A Proposal on the Identification, Histologic Reporting, and Implications of Intraductal Prostatic Carcinoma

Ronald J. Cohen, MBBCH, FFPATH, FRCPA, PhD; Thomas M. Wheeler, MD; Helmut Bonkhoff, MD; Mark A. Rubin, MD

Context.—Prostatic adenocarcinoma growing within acinar-ductal spaces (intraductal carcinoma) in contrast to high-grade prostatic intraepithelial neoplasia (HG-PIN) is defined by major criteria that include enlarged gland structures, neoplastic cells spanning the gland lumen, central comedonecrosis, and, further supported by minor diagnostic criteria including molecular biological markers, separate this entity from HG-PIN. Despite its perimeter basal elements, IDC-P should be interpreted as biologically equivalent to Gleason pattern 4 or 5 adenocarcinoma. Several hypotheses are proposed as to the evolution of IDC-P, which is almost always a late event in prostate carcinoma progression. Diagnosis of IDC-P on needle biopsy should prompt therapeutic intervention rather than surveillance or repeat biopsy, as is the case for HG-PIN.

Objective.—To define intraductal carcinoma of the prostate (IDC-P) with major and minor diagnostic criteria that clearly separate it from HG-PIN. The implications of such a lesion are discussed with proposals to incorporate this entity into the Gleason grading system.

Data Sources.—We reviewed all published data referring to intraductal spread of prostate carcinoma. Articles discussing endometrial, endometrioid, and ductal carcinoma are included.

It has been recognized for several decades that prostatic basal cells could be demonstrated by electron microscopy in benign proliferations, but were absent in invasive adenocarcinoma. With the advent of reliable basal cell–specific immunohistochemistry, many cases of presumed invasive Gleason pattern 3 and 4 cribriform carcinoma as diagnosed by routine hematoxylin-eosin stains were shown to have a complete or partial basal cell layer. This finding then separated “cribriform carcinoma” into two entities: cribriform carcinoma without basal cells, which then would be interpreted as invasive carcinoma Gleason pattern 3 or 4; and cribriform lesions with basal cells, which could be interpreted as high-grade prostatic intraepithelial neoplasia (HG-PIN) that to the clinician is no different from any of the other types or patterns of HG-PIN. McNeal and Yemoto questioned the wisdom of this approach as cribriform HG-PIN differs from all other subtypes of dysplasia (HG-PIN) in that it is almost never seen in the absence of invasive carcinoma, and the invasive elements are almost always high grade (Gleason patterns 4/5). Furthermore, in contrast to HG-PIN, cribriform lesions with basal cells significantly worsen prognosis and may extend beyond the peripheral zone to involve the prostatic urethra. This phenomenon of ductal permeation involving the prostatic urethra was initially referred to as endometrioid carcinoma owing to the belief that it arose from the prostatic utricle, which is considered the male equivalent of the uterus. Current terminology refers to this growth pattern as ductal features or, in its pure form, ductal carcinoma. Recognizing a significant clinical and pathologic difference between what they termed dysplasia (HG-PIN) and the intraductal permeation of tumor, McNeal and Yemoto referred to these cribriform lesions rimmed by basal cells under a unifying term, intraductal carcinoma. They described these changes in 30% of 476 radical prostatectomies seen at Stanford.

Several authors from different institutions have now confirmed this cribriform tumor pattern (in contrast to HG-PIN) to have poor prognostic implications, but at this time there is no consensus with regard to the name of the lesion or its implications and, therefore, how to advise clinicians when these lesions are identified in prostate biopsies. This distinction of intraductal carcinoma from PIN implies for both therapy as well as new chemoprevention trials that specifically apply to HG-PIN. The purpose of this article is to reach a consensus as to how lesions with complex papillary, cribriform, or solid growth with or without central comedonecrosis and surrounded by a perimeter of basal cells should be interpreted and reported to clinicians. Furthermore, we would like to justify the use of the term intraductal carcinoma of the prostate (ICD-P) to depict these intraductal cribriform and solid neoplastic lesions lined by a confluent or interrupted population of basal cells.

Conclusions.—Intraductal carcinoma of the prostate as defined by major criteria that include enlarged gland structures, neoplastic cells spanning the gland lumen, central comedonecrosis, and further supported by minor diagnostic criteria including molecular biological markers, separate this entity from HG-PIN. Despite its perimeter basal cells, IDC-P should be interpreted as biologically equivalent to Gleason pattern 4 or 5 adenocarcinoma. Several hypotheses are proposed as to the evolution of IDC-P, which is almost always a late event in prostate carcinoma progression. Diagnosis of IDC-P on needle biopsy should prompt therapeutic intervention rather than surveillance or repeat biopsy, as is the case for HG-PIN.

(Arch Pathol Lab Med. 2007;131:1103–1109)
HISTORIC PERSPECTIVE

Since the original description of “endometrial carcinoma” arising from the prostatic utricle that was made by Melicow and Pachter, it has been increasingly recognized that cribriform/papillary growth of prostate cancer is a tumor pattern with a propensity for intraductal extension that is not infrequently encountered. Early case reports also described, in addition to this cribriform carcinoma, frequent coexistence of “common acinar” carcinoma that was often present adjacent to the endometrial-endometrioid tumor areas. Further, with the reemergence of radical prostatectomy in the early 1980s, it was noted that, although there may be involvement of the utricle and prostatic urethra, much of the tumor was located in the gland periphery. These reports also confirmed the highly aggressive clinical behavior of this tumor. With the recognition that the utricle played no role in this disease and that the tumor gland caliber was significantly larger than common “acinar” carcinoma, the disease was then renamed ductal carcinoma. This term was based on the misconception that normal prostatic ducts are of larger caliber when compared with prostatic acini, a fact that to this day remains unproven. Bock and Bostwick have also questioned and rejected the term ductal carcinoma on the basis of location or architecture. Furthermore, when ductal carcinoma was studied in radical prostatectomy specimens, no difference was noted between the larger caliber ductal carcinoma or the smaller caliber acinar cancer with respect to location or extraprostatic spread. Both patterns were admixed in all areas and pure ductal carcinoma is extraordinarily rare, supporting a common origin rather than two separate tumor types.

Kovi et al were the first to postulate a mechanism of intraductal spread of cancer, and with the publication of the article by McNeal and Yemoto in 1996, the unifying term intraductal carcinoma of the prostate was proposed. It was recognized from detailed tumor mapping in radical prostatectomy cases that IDC-P originated in the gland perimeter surrounded by invasive carcinoma and only occasionally did it track the entire length of the ductal array to eventually invade prostatic urethra, where it manifests as an exophytic complex papillary mass. Propensity for intraductal spread is sometimes manifest as extension, not only to the prostatic urethra, but continued spread along the urethra to the penile meatus. A recent case further demonstrates the ability of IDC-P to spread through natural passages to involve not only the urethra but also the seminal vesicles without stromal invasion. The terms endometrioid, ductal, and large-duct carcinoma can now be superseded by a unifying term intraductal carcinoma of the prostate.

POSSIBLE MECHANISM OF EVOLUTION OF IDC-P

Autopsy survey studies suggest that HG-PIN develops by the fourth decade in 5% to 10% of men and in 40% to 50% by age 60 years. It is likely that some portion of these foci will progress to invasive carcinoma within 10 years, which may explain the high incidence of small-volume, low-grade carcinoma that is ubiquitous in all communities. This view that HG-PIN may progress to invasive Gleason pattern 3 adenocarcinoma is widely accepted by pathologists, clinicians, and researchers as one possible route of prostatic carcinogenesis in the peripheral zone of the gland. However, this evidence is based on topographic associations of HG-PIN foci and the fact that microinvasion in HG-PIN foci is sometimes (although rarely) seen. This latter fact, along with the observation that HG-PIN is rare in the transition zone, where up to one fourth of tumors arise, suggests that other alternative routes to prostate cancer evolution need to be considered. One potentially intriguing alternative route is the development of molecular alterations associated with proliferative inflammatory atrophy. In summary, it is not clear how proliferative inflammatory atrophy and/or HG-PIN progress to invasive carcinoma. A large number of molecular alterations have been evaluated with the general finding that HG-PIN shares many of the same alterations as invasive cancer. This would include decreased expression of p27, higher AMACR (α-methylacyl-CoA racemase) and Ki-67 expression, and gain of chromosome 8q with loss of 8p.

The development of high-grade carcinoma (Gleason pattern 4/5) is even less clearly understood. It may evolve from low-grade tumors or, alternatively, directly from HG-PIN, but there is little evidence to support these concepts. Recently, it has been demonstrated in a whole-genome scan using high-density single nucleotide polymorphism arrays, that allelic imbalance (ie, loss of heterozygosity, amplifications, and deletions) becomes progressively more common in higher Gleason grade prostate cancers. Gleason pattern 4/5 carcinoma demonstrates more genomic instability when compared with lower Gleason grade prostate cancer as determined by loss of heterozygosity. Interestingly, similar frequencies of loss of heterozygosity are observed in IDC-P and in Gleason pattern 4/5 carcinoma. The incidence of several chromosomal anomalies including c-myc gene amplification (8q24) are almost identical in cribriform PIN, cribriform carcinoma, and Gleason primary pattern 5 tumors. Finally, in recent work examining the frequency of the TMPRSS2-ERG gene fusion in prostate cancer, gene fusion is seen in approximately 20% of HG-PIN but is intriguingly enriched in IDC-P (Figure 1, A and B). Emerging data suggest that the TMPRSS2-ERG gene fusion is associated with more aggressive prostate cancer.

In addition to similar chromosomal and genetic aberrations, there are several pathologic features common to both IDC-P and Gleason 4/5 carcinoma. The cribriform pattern of IDC-P is morphologically identical to Gleason grade 4 carcinoma, with the exception that grade 4 has irregular and infiltrating margins and is frequently composed of a larger mass of cells than the greatest diameter of a preexisting duct. Gleason did not appreciate that the smooth outlines and well-defined borders of Gleason cribriform grade 3 (now recognized as IDC-P) are not attributed to some inherent low-grade growth potential but to its intraglandular/ductal spread and the smooth contours of basal cells and basement membrane rimming these structures. It can be proposed that the cribriform pattern of IDC-P is partly attributed to the ability of tumor cells to survive and grow distant from direct contact with stroma (in most cases of common acinar carcinoma, malignant glands are lined by one layer of malignant cells that are in direct contact with stroma). Such ability of prostatic tumor cells to grow without stromal attachment is commonplace in Gleason patterns 4/5, but is not seen in lower Gleason patterns of carcinoma, with the exception of the cribriform type (IDC-P).

Based on our current observation and understanding,
there appear to be 2 possible hypotheses of IDC-P evolution (Figure 2). These mechanisms are not exclusive and may occur concurrently. The first and most straightforward explanation of IDC-P origin is simply the spread of established Gleason grade 4/5 back into preexisting ducts using these natural passages as low-resistance highways of rapid spread. The second is that IDC-P evolves directly from HG-PIN. This second mechanism is probably the less common pathway given that pure ductal cancers are rare but, as illustrated in a recent case report, can occur without high-grade invasive carcinoma. Both explanations are feasible and not in any way mutually exclusive. In either event, close biological association of IDC-P with Gleason grade 4/5 is clear and, in this regard it may be distinct from HG-PIN. Therefore, it seems that stromal invasion represents only one measure of tumor progression and this, in most cases, leads to Gleason pattern 3 carcinoma. The ability of tumor cells to grow and proliferate independent of stroma represents a second unrelated measure of progression that develops later in the disease process, resulting in evolution of Gleason patterns 4 or 5 carcinoma or in cells confined to ducts, IDC-P.

**IDENTIFICATION OF IDC-P IN TISSUE SECTIONS**

There are several major and minor criteria that define IDC-P and separate it from HG-PIN (Table). Five major criteria (M) are critical to the diagnosis of IDC-P and multiple minor criteria (m) are helpful and support this diagnosis. The first 4 major criteria are always present in IDC-P and include large-caliber glands (M1) that are more than twice the diameter of normal peripheral zone gland structures (approximately 300 μm) that are surrounded by basal cells (M2) as identified with cell markers (34βE12, p63). These glands are filled with cytologically malignant cells (M3) that, in contrast to those of HG-PIN, by definition always span the gland lumen (M4). The fifth major criterion, central comedonecrosis (M5), although not always present, is considered a major criterion as it is a common finding in IDC-P but is never a feature of HG-PIN. Minor criteria (m) include gland structure where IDC-P glands branch at almost right angles (m1) and have smooth rounded outlines (m2) in contrast to the undulating margins of benign glands and HG-PIN. Intraductal carcinoma of the prostate glands frequently has 2 cell populations (m3): an outer perimeter cell group that are tall, pleomorphic, and mitotically active (proliferative layer) 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 (secretory layer). Several IDC-P architectural patterns are noted that range from what has previously been described as trabecular (pattern A) (Figure 3, a and b), in which the cells spanning the lumen do so via thin cords often only 2 cells thick, creating elongated elliptical and crescent-shaped spaces between them. The 2 cell types are clearly evident in this pattern of IDC-P (Figure 3, a, inset). Sometimes these cords fail to span the total gland lumen and create a focal papillary pattern. Occasionally in addition to the cell bridges, a solid mass of cells is seen centrally. Pattern A represents the lowest “grade” of IDC-P in that it is associated with the smallest component of invasive Gleason grade 4/5. The few cases that have been described and followed yielded the best results with regard to PSA-free survival when compared with other patterns of IDC-P. The second pattern (B) is the better recognized cribriform type (Figure 3, c and d) with thick cell cords and punched-out round spaces that separate them. The distinction between the 2 cell types is recognizable in most cases but less clear than in pattern A. Occasionally, central comedonecrosis is identified (Figure 3, c and d). The third pattern (C) is associated with the greatest vol-
Intraductal Prostatic Carcinoma Review—Cohen et al

Figure 2. Diagrammatic representation of the theoretic progression of high-grade prostatic intraepithelial neoplasia (HG-PIN) to invasive carcinoma (left side) and intraductal carcinoma (right side). The dynamic relationship between intraductal carcinoma of the prostate (IDC-P) and Gleason grade 4 and 5 carcinoma is demonstrated. Despite the inability of IDC-P to invade stroma, it has the ability to grow and proliferate independent of stromal attachment, as does Gleason pattern 4 and 5 carcinoma.

Microscopic Distinction of Intraductal Carcinoma of the Prostate (IDC-P) From High-Grade Prostatic Intraepithelial Neoplasia (HG-PIN)

<table>
<thead>
<tr>
<th>Pathologic Features</th>
<th>IDC-P</th>
<th>HG-PIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large glands (&gt;2 times normal)</td>
<td>Always present</td>
<td>Occasionally present</td>
</tr>
<tr>
<td>Basal cells (34βE12, p63)</td>
<td>Always present</td>
<td>Always present</td>
</tr>
<tr>
<td>Cytologically malignant cells</td>
<td>Always present</td>
<td>Always present</td>
</tr>
<tr>
<td>Cells spanning the gland lumen</td>
<td>Always present</td>
<td>Never present</td>
</tr>
<tr>
<td>Comedo necrosis</td>
<td>Often present</td>
<td>Never present</td>
</tr>
<tr>
<td><strong>Minor Criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glands branching</td>
<td>Right angles</td>
<td>Acute angles</td>
</tr>
<tr>
<td>Gland outline</td>
<td>Round glands, smooth outline</td>
<td>Irregular glands, undulating outline</td>
</tr>
<tr>
<td>Two populations of tumor cells</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Figure 3, e and f. In this type, the spaces between the cell cords are lost and the gland is filled by a solid mass of cells. The 2 cell types are rarely distinguishable and all cells appear to be proliferative with loss of the central secretory layer, in particular, PSA secretion. Extensive central comedonecrosis is common. Mixtures of these patterns are common, particularly between patterns B and C. Tissue immunostaining for PSA is variable, with only focal regions showing strong positivity (Figure 3, f, inset). Accordingly, serum PSA is variable, often unexpectedly low in patients with this tumor pattern reflecting the loss of secretory function.

Frequently, pattern C, and more rarely pattern B, is associated with central comedonecrosis; this was originally classified as invasive adenocarcinoma, Gleason pattern 5. A perimeter population of basal cells excludes current designation as invasive carcinoma, and this lesion should be termed IDC-P. If basal cells are absent, then designation as Gleason pattern 5 is correct. In addition to perimeter basal cells, individual basal cells or clusters of basal cells may be seen within the gland lumen admixed with tumor.
cells. This is most common in the higher grades of IDC-P (patterns B and C) and may reflect undermining and shedding of the basal cell layer (Figure 3, f).

The major differential diagnosis is intraductal urothelial carcinoma. In contrast to IDC-P, this is best developed in glands surrounding the urethra and only rarely is it seen peripherally. In biopsy material, this anatomic distribution is of little value and distinction can be achieved using immunostains. Intraductal carcinoma of the prostate stains strongly for PSA and prostatic acid phosphatase, while...
Intraductal Prostatic Carcinoma Review

As IDC-P imparts a poorer prognosis than otherwise would be attributed to either HG-PIN or Gleason grade 3 carcinoma, it is important that it be recognized and reported in radical prostatectomy samples. McNeal and Yemoto used an arbitrary minimum value of 10% IDC-P to qualify a tumor as having this type of carcinoma, but other authors have simply identified its presence or absence. The ability of IDC-P to predict treatment failure has been confirmed repeatedly, as has its association with high-grade, large-volume carcinoma. Multivariate analysis confirms independent prognostic value of IDC-P over tumor grade (Gleason) of the invasive elements, pathologic stage, and tumor volume. Extensive extraprostatic perineural invasion is also associated with this tumor type in which the extraprostatic, and therefore obviously invasive, carcinoma may mimic the intraductal pattern.

Reporting IDC-P in preoperative biopsy is more complex in that the absence of complete architecture impedes IDC-P recognition. When recognized and associated with invasive carcinoma Gleason grade 4 or 5, its specific recognition may be of questionable value. However, when associated with only grade 3 carcinoma it should be recognized and reported. As IDC-P has so many features linking it to Gleason grade 4, one solution that is currently used by several authors may be to interpret IDC-P as if it were grade 4 (or 5, if there is necrosis) when calculating final Gleason grade and sum.

One rare problem encountered by the current authors is the identification of IDC-P in core biopsy without associated invasive carcinoma. In these cases in which solid cribriform masses are seen with comedonecrosis, it is unnecessary to perform further diagnostic biopsies prior to radical intervention. In these cases, tumors should be graded as Gleason pattern 4 or 5, where pattern 5 is reserved for glands with comedonecrosis. In other cases in which IDC-P with thin trabecular architecture is seen, it may be difficult with limited biopsy material to distinguish IDC-P from micropapillary HG-PIN; in such cases it is prudent to recommend immediate repeat biopsy rather than delayed repeat biopsy, as is usual for HG-PIN.

**CONCLUSION**

The histologic appearance of enlarged prostatic ducts filled by trabecular, cribriform, or solid arrangements of tumor cells surrounded by a complete or partial basal cell layer should no longer be reported as HG-PIN. The term intraductal carcinoma of the prostate should be used with added explanation to the clinician that in contrast to HG-PIN, IDC-P nearly always evolves late in cancer progression, well after the development of Gleason grade 3 carcinoma, and it is closely associated with large-volume and high-grade invasive carcinoma (Gleason grade 4/5). If detected on biopsy without coexistent invasive carcinoma (rare occurrence), immediate repeat biopsy should be performed with the expectation of detecting high-grade invasive carcinoma. Failure to achieve this should prompt consideration of radical therapy despite the repeated inability to detect invasive elements. This approach differs dramatically from HG-PIN, in which repeat biopsy is often deferred for a year or more.

The morphologic spectrum of IDC-P has been extensively described and the overlap with what has been previously described as ductal and/or endometrioid carcinoma is so extensive that separation of these entities can no longer be justified. The term intraductal carcinoma of the prostate should be used to describe all trabecular, cribriform, and solid lesions in which tumor cells are within ductal spaces (basal cells detected), and the term invasive carcinoma Gleason grade 4/5 should be used when no basal cells are identified with immunostains. Although the term invasive ductal carcinoma has been previously used to depict a large gland caliber, there is no evidence that this lesion is different in any way from usual acinar carcinoma of equivalent Gleason grade. Most ductal carcinomas are admixed with acinar patterns (like IDC-P) and located in exactly the same geographic locations. In the prostate gland, distinction of duct and acinus is rarely possible based only on lumen caliber. Similarly, large invasive tumor masses with central comedonecrosis may mimic a ductal pattern and these should not be referred to as ductal carcinoma but invasive carcinoma Gleason pattern 5.

Other lesions that may mimic IDC-P include intraductal spread of urothelial carcinoma. This lesion can often be separated from IDC-P on morphologic features and clinical history. For complex cases, immunostains for PSA and prostatic acid phosphatase are usually positive in IDC-P and negative in urothelial carcinoma. In addition, immunostains for cytokeratins 34βE12 and 5, 6, or 20 are often positive in neoplastic urothelial cells and negative in neoplastic prostatic tumor cells.

The recognition of IDC-P represents a step forward in our understanding of the biological progression of prostate cancer and the appreciation of ductal spread as an important route of cancer migration through the gland. In addition, it is likely that IDC-P may represent a biological progression of HG-PIN. Its recognition and active reporting are strongly supported to provide improved appreci-
ation of aggressive biological potential in what previously would have been misinterpreted and reported at the very worst as an indolent carcinoma (Gleason pattern 3) or more likely at the least as a premalignant clinically benign process (PIN).

We acknowledge the late John McNeal, MD, for his insight and contribution to our understanding of intraductal prostatic carcinoma. ‘‘It is easy to run where other men have walked, we can only crawl where no men have walked before’’ (J. McNeal, oral communication, 2000).

References