Prostatic Ductal Adenocarcinoma: A Mini Review

Jonathan I. Epstein
Departments of Pathology, Urology, and Oncology, The Johns Hopkins Hospital, Baltimore, Md., USA

Key Words
Prostate adenocarcinoma • Ductal adenocarcinoma • Gleason grade

Abstract
Prostatic ductal adenocarcinomas may arise either in large primary periurethral prostatic ducts or in the peripheral prostatic ducts. Ductal adenocarcinomas are composed of tall columnar cells arranged in cribriform, papillary, solid, single glands, and PIN-like patterns. Other than the prostatic intraepithelial neoplasia (PIN)-like ductal pattern, which behaves like Gleason pattern 3, ductal adenocarcinoma is comparable to Gleason pattern 4 prostate cancer. Ductal adenocarcinoma can have a patchy basal cell layer and typically expresses prostate-specific antigen (PSA) immunohistochemically. Mimickers of ductal adenocarcinoma include prostatic urethral polyps, hyperplastic benign prostate glands, high-grade PIN, colorectal adenocarcinoma, and papillary urothelial carcinoma.

Prostatic duct adenocarcinomas arising in large primary periurethral prostatic ducts often are associated with a normal digital rectal examination. Patients typically present with either urinary obstructive symptoms or gross/microscopic hematuria, and are diagnosed on transurethral resection. These tumors grow as exophytic lesions into the urethra, most commonly in and around the verumontanum. Tumors arising in the more peripheral prostatic ducts present as usual acinar prostate adenocarcinoma and are diagnosed on needle biopsy. Ductal adenocarcinomas are associated with variable serum prostate-specific antigen (PSA) levels.

While most adenocarcinomas of the prostate are composed of cuboidal cells arranged in acini, 0.4–0.8% of prostate cancers show a pure tumor composed of distinctive tall columnar cells of prostatic duct adenocarcinoma. Prostatic duct adenocarcinomas show a variety of architectural patterns, often admixed in a single tumor. The two most common patterns are papillary and cribriform. The formation of papillary fronds is a distinctive architectural pattern not seen with usual acinar prostate adenocarcinoma, which is composed of cuboidal epithelium and punched-out round lumina. Prostatic duct adenocarcinomas may also grow as solid nests or cribriform glands.
with central necrosis; this pattern cannot be distin-
guished from poorly differentiated prostatic acinar ade-
ocarcinoma without seeing the solid pattern in associa-
tion with papillary or cribriform prostatic duct adenocar-
cinoma. Single glands lined by tall columnar epithelial
cells resembling adenocarcinoma of the colon represent
another relatively uncommon pattern of prostatic ductal
adenocarcinoma. A more recently described morpholog-
ic variant of ductal adenocarcinoma is composed of
simple glands lined by stratified columnar epithelium
with cytological and architectural features of flat and
tufting high-grade prostatic intraepithelial neoplasia, re-
ferred to as ‘PIN-like ductal adenocarcinoma’ [7, 8].

Ductal adenocarcinomas may show a range of cyto-
logical atypia ranging from very bland columnar cells to
those with overt malignant features. Most cases of pros-
tatic duct adenocarcinoma have amphophilic cytoplasm,
although occasional cases with predominantly clear cells
exist. In contrast to acinar carcinoma, ductal adenocar-
cinoma may be accompanied by a prominent stromal
desmoplastic reaction, sometimes with hemosiderin de-
position. While prostatic duct adenocarcinoma can be
the sole component, more frequently it is found admixed
with tumor showing acinar differentiation. In most cases
with mixed acinar and ductal features, the two compo-
nents are intimately com浔ed. One can also see a cen-
trally located duct carcinoma with a peripherally located
acinar tumor. Mixed ductal and acinar adenocarcino-
ma is encountered in about 5% of prostatic carcinoma
cases.

Ductal adenocarcinomas express PSA and prostatic-
specific acid phosphatase (PSAP), verifying their pros-
tatic origin. Ductal adenocarcinomas, as they arise in
ducts, may show residual staining for high molecular
weight cytokeratin. Basal cells are detectable by p63 and
HMWCK in a patchy fashion in about one third of ductal
adenocarcinomas, which is the same as is seen in cribr-
iform pattern 4 acinar adenocarcinomas [9]. Cases where
biopsy shows all of the ductal adenocarcinoma within
ducts outlined by basal cell staining should be treated the
same as ductal adenocarcinoma identified without a bas-
al cell layer. Seventy-seven percent of ductal prostatic ad-
encarcinomas show positive staining for AMACR,
which is similar to the expression seen in Gleason pattern
4 acinar adenocarcinoma [9].

Ductal adenocarcinoma can be mistaken for a wide
spectrum of benign, precancerous, and malignant enti-
ties. One of the lesions most frequently confused with
cytologically bland ductal adenocarcinoma is prostatic
urethral polyp. Whereas ductal adenocarcinomas are
composed of tall pseudostratified columnar cells, pros-
tatic urethral polyps are polyloid nodules made up of
entirely benign-appearing prostate acini lined by pros-
tatic glandular epithelium and urothelium. Ductal ade-
ocarcinoma on needle biopsy may be particularly dif-
cult to recognize as malignant, and can be underdiag-
nosed as ‘hyperplastic’ benign glands as there may be
mild cytological atypia without prominent nucleoli [1].
The other feature that can result in underdiagnosis of
prostatic duct adenocarcinoma on needle biopsy is tumor
fragmentation, resulting in small detached foci of carci-
oma.

A difficult distinction lies between cribriform high-
grade PIN and ductal adenocarcinoma of the prostate.
Ductal adenocarcinomas often contain true papillary
fronds with well-established fibrovascular cores, where-
as high-grade PIN more frequently reveals micropapil-
lary fronds with tall columns of epithelium without fi-
brovascular stalks. Ductal adenocarcinomas frequently
contain comedonecrosis, which may be extensive. High-
grade PIN typically lacks comedonecrosis, and when ne-
crosis is present, it is focal. Finally, ductal adenocarci-
nomas may consist of very large and/or back-to-back glands,
whereas glands involved in PIN are of the size and dis-
tribution of benign glands. The use of basal cell markers
in this differential diagnosis may be problematic, as
both high-grade PIN and ductal adenocarcinoma may
display a patchy basal cell layer. However, absence of a
basal cell layer in numerous glands rules out PIN [10].
PIN-like ductal adenocarcinoma is even more difficult
to differentiate from high-grade PIN [7]. Ductal adeno-
carcinoma can be diagnosed either because the atypical
glands are too crowded to represent high-grade PIN or
there are too many atypical glands that are negative for
basal cell markers to be consistent with high-grade PIN.
In some needle biopsy specimens, there are only a few
atypical glands with papillary fronds that are negative
for basal cell markers that are highly suspicious for duc-
tal adenocarcinoma, yet due to the limited number of
atypical glands, high-grade PIN can not be ruled out
with certainty. These cases can be reported as: ‘Atypical
glands where the differential diagnosis is between high-
grade PIN and ductal adenocarcinoma. Repeat biopsy is
recommended.’

Ductal adenocarcinoma, especially the pattern char-
erized by single non-cribriform glands, can be diffi-
cult to distinguish from colorectal adenocarcinoma in-
vading the prostate. Immunohistochemical demonstra-
tion of PSA and PSAP in ductal adenocarcinoma can
verify the diagnosis. The finding of more characteristic

Prostatic Ductal Adenocarcinoma

Med Princ Pract 2010;19:82–85
patterns of prostatic ductal adenocarcinoma, such as the papillary pattern, or identifying admixed usual acinar adenocarcinoma can also aid in ruling out colonic adenocarcinoma. Only rarely are ductal adenocarcinomas associated with either extracellular or intracellular mucin. Negative immunohistochemical staining for B-catenin, CDX-2, and villin can be of further utility in excluding colon cancer [7, 11].

Prostatic duct adenocarcinoma on transurethral resection specimens can also mimic papillary urothelial carcinoma. The nuclei in urothelial carcinoma tend to be more pleomorphic, angulated in shape, contain variably numbered and sized nucleoli, and lack the columnar appearance of ductal adenocarcinoma [12]. Immunohistochemical demonstration of PSA and PSAP positivity and negative thrombomodulin and uroplakin staining in prostatic duct adenocarcinoma can confirm the diagnosis in difficult cases [13–15].

Prostatic ductal adenocarcinoma generally spreads in the same manner and should be treated in an analogous fashion to usual acinar adenocarcinoma of the prostate. There is, however, a greater propensity to spread to the testis and penis [16]. Ductal adenocarcinoma metastatic to the lung may be misdiagnosed as a primary lung tumor [17].

A unique aspect of this entity is that the urologist takes only a limited transurethral biopsy of the prostate, with the entire specimen consisting of only a small focus of prostatic duct adenocarcinoma. These tumor foci represent the ‘tip of the iceberg’, where there is more extensive unsampled carcinoma involving the underlying ductal system. Despite the limited tumor on biopsy or visible at cystoscopy, these tumors should be considered as aggressive lesions and treated accordingly. The one exception to considering ductal adenocarcinoma as aggressive tumors is the rare case when there is good sampling of the prostate with a sizable transurethral resection, and there is only a small focus of ductal adenocarcinoma; the prognosis in this situation is unknown.

Most studies have demonstrated that ductal morphology connotes a more aggressive course than acinar prostate cancer [18]. Men with ductal adenocarcinoma on needle biopsy who subsequently undergo radical prostatectomy have larger tumors with more advanced pathologic stage compared to acinar carcinoma and a shortened time to progression. Most ductal adenocarcinomas should be graded as Gleason score $4 + 4 = 8$, while retaining the diagnostic term of ductal adenocarcinoma to denote their unique clinical and pathological findings [19]. This can be achieved by diagnosing such a tumor as ‘prostatic ductal adenocarcinoma (Gleason score $4 + 4 = 8$)’. In cases with mixed ductal and acinar patterns, the ductal patterns should be assigned Gleason pattern 4. For PIN-like ductal adenocarcinomas, the evidence indicates that they behave comparable to Gleason pattern 4. For PIN-like ductal adenocarcinomas, the evidence indicates that they behave comparable to Gleason score $3 + 3 = 6$. The finding of comedonecrosis warrants assignment of Gleason pattern 5.

Summary

Ductal adenocarcinoma of the prostate is an unusual variant of prostate adenocarcinoma that has unique morphological and in some cases clinical features. It is critical to distinguish ductal adenocarcinoma from a variant of benign, premalignant, and malignant mimickers. Although typically ductal adenocarcinomas of the prostate are associated with a poor prognosis, there are several situations (i.e. limited cancer on an extensive transurethral resection, PIN-like ductal adenocarcinoma) in which the prognosis may not be as adverse.

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