Editor's comments:

Urothelial bladder carcinoma is a multifactorial disorder with diverse environmental and genetic etiologies. It comes out from literature that much effort has been put on the prognostic significance of some of the polymorphic variants associated with aggressive urothelial tumors and towards personalized therapeutic interventions. Special attention has been given to the elucidation of the genetic profile of patients in an effort to standardize alleles fro prognostic purposes. It appears that classical histology with traditional immunostaining lags behind since it can not give us consistent results with accuracy and reliability necessary for prognostic purposes.

In the current work an attempt is made in order to assess HE4 activity in urothelial tumors by means of immunohistochemistry in de-parafinized sections. The authors claim that the aim of this study is to evaluate the expression of HE4 and justify its prognostic significance. The study is based on a small sample of patients diagnosed with urothelial neoplasms. Immunohistochemistry is undertaken using classical methodologies and tumor grading was scored using an empirical method of "negative-weak-strong" as far as histological staining is concerned. No densitometric measurement were taken using appropriate instruments.

As the authors state in discussion, this study has limitations: The patient population is small and by no means it can be concluded (as they say) that HE4 may serve as a predictive protein for invasiveness in bladder carcinoma cases. Moreover, in conclusion, authors state again that the population was small and they hope their study to encourage researcher to study the subject. Overall, this study used weak statistical methodologies and oversimplified extrapolations. Finally, the manuscript is of inferior language quality and has to be revised by a language expert due to many language errors.

In conclusion,

I suggest that the following topics have to be addressed by the authors:

1/The help of a language expert is needed,

2/ thorough revision of the discussion including a critical analysis of international literature is necessary and

3/ having in mind that we talk about a clinical study, the conclusions could not possibly contain ambiguous expressions like "The Human Epididymis Protein 4 is infrequently expressed",or "slight difference was seen in invasive versus non-invasive groups" or "In conclusion, HE4 was seen mostly in invasive bladder carcinoma cases" .

The conclusions should be based on solid statistical data (bigger sample, improved random sampling etc.), real measurements, e.g. use of a microdensitometer (not simply weak or strong staining estimates, which is a naïve approach for prognostic markers) and not on simplifications. Alternatively authors could simply present their work as preliminary indicative results based on a small sample.

Author's feedback:

Thank you for your comments. We admit that that our manuscript is now more presentable along with your suggestions.

Here are changes we made in the manuscript:

1) When we noticed that we didn't include serum level and/or urine level measurements, we conducted another study prospectively. Sample collection and densitometric measurements were finalized and sent for statistics.

2) As it was proved for myometrial invasiveness, it may also predict urothelial tumor invasion status. Of course it is too early to claim that it may serve as a predictive protein for invasiveness in bladder carcinoma cases.

3) language check was done and highlighted

4) With 3 international literature, analysis of muscle invasion was included in the discussion section (ref-14,15,16)

5) In conclusion, ambiguous expressions like "infrequently", "slight difference", and "mostly" words were all deleted and the conclusion was re-written.

Thanks again for sparing your valuable time for reviewing our manuscript.