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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