



Review Article

# Updates of Prostate Cancer from the 2022 World Health Organization Classification of the Urinary and Male Genital Tumors



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## Abstract

Prostate cancer is a heterogeneous disease with a wide spectrum of pathological, clinical, and molecular features. The diagnosis and classification of prostate cancer have been constantly modified with the incorporation of new data. The 5<sup>th</sup> edition of the World Health Organization (WHO) Classification of Urinary and Genital Tumors was recently published six years after the 4<sup>th</sup> edition. In this new edition, the classification of prostate cancer has been refined in the diagnostic criteria, grading, nomenclature, and genomics. This paper reviews significant updates to the new WHO classification of prostate cancer, including high-grade prostatic intraepithelial neoplasia, acinar adenocarcinoma, intraductal carcinoma, ductal carcinoma, and neuroendocrine tumors. Controversial issues in the Gleason grading are discussed, such as intraductal carcinoma and tertiary grade. We also highlight distinct genetic and epigenetic alterations in prostate cancer that may contribute to its diverse clinicopathologic features. Overall, the 5<sup>th</sup> edition of the WHO classification provides a comprehensive assessment of prostate cancer with morphologic, immunohistochemical, genomic, and clinical data, which may represent an optimal paradigm for diagnosing and treating prostate cancer.

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**Keywords:** Prostate cancer; High-grade prostatic intraepithelial neoplasia; Intraductal carcinoma; Ductal carcinoma; Acinar carcinoma; Neuroendocrine differentiation.

**Abbreviations:** AIP, atypical intraductal proliferation; dMMR, DNA mismatch repair; GG, grade group; GU, genitourinary; GUPS, genitourinary pathology society; HGPIN, high-grade prostatic intraepithelial neoplasia; HRR, homologous recombination repair; IDC, intraductal carcinoma; IHC, immunohistochemistry; ISUP, international society of urological pathology; LCNEC, large-cell neuroendocrine carcinoma; NE, neuroendocrine; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; PARP, poly ADP-ribose polymerase; PIN, prostatic intraepithelial neoplasia; SCNEC, small-cell neuroendocrine carcinoma; t-NEPC, treatment-related neuroendocrine prostatic carcinoma; TRUS, transrectal ultrasound; WHO, world health organization.

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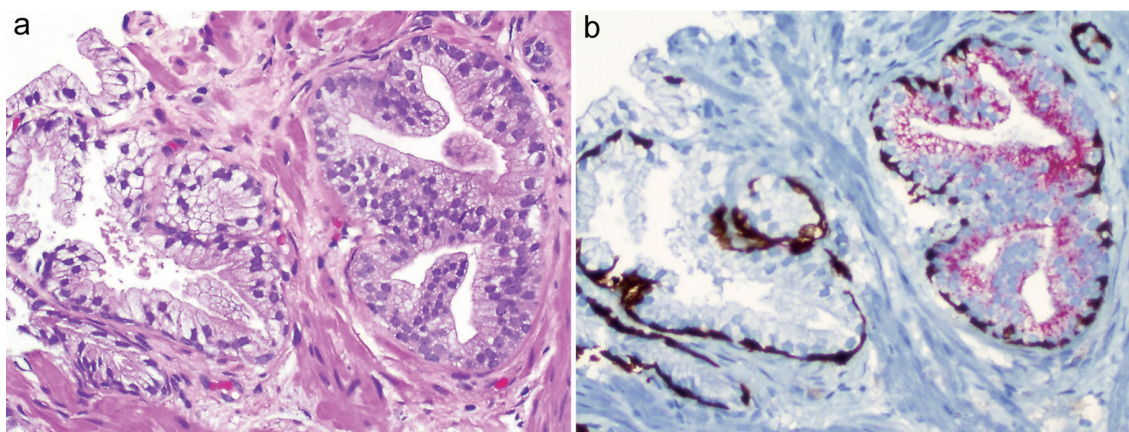
## Introduction

Prostate cancer is the 4<sup>th</sup> most common cancer worldwide, with an estimated 1,414,259 cases in 2020.<sup>1</sup> In the USA, prostate cancer is the most common cancer in men, with an estimated 268,490 cases in 2022, accounting for 27% of all male cancers.<sup>2</sup> One out of every nine American men will be diagnosed with prostate cancer during their lifetime.<sup>2</sup> However, autopsy studies have reported that the prevalence of prostate cancer in western countries is approximately 30–40% in men, which is even higher than that of clinically detected prostate cancer.<sup>3</sup> This indicates that a large proportion of prostate cancers are indolent and are not clinically diagnosed. On the other hand, a significant proportion of prostate cancers are clinically aggressive, resulting in the second leading cause of cancer-related death in men in the United States, with 34,500 prostate cancer-related deaths per year.<sup>2</sup>

The 5<sup>th</sup> edition of the World Health Organization (WHO) Classification of the Urinary and Male Genital Tumors was recently published in 2022.<sup>4</sup> The time interval between the 4<sup>th</sup> and 5<sup>th</sup> editions is six years, only half of that between the 3<sup>rd</sup> and 4<sup>th</sup> editions.<sup>4–6</sup> Still, substantial advancements in the pathology and genomics of prostate cancer have been included in the new edition. In this review, we will highlight new developments in the diagnosis, nomenclature, cancer grading, and molecular features of the most common malignancies in the prostate, i.e., prostatic adenocarcinoma and neuroendocrine tumors. Other uncommon tumors, such as squamous, urothelial, mesenchymal, and hematopoietic tumors, are beyond the scope of this paper.

## High-grade prostatic intraepithelial neoplasia

High-grade prostatic intraepithelial neoplasia (HGPIN) is the most common *in situ* precursor lesion of prostate cancer.<sup>7</sup> It shares some morphological features with prostatic adenocarcinoma, such as enlarged nuclei and hyperchromasia in the secretory epithelial cells (Fig. 1). The presence of prominent nucleoli in the epithelial cells is the key diagnostic feature of HGPIN. Unlike prostatic adenocarcinoma, HGPIN is usually characterized by large glands with irregular lumens lined by multilayered cells. The basal cells are always present in HGPIN, although in a reduced number. Immunohistochemistry (IHC) for basal cell markers, such as high molecular cytokeratin CK903 and p63, may be used to highlight the presence of scattered basal cells in HGPIN. At the molecular



**Fig. 1. High-grade prostatic intraepithelial neoplasia (HGPIN) shows flat and papillary growth patterns, with the overlying epithelial cells having enlarged nuclei with prominent nucleoli.** Note benign prostatic glands for comparison on the left (a) ( $\times 200$ ). Cribriform pattern is not recognized as HGPIN in the 5<sup>th</sup> edition. On immunostain, HGPIN is positive for racemase and basal cell markers (CK903 and p63) (b) ( $\times 200$ ).

level, HGPIN carries genetic and epigenetic alterations frequently observed in prostate cancer, such as TMPRSS2-ERG gene fusion, loss of PTEN, amplification of MYC, and telomere shortening.<sup>8–11</sup>

In the 5<sup>th</sup> edition, three common growth patterns, namely tufting, micropapillary, and flat, are described in HGPIN (Fig. 1). Some less frequent patterns, such as foamy, mucinous, inverted, signet ring-like, and small-cell, may also be observed in HGPIN.<sup>7,12</sup> However, the cribriform pattern is not recognized in HGPIN, as it may be associated with intraductal carcinoma (IDC).<sup>13,14</sup> It is now referred to as atypical intraductal proliferation (AIP), which encompasses a spectrum of intraductal proliferations that are architecturally more complex than HGPIN but fall short of IDC (Fig. 2).<sup>15</sup> Several studies have suggested that AIP shows clinical and molecular features similar to those in IDC.<sup>15–17</sup>

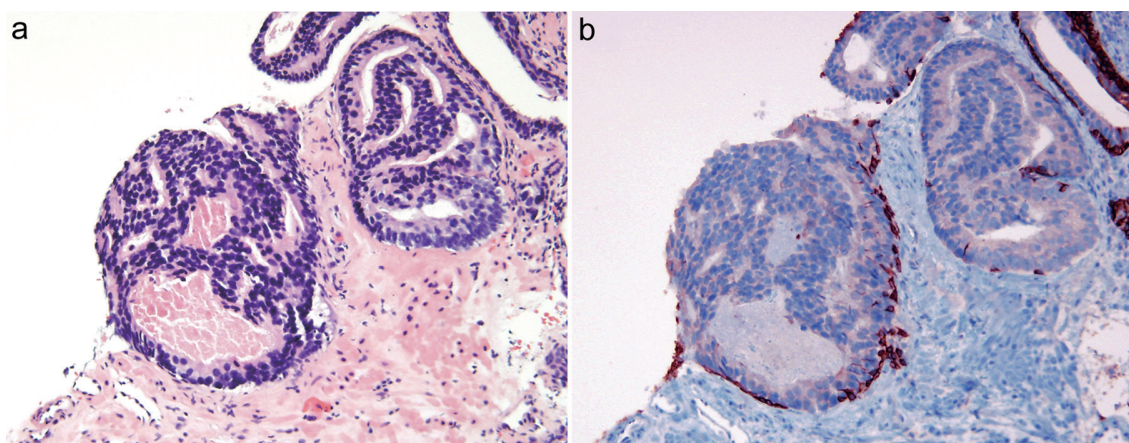
Like the previous 4<sup>th</sup> edition, the 5<sup>th</sup> edition does not recognize low-grade PIN, as it is generally difficult to differentiate it from benign prostatic glandular hyperplasia, and the frequency of diagnostic discrepancies among pathologists, including genitourinary (GU) pathology experts, is considerable.<sup>4,5</sup> Furthermore, the biological significance of low-grade PIN remains uncertain.

As a precursor lesion, HGPIN does not require treatment.

HGPIN is associated with an increased risk for prostate cancer in subsequent biopsies when it is found in a prostate biopsy with no prostate cancer. However, the risk associated with isolated HGPIN in a single biopsy tissue core has recently decreased to about 20% in patients who undergo regular PSA screening, similar to that in patients without HGPIN.<sup>18</sup> Patients with HGPIN in multiple biopsy tissue cores still carry a significant risk of prostate cancer (30–40%).<sup>19,20</sup> Therefore, it is recommended that the patients with multifocal HGPIN in prostate needle biopsy undergo another biopsy within a year.

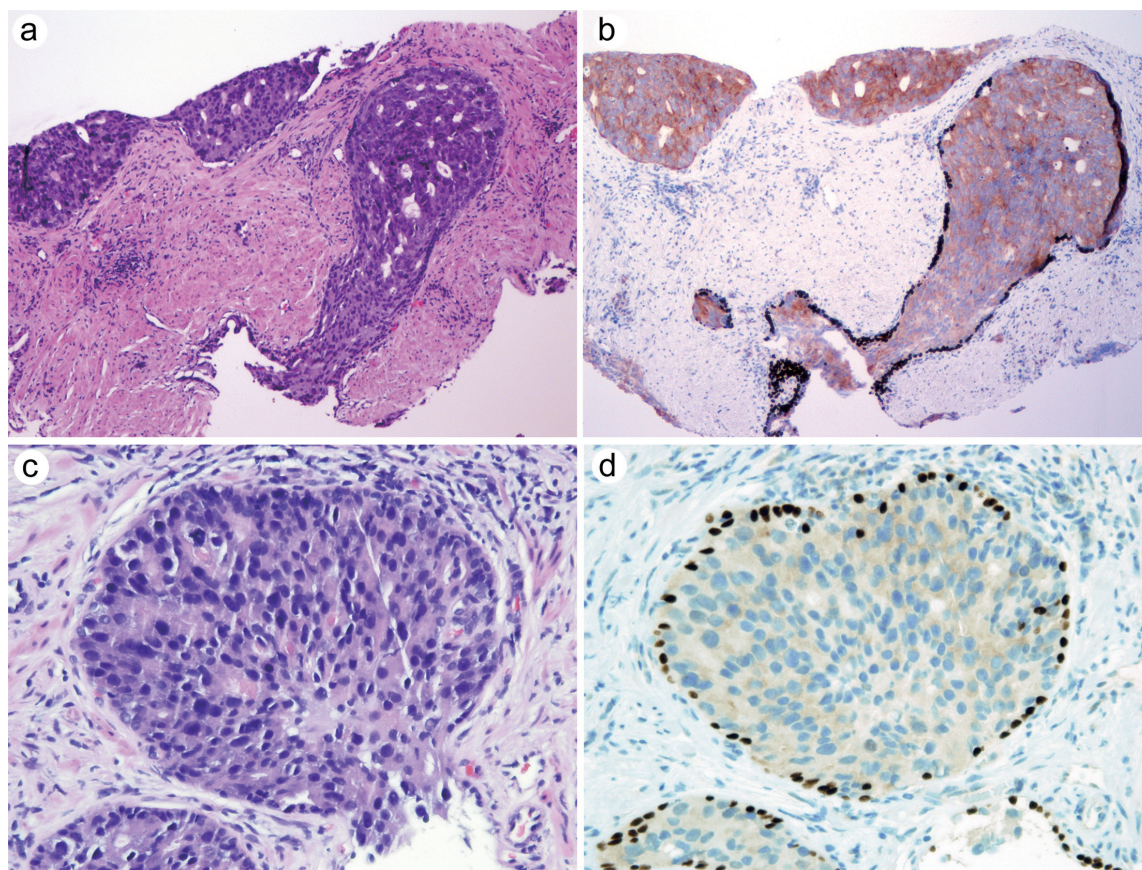
### Intraductal carcinoma

IDC of the prostate is characterized by an atypical proliferation of epithelial cells in native prostatic ducts or acini, which are originally noncancerous, as they still retain the basal cell layer. In most cases, IDC represents an advanced phase in prostate cancer with a retrograde spread of cancer into benign prostatic ducts or acini. The presence of IDC in the prostate is often associated with high-grade and advanced-stage prostate cancer.<sup>14,21,22</sup> However, a small subset of IDC is not associated with invasive prostate cancer and may represent a precursor lesion that exhibits greater architectural and cytological atypia than HGPIN.<sup>23,24</sup>



**Fig. 2. Atypical intraductal proliferation (AIP) shows atypical loose cribriform glands (a) ( $\times 200$ ).** On immunostain, AIP is positive for racemase and basal cell markers (CK903 and p63) (b) ( $\times 200$ ).





**Fig. 3.** Intraductal carcinoma (IDC) shows atypical dense cribriform glands (a) ( $\times 100$ ), which are positive for racemase and basal cell markers (CK903 and p63) (b) ( $\times 100$ ). IDC exhibits a solid growth pattern (c) ( $\times 200$ ) and is positive for racemase and p63 (d) ( $\times 200$ ).

Like the 4<sup>th</sup> edition, the 5<sup>th</sup> edition largely adopts the diagnostic criteria of IDC proposed by Guo and Epstein.<sup>14</sup> The most common growth pattern in IDC is dense cribriform, in which malignant epithelial cells account for more than 50% of the cribriform area (Fig. 3).<sup>14,25</sup> Solid pattern without glandular spaces is also common in IDC. Sometimes, IDC may show loose cribriform or micropapillary patterns, often accompanied by comedonecrosis and marked cytological atypia. The marked cytological atypia was initially defined as enlarged nuclei that were more than six times larger than normal epithelial nuclei,<sup>14</sup> but this criterion may be too strict.<sup>26</sup> In the 5<sup>th</sup> edition, the nuclear size is not specified, but the variation in nuclear size and shape in IDC are more pronounced than in HGPIN.

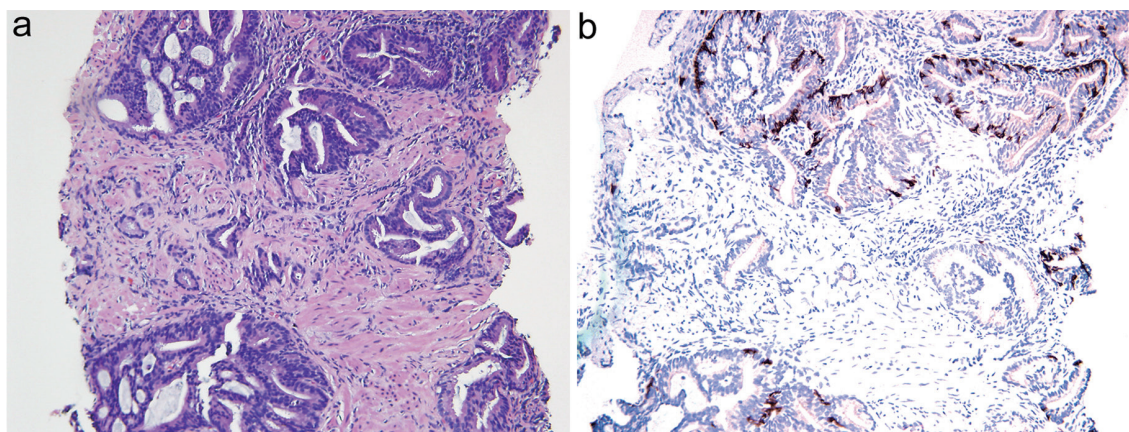
IDC should be reported in prostate biopsy and radical prostatectomy specimens, as it is an independent predictor of high-grade and advanced-stage prostate cancer.<sup>13,27</sup> In patients treated with radical prostatectomy, IDC is at significant risk for biochemical recurrence, decreased progression-free survival, and cancer-specific mortality.<sup>28,29</sup> There is consensus that IDC should not be graded when it is an isolated finding without concomitant invasive cancer in prostate biopsy.<sup>13,27</sup> However, whether IDC should be included in the Gleason score remains controversial when it coexists with invasive prostate cancer (Fig. 4).<sup>30</sup> The Genitourinary Pathology Society (GUPS) recommends that IDC should not be included in the Gleason score, as a small subset of IDC may represent an *in situ* lesion.<sup>13</sup> The International Society of Urological Pathology (ISUP) suggests that IDC may be in-

cluded in the Gleason score, as the incidence of IDC as an *in situ* lesion is so rare that its impact is insignificant.<sup>27</sup> The 5<sup>th</sup> edition does not endorse either recommendation because of insufficient data. Either GUPS or ISUP recommendation may be used, but pathologists should specify which version of the recommendation is used in pathology reports and publications, as it may facilitate meaningful comparison and analysis in different cohorts of patients.

It is important to differentiate IDC from HGPIN, as their clinical implications are significantly different. In general, HGPIN does not show cribriform or solid growth patterns, and cytological atypia is less pronounced than that in IDC. When the atypical glands demonstrate architectural disorder and cytological atypia that exceeds HGPIN but do not meet the criteria for IDC, the preferred term in the 5<sup>th</sup> edition is "atypical intraductal proliferation," although other terms, such as "atypical cribriform lesion," "atypical intraductal cribriform proliferation," and "low-grade ductal carcinoma," have also been used in literature.<sup>15,17,31</sup> Most (more than 90%) of AIP cases demonstrate loose cribriform architectures. When diagnosed on needle biopsy, AIP is considered a high risk of unsampled IDC and is associated with a significantly increased frequency (50%) of IDC on repeat biopsy.<sup>15</sup> Therefore, it is recommended that patients with only AIP but no invasive prostate cancer may undergo immediate rebiopsy.<sup>15,17,31</sup>

IHC is often employed to demonstrate the presence of basal cells in IDC, as it may be difficult to recognize basal cells on routine hematoxylin and eosin staining. Basal cell markers, such as p63 and high molecular weight cytokera-





**Fig. 4.** IDC coexists with acinar adenocarcinoma (a) ( $\times 100$ ). On immunostain, IDC is positive for racemase and CK903 and p63, while acinar carcinoma is positive for racemase and negative for CK903 and p63 (b) ( $\times 100$ ). Per the GUPS guidelines, the Gleason score is graded as 6 (3 + 3) with IDC, as IDC is not included in the Gleason score. Per the ISUP guidelines, the Gleason score is graded as 7 (4 + 3) with IDC, as IDC is included in the Gleason score.

tin CK903, are recommended for prostate biopsies displaying cribriform glands without concomitant invasive prostate cancer.<sup>13</sup> When cribriform glands are present in prostate biopsies with Gleason score 6 cancer, IHC may also be considered to differentiate IDC from Gleason pattern 4 cancer. However, it is not necessary to perform basal cell IHC on biopsies to identify IDC if the IHC results do not change the overall Gleason score. Germline BRCA2 testing has been recommended by the National Comprehensive Cancer Network, but it has not been endorsed in the 5<sup>th</sup> edition.<sup>32,33</sup> Additionally, urothelial carcinoma may show retrograde spread in the prostate, mimicking solid pattern IDC. IHC of prostatic markers (such as NKX3.1, PSA, PSAP, PSMA, and prostein) and urothelial markers (such as GATA3, p63, high molecular weight cytokeratin, and uroplakin II) can aid the differential diagnosis.<sup>14</sup>

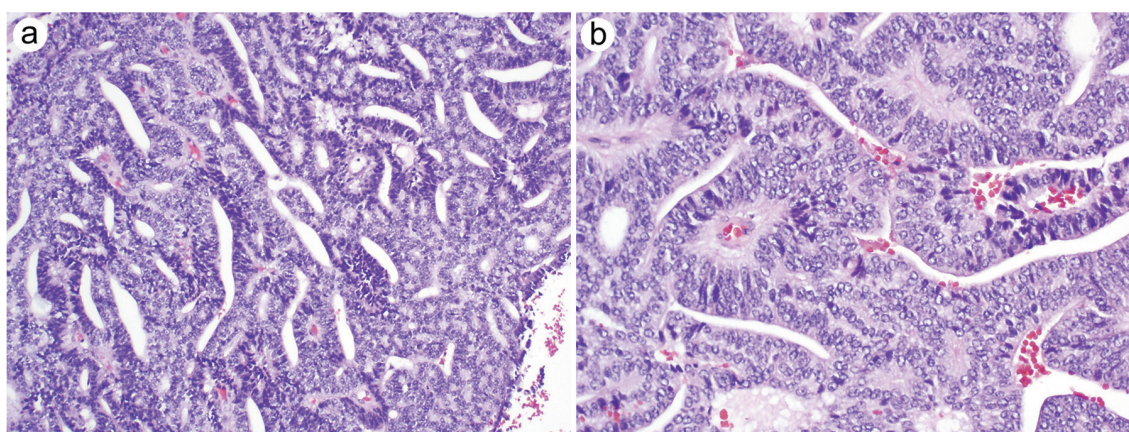
### Ductal adenocarcinoma

Ductal adenocarcinoma is a distinct subtype of prostatic adenocarcinoma characterized by large glands lined by tall pseudostratified columnar cells. It was originally thought to be derived from Mullerian duct remnants.<sup>34</sup> However, it is now believed to develop from the prostatic glandular cells,

like acinar adenocarcinoma, as they share similar IHC and molecular profiles.<sup>35,36</sup> It has been proposed that ductal adenocarcinoma may represent a subtype of acinar adenocarcinoma.<sup>4</sup> As insufficient data supports this view, ductal adenocarcinoma is still maintained as a separate type from acinar adenocarcinoma in the 5<sup>th</sup> edition.

Although most ductal adenocarcinomas are found in the peripheral zone, a small subset arises from the transition zone around the prostatic urethra, causing urinary obstruction and hematuria.<sup>37</sup> The level of PSA is elevated in ductal adenocarcinoma, but it is often lower than that in acinar adenocarcinoma. Ductal adenocarcinoma frequently metastasizes to visceral organs, such as the lungs and liver. Sometimes it metastasizes to the brain, skin, penis, and testis.<sup>38–40</sup>

Prostatic ductal adenocarcinoma typically shows papillary and large cribriform growth patterns (Fig. 5). The papillae often have fibrovascular cores, and the cribriform glands have slit-like lumens. The overlying malignant epithelium is often composed of pseudostratified columnar cells with abundant amphophilic or pale eosinophilic cytoplasm. The nucleoli are elongated and enlarged with prominent nucleoli and frequent mitotic figures. Ductal adenocarcinoma is present in 2.6% of prostate cancers and is mixed with acinar adenocarcinoma in most cases.<sup>41</sup> The pure form accounts for



**Fig. 5.** Ductal carcinoma exhibits cribriform and papillary growth patterns. The cribriform pattern shows small, narrow, slit-like spaces (a) ( $\times 200$ ), while the papillary pattern is characterized by the fibrovascular cores lined by columnar cells (b) ( $\times 200$ ).

only 0.2–0.4 % of prostate cancers.<sup>42,43</sup> In radical prostatectomies, the term “ductal adenocarcinoma” is reserved arbitrarily for those cancers with >50% ductal morphology. In biopsies, the term “adenocarcinoma with ductal features” is recommended even when it shows a pure ductal pattern. It is recommended that all ductal adenocarcinomas should be assigned Gleason grade 4 except for those with comedonecrosis, which are considered to represent Gleason grade 5.

Ductal adenocarcinoma should be differentiated from IDC and HGPIN. There is a significant morphological overlap between ductal adenocarcinoma and IDC. Nonetheless, ductal adenocarcinoma typically comprises tall pseudostratified columnar cells, which form cribriform glands with slit-like narrow spaces and/or papillary structures with true fibrovascular cores. In contrast, IDC comprises cuboidal cells, which form cribriform glands with round lumens and/or papillary structures without fibrovascular cores. In addition, basal cells are generally absent in ductal adenocarcinoma, while they are retained in IDC.<sup>14,35</sup> Unlike ductal adenocarcinoma, HGPIN lacks cribriform architectures and retains the basal cell layer.

PIN-like adenocarcinoma was previously considered a subtype of ductal adenocarcinoma in the 4<sup>th</sup> edition,<sup>5</sup> but it is now considered a subtype of acinar adenocarcinoma in the 5<sup>th</sup> edition.<sup>4</sup> It is characterized by large, discrete glands with a flat or tufted architecture lined by pseudostratified columnar cells with elongated hyperchromatic nuclei, mimicking high-grade PIN.<sup>44,45</sup> Unlike HGPIN, PIN-like carcinoma glands are more crowded and show the absence of basal cells on IHC. While ductal adenocarcinoma is characterized by true papillary and cribriform architectures, PIN-like carcinoma shows only flat and tufted growth patterns. It has a generally favorable prognosis and is assigned a Gleason score of 3 + 3 = 6.<sup>44,45</sup>

Ductal adenocarcinoma is an aggressive subtype of prostate cancer. The presence of ductal adenocarcinoma is a significant risk for biochemical failure and metastatic disease after definitive treatment, such as radical prostatectomy and radiotherapy.<sup>37,46</sup> Ductal adenocarcinoma appears less responsive to androgen deprivation therapy than acinar adenocarcinoma.<sup>46</sup> Patients with ductal adenocarcinoma treated by radical prostatectomy have a shorter disease-free survival time than those with acinar adenocarcinoma matched for a grade, stage, and nodal status.<sup>46</sup>

### Prostatic acinar adenocarcinoma

Most prostate cancers are acinar adenocarcinomas, which account for approximately 95% of all cancers in the prostate.<sup>1</sup> Prostate cancer is usually diagnosed by transrectal ultrasound (TRUS)-guided core needle biopsies. Typically, 10–14 tissue cores are obtained from different areas of the prostate, mostly corresponding to the peripheral zone.<sup>47</sup> Recently, multiparametric (mp) MRI has been used to guide the biopsies to specific lesions in the prostate.<sup>48</sup> This noninvasive technique shows a high sensitivity for clinically significant cancer with a Gleason score above 6.<sup>49</sup> Combining the two synergistic imaging techniques (i.e., mpMRI and real-time TRUS) may significantly improve the accuracy of targeting suspicious lesions in the prostate.

Prostatic acinar adenocarcinoma demonstrates a wide spectrum of morphology.<sup>13,27,50</sup> The major microscopic diagnostic criteria for prostate cancer include an infiltrative growth pattern, nuclear atypia, and loss of the basal cell layer. Minor criteria include prominent nucleoli, small round rigid lumens, intraluminal amorphous eosinophilic materials or crystalloids, blue-tinged mucinous secretions, and amphophilic cytoplasm. Only a few features are pathognomonic

of prostate cancer, including perineural invasion, glomerulation, and mucinous fibroplasia (or collagenous micronodules). Sometimes, prostatic acinar adenocarcinoma shows unusual growth patterns, such as atrophic, foamy gland, microcystic, and pseudohyperplastic, which mimic benign conditions and pose challenges to the diagnosis. Several histologic subtypes, including signet-ring-cell-like, sarcomatoid, and pleomorphic, are associated with highly aggressive clinical behavior.<sup>51</sup> Overall, the diagnosis of prostate cancer is based on a constellation of histologic features rather than relying on any single criterion alone.

The Gleason grading system is the cornerstone in the pathological evaluation of prostate cancer, which is largely based on architectural patterns and does not factor nuclear and cytological features into the grade. Since it was proposed in the 1960s, the Gleason grading system has undergone several modifications.<sup>13,27,52–54</sup> In biopsy specimens, the Gleason score is calculated by adding the primary grade to the highest grade, while the score in prostatectomy specimens is the sum of the primary grade and the second most prevalent grade. Currently, patterns 1 and 2 are no longer assigned to needle biopsy specimens and are rarely used in prostatectomy specimens. The percentage of pattern 4 should be reported in prostate biopsies containing Gleason score 7 tumors. Cribriform pattern and IDC should also be documented in prostate biopsies, as these features have prognostic significance.

A subset of prostatectomy specimens may show three different grading patterns, with the highest grade (pattern 5) being the least component. In these cases, pattern 5 is considered a tertiary pattern if it accounts for less than 5% of the tumor. Otherwise, pattern 5 will become the secondary pattern in the Gleason score. However, it remains controversial whether a tertiary Gleason pattern is recognized in radical prostatectomy specimens with Gleason scores of 3 + 3 = 6 and 4 + 4 = 8.<sup>13,27</sup>

An intuitive grade group (GG) system based on the Gleason grading system was initially proposed by the Johns Hopkins group and subsequently verified on a meta-analysis of more than 20,000 patients in a multi-institutional study.<sup>55,56</sup> This grade group has been adopted in the 4<sup>th</sup> WHO edition and referred to as “WHO grade.” The WHO GG closely correlates to the Gleason score and provides an advantage in communication with patients and clinicians, as it is a simpler categorization of prostate cancer. It is recommended in the 5<sup>th</sup> edition that this GG should be reported in conjunction with the Gleason score.

Recent genomic studies have revealed complex molecular alterations involved in the development of prostate cancer.<sup>57–59</sup> Genetic and epigenetic alterations, such as activation of MYC, shortening of telomeres, inactivation of GSTP1 by hypermethylation, and TMPRSS2-ERG gene fusion, are likely involved in the initial development of prostate cancer. Loss of PTEN, inactivation of TP53, gain of 8q24, and other mutations are associated with cancer progression. AR dysfunctions, such as AR gene amplification, mutation, rearrangement, and splice variants, lead to the failure of response to androgen deprivation treatment or castration resistance in prostate cancer.<sup>60,61</sup> Hereditary tumor syndromes, particularly homologous recombination repair defects and Lynch syndrome, are also implicated in the development of prostate cancer. Germline and somatic mutations in DNA repair genes, such as BRCA1, BRCA2, MSH2, ATM, and others, are present in up to 20% of aggressive prostatic carcinomas.<sup>62,63</sup> Patients with prostate cancer harboring homologous recombination repair (HRR) defects may respond favorably to the inhibition of poly (ADP-ribose) polymerase (PARP),<sup>64</sup> whereas



patients with DNA mismatch repair (dMMR)-deficient cancers are likely to benefit from immune checkpoint inhibitors.<sup>65</sup> Prostate cancer with distinct morphological features, such as IDC and cribriform histology, is more likely to harbor genetic defects of DNA repair genes.<sup>32,66</sup> It has been recommended that patients with aggressive prostate cancer may undergo germline and somatic testing for HRR mutations and dMMR deficiency to determine the eligibility for PARP inhibitor therapy or immune checkpoint blockade therapy.<sup>32</sup>

### Neuroendocrine tumors

Neuroendocrine (NE) tumors were previously discussed in separate GU organs in the 3<sup>rd</sup> and 4<sup>th</sup> editions,<sup>5,6</sup> but they are now consolidated into one chapter in the 5<sup>th</sup> edition, except for treatment-related neuroendocrine carcinoma.<sup>4</sup> The change is to be in alignment with the structure of the 5<sup>th</sup> edition WHO series.

In prostate cancer, NE differentiation is commonly defined as the expression of NE markers, such as synaptophysin, chromogranin, CD56, TTF1, NSE, and INSM1, by IHC. Almost all prostate cancers have scattered NE cells if studied extensively with multiple NE antibodies. However, the routine use of IHC for NE markers is not recommended for prostate cancer, as the clinical significance of focal NE neuroendocrine differentiation in otherwise conventional acinar adenocarcinoma remains uncertain. Prostate cancer may show Paneth cell-like NE differentiation characterized by coarse eosinophilic cytoplasmic granules. When present in cords or single cells, they may mimic Gleason pattern 5, but studies have shown that this morphology does not behave like high-grade prostate cancer. Therefore, excluding the non-gland-forming Paneth cell-like cells in the Gleason score is recommended.<sup>67,68</sup>

Well-differentiated neuroendocrine tumor (NET) (or carcinoid tumor) is extremely rare in the prostate.<sup>69,70</sup> It can only be diagnosed when it is not closely associated with conventional prostatic adenocarcinoma. The tumor typically shows bland, monotonous cells with mild nuclear atypia and speckled chromatin, which may form nests, acini, cords, or trabeculae. Mitoses are rare, and the Ki-67 labeling index is low. The tumor cells are immunoreactive for NE markers and negative for prostatic markers. Although it may present as a locally advanced disease, even with regional lymph node metastasis, prostatic well-differentiated NET has a favorable prognosis.

High-grade neuroendocrine carcinoma (NEC) is divided into small-cell and large-cell NECs based on nuclear size. An arbitrary cutoff of three lymphocyte diameters has been proposed in the 5<sup>th</sup> edition.<sup>4</sup> In the prostate, small-cell NEC (SCNEC) is far more common than large-cell NEC.<sup>69</sup> Like its lung counterpart, prostatic SCNEC may show solid, acinar, and trabecular growth patterns.<sup>71</sup> The tumor cells have a high nuclear/cytoplasmic ratio with "salt-and-pepper" chromatin, inconspicuous nucleoli, and scant cytoplasm. Nuclear molding may be present and geographic necrosis is common. Mitotic and apoptotic activities are high in SCNEC. A considerable subset (40–50%) of SCNECs are admixed with prostatic adenocarcinoma. Molecular studies indicate that SCNEC represents a progression of conventional prostatic adenocarcinoma with clonal expansion from its precursor lesion. Although a Gleason score is generally not assigned to SCNEC, it may be assigned to the adenocarcinoma component in mixed SCNECs. SCNEC is usually positive for various NE markers. While INSM1 shows a superior sensitivity for NE differentiation, CD56 is less specific for NE differentiation.<sup>72</sup> However, the expression of NE markers by IHC is not required if the tumor shows characteristic morphologic features

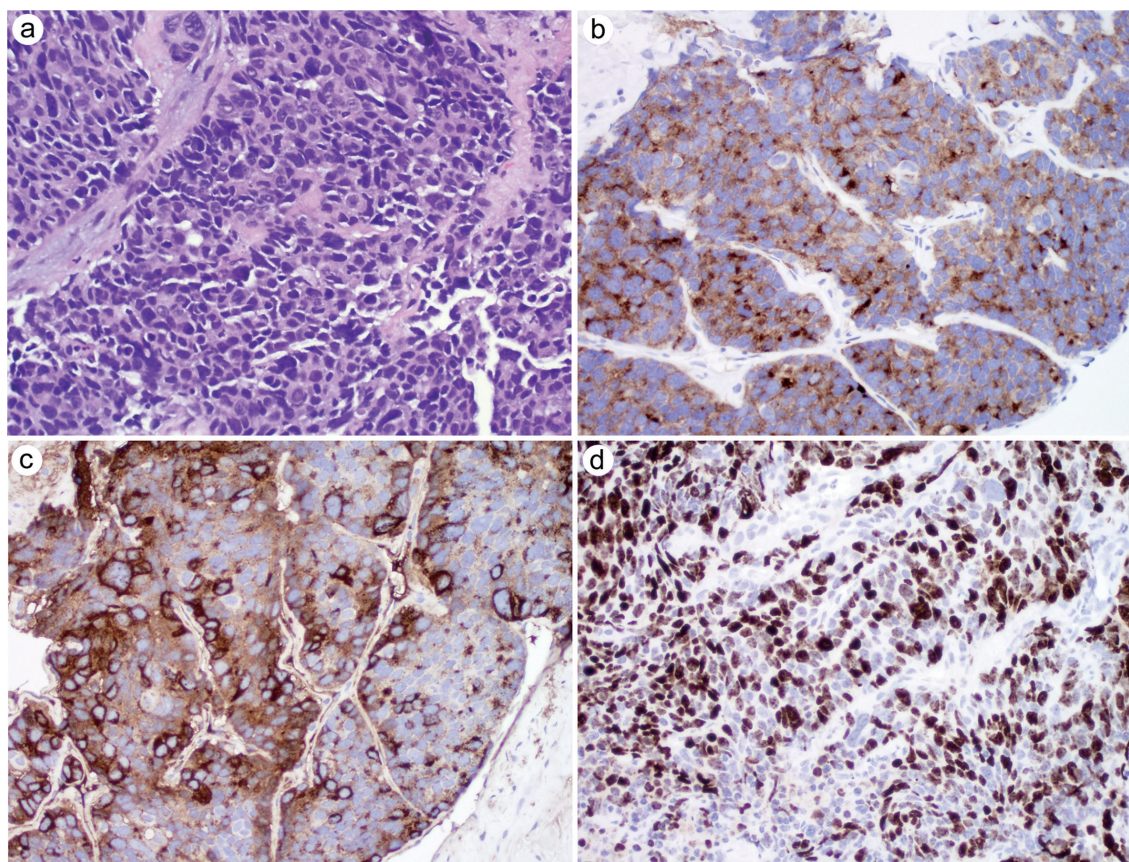
of SCNEC. Expressions of RB1, TP53, PTEN, and AR genes are often lost in SCNEC. Interestingly, the TMPRSS-ERG gene fusion can be detected in prostatic SCNEC by FISH or RT-PCR method, which may aid in determining the prostatic origin of SCNEC.<sup>73</sup> SCNEC is highly aggressive, and most patients develop metastatic disease with a dismal prognosis. Patients usually respond poorly to androgen deprivation treatment, but some may benefit from platinum-based chemotherapy regimens.<sup>74</sup>

Large-cell NEC (LCNEC) is extremely rare in the prostate. LCNEC may show nested, acinar, and trabecular growth patterns.<sup>75</sup> The tumor cells have high-grade large nuclei with prominent nucleoli. Necrosis and apoptosis are common. The mitotic activity is high, and the Ki-67 labeling index may be as high as 90%. The tumor is often diffusely positive for NE markers, such as synaptophysin, chromogranin, TTF1, INSM1, and CD56, but it is negative for prostatic markers, such as PSA, PSAP, and AR. Pure LCNEC is extremely rare. Most LCNECs are admixed with SCNEC or acinar adenocarcinoma in the prostate. LCNEC is a highly aggressive disease with rapid dissemination. Patients have a poor prognosis with a median survival time of less than one year.<sup>75</sup>

Treatment-related neuroendocrine prostatic carcinoma (t-NEPC) is a new entity in the 5<sup>th</sup> edition. It is designated as prostate cancer that exhibits complete or partial NE differentiation after androgen deprivation treatment. Studies have reported that t-NEPC is present in 10–15% of castration-resistant prostate cancers.<sup>76,77</sup> It is likely to be derived from transdifferentiation of castration-resistant prostate cancer via lineage plasticity characterized by AR indifference and activation of neural-like markers.<sup>78</sup> Genetic alterations, particularly mutations of the TP53, RB1, and PTEN genes, are likely to contribute to the transdifferentiation of castration-resistant prostate cancer to t-NEPC.<sup>76,78</sup> Patients with t-NEPC show clinical features similar to those with SCNEC. Morphologically, t-NEPC exhibits a spectrum of histological features, including pure SCNEC, mixed tumors with SCNEC and adenocarcinoma, and poorly differentiated adenocarcinoma (Fig. 6).<sup>77,79</sup> The IHC staining patterns of t-NEPC are similar to those of prostatic SCNEC. Patients with t-NEPC have a dismal prognosis with a median survival time of only seven months.<sup>76,79</sup> Pure SCNEC is associated with a significantly worse outcome than those with mixed histology.<sup>80</sup>

### Summary

Prostate cancer is a heterogeneous disease demonstrating a wide spectrum of pathological, clinical, and molecular variations. The 5<sup>th</sup> edition of the WHO Classification of Urinary and Male Genital Tumors makes important revisions in the diagnosis and classification of prostate cancer by incorporating new data. The cribriform pattern is not recognized as HG PIN and is now considered AIP, which is suspicious but falls short of IDC. The grading of IDC remains controversial, particularly when it is accompanied by invasive prostate cancer. PIN-like prostatic adenocarcinoma is now considered a subtype of acinar adenocarcinoma rather than ductal adenocarcinoma. Although t-NEPC shows a clinical behavior similar to SCNEC, it exhibits diverse histologic features ranging from high-grade adenocarcinoma to SCNEC. Recent molecular studies have revealed that genetic and epigenetic alterations in prostate cancer may contribute to its diverse clinicopathologic features. Although the application of molecular profiling has substantially impacted prostate cancer, morphology remains the foundation for diagnosing and classifying prostate cancer. The 5<sup>th</sup> edition provides a comprehensive approach with a combination of



**Fig. 6. Treatment-related neuroendocrine prostatic carcinoma.** It shows mixed features of small-cell carcinoma and poorly differentiated acinar adenocarcinoma (a) (×200). It is positive for synaptophysin (b) (×200) and chromogranin (c) (×200). It shows high mitotic activity with the K-67 labeling index >50% (d) (×200).

morphologic, immunohistochemical, genomic, and clinical data that may represent an optimal taxonomic paradigm of prostate cancer and improve the diagnosis and treatment of this complex disease.

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#### Author contributions

CCG was involved in study design, interpretation of data, manuscript writing, and critical revision. BC was involved in manuscript writing and critical revision. All authors have made a significant contribution to this study and have approved the final manuscript.

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