Reviewer's report

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

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Reviewer: Andreas Scorilas

Reviewer's report:

This is an interesting and well written research article that describes the prognostic significance of the uPA/uPAR/PAI-1 system for ccRCC patients, including the meaningful subgroup of patients with organ-confined disease. The sample size is adequate, the methodological approach is sound, the results are well documented and conclusions are reasonably derived. The following suggestions can further improve this work.

Major Compulsory Revisions

The background section needs to be shortened. For example, too many epidemiological data are presented. On the other hand, the medical need that this study aims to address should be emphasized: Why is important to provide early prognostic information for ccRCC patients? How can this affect the decision making process during ccRCC management (administration of adjuvant therapy, intense imaging/monitoring of patients)?

The inter- and intra-assay coefficients of variation (%CV) should be reported.

The advantages of using detergent based reagents should be described more clearly.

The use of the median levels as the cut-off point should be justified.

The authors mention that there is a significant association between the uPA system components in the tumor but not in the adjacent normal tissue. This is an important finding and should be discussed more extensively in parallel with findings in other tumor types.

The multivariate analysis needs to be adjusted. Given that stage and grade might be correlated they should not be included in the same multivariate model as this introduces multicollinearity. It is proposed that two base models are produced: one including stage and one including grade. For the same reason, the three components of the uPA system cannot be included in the same multivariate model. The development of reduced models could also be followed (uPA and stage only, uPA and grade only etc).

Minor Essential Revisions

Abstract, conclusions: The phrase “indicate and essential function” could be omitted.
It is mentioned that uPA levels are reduced in the tumor tissue parts and at the same time associated with poor prognosis. This should be discussed.

The Wilcoxon signed-rank test could be more appropriate for paired-samples analysis (Fig.1).

Discretionary Revisions

The title could be changed to indicate that this study was performed in patients without clinically detectable distant metastases at the time of diagnosis.

The prognostic relevance of the combination of the three molecules could also be assessed. For example, patients could be divided into three groups: all three uPA components low, uPA or uPAR or PAI-1 high, all three uPA components high.

**Level of interest:** An article of outstanding merit and interest 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