Editorial Commentary

Are we ready to include invasive cribriform and intraductal carcinoma into the prostate cancer grade grouping system?

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Prostatic adenocarcinoma (PCa) is one of the most heterogeneous tumors with great morphologic and biological diversity as well as variable clinical courses. It has been more than half a century since Dr. Gleason proposed the first PCa grading system. Over the years, even with emerging prognostic molecular biomarkers, Gleason grading based on the histomorphology is still the most powerful and widely used parameter in predicting the behavior of PCa as well as in determining the treatment modalities for PCa patients. Despite a huge success, its predictability for the clinical behavior of PCa is still limited, particularly for intermediate grade (grade groups 2 and 3) PCa. With growing knowledge and better understanding of PCa biology and its pathological features, the Gleason grading of PCa has been continuously evolving. To simplify and improve the group stratification of the PCa grading, a 5 Grade Group system has been developed based on modified original Gleason grading and is now incorporated into the 2016 WHO prostate cancer grading system (1). In the past decade, invasive cribriform PCa and intraductal carcinoma (IDC) have been increasingly recognized as independent adverse histomorphologic components in predicting the poor outcome of PCa (2-8), and the International Society of Urological Pathology has recently recommended to include the cribriform PCa and IDC in the routine pathology report.

In the recent article by van Leenders *et al.* published in *European Urology*, the authors incorporated the invasive cribriform PCa and IDC into the current grading group (GG) and analyzed this modified grade grouping (cGG) method in the prediction of the outcome of PCa patients (9). Their results have shown that the modified cGG system has better discriminative values for disease-specific survival as well as metastasis-free survival than the contemporary PCa grading group; especially, cGG significantly increases the eligibility for active surveillance. Overall it better predicts PCa outcome and might improve future treatment options as well.

The findings are appealing and promising. Although the underlying mechanisms for the aggressiveness of cribriform PCa are not fully understood, our recent study has shown overexpression of EGFR in the cribriform PCa in comparison with non-cribriform Gleason 4 PCa (10). Inclusion of invasive cribriform morphology in the grade group may additionally benefit patients for potential future treatment with the available EGFR inhibitors (e.g., Cetuximab, Gefitinib and Erlotinib) as well. Nevertheless, besides the need of further validation by independent studies, there are a few issues we raise regarding this proposed modified grade grouping.

The potential impact of Gleason 4 non-cribriform element might be overlooked

The authors demonstrated that downgrading of Gleason 3 + non-cribriform Gleason 4 (GG2) to cGG1 increased the eligibility for active surveillance. The clinical consequence is still uncertain at this moment. The non-cribriform Gleason 4 PCa is also a group of patterns with morphology varying from ill-formed glands to variably sized fused

glands. Some of the fused glands, to some extent, may be morphologically close to cribriform PCa. At present, the biologic difference between fused glands and cribriform is not yet known and it is unclear whether or not these non-cribriform Gleason 4 PCa variants behave differently. It has been known that the percentage of Gleason pattern 4 is also of prognostic value for PCa outcome (11), especially when the percentage/absolute volume of the non-cribriform Gleason 4 is at the high end of the 50% cutoff in GG2 disease. Although the authors did not find additive predictive value of the percentage of the Gleason pattern 4, as the authors mentioned it could have been caused by the way it was analyzed. Loosening of the stringency and over downgrading of the GG2 to cGG1 for surveillance eligibility might risk a subset of the patients with PCa of aggressive potential for disease progression if active surveillance is selected for them. One of the cautious options to avoid this potential adverse effect is to subgroup the cGG1 into "cGG1a" for Gleason 3+3 (GG1) and "cGG1b" for Gleason 3+noncribriform Gleason 4 (noncribriform GG2). Nevertheless, the benefit for the shift of morphologic surveillance criteria by the proposed cGG requires further assessment.

The potential impact of the morphologic variants of invasive cribriform PCa might need to be considered

Morphologically, the cribriform pattern of invasive PCa can be further classified into glomeruloid (intraglandular cribriform) and conventional cribriform. It has been shown that the prognosis of invasive PCa with conventional cribriform pattern is worse than that of PCa with glomeruloid cribriform pattern (12,13). Conventional non-glomeruloid cribriform PCa can also be divided into PCa of small cribriform, defined by the size equal or smaller than adjacent benign prostatic glands and without tangible expansion, and PCa of large expansible cribriform. We have recently demonstrated that lymphovascular invasion and lymph node metastasis are strongly associated with small cribriform PCa (14). On the other hand, large cribriform lesions, although often being called invasive PCa, not infrequently contain variable basal cells in the periphery if basal cell immunohistochemistry is performed, and, are actually non-invasive. Although these large cribriform lesions with basal cells could represent intraductal carcinomas, at least some of them could be precursor lesions (such as high grade PINs or carcinomas *in situ*) (15). It is conceivable that invasive small cribriform PCa is more accessible to the blood or lymphatic stream than invasive large cribriform PCa. More recently, some researchers have found that formation of small cell clusters/groups are essential for tumor cells to survive in blood or lymphatics as well as to initially establish tumor colonies at metastatic sites (16,17). In addition, detection of groups/clusters of tumor cells is found to signify a worse prognosis than dispersed tumor cells in the blood stream (18,19). These findings also support the importance of the ability of tumor cells to retain cohesion and form a group in the success of migration and distant seeding. Given the different pathologic presentations for different cribriform morphologies, the variants of invasive cribriform PCa may need to be considered as well in the cGG grade grouping for improvement of its accuracy.

Potential impact of the volume of cribriform PCa

Reporting of the percentage of Gleason 4/5 pattern has recently been implemented. Percentage or absolute volume of invasive cribriform PCa might also be important. Although no specific study has been conducted to evaluate and correlate the impact of percentage/volume of invasive cribriform PCa on clinical outcome. Low percentage or only one or a few invasive foci of cribriform PCa should apparently have more favorable overall outcome than high percentage or abundant invasive cribriform PCa. Therefore, the percentage/volume of invasive cribriform PCa might also need to be considered.

The intraductal carcinoma mystery

IDC is thought to represent intraductal spread and cancerization of preexisting ducts and/or acini by invasive carcinoma and is typically associated with high-grade and high-stage PCa (7,8). Definitive therapy or immediate re-biopsy is currently recommended if IDC is identified in a biopsy specimen. IDC is morphologically characterized by solid, dense cribriform, comedonecrosis, or a loose cribriform or micropapillary pattern with marked nuclear atypia (8,20). Despite the delineated morphologic criteria, in practice, distinction between noninvasive atypical cribriform lesion or atypical intraductal proliferation and IDC might not be so straightforward, and a gray zone exists with high inter-observer variability. In addition, recently we have shown that IDCs do not necessarily display the aforementioned cytological or architectural morphology

of classic IDCs (15). They can present with features of low-grade cytology as well as variable architectures (15). Furthermore, it is well known that no invasive carcinoma is found in at least 10% of the cases containing lesions with IDC morphology (7,21). This fact indicates that, at least some, if not most, of the IDCs are actually precursor lesions or carcinomas in situ rather than retrograde spreads of surrounding invasive PCa, which also seems to be endorsed by our study (15). So far, there are no definitive morphologic features, immunohistochemical or even molecular biomarkers that distinguish IDCs from the precursor lesions of PCa. Given the current relative uncertainty of the diagnosis of IDC, its weight in grade grouping may be variable and subject to inter-observer variation. Further studies and better definition of the criteria for this entity are warranted.

In summary, the authors presented a very interesting longitudinal study with a sound proposal for the improvement of PCa grade group. Future validation and comprehensive consideration is still needed. In the near future, we anticipate an improvement in the stratification of PCa patients by incorporating not only morphologic parameters but also potential molecular biomarkers, including genomic signatures.

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Footnote

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