Author's response to reviews

Title: The expression of type 1 plasminogen activator inhibitor (PAI-1) in clear cell renal cell carcinoma (CCRCC) and its impact on angiogenesis, progression and patient survival after radical nephrectomy

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Dear Editor,

We thank you for your letter with constructive criticism and advisees.

We hereby address point-by-point the comments detailed in reviewer’s report.

As far as possible we have implemented the changes recommended by the
reviewer and they are clearly marked in yellow in the revised manuscript.

Ad: Major concerns:

We agree the high correlation between PAI-1 expression and traditional clinical and pathological prognostic parameters like tumor stage, tumor size, nuclear grade, sarcomatoid differentiation may limit the added prognostic utility of this marker in RCC. However, our findings give strong support to the conclusion that PAI-1 may turn out to be a valuable molecular and biochemical marker for tumor aggressiveness, which can be used as a supplement or a possible substitute to standard morphological methods. (This has now been included in the Discussion page: 11)

Most of our patients with positive PAI-1 had stage T3/T4 tumours. Two of the 3 patients with stage T1/ T2 tumours died in RCC. Even though there were very few PAI-1 positive tumours in organ confined stages (T1/T2), this molecular marker turned out to be a highly significant predictor of developing metachronous metastasis in these patients with HR =13.71 (p=0.002). Further studies however seems necessary to fully reveal the prognostic impact of PAI-1 expression in T1-T2 tumours. (This has now been included in the discussion page 12.)

We do not think that 9% positivity makes it uninteresting to invest in terms of targeted therapeutics toward PAI-1. We agree however, that it might be discussible whether our findings deserves a tremendous investment or not. However, no doubt, it is of interest to illuminate the relationship between morphological and molecular features that may define the biology of RCC and open up for new therapeutic measures. It is not a part of our study to discuss the
pathways and mechanisms of the current targeted therapies for RCC.

Ethical consent:

Approval to use the biological material for research purposes was granted in 2004 by the local authority at Karlstad Central Hospital in Sweden according to Swedish regulations. In Norway the appropriate Norwegian authority, Norwegian Social Science Data Services, recognized this approval. The study was carried out in accordance with the standards of World Medical Association Declaration of Helsinki as revised in 2008. (Page 5.)