Editorial

Understanding pitfalls of grading prostate carcinoma between biopsy and prostatectomy

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I enthusiastically read the interesting manuscript by Gansler *et al.* This is a well-designed study incorporating the largest number of Gleason score (GS) 8 prostate adenocarcinoma (PCa) cases in National Cancer Registry Database (NCDB). Among 72,556 PCa patients, the authors excerpted 5,474 cases with GS8 on biopsy, PSA ≤20 ng/mL and clinical stage cT <3, and compared the GS modifications between the initial needle biopsy (NB) and the subsequent radical prostatectomy (RP). The study revealed downgraded GS8 in about 60% of their cohort, most notably in the GS (3+5) group. There was indirect correlation between the rate of downgraded GS8 and age [68% (82/121) in 5th decade *vs.* 52% (14/27) in 9th decade]. The authors concluded that GS discordance can potentially cause overtreatment in GS8 PCa patients and result in unnecessary complications.

Gleason grade plays a crucial role in personalized management of PCa. In practice, GS in NB dictates the management protocol and follow-up regimen; while GS in RP determines the prognosis of the disease (1). As a result, inaccurate grading of PCa may have a serious impact on patient care.

In order to facilitate accurate and reproducible grading in PCa, the 2005 International Society of Urological Pathologists (ISUP) Consensus Meeting revised Gleason grading and provided guidelines that are unanimously embraced by the pathology community. Based on these guidelines, the GS is different between NB and RP (2). In NB, the grade is determined by adding the most prevalent pattern and the highest grade tumor of any quantity. In RP, GS is calculated by adding the most prevalent pattern and the highest grade tumor provided that the latter comprises more than 5% of the entire tumor volume; highest grade tumor of less than 5% should be reported as a tertiary pattern and does not affect the GS. Also Gleason patterns 1 & 2 should not be used in NB. As a result of this, poor concordance of GS between the NB and RP is well-known; almost 50 % of GS6 prostate biopsies are GS7 at RP (3,4).

The ISUP consensus guidelines are proved to be efficient and for most part, reproducible. However subjective discrepancies still exist, mostly between genitourinary-trained (GU) pathologists and non-GU pathologists (5-7) and to a lesser degree among the GU pathologists (8). Studies have unraveled significant overgrading of Gleason pattern 4 and undergrading Gleason pattern 5 in NB by non-GU pathologists (7,9-11). The reported incidence of preoperative undergrading of PCa in the literature is between 6 and 36 % and that of overgrading is between 4% and 28% (5,7).

Recent studies show that the quantity of Gleason pattern 4, especially the cribriform subtype, affects the outcome of the disease (12,13). It is now recommended to quantitate Gleason pattern 4 in GS7 PCa (3+4 & 4+3). Gleason pattern 4 can be seen in several variants: cribriform, glomeruloid, poorly-formed glands and hypernephromatoid. Among these variant, detection of poorly-formed glands is most challenging and a source of controversy, since this pattern closely mimics tangentially sectioned small glands of Gleason pattern 3 (14).

Despite the intriguing results, the study by Gansler *et al.* has limitation, including inevitable selection bias (studying GS8 cases that underwent RP). The authors have not included variables like perineural invasion (in NB),

extraprostatic extension and the status of surgical margin and lymph nodes (in RP). As the authors testify, accounting for number of positive cores and the quantity of Gleason pattern 4 would add more value to the results. Also, based on the presented data, it seems that the authors were able to extract grade group of PCa in their study population from 2010 to 2013 which is puzzling, since grade grouping was introduced in 2012 (15).

One important limiting factor that is barely touched upon in this study is lack of expert review of the GS by GU pathologist. Based on the data provided in the study, the accuracy of GS in biopsy and RP has not been attested, and follow up of the study cohort is not provided; therefore it is not clear which GS reading was accurate. Finally, at a time when standard synoptic report administration is becoming more popular, discovering incomplete pathology reports in up to 20% of PCa in national database is alarming and inadmissible.

I personally agree with the authors that their findings are limited to the GS8 patient population who underwent RP, and cannot be expanded to GS8 cases for which RP is not the treatment of choice. I believe this study emphasizes the fact that for patients to receive optimum treatment and to improve outcome, accurate GS is vital; therefore it is crucial to obtain proper specimen followed by accurate and complete pathology assessment. There may also be a role for imaging technologies and supplemental molecular studies in the future management of PCa.

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Footnote

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