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The clinicopathologic relevance of prostate lesions and their link to prostatic adenocarcinoma are reviewed.

Premalignant and Malignant Prostate Lesions: Pathologic Review
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Background: High-grade prostatic intraepithelial neoplasia (HGPIN) is currently the only recognized premalignant lesion of prostatic carcinoma.

Methods: This review article discusses HGPIN, its link to prostatic adenocarcinoma, and the significance of its presence on needle biopsy. The criteria and clinical impact of the diagnosis of atypical small acinar proliferation on needle biopsy are reviewed. Certain subtypes of prostate cancer that are not associated with HGPIN are of clinical relevance, and the unique clinicopathologic features of these subtypes are discussed. Histologic variants of prostatic adenocarcinoma with distinct cell types are also described.

Results: HGPIN is the only known pathologic factor currently available to distinguish which patients may be at risk for detecting carcinoma on repeat biopsy. Histologic variants are recognized due to the inference of a particular Gleason grade pattern associated with the cell type, hence affecting prognosis. Typically, pure forms of these histologic variants are associated with worse prognosis due to the associated high Gleason grades.

Conclusions: HGPIN has a strong association with acinar-type prostatic adenocarcinoma. HGPIN and acinar-type prostatic adenocarcinoma both show similar molecular alterations, providing further evidence of their association.

Introduction
Prostate cancer is the most common malignancy in men in the United States, with approximately 192,280 cases diagnosed yearly.\(^1,2\) It is the second leading cause of death in the Western world. The incidence of prostate cancer has increased worldwide in the last two decades, partly due to serum prostate-specific antigen (PSA) screening.\(^3,4\) Acinar-type adenocarcinoma is the most common malignancy of the prostate, comprising more than 90% of malignant lesions.\(^5,6\) Acinar-type adenocarcinoma typically involves the peripheral zones and is associated with high-grade prostatic intraepithelial neoplasia (HGPIN), the only recognized premalignant prostate lesion.\(^6\)

Various subtypes of prostate cancer are of clinical relevance and have specific clinicopathologic features and prognosis. They include small-cell neuroendocrine, adenoid cystic and basal cell (basaloid), squamous cell, urothelial, and sarcomatoid carcinomas. They commonly occur in association with acinar-type adenocarcinoma, although they may occur in their pure forms.\(^5,7\) Gleason grade is not recommended for these subtypes. Furthermore, other primary malignant prostate lesions that are not adenocarcinomas are exceedingly rare and include...
primary prostate sarcomas, germ cell tumors, rhabdoid tumors, phyllodes tumors, malignant peripheral nerve sheath tumors, nephroblastoma, primary malignant melanoma, and Wilms’ tumor, as well as primary hematopoietic malignancies.8

**Small-cell Neuroendocrine Carcinoma**

Small-cell neuroendocrine carcinoma (Fig 1), accounting for less than 0.5% to 2% of malignant prostate lesions, is a distinct clinicopathologic entity. Up to 50% of cases are associated with acinar-type adenocarcinoma. About one-half of patients present with bladder outlet obstruction and one-third present with signs of metastatic disease such as neurologic signs, bone pain, hydronephrosis, abdominal pain, or hematochezia.9 Small-cell neuroendocrine carcinoma is commonly seen in patients treated with prior hormone therapy for prostate cancer who present with widespread metastases in unusual sites such as soft tissue, omentum, and pericardium. There is frequent widespread dissemination, particularly to visceral organs such as the liver and lung.5,10,11 The prostate may be extensively enlarged, usually without an associated elevation of serum PSA. Bone metastases tend to be osteolytic rather than osteoblastic. An associated paraneoplastic syndrome such as Cushing’s syndrome, hypercalcemia, hyperparathyroidism, thyrotoxicosis, or hyperglucagonemia occurs in a minority of patients. Any proportion of a small-cell neuroendocrine component imparts a worse prognosis regardless of the presence of acinar-type adenocarcinoma. Small-cell carcinoma has poor response to androgen ablation therapy. The median survival ranges from 5 to 17.5 months. Less than 5% of patients survive beyond 2 years.8,17 Prostate carcinoma with neuroendocrine differentiation expresses chromogranin A, a neuroendocrine marker. Berruti et al12 showed that detection of plasma and tissue chromogranin A in newly diagnosed prostate carcinoma is an independent predictive factor of hormone refractory disease in patients on early androgen deprivation therapy and is associated with decreased overall survival. Chromogranin A is known to activate androgen receptors in the absence of androgens and accounts for one of the mechanisms of androgen independence.12

**Basal Cell/Adenoid Cystic Carcinoma**

Basal cell/adenoid cystic (basaloid) carcinoma (Fig 2) is exceedingly rare, comprising < 0.01% of malignant lesions of the prostate. It is a distinct subtype of prostate carcinoma that arises from the periurethral transition zone basal cells.1,18,20 Therefore, it is usually discovered on transurethral resection specimens, particularly in patients presenting with prostatic hyperplasia and lower urinary tract symptoms. The age of patients is broad, ranging from the second to the eighth decade.3,18 Serum PSA is usually not elevated. Bone is not a common site of metastases. There is no standard guideline for the treatment of basaloid carcinoma due to the limited long-term data available on outcome. Life-long follow-up is recommended since recurrences can arise several years after the initial presentation. Although basaloid carcinoma is generally considered indolent, cases with more aggressive behavior showing extraprostatic extension and metastases leading to rapid demise have been reported.1,3,8,16,19-24

**Primary Squamous Cell Carcinoma**

Primary squamous cell of the prostate (Fig 3) is rare, accounting for < 1% of all prostate malignancies.5,6,8 There is an association with Schistosomiasis infection.8 Serum PSA is not usually elevated. A history of previous hormone or radiation therapy (ranging from 3 months to 9 years prior) is a common factor.5,8 Patients generally present with locally advanced disease with invasion

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**Fig 1.** — Small-cell neuroendocrine carcinoma. This clinicopathologic entity contains a sheet-like arrangement of small hyperchromatic cells with nuclear molding and numerous apoptotic bodies (hematoxylin-eosin, magnification ×200).

**Fig 2.** — Basaloid carcinoma. This rare lesion shows a multinodular growth pattern containing small hyperchromatic basaloid cells. Some glands show a cribriform pattern with round lumens. Intervening desmoplastic stroma are present with a fibrotic appearance (hematoxylin-eosin, magnification ×200).
into the bladder, rectum, and seminal vesicles. Bone metastases are typically osteolytic rather than osteoblastic. Widely disseminated disease has been reported in the peritoneum, diaphragm, liver, and lung. While data regarding response to treatment are insufficient, the mean survival is reported as 6 to 24 months.8,16,25

**Primary Urothelial Carcinoma**

Primary urothelial carcinoma of the prostate (Fig 4) comprises 0.7% to 2.8% of malignant prostate lesions. Since it arises in the periurethral transition zone, it commonly causes lower urinary tract symptoms and is more likely seen in transurethral resection specimens.1,2 Serum PSA may be elevated. The differential diagnosis includes secondary involvement by primary bladder carcinoma. Primary urothelial carcinoma can extend into ejaculatory ducts to involve the seminal vesicles. Bone metastases tend to be osteolytic. Stromal invasion is the most significant prognostic factor, with survival rates of 100% for noninvasive tumors treated by radical surgical resection. Patients with stromal invasion have poor prognosis; 5-year survival rates of 45% have been reported.8,16,26,27

**Primary Sarcomatoid Carcinoma**

Primary sarcomatoid carcinoma of the prostate (Fig 5) is rare. A history of prostate cancer treated by radiation and/or hormone therapy is present in over one-half of cases. Serum PSA levels may be lower than anticipated for the tumor volume. Patients may present with bladder outlet obstruction. There is an association with local recurrences and extension of the disease into the pelvis. Prognosis is poor, with 5- and 7-year survival rates reported as 41% and 14%, respectively. Primary prostate sarcomas such as leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, malignant fibrous histiocytoma, and synovial sarcoma are in the differential diagnosis. Nonetheless, in recurrent prostate tumors showing only a spindle cell (mesenchymal) pattern, a diagnosis of sarcomatoid carcinoma should be favored when there is a history of treated adenocarcinoma.8,16,28

**Histologic Variants of Prostatic Carcinoma**

There are also histologic variants of prostatic adenocarcinoma with unique cell types. These are recognized due to

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**Fig 3.** — Squamous cell carcinoma. Nests of infiltrating keratinizing cells are present (hematoxylin-eosin, magnification ×400).

**Fig 4.** — Urothelial carcinoma. Nests of infiltrating neoplastic urothelial cells are present (hematoxylin-eosin, magnification ×200).

**Fig 5.** — Sarcomatoid carcinoma. This tumor commonly is a sarcomatoid transformation of a prior prostatic adenocarcinoma that has undergone radiotherapy and/or hormonal therapy. Only the mesenchymal spindle cell component is present (hematoxylin-eosin, magnification ×200).

**Fig 6.** — Ductal adenocarcinoma. Arborizing papillary architecture contains stratified hyperchromatic oblong cells. Basal cells are sparse (hematoxylin-eosin, magnification ×100).
the implication of a specific Gleason grade, imparting a worse prognosis and/or the potential diagnostic pitfalls associated with the cell type. These variants include ductal, mucinous/colloid, signet ring cells, foamy xanthomatous glands, atrophic, oncocytic, carcinoid-like, Paneth-like, pseudohyperplastic, lymphoepithelioma-like, hypernephroid, and tubulocystic with clear cell features. Pure forms such as carcinoid tumors are rare.

The most common variant is ductal adenocarcinoma (Fig 6), which comprises 1% of malignant prostate lesions and is associated with the acinar pattern in > 80% of cases. Grade for grade and stage for stage, it is similar to acinar-type adenocarcinoma. Its presence imparts a worse prognosis, advanced disease, and shorter time to progression since it is considered a Gleason grade 4 pattern.8,16,29

Pure mucinous carcinoma of the prostate (Fig 7) is also rare, with an incidence of approximately 0.2%. It is defined as a tumor consisting of extravasated mucin comprising > 25% of its volume. It is clinically similar to acinar-type adenocarcinoma. Its presence imparts a worse prognosis, advanced disease, and shorter time to progression since it is considered a Gleason grade 4 pattern.8,16,29

Pure signet ring cell carcinoma (Fig 8), defined as signet ring cells comprising > 25% of the tumor volume, is exceedingly rare. It is associated with a significantly elevated serum PSA level. Signet ring cells may occur in association with acinar-type adenocarcinoma with any Gleason grade pattern in which its prognosis is similar, grade for grade and stage for stage, to the acinar component. Pure signet ring cell carcinomas present in advanced stages, with 3-year survival rates reported as 27%.8

**High-Grade Prostatic Intraepithelial Neoplasia**

HGPIN currently is the only recognized premalignant precursor to prostatic adenocarcinoma (Fig 9). In 1969, McNeal6 was the first to describe HGPIN as a precursor to prostatic carcinoma. In 1986, McNeal and Bostwick30 further defined HGPIN. In the past, other lesions have been assumed to be precursors to prostatic adenocarcinoma; these include adenosis (atypical adenomatous hyperplasia) and proliferative inflammatory atrophy. However, follow-up data do not link these to prostatic adenocarcinoma since there is no increased risk of carcinoma on repeat biopsy and it is rare to see carcinoma developing or associated with these lesions.6,31,32

Morphologic and molecular data are available that support HGPIN as a precursor to prostatic carcinoma.33,34 Increased foci of HGPIN are seen in association with carcinoma compared to benign prostate tissue (Fig 10). Multiple foci of HGPIN are associated with multifocal involvement by prostatic carcinoma. HGPIN dominates in the peripheral zone (up to 80%) and is more closely related to peripheral cancers than to transition zone...
cancers of the prostate. Transition and central zone involvement by HGPIN is less common. Moreover, prostatic carcinoma is observed budding off of HGPIN, further providing morphologic evidence supporting HGPIN as a precursor to carcinoma. The amount and degree of involvement by HGPIN decrease following complete androgen deprivation therapy. However, no morphologic changes in HGPIN are evident following 5-alpha-reductase inhibitor therapy or radiotherapy.6

Molecular data supporting the premalignant nature of HGPIN include the frequent losses of chromosome 8p and gains of 8q as well as telomere shortening and increased telomerase activity seen in both HGPIN and carcinoma. Other chromosomal abnormalities observed in both HGPIN and carcinoma include losses of 10q, 16q, and 18q with gains of chromosomes 7, 10, 12, and Y. HGPIN is also more frequently aneuploidy compared with benign prostate tissue. Glutathione S-transferase P1 is hypermethylated in the majority of HGPIN as well as carcinomas. Overexpression of p16, p53, Bcl-2, and MYC can be seen in both HGPIN and carcinoma. There may be decreased expression of NKX3.1 and p27 genes in both HGPIN and carcinoma.33,34 Furthermore, approximately 20% of HGPIN shows the TMPRSS2-ERG fusion gene abnormality, which is also observed in approximately 50% of prostatic carcinomas. Proliferative rate and apoptosis are also increased in HGPIN and carcinoma compared to benign prostate tissue.35-38

Histologically, HGPIN is characterized by prostate glands retaining a complete or partial basal cell layer lined by atypical cells with prominent nucleoli (Fig 11). The glands of HGPIN show a variety of patterns including flat, stratified, branching, micropapillary, (Fig 12) or cribriform architecture. The nuclei are typically overlapping, large, and hyperchromatic. In contrast, low-grade prostatic intraepithelial neoplasia (PIN), which is not considered premalignant, does not show prominent nucleoli and rarely shows micropapillary or cribriform architecture. HGPIN may also show signet ring, small cell neuroendocrine, mucinous, foamy gland, squamous, apocrine, or Paneth cells, thus making its distinction from carcinoma challenging. The presence of signet ring cells in HGPIN is rare. In almost all cases, an adjacent invasive signet ring cell carcinoma component has been reported.6,39-41

Currently, the incidence of HGPIN on needle biopsy is reported as 5% to 8%.39 HGPIN can be seen in men in their third decade of life preceding the development of carcinoma by 10 years. Its incidence in Caucasian men progressively increases with age. In prostatectomy specimens, the reported frequency of HGPIN ranges from 71% to 83%.42,43 African American men are reported to have higher incidence of HGPIN at autopsy. In the past, men living in Japan were reported to have a significantly lower incidence of HGPIN compared with men in the United States; however, most recently, the incidence of HGPIN in Asian men is reported to be
comparable to the Western world. Whether this represents an increase in the detection of HGPIN or an increase in its incidence is uncertain.44

A variety of benign lesions such as central zone histology and clear cell cribriform hyperplasia are not premalignant precursors, but they can be morphologically confused with HGPIN due to similarities in appearance. The central zone is at the base of the prostate adjacent to the ejaculatory ducts and seminal vesicles. The glands in the central zone may show complex papillary or cribriform architecture emulating HGPIN. There is dense muscular stroma at the base of the prostate that will aid in identifying its location at the base. Clear cell cribriform hyperplasia (Fig 13), in which the glands are crowded with pale cytoplasm, is usually located in the transition zone, whereas HGPIN dominates in the peripheral zone.6,33

Malignant lesions that can be morphologically confused with HGPIN on needle core biopsies include acinar adenocarcinoma with cribriform architecture, ductal adenocarcinoma, and the debatable entity intraductal carcinoma. In the presence of numerous cribriform glands, the absence of basal cells is usually diagnostic of carcinoma. However, the complete absence of basal cells in only a few cribriform glands is still not diagnostic of carcinoma given that HGPIN cannot be distinguished from cribriform carcinoma with certainty. The reason for this is that HGPIN can show a few glands that completely lack the basal layer. Repeat needle core biopsy is recommended in these cases. If only a few microacinar glands are present adjacent to HGPIN (Fig 14), then the differential diagnosis includes tangential sectioning or extensions of HGPIN vs a minute focus of adenocarcinoma adjacent to HGPIN. If the microacinar glands are numerous or farther away from the HGPIN, then a diagnosis of carcinoma can be made with certainty in the absence of a basal cells.6,45

Distinguishing ductal adenocarcinoma from HGPIN can also be challenging on core biopsies. Ductal adenocarcinoma is commonly located within the central perirethral region, whereas HGPIN is more often located peripherally. Therefore, prostatic ductal adenocarcinoma is more likely than HGPIN to be sampled on transurethral resection of the prostate (TURP). Ductal adenocarcinoma can be differentiated from HGPIN by the presence of true papillary fronds containing fibrovascular cores, comedo-necrosis, and crowded confluent glands. Ductal adenocarcinoma may show an uneven basal cell layer; therefore, the utility of basal cell markers (ie, antibodies to high-molecular-weight cytokeratin or p63) can be limited.32,43 If only a few atypical glands with papillary fronds lacking basal cells are present, then the diagnosis of highly suspicious for ductal adenocarcinoma is preferred since the differential diagnosis still includes HGPIN. Repeat needle core biopsy is also recommended in these cases.

Intraductal carcinoma is believed to represent the intraductal spread of carcinoma within prostate glands. It is not considered preinvasive, but rather a progression that occurs later in prostate cancer since it is nearly always associated with more advanced stage, higher Gleason score, and larger tumor volume. Carcinomas with an associated intraductal component are more likely to show poor prognosis and seminal vesicle involvement than those that lack an intraductal component. The differential diagnosis of intraductal carcinoma includes HGPIN and ductal adenocarcinoma. The differential diagnosis between HGPIN and intraductal carcinoma is considered if basal cells are unevenly distributed. Intraductal carcinoma can be distinguished from HGPIN by its solid growth pattern, marked pleomorphism, and the presence of comedo-necrosis; these

Fig 13. — Clear cell cribriform hyperplasia. This benign lesion is located in the transitional zone. It shows a gland-to-gland arrangement with cells containing clear cytoplasm, small round nuclei without prominent nucleoli, and a prominent basal cell layer (hematoxylin-eosin, magnification ×400).

Fig 14. — Atypical glands adjacent to HGPIN showing a cribriform pattern. Adjacent to the cribriform HGPIN, confirmed by the presence of an incomplete basal cell layer, are a few small round glands with prominent nucleoli that lack a basal cell layer. These atypical small glands may represent either tangentially sectioning of HGPIN or invasive carcinoma adjacent to HGPIN. Rebiopsy is recommended in these cases (hematoxylin-eosin, magnification ×400).
features are not characteristically seen in HGPIN. Intraductal carcinoma has micropapillary tufts lacking fibrovascular stacks that distinguish it from ductal adenocarcinoma, in which fibrovascular stacks may be present. Immediate repeat biopsy is generally recommended for lesions that cannot be definitely classified into either intraductal carcinoma or HGPIN.6,46

In recent studies, the median risk of detecting carcinoma on repeat biopsy following a diagnosis of HGPIN ranges from 22% to 24.1%, which is not statistically significant from the risk reported on repeat biopsy following a benign diagnosis.6,39 This is in part due to larger numbers of needle core biopsies sampled initially, which detects many associated cancers on initial biopsy. Likewise, the possibility of detecting isolated HGPIN on initial biopsy relies mainly on the quantity of core biopsies sampled initially. With greater amounts sampled initially, the incidence of isolated HGPIN decreases on repeat biopsy. In spite of this, HGPIN is the only pathologic factor currently available to predict which patients may be of higher risk for carcinoma on repeat biopsy. HGPIN may be a marker for concurrent carcinoma, and the risk of carcinoma depends on the amount of HGPIN rather than its mere presence.6,39 Specifically, HGPIN detected on more than three core biopsy specimens is associated with a significantly higher risk of carcinoma on repeat biopsy.6,39 Clinical parameters such as serum PSA level, digital rectal examination, and imaging studies are not as effective in identifying which patients with HGPIN are more likely to show carcinoma on repeat biopsy. Therefore, repeat biopsy is generally recommended within a year of the initial diagnosis of HGPIN, particularly if three or more cores show HGPIN. For one or two cores showing HGPIN, some recommend that repeat biopsy may not be needed within the first year following HGPIN if there are no clinical signs of possible cancer.6,49,51-56 However, whether HGPIN has prognostic significance in clinical decision making remains controversial. Overall, more studies are needed to resolve exactly how often and when a repeat biopsy should be performed following the initial diagnosis of HGPIN. Moreover, if small atypical glands are adjacent to HGPIN, the risk of cancer is reported to be similar to cases in which glands are suspicious for carcinoma. In these cases, repeat biopsy is recommended within 3 to 6 months of the initial diagnosis of atypical glands adjacent to HGPIN.40,49,51-56

Investigational studies are currently assessing the role of α-methylacyl-CoA racemase (AMACR) and the novel gene PTOV1 linked to prostate cancer in detecting the risk of carcinoma on repeat biopsy following a diagnosis of HGPIN. HGPIN adjacent to carcinoma is reported to show significantly more AMACR expression (56%) than HGPIN distant from carcinoma (14%).57-59 Patients with any HGPIN gland that is AMACR-positive are 5.2 times more likely to show carcinoma on repeat biopsy than those with completely AMACR-negative HGPIN.57-59 Further studies are needed to determine the utility of AMACR and PTOV1 gene in identifying which patients with HGPIN are at greater risk for carcinoma.

**Atypical Small Acinar Proliferation**

Another significant predictor of subsequent carcinoma on repeat biopsy is the presence of small atypical glands in which morphologic features are insufficient to definitively render a diagnosis of carcinoma. These cases are referred to as atypical small acinar proliferation (ASAP) suspicious but not diagnostic of carcinoma (Fig 15). The incidence of ASAP on needle biopsy is approximately 2% to 3%. Up to 60% of cases of ASAP show carcinoma on repeat biopsy.60-64 A considerable number of cases of ASAP represent cancer that was originally inadequately sampled on initial biopsy. Therefore, most authors believe that ASAP is a diagnostic risk category and not a valid pathologic entity.60-64 Its precise diagnostic cri-
teria is not well defined. However, foci of ASAP often lack one or more major diagnostic criteria and are of small size, often < 1 mm (Fig 16). The glands of ASAP often show distorted features including partial atrophic-like appearance, lack of significant nuclear enlargement, lack of enough cells showing prominent nucleoli (Fig 17), obscured associated inflammation, gland clustering mimicking adenosis, or incompletely sampled glands. Degenerative changes and nuclear hyperchromasia obscuring nuclear detail in a few atypical glands (Fig 18) may also be considered as ASAP. Minute foci of atypical glands that disappear on deeper levels obtained for immunohistochemical basal cell staining can also be referred to as ASAP. ASAP informs clinicians that an obvious malignant or definite benign diagnosis is not possible based on insufficient features and that repeat biopsy is necessary.60-64

Conclusions

Presently, no concise clinical or pathologic characteristic has been established that can assess which patients with HGPIN are at increased risk for carcinoma on repeat biopsy. Further studies are necessary to validate whether routine repeat biopsies should be performed following the diagnosis of HGPIN. Moreover, distinguishing between HGPIN and foci of ASAP suspicious for cancer is imperative since the risks of carcinoma on repeat biopsy and the recommendations for follow-up are different. Additional studies are necessary to resolve which parameters may be predictive of subsequent carcinoma detection.

References


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