Reviewer's report

Title: Prognostic impact of urokinase-type plasminogen activator system components in patients with clear cell renal cell carcinoma

Version: 1 Date: 15 August 2014

Reviewer: Fred Sweep

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The study “Prognostic impact of urokinase-type plasminogen activator system components in patients with clear cell renal cell carcinoma” by Fuessel et al. provides new insight in the potential role of components of the plasminogen activator system in Renal Cancer. Earlier studies yielded conflicting results obstructing further studies on the clinical role of these parameters. Most likely these discrepancies resulted from inclusion of a series of tumor tissue samples from inconsistent cohorts of patients with different RC subtypes, use of different assay types and ways of protein extraction. The present study provides elegant data on parallel assessment of antigen levels of uPA, its receptor and its inhibitor in a consistent cohort patients with ccRCC without clinically detectable distant metastasis at the time of diagnosis. In my view the paper therefore provides valuable clinically relevant data bringing theses proteases biomarkers back in picture in particular for organ-confined RC.

In general the outline to the study, patients and samples cohort, analytical and statistical methods and results are very well and clear described.

Minor revisions.

1) Abstract: last line please HR 9.8 by 9.83.

Materials and Methods. 2) No data are provided on storage time of the samples. What is time interval between collection of data and extraction and assessment of protease protein levels? Is this time interval equally distributed between all clinical pathological parameters? 3) Are the assays done in one assay run? If not what is the within and between assay run CV for the three parameters? 4) As the authors compare protein results between different institutes (papers table 6) could they provide data on between institute/lab CVs? 5) Info on external quality assessment performance with the used kits would be helpful in particular as most authors used the same commercial assay type.

Results. 6) Page 9. First paragraph: please refer to a figure or table. 7) Page 9, Line 21; could the authors explain why the correlation between uPA and its inhibitor (0.65) seems higher than between uPA and its receptor (0.51)? 8) Page 11, line 11-13. Why do the authors regard a p value of 0.064 (PAI-1) conversely to those of uPA and uPAR, while later on they explain an even higher p value of 0.077 a trend to significance (line 25)?

9) Discussion, some lines on the physiological interdependece of uPA, PAI-1 and
uPAR should be added. 10) Do the assays specifically measure each of these three components or are complexes between the components also detected? If so would for instance measurement of the uPA-uPAR complex be of any value regarding the high HR of “uPA and/or uPAR high”
11) Figure 2: please add the terms uPA, uPAR and PAI-1 in the figures itself.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'