Intraductal Carcinoma of the Prostate: the Whole Story

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Introduction:

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. Infrequently, cribriform or solid lesions comprise cytologically malignant cells spanning or expanding 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 of the two is of critical importance, especially in prostate needle biopsy, as IDC-P is almost always associated with high grade and high volume prostate cancer (PCa). A diagnosis of IDC-P in biopsy mandates immediate repeat biopsy or even definitive therapy in the absence of documented invasive PCa. In contrast, cribriform HGPIN is a putative precursor lesion to PCa. Recent data have questioned whether HGPIN on needle biopsy is associated with a significantly increased cancer risk in subsequent biopsies and whether repeat biopsy is necessary within the first year after its diagnosis, especially when HGPIN is focal 1, 2.

This lecture reviews the historical perspective, histological features, diagnostic criteria of IDC-P. The incidence and clinical significance of IDC-P in prostate biopsy specimens as well as the reporting of IDC-P in prostate biopsies is also discussed.

Historical Perspective:

In earlier literature 3, the term “intraductal carcinoma” was used variably to describe the extension of different carcinomas, including prostatic acinar carcinoma, prostatic ductal carcinoma and urothelial carcinoma, into prostatic ducts and acini. Currently
IDC-P refers specifically to a lumen-spanning proliferation of malignant cells within prostatic ducts and acini, resulting from spread of prostate cancer cells within pre-existing prostatic glandular structures.

The first detailed analysis of such phenomenon was credited to Kovi et al, who studied 139 cases of PCa diagnosed on transurethral resection, suprapubic prostatectomy and needle biopsy specimens and found spread of PCa cells into the pre-existing 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.

While studying cribriform PCa, McNeal et al found that in most cases cribriform PCa was predominantly located within prostatic ducts and acini with cancer cells following normal duct contour or showing a basal cell layer on morphological 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 the majority of cases. The term “intraductal carcinoma of the prostate (IDC-P)” was introduced to emphasize the unique histological and clinical features of this lesion.

Since PIN glands also comprise cytologically atypical or malignant secretory cells within prostatic ducts and acini, the relationship between PIN and IDC-P was debated. In a subsequent study, McNeal and Yemoto presented evidence that IDC-P was different from PIN and suggested rather that it represented a distinct form of PCa with 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 almost always high grade. Furthermore, PCa with IDC-P component had a
significantly worse prognosis than those without. The authors concluded that IDC-P was an entity with precisely defined histological criteria and unique biological and clinical significance. Morphologically, IDC-P and PIN could be reliably distinguished from each other.

Several subsequent studies also demonstrated the association of IDC-P with other adverse pathological features such as higher Gleason score, larger tumor volume, greater probability of extraprostatic extension and poorer clinical outcomes\(^9-12\). 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 form of PCa with propensity for intraductal growth\(^13,14\).

**Histological features and diagnosis of IDC-P**

The hallmark of IDC-P is the expansile proliferation of PCa cells within the native prostatic glands with at least partially preserved basal cell layer. McNeal and Yemoto 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 histological features of IDC-P (Table 1)\(^10,11,14-17\). Classical examples of IDC-P usually comprise many glands, often > 6 per radical prostatectomy specimen\(^17\), and the glands are larger than normal peripheral zone glands\(^13,17\) with irregular and branching contours\(^8,13,17\). The neoplastic cells in IDC-P grow in several architectural patterns, including trabecular, loose cribriform, dense cribriform and solid, that represent progressive dedifferentiation with a reciprocal increase in proliferation and correlated with cancer stage, grade, and clinical course\(^10\).
Neoplastic cells in classical IDC-P are pleomorphic, some 6X larger than adjacent non-neoplastic nuclei. Comedonecrosis is diagnostic of IDC-P, but is only present in a subset of cases.

Cohen et al. proposed a set of criteria for diagnosing IDC-P \textsuperscript{13}, which included five major and three 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 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 biopsy (Table 2) that have subsequently been used in a larger study of IDC-P from the same institution \textsuperscript{14,16}. In these two 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, where punched-out luminal spaces account for <50% of the central cellular mass; or 2) marked nuclear atypia, where nuclei are at least 6x larger than adjacent benign nuclei; or 3) nonfocal comedonecrosis. Lesions that fall short of these criteria but are still felt to be more ominous than HGPIN are labeled as “atypical intraductal proliferations” where the differential
diagnosis rests between HGPIN and IDC-P. Any atypical cribriform lesions that do not meet the diagnostic criteria for IDC-P are termed “atypical cribriform lesions” and additional work-up is warranted.

**Differential Diagnosis of IDC-P**

IDC-P should be differentiated from a broad spectrum of other prostate lesions with cribriform and/or solid architecture, ranging from normal histological structures or benign lesions to premalignant lesions and frank malignancies (Table 3).

**Normal prostatic structures and benign lesions**

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

**High-grade prostatic intraepithelial neoplasia**

The distinction between isolated IDC-P from cribriform HGPIN in prostate biopsy is the most important one as management for these two conditions are drastically different.

Both HGPIN and IDC-P represent the presence of cytologically atypical or malignant cells within prostatic ducts and acini, although the architectural and cytological 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 and solid patterns and comedonecrosis are not seen in HGPIN. To establish the diagnosis of IDC-P in the loose cribriform and
micropapillary patterns, other cytological features such as markedly enlarged and pleomorphic nuclei (> 6X of adjacent non-neoplastic glands), and non-focal comedonecrosis, are required.

These criteria can reliably distinguish IDC-P and HGPIN in most cases. However, some IDC-P glands have morphological features that overlap with HGPIN. In two recent studies, Shah et al and Han et al demonstrated that some IDC-P glands that were intermixed with 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 were comprised of small cribriform glands with round and smooth contours and were 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 merits aggressive work-up.

**Invasive cribriform acinar adenocarcinoma of prostate**

Infiltrating cribriform acinar adenocarcinoma (Gleason pattern 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, though, is not critical as IDC-P is almost always 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 focally have ductal adenocarcinoma features. It is defined by morphological features including tall pseudostratified columnar epithelium arranged in cribriform patterns with slit-like 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 PCa, ductal PCa is also prone to intraductal spread. Residual basal cells are therefore often demonstrated in ductal PCa. Ductal PCa with basal cells is mechanistically IDC-P and Cohen et al proposed to classify ductal PCa as IDC-P. However, “ductal PCa” is not synonymous with IDC-P, as it has characteristic morphological 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, or exceedingly rarely from a prostate primary, may mimic IDC-P. Urothelial carcinoma cells may fill and distend the lumen of prostatic ducts and central necrosis may occur, imparting a morphology similar to IDC-P. However, urothelial carcinoma is typically more pleomorphic than IDC-P cytologically, and it often has a dense pink, “hard” cytoplasmic quality. A panel of immunostains can often resolve the diagnostic ambiguity. IDC-P stains positive for prostate specific markers, including PSA, prostate specific acid phosphatase (PSAP), prostate specific membrane antigen (PSMA) and P501S, while 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 PSAP) and is positive in 2/3 of cases for markers that recognize the prostate basal cells (cytokeratin 34βE12 and p63).

**Metastatic adenocarcinoma**

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

**Incidence and Clinical Significance of IDC-P in Prostate Biopsy**

Since the initial studies by Kovi et al and McNeal et al\(^4,8\), several other studies have investigated IDC-P in radical prostatectomy and found consistently that the presence of IDC-P correlated with other adverse pathological 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 postsurgical biochemical recurrence\(^10-12,15,17\).

In a recent study, we investigated the incidence of IDC-P in prospectively examined prostate biopsies\(^25\). The incidence of IDC-P in our prospective PBx cohort was 2.8% (33/1176) during a 23-month period. IDC-P was identified in 10.6% (33/312) of cancer-containing PBx. The incidence of IDC-P without associated invasive PCa on PBx was 0.26% in our study. This study demonstrates that IDC-P is uncommon in prostate biopsies, and even rarer as an isolated finding without concomitant PCa. However, IDC-P identified in prostate biopsies correlates with high grade and high volume PCa, consistent with other studies. In this study, 26 of 30
(86.7%) PBx with PCa and concomitant IDC-P had a primary Gleason pattern 4 or 5, including 4+3=7 in 12 (40%), 8 in 4 (13.3%) and 9 in 10 (33.3%) cases. The mean number of biopsy cores involved by PCa was 7.2. These findings suggest that many of these patients harbor high grade, large volume disease. This conclusion is further supported by the finding in the corresponding radical prostatectomy specimens where 8 of 9 (88.9%) patients had a primary Gleason pattern 4 or 5, including GS 4+3=7 in 3 (33.3%), GS8 in 1 (11.1%) and GS9 in 4 (44.4%). Poor prognostic factors including EPE and SVI were identified in 67% and 44% of patients, respectively. Compared with the incidence predicted by Partin Tables, the incidence of SVI in our cohort (44%) was significantly higher than that predicted by Partin Tables (12%). Our study suggests that IDC-P in prostate biopsies may provide additional prognostic values beyond that provided by conventional pathological parameters such as Gleason score and tumor volume.

Cohen et al. studied a small series of radical prostatectomy (RP) with matching pre-operative needle biopsies and found that the inclusion of IDC-P in prostate biopsies in a preoperative model could improve the prediction of pathological stage of RP specimens. Furthermore, the presence of IDC-P on biopsy correlated strongly with biochemical failure. This study also found that serum PSA levels correlated with tumor volume only when IDC-P was not present in biopsy, similar to an earlier study. These findings suggest that IDC-P identified in prostate biopsy is a very powerful parameter that counteracts the predictive values of other commonly used clinicopathological parameters, including serum PSA and biopsy Gleason score. This has potentially profound clinical significance, as 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 al also found that inclusion of several new pathological variables including IDC-P significantly improved the
predictive accuracy of a postoperative nomogram that used preoperative clinicopathological 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, as it may provide additional prognostic information.

Guo and Epstein initially reported a small series of cases of IDC-P without invasive carcinoma on biopsy, and more recently Robinson and Epstein updated and expanded this series to include a total of 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 two studies, 8 of 66 (12%) patients 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 PCa were Gleason score ≥7, and nearly half of the cases contained some Gleason pattern 5 components. Tumors were also of relatively high volume (mean: 2.85 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 RP without 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 beyond what we recognize as HGPIN morphologically but before invasive cancer develops.
Based on their studies of needle biopsy with IDC-P, and previous studies in the literature that demonstrated consistent association of IDC-P at RP with multiple adverse prognostic factors, Robinson et al recommend definitive therapy in men with IDC-P on needle biopsy even in the absence of pathologically documented invasive PCa.

Reporting of IDC-P in prostate biopsy:

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

In the majority of cases, IDC-P is identified with a concomitant invasive PCa that almost always contains Gleason patterns 4 or 5 cancer. In these cases, reporting of IDC-P is recommended as it may provide additional prognostic information.

Rarely, IDC-P is seen on biopsy with only Gleason pattern 3 PCa. In these cases, it is imperative to document presence of IDC-P, and this can be done in two ways. Either IDC-P can be regarded as and graded like invasive PCa (Gleason patterns 4 or 5, depending on the absence or presence of solid and/or necrosis, respectively). Alternatively, one can grade only the invasive Gleason pattern 3 PCa 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 PCa, pathologists should report the presence of IDC-P with a comment stating that IDC-P is almost always associated with a high grade and high volume PCa and that definitive therapy is indicated for these patients. 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 exceed the criteria for HGPIN, should be reported on biopsy as “atypical cribriform lesion (ACLs)” with a recommendation of immediate repeat biopsy as it may represent IDC-P.

**Conclusion:**

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

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Table 1. Histological Features That May Be Seen in Intraductal Carcinoma of the Prostate

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of IDC-P glands, No.</td>
<td>Many, ; often &gt;6 / per prostate gland</td>
</tr>
<tr>
<td>Size</td>
<td>Larger than normal glands, ; may 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 two 2 cells thick), ; spanning lumen without stromal support and intersecting randomly to form an orderly lacework of empty spaces</td>
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<tr>
<td></td>
<td>2. Micropapillary with cells forming papillae with inconspicuous fibrovascular cores</td>
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</tbody>
</table>
3. Dense cribriform with cells forming small, round “punched out” lumens which comprise > 50% of the luminal space
4. Solid cell mass

Cytology

1. Cuboidal or low columnar
2. Significant nuclear atypia
3. Nuclei ×6 times larger than adjacent non-nonneoplastic nuclei
4. 2 cell populations with central small and uniform nuclei and peripheral pleomorphic nuclei may be seen in dense cribriform and solid patterns

Comedonecrosis

May be present

Basal cell layer

Preserved, at least focally

IDC-P: intraductal carcinoma of the prostate

Table 2. Diagnostic Criteria for Intraductal Carcinoma of the Prostate

Malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells and:

• Solid or dense cribriform pattern
Or

- Loose cribriform or micropapillary pattern with either
  - Marked nuclear atypia: nuclear size ×6 normal or larger
  - Non-Nonfocal comedonecrosis
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</th>
<th>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>
<td></td>
</tr>
<tr>
<td>Gland size</td>
<td>Increased (≠ 2X times size of Normal normal glands)</td>
<td>Variable</td>
<td>Variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen-spanning cell mass</td>
<td>Present</td>
<td>Present in cribriform</td>
<td>Present</td>
<td>Present</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Absent in other types</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Cribriform (loose/, dense)</td>
<td>2. Cribriform (loose)</td>
<td>2. Solid</td>
<td>2. Cribriform</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Solid</td>
<td>3. Flat</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>4. Tufting</td>
<td></td>
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</tr>
<tr>
<td>Comedonecrosis</td>
<td>±</td>
<td>−</td>
<td>±</td>
<td>±</td>
<td></td>
</tr>
<tr>
<td>Basal cells</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations:
IDC-P: intraductal carcinoma of the prostate; HGPIN: high- grade prostatic intraepithelial neoplasia; PCa: prostate carcinoma.
Intraductal Carcinoma of the Prostate - the Whole Story!

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Case
➢ 75 y.o. male with persistently elevated PSA for 12 years
Differential Diagnosis of Atypical Cribriform Lesions of the Prostate

- Intraductal carcinoma of the prostate
- Invasive cribriform prostatic carcinoma
- Ductal adenocarcinoma of the prostate
- Cribriform high grade PIN
- Urothelial carcinoma involving the prostate
- Metastatic (colorectal) adenocarcinoma

Outline

- Historical perspective
- Histological features and diagnostic criteria
- Differential diagnosis
- Incidence and clinical significance of IDC-P in prostate biopsies
- Reporting
Intraductal Carcinoma of the Prostate (IDC-P)

**Historical Perspective**
- Used variably for extension into prostatic ducts and acini of prostatic acinar carcinoma, ductal carcinoma, urothelial and colorectal carcinoma in early literatures.
- Currently only refers to lumen-spanning proliferation of prostate cancer cells within prostatic ducts and acini caused by the spread of prostate cancer cells into preexisting prostatic glandular structures.

**Current Concept**
- Intraductal spread and growth of advanced-stage PCa
  (Cohen, Br J Urol, 1998; Rubin, AJSP, 1998; Wilcox, Hum Pathol, 1998; Cohen, Prostate, 2000)
- Rarely a form of PCa with predominant/exclusive intraductal growth with little/no invasive PCa
  (Cohen, Arch Pathol Lab Med, 2007; Robinson and Epstein, J Urol, 2010)

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

**Intraductal Carcinoma of the Prostate (IDC-P)**

- Intraductal spread by invasive prostate cancer (Pca) (Kovi et al, Cancer, 1985)
- IDC-P is a distinct form of aggressive PCa with a propensity for intraductal spread and growth (McNeal & Yemoto, AJSP, 1996)
  - Almost never seen in the absence of invasive carcinoma
  - Concomitant invasive carcinoma almost always high grade and high volume
  - PCa with IDC-P component has significantly worse prognosis than PCa without a component of IDC-P

**Intraductal Carcinoma of the Prostate (IDC-P)**

- Cribriform or solid architecture
- Basal cell layer at least partially preserved
Intraductal Carcinoma of the Prostate (IDC-P)

Diagnostic Criteria

- Morphological features not specific
- Use a constellation of morphological features
- Use stringent diagnostic criteria to ensure its unique clinical significance, ie, association with adverse outcomes
Diagnostic Criteria for IDC-P
(Cohen RJ et al., Arch Pathol Lab Med; 2007)

**Five major criteria:**
- Large-caliber glands that are twice the diameter of normal glands
- Preserved basal cells as identified with basal cell markers
- Cytologically malignant cells
- Expansile cell mass that spans the glandular lumen
- Central comedonecrosis (diagnostic of IDC-P but not always present)

**Three minor criteria:**
- Right-angle branching
- Smooth rounded outlines
- Two cell populations with an outer pleomorphic cells and a central cuboidal monomorphic cells

Diagnostic Criteria for IDC-P
(Guo CC and Epstein JI, Mod Pathol. 2006)

Malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells require either:
- A Solid or Classical cribriform pattern
- Marked nuclear atypia/nuclei 6x larger than adjacent benign nuclei
- Non-focal comedonecrosis

Lesions that fall short of these criteria:
“Atypical intraductal proliferations”

Intraductal Carcinoma of the Prostate
Atypical intraductal proliferations

Differential Diagnosis of Intraductal Carcinoma of the Prostate
(DDX for Atypical Cribriform/Solid Lesions)

- Intraductal carcinoma of the prostate
- Invasive cribriform prostatic carcinoma
- Ductal adenocarcinoma of the prostate
- Cribriform high grade PIN
- Urothelial carcinoma involving the prostate
- Metastatic (colorectal) adenocarcinoma

Difference between IDC-P and Cribriform High Grade PIN

<table>
<thead>
<tr>
<th></th>
<th>Cribiform HGPIN</th>
<th>IDC-P</th>
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<tbody>
<tr>
<td>Definition</td>
<td>Putative precursor lesion to PCa</td>
<td>Intraductal spread of advanced stage PCa</td>
</tr>
<tr>
<td>Clinical</td>
<td>Cancer risk associated with the diagnosis of HGPIN in prostate biopsy: ~ 25%</td>
<td>Almost always associated with high grade/volume PCa</td>
</tr>
<tr>
<td>Significance in Prostate Biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>HGPIN diagnosed in prostate biopsy does not mandate a repeat biopsy</td>
<td>Definitive treatment recommended</td>
</tr>
<tr>
<td>Management</td>
<td>within 1st year when HGPIN is focal</td>
<td></td>
</tr>
</tbody>
</table>

IDC-P versus Cribriform HGPIN

- Atypical cribriform lesion with basal cells intermixed with or within 3 mm from the border of invasive cancer
- ERG gene fusion: 72%
- ERG fusion status concordant between IDC-P and adjacent Pca in 100% cases

- Atypical cribriform lesion with basal cells > 3 mm from the border of invasive cancer
- ERG gene fusion: 0%

- IDC-P and cribriform HGPIN are genetically distinct
- ERG gene status identical between IDC-P and Pca
- IDC-P resulting from intraductal spread of PCa

(Han et al AJSP 2010)
### Morphological Difference b/w of IDC-P and Cribriform HGPIN

(Shah, Magi-Galluzzi, Han, Zhou, AJSP 2010)

<table>
<thead>
<tr>
<th># cases</th>
<th>IDC-P</th>
<th>Cribriform HGPIN</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td># atypical cribriform lesion prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>23.8</td>
<td>2.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Range</td>
<td>9-145</td>
<td>1-6</td>
<td></td>
</tr>
<tr>
<td>Smallest size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>0.32 ± 0.39</td>
<td>0.32 ± 0.33</td>
<td>0.048</td>
</tr>
<tr>
<td>Range</td>
<td>0.2-1.1</td>
<td>0.2-1.1</td>
<td></td>
</tr>
<tr>
<td>Largest size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>1.5 ± 1.3</td>
<td>0.43 ± 0.15</td>
<td>0.003</td>
</tr>
<tr>
<td>Range</td>
<td>0.6-2.6</td>
<td>0.2-1.8</td>
<td></td>
</tr>
<tr>
<td>Glandular contour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>29 (67.4%)</td>
<td>19 (87.6%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Irregular</td>
<td>17 (32.6%)</td>
<td>4 (12.4%)</td>
<td></td>
</tr>
<tr>
<td>Branching</td>
<td>36 (85.3%)</td>
<td>10 (40%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Architecture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cribiform/circleform</td>
<td>41 (95.3%)</td>
<td>23 (100%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Dense cribriform or solid</td>
<td>10 (23.3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Camcan necrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uniform</td>
<td>15 (33.8%)</td>
<td>14 (60.9%)</td>
<td>0.054</td>
</tr>
<tr>
<td>Variable</td>
<td>22 (47.9%)</td>
<td>10 (40%)</td>
<td>0.058</td>
</tr>
<tr>
<td>&gt; 6X or pleomorphic</td>
<td>12 (27.9%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

IDC-P with “Low Grade Morphology”

**Cribiform HGPIN**
IDC-P with “Low Grade Morphology”

Difference between IDC-P and Cribriform High Grade PIN

- IDC-P is much more common than cribriform HGPIN
- Defining features of IDC-P
  - Large branching architecture
  - Dense cribriform/solid
  - Comedonecrosis
  - Pleomorphic nuclei (>6X adjacent nuclei)
- IDC-P may have “low grade morphology”
  - Any “atypical cribriform lesions”, even without high grade morphology, should be worked up in prostate biopsy

Cribriform HGPIN

Atypical intraductal proliferations

Cribriform PCA
Incidence and Significance of IDC-P in Prostate Biopsy

- 33/1176 (2.8%) of prospectively examined prostate biopsies
- 3 (0.26%) not associated with PCa
- 9 underwent radical prostatectomy

Extraprostatic

Risk of adverse
Pathological features Patients with IDC Predicted by Partin tables P value
Extraprostatic extension 6/9 (67%) 41% 0.173
Seminal vesicle invasion 4/9 (44%) 12% 0.002
Lymph node metastasis 1/9 (11%) 5% 0.383

Watts KE et al, *Mod Pathol* 2012;25:250A
Significance of IDC-P in Prostate Biopsy

- IDC-P in prostate biopsies provided additional prognostic value independent of other histologic parameters (Cohen et al., *Br J Urol*, 1998; O’Brien et al., *Br J Urol*, 2011)


- IDC-P in prostate biopsies should be reported even when it is associated with an extensive and high-grade PCA, as it may provide additional prognostic value

Reporting Recommendations for Prostate Biopsy with IDC-P

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Reporting recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC-P with high-grade PCs</td>
<td>Document IDC-P (may provide an additional prognostic value)</td>
</tr>
</tbody>
</table>
| IDC-P with Gleason pattern 3 PCs    | • Grade PCs and document IDC-P and its poor prognostic significance in the report  
• Grade IDC-P as pattern 4 or 5  |
| IDC-P without PCs                   | • Document IDC-P and its poor prognostic significance in the report  
• Advise immediate rebiopsy or recommend definitive therapy  |
| Atypical cribriform lesions that do not meet the criteria for cribriform HGPIN and IDC-P | • Diagnosis of an atypical cribriform lesion, cannot rule out IDC-P  
• Recommend immediate repeat biopsy |

Intraductal Carcinoma of the Prostate: Summary

- A distinct clinicopathologic entity
- Cribriform/solid proliferation of PCs cells that expand the preexisting ducts and acini
- Strongly associated with aggressive, high grade/volume PCs
- Morphologic criteria have been established to diagnose and distinguish IDC-P from several other lesions with similar histologic appearance
- It is critical to recognize and report IDC-P in prostate specimens, especially in prostate biopsies reports, for patient management
Acknowledgement

Dr. Rajal Shah, Miraca Life Sciences, Dallas, TX

Questions?