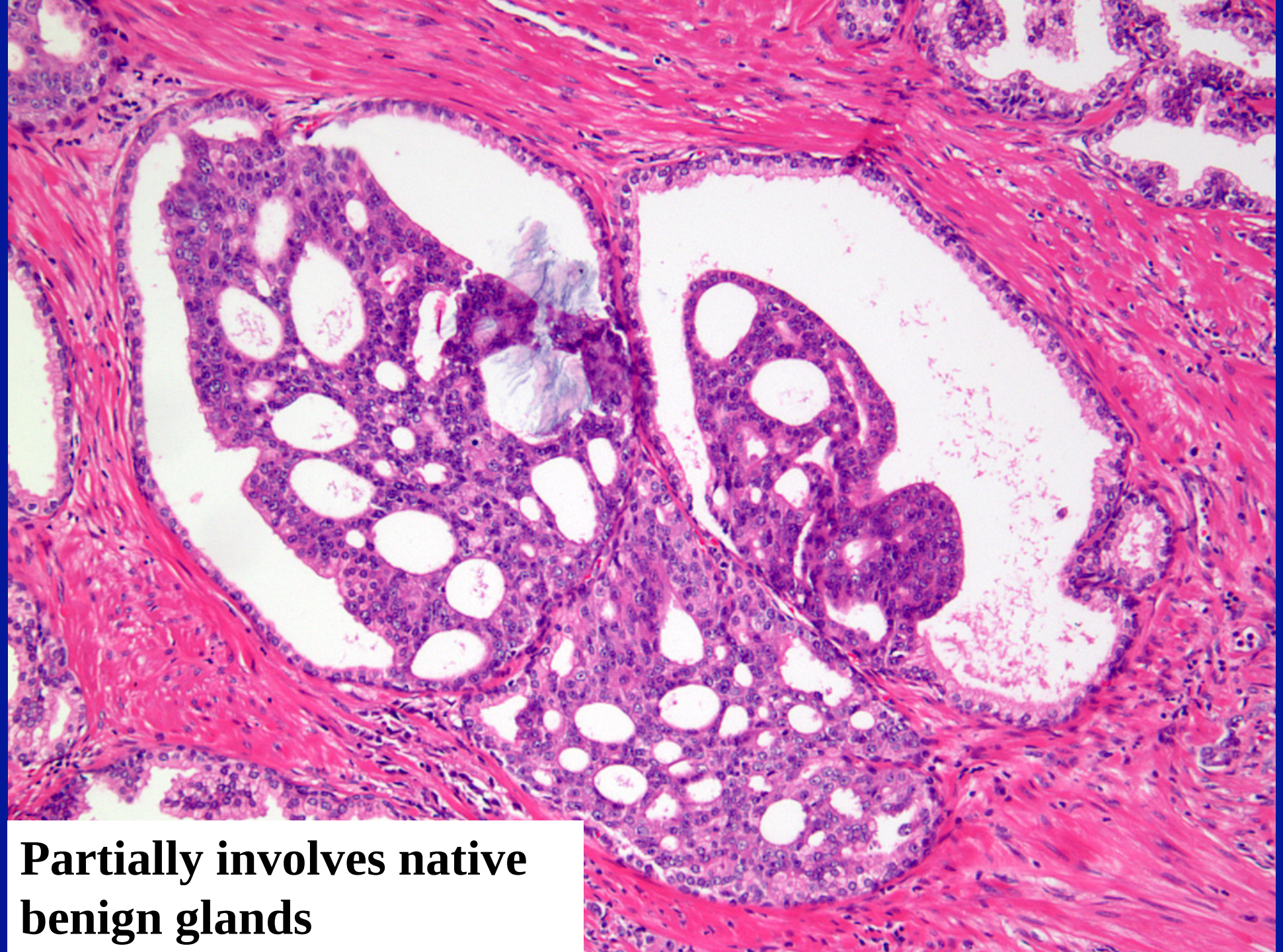
(Cohen RJ et al, *Arch Pathol Lab Med*; 2007
Shah RB et al, *Am J Surg Pathol*; 2010)

- ✓ 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





Two cell population with outer pleomorphic and inner small cells



Partially involves native benign glands

Intraductal Carcinoma of the Prostate (IDC-P)

Diagnostic Criteria

- Use a constellation of architectural and cytological features
- 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

Modern Pathology (2006) 19, 1528–1535

www.modernpathology.org

Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance

Charles C Guo[1] and Jonathan I Epstein[1,2,3]

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Intraductal carcinoma of the prostate (IDC-P) has been described in radical prostatectomies. However, there is limited information as to its histologic features and clinical significance when seen on prostate biopsy. A total of 27 cases of prostate biopsies with only IDC-P (ie no infiltrating cancer anywhere on the biopsy) were studied from the consult files of one of the authors. IDC-P was defined as malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells forming either: (1) solid or dense cribriform patterns or; (2) loose cribriform or micropapillary patterns with either marked nuclear atypia (nuclear size 6 × normal or larger) or comedonecrosis. The numbers of cores involved by IDC-P in the biopsies ranged from 1 to 7, with >1 core involved in 17 cases. The architectural patterns of IDC-P were solid (12), dense cribriform (19), loose cribriform (17), and micropapillary (5). More than one pattern was present in 24 of 27 cases. The cytological features frequently observed in IDC-P were marked pleomorphism (18), non-focal comedonecrosis (22), and mitoses (20). Basal cells were observed on regular hematoxylin and eosin stained slides in 14 cases; in all the cases, basal cells were confirmed by immunohistochemical stains for high molecular weight cytokeratin (*n* = 25) and/or p63 (*n* = 4). After the diagnosis of IDC-P on prostate biopsies, patients were treated by radical prostatectomy (6), radiation (7), hormone (5), combined radiation and hormone (1), or watchful waiting (2). The follow-up information was not available for six patients. The follow-up times ranged up to 4 years with an average of 2.1 years. In all six radical prostatectomy specimens, high-grade infiltrating carcinoma with Gleason score 8 or 9 was present with five cases also revealing prominent IDC-P. Non-focal extraprostatic extension of carcinoma

- N= 27 only IDC on bx
- 6 RPs:
  - all grade 8-9
  - 5 of 6 EPE
- 3/16 without therapy
  - bone mets

Intraductal Carcinoma of the Prostate Without Invasive Carcinoma on Needle Biopsy: Emphasis on Radical Prostatectomy Findings

Brian D. Robinson and Jonathan I. Epstein*

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Abbreviations and Acronyms

EPE = extraprostatic extension
GS = Gleason score
HT = hormone therapy
IDC-P = intraductal carcinoma of the prostate
PIN = high grade prostatic intraepithelial neoplasia
PSA = prostate specific antigen
RP = radical prostatectomy
RT = radiation therapy

Submitted for publication February 24, 2010.
Study received institutional review board approval.

* Correspondence: The Johns Hopkins Hospital, Weinberg Building, Suite 2242, 401 North Broadway, Baltimore, Maryland 21231 (telephone: 410-614-4330; FAX: 443-287-3818; e-mail: jepstein@jhmi.edu).

Purpose: Limited information is available on radical prostatectomy findings in men with intraductal carcinoma of the prostate on needle core biopsy in the absence of invasive prostate cancer.

Materials and Methods: From the consulting files of one of us we identified 83 men in whom biopsy showed only intraductal prostate cancer. Followup was available in 66 cases. We reviewed slides in 21 radical prostatectomy cases.

Results: Treatment was radical prostatectomy in 23 men, radiation therapy in 15, hormone therapy in 8 and radiation plus hormone therapy in 15 while 5 underwent no treatment or repeat biopsy. Of the 21 radical prostatectomies available for review findings revealed pathological stage pT3a in 8 (38%), pT3b in 3 (13%), pT2 in 8 (38%) and intraductal carcinoma without identifiable invasive cancer in 2 (10%). One patient with pT3a had a positive lymph node at surgery. Average Gleason score was 7.9. Three patients (14%) experienced post-prostatectomy biochemical failure and another (5%) had bone metastases 2.5 years after prostatectomy. In 15 prostatectomies (71%) there was extensive intraductal carcinoma, defined as greater than 10% of tumor being intraductal, including the 2 cases of intraductal carcinoma only. Of the 19 prostatectomies with invasive adenocarcinoma 16 (84%) were conventional acinar adenocarcinoma, 2 (11%) ductal adenocarcinoma, and 1 (5%) mixed ductal and acinar adenocarcinoma.

Conclusions: At radical prostatectomy men in whom prior biopsies showed only intraductal carcinoma of the prostate typically have high grade (Gleason score 7 or greater) invasive adenocarcinoma and most have advanced stage disease (pT3). Definitive therapy is recommended in men with intraductal carcinoma of the prostate on needle biopsy even in the absence of pathologically documented invasive

Journal of Urology 2010; 184, 1328-1333

N= 23 patients with IDC-P only on biopsy

38%: pT3a

13%: pT3b

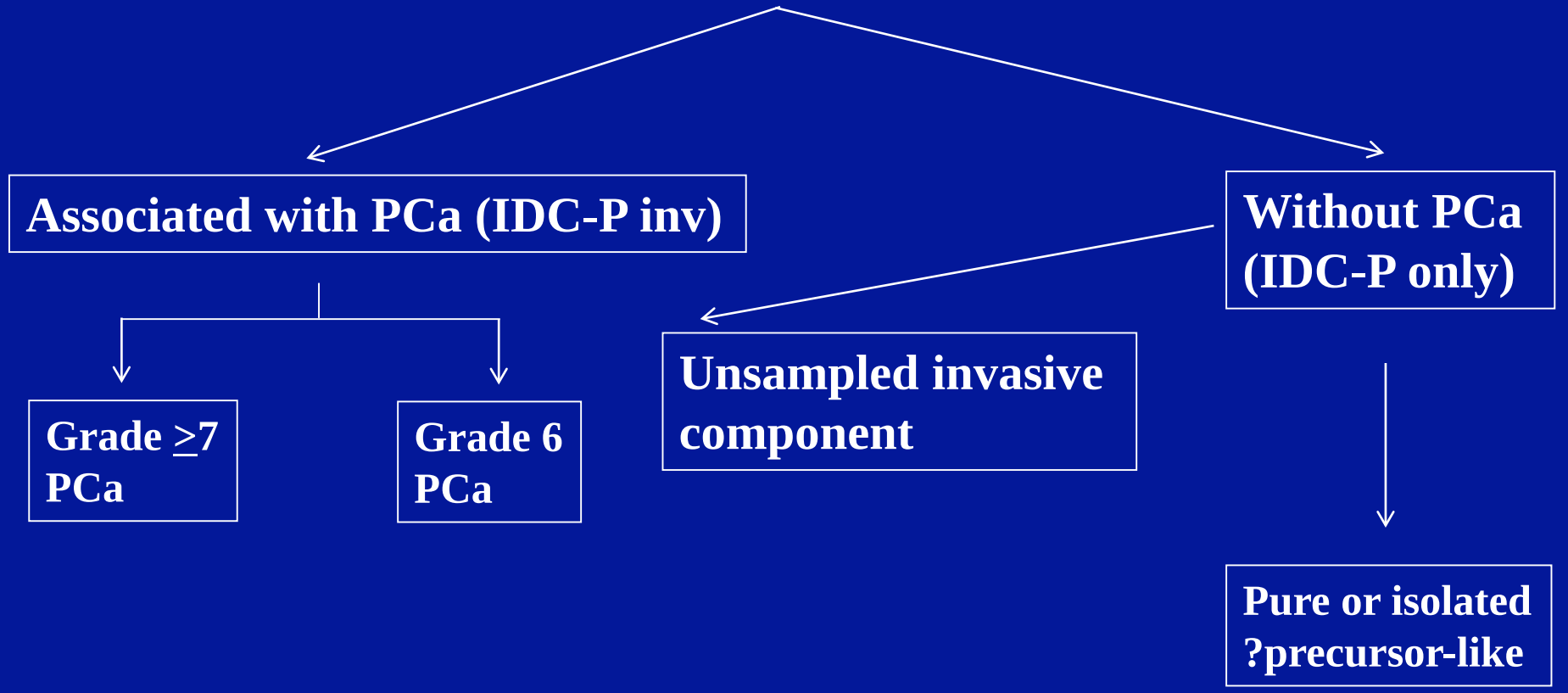
38%: pT2

10%: IDC-P only

IDC-P WITH INVASIVE PROSTATE CANCER: OUTCOME

- Independent predictor of various adverse outcomes in both biopsy and RP:
  - *Biochemical recurrence*
  - *Metastasis*
  - *Disease specific death*

PRESENTATION OF IDC-P IN BIOPSY



INTRADUCTAL CARCINOMA OF THE PROSTATE WITHOUT INVASIVE CANCER IN BIOPSY: TREATMENT IMPLICATIONS

- Definitive therapy may be indicated
- Some 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

ARTICLE

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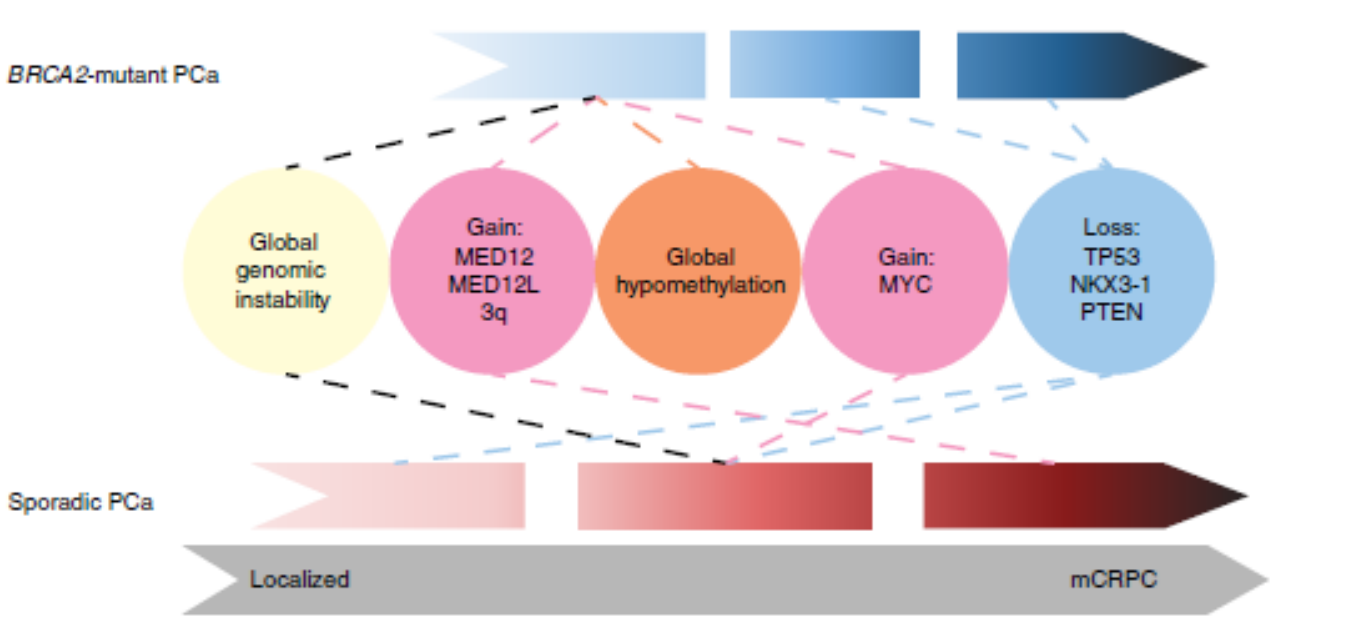
Germline *BRCA2* mutations drive prostate cancers with distinct evolutionary trajectories

Renea A. Taylor[1,*], Michael Fraser[2,*], Julie Livingstone[3,*], Shadrielle Melijah G. Espiritu[3,*], Heather Thorne[4,5,*], Vincent Huang[3], Winnie Lo[2], Yu-Jia Shiah[3], Takafumi N. Yamaguchi[3], Ania Sliwinski[5,6], Sheri Horsburgh[2], Alice Meng[2], Lawrence E. Heisler[3], Nancy Yu[3], Fouad Yousif[3], Melissa Papargiris[7], Mitchell G. Lawrence[7], Lee Timms[8], Declan G. Murphy[9], Mark Frydenberg[7], Julia F. Hopkins[3], Damien Bolton[7], David Clouston[10], John D. McPherson[8], Theodorus van der Kwast[2], Paul C. Boutros[3,11,12,**], Gail P. Risbridger[7,**] & Robert G. Bristow[2,11,**]



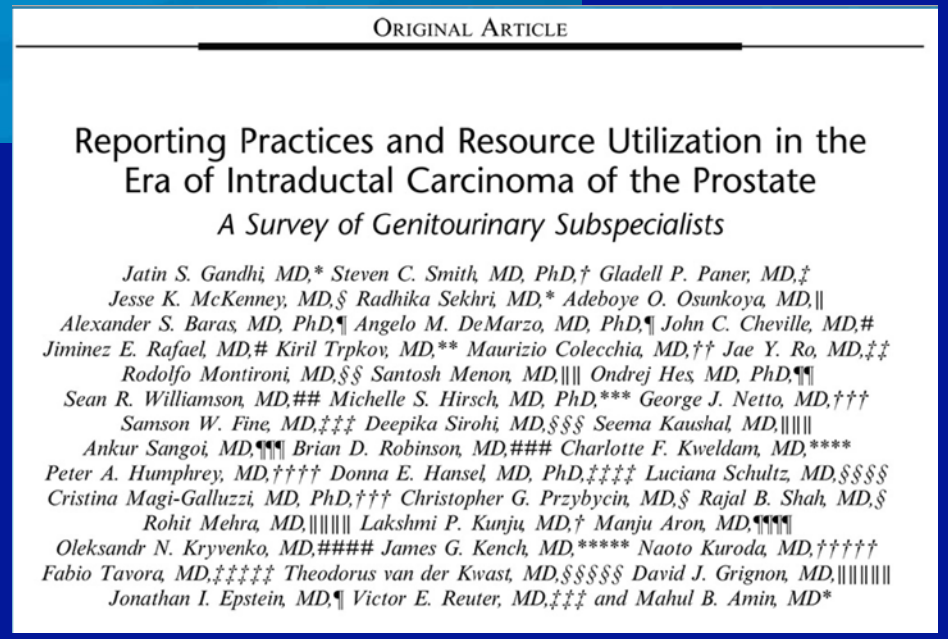
NCCN recommends germline mutation study for patients with high grade prostate cancer with IDC-P

- BRCA2 mutant PCa exhibit increased genomic instability and mutational profile that closely resembles metastatic than localized PCa
- Genomic and epigenomic dysregulation of the *MED12L/MED12* axis is frequently dysregulated in metastatic castration-resistant PCa
- This dysregulation is enriched in BRCA2-mutant PCa harboring IDC-P

PROBLEM AREAS

1) Borderline Cases
2) Cancer quantitation
3) Cancer grading

→ Reporting variability

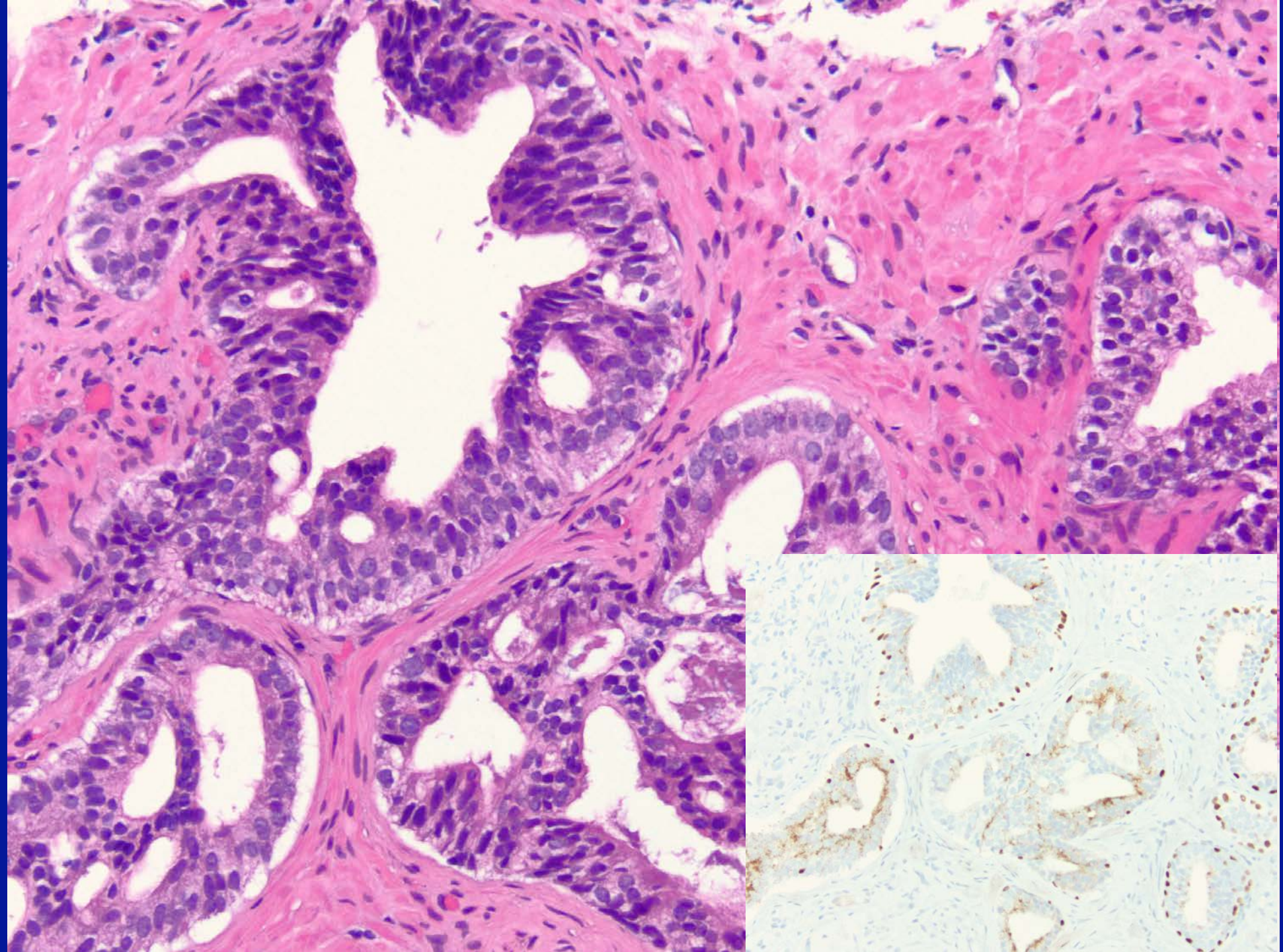


ORIGINAL ARTICLE

Reporting Practices and Resource Utilization in the Era of Intraductal Carcinoma of the Prostate

A Survey of Genitourinary Subspecialists

Jatin S. Gandhi, MD, Steven C. Smith, MD, PhD,† Gladell P. Paner, MD,‡ Jesse K. McKenney, MD,§ Radhika Sekhri, MD,* Adeboye O. Osunkoya, MD,‖ Alexander S. Baras, MD, PhD,¶ Angelo M. DeMarzo, MD, PhD,¶ John C. Cheville, MD,# Jiminez E. Rafael, MD,# Kiril Trpkov, MD,** Maurizio Colecchia, MD,†† Jae Y. Ro, MD,‡‡ Rodolfo Montironi, MD,§§ Santosh Menon, MD,‖‖ Ondrej Hes, MD, PhD,¶¶ Sean R. Williamson, MD,## Michelle S. Hirsch, MD, PhD,*** George J. Netto, MD,††† Samson W. Fine, MD,‡‡‡ Deepika Sirohi, MD,§§§ Seema Kaushal, MD,‖‖‖ Ankur Sangoi, MD,¶¶¶ Brian D. Robinson, MD,### Charlotte F. Kweldam, MD,**** Peter A. Humphrey, MD,†††† Donna E. Hansel, MD, PhD,‡‡‡‡ Luciana Schultz, MD,§§§§ Cristina Magi-Galluzzi, MD, PhD,††† Christopher G. Przybycin, MD,§ Rajal B. Shah, MD,§ Rohit Mehra, MD,‖‖‖‖ Lakshmi P. Kunju, MD,† Manju Aron, MD,¶¶¶¶ Oleksandr N. Kryvenko, MD,#### James G. Kench, MD,***** Naoto Kuroda, MD,†††† Fabio Tavora, MD,‡‡‡‡‡ Theodorus van der Kwast, MD,§§§§§ David J. Grignon, MD,‖‖‖‖‖ Jonathan I. Epstein, MD,¶ Victor E. Reuter, MD,‡‡‡ and Mahul B. Amin, MD**



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

Rajal B Shah[1] Jane K Nguyen,[1] Christopher G Przybycin,[1] Jordan P Reynolds,[1] Roni Cox,[1] Jonathan Myles,[1] Eric Klein[2] & Jesse K McKenney[1,2]

[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.

- Patients with isolated AIP require immediate re-biopsy to rule out significant PCa
- Patients with AIP + GG1/GG2 without "cribriform" architecture may not be good active surveillance candidates

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%)

Histopathology

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

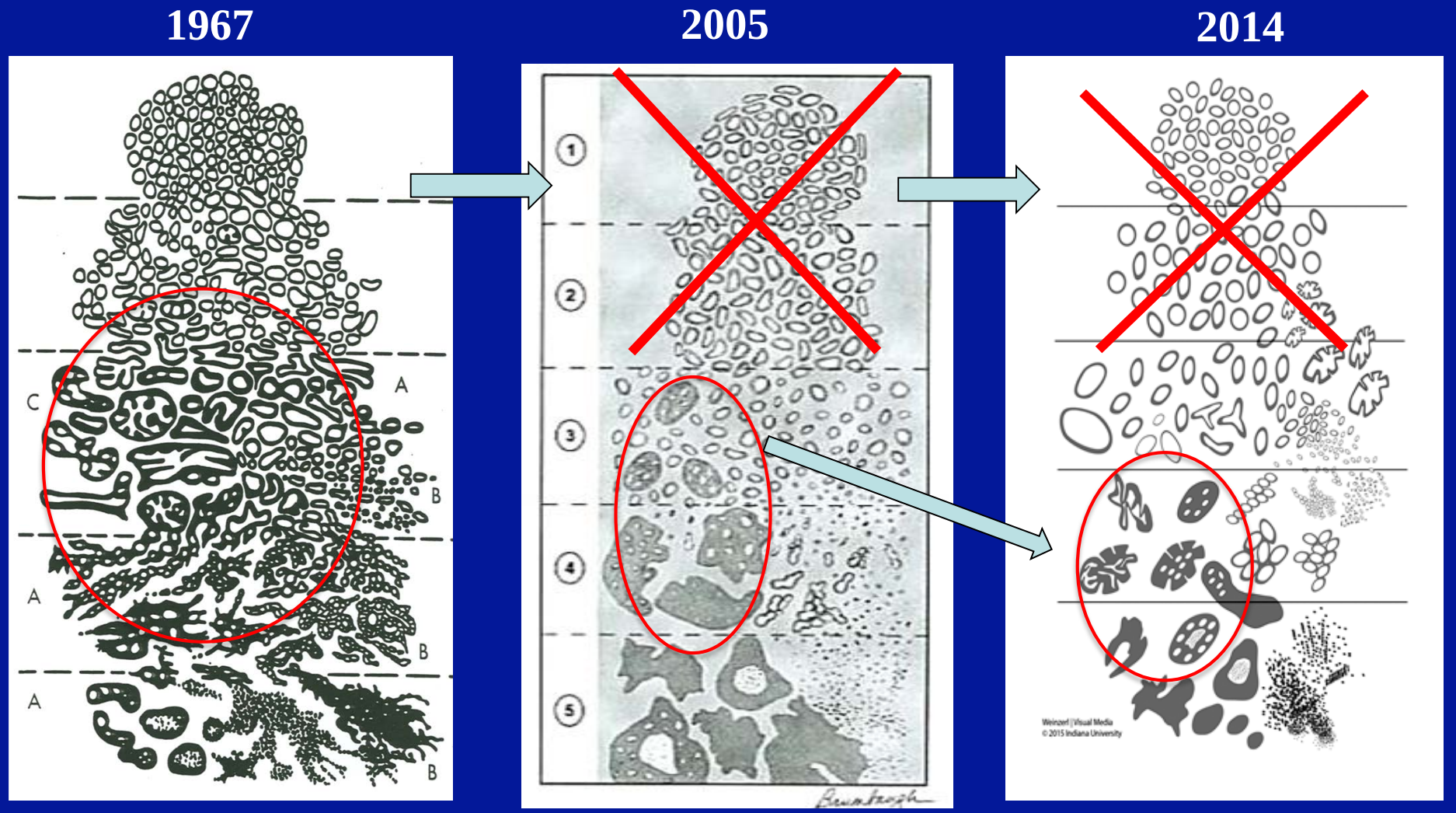
Atypical intraductal proliferation and intraductal carcinoma of the prostate on core needle biopsy: a comparative clinicopathological and molecular study with a proposal to expand the morphological spectrum of intraductal carcinoma

Rajal B Shah,[1,2] Jiyoon Yoon,[1] Gang Liu[3] & Wei Tian[1]

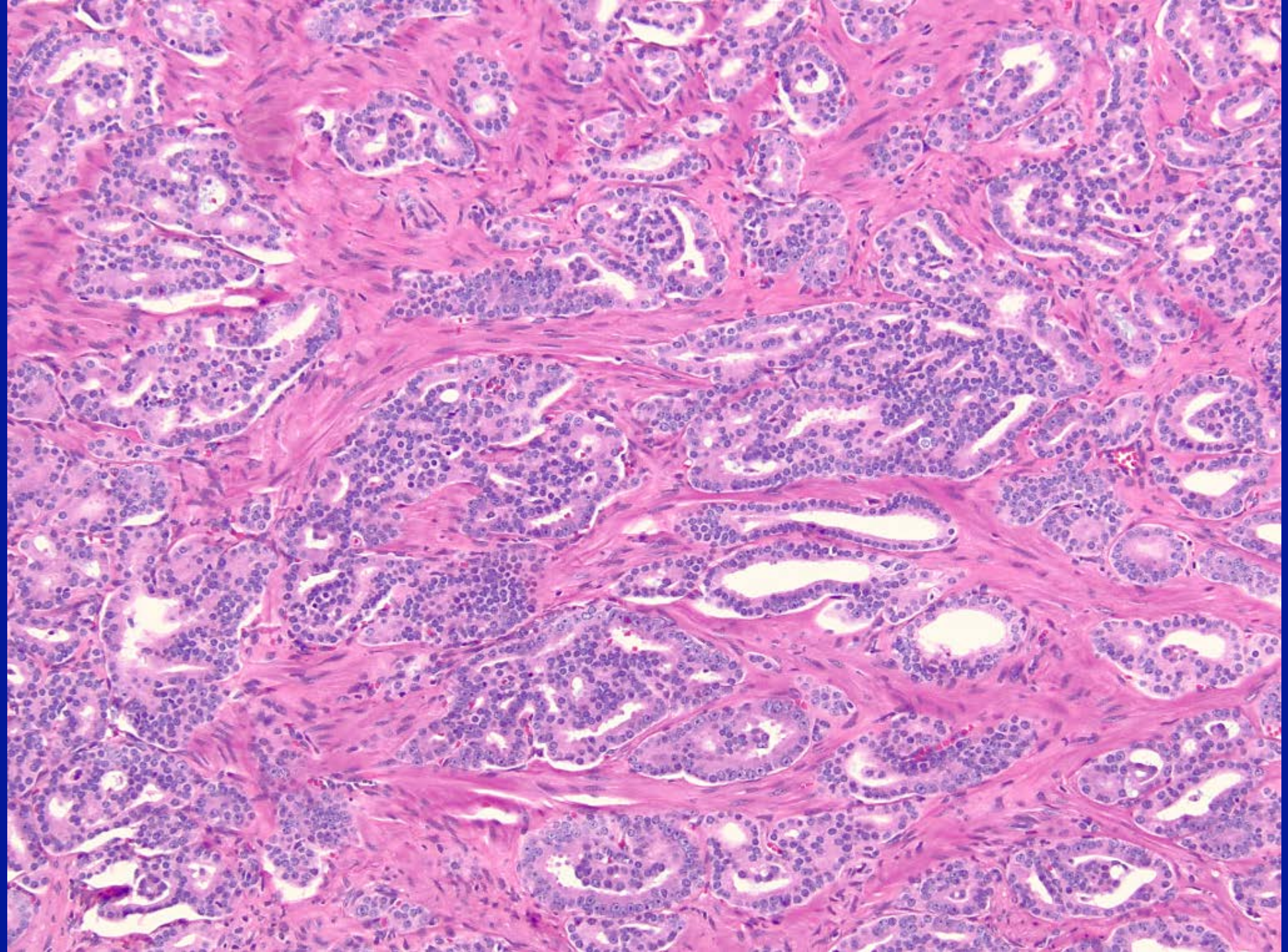
[1]Division of Pathology, Miraca Life Sciences, Irving, TX, USA, [2]Department of Pathology, Baylor College of Medicine, Houston, TX, USA, and [3]University of Toledo, Toledo, OH, USA

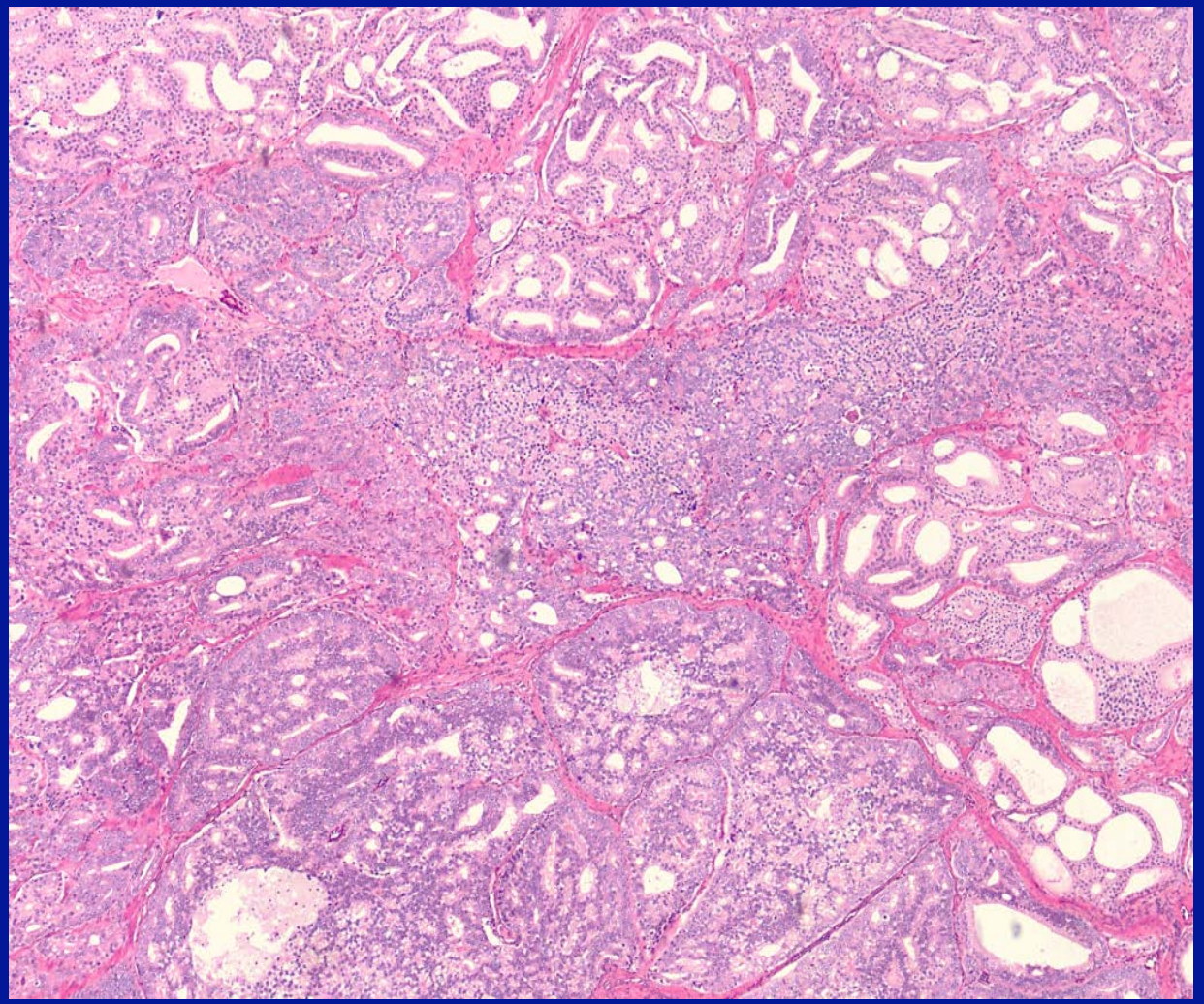
	Concordance of molecular markers expression pattern in AIP, IDC-P and Invasive PCa	
	ERG	PTEN
Hickman et al, AJSP, 2017	100%	95%
Shah RB et al, Histopathol, 2017	96%	89%

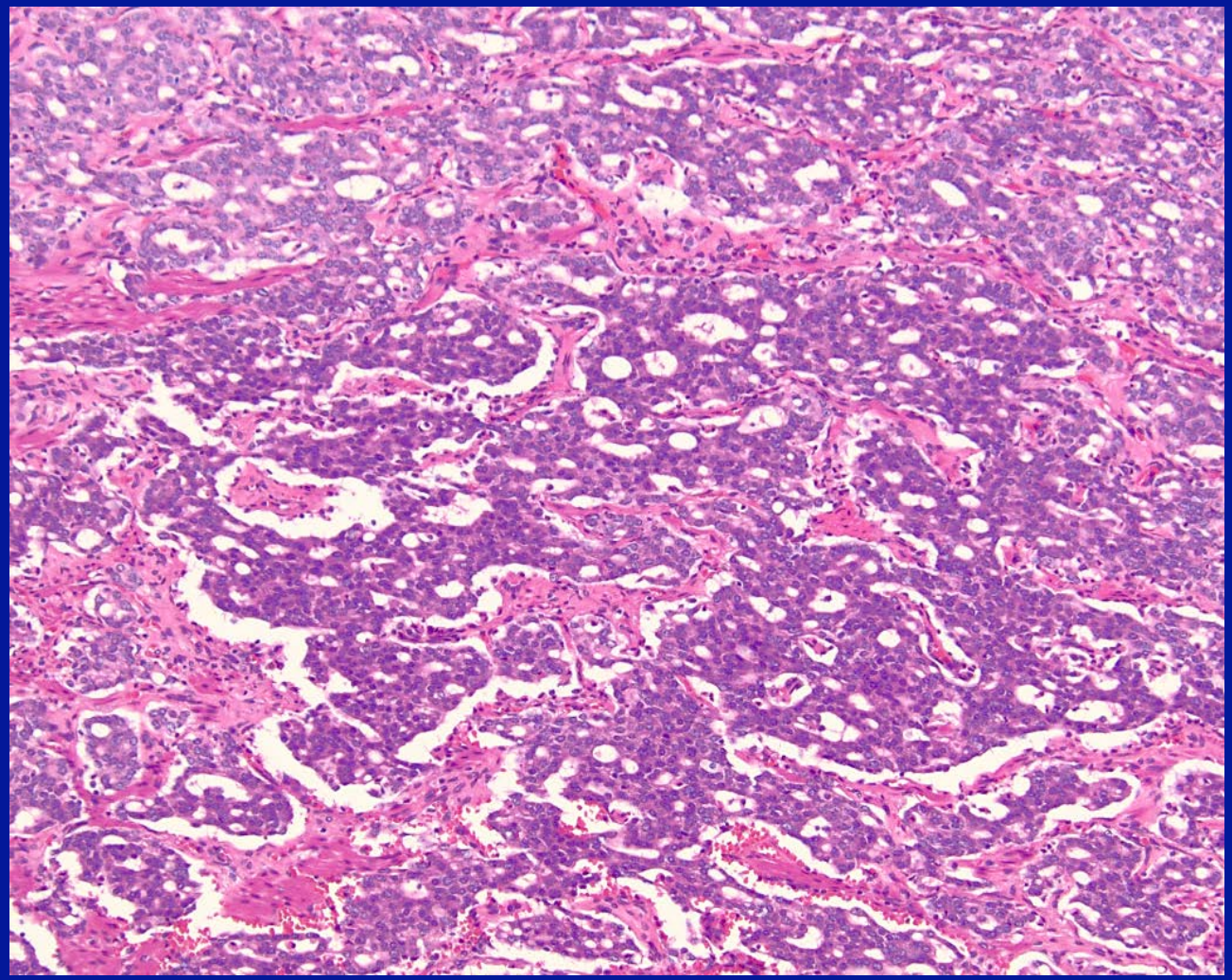
EVOLUTION OF CRIBRIFORM PROSTATE CANCER

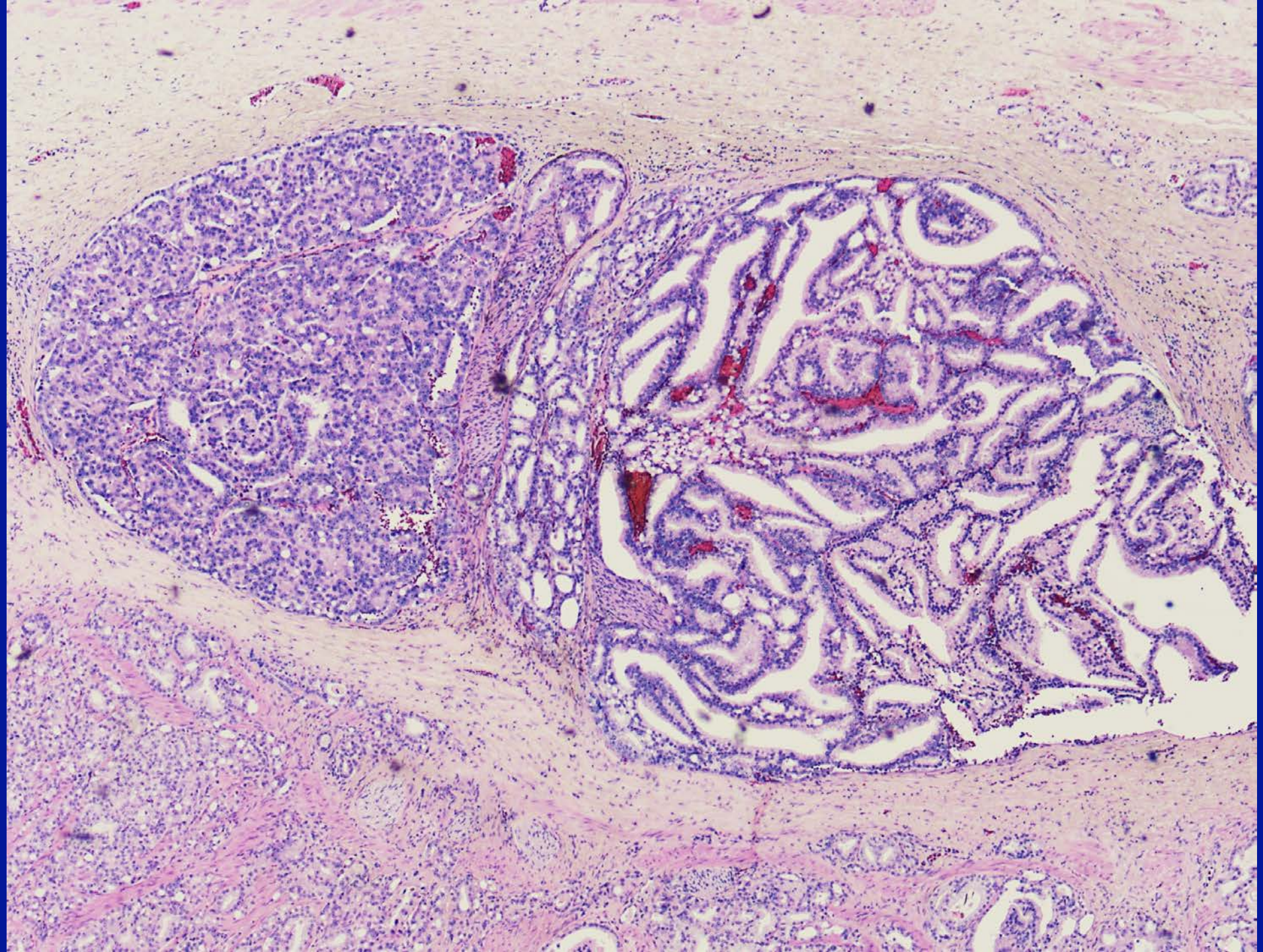


All cribriform cancers (large and small) are pattern 4 or 5 if associated with necrosis









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

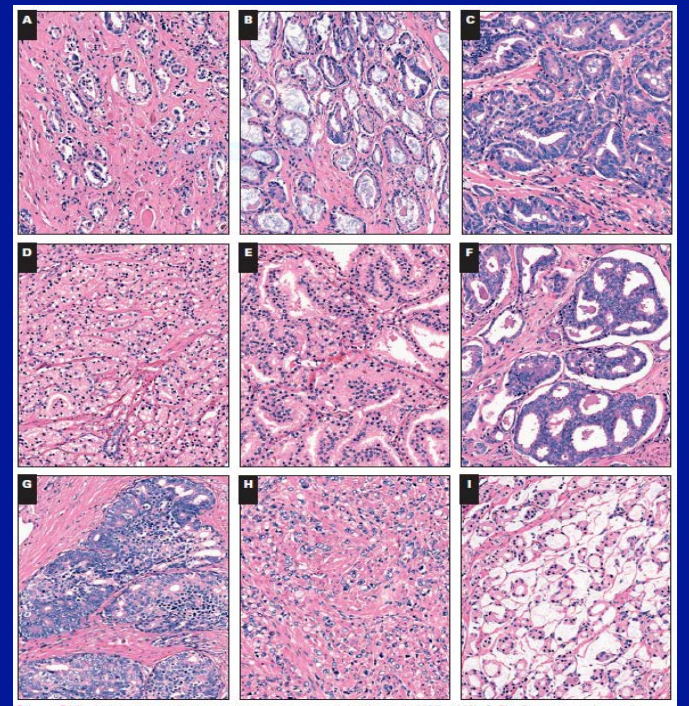


Image 1 Nine histologic prostate cancer patterns were annotated in the study (H&E, ×100). **A**, The S pattern, single, small separate acini. **B**, The B pattern, luminal blue mucin–containing single, separate acini. **C**, The U pattern, undulating, branched, or angulated larger acini that are not truly papillary—no bridging or stromal cores. **D**, The F pattern, fused small acini. **E**, The P pattern, true papillary with stromal cores or bridging across acinar spaces. **F**, The SC pattern, small cribriform, defined as rounded acinar spaces with ≤12 lumens and no solid area. **G**, The LC pattern, large cribriform, with more sprawling, cribriform to focally solid formations. **H**, The I pattern, individual cells. **I**, The M pattern, mucinous/colloid carcinoma without fusion or individual cells.

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

MODERN PATHOLOGY (2015) 28, 457–464

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]

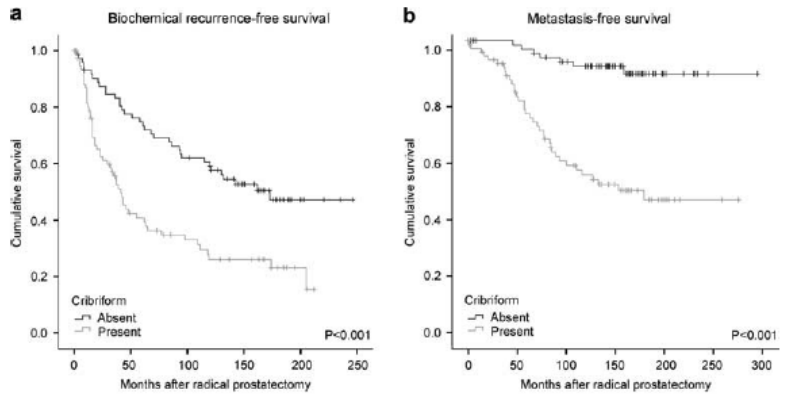
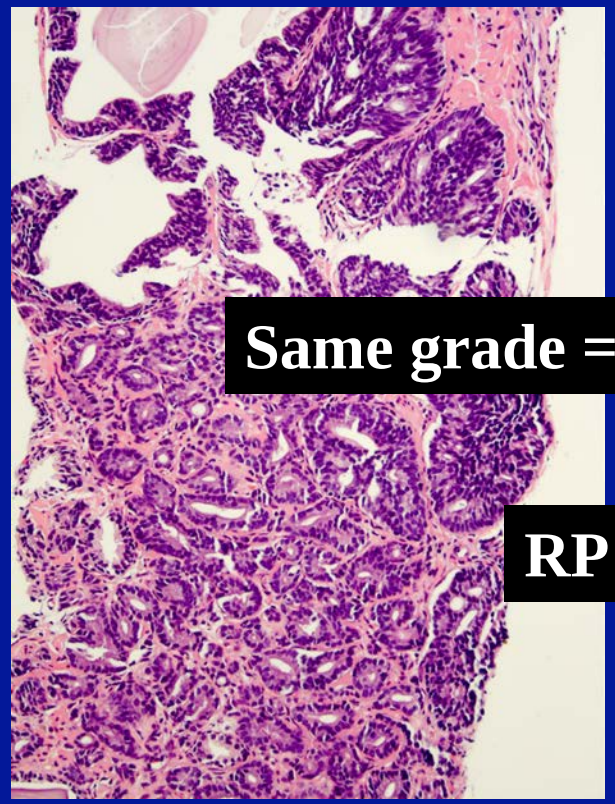
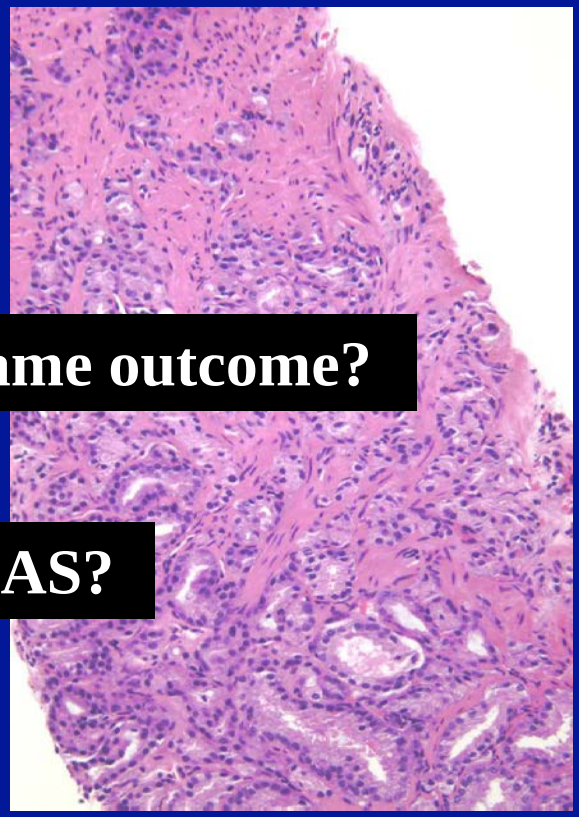


Figure 2 Kaplan–Meier estimates on impact of cribriform growth pattern in (**a**) biochemical recurrence-free survival; (**b**) distant metastasis-free survival; (**c**) disease-specific survival; and (**d**) overall survival.



Same grade = Same outcome?

RP vs AS?



3+4=7 with cribriform pattern (30% pattern 4)

3+4=7 with poorly formed glands (30% pattern 4)

“Cribriform Architecture”

- Invasive cribriform pattern 4 and IDC-P lumped as “Cribriform architecture” for prognostic and therapy decisions purposes

- *Both independent adverse prognostic features*
- *Majority of IDC-P present with cribriform morphology*
- *Both associated with aggressive molecular features*

Cribriform growth pattern in prostate 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

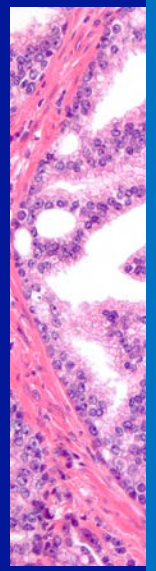
*Generally defined as a postoperative rise in serum PSA to ≥ 0.2 ng/mL.
BCR indicates biochemical recurrence; IDC, intraductal carcinoma; OR, odds ratio; PSA, prostate-specific antigen.

Cribriform growth pattern in prostate cancer and prediction of metastasis and death

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

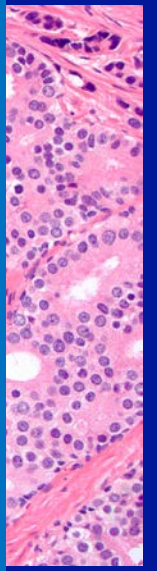
Studies	Median Follow-up (y)	Metastasis	Cancer-specific Death
Prostatectomy:			
Dong et al[10]	10	Grade 4 cribriform 13.3% vs. without cribriform 2.6%, OR = 5.6, $P = 0.02$	
Kweldam et al[16]	10	Cribriform pattern was the only independent predictor for metastasis, OR = 8.0, $P < 0.001$	Other than Gleason 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

Problem areas: Standardization of Definition

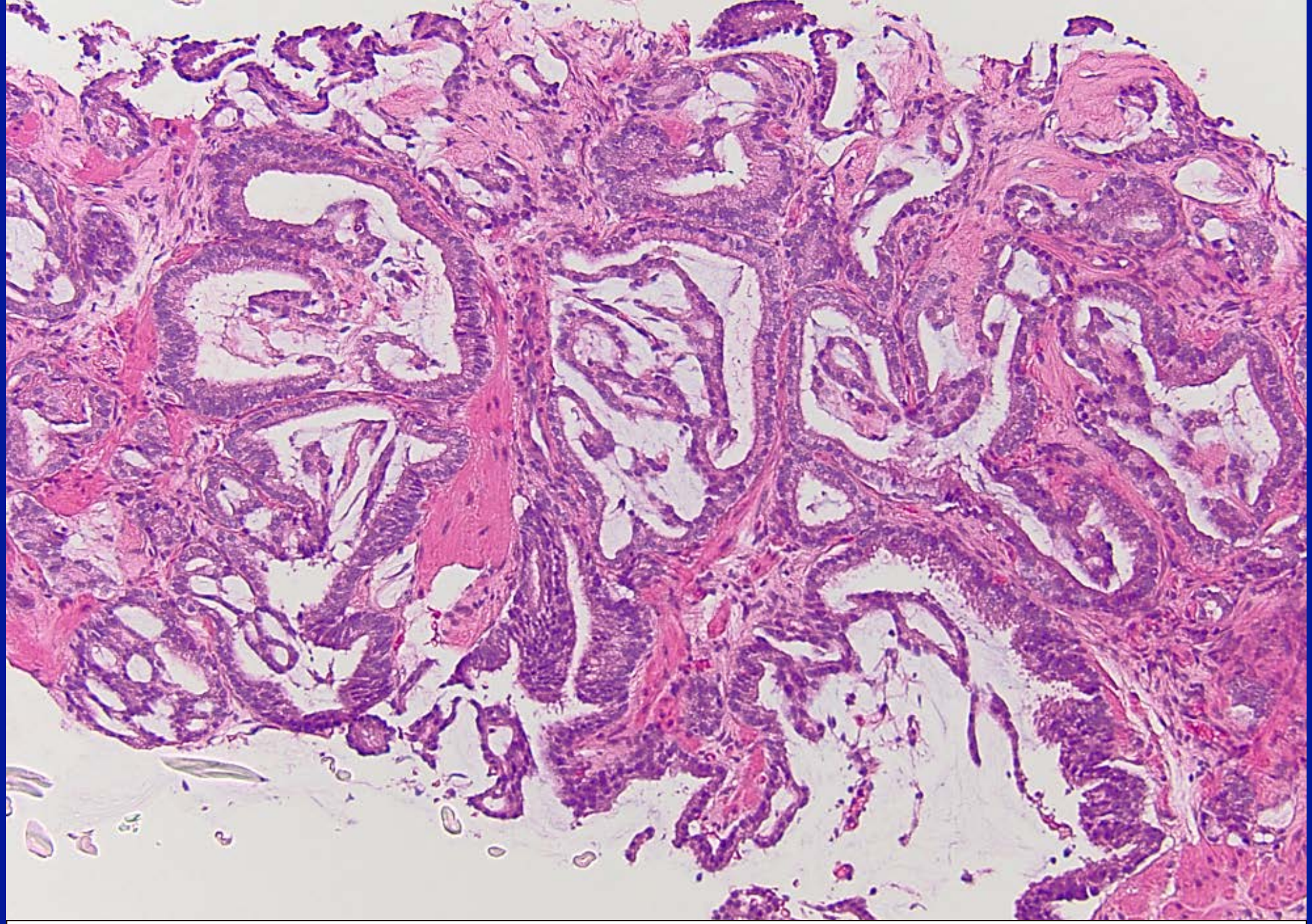


Problem areas affecting reproducibility:

-Mucin rupture pattern
-Glomerulation, small vs large
-Size of cribriform glands: small vs large
-Fusion vs cribriform
-Quantity of cribriform glands: few vs extensive

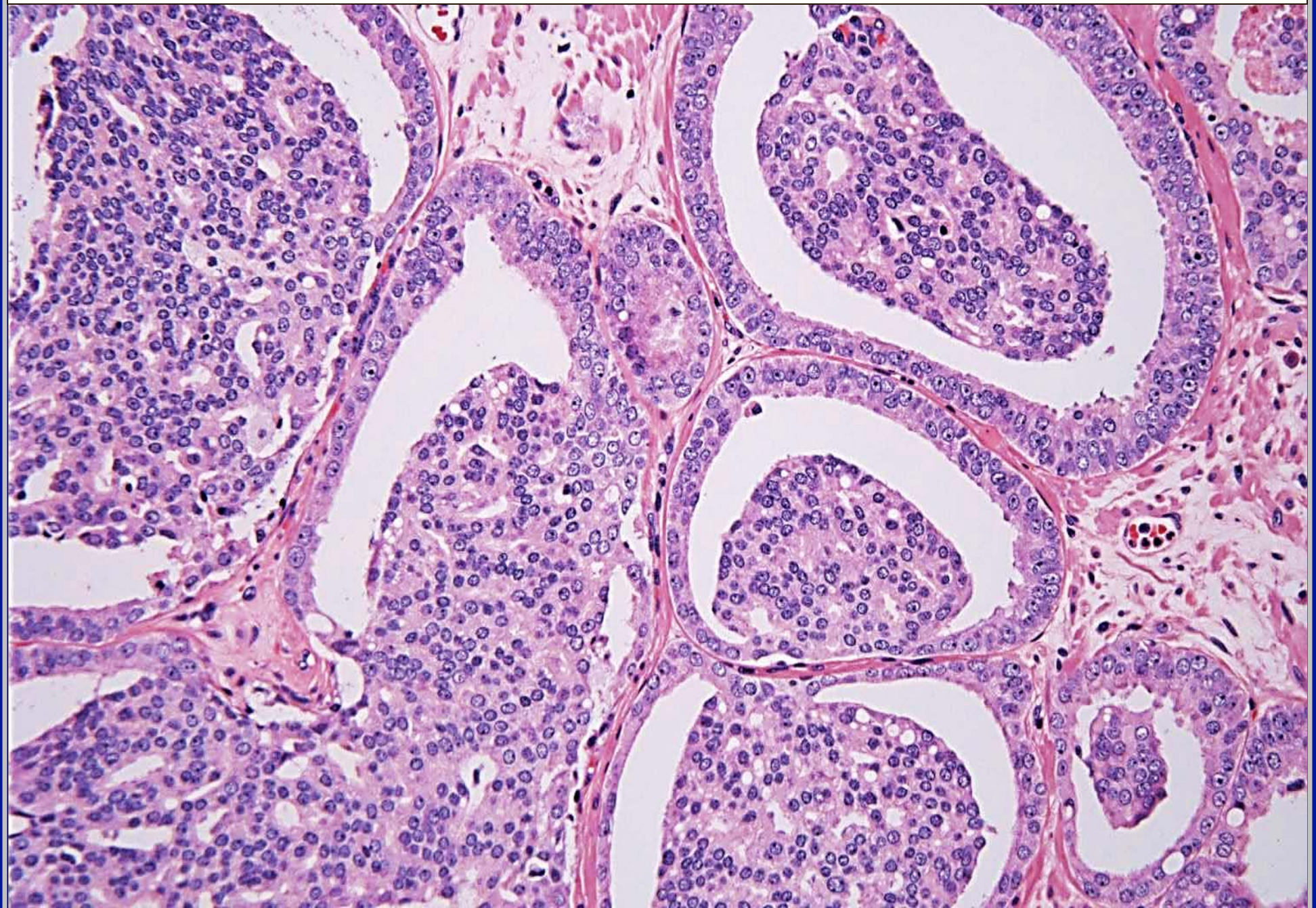


Proliferation of glandular epithelial cells to form lumen-spanning mass with distinctive “spaces” or “holes” in between cells, imparting a “Swiss cheese” appearance

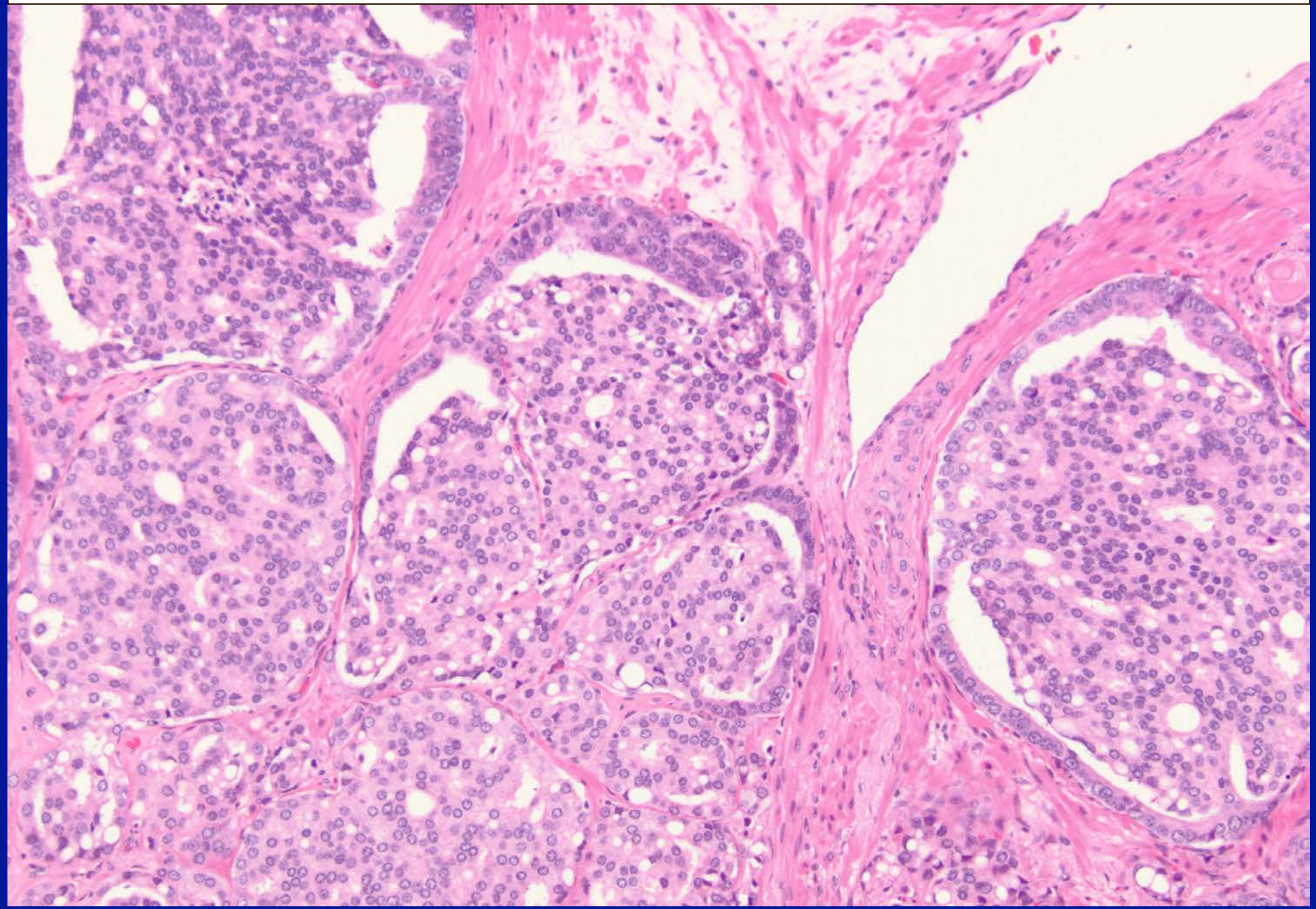


Complex mucin extravasation pattern : 3+4=7, GG2

Large Glomeruloid structures – ? Significance as Cribriform



Cribriform glands?



Histologic Grading of Prostatic Adenocarcinoma Can Be Further Optimized

Analysis of the Relative Prognostic Strength of Individual Architectural Patterns in 1275 Patients From the Canary Retrospective Cohort

Jesse K. McKenney, MD, Wei Wei, MS,† Sarah Hawley, MS,‡ Heidi Auman, PhD,‡ Lisa F. Newcomb, PhD,§‖ Hilary D. Boyer, BSc,§ Ladan Fazli, MD,¶ Jeff Simko, MD, PhD,# Antonio Hurtado-Coll, MD,¶ Dean A. Troyer, MD, PhD,** Maria S. Tretiakova, MD, PhD,‖ Funda Vakar-Lopez, MD,‖ Peter R. Carroll, MD, MPH,# Matthew R. Cooperberg, MD, MPH,# Martin E. Gleave, MD,¶ Raymond S. Lance, MD,** Dan W. Lin, MD,§‖ Peter S. Nelson, MD,§‖ Ian M. Thompson, MD,†† Lawrence D. True, MD,‖ Ziding Feng, PhD,† and James D. Brooks, MD‡‡*

Abstract: Histologic grading remains the gold standard for prognosis in prostate cancer, and assessment of Gleason score plays a critical role in active surveillance management. We sought to optimize the prognostic stratification of grading and developed a method of recording and studying individual architectural patterns by light microscopic evaluation that is independent of standard Gleason grade. Some of the evaluated patterns are not assessed by current Gleason grading (eg, reactive stromal response). Individual histologic patterns were correlated with recurrence-free survival in a retrospective post-radical prostatectomy cohort of 1275 patients represented by the highest-grade foci of carcinoma in tissue microarrays. In univariable analysis, fibromucinous rupture with varied epithelial complexity had a significantly lower relative risk of recurrence-free survival in cases graded as 3+4 = 7. Cases having focal "poorly formed glands," which could be designated as pattern 3+4 = 7, had lower risk than cribriform patterns with either small cribriform glands or expansile cribriform growth. In separate multivariable Cox proportional hazard analyses of both Gleason score 3+3 = 6 and 3+4 = 7 carcinomas, reactive stromal patterns were associated with worse recurrence-free survival. Decision tree models demonstrate potential regrouping of architectural patterns into categories with similar risk. In summary, we argue that Gleason score assignment by current consensus guidelines are not entirely optimized for clinical use, including active surveillance. Our data suggest that focal poorly formed gland and cribriform patterns, currently classified as Gleason pattern 4, should be in separate prognostic groups, as the latter is associated with worse outcome. Patterns with extravasated mucin are likely overgraded in a subset of cases with more complex epithelial bridges, whereas stromogenic cancers have a worse outcome than conveyed by Gleason grade alone. These findings serve as a foundation to facilitate optimization of histologic grading and strongly support incorporating reactive stroma into routine assessment.

Key Words: prostate, adenocarcinoma, Gleason, grade, cribriform, stromal reaction, mucin, stromogenic

(*Am J Surg Pathol* 2016;40:1439–1456)

From the *Cleveland Clinic, Cleveland, OH; †University of Texas MD

Glomerulation and Mucin rupture do NOT represent high-risk pattern

ORIGINAL ARTICLE

Prognostic Significance of Percentage and Architectural Types of Contemporary Gleason Pattern 4 Prostate Cancer in Radical Prostatectomy

Bonnie Choy, MD, Shane M. Pearce, MD,† Blake B. Anderson, MD,† Arieh L. Shalhav, MD,† Gregory Zagaja, MD,† Scott E. Eggener, MD,† and Gladell P. Paner, MD*†*

Abstract: The International Society of Urological Pathology (ISUP) 2014 consensus meeting recommended a novel grade grouping for prostate cancer that included dividing Gleason score (GS) 7 into grade groups 2 (GS 3+4) and 3 (GS 4+3). This division of GS 7, essentially determined by the percent of Gleason pattern (GP) 4 (< or >50%), raises the question of whether a more exact quantification of the percent GP 4 within GS 7 will yield additional prognostic information. Modifications were also made by ISUP regarding the definition of GP 4, now including 4 main architectural types: cribriform, glomeruloid, poorly formed, and fused glands. This study was conducted to analyze the prognostic significance of the percent GP 4 and main architectural types of GP 4 according to the 2014 ISUP grading criteria in radical prostatectomies (RPs). The cohort included 585 RP cases of GS 6 (40.2%), 3+4 (49.0%), and 4+3 (10.8%) prostate cancers. Significantly different 5-year biochemical recurrence (BCR)-free survival rates were observed among GS 6 architecture was associated with improved 5-year BCR-free survival when compared with GS 7 cancers without this architecture (87% vs. 75%, $P = 0.01$). However, GS 7 disease having only the glomeruloid architecture had significantly lower 5-year BCR-free survival than GS 6 cancers (86% vs. 99%, $P < 0.01$). Multivariable Cox proportional hazards regression model for factors associated with BCR among GS 7 cancers identified age (hazard ratio [HR] 0.95, $P < 0.01$), preoperative prostate-specific antigen (HR 1.07, $P < 0.01$), positive surgical margin (HR 2.70, $P < 0.01$), percent of GP 4 (21% to 50% [HR 2.21], 51% to 70% [HR 2.59], >70% [HR 6.57], all $P < 0.01$), presence of cribriform glands (HR 1.78, $P = 0.02$), and presence of glomeruloid glands (HR 0.43, $P = 0.03$) as independent predictors. In conclusion, our study shows that increments in percent of GP 4 correlate with increased risk for BCR supporting the ISUP recommendation of recording the percent of GP 4 in GS 7 prostate cancers at RP. However, additional larger studies are needed to establish the optimal interval for reporting percent GP

SHOULD IDC-P BE GRADED?

- PROS:

-Invasive cribriform cancer and IDC-P have same clinical significance

-Potential under recognition of aggressive disease

-Overutilization of IHC

-Was done in most outcome studies

-Uniform communication to Urologists and Patients

SHOULD IDC-P BE GRADED?

- CONS:

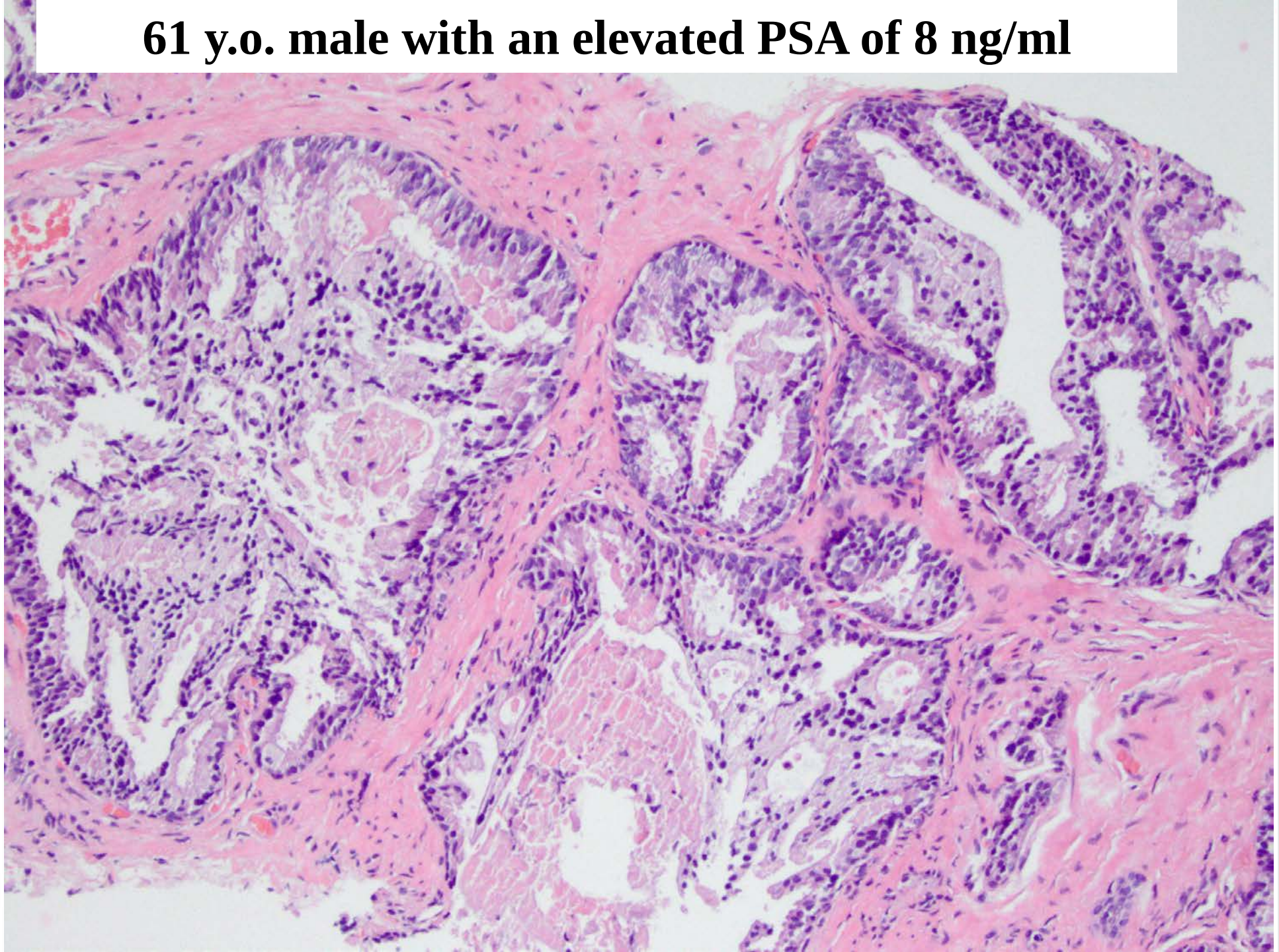
-IDC-P only and IDC-P + Grade group 1 would be labeled as Grade group 5 when patient could potentially be cured

-No other organ system considers in-situ disease as invasive

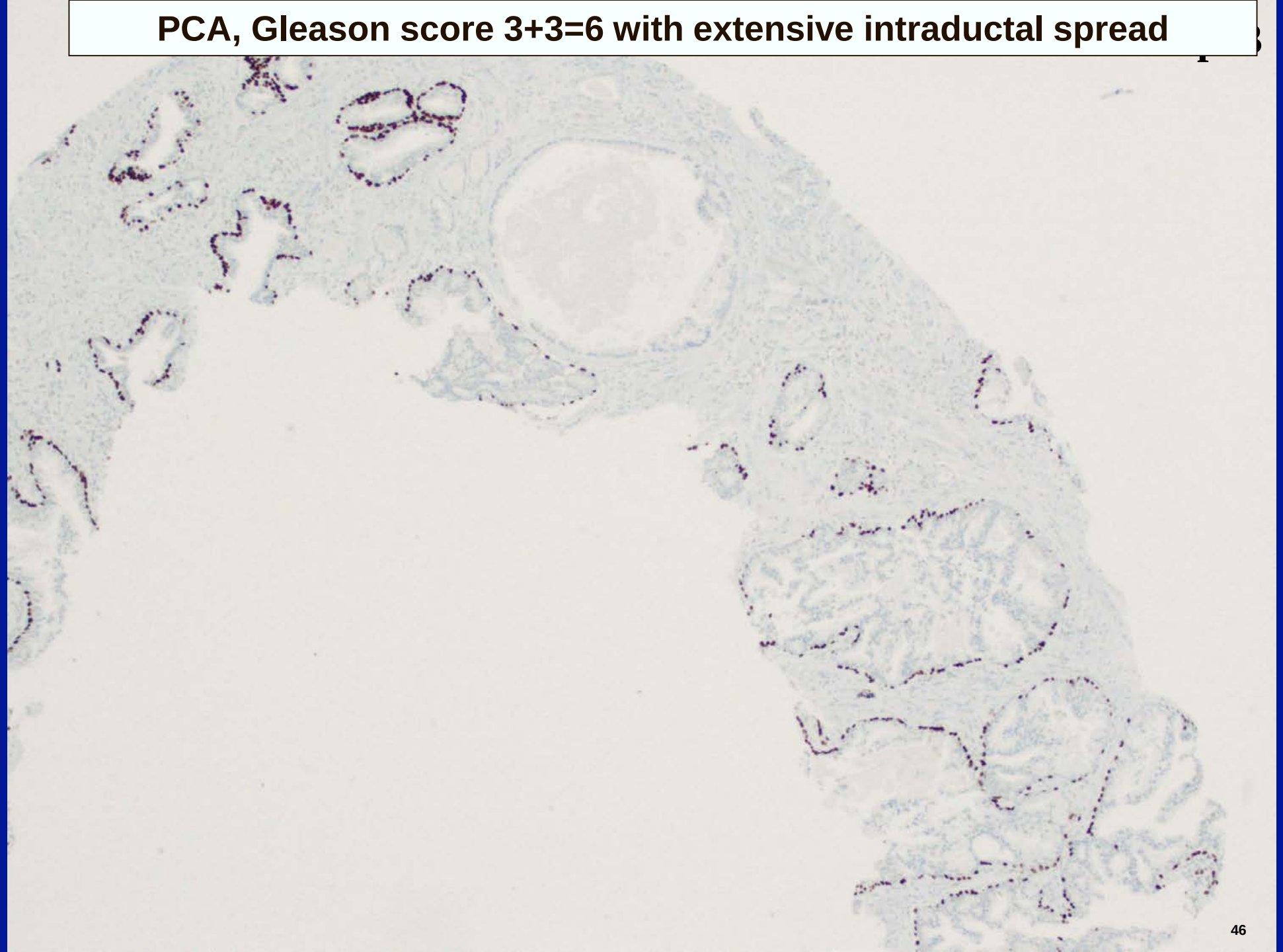
WHEN TO PERFORM BASAL CELL STAINING?

- 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”

61 y.o. male with an elevated PSA of 8 ng/ml



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



Sensitivity/Specificity of Biopsy for IDC-P/Invasive Cribriform Carcinoma

- Sensitivity: 43-56%
- Specificity: 88-97%
- Not improved by MRI fusion

Review Article

The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer

Jonathan I. Epstein, MD; Mahul B. Amin, MD; Samson W. Fine, MD; Ferran Algaba, MD, PhD; Manju Aron, MD; Dilek E. Baydar, MD; Antonio Lopez Beltran, MD, PhD; Fadi Brimo, MD; John C. Cheville, MD; Maurizio Colecchia, MD; Eva Comperat, MD, PhD; Isabela Werneck da Cunha, MD, PhD; Warick Delprado, MD; Angelo M. DeMarzo, MD, PhD; Giovanna A. Giannico, MD; Jennifer B. Gordetsky, MD; Charles C. Guo, MD; Donna E. Hansel, MD, PhD; Michelle S. Hirsch, MD, PhD; Jiaoti Huang, MD, PhD; Peter A. Humphrey, MD, PhD; Rafael E. Jimenez, MD; Francesca Khani, MD; Qingnuan Kong, MD; Oleksandr N. Kryvenko, MD; L. Priya Kunju, MD; Priti Lal, MD; Mathieu Latour, MD; Tamara Lotan, MD; Fiona Maclean, MD; Cristina Magi-Galluzzi, MD, PhD; Rohit Mehra, MD; Santosh Menon, MD; Hiroshi Miyamoto, MD, PhD; Rodolfo Montironi, MD; George J. Netto, MD; Jane K. Nguyen, MD, PhD; Adeboye O. Osunkoya, MD; Anil Parwani, MD; Brian D. Robinson, MD; Mark A. Rubin, MD; Rajal B. Shah, MD; Jeffrey S. So, MD; Hiroyuki Takahashi, MD, PhD; Fabio Tavora, MD, PhD; Maria S. Tretiakova, MD, PhD; Lawrence True, MD; Sara E. Wobker, MD; Ximing J. Yang, MD, PhD; Ming Zhou MD, PhD; Debra L. Zynger, MD; Kiril Trpkov, MD

Arch Pathol Lab Med. doi: 10.5858/arpa.2020-0015-RA

e SPECIAL ARTICLE

OPEN

The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma

Geert J.L.H. van Leenders, MD,* Theodorus H. van der Kwast, MD,† David J. Grignon, MD,‡ Andrew J. Evans, MD,§ Glen Kristiansen, MD,‖ Charlotte F. Kweldam, MD,* Geert Litjens, PhD,¶ Jesse K. McKenney, MD,# Jonathan Melamed, MD,** Nicholas Mottet, MD,†† ‡‡ Gladell P. Paner, MD,§§ Hemamali Samaratunga, FRCPA,‖‖ Ivo G. Schoots, MD,¶¶ Jeffry P. Simko, MD,## Toyonori Tsuzuki, MD,*** Murali Varma, MD,††† Anne Y. Warren, MD, FRCPath,‡‡‡ Thomas M. Wheeler, MD,§§§ Sean R. Williamson, MD,‖‖‖ ISUP Grading Workshop Panel Members, and Kenneth A. Iczkowski, MD¶¶¶

Am J Surg Pathol 2020;44:e87–e99)

Take Home Messages

- Both IDC-P and invasive cribriform pattern 4 should be reported due to its independent adverse associations with various clinical outcomes
- Whether IDC-P should be included in grading or not remains controversial
- Basal cell staining should be utilized judiciously
- Further refinement in grading system is expected


thank you so much