

## First clinico-pathological evidence of a non PSMA-related uptake mechanism for Ga-PSMA-11 in salivary glands

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The intense accumulation of PSMA radioligands in salivary glands is still not well understood. It is of concern for therapeutic applications of PSMA radioligands, as therapeutic radiation will damage these glands. A better understanding of the uptake mechanism is, therefore, crucial to allow the finding of solutions to reduce toxicity. The aim of this study was to investigate on whether or not the accumulation of PSMA-targeting radioligands in submandibular glands (SMG) can be explained with PSMA expression levels using the methods of autoradiography (ARG) and immunohistochemistry (IHC). All patients gave written informed consent for further utility of the biological material. SMG of 9 patients, pancreatic tissue of 4 patients and prostate cancer (PCA) lesions of 9 patients were analyzed. Fresh tissue specimen were analyzed by means of PSMA-IHC (using an anti-PSMA-antibody and an immunoreactivity score system - IRS) and ARG using Lu-PSMA-617 (with quantification of the relative signal intensity compared to a PSMA-positive standard). The SUV in salivary glands, pancreas and PCA tissues were quantified in 60 clinical Ga-PSMA-11 PET scans for recurrent disease, as well as the 9 primary tumors selected for ARG and IHC. PCA tissue samples revealed a wide range of PSMA staining intensity on IHC (IRS 70-300) as well as in ARG (1.33 - 21.98%). This variability on PCA tissue could also be observed in Ga-PSMA-11 PET (SUV 4.4-16) with a significant correlation between ARG and SUV ( $< 0.001$ ,  $R^2 = 0.897$ ). On IHC, ARG and Ga-PSMA-11 PET, the pancreatic tissue was negative (IRS = 0, ARG =  $0.1 \pm 0.05\%$ , SUV of  $3.1 \pm 1.1$ ). The SMG tissue displayed only focal expression of PSMA limited to the intercalated ducts on IHC (IRS 10-15) and a minimal signal on ARG ( $1.3 \pm 0.9\%$ ). In contrast, all SMG showed a high Ga-PSMA-11 accumulation on PET scans (SUV  $23.5 \pm 5.2$ ). Our results indicate that the high accumulation of PSMA radioligands in salivary glands does not correspond to a high PSMA expression levels determined using ARG and IHC. These findings provide evidence, that the significant accumulation of PSMA radioligands in SMG is not primarily a result of PSMA-mediated uptake.

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