Prostate-specific membrane antigen and renal cell carcinoma: a new diagnostic and therapeutic target?

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The prostate-specific membrane antigen (PSMA) is a membrane glycoprotein (type II-carboxypeptidase) encoded by the FOLH1 gene, which is hyper-expressed in prostate cancer (PCa). 68Ga-PSMA PET/CT is a new diagnostic tool for the localization of PCa foci in patients with biochemical recurrence. Its use in pre-surgical staging as well as in early treatment evaluation is also under investigation (1). Moreover, the possibility of labeling PSMA antagonists with radionuclides emitting α and/or β-particles is becoming an interesting therapeutic application for the same molecule (2). However, PSMA, despite its name, is not really specific for PCa as it is also expressed by endothelial cells in the neovascular tissue of many solid tumors including kidney cancer. It has also been reported that the expression of PSMA in normal renal parenchyma can be detected within the brush borders and apical cytoplasm in a subset of proximal tubules (3,4).

Recently, Spatz *et al.* (5) evaluated PSMA immunohistochemical expression in neovascularized tissue in a cohort of 257 patients with renal cell carcinoma (RCC), mostly clear cell RCC (ccRCC) and, to a lesser extent, papillary RCC (pRCC) and chromophobe RCC (chRCC). The authors correlated PSMA expression with clinical-pathological parameters related to 68Ga-PSMA PET/CT. They also investigated the possible prognostic role of *FOLH1* (folate hydrolysis 1) gene encoding for PSMA in patients with ccRCC and pRCC. Results of immunohistochemical analysis revealed that PSMA hyperexpression was only present in the endothelium of neovascular tissue in RCC samples. In particular, 82.5% of ccCRCC and 71.4% of chRCC samples expressed PSMA glycoprotein, whereas only 13.6% of pRCC showed PSMA staining.

For the first time, Spatz *et al.* highlighted a significant correlation between increasing levels of PSMA expression and overall survival among patients with ccRCC. The association between PSMA expression and overall survival also maintained its significance (HR 2.02; 95% CI: 1.08–3.79) after correlation with key clinical features such as tumor grade, primary tumor stage and metastases. These results were largely supported by the data analysis of RNA expression from the Cancer Genome Atlas (TCGA). The authors reported a significant correlation between the expression of FOLH1 mRNA and survival in both univariate and multivariate analysis in pRCC patients, whereas it was only significant in univariate analysis in ccRCC patients. These results allow us to hypothesize an important role of PSMA in the management of RCC patients.

Recently, a potential role of 68Ga-PSMA PET/CT was reported in the preoperative evaluation of patients with RCC (6,7). The main advantage of 68Ga-PSMA PET/CT compared to conventional methods, in particular CT, lies in its ability to detect small lymph node lesions that do not exceed CT volumetric limit. In addition, the possibility of performing a whole body scan enables distant metastases to be detected.

PSMA could also be used to evaluate response to therapy in RCC. At present, inhibition of angiogenesis represents a new treatment strategy for RCC.

It is estimated that more than 300 compounds are currently being investigated for their potential anti-angiogenic effect, and a large series of inhibitors of angiogenesis have shown great potential in (pre)clinical studies for the treatment of many tumors.

Sorafenib and sunitinib, two tyrosine kinase inhibitors of the VEGF and PDGF receptor, were recently registered for the treatment of metastatic RCC.

68Ga-PSMA PET/CT could be a triage test for

antiangiogenic therapy and for subsequent evaluation of the response, monitoring the variations of "PSMA expression" as a surrogate of neo-angiogenesis *in vivo*. To date, only one study performed in eight RCC patients revealed a potential role of 68Ga-PSMA PET/CT in the evaluation of early response to systemic therapy compared to MRI and CT (8).

According to Spatz *et al.*, PSMA may represent a molecule to be used as both a diagnostic and therapeutic agent in RCC. The latter application could be very important if we consider that RCC remains largely incurable, despite the increasing number of currently available drugs.

Like PCa, the possibility of labeling PSMA antagonists with α and/or β particles (9,10) could also pave the way for an effective radionuclide therapy in patients with RCC.

Although there is still a long way to go, in our opinion we are heading in the right direction. However, large-scale prospective studies are warranted.

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Footnote

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