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European Association of Urology

Platinum Opinion

Grading Noninvasive Bladder Cancer: World Health Organisation 1973 or 2004 May Be the Wrong Question

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Tumour grade is a critical parameter in determining the management approach for patients with non-muscle-invasive bladder cancer. In 1998 a consensus conference convened by the International Society of Urological Pathology (ISUP) proposed a novel system to replace the World Health Organisation (WHO) 1973 grading system [1] and this recommendation was incorporated into the WHO classification of bladder tumours in 2004 (Fig. 1) [2]. The 2004 grading system has been adopted globally to the extent that several countries have largely abandoned the WHO 1973 system [3]. Here we discuss issues associated with this approach and suggest an alternate strategy for bladder cancer grading.

The ISUP 1998/WHO 2004 grading system was designed to overcome inherent problems with the WHO 1973 grading system. It is generally recognised that in the WHO 1973 system, grade 2 is a widely heterogeneous category, with the reported proportion of bladder tumours categorised as grade 2 varying from 13% to 69%, suggesting significant interobserver variation [4,5]. Moreover, noninvasive grade 2 urothelial carcinoma is associated with a progression risk of up to 20%, suggesting that a significant number of these patients have been undertreated [6]. To rectify this situation, the ISUP 1998/WHO 2004 classification categorised more atypical grade 2 tumours, which would be suitable for consideration of bacillus Calmette-Guérin (BCG) therapy, into the high-grade class. The criterion for urothelial carcinoma in situ was also slightly relaxed to include flat lesions with cytological atypia, corresponding to more atypical grade 2 papillary urothelial carcinomas.

The WHO 2004 grading system has resulted in a significant increase in high-risk category tumours with a consequent risk of overtreatment. This is important as BCG therapy can have significant side effects, while in rare cases a patient may even undergo cystectomy for intractable BCG symptoms, which would be a tragedy if the risk of tumour progression had been relatively low. The risk of overtreatment is particularly significant in the post-BCG therapy setting, in which recurrence of high-grade tumour would be an indication for cystectomy. A urologist faced with a report of recurrent high-grade urothelial carcinoma or carcinoma in situ would be unable to decipher where the tumour lies within the high-grade spectrum. Cystectomy might be appropriate for a high-grade recurrence corresponding to WHO 1973 grade 3, but not for a tumour that is at the lower end of the high-grade spectrum.

Although low-grade and high-grade bladder cancer may have different pathogenic pathways, it must be recognised that tumour grade represents a biological spectrum with a continuum of risk of tumour progression and that the “cutoffs” are essentially arbitrary and artificial. There has been a general tendency for all organ systems to reduce the number of grade categories, generally to low grade and high grade, which usually facilitates statistical analysis by increasing the number of patients in each group. A binary system may also simplify clinical decision-making as it eliminates the ambiguous intermediate category. However, a reduction in the number of grade categories, resulting in wider, more heterogeneous groups, is the antithesis of personalised medicine. Reporting fewer grade categories is also more difficult for pathologists as the distinction between the two groups for borderline cancers is observer-dependent and may be clinically critical. Conversely, reporting narrower grade categories would provide improved stratification, with the distinction between adjacent

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https://doi.org/10.1016/j.eururo.2019.05.001

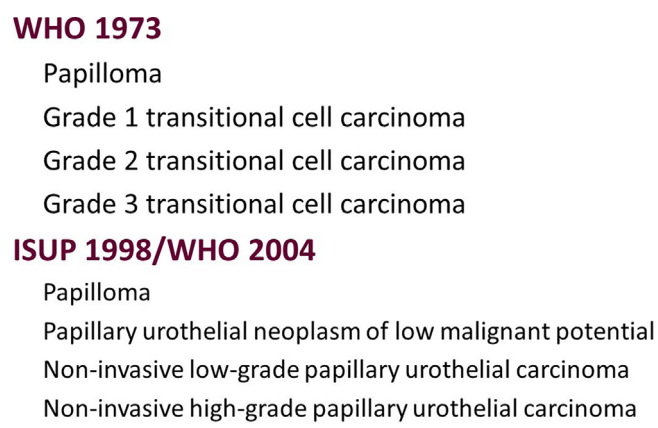

Fig. 1 – World Health Organisation (WHO) 1973 and International Society of Urological Pathology (ISUP) 1998/WHO 2004 classifications of urothelial carcinoma.

grades becoming less critical. A classic example of this approach is the recommendation to report the percentage of pattern 4 in Gleason score 7 prostate cancer. This has resulted in an evolution from reporting a single-tier Gleason score 7 to a two-tier system (3 + 4 and 4 + 3 [ISUP grades 2 and 3]), and an 11-tier system based on the percentage of pattern 4 (<10%, 10%, ... 90%, >90% pattern 4). This enables urologists to clearly identify a patient with 50% pattern 4 tumour and treat him according to either 3 + 4 or 4 + 3 treatment protocols after consideration of other factors such as prostate-specific antigen, tumour size, and the patient's risk tolerance.

Cheng et al. [6] proposed a four-tier grading system in which the category of papillary urothelial neoplasm of low malignant potential (PUNLMP) was abandoned and the ISUP 1998/WHO 2004 high-grade category was split into grades 3 and 4. Although this proposal would improve risk stratification, it has not gained widespread acceptance, perhaps because there was a potential for confusion as their grade 3 would be very different from WHO 1973 grade 3.

Another option would be to report both WHO 1973 and ISUP 1998/WHO 2004 grading systems in parallel, as currently recommended by the European Association of Urology guidelines [7] because of a lack of evidence that WHO 2004 grading is superior to WHO 1973 grading [4]. This would amount to a five-tier system and result in improved patient stratification (Fig. 2). Thus, in the post-BCG recurrence scenario, cystectomy could be offered for high-grade/grade 3 but not for high-grade/grade 2 tumours. This approach would also permit urologists to use tumour grade more effectively with other parameters, such as tumour size, multifocality, and interval to first recurrence. For example, BCG therapy could be recommended for larger or multifocal high-grade/grade 2 tumours, but only for small unifocal tumours on first presentation if they are high-grade/grade 3.

Another problem with the ISUP 1998/WHO 2004 system relates to the difficulty in mapping back to the WHO 1973 grade, which creates problems for epidemiological databases and use of the well-established EORTC risk score for patient stratification in Europe [8]. Moreover, if only the ISUP 1998/WHO 2004 scheme is reported then it is difficult to use the considerable volume of historical data with long-term follow-up that is based on the WHO 1973 system. Both these issues would be mitigated by reporting both systems.

In summary, while the development of the ISUP 1998/WHO 2004 grading classification was a commendable attempt to deal with problems associated with the WHO 1973 grading of bladder cancer, it has created further problems. In particular, while the widely heterogeneous WHO 1973 grade 2 category has resulted in therapeutic uncertainty and potential undertreatment, the creation of an equally wide heterogeneous high-grade category poses a serious risk of patient overtreatment. The reporting of both systems in parallel would promote improved risk stratification and better enable clinicians and patients to make

Fig. 2 – Relationship of World Health Organisation (WHO) 1973 and International Society of Urological Pathology (ISUP) 1998/WHO 2004 classifications of urothelial carcinoma. Concurrent use of both systems improves risk stratification. G = grade; PUNLMP = papillary urothelial neoplasm of low malignant potential; LG = low grade; HG = high grade.

evidence-based informed decisions regarding the management of noninvasive bladder cancers.

Conflicts of interest: The authors have nothing to disclose.

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