Analysis of papillary urothelial carcinomas of the bladder with grade heterogeneity: supportive evidence for an early role of CDKN2A deletions in the FGFR3 pathway.

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Justine Varinot, Eva Compérat

Dpt of Pathology

Hôpital Tenon, Assistance Publique- Hôpitaux de Paris, UPMC Paris VI, Paris, France

Expert's summary

This pathological study examines histologically heterogeneous cases of papillary non muscle invasive bladder carcinomas (NMIBC) on a morphologic, protein and molecular level. The authors working hypothesis is that molecular alterations already take place in histological low grade aspects of heterogeneous tumors and the changes predate the morphological appearance.

The authors show that even low grade aspects display several molecular changes, such as increased expression of MIB-1, representing the proliferation index of the tumour. This is particularly true for areas affected by the *FGFR3* mutant pathway, known to be overexpressed in low grade tumours. Furthermore they show that homozygous deletions of CDKN2A, located on 9p21, frequently deleted and probably playing a role in stage progression, are found in low and high grade areas, suggesting that these deletions occur earlier than morphological changes can be detected microscopically.

Expert's opinion

Grading of NMIBC is an important prognostic factor. One of the major challenges in pathology is the grading of heterogeneous (low and high grade) lesions. The current convention suggests reporting the tumor as high grade, if the high grade component represents more than 5% (1). Recent data of clinical studies have shown that even a cut-off of 10% could be acceptable to consider a lesion still as low grade (2). Some newer studies show that if untreated, these mixed carcinomas might have a higher

rate of grade progression, but little is known about the carcinogenesis in the different tumor areas and the different pathways, which might impact on grading (3, 4).

From a clinical point of view the findings of the paper underline the current practice of reporting the highest grade on these mixed NMIBC, even if the high grade part represents only a small amount of the tumour (5%). Obviously the presence of increased MIB-1, but also several mutations already occur in the histological low-grade parts.

One of the major problems of the study is the low sample number (19 cases), on the other hand the results were very clear with 88% displaying a homozygous CDKN2A deletion in the low grade areas and increased expression of MIB-1 in 12/19 cases.

The cut off of 5% should probably be reconsidered. Maybe all heterogeneous tumors, independently from the amount of high grade, should be considered as high grade lesions. Nevertheless larger studies would be requested to have further insights in one of the most difficult problems of uropathology.

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