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PIN-like (Ductal) Adenocarcinoma of the Prostate

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汇报人：李擒龙

WHO classification of tumours of the prostate

Epithelial Tumours	
Glandular neoplasms	
Acinar adenocarcinoma	8140/3
Atrophic	
Pseudohyperplastic	
Microcystic	
Foamy gland	
Mucinous (colloid)	8480/3
Signet ring	8490/3
Pleomorphic giant cell adenocarcinoma	
Sarcomatoid carcinoma	8572/3
Prostatic intraepithelial neoplasia (PIN), high grade	8148/2
Intraductal carcinoma NOS	8500/2
Ductal adenocarcinoma	8500/3
Cribriform	8201/3
Papillary	8260/3
Solid	8230/3
Urothelial carcinoma	8120/3
Squamous neoplasms	
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Basal cell carcinoma of the prostate	8147/3

2016 WHO Classifcation of Tumours of the Urinary System and Male Genital Organs

High-grade PIN

Definition

•High-grade prostatic intraepithelial neoplasia (HGPIN) constitutes the preinvasive end of the continuum of neoplastic proliferations of secretory cells within the lining of the prostatic ducts and acini.

Synonyms

•Grades II and III prostatic intraepithelial neoplasia (obsolete)

Histopathology

•HGPIN is characterized by a neoplastic proliferation of secretory cells within preexisting ducts and acini, with cytological changes resembling those seen in cancer, including nuclear enlargement and numerous prominent nucleoli.

•Four main patterns: tufting, micropapillary, cribriform, and flat.

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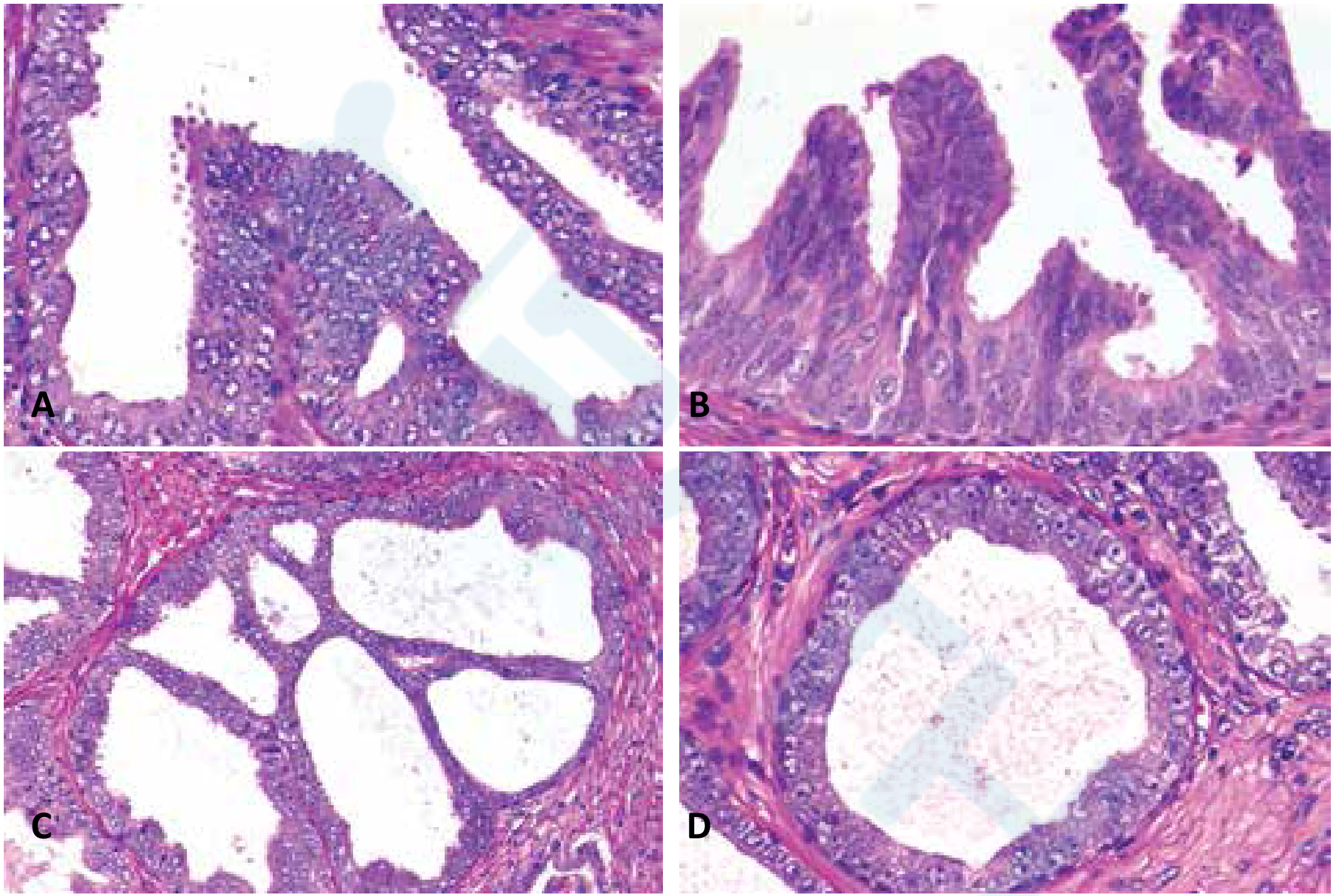

Fig. 3.24 Prostatic intraepithelial neoplasia.
A Tufting pattern. **B** Micropapillary pattern. **C** Cribriform pattern. **D** Flat pattern.

Ductal adenocarcinoma

Definition

Ductal adenocarcinoma is a subtype of prostatic adenocarcinoma with large glands lined by tall pseudostratified columnar cells.

ICD-O codes

Ductal adenocarcinoma 8500/3
- Cribriform 8201/3
- Papillary 8260/3
- Solid 8230/3

Epidemiology

Ductal adenocarcinoma accounts for 3.2% of all prostate cancers. In most cases, this subtype is combined with acinar adenocarcinoma. Pure ductal adenocarcinoma is only seen in 0.2–0.4% of prostate cancers.

Ductal adenocarcinoma

Histopathology

•The glands of ductal adenocarcinoma are lined by tall columnar pseudostratified epithelium.

•The nuclei may be elongated and show more severe atypia than seen in most acinar adenocarcinomas. Prominent nucleoli, coarse chromatin, and mitotic figures are common findings.

•Intraluminal necrotic debris is commonly seen in both the intraductal and invasive components.

•The glandular architecture is more complex than that of acinar adenocarcinoma. Papillary and cribriform glands are the most common patterns, and combinations are often seen.

•Not all ductal adenocarcinomas have papillary architecture, but when found, it is a useful diagnostic feature.

•Poorly differentiated ductal cancers have a solid component with no luminal differentiation. The solid pattern is nonspecific and must be combined with other patterns of ductal adenocarcinoma to justify this diagnosis.

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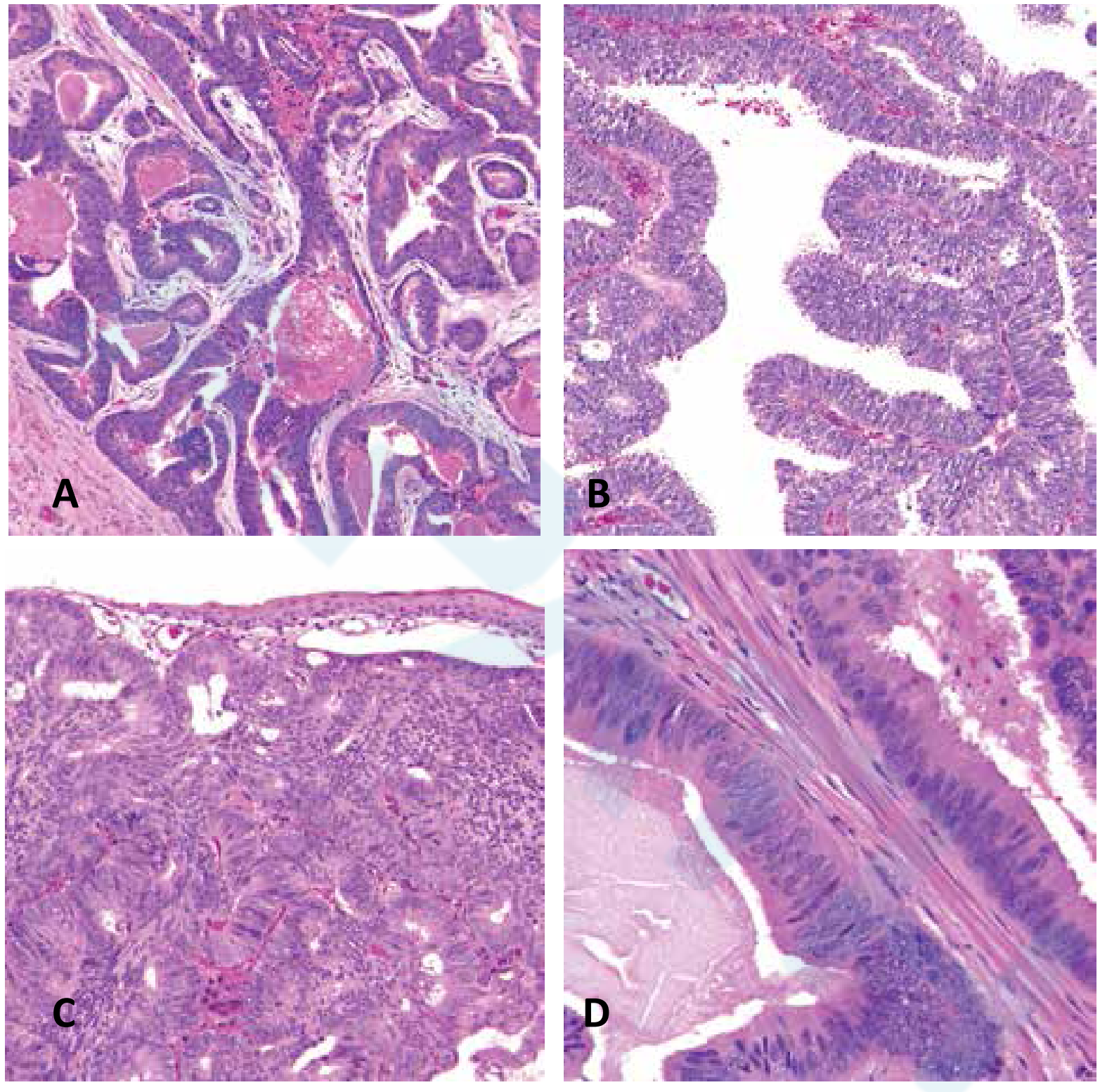

Fig. 3.29 Ductal adenocarcinoma. **A,** Growth along ducts and invasion of the stroma. **B,** Papillary growth pattern. **C,** Cribriform growth pattern. **D,** Elongated high-grade nuclei.

Ductal adenocarcinoma

Prognosis and predictive factors

•Ductal adenocarcinoma is more aggressive than the average acinar adenocarcinoma, with higher stage and greater risk of biochemical recurrence after radical prostatectomy and increased mortality.

Grading

•Cribriform and papillary ductal adenocarcinoma components should be assigned Gleason pattern 4.

•Similar to acinar adenocarcinoma, the presence of comedonecrosis should be considered Gleason pattern 5.

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PIN-like ductal adenocarcinoma

Histopathology

•A pattern consisting of separate non-cribriform glands is called **prostatic intraepithelial neoplasia–like (PIN-like) ductal adenocarcinoma.** Unlike in PIN, the glands are more crowded and often cystically dilated, with a flat lining. All glands lack basal cells . {1107, 2683}

Grading

•**PIN-like ductal adenocarcinoma** has a prognosis corresponding to a Gleason score of 6 (3 + 3). {1107, 2683}

1107. Hameed O, Humphrey PA. Stratified epithelium in prostatic adenocarcinoma: a mimic of high-grade prostatic intraepithelial neoplasia. Mod Pathol. 2006;19:899–906.

2683. Tavora F, Epstein JI. High-grade prostatic intraepithelial neoplasia like ductal adenocarcinoma of the prostate: a clinicopathologic study of 28 cases. Am J Surg Pathol. 2008;32:1060–1067.

2016 WHO Classifcation of Tumours of the Urinary System and Male Genital Organs

Stratified epithelium in prostatic adenocarcinoma: a mimic of high-grade prostatic intraepithelial neoplasia

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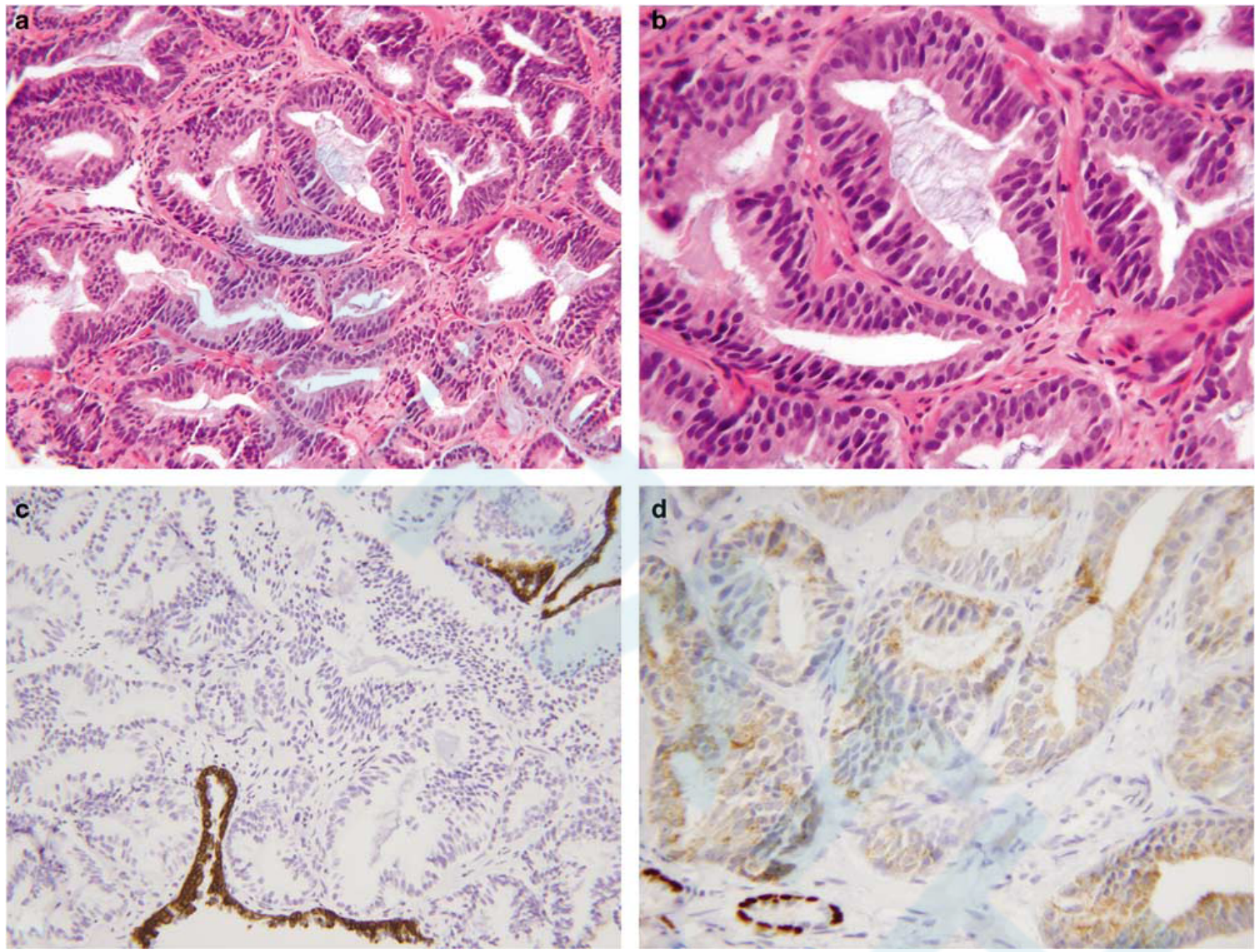
Typically glands of prostatic adenocarcinoma have a single cell lining, although stratification can be seen in invasive carcinomas with a cribriform architecture, including ductal carcinoma. The presence and diagnostic significance of stratified cells within non-cribriform carcinomatous prostatic glands has not been well addressed. The histomorphological features and immunohistochemical profile of cases of non-cribriform prostatic adenocarcinoma with stratified malignant glandular epithelium were analyzed. These cases were identified from needle biopsy cases from the consultation files of one of the authors and from a review of 150 consecutive in-house needle biopsy cases of prostatic adenocarcinoma. Immunohistochemistry was performed utilizing antibodies reactive against high molecular weight cytokeratin (34βE12), p63 and α-methylacyl-coenzyme-A racemase (AMACR). A total of 8 cases were identified, including 2 from the 150 consecutive in-house cases (1.3%). In 4 cases, the focus with glands having stratified epithelium was the sole carcinomatous component in the biopsy, while such a component represented 5–30% of the invasive carcinoma seen elsewhere in the remaining cases. The main attribute in all these foci was the presence of glandular profiles lined by several layers of epithelial cells with cytological and architectural features resembling flat or tufted high-grade prostatic intraepithelial neoplasia, but lacking basal cells as confirmed by negative 34βE12 and/or p63 immunostains in all cases. The AMACR staining profile of the stratified foci was variable, with 4 foci showing positivity, and 3 foci being negative, including two cases that displayed AMACR positivity in adjacent non-stratified prostatic adenocarcinoma. Prostatic adenocarcinoma with stratified malignant glandular epithelium can be identified in prostate needle biopsy samples harboring non-cribriform prostatic adenocarcinoma and resembles glands with high-grade prostatic intraepithelial neoplasia. These 'PIN-like' carcinomas can present in pure form. Recognition of this pattern of prostatic adenocarcinoma is necessary to correctly diagnose such cases as invasive carcinoma.

Modern Pathology (2006) **19**, 899–906. doi:10.1038/modpathol.3800601; published online 7 April 2006



A case of prostatic adenocarcinoma composed of small to medium-sized glands lined by stratified epithelium resembling HG-PIN. The degree of glandular crowding is more than what one usually sees with PIN. The malignant glands lack a basal cell lining (a, b) as confirmed by a negative 34bE12 immunostain (c) as well as a negative p63 immunostain, as demonstrated by a p63/AMACR antibody cocktail (d) that also demonstrates AMACR positivity in these glands, a profile similar to the non-stratified component of the tumor seen elsewhere on the slide (not shown).

Table 1 Clinical and pathological findings of eight cases of prostatic adenocarcinoma with stratified malignant glandular epithelium

Case no.	*Age*	*PSA level (ng/ml)*	*Light microscopic findings*			*Immunohistochemical findings*				
			Carcinoma extent		*Grade*	*% carcinoma stratified*	*34βE12*	*p63*	*AMACR*	
			Length (in mm)	*% of tissue*					*Stratified*	*Non-stratified*
1	61	4.6	11	45	3+3	30	Negative	Negative	Positive	Positive
2[a]	89	66.2	17	55	3+3	100	Negative	Negative	Positive	NA
3[a]	71	U	1.5	<5	3+3	100	Negative	NC	NC	NA
4	68	23.0	21	75	3+4[b]	5	—	Negative	Negative	Positive
5[a]	73	5.8	<1	<5	3+3	100	Negative	Negative	Negative	NA
6[a]	64	4.3	<1	<5	3+3	100	—	Negative	Positive	NA
7	74	5.2	3	10	3+3	15	—	Negative	Positive	Positive
8	81	U	26	70	3+4[b]	10	—	Negative	Negative	Positive

AMACR, α-methylacyl-coenzyme-A racemase; PSA, prostate-specific antigen; U, unknown; NC, non-contributory (focus no longer present on section); NA, not applicable.

[a]Immunohistochemistry was performed during original evaluation of the case.

[b]Gleason pattern 4 carcinoma was limited to the non-stratified component.

ORIGINAL ARTICLE

High-grade Prostatic Intraepithelial Neoplasialike Ductal Adenocarcinoma of the Prostate: A Clinicopathologic Study of 28 Cases

Fabio Tavora, MD and Jonathan I. Epstein, MD*† ‡*

Abstract: Most of the prostatic ductal adenocarcinomas of the prostate are characterized by cribriform and/or papillary architecture lined by columnar pseudostratified malignant epithelium. We report 28 cases of ductal adenocarcinomas on needle biopsy and transurethral resection of prostate closely resembling high-grade prostatic intraepithelial neoplasia (HGPIN) composed of simple glands with flat, tufting, or micropapillary architecture. The mean age of the patients was 68 years (range, 50 to 91 y). Prostate specific antigen serum level at diagnosis ranged from 1.2 to 12.1 ng/mL. Treatment included radical prostatectomy (n = 9), hormone therapy (n = 7), radiotherapy (n = 5), and cryotherapy (n = 1). Three patients had greater predominance of flat architecture, and less frequently prominent nucleoli. Verification often requires the immunohistochemical documentation of the absence of basal cells in numerous atypical glands. Although usual ductal adenocarcinoma is considered comparable to Gleason score 8, PIN-like ductal adenocarcinoma was accompanied by Gleason score 6 acinar carcinoma and behaved similar to Gleason score 6 acinar cancer. Recognition of this entity is critical to differentiate it from both HGPIN and conventional ductal adenocarcinoma.

Key Words: prostate cancer, high-grade intraepithelial neoplasia, ductal adenocarcinoma of the prostate

TABLE 1. Clinicopathologic Features

Study No.	Age	No. Cores Involved/ Total No. Cores	Percent Overall Involvement	Treatment	Findings at RP	Pathologic Stage	Follow-up (mo)
1	54	3/6	5	RP	PLDCA and 3+3=6	T2	NED (25)
2	66	1/4	40				LFU
3	70	1/5	20	BT			NED (26)
4	54	3/5	70	RP	PLDCA and 3+3=6	T3a	NED (8)
5	70	5/6	50	HT			NED (32)
6	61	1/1	45				LFU
7	68	2/3	60	HT			NED (17)
8	83	2/3	30	HT			NED (2)
9	68	4/6	60	XRT			NED (2)
10	77	2/3	40	HT			NED (8)
11	74	1/3	25	CT			NED (4)
12	69	8/10	40				LFU
13	63	1/2	10	RP	PLDCA and 3+3=6	T2	NED (5)
14	73	8/9	30	HT			NED (8)
15	91	1/2	90	BT			NED (9)
16	63	2/5	10	BT			NED (6)
17	85	1/1	70	HT			NED (5)
18	75	9/13	80	XRT			NED (8)
19	77	5/8	50	HT			NED (3)
20	50	4/10	30	RP	PLDCA and 3+3=6	T2	NED (4)
21	65	2/4	25	RP	PLDCA and 3+3=6	T2	NED (2)
22	71	18/24	20	RP	PLDCA and 3+3=6	T2	NED (3)
23	51	2/4	5	RP	PLDCA	T2	NED (3)
24	70	4/5	50	RP	PLDCA	T2	NED (5)
25	59	1/4	20				Recent
26	63	11/13	90	RP	PLDCA	T2	Recent
27	77	TURP	20				Recent
28	65	3/8	10				Recent

BT indicates brachytherapy; CT, cryotherapy; HT, hormone therapy; LFU, lost to follow-up; NED, no evidence of disease; PLDCA, PIN-like ductal adenocarcinoma; RP, radical prostatectomy; TURP, transurethral resection; XRT, external beam radiotherapy.

Histology

•Flat was the most common pattern (42%), followed by tufted (41%), and micropapillary (17%) (some with more than 1 pattern).

Findings at Radical Prostatectomy (RP)

•Tumor was primarily composed of small (25%), medium (17%), or cystically dilated (58%) cancer glands, with all cases demonstrating a mixture of different gland sizes.

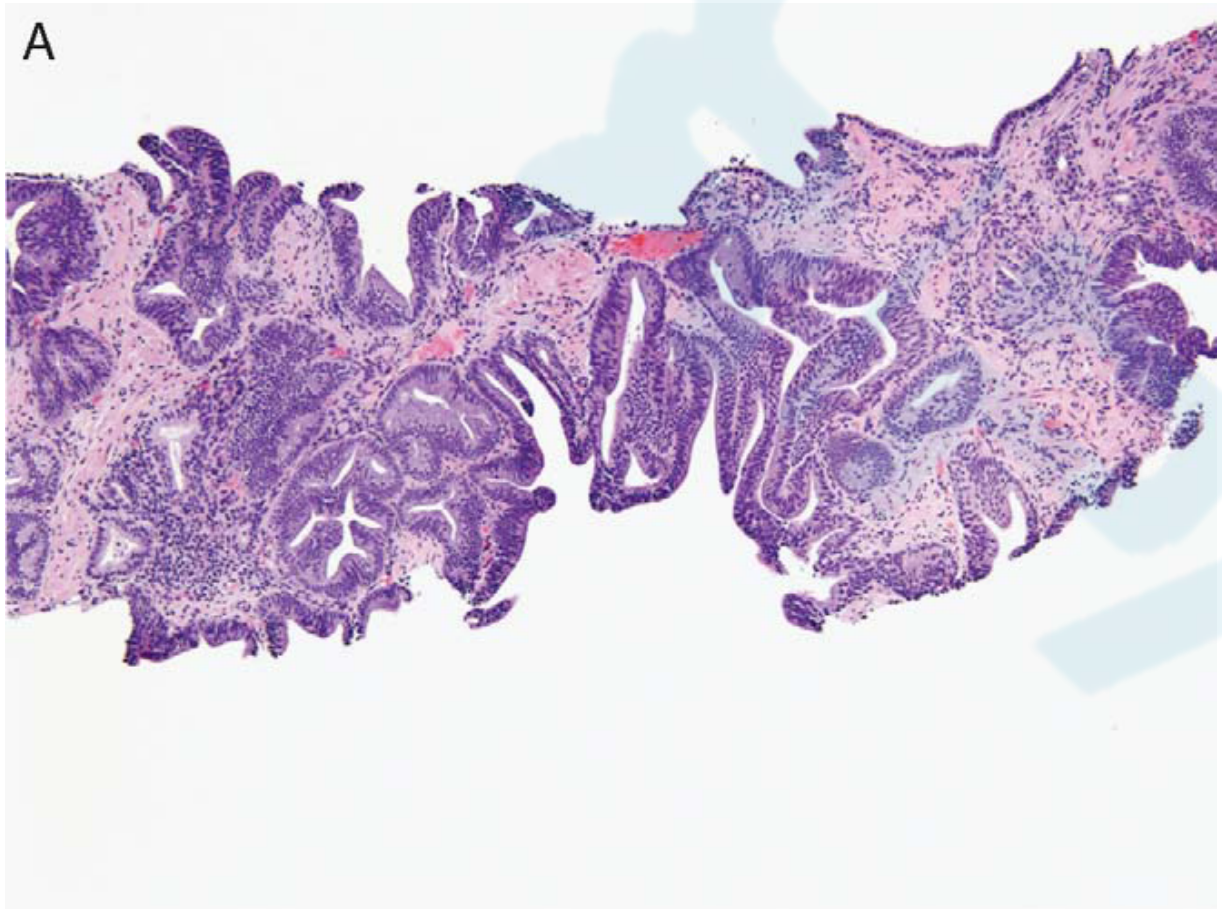
•Cytologically, tumors were characterized by tall columnar atypical cells, basally located nuclei, and amphophilic cytoplasm.

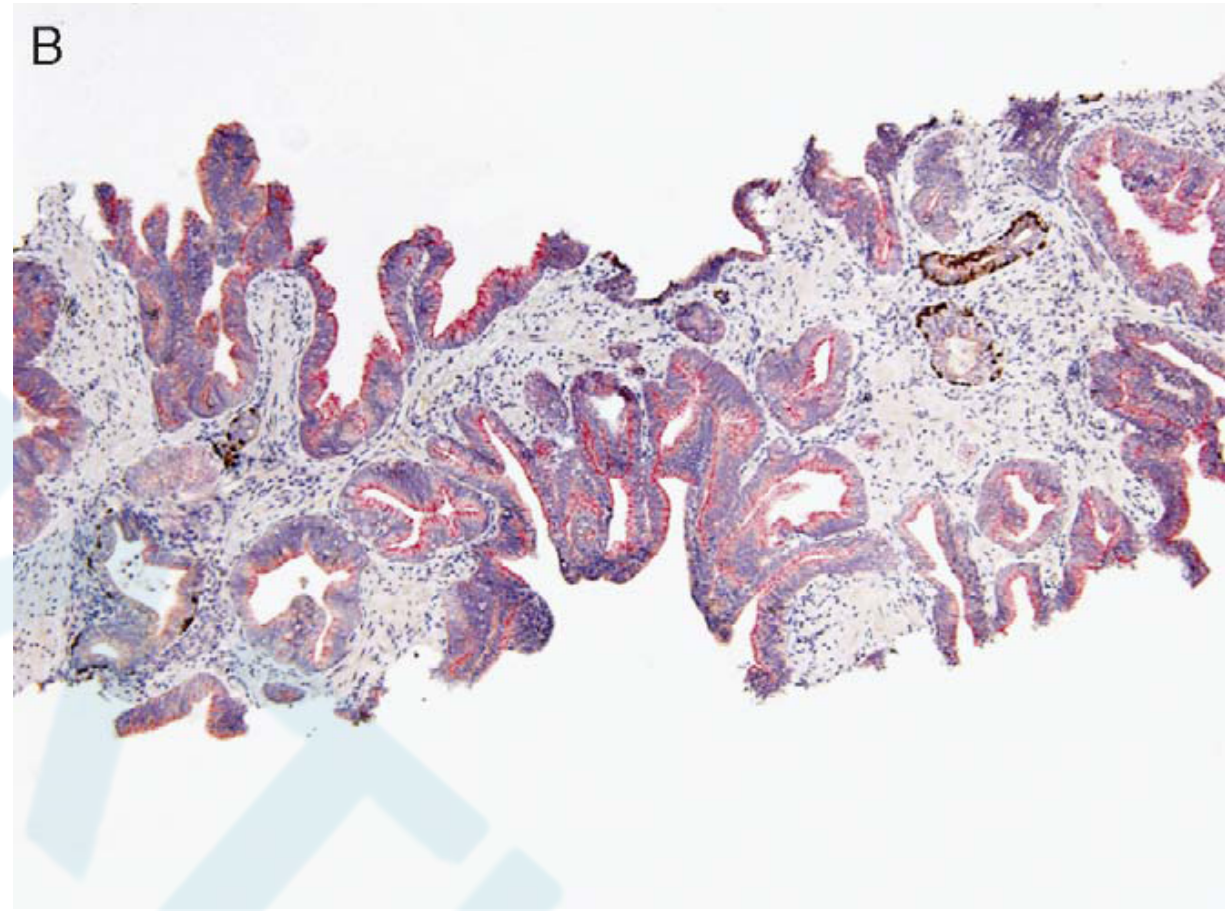
•The tumors lacked marked pleomorphism, necrosis, solid areas, cribriform formation, or true papillary fronds.

•Only one (1/9) of the PIN-like ductal adenocarcinomas at RP had extraprostatic extension(EPE), which was focal.

Follow-up

•In none of the patients has there been evidence of biochemical progression, local recurrence, or metastatic disease.





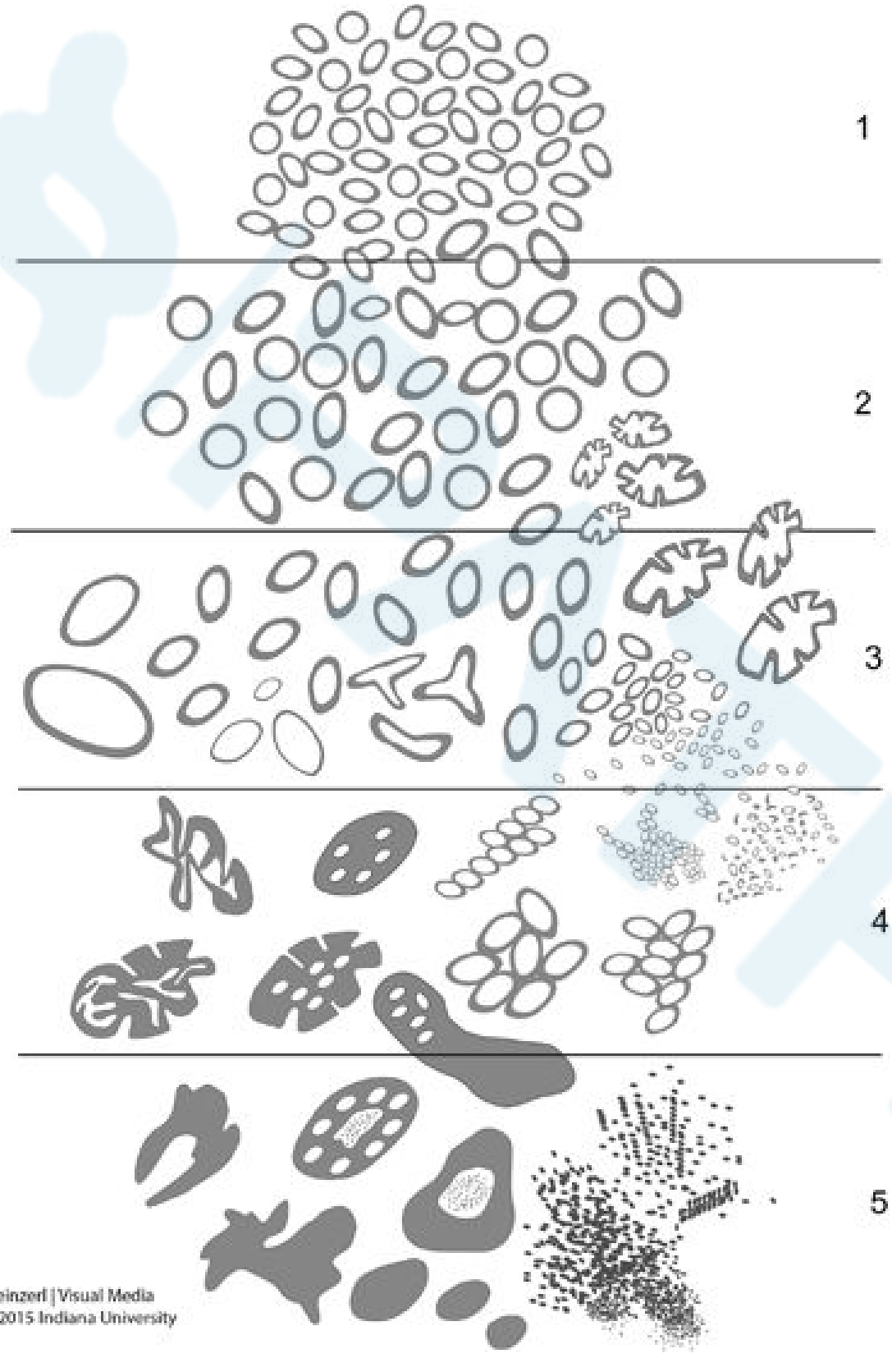
A, Low-power view of PIN-like ductal adenocarcinoma on needle biopsy showing crowded glands lined by columnar epithelium with a flat and tufting pattern. B, Triple antibody cocktail with intense AMACR positivity in PIN-like ductal adenocarcinoma and absence of basal cells (p63 and HMWCK).

	HGPIN	Ductal adenocarcinoma	PIN-like Ductal adenocarcinoma
Architecture	Four main patterns: tufting, micropapillary, cribriform, and flat.	large glands lined by tall pseudostratified columnar cells. glands are crowded and extensive and display expansile morphology with true papillae, cribriform,	large glands lined with stratified nuclei. the glands are crowded and often cystically dilated. only flat and tufted patterns are seen
Cytology	nuclear enlargement and numerous prominent nucleoli	The nuclei may be elongated and show more severe atypia than seen in most acinar adenocarcinomas. Prominent nucleoli, coarse chromatin, and mitotic figures	The nuclei are either round or elongated. PIN-like carcinoma usually shows less prominent nucleoli than HGPIN.
Basal cells	always present. occasionally be absent in one or a few glands	Majority of cases lack basal cells	entirely devoid of basal cells
Gleason pattern	NA	4/5	3

Aims

The largest series of PIN-like ductal adenocarcinomas from our institution found a behavior similar to Gleason score 3+3 =6 (grade group [GG1]), with only rare extraprostatic extension (EPE). However, this series consisted of only 28 biopsies and 9 radical prostatectomies (RPs). We sought to further investigate the behavior and molecular phenotype of this rare tumor within a larger series.

Gleason Pattern



Gleason Scores（GS）

- The primary (predominant) and secondary (second most prevalent) architectural patterns are assigned a number from 1 (the most differentiated) to 5 (the least differentiated).
- Gleason scores range from 2 (1 + 1) to 10 (5 + 5).

Grade groups (GGs) of prostate carcinoma

Table 3.03 Grade groups

Grade group 1: Gleason scores 2–6
Grade group 2: Gleason score 7 (3 + 4)
Grade group 3: Gleason score 7 (4 + 3)
Grade group 4: Gleason score 8
Grade group 5: Gleason scores 9–10
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MATERIALS AND METHODS

- A total of 190 cases of PIN-like carcinoma, 2008 -2017
- Johns Hopkins Hospital, in-house and consult cases
- the percentage of biopsy cores involved by PIN-like carcinoma
- the maximum percentage of involvement of positive cores
- presence and grade of associated acinar carcinoma, and the association of papillary or cribriform ductal carcinoma
- Clinical treatment data was sought in all cases where the patient was eligible for either active surveillance or RP and available in 48 cases.
- Of those patients who underwent RP, slides were requested and when available reviewed by a urologic pathologist for size and location of the PIN-like carcinoma component, association with acinar carcinoma, GG, and presence of EPE and positive margins.

- PIN-like carcinoma glands consisting of flat, tufted, or simple dilated architecture were graded as Gleason pattern 3.

- A unique finding in this series was the presence of typical dilated PIN-like carcinoma glands with thin intraluminal papillary projections, which we graded as Gleason pattern 4. For the purposes of this study, we distinguished these papillary fronds with tall thin projections lacking prominent fibrovascular cores from usual papillary prostatic ductal adenocarcinoma.

- The overall grade for a case was based on the part with the highest GG.

- In cases where there was a PIN-like carcinoma component identified on the RP, immunohistochemical studies were performed on 10 cases with available paraffin blocks.

- Immunohistochemistry was performed at our institution using antibodies against PTEN (predilutes, Ventana, Tucson, AZ) and ERG (1:100; Ventana).

- PTEN was considered to be negative if there was markedly decreased staining in >10% of tumor cells compared with background.
- ERG was considered positive if any tumor cells showed nuclear staining.

RESULTS

Patient Demographics

- A total of 190 cases with a PIN-like carcinoma component were identified (in-house cases n =8, 4.2%, consult cases n = 182, 95.8%).
- needle biopsy (n =181), transurethral resection (TURP, n= 5), radical prostatectomies (RP, n =4).
- The average age of patients was 70 years (range: 45 to 91 y).
- The average number of cores with involvement by PIN-like carcinoma was 2 (1 to 12).
- The average maximum percentage by a PIN-like carcinoma component of any core was 43.5% (5% to 90%).

Association With Acinar Component on Biopsy

- In 58/181 (32.0%) biopsy cases, due to selective parts having been submitted for consultation, it was unknown whether there was an association with acinar carcinoma.
- Of the remaining 123 biopsy cases where it was known whether acinar carcinoma was present, 72 cases (58.5%) showed exclusively PIN-like carcinoma without associated acinar or papillary/cribriform ductal adenocarcinoma.
- GGs on the 51/123 biopsies where there was known acinar or papillary/cribriform ductal adenocarcinoma and where the PIN-like carcinoma component was graded as Gleason pattern 3, were GG1 (n =23, 45.1%), GG2 (n= 14, 27.5%), GG3 (n= 9, 17.6%), GG4 (n =4, 7.8%), and GG5 (n = 1, 2.0%).
- Papillary ductal adenocarcinoma associated with the PIN-like carcinoma was seen in 9/51 (17.6%) of the cases, either with (n =7) or without (n= 2) an acinar component.

Treatment Follow-up

- Information regarding treatment was available in 44 cases of biopsies or TURP where the patient would be considered eligible for active surveillance(主动监测).
- 18/44 (41.0%) underwent RP
- active surveillance or no additional treatment (n=8)
- external radiotherapy exclusively单纯外放射治疗(n=3)
- brachytherapy近距离放疗(n=2)
- cyberknife射波刀(n=1)
- antiandrogen therapy (n=2)
- proton beam radiation质子束放疗(n=1)
- In 9 cases, the patient did not have a prostatectomy, but the alternate treatment was unknown.

Findings on RP

- RP reports were available in 20 cases, with slides available for review in 16/20 (80.0%).
- In 3/16 (18.8%) cases diagnosed with PIN-like carcinoma on biopsy, a PIN-like carcinoma component was not evident on review of RP slides; in all 3 cases, only representative sections of the RP had been submitted for histologic examination.
- The remainder of cases showed a PIN-like carcinoma tumor with classic architecture of glands resembling HGPIN but with a greater degree of crowding and dilatation, and columnar pseudostratified cytology or large cystic dilated glands with ductal type epithelium.

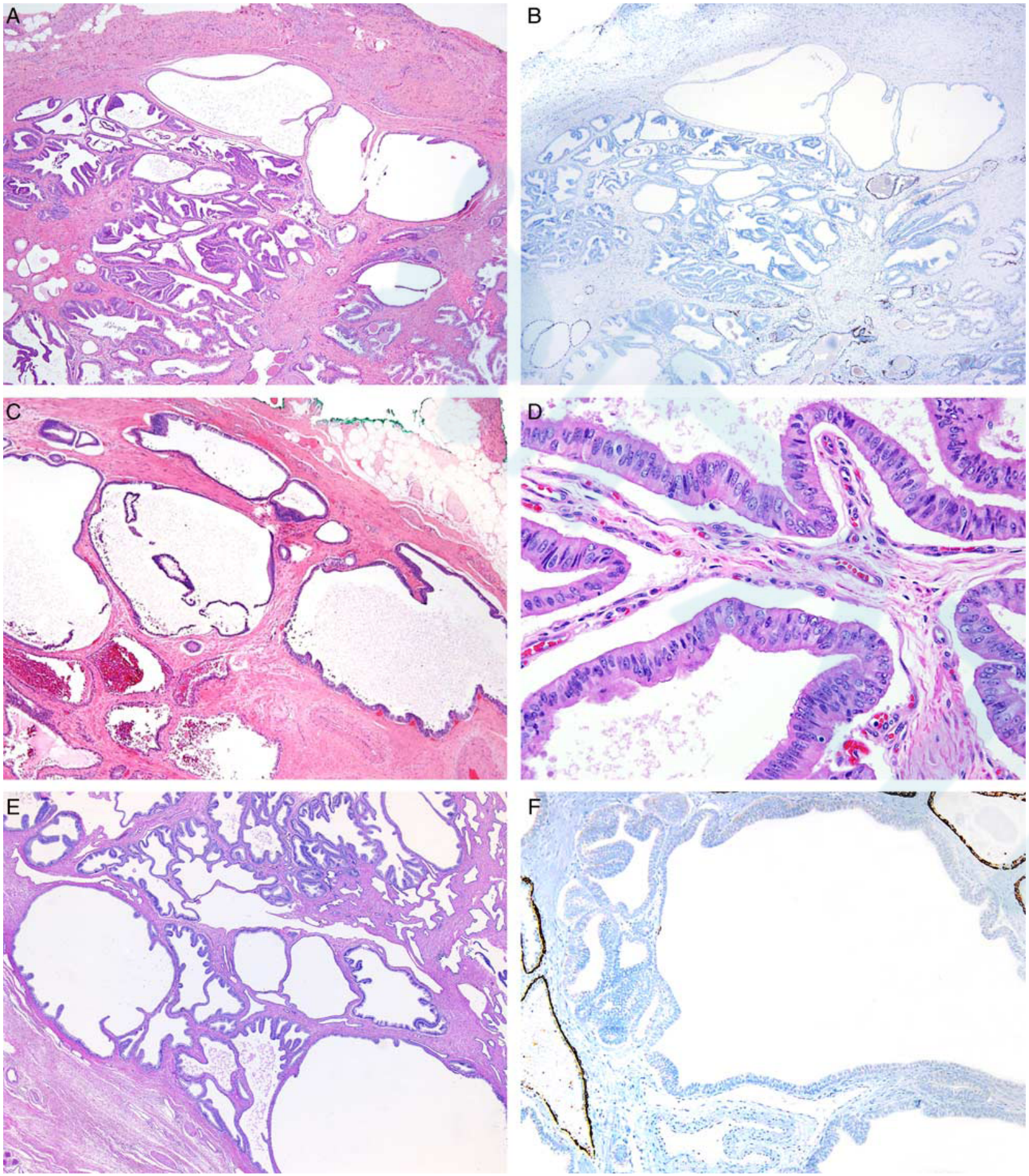

FIGURE 1.
A.Classic architecture of PIN-like carcinoma, with glands resembling HGPIN but with greater degree of crowding and dilatation.
B.Same case as (A) where PIN4 immunostain show lack of basal cells in PIN-like carcinoma glands.
C.Large cystic dilated glands of PIN-like carcinoma.
D.higher power of (C) with cystic glands lined by columnar pseudostratified epithelium.
E.Large cystic glands of PIN-like carcinoma with atrophic appearing epithelium.
F.Same case as (E) with cystic PIN-like carcinoma glands lacking basal cells by PIN immunostain.

- In 3 cases, there was a peculiar finding of very large, cystic dilated tumor glands with areas of atrophic epithelium; in 2 cases these glands involved extraprostatic tissue, with one case at a margin of resection.

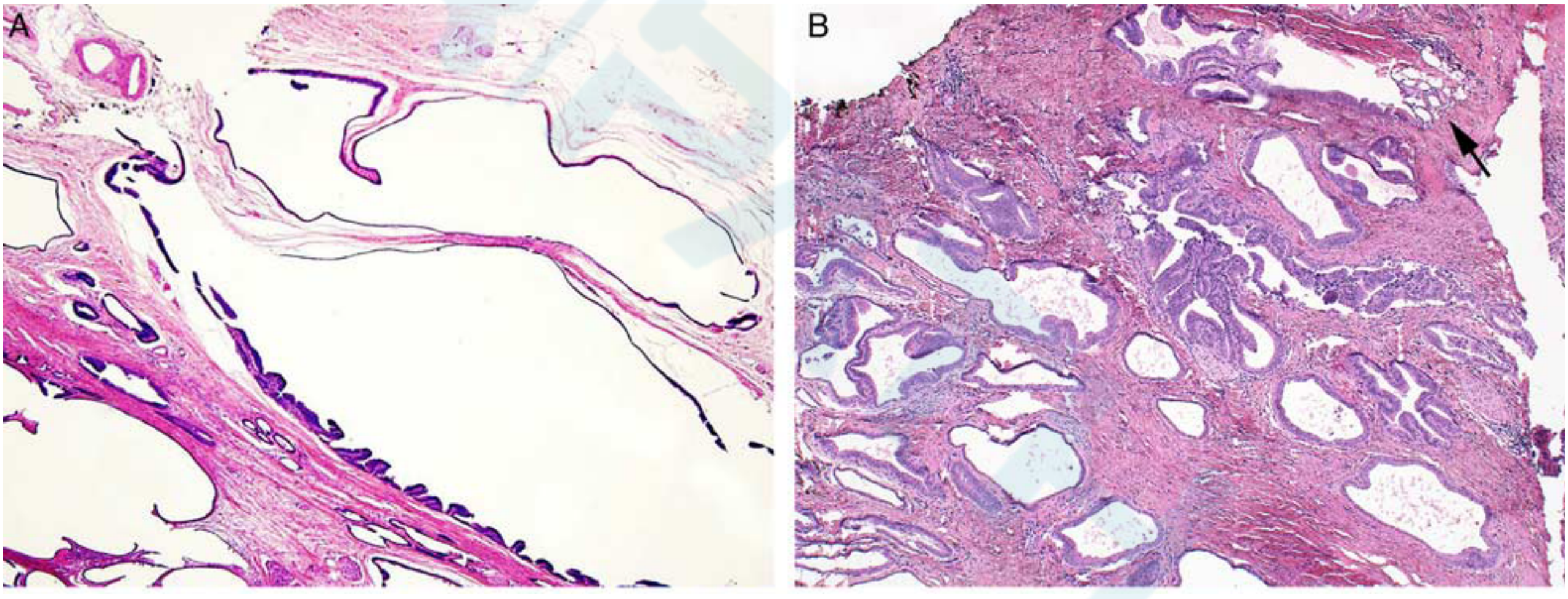

FIGURE 2
A, Large cystic PIN-like carcinoma glands extending into periprostatic adipose tissue.
B, Dilated PIN-like carcinoma glands adjacent to periprostatic adipose tissue (black arrow). This case showed PIN-like carcinoma involving a margin with recurrence in the bladder 6 years following RP.

TABLE 1. Histologic Features of PLC on Radical Prostatectomy

Case	Size of PLC (mm)	Overall Gleason Grade	Separate Acinar Gleason	Dominant Tumor	EPE	Type of Pattern 4
1	7	3+4=7; GP4=5%	3+4=7; GP4=5%	Acinar	0	Fused, poorly formed acinar
2	6	3+4=7; GP4=5%	3+4=7; GP4≤5%	Acinar	Acinar	PLC with thin papillary projections into cystic dilated glands; fused acinar
3	10	3+4=7; GP4≤5%	3+4=7; GP4=5%	Acinar	0	Fused acinar glands
4	5	3+3=6	3+3=6	Acinar	0	
5	10	3+3=6	NT	PLC	0	
6	15	3+4=7; GP4≤5%	3+3=6	PLC	PLC	PLC with thin papillary projections into cystic dilated glands
7	4	3+4=7; GP4≤5%	3+4=7; GP4=5%	Acinar	0	Poor formed acinar
8	18	3+3=6	NT	PLC	PLC	
9	3	3+3=6	3+3=6	Acinar	0	
10	45	3+4=7; GP4=5%	NT	PLC	PLC	PLC with thin papillary projections into cystic dilated glands
11	26	3+4=7; GP4=5%	3+3=6	PLC	PLC	PLC with thin papillary projections into cystic dilated glands
12	6	3+3=6	3+3=6	Acinar	0	
13	10	3+4=7; GP4=10%	3+3=6	PLC	PLC	Papillary ductal and PLC with thin papillary projections into cystic dilated glands

GP4 indicates percent Gleason pattern 4; NT, no tumor; PLC, Pin-like carcinoma.

- The overall grade at RP, based on the nodule with the highest grade, was GG1 (5/13, 38.5%) and GG2 (8/13, 61.5%).
- Of the 13 cases, PIN-like carcinoma was present without an associated acinar tumor in 3 (23.1%) cases.
- In all 10 cases with an acinar component, the acinar tumor was anatomically distinct from the PIN-like carcinoma tumor. With the exception of one case where there was adjacent classic papillary ductal adenocarcinoma, all our RP specimens showed pure 100% PIN-like carcinomas. The GGs of the separate acinar tumors were GG1 (6/10) and GG2 (4/10) with percent pattern 4 $\leqslant$5% in all 4 cases.
- The average size of the PIN-like carcinoma component was 12.8mm (range: 3 to 45mm).
- No cases were associated with metastases to lymph nodes or seminal vesicle invasion.

Percent and Type of Pattern 4

➢Of the 8 cases with an overall grade of GG2 (3+4=7) on RP, the percent pattern 4 included: ≤5% (n=7, 87.5%) and 10% (n=1, 12.5%).

➢The type of Gleason pattern 4 present was fused or poorly formed acinar glands in separate acinar tumors (n=4, 50.0%), papillary ductal adenocarcinoma (n=1, 12.5%) ,

➢thin papillary projections of ductal glands into cystic dilated glands of PIN-like carcinoma (n=5, 62.5%)

TABLE 1. Histologic Features of PLC on Radical Prostatectomy

Case	Size of PLC (mm)	Overall Gleason Grade	Separate Acinar Gleason	Dominant Tumor	EPE	Type of Pattern 4
1	7	3+4=7; GP4=5%	3+4=7; GP4=5%	Acinar	0	Fused, poorly formed acinar
2	6	3+4=7; GP4=5%	3+4=7; GP4≤5%	Acinar	Acinar	PLC with thin papillary projections into cystic dilated glands; fused acinar
3	10	3+4=7; GP4≤5%	3+4=7; GP4=5%	Acinar	0	Fused acinar glands
4	5	3+3=6	3+3=6	Acinar	0	
5	10	3+3=6	NT	PLC	0	
6	15	3+4=7; GP4≤5%	3+3=6	PLC	PLC	PLC with thin papillary projections into cystic dilated glands
7	4	3+4=7; GP4≤5%	3+4=7; GP4=5%	Acinar	0	Poor formed acinar
8	18	3+3=6	NT	PLC	PLC	
9	3	3+3=6	3+3=6	Acinar	0	
10	45	3+4=7; GP4=5%	NT	PLC	PLC	PLC with thin papillary projections into cystic dilated glands
11	26	3+4=7; GP4=5%	3+3=6	PLC	PLC	PLC with thin papillary projections into cystic dilated glands
12	6	3+3=6	3+3=6	Acinar	0	
13	10	3+4=7; GP4=10%	3+3=6	PLC	PLC	Papillary ductal and PLC with thin papillary projections into cystic dilated glands

GP4 indicates percent Gleason pattern 4; NT, no tumor; PLC, Pin-like carcinoma.

Architecture of the PIN-like Carcinoma Component

•In 3 cases, there was a peculiar finding of very large, cystic dilated tumor glands with areas of atrophic epithelium; in 2 cases these glands involved extraprostatic tissue, with one case at a margin of resection.

•EPE was present in 6/13 (46.1%) cases, from the acinar component in 1 (7.7%) case and the PIN-like carcinoma component in 5 (83.3%) cases. In all 5 PIN-like carcinoma cases, there was a peculiar morphology of thin papillary projections into cystic dilated PIN-like carcinoma glands (Figs. 2D–F).

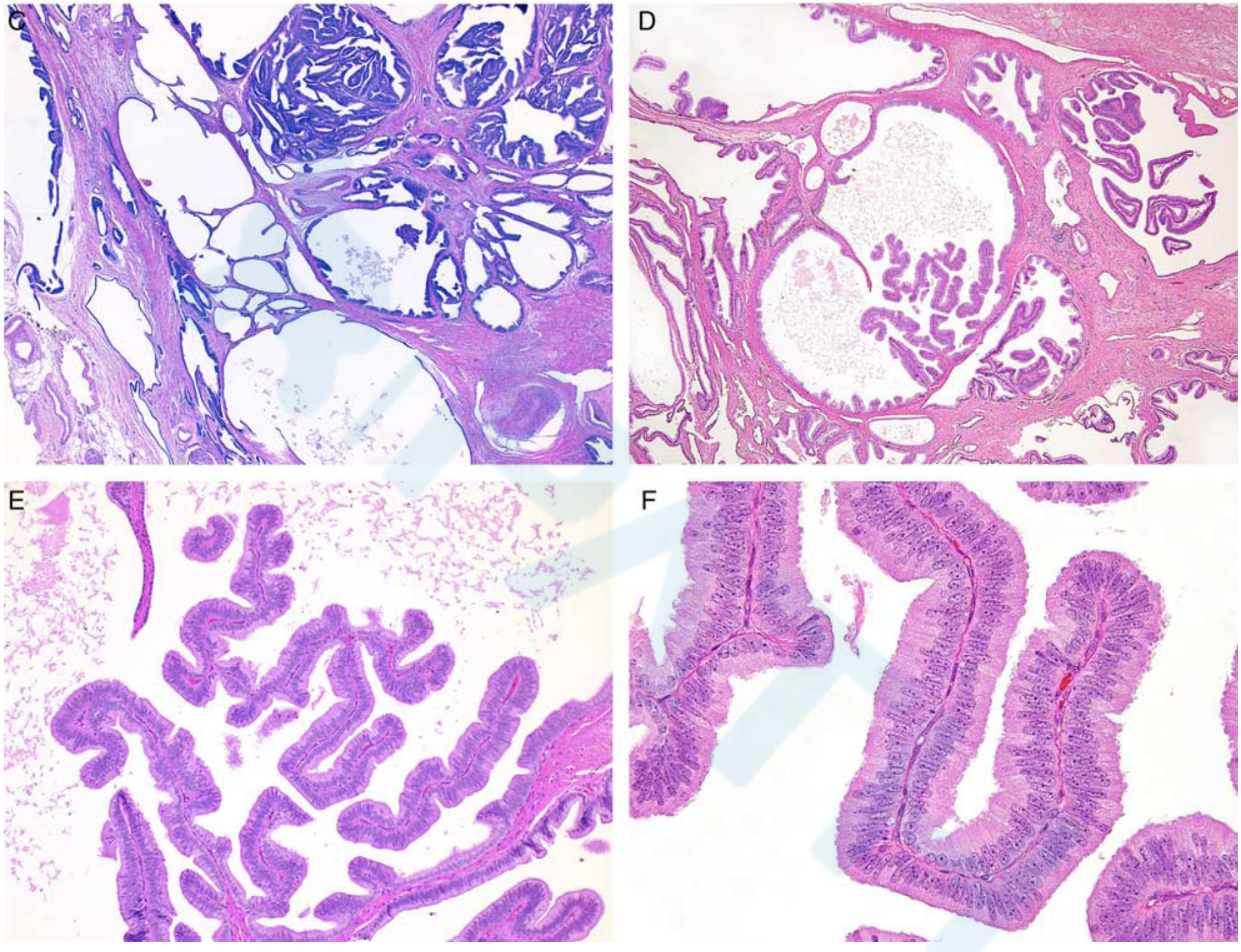

FIGURE 2. **C**, One case showed usual papillary ductal carcinoma (upper right) adjacent to PIN-like carcinoma (left). **D**, Thin papillary projections into cystically dilated PIN-like carcinoma glands. **E**, Medium power of (D) with thin papillary projections of PIN-like carcinoma, graded as Gleason pattern 4. **F**, High power of (D) thin papillary projections with columnar pseudostratified epithelium with prominent nucleoli.

- In 6/13 (46.1%) of cases the PIN-like carcinoma component was the dominant tumor, whereas in 7/13 cases (53.8%), the acinar component was the dominant tumor and the PIN-like carcinoma component was small (<1 cm) (Figs. 3A, B).

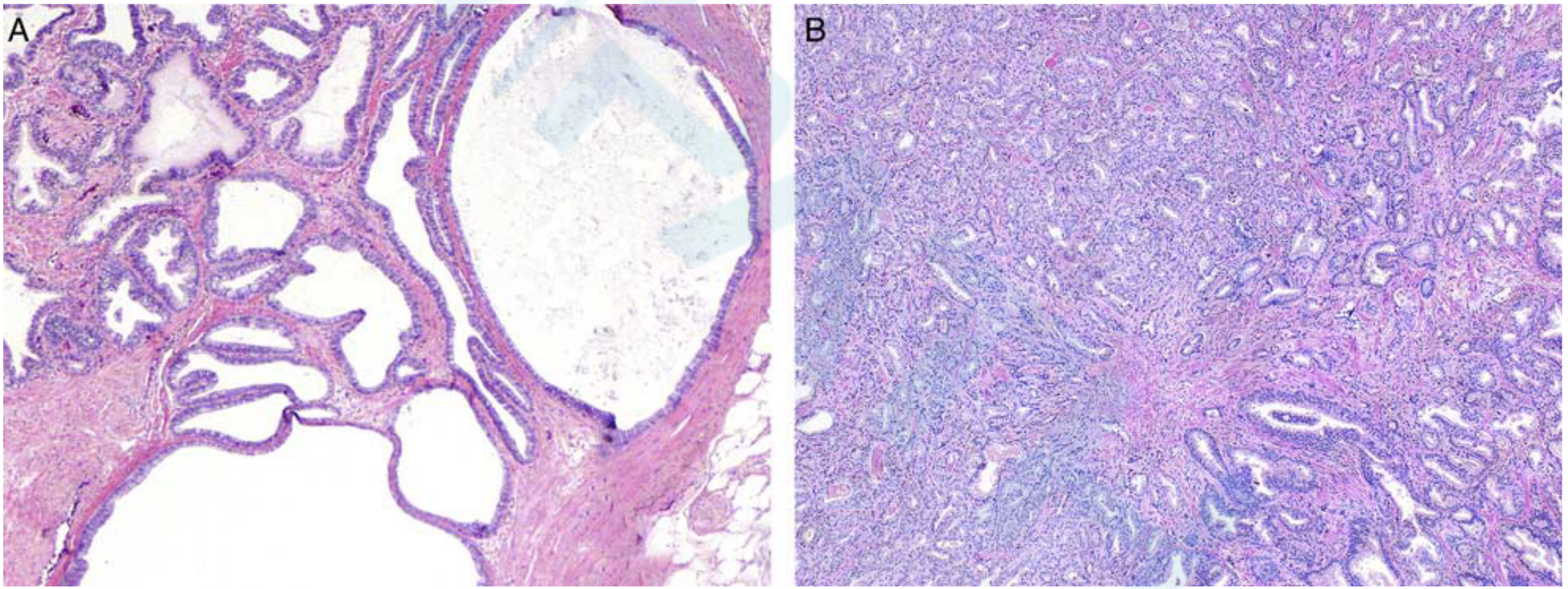

FIGURE 3
A, Small PIN-like carcinoma tumor where this image represents entire PIN-like carcinoma tumor in RP. **B**, Separate tumor in same case as (A), where acinar Gleason score 3+4= 7 (GG2) tumor was much larger than PIN-like carcinoma tumor.

- In all cases where there was PIN-like carcinoma with extraprostatic extension, the PIN-like carcinoma was the dominant component.
- In all cases the PIN-like carcinoma was located in the peripheral zone, and anatomically distinct from the acinar tumor, without intermingling of tumor types.

ERG and PTEN Expression

•IHC expression of ERG was positive in 1/11 (9.1%); the acinar component was also positive.

•IHC expression of PTEN showed heterogenous loss in 1/11 (9.1%) case within the PIN-like carcinoma tumor. In all other cases, both the acinar and PIN-like carcinoma tumors retained PTEN.

DISCUSSION

- In the first series looking at RP findings in PIN-like carcinomas, we named these cancers PIN-like ductal carcinomas, based on the cytologic resemblance to ductal adenocarcinoma and their architectural similarity to HGPIN.

- In that series, only 1 in 9 of the PIN-like carcinoma tumors showed EPE in the RP specimen; no tumors showed positive margins or seminal vesicle invasion. In addition, the associated acinar carcinoma in that series was entirely Gleason pattern 3 (GG1). On the basis of these findings, it was suggested that until long-term follow-up studies are available, what we termed “PIN-like ductal carcinoma” should be graded as Gleason pattern 3.

- Compared with our prior series, the current study found a higher frequency of EPE with PIN-like carcinoma, which was present in approximately half of cases on RP.
- On the basis of the low association with pattern 4 Gleason and cribriform cancer, lack of seminal vesicle invasion and low incidence of positive margins, we consider our results concordant with the original suggestion that PIN-like carcinomas be considered as pattern 3.

- Unlike our prior series, some percentage of Gleason pattern 4 was present in a majority of cases on RP. However, in all cases the percent pattern 4 was very low (5% to 10%).
- In half of cases classified as GG2, the pattern 4 consisted of thin papillary projections of the PIN-like carcinoma tumor, sometimes into cystic dilated glands.
- We consider that the glands containing these projections are identical to the cystically dilated glands of PIN-like carcinoma and the nature of the papillary projections also differ from those seen in classic papillary ductal adenocarcinoma.
- Whether these glands are considered a pattern of PIN-like carcinoma seen with more aggressive local infiltration or an unusual pattern of classic papillary prostatic duct adenocarcinoma, we agree they currently should be graded as Gleason pattern 4, and long-term studies are needed to understand its clinical significance.

- TMPRSS2-ERG rearrangement, present in ~ 50% of peripherally located tumors was found to be lower in usual ductal adenocarcinoma and their associated acinar tumors (11% and 6%, respectively) in a surgical cohort series by our institution.
- Our study found a similarly low rate of ERG expression and PTEN loss in PIN-like carcinoma tumors, with 1/11(9.1%) tumors showing positive ERG staining and only 1/11 (9.1%) case showing heterogenous loss of PTEN.

- One of **the limitations of our study** is the relatively small sample size of RP specimens, in part due to the rarity of the tumor and as well likely due to a decreased rate of RP among patients with this tumor.
- In addition, while we can report prostatectomy findings, the long-term follow up data is not yet available.
- The clinical significance of several findings on RP in our series, including EPE by dilated PIN-like carcinoma glands, or the significance of PIN-like carcinoma glands which form thin papillary projections into cystic dilated glands, is as of yet uncertain. Longer term studies will be needed to determine the clinical significance.

- **The current study expands on our prior study of PIN-like carcinomas by describing:**

(1) a new set of cases, where there was increased EPE, and the unique finding of large, cystic, extraprostatic glands of PIN-like carcinoma lined by atrophic epithelium;

(2) typical dilated PIN-like carcinoma glands with thin intraluminal papillary projections, which we graded as Gleason pattern 4;

(3) for the first time ERG and PTEN expression in these tumors.

- On needle biopsy, PIN-like carcinoma tumors may be particularly challenging to diagnose, as they may show less prominent nucleoli than HGPIN, and architecturally resemble benign glands.
- The diagnosis can only be made in the presence of numerous crowded glands with columnar pseudostratified architecture which also lack basal cells verified by IHC.

- Occasionally, the tumor may be seen as long strips of columnar epithelium along the edge of needle cores, due to the tendency of PIN-like carcinoma tumors to grow as large, dilated cysts.
- As a limited number of glands with HGPIN may have negative basal cells in a plane of section, a definitive diagnosis of PIN-like carcinoma on needle biopsy typically requires multiple glands negative for basal cell markers with morphology suggestive of PIN-like carcinoma to establish a definitive diagnosis.

- The current study showed an increased association of PIN-like carcinoma with EPE compared with our prior series, raising concerns that PIN-like carcinoma may be more aggressive than previously thought, although longer follow-up is needed to determine whether the peculiar morphology seen with EPE is associated with increased mortality.

Thanks for your attention!