Review article

68Ga-prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography for Prostate Cancer Imaging: A Narrative Literature Review

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Abstract

The 68Ga-prostate-specific membrane antigen (68Ga-PSMA) has been recently developed to be used, as a ligand, in positron emission tomography/computed tomography (PET/CT) prostate cancer imaging, to detect prostate disease. The main objective of this review was to collect data and findings from other studies and articles to assess, theoretically, if 68Ga-PSMA PET/CT is a more appropriate prostate cancer diagnostic technique in comparison with others available such as CT, 18F-fluorodeoxyglucose PET/CT, or 18F-fluoromethylcholine (18F-choline) PET/CT. For that purpose, PubMed, the online scientific articles’ database, was consulted where the keywords “PSMA” and “PET” were used to find relevant articles. The clinicaltrials.gov, clinical trials’ database, was also consulted where the keywords “68Ga-PSMA” and “prostate” were used to search clinical trials. Based on the reviewed scientific literature, several studies were conducted to assess and compare the 68Ga-PSMA PET/CT detection rate in prostate cancer with other available techniques. One of those studies, conducted by Giesel et al., concluded, within study sample, that 75% of patients with lymph nodes detected by 68Ga-PSMA PET/CT would have not been identified using other conventional morphological criteria based techniques. In Eiber et al.’s study, 68Ga-PSMA PET detected prostatic disease findings in 67% of patients with prostate-specific antigen levels <1 ng/mL, when compared with choline-based PET that presented detection rates between 19% and 36%. In Bluemel et al.’s study, 68Ga-PSMA identified positive prostatic disease in 43.8% of the patients with negative findings in F-choline PET/CT. Findings from this review demonstrate that 68Ga-PSMA PET/CT is more effective in detecting metastases, lymph nodes, and recurrent prostate cancer when compared to 18F-choline-based PET/CT and CT. 68Ga-PSMA PET/CT presents also more imaging contrast and can be more cost-effective. 68Ga-PSMA has already been subjected to first-in-human trials, and it is now being tested in Phase II and III trials.

Keywords: 68Ga-prostate-specific membrane antigen, positron emission tomography/computed tomography, prostate cancer

Introduction

Portugal, in 2012, presented 6022 individuals with prostate cancer, corresponding to 23% of all cancers reported. Worldwide, in 2012, 1.1 million men had prostate cancer. The therapeutic decision in these patients depends, essentially, on the prostate cancer staging and on the presence or absence of metastases. For localized prostate cancer, usually, the first-line treatment is radical prostatectomy or radiation

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The prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II, is a membrane-type zinc protease which is overexpressed in almost all patients with prostate cancer. Practically, all prostate gland adenocarcinomas overexpress PSMA although it can be expressed in other tissues such as kidney, proximal small intestine, and salivary glands. This overexpression is proportional to tumor aggressiveness, metastatic disease, and disease recurrence.\cite{6,7,10} Contrarily, choline metabolism is not overexpressed in a significant number of cases.\cite{11} The potential of targeting PSMA with $^{68}$Ga and $^{11}$F-labelled in PET/CT was already demonstrated as clinically significant for prostate cancer imaging in first-in-human trials.\cite{6,7,10}

The $^{68}$Ga-PSMA has been recently developed to be used as a PSMA ligand in PET/CT prostate cancer imaging to trace prostatic disease presence and location.\cite{8,11}

**Objective**

This narrative review was conducted to collect data and findings from other studies and articles to assess, theoretically, if $^{68}$Ga-PSMA PET/CT is a more appropriate diagnostic technique when compared with others available such as CT, $^{18}$F-FDG PET/CT, or $^{11}$F-choline PET/CT.

**Methods**

For the present review, PubMed, the online scientific articles’ database, was consulted where the keywords “PSMA” and “PET” were used to find relevant articles. Thirteen articles were selected with relevant data on $^{68}$Ga-PSMA and PET, with publication dates from 2014 to 2016. The clinicaltrials.gov, clinical trials’ database, was also consulted where the keywords \"$^{68}$Ga-PSMA\" and \"prostate\" were used to search clinical trials. There are eight clinical trials registered, but only five of them included PET/CT procedure, being two of them in \"not yet recruiting\" phase, two in \"recruiting\" phase, and one \"active but not recruiting.\"

**Discussion and Conclusions**

Based on the reviewed scientific literature, several studies demonstrate the utility of $^{68}$Ga-PSMA PET/CT. Afshar-Oromieh et al. performed a study on 37 male patients with biochemical relapse, to compare $^{11}$F-choline PET/CT and the novel $^{68}$Ga-PSMA PET/CT, for the diagnosis of recurrent prostate cancer. The patients were subjected to $^{11}$F-choline PET/CT and then to $^{68}$Ga-PSMA PET/CT, within a 30-day period. In this study, 86.7\% of patients presented at least one lesion of prostate cancer when using $^{68}$Ga-PSMA PET/CT, in comparison with $^{11}$F-choline PET/CT that only detected prostatic disease in 70.3\% of patients [Table 1]. They also refer that lesions with lymph node metastases’ characteristics, using $^{68}$Ga-PSMA, presented, usually, very high contrast when compared with choline-based PET/CT. This higher contrast was also present in most skeletal metastases and local relapses.\cite{12}

Afshar-Oromieh et al. performed a retrospective study of 319 patients who had been subjected to $^{68}$Ga-PSMA PET/CT examination from 2011 to 2014. About 83\% of the patients presented at least one prostate cancer lesion with this technique [Table 1].\cite{8,9,12-14} With this study, they were also able to provide information on Vitamin C, which demonstrated to have no influence in $^{68}$Ga-PSMA uptake in the salivary glands. The PSA levels and androgen deprivation therapy influenced positively the prostate cancer detection. In this study, 42 patients with

| Study                        | $^{18}$F-fluoromethylcholine Detection rate (%) | $^{68}$Ga-PSMA Detection rate (%) |
|------------------------------|-----------------------------------------------|---------------------------------|
| Afshar-Oromieh et al.\cite{11} | 70.3                                          | 86.7                            |
| Afshar-Oromieh et al.\cite{11} | -                                             | 83                              |
| Elber et al.\cite{9}         | -                                             | 89.5                            |
| Ceci et al.\cite{10}         | -                                             | 74.2                            |
| Blumen et al.\cite{8}        | 74.4                                          | 85.6 ($^{18}$F-fluoromethylcholine + $^{68}$Ga-PSMA) |

PSMA: Prostate-specific membrane antigen
lesions detected by ⁶⁸Ga-PSMA PET/CT were subjected to further biopsy or surgery. The patient-based analysis revealed a sensitivity value of 88.1%. The lesion-based analysis presented values of 76.6% for sensitivity, 100% for specificity, 91.4% for negative predictive value (NPV), and 100% for positive predictive value (PPV).[⁸]

In the retrospective study performed by Ceci et al. with a sample of seventy patients, a detection rate of 74.2% was registered. Concerning PSA levels, patients with PSA <2 ng/mL and PSA doubling time of <6.5 months, the positivity rate was 85%; in PSA <2 ng/mL and PSA doubling time of ≥6.5 months, the positivity value was 18.7%; showing a negative relation between PSA doubling time and ⁶⁸Ga-PSMA detection rate [Table 1].[¹³]

Giesel et al. compared ⁶⁸Ga-PSMA PET/CT with three-dimensional CT volumetric lymph node assessment. It was demonstrated that in seven patients (total sample = 21) with 31 PSMA-positive nodes, only 11 of the nodes were morphologically positive based on diameters ≥8 mm on CT. In the other 14 patients, 18 of PSMA-positive nodes had diameters shorter than 8 mm, with a range between 2.4 and 7.9 mm. It was concluded within study population that 75% of patients with lymph nodes detected by ⁶⁸Ga-PSMA PET/CT would have not been detected using conventional morphological criteria techniques.[¹⁵]

Eiber et al. conducted a retrospective study of 248 patients. About 89.5% of the patients showed disease findings in ⁶⁸Ga-PSMA PET/CT [Table 1]. The detection rates were 96.8% for PSA ≥2, 93% for PSA 1 < 2, 72.7% for PSA 0.5 < 1, and 57.9% for PSA with levels 0.2 < 0.5 ng/mL/year [Table 2]. The detection efficacy was considered related to higher Gleason scores. They found that in 33% of patients, the site of recurrence could only be detected by PET. The literature refers that staging detection rates for ¹¹C-choline range from 34% to 88%, for ¹⁸F-choline from 43% to 79%, for ¹³C-acetate from 59% to 80%, when compared to, as seen in this study, 57.9%–96.8% for ⁶⁸Ga-PSMA PET/CT. In this study, ⁶⁸Ga-PSMA PET/CT detected findings in 67% of patients with PSA levels of <1 ng/mL while choline-based PET presents a detection rate between 19% and 36%.[⁹]

Bluemel et al. performed a study on 125 patients to assess the value of ⁶⁸Ga-PSMA in patients with biochemical prostate cancer recurrence and negative ¹⁸F-choline PET/CT. Thirty-two patients showed negative results in ¹⁸F-choline PET/CT and were, then, subjected to ⁶⁸Ga-PSMA. The detection rate calculated was 85.6% for the sequential imaging approach with ¹⁸F-choline followed by ⁶⁸Ga-PSMA, while for ⁶⁸Ga-PSMA alone, the detection rate was only 74.4% [Table 1]. For ⁶⁸Ga-PSMA patients, the detection rates were 28.6% for PSA levels of 0.2 < 1 ng/mL, 45.4% for 1–2 ng/mL, and 71.4% for ≥2 ng/mL [Table 2]. ⁶⁸Ga-PSMA identified positive findings in 43.8% of the patients with negative ¹⁸F-choline PET/CT.[¹⁴]

Budäus et al. performed a study with thirty patients, where the intraprostatic tumor foci were correctly detected in 92.9% of them, using ⁶⁸Ga-PSMA PET/CT. The sensitivity was 33.3%, specificity was 100%, PPV was 100%, NPV was 69.2%, and accuracy registered was 73.3%, for initial prostate cancer nodal staging [Table 2].[¹⁶]

Pfister et al. studied the accuracy of ⁶⁸Ga-PSMA PET/CT in comparison with ¹⁸F-choline PET/CT, in a sample of 66 patients. Thirty-eight patients underwent ¹⁸F-choline, while 28 were subjected to ⁶⁸Ga-PSMA. The results were 71.2% of sensitivity for ¹⁸F-choline and 86.9% for ⁶⁸Ga-PSMA; 86.9% of specificity for ¹⁸F-choline, and 93.1% for ⁶⁸Ga-PSMA; PPV of 67.3% for ¹⁸F-choline and 75.7% for ⁶⁸Ga-PSMA; NPV of 88.8% for ¹⁸F-choline and 96.6% for ⁶⁸Ga-PSMA; and accuracy of 82.5% for ¹⁸F-choline and 91.9% for ⁶⁸Ga-PSMA [Table 3].[¹¹]

Verburg et al. conducted a retrospective study with 155 patients with recurrent prostate cancer, to assess the relation between extending of disease determined by ⁶⁸Ga-PSMA PET/CT, PSA values, PSA doubling time, and Gleason score. The detection rate registered was 44% for PSA levels of ≤1, 79% for PSA doubling time of 1–2 ng/mL, and 89% for ≥2 ng/mL, showing a positive relation between PSA levels and ⁶⁸Ga-PSMA detection

Table 2: Summary of detection rates of ⁶⁸Ga-prostate-specific membrane antigen for different prostate-specific antigen levels

| Study          | Detection rates (%) | 2 ng/mL | <2 ng/mL | 0.5<1 ng/mL | 0.2<0.5 ng/mL |
|----------------|---------------------|---------|----------|-------------|--------------|
| Eiber et al.   | 96.8                | 93      | 72.7     | 57.9        |
| Verburg et al. | 89                  | 79      | 44       | 28.6        |
| Bluemel et al. | 71.4                | 45.4    | 28.6     |             |
rate [Table 2]. With PSA doubling time values of <6 months and PSA of ≥2 ng/mL, 95% showed a positive scan, while with PSA level of <1 ng/mL and PSA doubling time of >6 months, only 36% had a positive scan, which indicates, once more, a negative relation between PSA doubling time and ⁶⁸Ga-PSMA detection rate.[¹⁷]

From the five clinical trials registered in clinicaltrials.gov, two correspond to Phase II (one not yet recruiting and one recruiting), two of Phase III (one not yet recruiting and one recruiting), and one feasibility (ongoing, not recruiting) which shows that the first-in-human trials have demonstrated positive results concerning safety issues, and further efficacy and safety studies, in larger populations, are being conducted.[¹⁰,¹⁸]

**Conclusion**

The literature consulted to elaborate this narrative review presents findings which demonstrate that ⁶⁸Ga-PSMA PET/CT is more effective in detecting metastases, lymph nodes, and recurrent prostate cancer when compared with ¹⁸F-choline-based PET/CT and CT. The image acquired by ⁶⁸Ga-PSMA PET/CT presents also more contrast, and the technique can be more cost-effective since ⁶⁸Ga is made available by ⁶⁷Ge/⁶⁸Ga radionuclide generators and no cyclotron is needed. This hybrid imaging technique is also effective in patients with low PSA levels, being positively related with rising levels of this biomarker and tumor size. This early detection is crucial to stage the prostate cancer and to manage the most appropriate therapy for the patient. The technique was assessed in several retrospective studies which showed good safety profiles and better efficacy among others available. This method was also tested through first-in-human trials proving its safety, and it is now being subjected to Phase II and III clinical trials to explore ⁶⁸Ga-PSMA safety and efficacy, in larger populations.[¹,²,⁵-¹⁸]

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**Conflicts of interest**

There are no conflicts of interest.

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**Table 3: Summary of Pfister et al. study for ⁶⁸Ga-prostate-specific membrane antigen positron emission tomography/computed tomography parameters**

| Study          | Ligand                  | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|----------------|-------------------------|-----------------|-----------------|---------|---------|--------------|
| Pfister et al. | ¹⁸F-fluoromethylcholine | 71.2            | 86.9            | 67.3    | 88.8    | 92.5         |
|                | ⁶⁸Ga-PSMA               | 86.9            | 93.1            | 75.7    | 96.6    | 91.9         |

PPV: Positive predictive value; NPV: Negative predictive value; PSMA: Prostate-specific membrane antigen

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