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Intraductal carcinoma of the prostate: interobserver reproducibility survey of 39 urologic pathologists ☆

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ABSTRACT

The diagnosis of intraductal carcinoma (IDC) of the prostate remains subjective because 3 sets of diagnostic criteria are in use. An internet survey was compiled from 38 photomicrographs showing duct proliferations: 14 signed out as high-grade prostatic intraepithelial neoplasia (HGPIN), 17 IDC, and 7 invasive cribriform/ductal carcinoma. Each image was assessed for the presence of 9 histologic criteria ascribed to IDC. Thirty-nine respondents were asked to rate images as (1) benign/reactive, (2) HGPIN, (3) borderline between HGPIN and IDC, (4) IDC, or (5) invasive cribriform/ductal carcinoma. Intraclass correlation coefficient was 0.68. There was 70% overall agreement with HGPIN, 43% with IDC, and 73% with invasive carcinoma ($P < .001$, χ^2). Respondents considered 19 (50%) of 38 cases as IDC candidates, of which 5 (26%) had a two-thirds consensus for IDC; two-thirds consensus for either borderline or IDC was reached in 9 (47%). Two-thirds consensus other than IDC was reached in the remaining 19 of 38 cases, with 15 supporting HGPIN and 4 supporting invasive carcinoma. Findings that differed across diagnostic categories were lumen-spanning neoplastic cells ($P < .001$), 2× benign duct diameters ($P < .001$), duct space contours (round, irregular, and branched) ($P < .001$), papillary growth ($P = .048$), dense cribriform or solid growth (both $P = .023$), and comedonecrosis ($P = .015$). When the 19 of 38 images that attained consensus for HGPIN or invasive carcinoma were removed from consideration, lack of IDC consensus was most often attributable to only loose cribriform growth (5/19), central nuclear maturation (5/19), or comedonecrosis (3/19). Of the 9 histologic criteria, only 1 retained significant correlation with a consensus diagnosis of IDC: the presence of solid areas ($P = .038$). One case that attained IDC consensus had less than 2× duct enlargement yet still had severe nuclear atypia and nucleomegaly. Six fold nuclear enlargement was not significant ($P = .083$), although no image had both 6× nuclei and papillary or loose cribriform growth: a combination postulated as sufficient criteria for IDC. Finally, 20.5% of respondents agreed that an isolated diagnosis of IDC on needle biopsy warrants definitive therapy, 20.5% disagreed, and 59.0% considered the decision to depend upon clinicopathologic variables. Although IDC diagnosis remains challenging, we propose these criteria: a lumen-spanning proliferation of neoplastic cells in preexisting ducts with a dense cribriform or partial solid growth pattern. Solid growth, in any part of the duct space, emerges as the most reproducible finding to rule in a diagnosis of IDC. Comedonecrosis is a rarer finding, but in most cases, it should rule in IDC. Duct space enlargement to greater than 2× the diameter of the largest, adjacent benign spaces is usually present in IDC, although there may be rare exceptions.

1. Introduction

Intraductal carcinoma (IDC) is considered as a lumen-spanning proliferation of neoplastic prostate epithelium within enlarged, preexisting ducts. Intraductal carcinoma is distinguished from high-grade prostatic intraepithelial neoplasia (HGPIN) by duct size, cellularity, and functionally, by prognosis and molecular markers [1-3]. Evidence exists on both sides as to whether IDC represents colonization of benign ducts by preexisting acinar carcinoma or a progression from HGPIN.

Possibly because they lack awareness of IDC as a separate entity or due to conflicting criteria, only 44% of pathologists surveyed as of 2006 were willing to diagnose IDC [1]. Intraductal carcinoma had generated little attention from uropathologists until recent years. This is because it occurs as an isolated finding (no invasive cancer) in only 0% [2] to 0.26% [3] of prostate needle biopsy sets. More than 99% of IDC is a minor component in a prostate with invasive high-grade (Gleason score always at least 7 [2,3]) and high-volume [4] carcinoma, usually greater than 2 mL [3]. Intraductal carcinoma usually arises amid acinar carcinoma, but 11% of cases are associated with invasive ductal carcinoma and 5%, with mixed ductal-acinar carcinoma [5].

The diagnosis of IDC is hampered by having 3 discrepant sets of diagnostic criteria in use (Table 1), and no consensus exists about which criteria to prioritize. The first set of criteria, published in 1996 [6] and used subsequently [7], included trabecular, cribriform, and solid growth patterns. Guo and Epstein [1] in 2006 additionally stipulated that papillary and "loose" cribriform patterns qualified as IDC only if their nuclei were enlarged to 6× the size of nuclei in adjacent benign epithelium, or if comedonecrosis was also present. Cohen et al [8] in 2007 gave no size criterion for the nuclei but stipulated that the duct space must be enlarged to at least twice (2×) that of benign acini and placed emphasis on the duct space contour (round vs irregular) and branching.

Because of the morphologic overlap of IDC with cribriform and noncribriform HGPIN, some pathologists have devised a borderline category between HGPIN and IDC, termed *atypical cribriform proliferation*

Table 1
Proposed criteria for IDC of the prostate

Characteristic:	First author:		
	McNeal and Yemoto [6], 1996	Guo and Epstein [1], 2006	Cohen et al [8], 2007
Lumen-spanning neoplastic cell proliferation	Yes	Yes	Yes, adds that the duct diameter must exceed 2× that of benign peripheral zone glands
Basal cell layer (mostly) intact	Yes	Yes	Yes
Nuclei and necrosis	Atypical nuclei	If papillary or loose cribriform growth, size at least 6× that of a benign nucleus, or comedonecrosis present	Atypical nuclei; may have necrosis
Patterns	Trabecular, cribriform, solid/comedo	Same but adds papillary pattern without fibrovascular cores	Proposes to rename ductal carcinoma and includes it as part of IDC
Minor criteria	None	None	1) Right-angle branching; 2) smooth contours; 3) dimorphic cell population with peripheral columnar PSA-negative and central cuboidal PSA-positive cells

[9-13]. In a study of 53 patients with borderline lesions on biopsy, Han et al [9] recommended repeat biopsy for all. Among 22 patients with clinical follow-up, the predictive value of a borderline lesion for invasive cancer (10 cases) or IDC (2 cases) on repeat biopsy was 55%. Given the uncertainty of the histologic features of IDC, we assessed the interobserver reproducibility of an IDC diagnosis, questioning whether it rivals the "good-to-excellent" reproducibility ascribed to HGPIN [14] and determined which histologic findings were significant discriminators.

2. Materials and methods

Thirty-eight images were compiled with assistance from JM and DGB; 4 were composites of low and high magnifications. Fourteen images were diagnosed HGPIN at sign-out, 17 were IDC under current criteria [1,6-8], and 7 were invasive carcinoma. Although immunohistochemical stain results were available for most of the cases, we chose not to include them in the survey because the survey's focus was on distinguishing HGPIN vs IDC. The rationale was that an immunostain is useful only in the distinction of IDC from invasive carcinoma, whereas HGPIN and IDC can usually be perceived by hematoxylin-eosin stain to arise in preexisting duct spaces with at least focal basal cells. Prospectively, the presence or absence of 9 criteria was assessed for each image including duct size, growth pattern, and cytologic features believed relevant to an IDC diagnosis. Using SurveyMonkey.com, a survey was constructed that gave respondents 5 diagnostic choices for each image: (1) benign/reactive, (2) HGPIN, (3) borderline between HGPIN and IDC, (4) IDC, or (5) invasive cribriform or ductal carcinoma. The survey was sent to 39 pathologists (1 declined authorship). Group 1 comprised 19 urologic pathologists who have authored articles or book chapters on the topic of intraductal and large-gland carcinoma and are thus presumed to have an "expert" level of awareness about IDC, and group 2 comprised 20 pathologists who practice largely or entirely urologic pathology but who have not authored any writings on intraductal and large-gland carcinoma. Raw data were tabulated; the above diagnostic categories were assigned numeric values of 1 to 5, and the mean and SD for each image were calculated. The intraclass correlation coefficient (ICC) for a fixed set (set of respondents is the same for all cases) was used to determine associations across all 5 categories of response for group 1 and for group 2. The ICC usually ranges from 0 (no association) to 1.0 (perfect association). To determine agreement with the original diagnoses of HGPIN, IDC, or invasive carcinoma, logistic regression with repeated measures on observers was used.

Consensus, in this study, was defined as a vote by two-thirds or more of respondents in favor of any 1 of the 5 diagnoses. This followed the precedent set in a consensus survey on ductal carcinoma [15]. A minority opinion for a given alternative diagnostic choice required at least 5 votes favoring that diagnosis, for the purpose of this study.

Respondents were asked their opinion regarding the statement, "Isolated IDC (no invasion) diagnosis on needle core biopsy is sufficient evidence to perform definitive therapy (radical prostatectomy or radiation brachytherapy)." Choices were (1) agree, (2) disagree, and (3) it depends on clinicopathologic variables such as linear extent, number of cores, urologist's judgment, etc.

3. Results

The ICC (all 5 diagnostic choices) for group 1 (19 experts) was 0.70. The ICC for group 2 was marginally lower, at 0.68, and for the combined groups, it was 0.68. Thus, further analyses were performed on the combined groups. Taking all responses for all images as "agree" or "disagree" with the original diagnoses and excluding benign/reactive and borderline, there was 70% overall agreement with HGPIN, 43% with IDC, and 73% with invasive carcinoma ($P < .001$, χ^2). The weighted κ values for multiple observers were 0.13, 0.13, and 0.23, respectively.

Consensus results are shown in Table 2. Keeping the focus of the study on the HGPIN vs IDC distinction, attention was given to HGPIN, borderline, and IDC diagnoses. Candidates for IDC comprised 19 of 38 cases; 5 (26%) had a consensus for IDC, and the correlation of the resulting diagnostic categories with histologic findings is shown (Table 3). Because few images attained consensus for IDC alone, the consensus for either IDC or borderline was studied. Consensus for either borderline or IDC occurred in 9 (47%) of cases (Table 4) (it rose to 10 [53%] among group 1 respondents only). A two-thirds consensus against IDC was reached in 19 (50%) of 38 cases, with 15 in the direction of HGPIN and 4 in the direction of invasive carcinoma.

Table 2
Attainment of two-thirds consensus on images

Among images with no consensus against IDC:	Group results (n = 19)
For IDC	5/19 (26%)
For either IDC or borderline	9/19 (47%)
No consensus for IDC	14/19 (74%)
No consensus for either IDC or borderline	10/19 (53%)
Among all images:	(n = 38)
Consensus against IDC, for HGPIN	14/38 (37%)
Consensus against IDC, for invasive carcinoma	5/38 (11%)

3.1. Duct features

Findings that reliably distinguished diagnostic categories (Table 3) were lumen-spanning neoplastic cells ($P < .001$), duct diameters 2× those of neighboring benign spaces ($P < .001$), and contours (round, irregular, or branched) ($P < .001$). When the 19 of 38 images that had a consensus for either HGPIN or invasive carcinoma were removed from consideration, no duct features retained a significant correlation with IDC (Table 3) or either borderline lesion or IDC (Table 4).

3.2. Growth pattern

Dense cribriform ($P = .008$) or solid ($P = .002$) growth demonstrated a correlation with an IDC diagnosis (Table 3) and also with either IDC or borderline diagnosis (Table 4) (both $P = .023$). "Loose" cribriform [1] growth, in the current study, was considered less than 50% filling of the duct space by epithelium. Papillary growth and loose cribriform growth did not correlate with IDC diagnosis (Table 3), although an absence of papillary growth correlated with IDC or borderline lesion (Table 4, $P = .048$). After excluding the 19 (of 38) images that had a consensus of HGPIN or invasive carcinoma, the presence of solid areas was the only one among all 9 histologic criteria that retained significant correlation with a consensus-based diagnosis of IDC ($P = .038$).

3.3. Nuclear features

The IDC criterion of 6× nuclear enlargement within papillary or loose cribriform growth patterns [1] was scrutinized. Six fold nuclear enlargement was present in 5 cases, and all had foci of solid growth; in no instance was papillary or loose cribriform growth present. The consensus was for IDC in 2 of these cases, for either IDC or borderline in 1 and no consensus in 2. Six fold nuclear enlargement never occurred, where the consensus was HGPIN or invasive carcinoma. Across all categories, 6× nuclei was marginally significant ($P = .053$). In the 19 cases without a consensus for HGPIN or invasive carcinoma, 6× nuclei was not significant in reaching a consensus of IDC only ($P = .084$) or either borderline or IDC ($P = .628$). The small number of cases with 6× nuclei may have precluded attainment of significance, but the survey was not able to establish a correlation between 6× nuclei and IDC. Nuclear maturation was most common in HGPIN (6 cases, 43%) but was present in 4 cases with no consensus and 1 with IDC consensus. It did not differ significantly across categories.

Table 3
Correlation of histologic features with consensus for IDC

Variables	Total, n = 38 (%)	2/3 Consensus for IDC or for HGPIN or invasive carcinoma: For HGPIN, n = 14 (%)	For invasive carcinoma, n = 5 (%)	No consensus, n = 14 (%)	Consensus for IDC, n = 5 (%)	*P* value across 4 categories, n = 38*	*P* value excluding HGPIN or invasive carcinoma, n = 19*
Lumen-spanning neoplastic cells						<.01	NA
No	14 (37)	14 (100)	0	0	0		
Yes	24 (63)	0 (0)	5 (100)	14 (100)	5 (100)		
Duct diameter (2×)						<.01	.263
No	15 (40)	14 (100)	0	0	1 (20)		
Yes	23 (61)	0	5 (100)	14 (100)	4 (80)		
Duct contour						.002	.480
Round	23 (70)	14 (100)	0	5 (36)	4 (80)		
Irregular	9 (27)	0	0	8 (57)	1 (20)		
Branching	1 (3)	0	0	1 (7)	0		
Disrupted basement membrane	5	0	5	0	0		
Papillary pattern						.060	.591
No	30 (79)	8 (57)	5 (100)	12 (86)	5 (100)		
Yes	8 (21)	6 (43)	0	2 (14)	0		
Cribriform pattern (loose)						.077	.128
No	30 (79)	13 (93)	4 (80)	8 (57)	5 (100)		
Yes	8 (21)	1 (7)	1 (20)	6 (43)	0		
Cribriform pattern (dense)						.008	.305
No	28 (74)	14 (100)	2 (40)	10 (71)	2 (40)		
Yes	10 (26)	0	3 (60)	4 (29)	3 (60)		
Solid areas						.002	.038
No	28 (74)	14 (100)	2 (40)	11 (79)	1 (20)		
Yes	10 (26)	0	3 (60)	3 (21)	4 (80)		
Nuclear enlargement (6×)						.008	.084
No	33 (87)	14 (100)	5 (100)	12 (86)	2 (40)		
Yes	5 (13)	0 (0)	0	2 (14)	3 (60)		
Nuclear maturation in center						.348	1.000
No	27 (71)	8 (57)	5 (100)	10 (71)	4 (80)		
Yes	11 (29)	6 (43)	0	4 (29)	1 (20)		
Comedonecrosis						.064	.570
No	33 (87)	14 (100)	5 (100)	11 (79)	3 (60)		
Yes	5 (13)	0	0	3 (21)	2 (40)		

* ANOVA (Analysis of variance), Fisher exact test.

3.4. Luminal features

Across diagnostic categories, frequency of comedonecrosis differed ($P = .015$). It was never seen when the consensus was HGPIN. Excluding the 19 of 38 images with HGPIN or invasive carcinoma consensus, significance was not retained.

Also excluding the 19 images with HGPIN or invasive carcinoma consensus, a lack of IDC consensus was most often attributable to only loose cribriform growth (5/19), central nuclear maturation (5/19), or comedonecrosis (3/19). Certain images best illustrate the main diagnostic conflicts:

3.5. HGPIN vs borderline

Lumen-spanning cells and 2× duct space enlargement were present in only 1 (Fig. 1) of 5 cases in this category of diagnostic conflict. None had a dense cribriform or solid pattern, 6× nuclei, or comedonecrosis. Two had central nuclear maturation.

3.6. HGPIN vs borderline vs IDC

All 9 cases had lumen-spanning cells and 2× duct enlargement. Five had loose cribriform growth, 2 had dense cribriform, and 1 (Fig. 2) had solid growth. Six fold nuclear enlargement was present in 1 case, but there was nuclear maturation; the growth pattern was dense cribriform (Fig. 3). Central nuclear shrinkage was present in 3 of 9 cases and 2 had comedonecrosis (Figs. 4 and 5).

3.7. Borderline vs IDC vs invasive carcinoma

Only 1 case fell into this category, and it had the lowest concordance of all 38. This image had lumen-spanning neoplastic cells, 2× duct enlargement, a dense cribriform pattern, and comedonecrosis; but nuclear maturation was evident (Fig. 6). The immunohistochemical stain corresponding to this focus showed basal cells present (Fig. 7), so if that immunostain had been furnished to participants, they may have agreed on either IDC or borderline. This highlights the diagnostic difficulty posed by nuclear shrinkage/maturation.

3.8. Other diagnostic categories

Of all histologic features examined, papillary growth was present in 2 HGPIN consensus cases, and nuclear maturation was evident in 1 of 3. Two-thirds consensus on IDC was reached in 5 cases, but only 1 case had fewer than 3 dissenting votes. This strong-consensus lesion had dense cribriform growth, 6× nuclei, and an obvious basal cell layer (Fig. 8).

Nine cases had a main conflict of IDC vs invasive carcinoma (at least 5 votes for a category); all had lumen-spanning cells, and all but 1 had 2× duct space enlargement. The image without 2× duct space enlargement had 6× nuclear enlargement and solid, lumen-spanning cell growth (Fig. 9). All 9 had either dense cribriform growth, solid growth, or both.

3.9. Therapeutic significance of IDC

Respondents were asked for their opinion as to whether an isolated diagnosis of IDC on needle biopsy warrants definitive therapy. Eight

Table 4
Correlation of histologic features with consensus for either borderline lesion or IDC

Variables	Total, n = 38 (%)	2/3 Consensus for †either IDC or borderline or for HGPIN or invasive carcinoma: For HGPIN, n = 14(%)	For invasive carcinoma, n = 5 (%)	No consensus, n = 10 (%)	Consensus for either†, n = 9 (%)	*P* value across 3 categories, n = 38*	*P* value excluding HGPIN or invasive carcinoma, n = 19*
Lumen-spanning neoplastic cells						<.001	NA
No	14 (37)	14 (100)	0	0	0		
Yes	24 (63)	0	5 (100)	10 (100)	9 (100)		
Duct diameter (2×)						<.001	.474
No	15 (40)	14 (100)	0	0	1 (11)		
Yes	23 (61)	0	5 (100)	10 (100)	8 (89)		
Duct contour						.001	.255
Round	23 (70)	14 (100)	0	3 (30)	6 (67)		
Irregular	9 (27)	0	0	6 (60)	3 (33)		
Branching	1 (3)	0	0	1 (10)	0 (0)		
Disrupted basement membrane	5	0	5	0	0		
Papillary pattern						.048	.474
No	30 (79)	8 (57)	5 (100)	8 (80)	9 (100)		
Yes	8 (21.0)	6 (43)	0	2 (20)	0		
Cribriform pattern (loose)						.473	1.000
No	30 (79)	13 (93)	4 (80)	7 (70)	6 (67)		
Yes	8 (21)	1 (7)	1 (20)	3 (30)	3 (33)		
Cribriform pattern (dense)						.023	.650
No	28 (74)	14 (100)	2 (40)	7 (70)	5 (56)		
Yes	10 (26)	0	3 (60)	3 (30)	4 (44)		
Solid areas						.023	.650
No	28 (74)	14 (100)	2 (40)	7 (70)	5 (56)		
Yes	10 (26)	0	3 (60)	3 (30)	4 (44)		
Nuclear enlargement (6×)						.053	.628
No	33 (87)	14 (100)	5 (100)	8 (80)	6 (67)		
Yes	5 (13)	0	0	2 (20)	3 (33)		
Nuclear maturation in center						.340	1.000
No	27 (71)	8 (57)	5 (100)	7 (70)	7 (78)		
Yes	11 (29)	6 (43)	0	3 (30)	2 (22)		
Comedonecrosis						.015	.141
No	33 (87)	14 (100)	5 (100)	9 (90)	5 (56)		
Yes	5 (13)	0	0	1 (10)	4 (44)		

† Responses of borderline lesion were summed with responses of IDC for each image to determine consensus.
* ANOVA Fisher exact test.

(20.5%) of respondents agreed, 8 (20.5%) disagreed, and 23 (59.0%) considered the decision to depend upon clinicopathologic variables. Respondents mentioned high-serum prostate-specific antigen (PSA), number of cores involved, and clinical findings as considerations. One commented, "Another option would be to make a statement comment requiring follow-up rebiopsy within a short (1-2–month) time frame." Another remark was, "I worry that some pathologists have too low of a threshold for IDC."

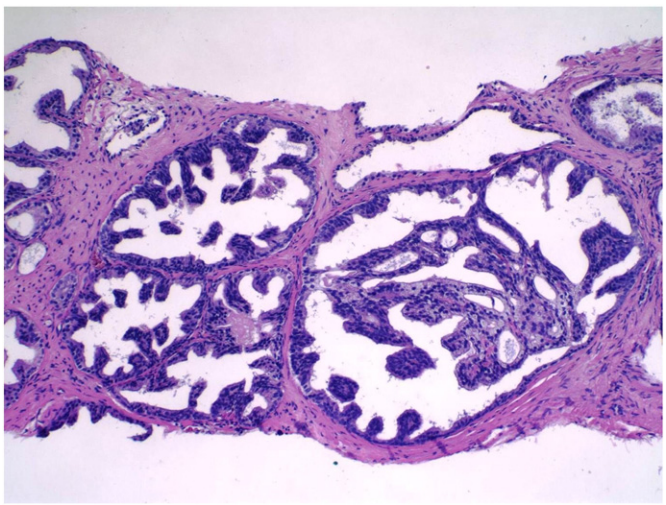

Fig. 1. No consensus. Fourteen votes for HGPIN, 15 for borderline, and 2 for IDC. Loose cribriform growth is present.

4. Discussion

The overall percentage agreement in this study was lower for IDC (43%) than for HGPIN (70%) or invasive carcinoma (73%). The κ values were 0.13, 0.23, and 0.13, respectively; this may have been attributable to sample size limitations and to large differences in the prevalence of agreement from case to case. After excluding 19 cases, where the consensus was against IDC (for HGPIN or invasive carcinoma), the rate of two-thirds consensus for IDC including the "borderline" designation was 47%. For comparison, a recent survey on ductal carcinoma of the prostate found that a two-thirds consensus was reached in 11 (52%) of 21 cases, and 5 cases (24%) had a consensus against [15]. However, the option to use the borderline designation in our survey renders it not strictly comparable with the ductal carcinoma survey.

Several histologic features were associated with the most discordance between HGPIN and IDC. When the diagnostic split was between HGPIN and borderline, an absence of lumen-spanning cells or 2× duct enlargement was a frequent occurrence. Conversely, of the 5 cases with an IDC consensus, 1 had minimal duct enlargement, less than 2× [8] (Fig. 9). In the HGPIN vs borderline vs IDC category, a common problem was having only papillary or loose cribriform growth rather than dense cribriform or solid growth. In fact, 2 cases in this category had comedonecrosis, but the growth pattern was only loose cribriform. Finally, 1 case in this category (Fig. 6) had 6× nuclear enlargement but with central nuclear shrinkage. This shrinkage may be artifact but may also be maturation, a noted feature of cribriform HGPIN [16].

When the 19 (of 38) images that had a consensus against IDC (for either HGPIN or invasive carcinoma) were removed from consideration, the only histologic criterion that correlated significantly with an IDC consensus was the presence of solid areas. This seems logical because

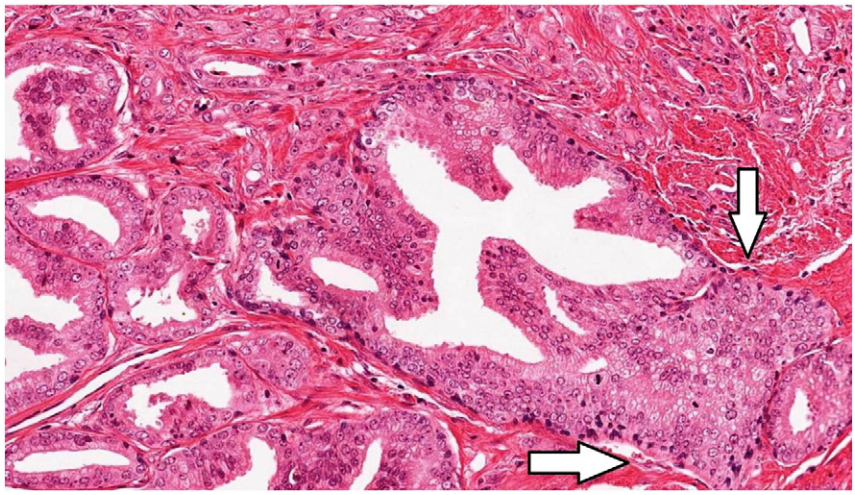

Fig. 2. No consensus. Respondents were asked to evaluate the duct between the arrows. Sixteen votes for HGPIN, 10 for borderline, 8 for IDC, and 4 for invasive. Partial solid growth is present on the right side of the duct.

HGPIN can be papillary or cribriform, but it is never solid. Solid growth of neoplastic cells should preclude a diagnosis of HGPIN.

Six fold nuclear enlargement in the setting of a papillary or loose cribriform growth pattern has been proposed as sufficient to diagnose IDC [1]. However, in the current study, all 5 (of 39) images that had 6× nuclei also had solid growth. Moreover, solid growth, but not 6× nuclei, was significant in determining whether a consensus for IDC was reached in the 19 cases that did not have a consensus against IDC (ie, either HGPIN or invasive carcinoma). In the 5 cases in which a consensus for IDC was reached, none had 6× nuclei. However, it is not possible to assess the utility of 6× nuclei in a loose cribriform or papillary growth pattern [1] from this survey. Notably, cribriform lesions with low-grade cytologic change have rates of ETS-related gene (ERG) fusion similar to classic IDC with high-grade cytology [11], arguing against the preeminence of cytologic criteria for diagnosing IDC.

4.1. Inherent adverse impact of cribriform growth

Rubin et al [17] described a set of lesions designated as "cribriform PIN." Some of their illustrations have sufficient nuclear pleomorphism that they would qualify as IDC by today's standards. Their cases of cribriform PIN had a 61% cumulative PSA failure rate in contrast to cribriform carcinoma at 15% and noncribriform acinar carcinoma at 13%. The presence of IDC according to criteria set by McNeal and Yemoto [6] correlated with higher Gleason score and tumor volume and was an independent risk factor for progression after prostatectomy [4]. The adverse impact of cribriform growth generalizes to invasive carcinoma. Invasive cribriform carcinoma, compared with other Gleason grade 4 patterns, was present in 61% of men who experienced PSA failure, but only 16% of controls matched for follow-up duration and other clinicopathologic variables [18]. It seems that whenever a duct proliferation attains a large or small cribriform pattern, with or without basal cells remaining, it predicts positive margin, extraprostatic extension [18-20], and biochemical recurrence [21].

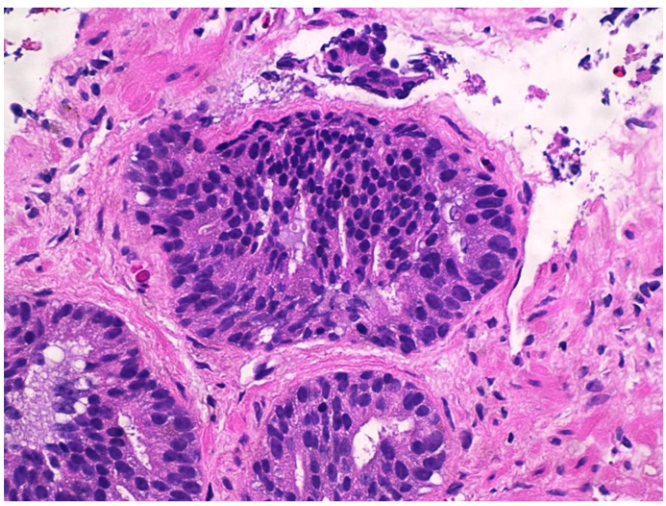

Fig. 3. No consensus. Twelve votes for HGPIN, 12 for borderline, 11 for IDC, and 4 for invasive. Dense cribriform growth is present, but smaller nuclear size (maturation) is noted toward the center.

For noninvasive lesions, our survey supports requiring dense cribriform/solid growth to diagnose most IDC. Isolated HGPIN with a cribriform/papillary pattern on needle biopsy did not significantly predict cancer on repeat biopsy, compared with other architectural HGPIN patterns in 100 cases [22]. Recently, however, others suggested that these patterns had a 58% risk for cancer on repeat biopsy, compared with 17% for other HGPIN patterns [23], and arguably, this supports classifying isolated cribriform HGPIN in the borderline category [11]. With use of the proper criteria for IDC, IDC has a distinctly worse outcome than cribriform HGPIN. In a study of 83 men with isolated IDC on needle biopsy, follow-up was available in 66; more than half underwent definitive treatment. In 21 prostatectomy specimens examined, all but 2 disclosed invasive tumor of high grade and stage. Two specimens had only IDC without an invasive component [5].

4.2. Borderline lesions

Lotan et al [10] defined the borderline category as a "loose cribriform proliferation without marked atypia or necrosis." Shah et al [11] designated these intermediate lesions in radical prostatectomy specimens as "isolated atypical cribriform lesion" or ACL. Eighteen percent of cases had ACLs that were within or less than 3 mm from invasive cancer, whereas ACLs isolated from cancer were found in 13%. Atypical cribriform lesions within invasive cancer outnumbered isolated ones (23.8 per specimen vs 2.4), ranged up to 9 mm (vs up to 1 mm), usually had an undulated or branching contour as opposed to a round one, had comedonecrosis in 33% as opposed to none, had 6× nuclear enlargement in 28% as opposed to none, and accompanied an invasive component with higher Gleason score and tumor volume. These criteria were then proposed as ways to distinguish true IDC from ACL in prostate biopsies. Topographic closeness to invasive cancer per se may not be

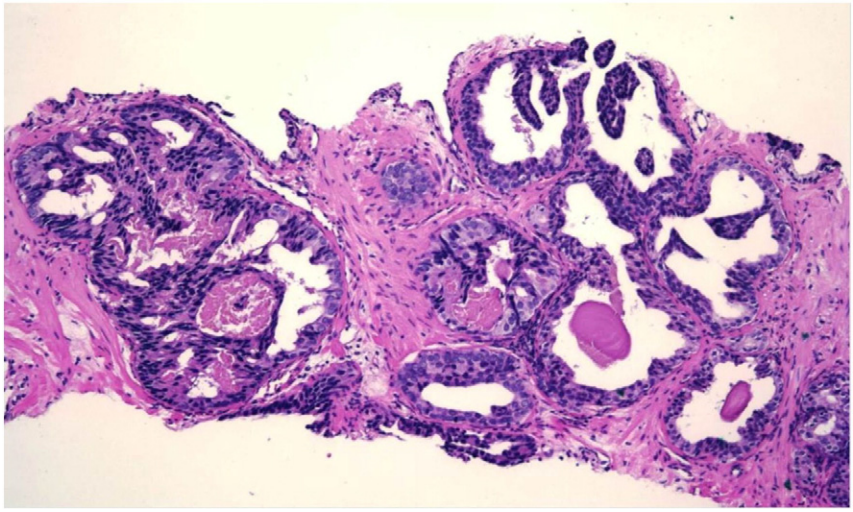

Fig. 4. Consensus for either borderline or IDC but not for IDC alone. One vote for benign, 9 for HGPIN, 12 for borderline, 15 for IDC, and 1 for invasive. Comedonecrosis is noted.

sufficient to presume that an ACL is IDC, however, our prior study showed 75% of foci of HGPIN to be closely associated with cancer [24]. Atypical cribriform lesion in prostatectomy specimens carried a risk of biochemical recurrence of the invasive component, intermediate between HGPIN and IDC [13].

In IDC, the rates of ERG fusion and phosphatase and tensin homolog (PTEN) loss are at least commensurate with those of invasive carcinoma [10] and exceed the corresponding rates for HGPIN. Cytoplasmic PTEN loss has been suggested as a marker to distinguish IDC from HGPIN, being observed in 84% of IDC and 100% of lesions intermediate between IDC and HGPIN but never in HGPIN [10]. Nuclear reactivity for PTEN may be retained in IDC [8]. Intraductal carcinoma's rate of PTEN loss exceeds the 35% to 45% rates reported for acinar carcinoma [10,25-28] and is actually similar to the much higher PTEN loss rates in Gleason grades 4 to 5 cancer [25].

Immunoreactivity for ERG protein, reflecting a transmembrane protease, serine 2-ERG gene fusion, has been reported in 35% to 75% [10,12,25,26,29] of IDC. Intraductal carcinoma rearrangement status of ERG (deletion or insertion) was always concordant with rearrangement status of invasive carcinoma, and whether 6× nuclear enlargement was present did not affect the rate of rearrangement [12]. In a topographic study using proximity to invasive cancer to discriminate IDC [11], this provided a molecular justification for the discriminatory value of topography. Schneider and Osunkoya [29] agreed that the presence or absence of ERG reactivity in IDC always matched that of the acinar carcinoma; but the 35% rate of expression in the invasive carcinoma associated with IDC was less than that away from IDC, suggesting that when IDC is present, the accompanying invasive component tends to have a unique phenotype. We have reviewed the molecular findings on rates of PTEN loss and ERG expression in borderline lesions [30], and they overlap significantly with cribriform HGPIN [12]. Given the difficulties in reproducibility of the IDC diagnosis in the present study and the molecular findings in atypical cribriform proliferation, the latter diagnosis is justified when not all IDC criteria are fulfilled, particularly solid/dense cribriform growth.

4.3. Nuclear maturation

Uncertainty may also arise when "maturation" of nuclei is observed—smaller nuclear size and loss of prominent nucleoli going from the periphery of the duct space toward the center. Nuclear maturation has been cited as a feature of cribriform HGPIN [16]. On the other hand, a different article designates a frequent dual-cell population with central maturation as a feature of IDC [8]. Other authors believe that IDC may (if trabecular or cribriform) or may not (if solid) have central maturation [6,21]. In a recently published article, pictures proposed to be HGPIN and

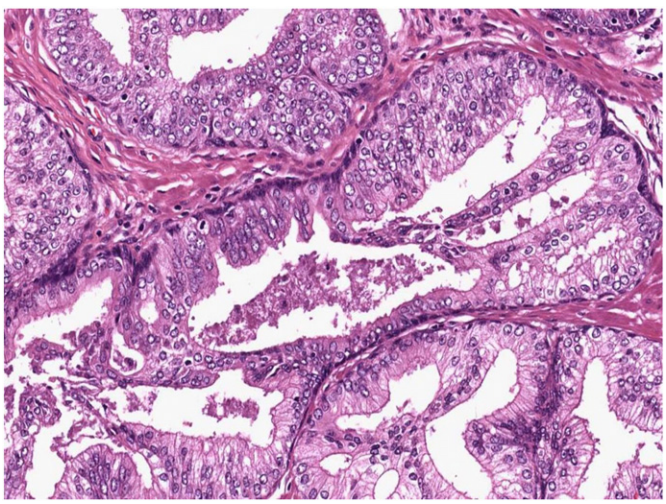

Fig. 5. Consensus for either borderline or IDC but not for IDC alone. Two votes for benign, 9 for HGPIN, 16 for borderline, 11 for IDC, and 1 for invasive. Comedonecrosis is noted centrally.

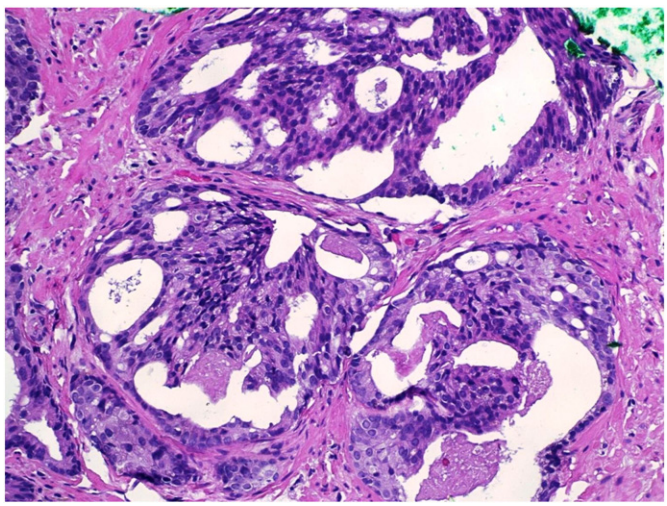

Fig. 6. No consensus. One vote for benign, 4 for HGPIN, 10 for borderline, 14 for IDC, and 10 for invasive. Central nuclear maturation may have discouraged some respondents from a definite IDC diagnosis.

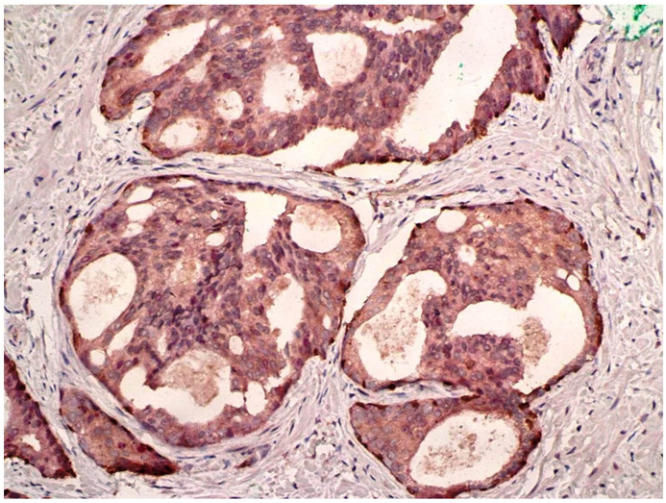

Fig. 7. Combined basal cell markers and P504S immunostain, not furnished to participants, demonstrate a basal cell layer. If this image had been provided to participants, consensus for IDC may have been met.

IDC were presented side by side, with the main difference between the 2 being smaller size of nuclei evident in the one designated HGPIN [31]. Most IDC ducts contained a dual-cell population, wherein the peripheral cells were alpha-methylacyl coA racemase (P504S)-positive, whereas central small cells were P504S-negative [32]. Thus, it would appear that a 2× enlarged duct space with nuclear atypia but smaller central cell nuclei is the prototype for classification as a borderline lesion.

4.4. Impact on biopsy diagnosis

We queried survey participants whether isolated IDC was sufficient for definitive therapy. A majority of participants considered that this decision depended on clinical and pathologic findings. Isolated IDC is a major diagnostic issue mostly for biopsies and only then in fewer than 1/200 cases. The finding of isolated IDC (no invasive cancer) was noted in only 0% [2] to 0.26% [3] of cases. In prostatic needle biopsy sets, the total rate of IDC, isolated or not, was reported as 1.5% [1] to 2.8% [3]. However, among intermediate-risk and high-risk prostate cancer patients, IDC was recently reported in their biopsy and transurethral resection specimens at rates of 19% and 22%, respectively, serving as a prognostic risk factor independent of Gleason score [33]. Isolated high-grade PIN, as of 2004, had a much higher 9% mean reported incidence (range, 4%-16%) in prostatic biopsy sets [16]. Some pathologists propose that isolated IDC on needle biopsy should prompt definitive therapy [1,5,8]. Not all pathologists agree, although, that isolated IDC warrants prostatectomy [21]. At least, immediate repeat biopsy is warranted [8] unlike with HGPIN, which calls for repeat biopsy at 1 year or just surveillance.

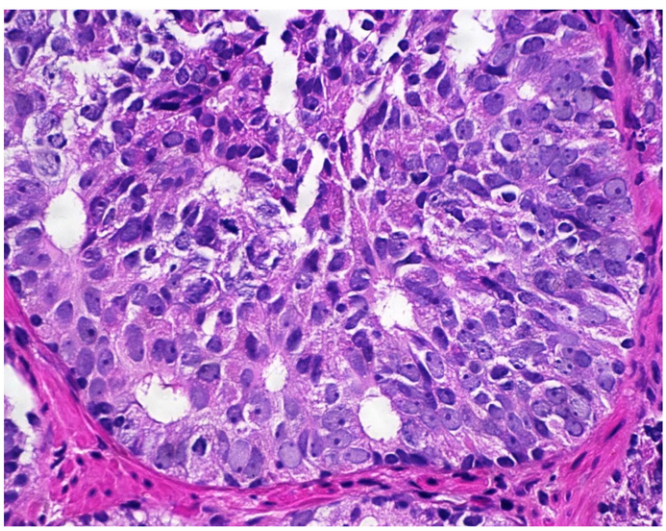

Fig. 8. Strong consensus for IDC among 34 respondents, with only 4 votes for borderline and 1 for invasive. Largely solid growth pattern, 6× nuclear enlargement, and a definite basal cell layer help establish an IDC diagnosis. Negligible central nuclear shrinkage is observed.

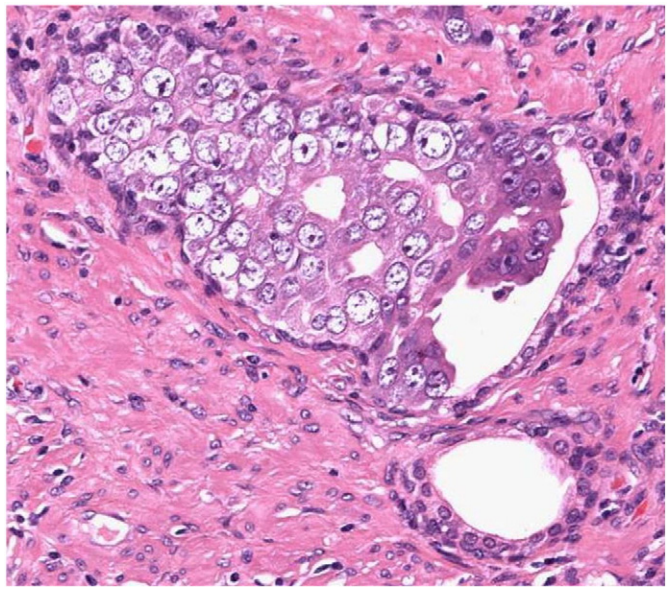

Fig. 9. Consensus for IDC among 29 respondents, with 1 vote for benign, 2 for HGPIN, 3 for borderline, and 4 for invasive. Although the duct space is not enlarged 2× compared with neighboring benign spaces (not shown), it has solid growth pattern, 6× nuclear enlargement, and a definite basal cell layer. These features support the IDC diagnosis.

4.5. Differential diagnosis

The differential diagnosis for IDC includes HGPIN, invasive carcinoma, ductal carcinoma, and urothelial carcinoma. Ductal carcinoma is sufficiently different from IDC that it rarely poses a problem. Classically, basal cells are absent, and there are often papillae with fibrovascular cores. The lining epithelium is usually pseudostratified columnar with basally situated nuclei, often imparting an “endometrioid” appearance consistent with its former name of endometrioid carcinoma. Intraductal carcinoma was the most common differential diagnosis for ductal carcinoma (52% of cases in a recent survey) [15], the only difference being presence or absence of basal cells. Ductal carcinoma has been proposed to be subsumed under IDC [8]. Bostwick and Cheng [34] argue the reverse: that IDC is actually a subset of ductal carcinoma, not a unique entity, and is a noninvasive type of ductal carcinoma that can get Gleason graded. The rare entity of adenoid cystic/basal cell carcinoma of the prostate can have a cribriform pattern. However, adenoid cystic/basal cell carcinoma has a distinctive dual-cell population [35] with basaloid cells with angulated nuclear contours, plus central, adluminal cells, with dark dense nuclei. A fifth consideration is intraductal spread of high-grade urothelial carcinoma, which can somewhat mimic IDC. Support for this diagnosis can come from lack of cribriform/glandular structures and from nuclear reactivity for p63, cytoplasmic reactivity for keratins 5/6 or 34βE12, and absence of PSA and prostatic acid phosphatase.

Our study has some limitations. The greatest limitation was that acini surrounding the focus of interest were not viewed; only 1 microscopic field from each case was shown, rather than using glass slides or scanned whole slides. The latter option would have required much

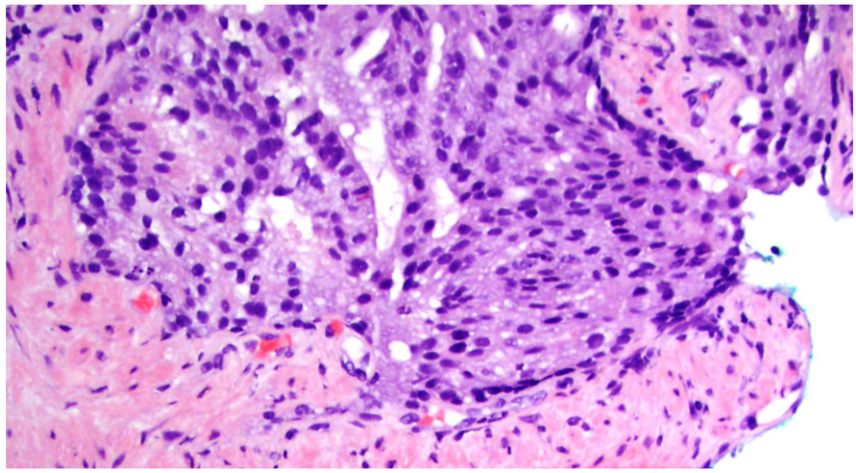

Fig. 10. Basal cells are present in central portion but not on the far right or left of the duct.

more time from the participants, whereas choosing to present only 1 to 2 microscopic fields per case allowed the testing of a larger sample of cases. Immunostains were not provided, although our goal was to study the boundary between HGPIN vs IDC, rather than IDC vs invasive cancer. Large duct spaces are often hybrids of IDC and invasive cancer (Fig. 10), so in biopsy core specimens with such large-duct proliferations, the decision to order immunostains usually requires a suspicion of IDC. Finally, we gave respondents a "borderline" option between HGPIN and IDC, so we cannot know the outcome had this choice that has not been available. However, the inclusion of this choice helped in teasing out IDC's discriminatory findings.

In conclusion, we propose the following criteria for IDC: a lumen-spanning proliferation of neoplastic cells in preexisting ducts, with a dense cribriform or solid growth pattern, which might occupy part of the duct space. After these criteria are fulfilled, solid growth in any part of the duct space is the most frequently useful feature to rule in a diagnosis of IDC. Although rare, comedonecrosis in most cases can rule in IDC. Two fold duct diameter enlargement, although frequent, is not essential to diagnose IDC. Nuclear maturation, a HGPIN feature, was present in some of our cases that lacked consensus, suggesting that this phenomenon deserves molecular study.

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