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Selective Intra-Arterial ^{177}Lu-PSMA Therapy for Castration Resistant Prostate Cancer: Initial Results

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Letter

Prostate-specific membrane antigen (PSMA)-based radionuclide therapy has been shown to be an efficient and well-tolerated option in patients with metastatic castration resistant prostate cancer (mCRPC). Initial results of an ongoing prospective study to assess the intra-arterial (*IA*) administration of lutetium-177 (^{177}Lu-)-labeled PSMA compared to conventional intravenous (*IV*) administration in patients with mCRPC is presented. *IA* administration is promising to increase delivery efficacy and safe. Following approval by the institutional review board, four patients were treated with ^{177}Lu-PSMA (median age, 62.5 years (range, 53–72); median PSA, 89.75 (range, 11.74–173)). Each patient received their treatment dose in two visits (Fig 1). The first half of the dose (3700 MBq) was administered using the routine IV administration route. The second half of the dose was administered a week later selectively from bilateral internal iliac arteries under fluoroscopic guidance (Allura Xper FD20/10 Philips Medical Systems, the Netherlands). Pelvic angiography from the distal aorta was performed using a 4-F pigtail catheter (TEMPO AQUA®, Cordis, Miami, FL). Each internal iliac artery was selectively catheterized using a 4-F cobra catheter

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Conflicts of interest: None

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(TEMPO AQUA®, Cordis, Miami, FL). With the tip of the Cobra catheter positioned proximal to the anterior branches of the internal iliac artery, the dose was split and each half of the ^{177}Lu-PSMA was infused in the left and right internal iliac arteries successively. SPECT-CT imaging (Siemens Medical Solutions, Erlangen, Germany) of the prostate and metastatic lesion sites following *IV* and *IA* administrations, was performed to calculate the absorbed dose. Regions of interest (ROIs) were drawn over the composite image of all axial SPECT slices with increased tracer uptake, with anatomic correlation using low-dose CT.

Absorbed doses in all metastatic lesions, kidneys, liver, bone marrow (BM), prostate, and whole body (WB) were determined for each patient using the OLINDA/EXM 1.0 software (Vanderbilt University, Nashville, TN) according to the Medical Internal Radiation Dose schema. Mean absorbed dose values of the dominant lesion (i.e., the metastatic lesion with the highest radioactivity count), all lesions and organs were compared between administration routes. Additionally, the absorbed dose value of the dominant lesion and the mean absorbed dose value across all lesions were used to calculate and compare all lesions-to-liver, all lesions-to-BM, and all lesions-to-WB ratios. All comparisons were made using Student's *t*-test using Excel.

Absorbed doses following *IA* administration compared with *IV* administration are shown in Fig 2. Although dominant lesions had a higher mean absorbed dose with *IA* versus *IV* administration (2.23 vs 1.67 MGy/MBq), the difference was not significant ($P = 0.10$). By contrast, the mean total absorbed dose of all lesions was significantly higher with *IA* versus *IV* administration (1.67 vs 1.26 MGy/MBq; $P = 0.02$). The prostate gland had a lower mean absorbed dose with *IA* versus *IV* administration (0.27 vs 0.36 MGy/MBq) but this difference was not significant ($P = 0.44$). By contrast, the liver mean absorbed dose was significantly lower with *IA* versus *IV* administration (0.11 vs 0.13; $P = 0.04$). Although not statistically significant (0.05 vs 0.07; P = 0.18), patients received lower total body radiation with *IA* versus *IV* administration. When lesion-to-liver, lesion-to-BM, lesion-to-prostate, and lesion-to-WB ratios were compared between administration routes, the differences between *IA* and *IV* administration were significant ($P = 0.039$ when only the dominant lesions were used to calculate ratios; $P = 0.01$ when all lesions were used to calculate ratios).

There were no unexpected side effects during the early post-therapy period for *IA* administration in all patients; after a one-night stay, patients were discharged. Several grade 1 adverse effects (xerostomia, nausea, and fatigue) occurred in the first 8–16 weeks of follow-up.

The goal of *IA* is to increase the local (and subsequently intra-tumoral) concentration of chemotherapeutic agents, decrease systemic adverse effects, and generate greater tumor response.[1] In one study, Ga-68 DOTATOC positron emission tomography/computed tomography (PET/CT) was performed after both *IV* and *IA* administration; the standardized uptake values of DOTATOC in neuroendocrine tumors were approximately 3.75 times higher after *IA* administration.[2] The LUTIA (Lutetium Intra-Arterial) study, an ongoing study in patients with neuroendocrine tumors, aims to increase the tumor-absorbed dose in liver metastases with *IA* versus *IV* administration of ^{177}Lu-Dotate.[3]

There are limitations in this study. First, there could have been possible saturation of PSMA receptors because the two treatments were performed one week apart. Second, it was difficult to draw ROIs on the prostate due to the low spatial resolution of SPECT/CT images. This, along with high activity crossover from the urinary bladder, could have led to the result that the absorbed dose to the prostate was similar between both administrations. Despite the finding, this study suggests that *IA* administration could have a lower radiation burden on the liver and more favorable therapeutic effects in distant metastatic lesions. Lastly, it is a small sample size. The study will continue with a larger number of patients, with endpoints such as progression-free survival and overall survival.

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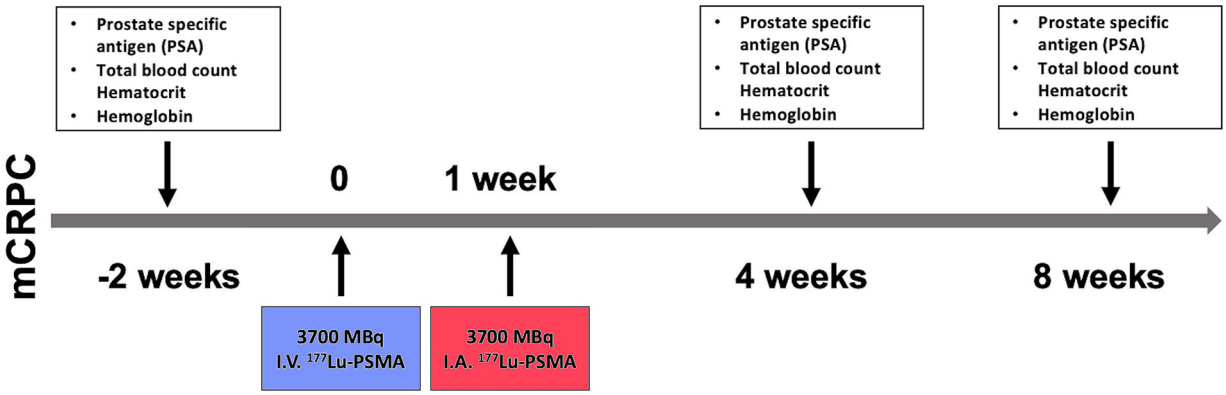
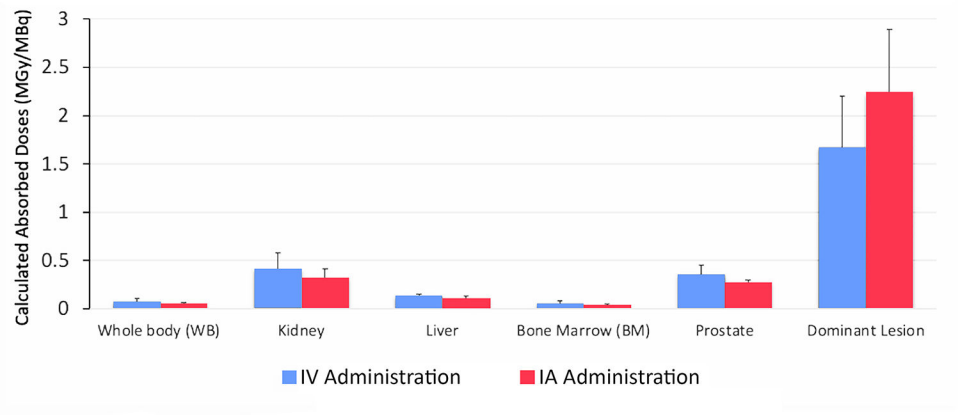
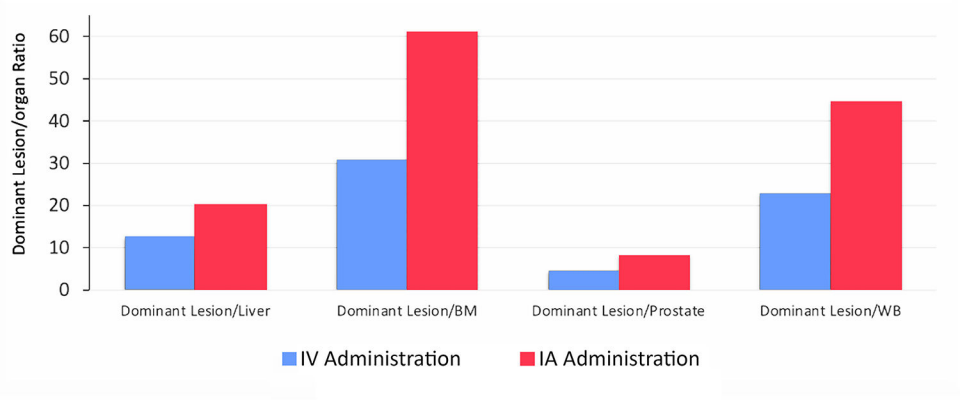


Figure 1.
Study design and timeline of Lu-177 PSMA therapy.





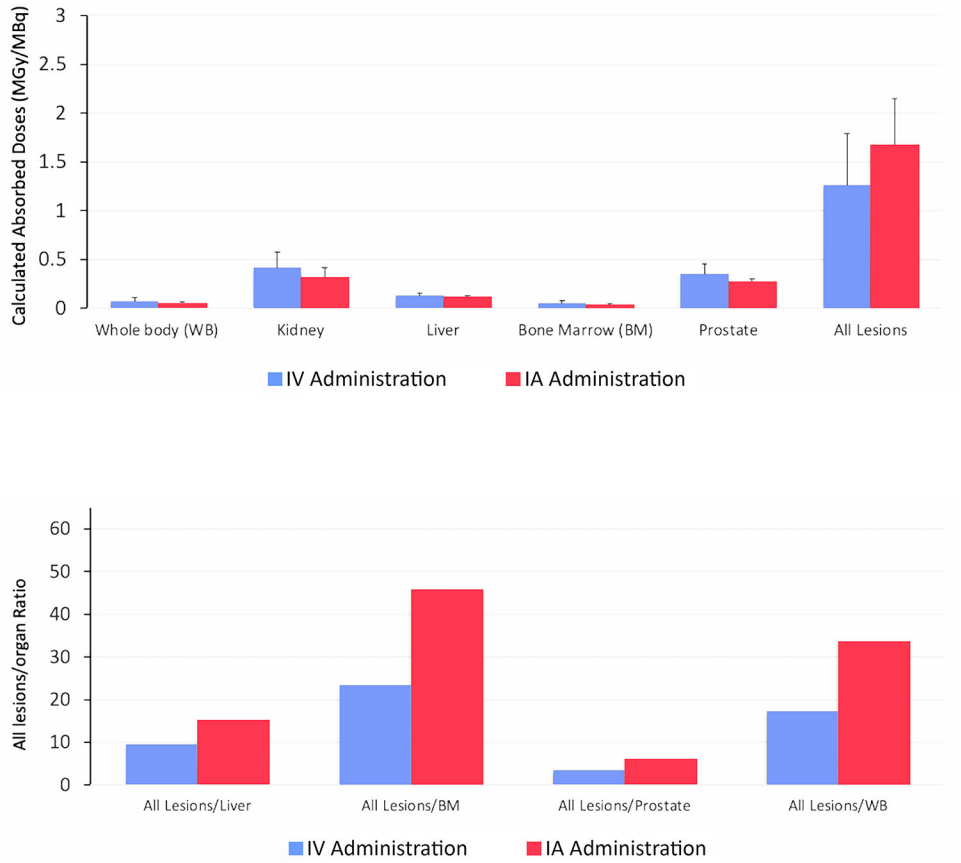


Figure 2.

(a) Comparison of intravenous (IV) and intra-arterial (IA) applications by calculated absorbed doses (MGy/MBq) in the dominant lesion with respect to calculated absorbed doses in the the liver, bone marrow (BM), prostate, and whole body (WB). (b). Comparison of intravenous (IV) and intra-arterial (IA) applications by calculated absorbed doses (MGy/MBq) of all lesions with respect to calculated absored doses in the liver, bone marrow (BM), prostate and whole body (WB). Each bar in calculated absorbed doses (MGy/MBq) represents mean ± SEM