Prostate cancer glands with cribriform architecture and with glomeruloid features should be considered as Gleason pattern 4 and not pattern 3

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Experts' experience

Loeb et al. [1] published the results of a study on 5880 men diagnosed with prostate cancer from 2005 to 2007, including 4325 who had radical prostatectomy (RP) and 1555 treated with radiation therapy. They adopted the recently proposed five-tiered Gleason grade groups (GGGs; i.e., Prognostic grade groups [PGGs]), in which Gleason 6 is GGG 1, Gleason 3 + 4 is GGG 2, Gleason 4 + 3 is GGG 3, Gleason 8 is GGG 4 and Gleason 9–10 is GGG 5. The authors found that the newly proposed GGGs offer a simplified, user-friendly nomenclature to aid in patient counseling, with similar predictive accuracy in a population-based setting to previous classifications.

Minardi, D., Mazzucchelli, R., Scarpelli, M., Massari, F., Ciccarese, C., Lopez-Beltran, A., … Montironi, R. (2016). Prostate cancer glands with cribriform architecture and with glomeruloid features should be considered as Gleason pattern 4 and not pattern 3. Future Oncology, 12(12), 1431–1433. https://doi.org/10.2217/fon-2016-0113

The study published by Loeb et al. [1] has suggested to our transnational group of pathologists, to investigate the prognosis in a series of RP with acinar adenocarcinoma diagnosed in Ancona from 2005 to 2007 with Gleason score 3 + 3 = 6 (i.e., GGG 1) based on the 2005 International Society of Urological Pathology (IUSP) Modified Gleason System [2]. In a group of 395 cases, 151 patients with Gleason score 3 + 3 = 6 (GGG 1) acinar adenocarcinoma were identified. 147 (97%) out of 151 patients are alive without tumor relapse and biochemical recurrence after a period of follow-up ranged from 8 to 10 years.

Four (3%) out of 151 patients had relapse at the pelvic lymph nodes and then distant metastases, three of them were still alive at a mean follow-up of 82 months and one dead after 108 months. The histological slides of these four patients were reviewed, applying the Gleason grading based on the 2014 ISUP Modified Gleason System [3]. One of the three patients, still alive, had a Gleason score 6 (GGG 1) and nonfocal intraprostatic positive margins. The other two patients, still alive, showed a cribriform component composed of small cribriform glands with smooth contours and the dead patient had glands with glomeruloid features. The cribriform glands and glomeruloid pattern represented approximately 5% of the acinar adenocarcinoma in each case.

Experts' comments

Our observations in terms of morphology and prognosis are not different from those made by Ross et al. [4], who reviewed the slides of 19 cases of radical prostatectomy with adenocarcinoma Gleason score <6 that showed pelvic lymph node metastases. All cases submitted to histopathologic review showed higher grade than originally reported by the pathologists. In particular, two cases were upgraded to 4 + 3 = 7 with both poorly formed and cribriform glands; eleven cases with glomeruloid structures and small to large cribriform glands were upgraded to 3 + 4 = 7.

The cribriform component observed in our two cases was composed of small cribriform glands with smooth contours, considered as Gleason pattern 3 on the base of 2005 ISUP Modified Gleason System [5].

In 2008, Latour et al. [6] presented a set of images representing examples of cribriform pattern 3 to experts in uropathology. The majority of the participants to this study have considered the cribriform patterns as pattern 4; furthermore, the most of the cribriform lesions (i.e., 73%) were associated with a pattern 4 in other parts of the biopsy. The conclusion of this study was that the vast majority of small cribriform glands should be considered as Gleason pattern 4.

In the 2005 conference organized by the ISUP [5], the few cases of adenocarcinoma with glomeruloid features were considered as Gleason score 3 + 3 = 6, only some participants supported the idea that all small glomeruloid structures had to be reported as a pattern 4. In a subsequent study, prostate biopsies with adenocarcinoma with glomeruloid features were assessed to see whether glomerulations and concurrent high-grade adenocarcinoma were associated in the same core. Glomerulations were associated with high-grade adenocarcinoma, predominantly of pattern 4 in 80% of the cases in the same biopsy, and often with a transition to larger cribriform glands. Only in 16% of the cases the glomeruloid structures were associated with pattern 3 adenocarcinoma [7]. On the base of such an observation, it was suggested that glomeruloid structures represent an early stage in the formation of cribriform pattern 4 and should be all reported as pattern 4 [8].

In the 2014 ISUP Modified Gleason System [3], the cribriform glands, regardless of their border, and the glands with glomeruloid features have to be considered as a Gleason pattern 4. This means that three of our patients belong to the GGG 2 when the 2014 ISUP Modified Gleason System is applied.

In our three cases (GGG 1) that showed metastasis, the percentage of Gleason pattern 4 represented approximately 5% of the tumor. Originally, McNeal et al. [9] had proposed to report the percentage of Gleason grade 4/5, afterward the same group showed that this feature was an independent predictor of recurrence after RP [10]. In 2007, in a paper entitled ‘Should the Gleason score be replaced with the amount of high-grade prostate cancer?’, Vis et al. demonstrated that the amount of high-grade cancer is more important than the Gleason system in predicting prognosis, both in biopsy and in RP specimens [11]. In particular, the authors have suggested that in addition to the Gleason score, the amount

of Gleason patterns 4/5 should also be mentioned in the pathology report [11]. In the 2014 ISUP conference, emerging issues related to grading of adenocarcinoma were also discussed; in addition to the prognostic grade groups, the percentage Gleason pattern 4 present in biopsy cores should be present in the pathological report. As quoted in a recent editorial by Egevad et al., “The reporting of percentage Gleason 4 tumor tissue has the advantage that this highlights if a cancer is at the lower or higher end of a grade” [12]. As shown by Sauter et al. in a very recent publication, “there is a biological continuum within Gleason score 3 + 4 = 7 and 4 + 3 = 7 tumors that is reflected in clinical outcome” [13].

We have also revised the slides of the other 147 patients alive without biochemical recurrence and no tumor relapse. A Gleason score 3 + 3 = 6, that is, GGG 1, was confirmed in all cases. Our results are in agreement with the study by Kweldam et al. [14]. Their investigation was based on 1101 consecutive RP patients operated between March 1985 and July 2013. They demonstrated that “disease-specific death and metastasis do not occur in patients with Gleason score ≤6 at radical prostatectomy” [14], that is, none of their 449 patients with Gleason score ≤6 showed disease-specific death and metastasis.

Our findings on GGG1 cases are in agreement with the observation made by Epstein et al. [15] in a recently published study on contemporary prostate cancer grading issue, in which they showed that the GGG system is a validated alternative to the Gleason score. In agreement with these authors, the new prostate cancer grading system reflects prognosis more accurately, being at the same time simpler to define.

Our findings are supported by a recent observation made in a study, in which Rubin and his coworkers [16] have investigated the genomic background for PGGs using whole-exome and whole-genome sequencing data from 426 localized prostatic adenocarcinomas treated by RP. These authors have observed a significant increase in frequency of both genomic amplifications and deletions with increasing risk strata and of nonsynonymous point mutations. In particular, PGG 1 was haploid, whereas, groups 2–5

showed an increasing frequency of polyploidy. Such findings have given support for increasing genomic alterations with increasing PGGs [16].

Conclusion

Our findings give further support to the fact that prostate cancer glands with cribriform architecture and with glomeruloid features should be considered as a Gleason pattern 4 and not pattern 3. In particular, acinar adenocarcinoma with a Gleason score 3 + 3 = 6, based on the 2014 ISUP modification, has an excellent prognosis. In addition, the new prognostic grade grouping system represents a validated alternative to the Gleason score.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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