



Novel ^{99m}Tc -labeled Small Molecule Inhibitors of Prostate Specific Membrane Antigen (PSMA): Initial experience in healthy volunteers and men with metastatic prostate adenocarcinoma (PCa).

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Abstract:

Background: ^{99m}Tc -MIP1404 and ^{99m}Tc -MIP1405 are small molecule inhibitors of PSMA based on glutamate-urea-glutamate and glutamate-urea-lysine pharmacophores, respectively, and contain a bis-imidazole chelator capable of complexing $\text{Tc}(\text{CO})_3^+$. Both exhibit high affinity to the extracellular domain of PSMA, an emerging and validated target for the detection of metastatic PCa. Both agents specifically localize in human PCa xenografts. The aim of this study was to assess the pharmacokinetics and tumor localizing characteristics of these agents in healthy men and in men with metastatic PCa.

Methods: Tissue kinetics, blood clearance and excretion were evaluated post i.v. injection (PI) of 20 mCi of ^{99m}Tc -MIP1404 and ^{99m}Tc -MIP1405 in 6 healthy men and 6 men with radiographic evidence of metastatic PCa. Subjects received both agents, two weeks apart. Planar whole body images (WBI) were obtained at 0, 1, 2, 4 and 24 hr and blood & urine collected over 24 hrs. ROI analysis of WBI was used to assess radioactive uptake for each identifiable organ and tissue including suspected tumor lesions.

Results: In healthy volunteers, WBI demonstrated, for both agents, rapid and persistent uptake in the salivary, lacrimal and parotid glands. Liver and kidney uptake was also evident, with greater uptake and retention with ^{99m}Tc -MIP1404. Both cleared the blood in a biphasic manner, with ^{99m}Tc -MIP1404 demonstrating significantly lower urinary activity compared to ^{99m}Tc -MIP1405. In men with PCa, ^{99m}Tc -MIP1404 and ^{99m}Tc -MIP1405 rapidly localized lesions in lymph nodes and bone on WBI as early as 1 hr PI. SPECT/CT images at 4 and 24 hrs demonstrated excellent lesion contrast. Good correlation was seen with bone scans in most patients though in general more lesions were demonstrated with ^{99m}Tc -MIP1404 and ^{99m}Tc -MIP1405 than bone scan. Both agents also detected metastatic tumors with a similarly high target to background ratios ranging from 3:1 to 28:1 at 4 to 24 hr.

Conclusion: Both agents rapidly detect metastatic PCa in soft tissues and bone and both also demonstrated a greater number of lesions in bone than bone scans. Enlarged and sub-centimeter lymph nodes were also clearly visualized. Further work is planned with these novel Tc-99m labeled PSMA targeted agents to correlate imaging findings with histopathological findings.