

Prostatic cancers: understanding their molecular pathology and the 2016 WHO classification

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ABSTRACT

Accumulating evidence suggests that prostatic cancers represent a group of histologically and molecularly heterogeneous diseases with variable clinical courses. In accordance with the increased knowledge of their clinicopathologies and genetics, the World Health Organization (WHO) classification of prostatic cancers has been revised. Additionally, recent data on their comprehensive molecular characterization have increased our understanding of the genomic basis of prostatic cancers and enabled us to classify them into subtypes with distinct molecular pathologies and clinical features. Our increased understanding of the molecular pathologies of prostatic cancers has permitted their evolution from a poorly understood, heterogeneous group of diseases with variable clinical courses to characteristic molecular subtypes that allow the implementation of personalized therapies and better patient management. This review provides perspectives on the new 2016 WHO classification of prostatic cancers as well as recent knowledge of their molecular pathologies. The WHO classification of prostatic cancers will require additional revisions to allow for reliable and clinically meaningful cancer diagnoses as a better understanding of their molecular characteristics is obtained.

INTRODUCTION

Prostatic cancers possess substantial heterogeneity in their molecular alterations and variable clinical courses [1–43]. An increased understanding of their morphologies, immunohistochemistries, and associations with clinical features has mandated the World Health Organization (WHO) to revise its classification of prostatic cancers. Additionally, emerging evidence suggests that prostatic cancers can be classified into various subtypes, which have distinct molecular pathologies and clinical features. This review introduces and briefly summarizes the clinicopathologically important issues of the new 2016 WHO classification of prostatic cancers [1] as well as presents a new understanding of their molecular characteristics.

THE 2016 WHO CLASSIFICATION

The 2004 WHO classification of prostatic cancers [44] precedes the current 2016 classification [1] that

reflects the remarkable gains in our knowledge of the pathologies and genetics of prostatic cancers acquired during the intervening 12 years. The main differences between the previous and new WHO classifications are as follows: i) The Gleason grading system is modified to more accurately represent clinical outcomes. ii) Intraductal carcinoma of the prostate (IDC-P) and large cell neuroendocrine carcinoma (LCNEC) are newly recognized as subtypes of prostatic carcinoma. iii) The histological variants of acinar adenocarcinoma are updated. iv) New immunohistochemical markers are described, which are useful for diagnosis. Perspectives on the important issues addressed in the revised 2016 WHO classification are described below.

Grading of prostatic adenocarcinoma

Gleason grading, the standard approach for assigning a histological grade to prostatic adenocarcinomas (Figure 1), is modified in the 2016 WHO classification

[1, 4] according to discussions at the meeting of the International Society of Urological Pathology (ISUP) in 2014 [45]. The modifications are as follows: i) Cribriform glands and glomeruloid glands should be assigned Gleason pattern (GP) 4, regardless of morphology. ii) The GP of mucinous adenocarcinoma should be determined according to its underlying growth pattern. iii) IDC-P should not be assigned a GP, and a comment about its association with aggressive prostatic cancer should be provided. iv) GP 4 should include cribriform, fused, and poorly formed glands. v) GP 4 should be diagnosed under $10 \times$ magnification. vi) Occasional/seemingly poorly formed glands between well-formed glands should be assigned GP 3. vii) In cases with a borderline morphology between GP 3 and GP 4, with crush artifacts, GP 3 should be favored. viii) Solid medium-to-large nests with a rosette-like structure should be assigned GP 5. ix) The presence of unequivocal comedonecrosis, even if focally observed, should be assigned GP 5. x) When the highest GS is $3 + 4 = 7$ or $4 + 3 = 7$, the percentage of GP 4 tumors should be reported [1, 45].

A new grading system specified by the 2016 WHO classification is supported by a broad consensus reached at the 2014 ISUP conference [45]. The histological definitions within this new grading system are provided in Table 1. The basis of this new grading system was proposed in 2013 [46] and was subsequently validated by a multi-institutional study [47]. The 5-year biochemical risk-free survival rates for the grade groups 1–5 are 96%, 88%, 63%, 48%, and 26%, respectively [47]. This new grading system can be used to predict mortality risk after radical prostatectomy for patients with grade groups 4 and 5. Prostatic cancer-specific survival is significantly shorter for patients with grade group 5 than patients with grade group 4 for the biopsy (hazard ratio [HR] = 2.13, 95% confidence interval [CI] = 1.37–3.30) and radical prostatectomy groups (HR = 2.38, 95% CI = 1.74–3.28) [48].

Subtypes of prostatic carcinoma

The new 2016 WHO classification updates the subtypes of prostatic carcinoma, as shown in Table 2. The newly adopted IDC-P and modification of

neuroendocrine carcinoma (see below) are novel changes, acquired through updated knowledge of their biology and clinical usefulness. The histopathological and molecular characteristics of each subtype are discussed below, except for acinar adenocarcinoma. The latter comprises most prostatic cancers and is described according to histopathology and genomics in other sections.

IDC-P

The 2016 WHO classification includes IDC-P as a new subtype of prostatic cancer [1, 4]. The definition of IDC-P is an “intra-acinar and/or intraductal neoplastic epithelial proliferation that has some features of high-grade prostatic intraepithelial neoplasia (HGPIN) but exhibits much greater architectural and/or cytological atypia, typically associated with high-grade, high-stage prostate carcinoma” [1, 4]. IDC-P manifests as the intraductal spread of advanced prostatic carcinoma, but may also reflect a preinvasive carcinoma derived from HGPIN [49, 50]. Isolated IDC-P without concomitant prostate carcinoma is detected in only 0.26% of prostate biopsies [51].

Genetically, in radical prostatectomy specimens, loss of heterozygosity (LOH) is detected in 29% and 60% in GP 4 carcinomas and IDC-Ps, respectively, whereas LOH is rarely observed in GP 3 carcinomas or HGPINs [52]. Although *ERG* rearrangement is less common in HGPINs, it is frequently observed (75%) in IDC-Ps [1, 53]. Loss of immunohistochemical detection of cytoplasmic PTEN is frequently observed (84%) in IDC-Ps, but rarely in HGPINs [1, 54]. Results from the above-mentioned genetic and immunohistochemical studies support the view that IDC-P represents a lesion distinct from HGPIN and a late event in prostate carcinogenesis [1, 4].

Ductal adenocarcinoma

Ductal adenocarcinoma is the second most common (3%) subtype of prostatic carcinoma, which is better characterized clinically, histologically, and molecularly than other subtypes. Mixed ductal–acinar adenocarcinoma is more common than pure ductal adenocarcinoma, which accounts for only 0.2%–0.4% of prostatic carcinomas [1]. Ductal adenocarcinomas are

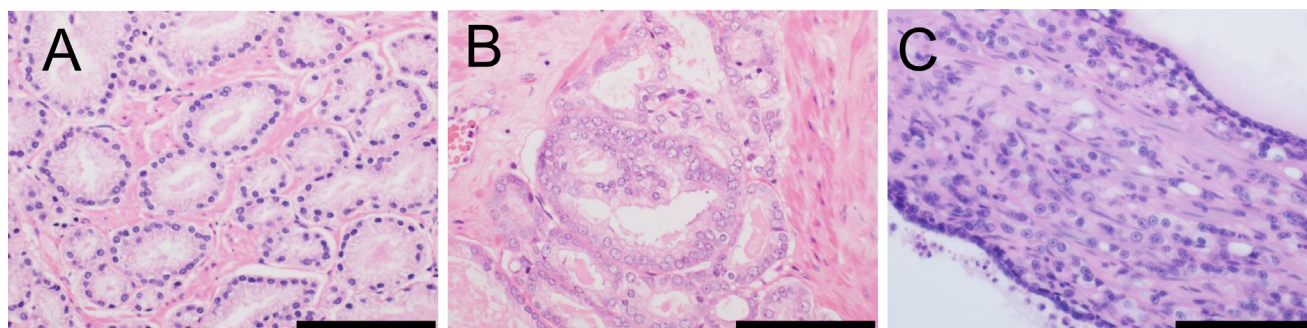


Figure 1: Morphology of distinct Gleason patterns (GPs). (A) Individual, discrete, well-formed glands (GP 3). (B) Fused/cribriform glands (GP 4). (C) Individual neoplastic cells infiltrating the stroma between benign glands (GP 5). Scale bar, 100 μ m.

Table 1: Histological definitions of the new grading system (Grade Groups) [1]

Grade Groups	Histological Definitions
Grade Group 1	Gleason score ≤ 6 Only individual, discrete, well-formed glands
Grade Group 2	Gleason score $3 + 4 = 7$ Predominantly well-formed glands with a few poorly-formed/fused/cribriform glands
Grade Group 3	Gleason score $4 + 3 = 7$ Predominantly poorly-formed/fused/cribriform glands with a few well-formed glands
Grade Group 4	Gleason score $4 + 4 = 8$; $3 + 5 = 8$; $5 + 3 = 8$ Only poorly-formed/fused/cribriform glands; Predominantly well-formed glands with a few areas lacking glands (or with comedonecrosis); Predominantly lacking glands (or with comedonecrosis) and a few well-formed glands
Grade Group 5	Gleason score 9–10 Lacking gland formation (or with comedonecrosis) with/without poorly-formed/fused/cribriform glands

frequently located in the periurethral area. Periurethral ductal adenocarcinomas often protrude into the urethra; hematuria and other urinary tract symptoms are common manifestations. The clinical findings for peripheral ductal adenocarcinomas are similar to those of acinar adenocarcinomas. For example, most patients have elevated levels of serum prostate-specific antigen (PSA); however, the levels are lower than those in patients with acinar adenocarcinoma. Clinical stage is often more advanced than that of typical acinar adenocarcinoma. In a population-based study, 12% of patients with ductal adenocarcinoma presented with distant metastasis compared with 4% of patients with acinar adenocarcinoma [55]. Ductal adenocarcinoma may metastasize to the penis, testis, and lung [1, 2, 56].

Ductal adenocarcinoma often presents as an exophytic, villous/polypoid mass arising from the verumontanum. The macroscopic appearance of peripheral ductal adenocarcinoma is similar to that of acinar adenocarcinoma [1, 2]. Ductal adenocarcinomas form ducts/acini with cribriform or papillary growth of tall columnar cells with elongated, frequently pseudostratified nuclei and an amphophilic, but occasionally clear, cytoplasm. Typical observations include large nucleoli, coarse chromatin, mitotic figures, and intraluminal necrotic debris. Papillary infoldings have fibrovascular cores, and cribriform spaces are typically slit-like. GP is usually 4 and is less frequently assigned GP 3 (PIN-like pattern) or GP 5 (solid or comedo pattern).

TMPRSS2-ERG fusion occurs in 11% of the ductal component and in 5% of the acinar component of a mixed tumor, compared with 45%–50% of pure acinar adenocarcinomas [57, 58]. Similarly, *PTEN* is infrequently lost in the ductal and acinar components of mixed tumors and more often lost in pure acinar adenocarcinoma cells. These concordant characteristics of ductal and acinar components of mixed tumors suggest their clonal relationship. Gene expression profiling revealed remarkable similarity between ductal and typical acinar

adenocarcinomas, with only 25 gene transcripts showing significant differences [59]. Transcripts significantly overexpressed in ductal adenocarcinomas include *CD24*, *CDH23* (cadherin-like 23), and *PRLR* (prolactin receptor). *CD24* and *CDH23* encode proteins with cell adhesion-related properties. *CD24* is a potential oncogene that is overexpressed in diverse malignancies, including prostatic cancer [60]. *PRLP* promotes ductal morphogenesis and is implicated in the development of the normal, hyperplastic, and neoplastic prostate. PRLP signaling contributes to tumorigenesis of the prostate and breast; therefore, targeting PRLP signaling attracts attention as a potential personalized therapy for prostatic cancer [61]. According to a recent study, somatic copy-number alterations (SCNAs) of ductal adenocarcinomas are similar to those of acinar adenocarcinomas of patients with a high GS (8–9) [62]. Chromosome 6q15 is frequently deleted in ductal adenocarcinoma cells, and deletions of *MAP3K7*, which is harbored in this locus, are associated with early biochemical recurrence, advanced tumor stage, and high GS. *MAP3K7* deletions are associated well with the *TMPRSS2-ERG* absence, which is more common in ductal than acinar adenocarcinomas [58, 63].

Neuroendocrine carcinoma

LCNEC is newly adopted as a variant of neuroendocrine carcinoma, which comprises adenocarcinoma with neuroendocrine differentiation, small cell neuroendocrine carcinoma (or small cell carcinoma [SmCC]), and LCNEC.

Adenocarcinoma with neuroendocrine differentiation is defined as typical acinar or ductal adenocarcinoma without a detectable neuroendocrine morphology (such as nuclear molding and peripheral palisading) and with neuroendocrine differentiation, demonstrated only by immunohistochemical detection of at least one of three neuroendocrine markers (CHGA [chromogranin A], SYP [synaptophysin], or NCAM1 [CD56, NCAM]). Most studies did not detect an effect of neuroendocrine

Table 2: The 2016 and 2004 WHO classifications of prostatic carcinoma [1, 44]

2016 WHO classification	2004 WHO classification
Glandular neoplasms	Glandular neoplasms
Acinar adenocarcinoma	Acinar adenocarcinoma
Intraductal carcinoma	Ductal adenocarcinoma
Ductal adenocarcinoma	
Urothelial carcinoma	Urothelial carcinoma
Squamous neoplasms	Squamous neoplasms
Adenosquamous carcinoma	Adenosquamous carcinoma
Squamous cell carcinoma	Squamous cell carcinoma
Basal cell carcinoma	Basal cell carcinoma
Neuroendocrine tumors	Neuroendocrine tumors
Adenocarcinoma with neuroendocrine differentiation	Endocrine differentiation within adenocarcinoma
Small cell neuroendocrine carcinoma	Small cell carcinoma
Large cell neuroendocrine carcinoma	

WHO, World Health Organization.

differentiation on clinical outcomes [1, 64]. Therefore, routine use of immunohistochemistry is not recommended to detect neuroendocrine differentiation in typical adenocarcinomas that lack neuroendocrine morphology.

Prostatic SmCC is extremely aggressive and is resistant to androgen-deprivation therapy (ADT). SmCC is characterized by scant cytoplasm (high nuclear to cytoplasmic ratio), hyperchromatic nuclei without conspicuous nucleoli, frequent mitosis, fragility, crush artifacts, nuclear molding, rosette-like structures, and geographic necrosis [1–3, 64]. Of importance, adenocarcinoma is initially diagnosed in one-third of patients with SmCC, followed by ADT, and subsequent diagnosis of SmCC. Approximately 50% of patients with SmCC present pure SmCC, whereas there is an admixture with acinar adenocarcinoma in the remaining patients. Immunohistochemically, prostatic SmCCs are positive for one or more of the three neuroendocrine markers and are infrequently positive for PSA and other prostatic markers. Immunohistochemistry reveals that SmCCs infrequently express TP63 (p63) and high-molecular weight cytokeratins, which are not detectably expressed by adenocarcinomas. Further, > 50% of prostatic SmCCs express NKX2-1 (TTF-1), limiting the utility of excluding a lung origin [1–3, 64].

Approximately 50% of prostatic SmCCs harbor *TMPRSS2-ERG*. Notably, unlike typical adenocarcinomas, such SmCCs do not consistently express ERG immunohistochemically, likely because of the lower frequency of expression of the androgen receptor (AR) by these cells [1–3, 64]. Further, an increased *AR* copy number may be associated with *TMPRSS2-ERG* in SmCCs. Inactivation of the tumor suppressors *RB1* and *TP53* commonly occurs in prostatic SmCCs, similar to their counterparts in the lung and other organs [65].

Inactivation of these genes through allelic loss or mutation, as well as lack of expression of their encoded proteins, is characteristic of prostatic SmCCs. The loss of *RB1* expression occurs nearly universally in SmCCs and rarely occurs in high-grade acinar adenocarcinoma. Therefore, the loss of *RB1* likely represents a critical event in the development of prostatic SmCC and may serve as a diagnostic marker and potential therapeutic target [65]. In xenograft models, prostatic SmCC is characterized by marked upregulation of *UBE2C* and other mitotic genes in the absence of *AR*, *RB1*, and *CCND1* (*cyclin D1*) expression [66].

Prostatic LCNEC is an aggressive tumor, with a mean survival of seven months, similar to SmCC [67]. LCNEC is extremely rare, particularly in its pure form. The largest series analyzed documents seven cases of LCNEC, among which only one case was a pure LCNEC and apparently de novo. Most cases arise in the setting of an existing acinar adenocarcinoma with a history of long-term ADT [67]. LCNEC is characterized by tumor cells with abundant cytoplasm, coarse nuclei with prominent nucleoli, and growth patterns of large nests, sheets, cords, and peripheral palisading. Diagnosing LCNEC requires observing these characteristic morphologies combined with immunohistochemical detection of at least one of the three neuroendocrine markers. LCNEC is negative or only focally positive for PSA using immunohistochemical detection. The Ki-67 index is typically > 50% and regional necrosis is commonly observed [1–3, 64]. Further accumulation of LCNEC cases is required to identify the clinicopathological and molecular hallmarks of this disease.

Basal cell carcinoma (BCC)

BCC, which is extremely rare, resembles adenoid cystic carcinomas of the salivary glands. Microscopically, typical growth structures of BCC include adenoid cystic/

cribriform patterns and small solid nests with palisading. BCC is typically characterized by hyperchromatic nuclei, a high nuclear to cytoplasmic ratio, lumens lined by eosinophilic cells, and desmoplastic or myxoid stroma. Immunohistochemical detection of BCL2 and a higher Ki-67 index favor a diagnosis of BCC vs basal cell hyperplasia [1, 2]. A subset of prostatic BCCs with adenoid cystic-like histology exhibits the *MYB* rearrangement, suggesting an independent entity [68].

Squamous cell carcinoma (SqCC) and adenosquamous carcinoma

Squamous neoplasms comprise SqCC and adenosquamous carcinoma [1–3, 69]. Prostatic SqCC accounts for < 0.6% of prostatic cancers. Adenosquamous carcinomas occur less frequently. SqCC can originate in the periurethral glands or prostatic acini as well as from the lining basal cells. Patients with SqCC or adenosquamous carcinoma present with bladder-outlet obstruction and dysuria. The mean survival of patients with SqCC ranges from 6 to 24 months. Approximately 50% of SqCCs and adenosquamous carcinomas arise in patients with prostatic acinar adenocarcinoma, subsequent to ADT or radiotherapy, and may occur in association with prostatic schistosomiasis. SqCC often metastasizes to the bone, and the metastases are more frequently osteolytic than osteoblastic, which is observed in typical prostatic adenocarcinomas [1–3, 69].

The tumors are usually large, reaching 65 mm in the largest dimension. Prostatic SqCC must be distinguished from the involvement of SqCC of bladder origin and from squamous metaplasia occurring after ADT. Adenosquamous carcinoma is defined by the presence of SqCC and a glandular (acinar) adenocarcinoma component. The adenocarcinoma component is often of a high grade, whereas the grade of the SqCC component varies. Malignant squamous cells are often negative for PSA using immunohistochemistry [1–3, 69]. To my knowledge, molecular studies of prostatic SqCC or adenosquamous carcinoma are not published.

Urothelial carcinoma

Prostatic urothelial carcinoma can arise from the urothelium of the prostatic urethra and the proximal portions of the prostatic ducts [1–3, 70]. Most cases of prostatic urothelial carcinoma present concurrently with bladder carcinoma. Patients present with hematuria, irritation, and obstructive symptoms. The clinical outcome of patients with prostatic urothelial carcinoma is usually dismal; however, the prognosis of patients with pure urothelial carcinoma *in situ* is excellent.

Prostatic urothelial carcinoma has a marked propensity for growth within prostatic ducts and acini with solid cylinders, with or without comedo necrosis [1–3, 70]. The tumor cells exhibit marked nuclear pleomorphism with numerous mitoses. Spreads between the basal cells and secretory cells in a single-cell pagetoid pattern are

frequently observed. Stromal invasion is characterized by irregular nests and cords with a desmoplastic response. Immunohistochemically, tumors are positive for urothelial markers, including GATA3, and negative for prostate markers, including PSA and NKX3-1 (NKX3.1). There is no information, to my knowledge, indicating that the molecular features of this tumor differ from those of bladder urothelial carcinoma [1–3, 70].

New variants of acinar adenocarcinoma of the prostate

The histological variants of acinar adenocarcinoma are updated in the 2016 WHO classification (Table 3). These variants are clinically important due to difficult diagnoses and prognostic differences, compared with typical acinar adenocarcinoma [3]. The histological variants are atrophic, pseudohyperplastic, microcystic, foamy gland, mucinous (colloid), signet ring-like cell, pleomorphic giant cell, and sarcomatoid. The newly recognized variants in the 2016 WHO classification are microcystic and pleomorphic giant cell [1]. Variants that are challenging to diagnose include benign-looking atrophic, pseudohyperplastic, microcystic, and foamy gland. The signet ring-like cell, pleomorphic giant cell, and sarcomatoid variants are associated with higher mortality than typical acinar adenocarcinomas.

Sarcomatoid carcinoma, a variant of acinar adenocarcinoma, is also known as so-called carcinosarcoma. Sarcomatoid carcinoma represents a biphasic malignant tumor comprising adenocarcinoma and sarcomatoid components [1–3, 71]. Immunohistochemical analysis detects the expression of prostate markers, including PSA and NKX3-1, in cells of the adenocarcinoma component, whereas mesenchymal markers are detected in the sarcomatoid component. Approximately 50% of patients have a history of acinar adenocarcinoma treated with ADT, radiotherapy, or both. Therefore, the sarcomatoid component is likely to have evolved from the adenocarcinoma component. An LOH analysis found that adenocarcinoma and sarcomatoid components share a clonal origin [72]. A recent genomic assay using fluorescence in-situ hybridization found that the adenocarcinoma and sarcomatoid components harbor *ERG* fusions, indicating the epithelial origin of the sarcomatoid component [73].

Microcystic adenocarcinoma is a deceptively benign-appearing variant of acinar adenocarcinoma [74]. Microcystic glands are, on average, 10-times larger than glands of typical acinar adenocarcinoma. Intraluminal crystalloids and wispy blue intraluminal mucin are often detected. Atrophic features are observed focally, however the neoplastic lining cells exhibit a moderate amount of cytoplasm. Most microcystic adenocarcinomas possess alpha-methylacyl-CoA racemase (AMACR), and all of these tumors show

Table 3: Variants of acinar adenocarcinoma (AC) of the prostate in the 2016 WHO classification [1]

Variants	Clinical Features
Atrophic	Resembling benign atrophic glands; cytoplasmic volume loss; GP 3
Pseudohyperplastic	Resembling benign luminal cell hyperplasia with papillary infoldings; GP 3; <i>HOXB3</i> G84E-related familial prostate cancer [36]
Microcystic	Benign-looking; dilated glands 10-times larger than glands of typical acinar AC; intraluminal crystalloids and wispy blue mucin; GP 3
Foamy gland	Benign-looking, abundant foamy cytoplasm; pyknotic nuclei
Mucinous (colloid)	At least 25% composed of extracellular mucin pools
Signet ring-like cell	Very aggressive; at least 25% composed of signet ring-like cells
Pleomorphic giant cell	Very aggressive; giant anaplastic cells with pleomorphic nuclei; lacking a spindle cell component
Sarcomatoid	Very aggressive; biphasic exhibiting epithelial and mesenchymal differentiations

AC, adenocarcinoma; GP, Gleason pattern; WHO, World Health Organization.

evidence of complete basal cell loss, as determined by the immunohistochemical analysis of TP63 and 34 β E12. The assigned GP is 3.

Pleomorphic giant cell adenocarcinoma, which is an extremely rare variant, comprises giant anaplastic cells with pleomorphic nuclei and lacks a spindle cell component [75, 76]. In addition to the pleomorphic giant cell element, a coexistent adenocarcinoma of Gleason score (GS) 9 is usually present. Evidence of focal ductal adenocarcinoma, squamous cell carcinoma, or SmCC is observed in some cases. The clinical course is typically very aggressive [1, 75, 76].

Immunophenotype

For a diagnosis of prostate cancer, immunohistochemical analyses of expressions of PSA, prostatic acid phosphatase (PAP), high-molecular-weight cytokeratin (34 β E12), TP63, and AMACR are helpful. The 2016 WHO classification introduces new immunohistochemical markers, including prostein (also known as P501S) and NKX3-1. Because PSA and PAP expression can decrease after ADT, NKX3-1 and prostein can be of use in such cases. Staining for prostein can be detected in cases of urinary bladder adenocarcinoma; however, its characteristic granular perinuclear pattern is not observed [77]. Nuclear NKX3-1 staining is highly specific for prostatic adenocarcinoma [78]. Prostatic markers of limited diagnostic utility, due to sensitivity and/or specificity, include prostate-specific membrane antigen (PSMA), ERG, AR, and AMACR.

An example of metastatic carcinoma of unknown origin that has spread to a neck lymph node is shown in Figure 2. Microscopically, the tumor is shown to be composed of round cells with solid growth (Figure 2A). The tumor stained positive for NKX3-1 (nuclear staining; Figure 2B), prostein (P501S) (granular perinuclear pattern;

Figure 2C), PSA (Figure 2D), PSMA (Figure 2E), and AR (nuclear staining; Figure 2F). These immunohistochemical results support a diagnosis of metastatic prostatic cancer.

MOLECULAR CHARACTERISTICS OF PROSTATIC CANCER

With the emergence of high-throughput sequencing techniques, detailed molecular profiles of prostatic cancer subtypes have been identified. The Cancer Genome Atlas (TCGA) research network identified genomic and other molecular alterations in different types of cancers, including prostatic cancers. The identification of subtypes with specific underlying genetic abnormalities can help identify potential therapeutic targets and predict effects on patient prognosis. In this section, the recently identified molecular characteristics of prostatic cancers are introduced.

Comprehensive molecular subtyping by TCGA research network [5]

The TCGA research network conducted a comprehensive molecular characterization of 333 primary prostatic cancers, including data on somatic mutations, gene fusions, SCNAs, gene expression, and DNA methylation [5]. Of these primary cancers, 75% were classified into seven subtypes, defined by either specific gene fusions of *ETS* transcription family members (*ERG*, *ETV1*, *ETV4*, and *FLII*) or mutations (*SPOP*, *FOXA1*, and *IDH1*) (Figure 3). The *ETS*-positive subset, comprising 59% of all cases, was enriched in *PTEN* deletions. The *SPOP*-mutant subset, comprising 11% of all cases, harbored distinct SCNA profiles (including deletions of *CHD1*, 6q, and 2q), consistent with results from previous studies [14, 79]. The *SPOP*-mutant/*CHD1*-deleted subset harbored specific molecular characteristics, including high

levels of DNA methylation, homogeneous gene expression patterns, and frequent overexpression of *SPINK1* mRNA. *SPOP*- and *FOXA1*-mutant subsets shared similar mRNA, SCNA, and DNA methylation profiles. Furthermore, a new and genomically distinct *IDHI*-mutant subset was identified. The mRNA clusters were tightly correlated with the *ETS*-fusion status: mRNA cluster 1 consisted of the *ETS*-negative subset, whereas mRNA clusters 2 and 3 both contained elements of the *ETS*-positive subset. MicroRNA results showed a similar pattern, indicating a general difference between the *ETS*-positive and -negative subsets. Clustering of expressed protein resulted in three distinct subgroups, with protein cluster 3 exhibiting elevated PIK3/AKT, MAP kinase, and receptor tyrosine kinase activities. However, this cluster was not enriched in genomic alterations of the analogous signaling pathways, and there were few associations of increased pathway activity.

The overall mutational burden was 0.94 mutations per megabase (median, range 0.04–24 per megabase), which corresponds to 19 nonsynonymous mutations per tumor genome (median, 13–25, 25th and 75th percentiles, respectively) [5]. This result is consistent with data from previous genome-scale sequencing studies of localized prostatic cancers [7, 14] and is lower than the mutational burden of metastatic prostatic cancers [8, 20, 21]. These findings confirmed that prostatic cancers carry a lower mutational burden than many other types of carcinoma that are not associated with a substantial exposure to a mutagen [80, 81]. The mutational significance analysis yielded 13 significantly mutated genes, including six previously identified mutations (*SPOP*, *TP53*, *FOXA1*, *PTEN*, *MED12*, and *CDKN1B*) and seven previously unidentified mutations (*BRAF*, *CTNNB1*, *HRAS*, *ATM*, *NKX3-1*, *AKT1*, and *ZMYM3*). Novel somatic mutations of *BRAF* (2.4%),

NKX3-1 (1%), and *ZMYM3* (2%) were included. Although the overall mutational burden was substantially higher in metastatic cancers, consistent with previous studies [20, 22], the primary and metastatic cancers were remarkably similar in their subtype distributions, except that metastatic cancers harbored no *IDHI* mutations.

Clustering results of the most variably hypermethylated CpG islands led to the identification of four epigenetically distinct groups. Nearly two-thirds of all *ERG*-rearranged cancers belonged to a cluster with only moderately elevated levels of methylation (DNA methylation cluster 3), whereas the remaining *ERG*-rearranged cancers comprised a distinct hypermethylated cluster (cluster 1) that was almost exclusively occupied by *ERG*-rearranged cancers. DNA methylation cluster 1 contained twice the number of hypermethylated loci in comparison with cluster 3, and the epigenetic patterns were substantially different from those of *ETV1*- and *ETV4*-rearranged cancers, which exhibit more heterogeneous methylation levels. This diversity among *ETS*-positive subtypes is consistent with results from previous studies that suggest substantial molecular and clinicopathological differences between *ERG*- and non-*ERG* *ETS*-rearranged cancers [82, 83]. *SPOP*- and *FOXA1*-mutant subsets showed homogeneous epigenetic profiles. These subsets belong almost exclusively to DNA methylation cluster 2, a cluster that also contains a majority of *ETV1*- and *ETV4*-, but not *ERG*-, rearranged subsets. Importantly, the *IDHI*-mutant subset harbors greater levels of genome-wide DNA hypermethylation. Integration of these epigenetic data with mRNA expression results yielded 164 genes that were epigenetically silenced in the subsets examined. *STAT6* was silenced predominantly in *ETS*-rearranged subsets, whereas *HEXA* was silenced frequently in the *SPOP*-mutant subset. As expected, the *IDHI*-mutant

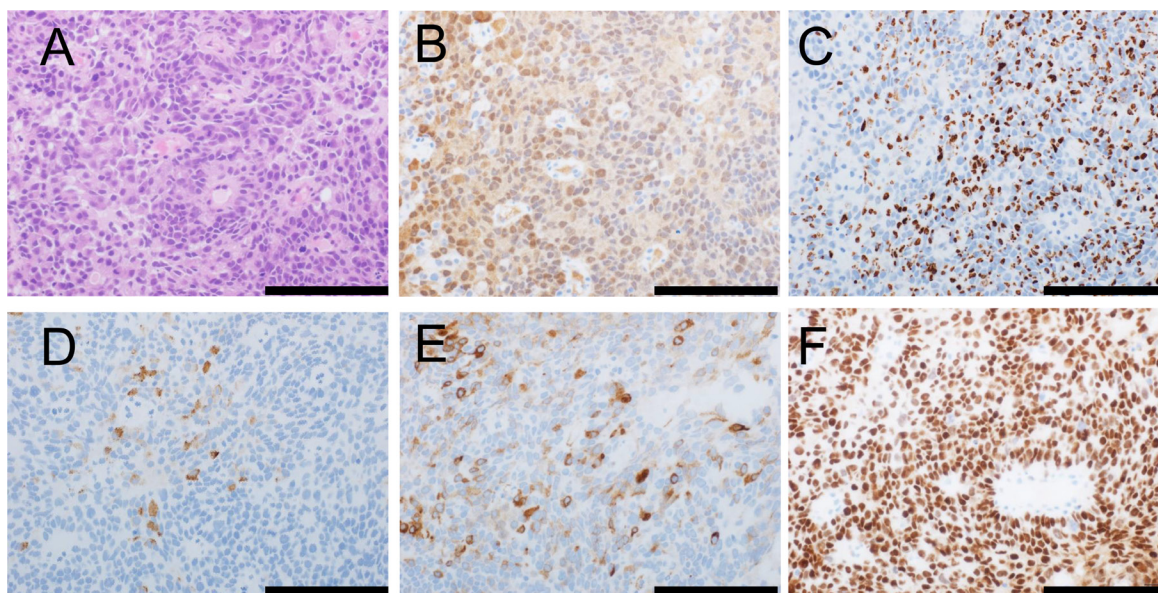


Figure 2: Morphology and immunophenotype of metastatic prostatic cancer in a neck lymph node. Morphologically, the tumor is composed of round cells with solid growth (hematoxylin and eosin staining) (A). The tumor stained positive for NKX3-1 (B; nuclear staining), prostatein (P501S) (C; granular perinuclear pattern), PSA (D), PSMA (E), and AR (F; nuclear staining). Scale bar, 100 μ m.

subset harbored the greatest number of epigenetically silenced genes among all prostatic cancers.

During assessments of AR activity, *ETS*-rearranged subsets showed variable AR transcriptional activity, whereas *SPOP*- and *FOXA1*-mutant subsets showed the highest AR transcriptional activity among all genotypically distinct subsets. Consistent with these findings, *SPOP* mutations were previously implicated in androgen signaling because both AR and AR coactivators undergo deregulation in the presence of *SPOP* mutations [84–86]. AR signaling was more frequently altered in metastatic samples, most often by amplifications or mutations of *AR*, which were essentially absent in localized prostatic cancers [87].

Several studies have indicated that DNA repair pathways are disrupted in a subgroup of prostatic cancers [38, 88, 89]. The poly ADP ribose polymerase (PARP) inhibitor olaparib is effective in some patients with prostate cancer [90]. Nearly 20% of all cases harbored the inactivation of DNA repair genes, including *BRCA2* (3%), *BRCA1* (1%), *CDK12* (2%), *ATM* (4%), *FANCD2* (7%), and *RAD51C* (3%) [5]. Recent evidence suggests that the incidence of germline mutations in genes mediating DNA repair processes was 11.8% in patients with metastatic

prostatic cancer, which is significantly higher than in patients with localized prostatic cancer [38].

ETS family

In 2005, genetic rearrangements of androgen-regulated genes with members of the *ETS* transcription factor family were identified in more than half of prostatic cancer cases [6, 10, 91, 92]. The most common rearrangement manifests as a fusion of the 5' untranslated region of the androgen-regulated *TMPRSS2* gene with the coding area of *ERG*, accounting for 90% of *ETS* family fusions [92, 93]. Other members of the *ETS* family members include *ETV1*, *ETV4*, *ETV5*, and *FLI1* [93, 94]. *ETS* rearrangements have been occasionally detected in HGPIN and appear to be an early event in prostate carcinogenesis [95–97]. *ETS*-rearranged cancers are notably enriched in genomic alterations in a number of canonical pathways, including *PTEN* deletions, *TP53* alterations, PIK3 pathway alterations, and the specific amplification of 3p [98]. *ERG* overexpression accelerates prostatic carcinogenesis when combined with *PTEN* deletions [12, 13]. *PTEN* deletions are associated with metastatic disease, higher GP, higher risk of progression, recurrence after

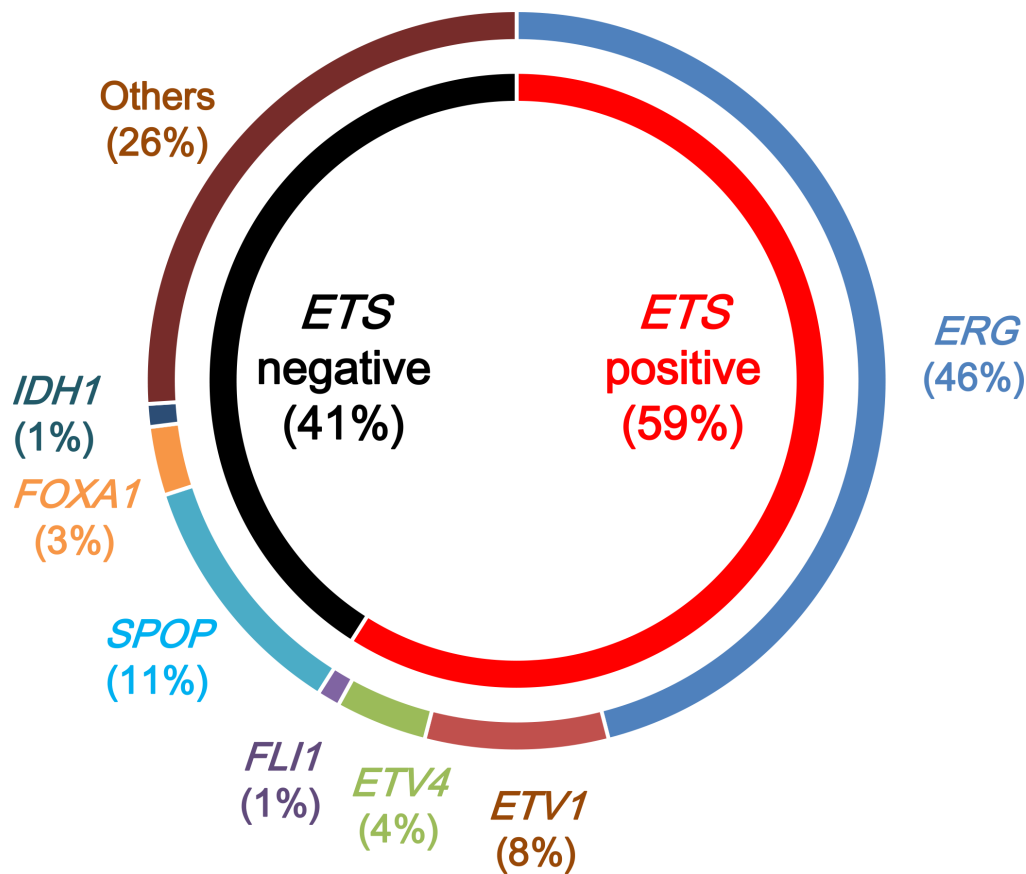


Figure 3: Molecular subtypes of primary prostatic cancers by The Cancer Genome Atlas. Primary prostatic cancers can be classified into those with rearrangements in *ETS* family transcription factors (*ERG*, *ETV1*, *ETV4*, and *FLI1*) (*ETS* positive) and those without *ETS* rearrangements (*ETS* negative). *ETS*-positive prostatic cancers are classified by the specific *ETS*-fusion gene member involved: *ERG*, *ETV1*, *ETV4*, or *FLI1*. *ETS*-negative prostatic cancers are classified by mutations in *SPOP*, *FOXA1*, and *IDH1*.

therapy, and death from diseases [99–104]. *ETS*-rearranged prostatic cancers exhibit characteristic SCNAs with a specific pattern of genomic rearrangements that involve chains of balanced alterations, a phenomenon known as “chromoplexy” [7, 18, 20, 105–107]. The *TMPRSS2-ERG* fusion increases bone tropism of prostatic cancers and promotes their metastases in bone [108]. Although the prognostic implications of *ETS* rearrangements remain unclear, recent evidence suggests that *TMPRSS2-ERG* fusions are associated with young patients and low-grade prostatic cancer [109]. A recent study demonstrates that small molecules targeting the DNA-binding ETS domain of *ERG* can suppress its transcriptional activity and reverse transformed characteristics of prostate cancers aberrantly expressing ERG [110].

***SPOP* mutation**

The *SPOP* mutation is the most common point mutation (6%–15%) in all prostatic cancers [14, 79, 111, 112]. The *SPOP* gene encodes the substrate-recognition component of the Cullin3-based E3-ubiquitin ligase; missense mutations are found exclusively in the substrate-binding cleft of *SPOP*, indicating that this mutation alters substrate binding [14]. *SPOP* mutations and *ETS* rearrangements are mutually exclusive. Because *SPOP* mutations can be detected in HGPINs adjacent to cancers, *SPOP* mutations are likely to be early events in prostatic carcinogenesis. Functionally, *SPOP* mutation promotes oncogenesis by preventing the degradation of oncogenic factors including ERG and AR [84, 85, 113–115]. *SPOP*-mutant cancers generally lack genetic alterations in the PIK3 pathway [14, 20] but show a distinct pattern of genomic alterations, including losses of *CHD1* at 5q21, 2q, and 6q [14, 79]. *CHD1* is an ATP-dependent chromatin-remodeling enzyme, whose genomic locus is lost in 5%–10% of all prostatic cancers [116, 117]. A recent study demonstrated that *CHD1* is a putative synthetic-essential gene in *PTEN*-deficient cancers, and *CHD1* depletion profoundly and specifically suppresses cell proliferation in *PTEN*-deficient prostate cancers [118]. Another recent study showed that *SPOP* mutations activate both PIK3/MTOR and AR signaling pathways, effectively uncoupling the normal negative-feedback mechanism between these two pathways [86].

***SPINK1* overexpression**

SPINK1 is commonly overexpressed in *SPOP*-mutant and other *ETS*-negative prostatic cancers. *SPINK1* is overexpressed in approximately 10% of prostate cancers, and *SPINK1* overexpression and *ERG* rearrangement appear to be mutually exclusive. *SPINK1* overexpression is associated with an increased risk of biochemical recurrence [23]. Because *SPINK1* partially exhibits its neoplastic effects through its interaction with EGFR, EGFR inhibitors may be a potential targeted therapy for *SPINK1*-overexpressing prostatic cancers [119].

***FOXA1* mutation**

FOXA1 is an AR transcription factor that promotes prostatic cancer oncogenesis and progression mainly by increasing the transcriptional activity of AR [120]. *FOXA1*-mutant cancers share similar molecular features with *SPOP*-mutant cancers [5]. Along with *SPOP*-mutant cancers, *FOXA1*-mutant cancers have been associated with the highest levels of AR transcriptional activity [5]. A recent study suggested that NONOG, a pluripotency transcription factor, reprograms prostatic cancers to become castration resistant by dynamically repressing and engaging the AR/FOXA1 signaling axis [121]. Another recent study suggests that AR variants are dependent on FOXA1 for sustaining a pro-proliferative gene signatures and agents targeting FOXA1 may represent novel therapeutic options for patients with castrate-resistant prostatic cancer [122].

***IDH1* mutation**

IDH1, which encodes a metabolic enzyme, is recurrently mutated in prostatic cancers, resulting in a methylator phenotype [5]. The presence of *IDH1* mutations appears to represent a rare and unique subset of early onset prostate cancers, with relatively few SCNAs and high levels of genomic hypermethylation [5]. Patients with *IDH1*-mutant cancers might be candidates for treatment with *IDH1*-specific therapies that are currently under development [123–125].

CONCLUSIONS AND FUTURE DIRECTIONS

This review provides perspectives on the new 2016 WHO classification of prostatic cancers as well as recent knowledge of their molecular pathologies. The comprehensive molecular characterization of prostatic cancers enabled their classification into subgroups, permitting their evolution from a poorly understood, heterogeneous group of diseases with variable clinical courses to characteristic molecular subtypes that could allow the implementation of personalized therapies and better patient management. In the clinical practice, although we have got to know the more precise prediction of prognosis or rough sensitivity for ADT by the histopathological and/or immunohistological examinations, the increased understanding of the molecular pathologies via high-throughput analyses are currently less useful for clinicians and pathologists to offer the meaningful therapeutic suggestions for patients with prostatic cancer. Actually, we continue to use mostly traditional approaches for the treatment of patients with prostatic cancer. Using the molecular knowledge of prostatic cancer, we really need to press forward the clinical translation and precision medicine for the patients. In accordance with the increased

clinicopathological and molecular knowledge of prostatic cancers, the WHO classification will also require additional revisions to allow for reliable and clinically meaningful cancer diagnoses.

Abbreviations

ADT, androgen deprivation therapy; AMACR, alpha-methylacyl-CoA racemase; AR, androgen receptor; BCC, basal cell carcinoma; CI, confidence interval; GP, Gleason pattern; GS, Gleason score; HGPIN, high-grade prostatic intraepithelial neoplasia; HR, hazard ratio; IDC-P, intraductal carcinoma of the prostate; ISUP, International Society of Urological Pathology; LCNEC, large cell neuroendocrine carcinoma; LOH, loss of heterozygosity; PAP, prostatic acid phosphatase; PARP, poly ADP ribose polymerase; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SCNA, somatic copy-number alteration; SqCC, squamous cell carcinoma; SmCC, small cell carcinoma; TCGA, The Cancer Genome Atlas; WHO, World Health Organization.

Author contributions

K.I. conceived the review, wrote the text, and created the tables and figures. K.I. is responsible for the overall content as a guarantor.

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CONFLICTS OF INTEREST

K.I. declares no conflicts of interest.

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