Histopathology

Histopathology 2022, **81**, 447–458. DOI: 10.1111/his.14711

REVIEW

WHO Classification of Tumours fifth edition: evolving issues in the classification, diagnosis, and prognostication of prostate cancer

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(2022) *Histopathology* **81**, 447–458. https://doi.org/10.1111/his.14711

WHO Classification of Tumours fifth edition: evolving issues in the classification, diagnosis, and prognostication of prostate cancer

The fifth edition of the WHO Classification of Tumours of the Urinary and Male Genital Systems encompasses several updates to the classification and diagnosis of prostatic carcinoma as well as incorporating advancements in the assessment of its prognosis, including recent grading modifications. Some of the salient aspects include: (1) recognition that prostatic intraepithelial neoplasia (PIN)-like carcinoma is not synonymous with a pattern of ductal carcinoma, but better classified as a subtype of acinar adenocarcinoma; (2) a specific section on treatment-related neuroendocrine prostatic carcinoma in view of the tight correlation between androgen deprivation therapy and the development of prostatic carcinoma with neuroendocrine morphology, and the emerging data on lineage plasticity; (3) a terminology change of basal cell carcinoma to "adenoid cystic (basal cell) cell carcinoma" given the presence of an underlying *MYB::NFIB* gene fusion in many cases; (4) discussion of the current issues in the grading of acinar adenocarcinoma and

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the prognostic significance of cribriform growth patterns; and (5) more detailed coverage of intraductal carcinoma of prostate (IDC-P) reflecting our increased knowledge of this entity, while recommending the descriptive term atypical intraductal proliferation (AIP) for lesions falling short of IDC-P but containing more atypia than typically seen in high-grade prostatic intraepithelial neoplasia (HGPIN). Lesions previously regarded as cribriform patterns of HGPIN are now included in the AIP category. This review discusses these developments, summarising the existing literature, as well as the emerging morphological and molecular data that underpins the classification and prognostication of prostatic carcinoma.

Keywords: pathology, prostate carcinoma, WHO Classification

Introduction

Prostate cancer is a significant contributor to cancer morbidity and mortality as the fourth most common cancer and the eighth leading cause of cancer-associated death globally.[1] The Prostate chapter in the fifth edition of the WHO Classification of Tumours of the Urinary and Male Genital Systems[2] represents an evolution of diagnostic terminology and criteria based on significant prior changes in the third (e.g. acceptance of Gleason grading for prostate cancer) and fourth editions (concept of grade groupings and acceptance of intraductal carcinoma of prostate [IDC-P] as a new entity), which were published almost 20 and 6 years ago, respectively.[3,4] The importance of tumour growth patterns, for instance IDC-P or the variety of cribriform glands that may be seen in prostatic adenocarcinomas as part of the morphological spectrum of Gleason pattern 4, has received increasing recognition in the published literature in recent years. There have also been well publicised modifications to the grading of prostatic adenocarcinoma recently by the two major urological pathology societies, which have published broadly concordant proposals on most issues. However, there are some areas where the recommendations of the two societies currently diverge, such as whether or not to include IDC-P when assessing the Gleason score (GS).[2,5,6]

As in other books of the WHO Classification of Tumours fifth series, the term subtypes for distinct clinicopathological entities replaces the term variants, which is used for genomic rather than morphologic alterations. A subtype is defined as "a tumour subtype is a variant of a type in which one or two parameters (e.g. clinical, location, histopathological, and/or molecular) make it desirable to recognize it as being distinct from other subtypes but still related to the parent type." Tumours with unusual morphological appearances, such as atrophic or pseudohyperplastic acinar carcinoma, but which are less distinctive clinicopathological entities, have also been included as alternative histological patterns to aid pathologists in their recognition.

To minimize duplication of information, metastatic, haematolymphoid, mesenchymal, neuroendocrine, and genetic syndrome-related tumours are each consolidated across all genitourinary sites rather than being discussed separately in the chapter on each organ: the exceptions in the prostate chapter being mesenchymal tumours from the prostate stromal cells and treatment-related neuroendocrine prostatic carcinoma, due to the specialised nature of these malignancies involving the prostate versus other urological sites. Likewise, to reduce redundancy, urothelial carcinoma of prostate and prostatic urethra is covered in the urinary tract chapter of this book. While the classification of prostate cancer remains deeply rooted in morphology, the fifth edition and this review address some of the important emerging issues and molecular data in this field that have potential for significant diagnostic and management impact as this dynamic field continues to evolve.

Classification

Ductal adenocarcinoma and prostatic intraepithelial neoplasia (PIN)-like carcinoma

Ductal adenocarcinoma has been retained as a separate type of prostatic adenocarcinoma in the fifth edition,[2] although consideration was given as to whether it might be more accurately classified as a subtype of acinar adenocarcinoma. In most cases ductal adenocarcinoma is admixed with acinar adenocarcinoma, rather than occurring in a 'pure' form, and there is also a degree of interobserver variability in distinguishing between ductal adenocarcinoma and high-grade acinar adenocarcinoma, even among expert uropathologists, reflecting the morphological

overlap between the two entities and the lack of consensus diagnostic criteria for ductal adenocarcinoma.[7–10] In the WHO Classification fifth edition the term 'ductal adenocarcinoma' is now reserved for those radical prostatectomy cases with more than 50% ductal morphology, while in needle biopsy cases the term 'adenocarcinoma with ductal features' is recommended for both pure ductal and mixed ductal and acinar features. Interestingly, some studies have shown that ductal adenocarcinomas and their coincident acinar adenocarcinomas from the same patient may be clonally related, sharing *ERG* rearrangements, often other molecular aberrations, such as putative driver mutations in *SPOP* and *FOXA1*, and having similar levels of AR expression.[11,12] However, in some investigations there is a lower frequency of *ERG* fusions and expression in ductal adenocarcinoma and there are differences in molecular alterations, including more common mutations in the WNT-signalling pathway genes *CTNBB1* and *APC* in ductal adenocarcinomas compared to acinar carcinomas.[11–13] Aberrations in genes regulating DNA repair, including homologous recombination and mismatch repair genes, may also be more frequent in ductal adenocarcinoma, occurring in 49% of cases in one series of 51 patients.[13,14] One study reported similar levels of copy number alternations (CNA) between ductal adenocarcinoma and high-grade acinar adenocarcinoma, while another found a higher frequency of CNAs in ductal versus their coincident acinar adenocarcinomas.[12,15] The behaviour of ductal adenocarcinoma is clinically distinctive, with a higher rate of biochemical recurrence (BCR), worse metastasis-free survival (MFS), and overall survival (OS), lower salvage-free survival, and lower response rate to androgen deprivation therapy than high-grade acinar adenocarcinoma.[16–18] Moreover, ductal adenocarcinoma has a propensity to metastasise to lung and liver, as well as other sites that are unusual for prostate carcinoma metastases, such as brain, skin, penis, and testis.[18–22] Overall, given its distinctive clinical behaviour and metastatic pattern, ductal adenocarcinoma has been retained as a separate type in the fifth edition, while awaiting further evidence to resolve this issue more definitively.

In contrast, PIN-like carcinoma has been reclassified as a subtype of acinar rather than ductal adenocarcinoma in this edition. PIN-like carcinoma lacks the papillary or cribriform architecture typical of ductal adenocarcinoma (Figure 1A,B), but is instead characterised by large discrete glands lined by flat or tufted epithelium (Figure 1C,D). Although some cases have tall columnar epithelium with stratified nuclei resembling that of ductal adenocarcinoma, others have cuboidal epithelium with rounded nuclei, more in keeping with acinar adenocarcinoma.[23,24] PIN-like carcinoma also has a more favourable prognosis, similar to that of low-grade acinar adenocarcinoma and is assigned a GS of 6 only.[24,25] Finally, recent molecular studies have found frequent activating mutations in the RAF/RAS pathway, an uncommon finding in either typical ductal or acinar adenocarcinoma.[26]

TREATMENT-RELATED NEUROENDOCRINE PROSTATIC CARCINOMA

Although in general the WHO fifth edition series has consolidated neuroendocrine tumours from the various sites within each system into a separate chapter, treatment-related neuroendocrine prostatic carcinoma (t-NEPC) has been described in its own section in the prostate cancer chapter because of its distinctive clinical and biological behaviour.[2] This entity is now defined as "Tumours demonstrating complete neuroendocrine differentiation or partial neuroendocrine differentiation with adenocarcinoma following androgen deprivation therapy", and applies to both primary and metastatic tumours. The WHO fifth edition does not recommend routine use of immunohistochemistry (IHC) for synaptophysin and chromogranin, since almost all prostatic adenocarcinomas show some degree of neuroendocrine differentiation, albeit generally minor.[27] Moreover, there is insufficient evidence that these neuroendocrine markers have a therapeutic or prognostic role when used in this setting.[28–30]

Treatment-related neuroendocrine prostatic carcinoma is found in 10.5%–17% of patients with metastatic castration-resistant prostate cancer after treatment with androgen receptor signalling inhibitors.[31–33] These carcinomas usually arise during or after the use of potent androgen deprivation therapy, such as enzalutamide or abiraterone, which leads to a loss of response to the androgen axis targeting agents due to lineage plasticity, with the concordance of *ERG* rearrangements between the t-NEPC and the matched hormone-naïve carcinoma, or in mixed tumours, between the NEPC and adenocarcinoma components, implicating a shared clonal origin.[30,34] Emerging data suggest that such transdifferentiation may be driven by epigenetic changes occurring in a specific genomic context involving *TP53*, *RB1*, and *PTEN* loss.[31,35–38] Some cancers have the histological and immunohistochemical features of pure small cell, or less commonly large cell, neuroendocrine carcinoma, while others are mixed tumours with a component of high-grade

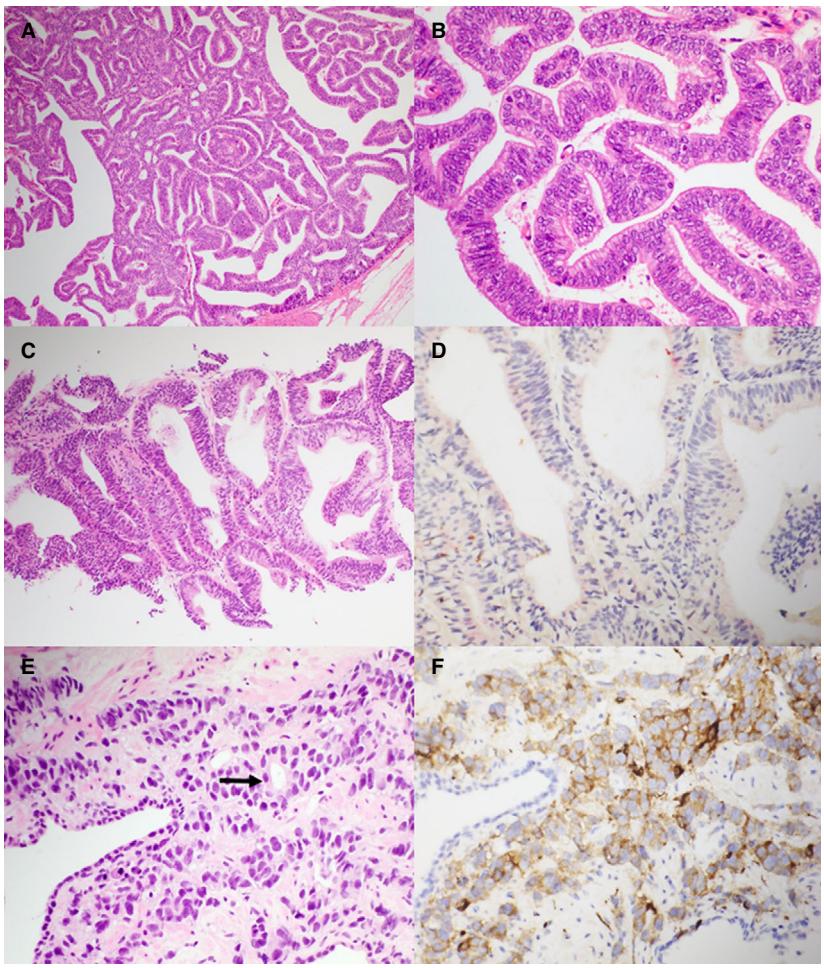

Figure 1. Ductal adenocarcinoma [(A), higher power in (B)] with papillary and cribriform architecture in contrast to the large discrete glands of PIN-like carcinoma (C,D). PIN-like carcinoma with simple discrete glands lined by flat and tufted tall columnar epithelium (C). The absence of basal cells is highlighted by immunohistochemistry (IHC) [(D), p63, cytokeratin 34βE12 and AMACR cocktail]. Treatment-related neuroendocrine prostatic carcinoma [(E), synaptophysin IHC in (F)]. Cords of cells with hyperchromatic crowded nuclei. Only rare gland formation is present [arrow in (E)].

adenocarcinoma (Figure 1E,F).[34,39,40] The neuroendocrine carcinoma component shows p53 immunostaining in most cases and TTF1 positivity in approximately half, while prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) are usually lost.[30] The prognosis is poor, with a median OS of 53.5 months after initial prostate cancer diagnosis in one study and median survival of only 7 months after diagnosis of t-NEPC in a pooled analysis of 123 cases in another.[39,41]

ADENOID CYSTIC (BASAL CELL) CARCINOMA OF THE PROSTATE

Adenoid cystic (basal cell) carcinoma is defined as a malignant neoplasm thought to be defined from prostatic basal cells. The name of this entity has been revised in the WHO Classification fifth edition to reflect the close morphological and molecular similarities between these tumours originating in the prostate and their salivary gland counterparts.[2] Histologically, this entity typically exhibits either: an adenoid cystic pattern with hyaline globules (inspissated secretion); a basal pattern comprising small solid nests of basal cells; or a mixture of both.[42,43] In recent years fluorescence in situ hybridisation (FISH) analysis has demonstrated that 29%–47% of these carcinomas harbour *MYB::NFIB* gene fusions, predominantly in those tumours with an adenoid cystic pattern.[44,45] No *TMPRSS2::ERG* fusion positive cases have been identified.[46] Similar *MYB* rearrangements occur in the majority of adenoid cystic carcinomas of salivary gland,[47] so exclusion of metastasis from salivary gland or other organs where adenoid cystic carcinomas may arise is an essential diagnostic criterion.[2]

Cribriform growth patterns

Over the last few years there has been an increasing focus on the impact of tumour growth patterns, particularly cribriform glands, on the behaviour of acinar adenocarcinoma of the prostate and in 2019 both

the International Society of Urological Pathology (ISUP) and Genitourinary Pathology Society (GUPS), in their respective consensus conference report and 'white paper', recommended specifically reporting the presence of invasive cribriform carcinoma.[5,6] ISUP has recently proposed a consensus definition of cribriform pattern in prostate carcinoma, namely, "A confluent sheet of contiguous malignant epithelial cells with multiple glandular lumina that are easily visible at low power (objective magnification ×10). There should be no intervening stroma or mucin separating individual or fused glandular structures."[48] Additionally, a 2021 interobserver reproducibility study among urological pathologists also found that transluminal bridging and a clear luminal space along the periphery of gland occupying <50% of gland circumference were reliable diagnostic features of cribriform adenocarcinoma.[49] In a 2011 case-matched study, Iczkowski *et al.* found that the cribriform growth pattern was an independent predictor of BCR with both large and small cribriform glands linked to adverse outcomes.[50] Since then, other groups have demonstrated that cribriform carcinoma in radical prostatectomy specimens is significantly correlated with lower rates of BCR-free survival (BCRFS), MFS, and disease-specific survival (DSS).[51–56] Analyses of cohorts comprising needle core biopsies, followed by either radical prostatectomy or radiation treatment, have also shown that the presence of cribriform glands in the pretreatment biopsy specimens was predictive of more advanced pathological stage at prostatectomy, upgrading, and poorer BCRFS, MFS, and DSS.[57–62] Most of these investigations have focussed on GS 7 carcinomas (WHO grade/Grade Groups [GGs] 2 and 3), although the presence of cribriform carcinoma was also of prognostic value in GS 8 (GG 4) tumours.[61,63,64]

However, most of the studies do not clearly state how invasive cribriform carcinoma was distinguished from IDC-P, which often also has a cribriform morphology, or whether or not IHC was utilised to identify basal cells and exclude IDC-P. Hence, it is not possible in those series to determine whether the adverse outcomes were associated with invasive cribriform carcinoma, IDC-P, or with both. Despite this, some of those investigations that did differentiate between these two entities immunohistochemically still found that invasive cribriform carcinoma had an independent predictive value for BCR and PCSS; however, not all did.[53,56,61,65]

Several authors have investigated the difference in prognosis between cases with small and large cribriform glands with varying results. Iczkowski *et al.* did not find an association between the size of the cribriform gland and BCR postprostatectomy, and Keefe *et al.* did not demonstrate any link between gland size in biopsies and upgrading or staging on subsequent prostatectomy.[50,58] In contrast, Hollemans *et al.* found that large cribriform glands were associated with worse BCRFS than small ones.[53] These discrepancies may be partly explained by the varying definitions of large versus small cribriform gland used in each study: Iczkowski *et al.* defined a large cribriform pattern as having >12 luminal spaces, while Hollemans *et al.* used twice the diameter of the adjacent benign glands as the cut point (Figure 2A,B).[50,53] A recent study by Chan *et al.* demonstrated that a cribriform gland size of >0.25 mm was significantly associated with BCR, MFS, and DSS.[66] Encouragingly, interobserver variability in the diagnosis of cribriform glands, whether large or small, appears relatively good. Flood *et al.* found near perfect interobserver agreement between two genitourinary pathologists for the presence of cribriform morphology on biopsy specimens, and although Kweldam *et al.* showed more interobserver variation among a panel of 26 genitourinary pathologists, there was substantially more agreement on the presence of cribriform architecture than for the other patterns included in the spectrum of Gleason pattern 4.[57,67] More recent studies by van der Slot *et al.* and Shah *et al.* have also demonstrated moderate or fair ($k = 0.40$) interobserver agreement for the identification of cribriform glands.[49,68]

The molecular differences between cribriform glands and noncribriform glands have also been investigated in recent studies. Immunohistochemical loss of expression of PTEN and p27 was more commonly present in cribriform prostate cancer, and loss of PTEN was demonstrated by *in situ* hybridisation.[69,70] Other investigators have shown increased genomic instability, more frequent mutations of *SPOP* and *ATM*, and increased expression of SChLAP1, although these studies did not distinguish between intraductal and invasive cribriform carcinoma, so it is unclear whether these molecular aberrations occur equally frequently in the intraductal or invasive cribriform glands.[71–73]

IDC-P, grading and related issues

The fifth Edition of the WHO Classification of Tumours of the Urinary and Male Genital Systems has retained and expanded the separate section on IDC-P that was introduced in the 2016 fourth edition given the clinical implications and prognostic significance of this lesion.[2,4] Although there are precise

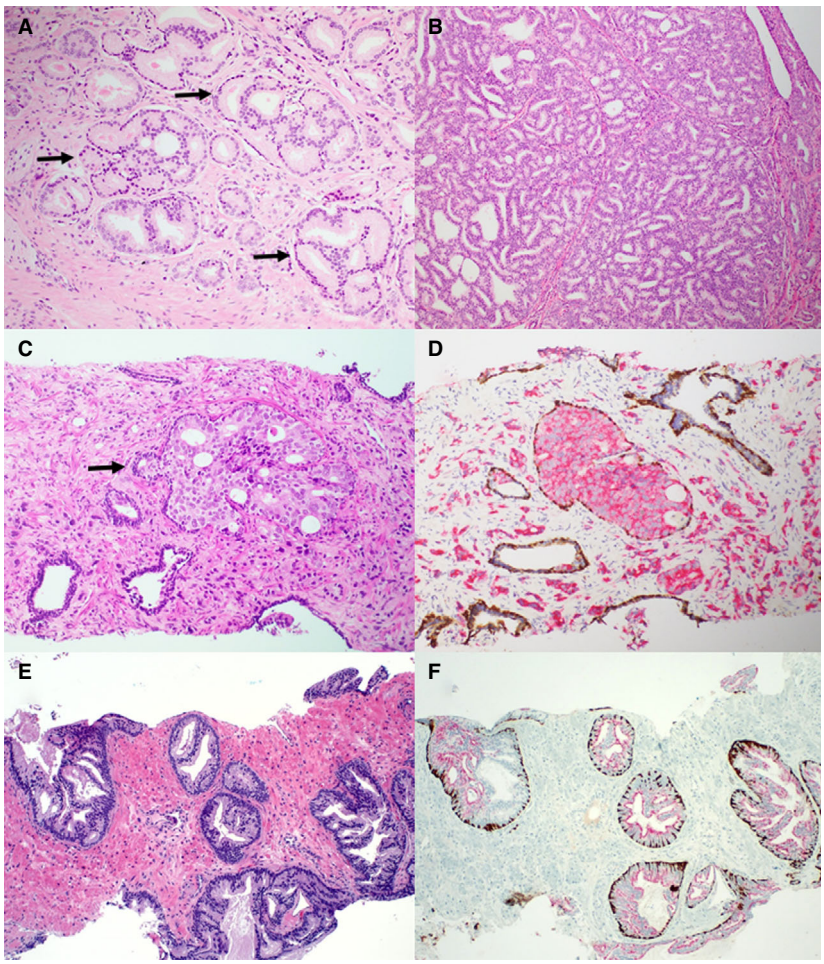

Figure 2. Small cribriform glands with ≤12 luminal spaces (A) contrasting with large cribriform glands (B). Intraductal carcinoma of prostate with retention of basal cells and surrounding adjacent high-grade invasive adenocarcinoma [(C), IDC-P indicated by arrow; (D), IHC for p63, cytokeratin 34βE12 stained brown, and AMACR red]. Atypical intraductal proliferation (AIP) with loose cribriform proliferations and only minor cytological atypia (E). No necrosis is seen and basal cells are retained [(F), p63, cytokeratin 34βE12, and AMACR cocktail].

definitional ambiguities that remain to be resolved, the core of the prescribed definition, i.e. "IDC-P is a neoplastic epithelial proliferation involving pre-existing, generally expanded, duct-acinar structures and characterized by architectural and cytological atypia beyond what is acceptable for HGPIN" (high-grade prostatic intraepithelial neoplasia [HGPIN]) is fairly broad-based and incorporates the key elements from previous formative publications (Figure 2C, D).[2,74–76] However, some of the diagnostic criteria previously suggested, which were problematic in terms of practical application and evidence base, such as the guideline that the nuclear size should be about 6× normal or larger when the architectural pattern was loose cribriform or micropapillary, have been removed in the fifth Edition.[75,77] Table 1 lists the essential and desirable diagnostic criteria for IDC-P from the WHO fifth edition.[2] IDC-P is associated with high-grade and high-stage prostate carcinoma in the vast majority of cases and considered to be a late 'colonization'-type event, but may rarely be found without concomitant invasive carcinoma or with only low-grade adenocarcinoma in radical prostatectomy specimens, raising the possibility that in some cases some IDC-P could represent a precursor or *in situ* lesion.[75,76,78–80] Isolated IDCP is slightly more commonly reported in prostate needle biopsies, 0.06%–0.26% of cases, but in this situation invasive carcinoma that was not sampled by the biopsies is nearly

Table 1. WHO fifth edition diagnostic criteria for intraductal carcinoma of the prostate

Essential criteria	• Expansile epithelial proliferation in the preexisting duct-acinar system • Lumen-spanning solid, cribriform, and/or cribriform patterns • Loose cribriform or micropapillary patterns with enlarged nuclei • Residual basal cells
Desirable criterion	• Immunohistochemistry demonstrating at least partial basal cell retention

always found in the associated radical prostatectomy specimens.[75,81] There is strong evidence that in association with invasive carcinoma, IDC-P is an independent adverse prognostic factor associated with BCR, progression-free survival, the likelihood of distant metastasis at clinical recurrence, and DSS.[82–88] Recently, revised clinical guidelines from the National Comprehensive Cancer Network (NCCN) and the Philadelphia Prostate Cancer Consensus Conference have recommended germline genetic testing for all patients with prostate cancer having an intraductal or cribriform morphology.[89,90] This recommendation is based on small retrospective series,[91,92] and is somewhat controversial, given that a larger case–control study found that there was no association between germline *BRCA2* mutations and IDC-P or cribriform glands.[93] However, this latter study did show that somatic bi-allelic loss in the primary carcinomas was significantly associated with IDC-P and cribriform glands.

A current controversy in prostate cancer pathology revolves around whether foci of IDC-P should be included when assessing the Gleason grade, and reporting practices vary between pathologists.[49,77,94–96] The 2014 ISUP Consensus Conference on the Gleason grading of prostatic carcinoma recommended that IDC-P without invasive carcinoma should not be assigned a Gleason grade; then the 2016 fourth Edition of the WHO Classification of Tumours of the Urinary System and Male Genital Organs went further and stated that "Intraductal carcinoma of the prostate should not be factored into the grading of a carcinoma."[97,98] However, in the last few years several authors have argued that IDC-P associated with invasive carcinoma should be incorporated into the tumour's GS or WHO grade/GG for a number of reasons.[5,95,98–100] Most studies correlating various outcomes with GS that incorporate cases reported before the 2014 ISUP consensus conference have not consistently distinguished between invasive carcinoma and IDC-P, and included the latter when assessing tumour grade. Moreover, the identification of basal cells to define preexisting duct-acinar structures, and hence reliably distinguish IDC-P from invasive cribriform carcinoma, is often difficult in routine haematoxylin and eosin-stained sections without using ancillary IHC, especially when the glands are distended and the basal cells are dispersed and attenuated.[101–103] Even when IHC is utilised it may not be definitive, since the basal cell layer is often fragmented in IDC-P and basal cells might not be present in the IHC plane of sectioning.[104] The consistent exclusion of IDC-P from Gleason grading would require much more frequent use of more expensive IHC, with attendant costs to health systems and accessibility issues in low- and middle-income countries. Interestingly, recent studies have shown that integrating IDC-P into the assignment of GGs may improve outcome predictions.[105,106] In their study of biopsies from 1031 men, Van Leenders *et al.* demonstrated that incorporation of IDC-P and invasive cribriform carcinoma into the GGs improved the value of the system for predicting MFS and DSS, although not for BCRFS.[106] Moreover, even in patients with distant metastasis at initial presentation, the presence of IDC-P in a needle biopsy is a significant prognostic factor.[107] Finally, the proponents of incorporating IDC-P into the GS/GG note that clinicians might overlook a separate comment on the presence of IDC-P in the pathology report and miss its prognostic significance for the patient, whereas if IDC-P were incorporated in the GS/GG a significant proportion, although not all, of its predictive value would be captured.[5,95] This is not without precedent, since a similar line of reasoning was used to justify the decision of the 2005 ISUP consensus conference to incorporate a minor component of higher grade into the biopsy GS.[108] The 2019 ISUP consensus conference endorsed this approach after 76% of participants voted in favour of the proposal that IDC-P associated with invasive carcinoma should be incorporated in the GS.[5]

In contrast, the 2019 GUPS 'white paper' recommended not to include IDC-P in determining the final GS on biopsy and/or radical prostatectomy, with only 23% of respondents to the associated survey including IDC-P when assigning the GS.[6] The proponents of this point of view argue that since a small subset of IDC-P, occurring either without associated invasive carcinoma or with low-grade (GS 3 + 3 = 6) carcinoma, may represent a precursor lesion it would be inappropriate to include it in the grading of the carcinoma.[6,80,95,109,110] Supporting this point of view, one study of radical prostatectomy specimens showed that the foci of IDC-P had different expression patterns of ERG and PTEN compared to the concurrent low-grade acinar adenocarcinoma.[79] The GUPS paper also contends that in historic studies of prostate cancer outcome there would have been only a small fraction of cases where the highest grade would have changed, depending on whether or not IDC-P was included in the grade assignment. A recent study supports this view and demonstrated that including IDC-P in grading led to a change in GG in only 1.6% of biopsy and 0.6% of radical prostatectomy specimens.[111] However, another small series of 123 IDC-P-positive biopsy cases found that the GG was

increased by 1–2 grades in 23%.[112] Finally, the GUPS recommends that it is not necessary to perform IHC to identify basal cells and IDC-P if this would not alter the highest GS/GG for the case.[6] Hence, the need to perform ancillary IHC could be significantly reduced.

Given the diverging recommendations of the two main urological pathology professional societies on whether IDC-P should be included in the grading of prostate cancer and the limited amount of data from studies designed to address this question, the fifth edition of the WHO Classification of Tumours of the Urinary and Male Genital Systems has not endorsed either position. Instead, it is recommended that pathologists should specify which variant of the Gleason grading recommendations is being used in their routine case reporting and publications to facilitate meaningful analyses and comparisons of cohorts.[2]

Some intraductal neoplastic proliferations fall short of either the architectural or cytological atypia required for a diagnosis of IDC-P but have more atypia than that usually seen in HGPIN. These lesions are designated "atypical intraductal proliferation (AIP)" in the fifth edition and in the GUPS 2019 white paper.[2,6] In particular, loose cribriform proliferations lacking severe nuclear atypia or necrosis fit into this category better than the alternative designation of cribriform HGPIN, since AIP-associated carcinoma has similar clinicopathological features to IDC-P-associated carcinoma.[113] AIP is a potential marker of unsampled high-grade prostate carcinoma and exhibits similar loss of PTEN expression and overexpression of ERG to IDC-P and the associated invasive carcinomas.[113–115] Some authors note that this terminology is nonspecific, as both HGPIN and IDC-P are also AIPs and suggest the alternative term "atypical proliferation suspicious for intraductal carcinoma (ASID)" to communicate diagnostic uncertainty.[104,116]

Conclusion

The fifth edition of the WHO Classification of Tumours of the Urinary and Male Genital Systems incorporates several significant advances in the pathology of prostate cancer. Some controversial issues cannot be resolved based on currently published evidence but it is likely that further studies will provide robust data and more clarity in subsequent editions. Emerging technologies, such as artificial intelligence-based decision support for prostate cancer imaging, histopathological diagnosis and grading, are also mentioned the fifth edition. Although these technologies are still in their infancy and not in widespread use in routine practice, it seems likely that they will become increasingly important in the future.

Author contributions

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Conflict of interest

The authors do not report any conflicts of interest.

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Acknowledgement

Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

References

1. Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2021; **71**; 209–249.
2. Netto GJ, Amin MB, Kench JG et al. Chapter 4: Tumours of the prostate. In Srigley JR, Amin MB, Rubin MA, Tsuzuki T, eds. *WHO classification of tumours: Urinary and male genital tumours*. Lyon, France: International Agency for Research on

Cancer, 2022. https://tumourclassification.iarc.who.int/chapters/36
3. Eble JNSG, Epstein JI, Sesterhenn IA. *World Health Organization classification of tumours. Pathology and genetics of tumours of the urinary system and male genital organs*. Lyon, France: IARC Press, 2004.
4. Moch HHP, Ulbright TM, Reuter V. *The WHO classification of tumours of the urinary system and male genital organs*. Lyon, France: IARC Press, 2016.
5. van Leenders G, van der Kwast TH, Grignon DJ et al. The 2019 International Society of Urological Pathology (ISUP) consensus conference on grading of prostatic carcinoma. *Am. J. Surg. Pathol.* 2020; **44**; e87–e99.
6. Epstein JI, Amin MB, Fine SW et al. The 2019 Genitourinary Pathology Society (GUPS) white paper on contemporary grading of prostate cancer. *Arch. Pathol. Lab. Med.* 2021; **145**; 461–493.
7. Epstein JI, Woodruff JM. Adenocarcinoma of the prostate with endometrioid features. A light microscopic and immunohistochemical study of ten cases. *Cancer* 1986; **57**; 111–119.
8. Samaratunga H, Duffy D, Yaxley J, Delahunt B. Any proportion of ductal adenocarcinoma in radical prostatectomy specimens predicts extraprostatic extension. *Hum. Pathol.* 2010; **41**; 281–285.
9. Seipel AH, Wiklund F, Wiklund NP, Egevad L. Histopathological features of ductal adenocarcinoma of the prostate in 1,051 radical prostatectomy specimens. *Virchows Arch.* 2013; **462**; 429–436.
10. Seipel AH, Delahunt B, Samaratunga H et al. Diagnostic criteria for ductal adenocarcinoma of the prostate: interobserver variability among 20 expert uropathologists. *Histopathology* 2014; **65**; 216–227.
11. Lotan TL, Toubaji A, Albadine R et al. TMPRSS2-ERG gene fusions are infrequent in prostatic ductal adenocarcinomas. *Mod. Pathol.* 2009; **22**; 359–365.
12. Gillard M, Lack J, Pontier A et al. Integrative genomic analysis of coincident cancer foci implicates CTNNB1 and PTEN alterations in ductal prostate cancer. *Eur. Urol. Focus* 2019; **5**; 433–442.
13. Schweizer MT, Antonarakis ES, Bismar TA et al. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. *JCO Precis Oncol.* 2019; **3**; 1–9.
14. Schweizer MT, Cheng HH, Tretiakova MS et al. Mismatch repair deficiency may be common in ductal adenocarcinoma of the prostate. *Oncotarget* 2016; **7**; 82504–82510.
15. Seipel AH, Whitington T, Delahunt B et al. Genetic profile of ductal adenocarcinoma of the prostate. *Hum. Pathol.* 2017; **69**; 1–7.
16. Brinker DA, Potter SR, Epstein JI. Ductal adenocarcinoma of the prostate diagnosed on needle biopsy: correlation with clinical and radical prostatectomy findings and progression. *Am. J. Surg. Pathol.* 1999; **23**; 1471–1479.
17. Chow K, Bedo J, Ryan A et al. Ductal variant prostate carcinoma is associated with a significantly shorter metastasis-free survival. *Eur. J. Cancer* 2021; **148**; 440–450.
18. Ranasinghe W, Shapiro DD, Hwang H et al. Ductal prostate cancers demonstrate poor outcomes with conventional therapies. *Eur. Urol.* 2021; **79**; 298–306.
19. Copeland JN, Amin MB, Humphrey PA, Tamboli P, Ro JY, Gal AA. The morphologic spectrum of metastatic prostatic adenocarcinoma to the lung: special emphasis on histologic features overlapping with other pulmonary neoplasms. *Am. J. Clin. Pathol.* 2002; **117**; 552–557.
20. Ellis CL, Epstein JI. Metastatic prostate adenocarcinoma to the penis: a series of 29 cases with predilection for ductal adenocarcinoma. *Am. J. Surg. Pathol.* 2015; **39**; 67–74.
21. Gzell CE, Kench JG, Stockler MR, Hruby G. Biopsy-proven brain metastases from prostate cancer: a series of four cases with review of the literature. *Int. Urol. Nephrol.* 2013; **45**; 735–742.
22. Tu SM, Reyes A, Maa A et al. Prostate carcinoma with testicular or penile metastases. Clinical, pathologic, and immunohistochemical features. *Cancer* 2002; **94**; 2610–2617.
23. Hameed O, Humphrey PA. Stratified epithelium in prostatic adenocarcinoma: a mimic of high-grade prostatic intraepithelial neoplasia. *Mod. Pathol.* 2006; **19**; 899–906.
24. Tavora F, Epstein JI. High-grade prostatic intraepithelial neoplasia like ductal adenocarcinoma of the prostate: a clinicopathologic study of 28 cases. *Am. J. Surg. Pathol.* 2008; **32**; 1060–1067.
25. Paulk A, Giannico G, Epstein JI. PIN-like (ductal) adenocarcinoma of the prostate. *Am. J. Surg. Pathol.* 2018; **42**; 1693–1700.
26. Kaur HB, Salles DC, Paulk A, Epstein JI, Eshleman JR, Lotan TL. PIN-like ductal carcinoma of the prostate has frequent activating ras/raf mutations. *Histopathology* 2021; **78**; 327–333.
27. Shehabeldin AN, Ro JY. Neuroendocrine tumors of genitourinary tract: recent advances. *Ann. Diagn. Pathol.* 2019; **42**; 48–58.
28. Priemer DS, Montironi R, Wang L, Williamson SR, Lopez-Beltran A, Cheng L. Neuroendocrine tumors of the prostate: emerging insights from molecular data and updates to the 2016 World Health Organization classification. *Endocr. Pathol.* 2016; **27**; 123–135.
29. Santoni M, Conti A, Burattini L et al. Neuroendocrine differentiation in prostate cancer: novel morphological insights and future therapeutic perspectives. *Biochim. Biophys. Acta* 2014; **1846**; 630–637.
30. Aggarwal R, Zhang T, Small EJ, Armstrong AJ. Neuroendocrine prostate cancer: subtypes, biology, and clinical outcomes. *J. Natl. Compr. Canc. Netw.* 2014; **12**; 719–726.
31. Abida W, Cyrta J, Heller G et al. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc. Natl. Acad. Sci. U. S. A.* 2019; **116**; 11428–11436.
32. Aggarwal R, Huang J, Alumkal JJ et al. Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. *J. Clin. Oncol.* 2018; **36**; 2492–2503.
33. Bluemn EG, Coleman IM, Lucas JM et al. Androgen receptor pathway-independent prostate cancer is sustained through FGF signaling. *Cancer Cell* 2017; **32**; 474–489.e6.
34. Mosquera JM, Beltran H, Park K et al. Concurrent AURKA and MYCN gene amplifications are harbingers of lethal treatment-related neuroendocrine prostate cancer. *Neoplasia* 2013; **15**; 1–10.
35. Beltran H, Prandi D, Mosquera JM et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. *Nat. Med.* 2016; **22**; 298–305.
36. Mu P, Zhang Z, Benelli M et al. SOX2 promotes lineage plasticity and antiandrogen resistance in tp53- and rb1-deficient prostate cancer. *Science* 2017; **355**; 84–88.

37. Park JW, Lee JK, Sheu KM et al. Reprogramming normal human epithelial tissues to a common, lethal neuroendocrine cancer lineage. *Science* 2018; **362**; 91–95.
38. Rubin MA, Bristow RG, Thienger PD, Dive C, Imielinski M. Impact of lineage plasticity to and from a neuroendocrine phenotype on progression and response in prostate and lung cancers. *Mol. Cell* 2020; **80**; 562–577.
39. Conteduca V, Oromendia C, Eng KW et al. Clinical features of neuroendocrine prostate cancer. *Eur. J. Cancer* 2019; **121**; 7–18.
40. Epstein JI, Amin MB, Beltran H et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. *Am. J. Surg. Pathol.* 2014; **38**; 756–767.
41. Wang HT, Yao YH, Li BG, Tang Y, Chang JW, Zhang J. Neuroendocrine prostate cancer (NEPC) progressing from conventional prostatic adenocarcinoma: factors associated with time to development of NEPC and survival from nepc diagnosis-a systematic review and pooled analysis. *J. Clin. Oncol.* 2014; **32**; 3383–3390.
42. Iczkowski KA, Ferguson KL, Grier DD et al. Adenoid cystic/basal cell carcinoma of the prostate: clinicopathologic findings in 19 cases. *Am. J. Surg. Pathol.* 2003; **27**; 1523–1529.
43. Ali TZ, Epstein JI. Basal cell carcinoma of the prostate: a clinicopathologic study of 29 cases. *Am. J. Surg. Pathol.* 2007; **31**; 697–705.
44. Bishop JA, Yonescu R, Epstein JI, Westra WH. A subset of prostatic basal cell carcinomas harbor the MYB rearrangement of adenoid cystic carcinoma. *Hum. Pathol.* 2015; **46**; 1204–1208.
45. Magers MJ, Iczkowski KA, Montironi R et al. MYB-NFIB gene fusion in prostatic basal cell carcinoma: clinicopathologic correlates and comparison with basal cell adenoma and florid basal cell hyperplasia. *Mod. Pathol.* 2019; **32**; 1666–1674.
46. Simper NB, Jones CL, MacLennan GT et al. Basal cell carcinoma of the prostate is an aggressive tumor with frequent loss of PTEN expression and overexpression of EGFR. *Hum. Pathol.* 2015; **46**; 805–812.
47. West RB, Kong C, Clarke N et al. MYB expression and translocation in adenoid cystic carcinomas and other salivary gland tumors with clinicopathologic correlation. *Am. J. Surg. Pathol.* 2011; **35**; 92–99.
48. van der Kwast TH, van Leenders GJ, Berney DM et al. ISUP consensus definition of cribriform pattern prostate cancer. *Am. J. Surg. Pathol.* 2021; **45**; 1118–1126.
49. Shah RB, Cai Q, Aron M et al. Diagnosis of "cribriform" prostatic adenocarcinoma: an interobserver reproducibility study among urologic pathologists with recommendations. *Am. J. Cancer Res.* 2021; **11**; 3990–4001.
50. Iczkowski KA, Torkko KC, Kotnis GR et al. Digital quantification of five high-grade prostate cancer patterns, including the cribriform pattern, and their association with adverse outcome. *Am. J. Clin. Pathol.* 2011; **136**; 98–107.
51. Choy B, Pearce SM, Anderson BB et al. Prognostic significance of percentage and architectural types of contemporary Gleason pattern 4 prostate cancer in radical prostatectomy. *Am. J. Surg. Pathol.* 2016; **40**; 1400–1406.
52. Dong F, Yang P, Wang C et al. Architectural heterogeneity and cribriform pattern predict adverse clinical outcome for Gleason grade 4 prostatic adenocarcinoma. *Am. J. Surg. Pathol.* 2013; **37**; 1855–1861.
53. Hollemans E, Verhoef EI, Bangma CH et al. Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis. *Mod. Pathol.* 2019; **32**; 139–146.
54. Kweldam CF, Wildhagen MF, Steyerberg EW, Bangma CH, van der Kwast TH, van Leenders GJ. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. *Mod. Pathol.* 2015; **28**; 457–464.
55. McKenney JK, Wei W, Hawley S et al. Histologic grading of prostatic adenocarcinoma can be further optimised: analysis of the relative prognostic strength of individual architectural patterns in 1275 patients from the canary retrospective cohort. *Am. J. Surg. Pathol.* 2016; **40**; 1439–1456.
56. Trudel D, Downes MR, Sykes J, Kron KJ, Trachtenberg J, van der Kwast TH. Prognostic impact of intraductal carcinoma and large cribriform carcinoma architecture after prostatectomy in a contemporary cohort. *Eur. J. Cancer* 2014; **50**; 1610–1616.
57. Flood TA, Schieda N, Keefe DT et al. Utility of Gleason pattern 4 morphologies detected on transrectal ultrasound (TRUS)-guided biopsies for prediction of upgrading or upstaging in Gleason score 3 + 4 = 7 prostate cancer. *Virchows Arch.* 2016; **469**; 313–319.
58. Keefe DT, Schieda N, El Hallani S et al. Cribriform morphology predicts upstaging after radical prostatectomy in patients with Gleason score 3 + 4 = 7 prostate cancer at transrectal ultrasound (TRUS)-guided needle biopsy. *Virchows Arch.* 2015; **467**; 437–442.
59. Kweldam CF, Kummerlin IP, Nieboer D et al. Presence of invasive cribriform or intraductal growth at biopsy outperforms percentage grade 4 in predicting outcome of Gleason score 3+4=7 prostate cancer. *Mod. Pathol.* 2017; **30**; 1126–1132.
60. Kweldam CF, Kummerlin IP, Nieboer D et al. Prostate cancer outcomes of men with biopsy Gleason score 6 and 7 without cribriform or intraductal carcinoma. *Eur. J. Cancer* 2016; **66**; 26–33.
61. Kweldam CF, Kummerlin IP, Nieboer D et al. Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. *Mod. Pathol.* 2016; **29**; 630–636.
62. Masoomian M, Downes MR, Sweet J et al. Concordance of biopsy and prostatectomy diagnosis of intraductal and cribriform carcinoma in a prospectively collected data set. *Histopathology* 2019; **74**; 474–482.
63. Harding-Jackson N, Kryvenko ON, Whittington EE et al. Outcome of Gleason 3 + 5 = 8 prostate cancer diagnosed on needle biopsy: prognostic comparison with Gleason 4 + 4 = 8. *J. Urol.* 2016; **196**; 1076–1081.
64. Hollemans E, Verhoef EI, Bangma CH et al. Cribriform architecture in radical prostatectomies predicts oncological outcome in Gleason score 8 prostate cancer patients. *Mod. Pathol.* 2021; **34**; 184–193.
65. Tom MC, Nguyen JK, Luciano R et al. Impact of cribriform pattern and intraductal carcinoma on Gleason 7 prostate cancer treated with external beam radiotherapy. *J. Urol.* 2019; **202**; 710–716.
66. Chan E, McKenney JK, Hawley S et al. Analysis of separate training and validation radical prostatectomy cohorts identifies 0.25 mm diameter as an optimal definition for “large” cribriform prostatic adenocarcinoma. *Mod. Pathol.* 2022; DOI: 10.1038/s41379-022-01009-7
67. Kweldam CF, Nieboer D, Algaba F et al. Gleason grade 4 prostate adenocarcinoma patterns: an interobserver

agreement study among genitourinary pathologists. *Histopathology* 2016; **69**; 441–449.
68. van der Slot MA, Hollemans E, den Bakker MA et al. Inter-observer variability of cribriform architecture and percent Gleason pattern 4 in prostate cancer: relation to clinical outcome. *Virchows Arch.* 2021; **478**; 249–256.
69. Ronen S, Abbott DW, Kravtsov O et al. PTEN loss and p27 loss differ among morphologic patterns of prostate cancer, including cribriform. *Hum. Pathol.* 2017; **65**; 85–91.
70. Shah RB, Shore KT, Yoon J, Mendrinos S, McKenney JK, Tian W. PTEN loss in prostatic adenocarcinoma correlates with specific adverse histologic features (intraductal carcinoma, cribriform Gleason pattern 4 and stromogenic carcinoma). *Prostate* 2019; **79**; 1267–1273.
71. Bottcher R, Kweldam CF, Livingstone J et al. Cribriform and intraductal prostate cancer are associated with increased genomic instability and distinct genomic alterations. *BMC Cancer* 2018; **18**; 8.
72. Chua MLK, Lo W, Pintilie M et al. A prostate cancer "nimbosus": genomic instability and schlap1 dysregulation underpin aggression of intraductal and cribriform subpathologies. *Eur. Urol.* 2017; **72**; 665–674.
73. Elfandy H, Armenia J, Pederzoli F et al. Genetic and epigenetic determinants of aggressiveness in cribriform carcinoma of the prostate. *Mol. Cancer Res.* 2019; **17**; 446–456.
74. Cohen RJ, Chan WC, Edgar SG et al. Prediction of pathological stage and clinical outcome in prostate cancer: an improved pre-operative model incorporating biopsy-determined intraductal carcinoma. *Br. J. Urol.* 1998; **81**; 413–418.
75. Guo CC, Epstein JI. Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance. *Mod. Pathol.* 2006; **19**; 1528–1535.
76. McNeal JE, Yemoto CE. Spread of adenocarcinoma within prostatic ducts and acini. Morphologic and clinical correlations. *Am. J. Surg. Pathol.* 1996; **20**; 802–814.
77. Varma M, Egevad L, Algaba F et al. Intraductal carcinoma of prostate reporting practice: a survey of expert european uropathologists. *J. Clin. Pathol.* 2016; **69**; 852–857.
78. Cohen RJ, Shannon BA, Weinstein SL. Intraductal carcinoma of the prostate gland with transmucosal spread to the seminal vesicle: a lesion distinct from high-grade prostatic intraepithelial neoplasia. *Arch. Pathol. Lab. Med.* 2007; **131**; 1122–1125.
79. Khani F, Wobker SE, Hicks JL et al. Intraductal carcinoma of the prostate in the absence of high-grade invasive carcinoma represents a molecularly distinct type of in situ carcinoma enriched with oncogenic driver mutations. *J. Pathol.* 2019; **249**; 79–89.
80. Robinson BD, Epstein JI. Intraductal carcinoma of the prostate without invasive carcinoma on needle biopsy: emphasis on radical prostatectomy findings. *J. Urol.* 2010; **184**; 1328–1333.
81. Watts K, Li J, Magi-Galluzzi C, Zhou M. Incidence and clinicopathological characteristics of intraductal carcinoma detected in prostate biopsies: a prospective cohort study. *Histopathology* 2013; **63**; 574–579.
82. Dinerman BF, Khani F, Golan R et al. Population-based study of the incidence and survival for intraductal carcinoma of the prostate. *Urol. Oncol.* 2017; **35**; 673.e9–673.e14.
83. Kimura K, Tsuzuki T, Kato M et al. Prognostic value of intraductal carcinoma of the prostate in radical prostatectomy specimens. *Prostate* 2014; **74**; 680–687.
84. Miyai K, Divatia MK, Shen SS, Miles BJ, Ayala AG, Ro JY. Clinicopathological analysis of intraductal proliferative lesions of prostate: intraductal carcinoma of prostate, high-grade prostatic intraepithelial neoplasia, and atypical cribriform lesion. *Hum. Pathol.* 2014; **45**; 1572–1581.
85. O'Brien C, True LD, Higano CS, Rademacher BL, Garzotto M, Beer TM. Histologic changes associated with neoadjuvant chemotherapy are predictive of nodal metastases in patients with high-risk prostate cancer. *Am. J. Clin. Pathol.* 2010; **133**; 654–661.
86. Saeter T, Vlatkovic L, Waaler G et al. Intraductal carcinoma of the prostate on diagnostic needle biopsy predicts prostate cancer mortality: a population-based study. *Prostate* 2017; **77**; 859–865.
87. Trinh VQ, Sirois J, Benzerdjeb N et al. The impact of intraductal carcinoma of the prostate on the site and timing of recurrence and cancer-specific survival. *Prostate* 2018; **78**; 697–706.
88. Van der Kwast T, Al Daoud N, Collette L et al. Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. *Eur. J. Cancer* 2012; **48**; 1318–1325.
89. Giri VN, Knudsen KE, Kelly WK et al. Implementation of germline testing for prostate cancer: Philadelphia prostate cancer consensus conference 2019. *J. Clin. Oncol.* 2020; **38**; 2798–2811.
90. Mohler JL, Antonarakis ES, Armstrong AJ et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. *J. Natl. Compr. Canc. Netw.* 2019; **17**; 479–505.
91. Risbridger GP, Taylor RA, Clouston D et al. Patient-derived xenografts reveal that intraductal carcinoma of the prostate is a prominent pathology in BRCA2 mutation carriers with prostate cancer and correlates with poor prognosis. *Eur. Urol.* 2015; **67**; 496–503.
92. Isaacsson Velho P, Silberstein JL, Markowski MC et al. Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. *Prostate* 2018; **78**; 401–407.
93. Lozano R, Salles DC, Sandhu S et al. Association between BRCA2 alterations and intraductal and cribriform histologies in prostate cancer. *Eur. J. Cancer* 2021; **147**; 74–83.
94. Epstein JI, Kryvenko ON. A comparison of genitourinary society pathology and international society of urological pathology prostate cancer guidelines. *Eur. Urol.* 2021; **79**; 3–5.
95. Varma M, Epstein JI. Head to head: should the intraductal component of invasive prostate cancer be graded? *Histopathology* 2021; **78**; 231–239.
96. Gandhi JS, Smith SC, Paner GP et al. Reporting practices and resource utilization in the era of intraductal carcinoma of the prostate: a survey of genitourinary subspecialists. *Am. J. Surg. Pathol.* 2020; **44**; 673–680.
97. Epstein JI, Egevad L, Amin MB et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. *Am. J. Surg. Pathol.* 2016; **40**; 244–252.
98. Humphrey PA, Amin M, Berney D et al. Acinar adenocarcinoma. In Moch H, Humphrey PA, Ulbright TM, Reuter VE eds. *WHO classification of tumours of the urinary system and male genital organs*. Lyon: IARC, 2016; 138–162.
99. Varma M, Egevad L, Delahunt B, Kristiansen G. Reporting intraductal carcinoma of the prostate: a plea for greater standardization. *Histopathology* 2017; **70**; 504–507.
100. Samaratunga H, Delahunt B, Egevad L et al. Intraductal carcinoma of the prostate is an aggressive form of invasive carcinoma and should be graded. *Pathology* 2020; **52**; 192–196.

101. Magers M, Kunju LP, Wu A. Intraductal carcinoma of the prostate: morphologic features, differential diagnoses, significance, and reporting practices. *Arch. Pathol. Lab. Med.* 2015; **139**; 1234–1241.
102. Fine SW, Al-Ahmadie HA, Chen YB, Gopalan A, Tickoo SK, Reuter VE. Comedonecrosis revisited: strong association with intraductal carcinoma of the prostate. *Am. J. Surg. Pathol.* 2018; **42**; 1036–1041.
103. Madan R, Deebajah M, Alanee S et al. Prostate cancer with comedonecrosis is frequently, but not exclusively, intraductal carcinoma: a need for reappraisal of grading criteria. *Histopathology* 2019; **74**; 1081–1087.
104. Varma M. Intraductal carcinoma of the prostate: a guide for the practicing pathologist. *Adv. Anat. Pathol.* 2021; **28**; 276–287.
105. Kato M, Hirakawa A, Kobayashi YM et al. The influence of the presence of intraductal carcinoma of the prostate on the grade group system's prognostic performance. *Prostate* 2019; **79**; 1065–1070.
106. van Leenders G, Kweldam CF, Hollemans E et al. Improved prostate cancer biopsy grading by incorporation of invasive cribriform and intraductal carcinoma in the 2014 grade groups. *Eur. Urol.* 2020; **77**; 191–198.
107. Kato M, Tsuzuki T, Kimura K et al. The presence of intraductal carcinoma of the prostate in needle biopsy is a significant prognostic factor for prostate cancer patients with distant metastasis at initial presentation. *Mod. Pathol.* 2016; **29**; 166–173.
108. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL, Committee IG. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *Am. J. Surg. Pathol.* 2005; **29**; 1228–1242.
109. Miyai K, Divatia MK, Shen SS, Miles BJ, Ayala AG, Ro JY. Heterogeneous clinicopathological features of intraductal carcinoma of the prostate: a comparison between "precursor-like" and "regular type" lesions. *Int. J. Clin. Exp. Pathol.* 2014; **7**; 2518–2526.
110. Khani F, Epstein JI. Prostate biopsy specimens with Gleason 3+3=6 and intraductal carcinoma: radical prostatectomy findings and clinical outcomes. *Am. J. Surg. Pathol.* 2015; **39**; 1383–1389.
111. Rijstenberg LL, Hansum T, Hollemans E et al. Intraductal carcinoma has a minimal impact on grade group assignment in prostate cancer biopsy and radical prostatectomy specimens. *Histopathology* 2020; **77**; 742–748.
112. Chen-Maxwell D, Prendeville S. Grading of prostate cancer: the impact of including intraductal carcinoma on the overall grade group assigned in diagnostic biopsies. *Histopathology* 2020; **77**; 503–507.
113. Hickman RA, Yu H, Li J et al. Atypical intraductal cribriform proliferations of the prostate exhibit similar molecular and clinicopathologic characteristics as intraductal carcinoma of the prostate. *Am. J. Surg. Pathol.* 2017; **41**; 550–556.
114. Shah RB, Nguyen JK, Przybycin CG et al. Atypical intraductal proliferation detected in prostate needle biopsy is a marker of unsampled intraductal carcinoma and other adverse pathological features: a prospective clinicopathological study of 62 cases with emphasis on pathological outcomes. *Histopathology* 2019; **75**; 346–353.
115. Shah RB, Yoon J, Liu G, Tian W. Atypical intraductal proliferation and intraductal carcinoma of the prostate on core needle biopsy: a comparative clinicopathological and molecular study with a proposal to expand the morphological spectrum of intraductal carcinoma. *Histopathology* 2017; **71**; 693–702.
116. Egevad L, Delahunt B, Kristiansen G, Samaratunga H, Varma M. Contemporary prognostic indicators for prostate cancer incorporating international society of urological pathology recommendations. *Pathology* 2018; **50**; 60–73.