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: 10 April 2006

Reviewer: Andrew Roddam

Reviewer's report:

General

This revised version of the manuscript is much improved on the first version I reviewed and I have only some minor revisions.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. I found Table 1 very difficult to read and interpret. There are many comparisons being made here and it is not immediately obvious to me that all of these comparisons are really necessary. Moreover there is no account made for multiple comparisons – I'm certain that if appropriate control were made then some of the significant associations presented would no longer remain significant. I would suggest that the authors attempt, as much as possible, to simplify this table to make it more accessible to readers.

2. In Table 2 it is not necessary to display the full correlation matrix – normally the lower triangle is adequate (as the upper triangle is simply a mirror image). Additionally it is only necessary to display at most 2 decimal places for a correlation.

3. My original concern over the degree of correlation between the markers and perhaps a degree of overfitting still remains. Whilst the use of ROC analysis is a good way to present the results, this does not overcome this problem and it is noteworthy that the two markers selected as the “best” virtual combination are those two markers which have the highest degree of correlation in Table 2. I would suggest that the authors consider including a cautionary note regarding interpretation of this “near-perfect” virtual classifier as I think this may be due to a high degree of co-linearity between the markers.

4. In Table 3, reduce the number of decimal places for the AUC to 2. Again in this table multiple comparisons are being made but no adjustment is given to the p-values for significance.

5. I appreciate the desire to show many different estimates of sensitivity and specificity in Table 4 but are these all really necessary for the purposes of this paper? Maybe simply presenting the optimal and 95% sensitivity/specificity would be adequate?

Discretionary Revisions (which the author can choose to ignore)

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