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The potential of ^{99m}Tc-PEI-MP for diagnosis and ^{188}Re-PEI-MP for therapy of bladder carcinoma

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Introduction: The water-soluble polymer PEI-MP (polyethyleneimine, functionalised with methylphosphonate groups) that might be labeled with ^{188}Re and ^{99m}Tc presents a strong potential for metabolic radiotherapy and diagnosis, respectively. The aim of this study was to evaluate *in vivo* the potential of ^{188}Re-PEI-MP as therapeutic agent for bladder carcinoma and ^{99m}Tc-PEI-MP for its diagnosis and follow up.

Material and Methods: Cytotoxicity of PEI-MP was investigated in bladder carcinoma cell line (CRL-1472) using the MTT test for different concentrations of PEI-MP (1 µM to 1000 µM) and incubation times (24h, 48h, 72h and 96h). Radiochemical purity of ^{99m}Tc-PEI-MP and ^{188}Re-PEI-MP was achieved using ascending microchromatography. For the *in vivo* studies six groups of Balb/c nu/nu mice were used: four normal groups injected with Na^{99m}TcO$_4$ (n=10), ^{99m}Tc-PEI-MP (n=10), Na^{188}ReO$_4$ (n=18) and ^{188}Re-PEI-MP (n=17), respectively; two with bladder carcinoma xenotransplants injected with Na^{188}ReO$_4$ (n=8) and ^{188}Re-PEI-MP (n=12), respectively. When the tumors reached the appropriate volume, radiopharmaceuticals were administered by an intravenous injection in the tail vein (22-37MBq), with the animal anesthetized and previously

placed on the gamma camera detector. Immediately, a dynamic acquisition followed, with a 128x128 matrix for 10 min (20 frames, 30 seconds). Static images (2 min) were performed with a 256x256 matrix, where each of the six groups was divided into two groups, of which one was imaged at 120 minutes, and the other at 240 minutes. For biodistribution proposes, mice were euthanized 2 and 4 hours after injection and organ samples were weighted and counted in a well-counter to obtain percentage injected activity per gram of organ (%ID/g).

Results and Discussion: The MTT assay showed that PEI-MP is not cytotoxic. The radiochemical purity of ^{188}Re-PEI-MP and ^{99m}Tc-PEI-MP was ≥85%. Biodistribution results, with $Na^{188}ReO_4$ and $Na^{99m}TcO_4$, showed a higher uptake by the thyroid, bladder and stomach, following a normal biodistribution. The biodistribution with ^{188}Re-PEI-MP and ^{99m}Tc-PEI-MP showed that the excretion of these complexes occurs primarily through the renal system, with a small fraction being eliminated by the hepatobiliary system. Tumor/muscle ratio for ^{188}Re-PEI-MP was greater than 1.5.

Conclusions: Given its biodistribution and tumor/muscle ratio, ^{188}Re-PEI-MP seems to be promising in the treatment of bladder cancer. Following the same biodistribution as ^{188}Re-PEI-MP, ^{99m}Tc-PEI-MP seems to be optimal for diagnosis and follow up of therapy.

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