Intraductal Carcinoma of the Prostate

Brian Robinson, MD; Cristina Magi-Galluzzi, MD, PhD; Ming Zhou, MD, PhD

• Context.—Intraductal carcinoma of the prostate (IDC-P) is a distinct clinicopathologic entity, characterized by an expansive proliferation of secretory cells within prostatic ducts and acini that demonstrate marked architectural and cytologic atypia. Intraductal carcinoma of the prostate is strongly associated with high-grade and high-volume, invasive prostate cancer and a poorer prognosis than cases without IDC-P.

Objective.—To review the historic perspectives, pathologic and genetic features, diagnostic criteria and differential diagnoses, and the clinical significance of IDC-P.

Data Sources.—Relevant studies indexed in PubMed.

Conclusions.—It is critical to recognize IDC-P, especially in prostate biopsies in which the clinical implications of IDC-P are greatest. Morphologic criteria have been proposed to distinguish IDC-P from several other lesions with similar histologic appearance such as high-grade prostatic intraepithelial neoplasia, invasive cribriform prostate cancer, and urothelial carcinoma involving the prostate. Intraductal carcinoma of the prostate is an uncommon finding in prostate biopsies, and it is even rarer as an isolated finding without concomitant prostate cancer in biopsies. However, patients with isolated IDC-P in biopsies are recommended for either definitive treatment or immediate repeat biopsy.


Prostate lesions with cribriform or solid architectures range from benign and proliferative, such as central zone glands, clear cell cribriform hyperplasia, and basal cell hyperplasia, to invasive cribriform carcinoma. Frequently, cribriform or solid lesions comprise cytologically malignant cells spanning or filling glandular lumens and yet preserve, at least focally, a basal cell lining. These atypical cribriform/solid lesions with basal cells represent either cribriform high-grade prostatic intraepithelial neoplasia (HGPIN) or intraductal carcinoma of the prostate (IDC-P). The distinction between these two is of paramount importance, especially in prostate needle biopsy, because IDC-P is usually associated with high-grade and high-volume prostate cancer (PCa). A diagnosis of IDC-P in a biopsy mandates an immediate repeat biopsy or even definitive therapy in the absence of documented invasive PCa. In contrast, cribriform HGPIN is a type of putative neoplastic precursor lesion. Recent data have caused researchers to question whether HGPIN on needle biopsy is an isolated finding without concomitant prostate cancer in most cases. The final multivariate analysis. The authors also depicted several morphologic patterns that represented various stages of the intraductal spread by PCa.

While studying cribriform PCa, McNeal et al3 found that, in most cases, cribriform PCa was predominantly located within prostatic ducts and acini with cancer cells following the normal duct contour or showing a basal cell layer on morphologic examination or basal cell immunostains. They found that the cribriform PCa with intraductal location was equivalent to Gleason patterns 4 and 5 PCa prognostically and was associated with high-grade and high-volume PCa in most cases. The term intraductal carcinoma of the prostate was introduced to emphasize the unique histologic and clinical features of this lesion.

Historic Perspective

Although in earlier literature, the term intraductal carcinoma of the prostate has been used variably to describe the extension of prostatic acinar carcinoma, prostatic ductal carcinoma, and urothelial carcinoma into prostatic ducts and acini, currently IDC-P refers to a lumen-spanning proliferation of malignant cells within prostatic ducts and acini caused by the spread of prostate cancer cells within preexisting prostatic glandular structures. The first detailed analysis of such phenomenon was credited to Kovi et al,4 who studied 139 cases of PCa diagnosed on transurethral resection, suprapubic prostatectomy, and needle biopsy specimens and found the spread of PCa cells into the preexisting prostate ducts and acini in 48% of PCa cases. Such “intraductal spread” was positively associated with both Gleason grade and tumor extent, although only tumor extent, not Gleason grade, remained significantly associated with the intraductal spread in the final multivariate analysis. The authors also depicted several morphologic patterns that represented various stages of the intraductal spread by PCa.

This article reviews the historic perspective, histologic features, diagnostic criteria, and molecular genetics of IDC-P. The clinical significance of finding IDC-P in both radical prostatectomy and prostate biopsy specimens as well as the reporting of IDC-P in prostate biopsies is also discussed.
Because prostatic intraepithelial neoplasia (PIN) glands also comprise cytologically atypical or malignant secretory cells within prostatic ducts and acini, the relationship between PIN and IDC-P was debated. Cribriform glands lined with cytologically atypical secretory cells were considered to represent a part of the morphologic spectrum and, therefore, a histologic subtype of PIN,6,7 because they were often present together with other types of PIN glands.6,7 However, some of these atypical cribriform glands fit the morphologic criteria for IDC-P. McNeal et al5 found that, in some cases, IDC-P was associated with HGPIN, with direct transition between the two or with both lesions adjacent to each other, suggesting that IDC-P arose primarily within ducts by evolution from the premalignant PIN.

In a subsequent study, McNeal and Yemoto8 presented evidence that IDC-P was different from PIN and suggested that it represented a distinct form of PCa with a peculiar propensity for intraductal spread and growth. They noted that the presence of cancer cells within prostatic ducts and acini, or IDC-P, was almost never seen in the absence of invasive carcinoma, and the concomitant invasive component was usually high grade.8 Furthermore, PCa with an IDC-P component had a significantly worse prognosis than did PCa without an IDC-P component. The authors concluded that IDC-P was an entity with precisely defined histologic criteria and unique biologic and clinical significance. Morphologically, IDC-P and PIN could be reliably distinguished from each other.

The concept that IDC-P represents intraductal growth of advanced-stage PCa is supported by several subsequent studies9–12 that also demonstrated the association of IDC-P with other adverse pathologic features, such as higher Gleason score, larger tumor volume, greater probability of extraprostatic extension, and poorer clinical outcomes. The current concept is that IDC-P represents intraductal extension of large-volume Gleason patterns 4 or 5 PCa. Rarely, IDC-P can be an isolated finding without a concomitant PCa and may represent a stage of prostate carcinogenesis that is later than what is recognized as HGPIN but before invasive PCa.13,14

**HISTOLOGIC FEATURES AND DIAGNOSIS OF IDC-P**

The hallmark of IDC-P is the expansile proliferation of PCa cells within the native prostatic glands with an at least partially preserved basal cell layer (Figure 1, A and B). McNeal and Yemoto8 first defined IDC-P as the “complete spanning of the ductal or acinar lumen by several trabeculae of malignant epithelial cells, with foci of trabecular fusion” in radical prostatectomy specimens. More-proliferative, denser lesions with cribriform or solid architecture were also included in their definition.8 Later studies refined the histologic features of IDC-P (Table 1).10,11,14–17 Classic examples of IDC-P usually comprise many glands, often greater than 6 per radical prostatectomy specimen,17 and the glands are larger than normal peripheral zone glands,13,17 with irregular and

**Figure 1.** A, Intraductal carcinoma of the prostate, with cancer cells filling and expanding several prostatic ducts. B, Double immunostains for p63 and AMACR, with AMACR+ staining in the proliferative cells and preserved basal cell layer (hematoxylin-eosin, original magnification ×40 [A]; original magnification ×40 [B]).

**Table 1.** Histologic Features That May Be Seen in Intraductal Carcinoma of the Prostate (IDC-P)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>IDC-P glands, No.</td>
<td>Many; often &gt;6 per prostate gland</td>
</tr>
<tr>
<td>Size</td>
<td>Larger than normal glands; can be &gt;1 mm</td>
</tr>
<tr>
<td>Ductal-lobular structure</td>
<td>Native ducts and acini are expanded and may show irregular and branching contours</td>
</tr>
<tr>
<td>Intraductal growth pattern</td>
<td>1. Loose cribriform with cells forming narrow strands (often 2 cells thick); spanning lumen without stromal support and intersecting randomly to form an orderly lacework of empty spaces</td>
</tr>
<tr>
<td></td>
<td>2. Micropapillary with cells forming papillae with inconspicuous fibrovascular cores</td>
</tr>
<tr>
<td></td>
<td>3. Dense cribriform with cells forming small, round “punched out” lumens that comprise &gt;50% of the luminal space</td>
</tr>
<tr>
<td></td>
<td>4. Solid cell mass</td>
</tr>
<tr>
<td>Cytology</td>
<td>1. Cuboidal or low columnar</td>
</tr>
<tr>
<td></td>
<td>2. Significant nuclear atypia</td>
</tr>
<tr>
<td></td>
<td>3. Nuclei 6 times larger than adjacent nonneoplastic nuclei</td>
</tr>
<tr>
<td></td>
<td>4. 2 cell populations with central small and uniform nuclei and peripheral pleomorphic nuclei may be seen in dense cribriform and solid patterns</td>
</tr>
<tr>
<td>Comedonecrosis</td>
<td>May be present</td>
</tr>
<tr>
<td>Basal cell layer</td>
<td>Preserved, at least focally</td>
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Figure 2. Histologic features of intraductal carcinoma of the prostate (IDC-P) include loose cribriform (A), dense cribriform (B), and solid growth patterns (C). Note the 2 cell populations with pleomorphic nuclei at the periphery and the smaller and more-uniform nuclei at the center (A and B). Nonfocal comedonecrosis (D) and marked nuclear pleomorphism with a size six times larger than the adjacent nonneoplastic cells (E) can also be seen. Two cell populations may be seen, with small and uniform nuclei in the center and pleomorphic nuclei at the periphery (F). Dense cribriform and solid patterns, nonfocal comedonecrosis, and marked pleomorphic nuclei are features diagnostic of IDC-P (hematoxylin-eosin, original magnifications [A through F]).
branching contours (Figure 2, A). The neoplastic cells in IDC-P grow in several architectural patterns, including trabecular, loose cribriform (Figure 2, A), dense cribriform (Figure 2, B), and solid (Figure 2, C), which represent progressive dedifferentiation, with a reciprocal increase in proliferation and correlated with cancer stage, grade, and clinical course. Neoplastic cells in classic IDC-P are pleomorphic, some 6 times larger than adjacent nonneoplastic nuclei (Figure 2, E). Two cell populations may be seen, usually in the dense cribriform and solid IDC-P, in which a central population of cells has small and uniform nuclei, and the peripheral population cells have pleomorphic nuclei (Figure 2, F). Comedonecrosis is diagnostic of IDC-P but is only present in a subset of cases (Figure 2, E).

Cohen et al proposed a set of criteria for diagnosing IDC-P, which included 5 major and 3 minor criteria. The first 4 major criteria are always present in IDC-P and include (1) large-caliber glands that are more than twice the diameter of normal peripheral zone glands, (2) preserved basal cells as identified with basal cell markers, (3) cytologically malignant cells, and (4) an expansile cell mass that spans the glandular lumen. The fifth major criterion, central comedonecrosis, is diagnostic of IDC-P but is not always present. Minor criteria include glands with (1) right-angle branching or (2) smooth, rounded outlines; and (3) 2 cell populations with an outer perimeter cell group composed of tall, pleomorphic, and mitotically active cells that stain poorly for prostate-specific antigen (PSA), and a central group that is cuboidal, monomorphic, and quiescent, with abundant cytoplasm containing abundant PSA and occasional extracellular mucin.

In 2006, Guo and Epstein proposed diagnostic criteria for IDC-P in prostate biopsies (Table 2), which were subsequently used in a larger study of IDC-P from the same institution. In these 2 studies, in addition to the presence of malignant epithelial cells filling large acini and prostatic ducts with preservation of basal cells, the diagnosis of IDC-P required the presence of (1) a solid or dense cribriform pattern (Figures 1 and 2, B and C), where punched-out, luminal spaces account for less than 50% of the central cellular mass; or (2) marked nuclear atypia, where the nuclei are at least 6 times larger than adjacent, benign nuclei (Figure 2, E); or (3) nonfocal comedonecrosis (Figure 2, D). Lesions that fell short of these criteria but were still felt to be more ominous than HGPIN were labeled atypical intraductal proliferations (Figure 3, A and B) when the differential diagnosis was between HGPIN and IDC-P. This diagnostic approach is summarized in Figure 4 and provides specific and reproducible criteria for the diagnosis of IDC-P.

Table 2. Diagnostic Criteria for Intraductal Carcinoma of the Prostate

<table>
<thead>
<tr>
<th>Malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells and:</th>
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<tbody>
<tr>
<td>• Solid or dense cribriform pattern</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>• Loose cribriform or micropapillary pattern with either</td>
</tr>
<tr>
<td>○ Marked nuclear atypia: nuclear size 6x normal or larger</td>
</tr>
<tr>
<td>○ Nonfocal comedonecrosis</td>
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Intraductal carcinoma of the prostate should be differentiated from other prostate lesions with cribriform and/or solid architecture, which range from normal histologic structures or benign lesions to premalignant lesions and frank malignancies (Table 3).

Normal Prostatic Structures and Benign Lesions

Normal histologic variations, such as central zone prostatic glands, and benign glandular proliferations, such as cribriform clear cell hyperplasia and basal cell hyperplasia, can be present as cribriform or, rarely, as solid structures. However, nuclear atypia, mitotic figures, and comedonecrosis are absent.

High-Grade PIN

The distinction of isolated IDC-P from cribriform HGPIN in prostate biopsy is the most important differential diagnosis because management for these 2 conditions is considerably different.
Both HGPIN and IDC-P represent the presence of cytologically atypical or malignant cells within prostatic ducts and acini, although the architectural and cytologic atypia is always more pronounced in IDC-P. Cribriform HGPIN is rare. The glands are small with smooth and round contours, and the cells are relatively uniform without marked nuclear pleomorphism or necrosis in cribriform HGPIN. Loose cribriform and micropapillary patterns can be seen in both HGPIN and IDC-P, but dense cribriform, solid patterns, and comedonecrosis are not seen in HGPIN. To establish the diagnosis of IDC-P in the loose cribriform and micropapillary patterns, other cyto-
logic features are required, such as markedly enlarged and pleomorphic nuclei (>6 times that of adjacent nonneoplastic glands) and nonfocal comedonecrosis.

These criteria can reliably distinguish IDC-P and HGPIN in most cases. However, some IDC-P glands have morphologic features that overlap with HGPIN. In 2 recent studies, Shah et al. and Han et al. demonstrated that some IDC-P glands that were intermixed and shared the same TMPRSS2-ERG gene fusion with invasive PCa were architecturally and cytologically similar to the HGPIN glands that were distant from the invasive PCa and lacked the TMPRSS2-ERG gene fusion. Both comprise small cribriform glands with round and smooth contours and are lined with low-grade nuclei. These findings suggest that IDC-P can occasionally exhibit a “low grade” morphology that overlaps with HGPIN and does not fit the diagnostic criteria for IDC-P. Therefore, any cribriform or lumen-spanning, atypical lesion may represent IDC-P, and its presence in prostate needle biopsies merits aggressive workup.

High-grade PIN and IDC-P share immunohistochemical profiles, including positive staining for PSA, α-methylacyl-coenzyme A racemase (AMACR), and basal cells. However, none of the stains is helpful in the differential diagnosis of these two entities.

### Invasive Cribriform Acinar Adenocarcinoma of Prostate

Infiltrating cribriform acinar adenocarcinoma (Gleason patterns 4 or 5, depending on whether comedonecrosis is present) closely mimics cribriform IDC-P. Invasive cribriform cancer, unlike IDC-P, lacks a basal cell lining. In some cases, the contour and branching pattern of normal duct architecture distinguishes IDC-P from infiltrating cribriform acinar adenocarcinoma. The distinction between invasive, high-grade PCa and IDC-P, however, is not critical because IDC-P is usually associated with a high-grade and high-volume PCa. Most cases of IDC-P would be diagnosed as cribriform acinar adenocarcinoma if immunohistochemistry for basal cells is performed.

### Ductal Adenocarcinoma of the Prostate

Ductal adenocarcinoma is an aggressive form of PCa and may occasionally arise in the peripheral zone, and ordinary acinar prostate carcinoma may have features of ductal adenocarcinoma focally. It is defined by morphologic features, including tall, pseudostratified, columnar

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**Table 3. Differential Diagnosis of Intraductal Carcinoma of the Prostate (IDC-P)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>IDC-P</th>
<th>HGPIN</th>
<th>Cribriform or Solid PCa</th>
<th>Urothelial Carcinoma Involving the Prostate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal-lobular structure</td>
<td>Expanded</td>
<td>Preserved</td>
<td>Distorted</td>
<td>Preserved (usually)</td>
</tr>
<tr>
<td>Gland size</td>
<td>Increased (&gt;2 times size of normal glands)</td>
<td>Normal</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Lumen-spanning cell mass</td>
<td>Present</td>
<td>Present in cribriform</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Comedonecrosis</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Basal cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: HGPIN, high-grade prostatic intraepithelial neoplasia; PCa, prostate cancer.

epithelium, arranged in cribriform patterns with slitlike spaces and/or true papillary fronds. The papillae in ductal adenocarcinoma have true fibrovascular cores, and the cells may show significant nuclear atypia with a high mitotic rate and extensive necrosis. Nuclei are large, mostly elongated or oval, and often contain a single macronucleolus. In contrast, IDC-P has cuboidal cells, cribriform pattern with rounded lumina, and micropapillary tufting without fibrovascular cores.

Similar to other high-grade and high-volume prostate cancers, ductal PCa is also prone to intraductal spread. Residual basal cells are, therefore, often found in ductal PCa.19 Ductal PCa with basal cells is mechanistically IDC-P, and Cohen et al13 proposed to classify ductal PCa as IDC-P. However, ductal PCa is not synonymous with IDC-P because IDC-P has characteristic morphologic features. Furthermore, not all ductal PCa cases have residual basal cells and, therefore, are not "intraductal carcinomas."

**Urothelial Carcinoma Involving the Prostate**

Intraductal spread of urothelial carcinoma, either from a bladder primary tumor or, in rare cases, from a prostate primary tumor, may mimic IDC-P. Urothelial carcinoma cells may fill and distend the lumen of the prostatic ducts, and central necrosis may occur, imparting a morphology similar to IDC-P. However, urothelial carcinoma is typically more pleomorphic than IDC-P is cytologically, and urothelial carcinoma often has a dense pink, "hard" cytoplasmic quality. A panel of immunostains can often resolve the diagnostic ambiguity. Intraductal carcinoma of the prostate stains positive for prostate-specific markers, including PSA, prostate-specific acid phosphatase, prostate-specific membrane antigen, and P501S, whereas stains for basal cells, such as CK5/6, 34βE12, and p63, are positive only in the basal cells at the periphery of the cancer glands. In contrast, urothelial carcinoma is negative for prostate specific markers (PSA and prostate-specific acid phosphatase) and is positive in two-thirds of cases for markers that recognize the prostate basal cells (cytokeratin 34βE12 and p63).20

**Metastatic Adenocarcinoma**

Metastatic adenocarcinoma from other sites, in particular, colorectal adenocarcinoma, may have extensive necrosis and mimic IDC-P. On hematoxylin-eosin stains, the presence of "dirty" necrosis, a columnar appearance of cells with basally located nuclei, and mucus secretions are features that suggest the enteric origin of the lesion. Clinical history and prudent use of immunostains (CDX-2, CK20, and β-catenin for colorectal adenocarcinoma) can lead to a correct diagnosis.

**MOLECULAR GENETICS OF IDC-P**

Molecular evidence to support the classification of IDC-P as a discrete entity comes from studies assessing loss of heterozygosity (LOH) at microsatellite loci often affected in PCa.

Dawkins et al15 studied allelic instability in prostate cancers to define the position of IDC-P in PCa progression. They compared the patterns of allelic loss in PIN, PCa with Gleason grade 3 and 4 patterns, and IDC-P. They observed no LOH in Gleason grade 3 carcinomas, and only a single example in PIN (1 of 11; 9%). In contrast, 60% of IDC-P cases (12 of 20) and 29% of Gleason grade 4 cancers (15 of 17) demonstrated LOH. The most frequently lost loci were 8p22 and 16q23.1-qter. In IDC-P with associated Gleason grade 4 invasive carcinoma, the authors reported 16 instances of LOH, 12 (75%) of which were not seen in the invasive tumor component. Similarly, of the 9 instances of LOH recorded in Gleason grade 4 cancers, 5 (56%) were not seen in the IDC-P from the same patient. The single case of PIN with LOH (at 2 loci) shared both of those losses with the coexistent IDC-P.

Bettendorf and colleagues20 analyzed 77 radical prostatectomy specimens for LOH of the tumor suppressor genes TP53, RBL, and P53, and they investigated IDC-P and PIN for chromosomal anomalies using comparative genomic hybridization. During comparative genomic hybridization analysis, 73% of IDC-P cases (8 of 11) showed several chromosomal imbalances, which is in stark contrast to PIN, wherein no comparative genomic hybridization changes were found. Five chromosomal gains and 19 chromosomal losses were detected in IDC-P: −1q23–q32, −5p, −6cen–q22, +7p, +7q, −8p, +8q21.1–qter, −10p, −10q, −10q21–qter, −13q, −13q14–qter, −16q, −16q13–qter, −17p, −18p, +19p, and +19q. Alterations of 7p, 7q, and 10q were previously identified as "late events" associated with recurrent or metastatic cancer. On the other end, loss at 8p is recognized as an early genetic change, which seems to link IDC-P to the PCa progression pathway involving PIN.21 Loss of heterozygosity for P7EN was found in 44% of PIN lesions, 48% of IDC-P, 49% of organ-confined (OC) PCa, and 50% of non-OC PCa. Loss of heterozygosity for TP53 was found in 30% of PIN, 60% of IDC-P, 40% of OC PCa, and 66% of non-OC PCa. Loss of heterozygosity of RB1 was detected in 53% of PIN, 81% of IDC-P, 60% of OC PCa, and 78% of non-OC PCa. Loss of heterozygosity of both tumor suppressor genes TP53 and RB1 was found in 52% of IDC-P compared with 19% of PIN, 24% of OC PCa, and 44% of non-OC PCa.20

To better understand the molecular and biologic basis of distinction between cribriform HGPIN and IDC-P, Han et al22 assessed ETS gene alterations using a break-apart fluorescence in situ hybridization assay. They found no ERG rearrangement in isolated cribriform HGPIN, whereas ERG was rearranged in 75% of IDC-P (36 of 48), of which 65% (23 of 31) were through deletion. The authors found 100% concordance of ERG gene fusion status between IDC-P and adjacent invasive PCa, suggesting that IDC-P is clonally related to the latter.

The allelic instability reported in IDC-P clearly distinguishes it from PIN. Although there is morphologic evidence that PIN can progress to IDC-P, the number and frequency of molecular changes in IDC-P (36 of 48), as compared with PIN, indicate that the former is a malignant progression far removed from PIN. Intraductal carcinoma of the prostate, in most cases, likely represents intraductal spread of nearby, well-established, invasive carcinoma and a late event in prostate carcinogenesis.

**CLINICAL SIGNIFICANCE OF IDC-P**

Studies have established that IDC-P represents an aggressive form of PCa and is an adverse pathologic parameter in both radical prostatectomy and needle biopsy specimens.

Since the initial studies by Kovari et al4 and McNeal et al,7 several other studies have investigated IDC-P in radical prostatectomy and consistently found that the presence of IDC-P correlated with other adverse pathologic features, including higher Gleason score, larger tumor volume, and...
greater probability of extraprostatic extension, seminal vesicle invasion, and pelvic lymph node metastasis. It also correlated with decreased progression-free survival and with postsurgical, biochemical recurrence.10,12,15,17

Only a few studies to date have examined the significance of IDC-P in needle core biopsy specimens, and, in 2 of these studies, IDC-P was present without associated invasive carcinoma in the biopsies,14,16 an exceedingly rare finding, involving less than 0.06% of all prostate biopsy specimens.

Cohen et al17 studied a small series of radical prostatectomy specimens with matching preoperative needle biopsy specimens and found that the inclusion of IDC-P in prostate biopsies in a preoperative model could improve the prediction of the pathologic stage of the radical prostatectomy specimens. Furthermore, the presence of IDC-P on biopsy correlated strongly with biochemical failure.9 This study also found that serum PSA levels correlated with tumor volume only when IDC-P was not present in the biopsy, similar to results in an earlier study.18 These findings suggest that IDC-P identified in prostate biopsy is a very powerful parameter that counteracts the predictive values of other commonly used clinicopathologic parameters, including serum PSA and biopsy Gleason score. This has potentially profound clinical significance because virtually all nomograms for predicting prostate cancer stage and outcome include serum PSA as a variable, yet none takes into account the presence of IDC-P as potentially masking a high-volume, high-stage tumor with relatively low serum PSA. Similarly, a recent study by O'Brien et al13 found that inclusion of several new pathologic variables, including IDC-P, significantly improved the predictive accuracy of a postoperative nomogram that used preoperative clinicopathologic variables to predict PSA recurrence after radical prostatectomy. These studies strongly suggest that the presence of IDC-P in prostate biopsies should be reported, even when it is associated with an extensive, high-grade PCA because it may provide additional prognostic information.

Guo and Epstein16 initially reported a small series of cases of IDC-P without invasive carcinoma on biopsy, and more recently, Robinson and Epstein14 updated and expanded that series to include 66 patients. Both studies found that the presence of IDC-P, even in the absence of documented invasive carcinoma, was associated with an aggressive clinical course. In the more contemporary of the 2 studies, 8 of 66 patients (12%) developed disease progression after definitive treatment, including 4 patients with distant metastasis at a mean of 22 months after diagnosis, and another 4 patients with PSA recurrence at a mean of only 8 months following definitive therapy. Furthermore, in patients who underwent radical prostatectomy, all prostate cancers had Gleason scores equal to or more than 7, and nearly one-half of the cases (9 of 21) contained some Gleason pattern 5 components. Tumors were also of relatively high volume (mean, 2.85 cm³; range, 0.05-13.1 cm³). Eight of 21 men (38%) had extraprostatic extension (pT3a), and another 3 (14%) had seminal vesicle invasion (pT3b). Nodal metastasis was seen in 1 (5%) of the men. Two patients (10%) had IDC-P only at radical prostatectomy, without an invasive PCA component. This latter finding suggests that IDC-P does not always represent intraductal spread of an invasive, high-grade carcinoma. In at least some cases, IDC-P represents a stage of prostate carcinogenesis that is greater than what we recognize as HGPIN morphologically but develops before invasive cancer.

Based on their studies of needle biopsy with IDC-P and previous studies in the literature that demonstrated consistent association of IDC-P at radical prostatectomy with multiple adverse prognostic factors, Robinson and Epstein14 recommend definitive therapy in men with IDC-P on needle biopsy, even in the absence of pathologically documented, invasive PCAs.

REPORTING OF IDC-P IN PROSTATE BIOPSY

Because of its frequent association with high-grade and high-volume PCAs, as well as its adverse prognostic significance, IDC-P should be reported in prostate biopsy reports.

In most cases, IDC-P is identified with a concomitant, invasive PCA that usually contains cancer with Gleason patterns 4 or 5. In these cases, reporting on the IDC-P is of questionable value. Nevertheless, we recommend the IDC-P be reported in these cases because IDC-P may provide additional prognostic information. Rarely, IDC-P is seen on a biopsy with PCa of only a Gleason pattern 3. In those cases, it is imperative to document the presence of IDC-P, and that can be done in 2 ways. IDC-P can be regarded as, and graded like, invasive PCa (Gleason patterns 4 or 5, depending on the absence or presence of solid architecture and/or necrosis, respectively). Alternatively, one can grade only the invasive PCA Gleason pattern 3 and then mention in a comment the presence of IDC-P and its clinical significance.

When IDC-P is identified on prostate biopsy without concomitant invasive PCAs, pathologists should report the presence of IDC-P with a comment stating that IDC-P is usually associated with a high-grade and high-volume PCa and that definitive therapy is indicated for those patients.14,16 However, some pathologists may still recommend immediate repeat biopsy, instead of definitive therapy, in these rare situations.

Finally, any cribriform lesion comprising cytologically atypical cells that do not satisfy the diagnostic criteria for IDC-P but that exceed the criteria for HGPIN should be reported as atypical cribriform lesion, with a recommendation for an immediate repeat biopsy because it may represent IDC-P.

CONCLUSIONS

Intraductal carcinoma of the prostate is a distinct clinicopathologic entity. Morphologically, it is characterized by lumen-spanning or solid proliferation of malignant cells that expand the preexisting ducts and acini. Intraductal carcinoma of the prostate is strongly associated with aggressive PCAs with a high Gleason grade and a large tumor volume. Therefore, it is critical for pathologists to recognize and report this lesion in prostate specimens, especially in prostate biopsy reports, for patient management. Morphologic criteria have been proposed to distinguish IDC-P from several other lesions with similar histologic appearance, such as HGPIN, invasive cribriform PCa, and urothelial carcinoma involving the prostate.

Reference


