Reviewer's report

Title: Matrix-metalloproteinases-1, -2, -3, -9, their inhibitors TIMP-1, -2, and the MMP1/TIMP1-complex in blood plasma as markers for transitional cell carcinoma of the bladder

Version: 4 Date: 7 April 2006

Reviewer: Cornelis Sier

Reviewer's report:

General
This manuscript contains convincing data about enhanced plasma levels of MMP-2 in bladder cancer patients. The usefulness as a stand-alone clinical marker is however still open for discussion, as the authors indeed indicate. Enhanced MMP-9 plasma levels seem primarily associated with patients with the highest grade cancers (G3) and perhaps with metastasis (mBCa). Decreased TIMP-1, TIMP-2 and MTC1 plasma levels seem also associated with the presence of bladder cancer, but their levels are not significantly decreased in patients with metastasis and G3. This defect, combined with the small detection ranges and strong overlap between patients and controls, makes them less fit as candidate tumour markers. That is in my opinion the essence of this manuscript.

To enhance the relevance of the manuscript the authors emphasized the possibility of using combinations of their parameters for clinical applications. The way they did it, using a not very common computer program as a black box, produced very nice results for some combinations with respect to specificity and sensitivity (both >90%). Because very few readers will be able to verify these data, that approach in my eyes needs visualization: Seeing is believing! Why didn't the authors choose to add a simple dot-plot for one of their successful combinations: All patients (black dots) and controls (white dots) with parameter A on the x-axis and parameter B on the y-axis, including indications of the used cut-off values on the respective axes? A simple graph like that would show in quadrants the performance of the single parameters and the combination.

Alternatively, to show the performance of all their parameters in combination, they could have chosen to add a dendrogram, showing that patients and healthy controls end up in different clusters based on parameters A, B, C... These simple statistical methods are on almost all statistical programs available and show exactly what is possibly relevant and what not.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
Table I: I understand that the data for the control group, previously presented as means, changed because they are now given as median values. But please explain why the median values for the patients also changed from the previous version.
Discussion: My previous opinion, that the discussion is too superficial does not change. The major part is filled with a repetition of the results section and the reason why plasma was used in this study and not serum.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Abstract:
Suggestive sentences in the result section of the abstract should be changed:
The MEDIAN MMP2 concentration was elevated in all patient GROUPS with TCC in comparison to controls.
‘non-invasive tumour detection’ as mentioned in the abstract (conclusion section) could be interpreted in 2 ways and should be avoided.
‘p=’ missing in table 1 for mBCa/TIMP1
Figure legend 1 should mention that the healthy controls are included.

Discretionary Revisions (which the author can choose to ignore)
none

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No