It has been 12 years since the publication of the last WHO classification of tumors of the prostate. During this time, significant new knowledge has been generated on pathology and genetics of tumors of the prostate. The aim of this review is to summarize the new additions to the 2016 WHO classification compared to the 2004 WHO classification, with emphasis on a new entity, new variants of acinar adenocarcinoma, new immunohistochemical stains for diagnosis, grading, risk stratification, and molecular genetics of acinar adenocarcinoma of the prostate.

New entity : Intraductal carcinoma

Intraductal carcinoma is newly recognized as an entity in the 2016 WHO classification. This term has been utilized for several decades, dating back at least to 1985 [Kovi, 1985], and it has been variably used to describe intraductal spread or in-situ growth of acinar or ductal adenocarcinoma of the prostate, and intraductal proliferation of urothelial carcinoma [Magers, 2015; Humphrey, 2015; McNeal, 1996; Tsuzuki, 2015; Robinson, 2012; Robinson, 2010; Watts, 2013; Guo, 2006; Miyai, 2014:]. The 2016 WHO definition is as follows:

“Intraductal carcinoma of the prostate is 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.”

Intraductal carcinoma is thought to represent a late event in prostate cancer evolution, with intraductal spread of aggressive prostatic carcinoma, with cancerization of pre-existing ducts and acini by high-grade prostatic adenocarcinoma. However, a minority of cases may be a precursor proliferation since in about 10% of radical prostatectomy cases following a needle biopsy diagnosis of intraductal carcinoma, the intraductal carcinoma in the whole prostate gland is found in pure form, without associated invasive adenocarcinoma [Robinson, 2010].

Intraductal carcinoma is rare in isolated form in needle biopsy tissue, being detected in 0.1% to 0.3 % of needle core cases [Robinson, 2010; Watts, 2013; Guo, 2006], and is uncommon in the presence of invasive adenocarcinoma in needle core tissue, being diagnosed in 2.8% of such cases [Guo, 2006]. In whole prostate glands the incidence is dependent on the grade and stage of the prostatic adenocarcinoma in
the series, and ranges from 20% to 40% of radical prostatectomy cases [McNeal, 1996; Miyai, 2014].

Diagnostic separation of intraductal carcinoma from HGPIN is critical due to the association of intraductal carcinoma with an average Gleason score of 8 and pT3 prostatic adenocarcinoma in the whole gland [Robinson, 2010]. In contrast to HGPIN, intraductal carcinoma exhibits a solid or dense cribriform pattern or a loose cribriform or micropapillary pattern with either marked nuclear atypia (that is, nuclear size 6x normal or larger) or comedonecrosis [Guo, 2006]. PTEN and ERG immunostaining may be a useful adjunctive method, since intraductal carcinoma commonly shows PTEN loss and ERG expression, whereas PTEN loss is rare in HGPIN and ERG expression is uncommon [Morais, 2015].

An important point is that intraductal carcinoma is not assigned a Gleason grade [Epstein, 2016].

Reporting of isolated intraductal carcinoma in needle biopsy should include a comment stating that intraductal carcinoma of the prostate is associated with high-grade and high-volume prostate carcinoma and that therapy may be indicated. Repeat biopsy may also be recommended.

New variants of acinar adenocarcinoma of the prostate

Variants of acinar adenocarcinoma of the prostate may be of significance due to difficulty in pathological diagnosis and due to prognostic and/or therapeutic differences compared to usual acinar adenocarcinoma [Humphrey, 2012]. The acinar adenocarcinoma variants that are difficult to diagnose are deceptively benign-looking and are highlighted in the WHO classification. These include atrophic, pseudohyperplastic, foamy gland, and microcystic adenocarcinomas. Variants of acinar adenocarcinoma with a worse prognosis compared to usual acinar adenocarcinoma include signet ring-like, sarcomatoid, and pleomorphic giant cell adenocarcinoma. The newly recognized acinar adenocarcinoma variants in the WHO 2016 classification are microcystic adenocarcinoma and pleomorphic giant cell adenocarcinoma.

Microcystic adenocarcinoma

Microcystic carcinoma is a deceptively benign-appearing variant of acinar adenocarcinoma of the prostate [Yaskiv, 2010]. Cystic change in prostatic adenocarcinoma glands is unusual and may be confused with cystic change in benign glands, which is common. These dilated malignant microcystic glands are, on average 10-fold larger than typical small gland adenocarcinoma of the prostate. Alpha-methylacyl CoA racemase (AMACR) is expressed in almost all cases and the glands uniformly lack basal cells in immunohistochemistry using p63 and 34betaE12 antibodies. The Gleason grade is pattern 3.
Pleomorphic giant cell adenocarcinoma

Pleomorphic giant cell adenocarcinoma is a rare variant of acinar adenocarcinoma with giant, bizarre, anaplastic cells harboring pleomorphic nuclei. Less than 10 cases have been reported [Parwani, 2006; Lopez-Beltran 2005]. Some patients have a history of hormonal or radiation therapy of usual acinar adenocarcinoma before the diagnosis of pleomorphic giant cell carcinoma is rendered. This variant is unusual in the degree of nuclear atypia since even the highest-grade usual acinar adenocarcinomas typically display relatively uniform nuclei. The clinical course is highly aggressive.

New variant of neuroendocrine tumors of the prostate: Large cell neuroendocrine carcinoma

Large cell neuroendocrine carcinoma of the prostate is a rare neuroendocrine tumor variant. It was not recognized in the 2004 WHO classification. The largest series, of 7 cases, was published in 2006 [Evans, 2006]. Almost all cases arose after hormonal treatment of adenocarcinoma of the prostate. The histological features are identical to large cell neuroendocrine carcinomas diagnosed in other anatomic sites such as the lung. Outcome is poor with a mean survival of 7 months after platinum-based chemotherapy.

Immunophenotype

In 2004 the prostate tissue markers most commonly targeted in diagnostic immunohistochemistry included prostate specific antigen (PSA), prostate specific acid phosphatase (PAP), high molecular weight cytokeratins (using monoclonal antibody 34betaE12), p63, and AMACR. These remain important immunostains in the diagnosis of selected cases of acinar adenocarcinoma of the prostate. In the 2016 WHO blue book utilization of these immunostains as well as additional others is presented in specific differential diagnostic scenarios. New immunostains that are discussed include the prostatic markers prostein (also known as P501S, a plasma membrane protein) and NKX3.1 (a homeobox-containing transcription factor) [Epstein, 2014; Gelmann, 2003; Gurel, 2010; Sheridan, 2007]. Immunohistochemical detection of NKX3.1 can be particularly valuable in the confirmation of a PSA and/or PAP-negative prostatic carcinoma when urothelial carcinoma is in the differential diagnosis and in the diagnosis of metastatic adenocarcinoma of the prostate. PSA, PAP, prostein, and NKX3.1 immunostains are all highly sensitive in diagnosis of metastatic prostatic adenocarcinoma, with each of the four markers displaying greater than 94% sensitivity [Epstein, 2014; Gurel, 2010]. PSA and PAP expression can be decreased after androgen deprivation therapy, and prostein and NKX3.1 immunostains can be of use in such cases.

Grading of adenocarcinoma of the prostate
Gleason grading remains the standard approach to histological grading of adenocarcinoma of the prostate. Since the 2004 WHO classification there have been modifications to the Gleason grading system and these are incorporated into the 2016 WHO section on grading of prostate cancer. Additionally, for Gleason score 7 adenocarcinomas, reporting of percentage adenocarcinoma that is pattern grade 4 is recommended, and grade groups are introduced.

2014 International Society of Urological Pathology (ISUP) modifications of Gleason grading

Significant evidence-based modifications of Gleason grading are presented, based on an ISUP meeting in 2014 [Epstein, 2016]. The major conclusions, which are rendered in that publication [Epstein, 2016] and the 2016 WHO blue book are as follows:

- Cribriform glands should be assigned a Gleason pattern 4
- Glomeruloid glands should be assigned a Gleason pattern 4
- Grading of mucinous carcinoma of the prostate should be based on its underlying growth pattern rather than grading them all as 4

Some cases of cribriform adenocarcinoma have been graded as pattern 3 in the past, and according to the 2004 WHO blue book [Epstein, 2004], rare cribriform glands could be diagnosed as pattern 3. However, recent data from several institutions have clearly demonstrated that cribriform adenocarcinoma is independently associated with biochemical failure after radical prostatectomy [Kir, 2014; Dong, 2013], with metastasis after radical prostatectomy [Kweldam, 2014], and with metastasis-free and disease specific survival [Kweldam, 2014]. All cribriform adenocarcinomas should be assigned pattern 4.

An additional change from the 2004 WHO is the addition of poorly-formed glands to pattern 4. So, high-grade pattern 4 is now comprised of cribriform glands, fused glands, poorly-formed glands, and glomeruloid glands.

A new modified Gleason grading diagram is presented in the ISUP publication [Epstein, 2016] and in the 2016 WHO blue book. This diagram is significantly different from the diagram published in the 2004 WHO blue book [Epstein, 2004]. Cribriform glands are now pattern 4 and poorly-formed glands are included as pattern 4 in the new diagram.

Reporting of adenocarcinoma that is pattern 4

It is recommended in the 2016 WHO blue book that percentage pattern 4 be reported for Gleason score 7s, when this is the highest grade in needle biopsy or radical prostatectomy cases. This is a change from the 2004 WHO blue book, which indicated that reporting of high-grade patterns 4 and 5 was not routine in clinical practice [Epstein 2004]. The percentage of pattern 4 may have implications for management strategies such as active surveillance since some patients with Gleason
grade $3 + 4 = 7$ with a low percentage of pattern 4 may be considered for active surveillance [Morash, 2015]. An abundance of data suggests that percentage of adenocarcinoma that is high-grade pattern 4/5 is an important prognostic indicator [Stamey, 1999; Cheng, 2007; Sauter, 2015]. The method for determination of percentage pattern 4 was not specified.

**Grade groups**

A new set of grade groups was recently developed [Pierorazio, 2013; Epstein, 2015], with a broad consensus for acceptance by expert urologic pathologists and clinicians at the 2014 International Society of Urological Pathology Consensus Conference on Gleason grading of prostatic carcinoma (Epstein, 2016). These grade groups are as follows:

- Grade group 1: Gleason score $\leq 6$
- Grade group 2: Gleason score $3 + 4 = 7$
- Grade group 3: Gleason score $4 + 3 = 7$
- Grade group 4: Gleason score $4 + 4 = 8; 3 + 5 = 8; 5 + 3 = 8$
- Grade group 5: Gleason scores 9-10

The rationale for the generation of the grade groups is that Gleason scores 2-5 are rarely used, Gleason scores have been grouped together in the past in arrangements that do not accurately reflect prognosis, and grade group 1 signifies to the clinician and patient that Gleason score 6 is the lowest possible grade, rather than an intermediate 6 of 10 grade. The latter point is critical and informs all that a diagnosis of adenocarcinoma of the prostate, grade group 1 carries an excellent prognosis [Pierorazio, 2013; Epstein, 2015]. Many patients with grade group 1 tumors, in the correct clinical context, with consideration of other parameters (such as serum PSA level, clinical stage, and amount of cancer in needle core tissue) could be candidates for active surveillance. The prognostic impact of the 5 grade groups have been validated in a large multi-institutional study of over 20,000 radical prostatectomy cases, over 16,000 needle biopsy cases, and over 5,000 biopsies followed by radiation therapy [Epstein, 2015]. Of interest, there are genomic correlates and molecular support for the grade group system [Rubin, 2015]. The 2016 WHO blue book states that the grade groups should be reported in conjunction with the 2014 modified ISUP Gleason scores.

**Risk stratification and active surveillance for acinar adenocarcinoma of prostate**

In the 2016 blue book the vital importance of risk stratification for patients for adenocarcinoma of the prostate is highlighted in a section on prognosis and predictive factors. In particular, there is much detail on pathologic prognostic factors for the different types of tissue samples – needle biopsy, transurethral resection, and radical prostatectomy tissues. Also, the 2015 National Comprehensive Cancer Network (NCCN) risk groups, which utilize clinical and
pathologic factors, are presented in a table. Since many prostate cancers (especially many grade group 1 tumors) are indolent and may be managed by active surveillance, a new discussion is provided on active surveillance, along with a table on clinical and pathologic inclusion criteria that are used by a number of large active surveillance programs.

**Genetic profile of adenocarcinoma of the prostate**

Since 2004 there has been a remarkable expansion of knowledge on the genetics of prostate cancer. Advances in sequencing technology have revealed complex rearrangements and marked heterogeneity [Barbieri, 2015; Barbieri, 2013; The Cancer Genome Atlas Research Network, 2015; Robinson, 2015]. Only a few abnormalities in specific genes are highly recurrent but alterations in certain signaling pathways do predominate, such as PI3K/PTEN/AKT, cell cycle regulation, and chromatin regulation [Barbieri, 2013]. The most common alterations, in both primary and metastatic prostate cancer, are fusions of androgen-regulated promoters with ERG and other members of the ETS family of transcription factors [The Cancer Genome Atlas Research Network, 2015; Robinson, 2015], particularly the TMPRSS2-ERG fusion, which is present in about 50% of all prostate cancers. In primary, clinically localized prostate cancer there are relatively few recurrent non-synonymous point mutations, including mutations in SPOP (11%) and FOXA1 (3%) genes [The Cancer Genome Atlas Research Network, 2015]. In comparison, in castration–resistant metastatic prostate cancer there are increased alteration rates in many genes and pathways, including abnormalities androgen receptor (AR) signaling (usually due to AR gene amplification or mutation), DNA repair and PI3K pathways, as well as mutations or deletions in TP53, RB1, KMT2C, and KMT2D genes [The Cancer Genome Atlas Research Network, 2015; Robinson, 2015]. This landscape of somatic genetic abnormalities in adenocarcinoma of the prostate is discussed in depth in a genetic profile section, and a model for molecular classification of prostate cancer is shown. While this molecular classification is not currently in clinical use, the discovery of these genetic abnormalities has led to a greater understanding of the molecular pathogenesis of prostate cancer and has demonstrated potentially therapeutically actionable molecular defects. Such molecular classifications may be incorporated into WHO classifications of prostate cancer in the future.

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