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Re: Anders Lidgren, Ylva Hedberg, Kjell Grankvist, Torgny Rasmuson, Anders Bergh and Börje Ljungberg. Hypoxia-Inducible Factor 1 α Expression in Renal Cell Carcinoma Analyzed by Tissue Microarray. *Eur Urol* 2006;50:1272–7

Dr. Lidgren and coworkers have to be congratulated for the presentation of their analysis of hypoxia-inducible factor 1 α (HIF-1 α) expression using tissue microarray in a large series of 216 patients with renal cell carcinoma (RCC) of any T stage, treated with radical nephrectomy [1]. The authors also reported on the possible correlation between HIF-1 α expression and other well-known clinicopathologic variables. It is very important to notice that the percentage of positively stained tumour cells was uniform throughout the study period, confirming that tissue microarray is a useful method that provides stable, feasible, and consistent results also if done on formalin-fixed tumour blocks. In this study, the HIF-1 α staining was detected using a monoclonal antibody (NB100-131; Novus Biologicals, Littleton, CO); the HIF-1 α staining was found mainly in the cytoplasm and nuclear staining was only sparsely observed and was disregarded. The level of HIF-1 α expression did not differ among the RCC subtypes and, interestingly, for patients with clear-cell RCC (cc-RCC), tumour size correlated inversely ($p = 0.012$) with HIF-1 α expression and high HIF-1 α cytoplasm staining correlated with longer survival with a p value that nearly reached significance ($p = 0.0553$). Intracapsular cc-RCCs are known to have an overall excellent prognosis, but 15–20% of patients with T1–T2 will have a recurrence and eventually die from the disease [2]. Therefore, to evaluate the prognostic significance of HIF-1 α cytoplasm staining in intracapsular cc-RCC, given the reported inverse correlation between HIF-1 α expression and tumour size in the whole series, it would have been interesting if the authors

could have provided their results in the 66 patients with cc-RCC limited to the kidney (pT1a, pT1b, pT2).

In most cancers and also in reports on cc-RCC, high HIF-1 α levels have been associated with an unfavourable prognosis [3–5]. On the contrary, Lidgren and coworkers indicate a trend towards better survival for patients with high HIF-1 α cytoplasmic protein expression but, given the nuclear transcriptional action of the HIF-1 α protein [6–8], the evaluation and detection of a high HIF-1 α nuclear staining in such patients with better prognosis, would have strengthened the authors thesis that “an upregulation of HIF-1 α is not necessarily all negative, at least not in conventional RCC” and that “a hypoxia-independent pathway, other than through HIF-1 α , might be present in this RCC type,” but unfortunately using the above-mentioned monoclonal antibody and tissue microarray, the nuclear staining was only sparsely detected. In a previous study, the same study group showed that HIF-1 α mRNA expression represents a favourable independent prognostic factor in RCC, although no information was available on the subcellular location of HIF-1 α [9]. The different subcellular location of HIF-1 α might constitute an important confounding factor in expression studies. Moreover, it would have been of great value if the authors could provide also the data about the von Hippel-Lindau tumour suppressor protein (pVHL) expression to confirm the inverse correlation among pVHL 19, pVHL 30, and HIF-1 α and therefore to show that not only high cytoplasmic HIF-1 α expression but also low pVHL expression correlate with longer survival in their series.

As far as we are concerned, being currently involved with the evaluation of pVHL and HIF-1 α expression using tissue microarray on formalin-fixed tumour blocks, the positive correlation between high HIF-1 α cytoplasmic staining and survival, without detecting the same correlation

between high HIF-1 α nuclear staining and survival cannot be considered enough to clear the field and further studies are needed to shed light on renal tumorigenesis.

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Reply to Andrea Minervini, Sergio Serni, Marco Carini and Claudio Di Cristofano's Letter to the Editor re: Anders Lidgren, Ylva Hedberg, Kjell Grankvist, Torgny Rasmuson, Anders Bergh and Börje Ljungberg. Hypoxia-Inducible Factor 1 α Expression in Renal Cell Carcinoma Analyzed by Tissue Microarray. *Eur Urol* 2006;50:1272–7

The comments on our study made by Minervini et al are much appreciated. They comment on the finding that in our study hypoxia-inducible factor 1 α (HIF-1 α) staining was found mainly in the cytoplasm, whereas nuclear staining was only sparsely observed. This was validated with repeated staining and also with staining on regular samples. With the antibody used, the HIF-1 α staining of the cytoplasm was mainly found. However, by using another antibody the staining of the renal cell carcinoma (RCC) tissue microarrays might have been different. Although the different RCC types did not differ with the immunohistochemical analysis in our study, it is important to analyze the different RCC types

separately. The trend that high HIF-1 α expression correlates with longer survival is supported by other studies [1,2]. Also in other recent studies by our group, as elevated vascular endothelial growth factor (VEGF) mRNA as well as elevated HIF-1 α protein analyzed by western blot correlated to better survival in patients with clear-cell RCC (cRCC) but not in those with papillary RCC [3,4]. When endoglin, a marker of angiogenesis evaluating intratumoral microvessel density was analyzed, the results indicated that endoglin expression was inversely related to stage and survival in cRCC [5]. Why higher levels of these angiogenic variables trend to associate with better prognosis in cRCC is unclear, but they indicate that mechanisms other than a hypoxia dependent-pathway are present in cRCC.

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