Reviewer's report

Title: Low Frequency of Defective Mismatch Repair in a Population-based Series of Upper Urothelial Carcinoma

Version: 1 Date: 17 December 2004

Reviewer: Arndt Hartmann

Reviewer's report:

Ericson and coworkers performed a population-based study of a defective mismatch repair (MMR) system on 216 tumors of the upper urinary tract (UUT) using microsatellite analysis (NCI consensus panel) and immunohistochemistry (MLH1, MSH2; MSH6, PMS2). The authors found 14/216 tumors showing microsatellite instability (MSI) consisting of 9/216 (4%) tumors with a MSI-high and 5/216 (2%) tumors with a MSI-low phenotype. 3/181 (1.6%) of the stable tumors and one tumor without information on the microsatellite instability status as well as 5/9 (55%) MSI-high tumors showed a loss of at least one MMR protein. The analysis of patients with metachronous and synchronous tumors showed MSI in the concomitant tumors in 5/6 analyzed tumors.

Major Compulsory Revisions:
The authors found a remarkably low frequency of MSI in the investigated tumors, which is in contrast to four published series from Germany, the US, France and the UK as listed in the comparison table. The authors described that they used tumor blocks containing at least 20% tumor tissue for DNA isolation without prior microdissection. This might be a reason for the low frequency of cases with MSI. Using material with only at least 20% tumor cells probably make it very difficult to detect microsatellite changes because the DNA form the tumor cells might be diluted during PCR analysis by the normal urothelial or inflammation cells. The authors should give a comment on this in the discussion. In addition, other possible explanations should be discussed (ethnic differences, selection bias in other studies, population-based study in this paper etc).

The authors also did not verify their MSI results. Own experience showed that microsatellite changes can be caused by PCR errors. The authors should repeat the analysis of the MSI positive cases.

Images of the MSI-positive cases, including the immunohistochemistry should be shown.

In previous studies (e.g. Hartmann et al., Human Pathology 34:222-227 (2003) a significant correlation of an inverted phenotype with MSI was found. How was the histology of the MSI-positive cases in this regard?

Minor Essential Revisions:
The authors defined MSI by the presence of extra peaks. This sounds a little bit confusing. Haven't the authors counted band-shifts as MSI? The authors should clarify this in the Materials & Methods section.

On page 11, discussion section, line 9 of the second paragraph the authors should correct a typing error: “…detected in or study,…”.

What next?: Accept after minor essential revisions
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.