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Review Article

Prostate-Specific Membrane Antigen Based Imaging Using ^{89}Zr-Labeled Monoclonal Antibody (J591)

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Abstract

Accurate and comprehensive imaging is vital for the subsequent management and treatment of prostate cancer. Conventional imaging modalities are of limited effectiveness in staging and re-staging disease. Prostate-specific membrane antigen (PSMA) is the most validated molecular target in prostate cancer, as it is specific and overexpressed in malignant cells. Therefore, PSMA positron emission tomography (PET) imaging is becoming more commonly used for both primary and metastatic prostate cancer. One conjugate involves the radionuclide ^{89}Zirconium (Zr) paired with the monoclonal antibody J591 directed toward PSMA, which we review in this article. A pilot study investigating ^{89}Zr-J591 PET in primary disease showed that the dominant nodule was identified in 8 out of 11 cases. Subsequent studies involving ^{89}Zr-J591 PET in metastatic disease found that the conjugate was safe and more effective than computed tomography (CT) and bone scan at detecting osseous lesions. 491 lesions were identified by ^{89}Zr-J591 PET, compared to 339 by traditional bone scan. In 22 biopsy-validated bone lesions, 21 were identified by ^{89}Zr-J591 PET. However, performance was poorer for soft tissue lesions, as CT identified more cancerous lymph nodes overall; this trend remained when scope was narrowed to biopsy-validated lymph nodes. ^{89}Zr-J591 PET had high specificity and positive predictive value. Challenges of ^{89}Zr-J591 PET include high uptake in liver and kidney and 8-day delay in imaging following radiotracer administration, owing to delayed clearance. These challenges are mitigated by the development of DF-IAB2M, a smaller derivative of J591. A pilot study involving ^{89}Zr conjugated to DF-IAB2M has shown promising results, and further studies are ongoing.

Keywords: Prostate Cancer; Prostate specific membrane antigen; 89Zr-J591 positron emission tomography

Introduction & Background

Prostate cancer is a common malignancy in men in the United States[1]. A significant proportion of cases progress to metastatic castration-resistant prostate cancer; bone is the most common site of metastasis[2,3]. Conventional imaging modalities, including CT and magnetic resonance tomography (MRI), are of limited efficacy in imaging both primary and metastatic prostate cancer. Prostate cancer has a lower glucose uptake compared to other solid tumor malignancies, and the prostate is small and compact, making resolution of lesions difficult[4]. Consequently, specialized imaging modalities have been developed for this disease, including Choline and Fluciclovine-based PET[4]. To date, prostate specific membrane antigen (PSMA) is the most validated target for prostate cancer imaging[5]. PSMA, a type II transmembrane glycoprotein with folate hydrolase activity, is found in the kidney, salivary glands, intestines, and prostate physiologically. Its expression is 100 to 1,000 times higher in prostatic adenocarcinoma as compared to expression in benign prostate[5,6]. Because of its expression profile, PSMA serves as an excellent target for both imaging and therapy of prostate cancer.

Many conjugates toward PSMA have been developed. One common combination employed for PSMA PET has been ^{68}Gallium (Ga) linked to the small molecule PSMA-11[7]. Another imaging agent is ^{89}Zr-J591; this is composed of Zirconium, a beta radiation emitter, and J591, a monoclonal antibody that has been used for radionuclide therapy in several clinical trials. Herein, we have reviewed and summarized the literature on published clinical trials involving ^{89}Zr-J591 PET imaging for prostate cancer. Only clinical trials with full-length published articles were included in this review.

^{89}Zr-J591 PET/CT imaging for localized prostate cancer

A pilot study conducted by Osborne et al. first explored the feasibility of ^{89}Zr labeled J591 PET in localized prostate cancer[8]. 11 patients with localized prostate cancer, scheduled to undergo radical prostatectomy, were enrolled. Median age was 61, and median PSA was 5.2 ng/mL. Each patient received an injection of ^{89}Zr-J591, followed by whole body positron emission tomography five to seven days later, and then radical prostatectomy the day after imaging. Prostatectomy specimens were imaged by ex-vivo micro positron emission tomography and a custom 3 Tesla magnetic resonance scanner coil. Both in-vivo and ex-vivo images and histopathology were correlated. In all patients, a total of 22 lesions, including 11 index lesions, were identified by histopathology with negative tumor margins and no lymph node metastasis. Eight out of 11 index lesions (72.7%) were identified on in-vivo PET while all index lesions were visualized by ex-vivo PET. Four out of 11 secondary nodules (36.4%) were visualized on ex-vivo PET. Seven out of these 11 secondary nodules, not seen on ex-vivo PET, were either low-grade tumors (six tumors, Gleason score of six) or small in size (one tumor, 2mm). The median size of dominant nodules was 5.5mm. For in-vivo PET and ex-vivo PET, lesion identification improved with increasing lesion size and Gleason score. One noted limitation of ^{89}Zr-J591 PET was the five to seven day waiting period between radiotracer injection and imaging due to the long clearance time of intact antibodies.

^{89}Zr-J591 PET/CT imaging for advanced metastatic prostate cancer

Soon after, Pandit-Taskar et al. conducted a phase I study using ^{89}Zr-huJ591 PET in patients with metastatic prostate cancer. This study demonstrated the safety of the radiotracer and showed accurate tumor targeting for bone as well as soft tissue[9]. It also determined the biodistribution, normal organ dosimetry, and optimal imaging time post ^{89}Zr-J591 injection. 10 patients with metastatic prostate cancer, median age 65 and median PSA 6.9 ng/mL, were imaged at multiple time points with PET following a 5mCi injection of ^{89}Zr-J591. Biopsies performed on eight patients showed 12 confirmed metastatic lesions. Only one biopsy-proven lesion was not detected on ^{89}Zr-J591 PET, compared to three missed lesions on conventional imaging modalities. The two additional lesions noted were both lymph nodes. The optimal time for imaging was determined to be 7±1 days following the injection. Critical organ dosimetry was also performed and dosimetry estimates were reported as follows: liver 7.7±1.5 cGy/mCi, renal cortex 3.5±0.4 cGy/mCi, and bone marrow 1.2±0.2 cGy/mCi. This indicated that there was relatively high uptake in the liver and renal cortex.

After the phase I study demonstrated safety and biodistribution of ^{89}Zr-J591 imaging in metastatic prostate cancer, the study was expanded to phase II, and 40 more patients with metastatic castration resistant prostate cancer were imaged with ^{89}Zr-J591 PET in order to assess the ability of ^{89}Zr-J591 to accurately detect bone and soft tissue involvement[10]. ^{89}Zr-J591 PET was compared to conventional imaging modalities: FDG PET, CT, and 99mTc-MDP bone scan. Overall, ^{89}Zr-J591 detected 491 osseous sites, compared to 339 by MDP, and 90 soft-tissue lesions, compared to 124 by CT. Of the 21 bone lesions confirmed by biopsy, 20 (95.2%) were detected by ^{89}Zr-J591; there was one biopsy-proven false positive. Of the 25 soft tissue sites confirmed by biopsy, 15 (60%) were detected by ^{89}Zr-J591; there were two false positives. The positive predictive value was estimated to be well above 90%. Given enhanced rates of detection of bone lesions compared to MDP bone scan, ^{89}Zr-J591 PET appeared to be the superior imaging modality. However, regarding lymph node metastases, its performance was equivocal. ^{89}Zr-J591 PET had 52% concordance with CT, and CT detected an additional 59 lesions. Of the 22 biopsy-proven soft tissue lesions, CT detected 18, ^{89}Zr-J591 detected 14, and FDG PET detected 13. Furthermore, uptake was lower in soft tissue lesions, less than 50% of bone SUVs, with variable overall performance. Of note, ^{89}Zr-J591 appeared to have the ability to detect disease in patients with low PSA. The lowest PSA associated with a positive scan was 0.23 ng/mL, and of the eight patients with PSA under 1 ng/mL, six had positive scans.

Some of the limitations of ^{89}Zr-J591 include long blood clearance time due to the large size of the antibody, requiring a six to eight-day delay between ^{89}Zr-J591 injection and imaging, and significant hepatorenal uptake that interferes with visualization. With the goal of reducing clearance time and increasing tumor penetrance, a smaller molecule, DF-IAB2M, was developed from the larger J591 antibody[11]. A pilot study of 20 patients with primary disease using ^{89}Zr-DF-IAB2M, conducted by Niaz et al., revealed an index lesion detection rate of 95%[12]. ^{89}Zr-DF-IAB2M also detected 11 extra-prostatic lesions in four patients; seven were confirmed by pathology and one was confirmed by bone scan two months post-operation. In this same pilot study, the ^{89}Zr-DF-IAB2M detection rate was compared to that of ^{68}Ga-PSMA-11, and both imaging agents showed similar lesion detection rates.

Conclusion

^{89}Zr-J591 PET has shown significant promise in imaging primary and metastatic prostate cancer. Pilot studies have shown

the radiotracer is safe and likely outperforms conventional imaging modalities in identifying bone lesions. Further studies are necessary to compare its efficacy in staging primary, intra-prostatic disease and identification of lymph node involvement. Further studies are also necessary to describe its efficacy relative to PSA levels in patients with biochemically recurrent disease. Challenges of ^{89}Zr-J591 imaging stem from the size of the antibody. However, with the development of the smaller DF-IAB2M, patients can be imaged more quickly, and the molecule may have increased tumor penetrance, leading to better imaging overall. The pilot study of DF-IAB2M demonstrated comparable efficacy with ^{68}Ga-PSMA-11. Additional studies involving DF-IAB2M, including those that compare it with ^{68}Ga-PSMA-11, are warranted.

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