Histological tumour grade (Required)

Reason/Evidentiary Support

Histologic grading of urothelial tumours is best considered in two categories, non-invasive papillary tumours and invasive carcinoma. For non-invasive papillary tumours the 2016 World Health Organization (WHO) remains the same as in the 2004 WHO and continues to recommend the grading system first put forward by the International Society of Urological Pathology (ISUP) in 1997.[1] The system is now recommended by almost all major pathology and urology organizations as the preferred grading system.[2,3]

This is a 3-tiered system with the lowest category of papillary urothelial neoplasm of low malignant potential considered to represent a tumour without the capacity to invade or metastasize and as such is considered to be a benign neoplasm.[4] This lesion represents up to one-third of newly diagnosed non-invasive papillary tumours. Papillary urothelial neoplasm of low malignant potential is not reported using this dataset. It is nonetheless a significant diagnosis and does indicate an increased risk for the development of other neoplasms in the urinary tract.

Grade heterogeneity is not uncommon in papillary urothelial carcinoma being reported in up to 32% of cases.[4,5] It is currently recommended that tumour grade be assigned based on the highest grade present. Some authors have recommended considering a tumour low grade if the high grade component accounts for less than 5% of the tumour volume.[4,6] Using the 1999 WHO grading system, Billis et al found that pure grade 3 tumours were more often muscle invasive than tumours with mixed grades 2 and 3.[5] They also reported that pure grade 1 tumours were invasive in 25% of cases compared to 66% of predominantly grade 1 tumours with a grade 2 component.[5] Specific percentages of the grades in the mixed grade cases were not provided. In another study Cheng et al studied grade heterogeneity in non-invasive papillary neoplasms using the 1998 ISUP grading system.[4] Tumours were evaluated based on predominant and secondary grades but secondary components were ignored if less than 5%.[4] In their study worst, predominant and average grade all were significant predictors of progression.[4] Progression was higher in pure high grade tumours (>95% high grade) than in mixed high/low grade tumours (5% to 95% high grade).[4] In another study tumours with less than 10% of high grade histology (5% of the cases) were compared with low and high-grade tumours.[7] The progression free and cancer specific survival of the mixed cases was similar to low grade tumours and significantly better than that of high grade cases.[7] The limited data does not allow for a definitive statement regarding reporting of cases with a small volume of high grade tumour or to determine what percentage of high grade tumour is necessary to indicate a significantly worse prognosis. The International Consultation on Urologic Disease recommended against the application of an arbitrary percentage of high grade tumour to ignore when assigning grade.[2] The 2016 WHO recommends grading based on the highest grade component and acknowledges the uncertainty of how to approach cases with a small proportion of high grade tumour. It does indicate that “it may be prudent to state the proportion of high-grade disease.”

The 1973 WHO grading system for papillary tumours remains in use in many regions and some published guidelines specifically recommend the reporting of both the current WHO grade with the 1973 grade,[3,8,9] while others provide for the 1973 grade to be included by institutional choice.[2,3,10] It is beyond the scope of this commentary to provide a detailed argument for or against the 1973

WHO. Interested readers can review those discussions elsewhere.[2,3,9,11] There is an extensive literature based on the 1973 WHO system documenting its significance as a predictor of outcome for papillary urothelial carcinoma. These include many studies using material from phase III clinical trials. The current European Organisation for Treatment and Research of Cancer (EORTC) risk tables, developed from the data of 8 phase III clinical trials use the 1973 WHO grading system.[12] The International Collaboration on Cancer Reporting (ICCR) dataset follows the WHO 2016 approach with reporting of the WHO 2016 grade as a required element and the inclusion of other grading systems as optional.

The grading of invasive urothelial carcinoma is another area of controversy. In North America the vast majority of invasive urothelial carcinomas have been diagnosed as high grade in contrast to European studies where a substantial percentage of invasive tumours have been graded as 2 or even 1. Currently there is general agreement that grade 1 tumours (WHO 1973), largely corresponding to papillary urothelial neoplasm of low malignant potential, lack the capacity to invade.[13-15] In studies using the 1998 ISUP/WHO 2004 grading system the vast majority of invasive tumours are high grade.[16,17] The conclusion of the International Consultation on Urologic Disease pathology group was that all invasive carcinomas should be considered high grade.[2,18] It has been noted that there are variants of urothelial carcinoma with low grade cytologic features, such as the nested variant, that appear to behave stage for stage like usual high grade carcinoma.[19-22] When variant histology such as this is present the tumours should be reported as high grade despite the bland cytology in order to reflect the biologic behaviour.[23] Nonetheless it is equally apparent that many pathologists have graded invasive urothelial carcinomas using the 1973 WHO and other systems and have demonstrated its prognostic significance.[12,14,24,25] We recommend the 2016 WHO approach of continuing to grade invasive carcinoma using the WHO 2004 system while recognising that the vast majority of tumours will be high grade. If invasive tumours are graded using an alternative grading system this should be indicated.

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