68Ga-PSMA-HBED-CC PET/MRI is superior to multiparametric magnetic resonance imaging in men with biochemical recurrent prostate cancer: A prospective single-institutional study

Juana Martinez, Kritika Subramanian, Daniel Margolis, Elisabeth O’Dwyer, Joseph Osborne, Yuliya Jhanwar, Himanshu Nagar, Nicholas Williams, Arindam RoyChoudhury, Gabriela Madera, John Babich, Sandra Huicochea Castellanos

Division of Molecular Imaging and Therapeutics, Department of Radiology, Weill Cornell Medicine, 525 E 68th Street, New York, NY 10065, USA
Division of Body Imaging, Department of Radiology, Weill Cornell Medicine, New York, NY, USA
Department of Radiation Oncology, Weill Cornell Medicine, New York, NY, USA
Department of Biostatistics, Department of Population Health Sciences, Weill Cornell Medicine, New York, NY, USA
Division of Radiology, Weill Cornell Medicine, New York, NY, USA
Division of Radiopharmaceutical Sciences, Department of Radiology, Weill Cornell Medicine, New York, NY, USA

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ABSTRACT

Background: The primary objective was to compare the overall diagnostic performance, presented as detection rate of 68Ga-PSMA-HBED-CC positron emission tomography/magnetic resonance imaging (PSMA PET/MRI) versus conventional, multiparametric MRI (mpMRI) in a population of patients with biochemically recurrent prostate cancer. In conjunction with this analysis, secondary objectives included the evaluation of the detection rate stratified by PSA levels and primary treatment modality.

Methods: A total of 165 PSMA PET MRI were performed from April 2018 to May 2021, of whom 108 were presenting for biochemical recurrent disease. The PSMA PET vertex to thigh were read by two different board-certified nuclear medicine physicians while the MRI head and neck, chest, abdomen, and pelvis (with dedicated, PI-RADS compliant multiparametric prostate MRI) were read by two board certified diagnostic radiologists.

Analysis: PSMA PET/MRI had a higher detection rate than mpMRI when evaluating patients with biochemical recurrence (BCR) with similar results demonstrated when sub-analysis was performed using PSA levels, primary treatment modality, and time since androgen deprivation therapy. Our study also showed PSMA PET/MRI had a higher sensitivity than mpMRI.

Discussion: Our findings demonstrate that PSMA PET/MRI is a better imaging modality in the detection of disease in the setting of BCR when compared to MRI alone. Combined utility with PSMA PET/MRI is a powerful tool which can aid in not only the detection of disease, but also guide in treatment planning for prostate cancer patients.

Introduction

3.1 million men in the US have a diagnosis of prostate cancer [1] with approximately 250,000 expected new diagnoses in 2021 alone. The predicted number of mortality cases attributed to prostate cancer in 2021 is approximately 34,000. Within 10 years of a prostate cancer diagnosis, 30% of the patients are expected to develop biochemical recurrence (BCR) [2]. BCR is defined as a PSA level equal to or greater than 0.2 ng/mL in post radical prostatectomy patients or 2 ng/mL greater than the nadir PSA after radiation therapy (Phoenix criteria) [3, 4]. BCR generally occurs before clinical and radiographic evidence of...
cancer is demonstrable. Conventional imaging techniques in asymptomatic patients with low serum prostate specific antigen (PSA) levels are not diagnostic [5]. Management of BCR includes observation with serial PSA monitoring, androgen deprivation therapy (ADT), and salvage radiation therapy (sRT). Despite advances made in prostate cancer and the inclusion of new therapies such as PSMA-based targeted treatment [6], salvage radiotherapy (sRT) to the prostatic bed +/- pelvic lymph nodes is still the only localized treatment option for patients with BCR following radical prostatectomy [7]. Furthermore, sRT has been associated with a 5-year progression free survival of 80% and 5-year overall survival of approximately 90%, with limited benefit in patients with extra-pelvic disease [8]. Therefore, the ability to identify and localize recurrent disease is crucial as it determines treatment course and patient prognosis.

The development of 68Ga-Prostate Specific Membrane Antigen (PSMA)-HBED-CC has improved the detection rate of prostate cancer related lesions, including in patients with low serum PSA values. PSMA positron emission tomography (PET)/computed tomography (CT) has the potential to detect disease at an earlier disease state and with low PSA values when compared to 18F-Choline PET/CT [9]. Crocò et al. [10] published a meta-analysis reporting a detection rate of 74.1% for PSMA PET/CT in BCR patients. Recently, studies have shown that PSMA PET/magnetic resonance imaging (MRI) have a high detection rate in detecting pathologic lesions in patients with low PSA levels, especially within the prostate/prostatic bed. Kranzbühler et al. [7] published a retrospective study with a cohort of 66 patients with BCR who underwent a PSMA PET/MRI and reported a detection rate of 65% in patients with PSA values between 0.2 and 0.5 ng/ml. In comparison, multiparametric MRI (mpMRI) has a reported sensitivity of 61% and specificity of 58.7% for the detection of local recurrence [11].

However, studies are yet to illustrate the value of PSMA PET/MRI when compared to mpMRI. For this reason, we designed this study to evaluate the detection rate of 68Ga-PSMA-HBED-CC positron emission tomography/magnetic resonance imaging (PSMA PET/MRI) in patients with BCR and compared it to MRI body with mpMRI prostate. We hypothesize that PSMA PET/MRI performance is superior to mpMRI with a greater detection rate of abnormal lesions in patients with biochemical recurrence.

**Objective**

The primary objective was to compare the overall diagnostic performance, presented as detection rate of 68Ga-PSMA-HBED-CC PET/MRI versus MRI vertex to thighs (MRI Body) with dedicated mpMRI prostate in a population of prostate cancer patients with BCR as determined by referring physician. In conjunction with this analysis, secondary objectives included the evaluation of the detection rate specifically in biochemical recurrent patients, subsequently stratified by serum PSA levels and primary treatment modality.

**Methods**

**Study design**

This was an observational study designed to evaluate detection rate and sensitivity of pathological lesions in PSMA PET/MRI and MRI Body with mpMRI prostate in a population of prostate cancer patients with BCR as determined by referring physician. In conjunction with this analysis, secondary objectives included the evaluation of the detection rate specifically in biochemical recurrent patients, subsequently stratified by serum PSA levels and primary treatment modality.

**Data sources/measurement**

The PSMA PET/MRIs were reviewed by two nuclear radiologists (S. H.C and J.J) while the MRI head, neck, chest, abdomen, and pelvis with dedicated mpMRI prostate were read by two diagnostic radiologists (D. M. and E.O). Study data were collected and managed using the REDCap (Research Electronic Data Capture) server hosted at Weill Cornell Medicine.
Medicine. REDCap is a secure, web-based software platform designed to support data capture for research studies [12].

**Bias**

To prevent biased interpretation, the PSMA PET/MRI and mpMRI were independently read and dictated.

**Study size**

A total of 108 patients were enrolled for the indication of BCR.

**Quantitative variables**

PSMA positivity was defined as having an SUV value above that of the reference blood pool, liver, and/or salivary glands when evaluating the N1 lymph nodes (or lymph nodes below the level of the aortic bifurcation), N2 lymph nodes (lymph nodes above the level of the aortic bifurcation), osseous, prostate/prostatic bed and other lesions, as described using the PROMISE criteria [13]. Additionally, detection of extracapsular extension, seminal vesicle and neurovascular bundle involvement on MRI was also extracted. T2 low signal lesions within the prostate/prostatic bed with focal early arterial enhancement on dynamic contrast-enhancing images were suspicious for recurrent disease. Diffusion weighted imaging demonstrated corresponding high signal intensity on high b-value images with low-signal intensity on apparent diffusion coefficient images. Imaging where the dictation mentioned multiple abnormal lymph nodes or osseous lesions were re-reviewed by two dual radiologists-nuclear medicine physicians for further quantification.

**Statistical methods**

First, the description analysis for patient demographics was performed (Table 1). Then, the true positive rates between PSMA PET/MRI and MRI were compared. The reference gold standard was either a recent biopsy report (biopsy done after the PSMA PET/MRI) or in patients subsequently treated with sRT with down-trending serum PSA and positive rate was defined as any true abnormal lesion detected in the prostate/prostatic bed with focal early arterial enhancement on dynamic contrast-enhancing images were suspicious for recurrent disease. Diffusion weighted imaging demonstrated corresponding high signal intensity on high b-value images with low-signal intensity on apparent diffusion coefficient images. Imaging where the dictation mentioned multiple abnormal lymph nodes or osseous lesions were re-reviewed by two dual radiologists-nuclear medicine physicians for further quantification.

**Results**

**Patient demographics**

114 patients were enrolled in this study with the indication of BCR. Population characteristics are shown in Table 1. The average age was 69 years +/- 9.1 years, and the average PSA level was 5.56 +/- 11.1. 109 (95.6%) patients had information about the primary treatment received, out of which 77.1% (n = 84) were post radical prostatectomy. Similarly, 113 patients had information about when they last received androgen deprivation therapy (ADT), and 72.6% (n = 82) did not receive a dose within the last 6 months of the scan.

**True positive rates of PSMA PET/MRI and MRI by anatomical region**

PSMA PET/MRI had a significantly higher number of positive reads than MRI for biochemically recurrent patients (p = 0.009, Table 2). This pattern was re-demonstrated when reviewing the number of abnormal N1 lymph nodes, N2 lymph nodes, osseous, prostate/prostatic bed, and other lesions. MRI detected more abnormal lesions in the prostate.

**Determining the interpretation of equivocal lesions on MRI**

On MRI, there were several lesions determined as equivocal primarily within prostate/prostatic bed and osseous lesions. For example, 6 patients had equivocal osseous findings on MRI. These 6 patients also had other suspicions findings on MRI consistent with recurrent disease. 2 of these patients were found to have congruent osseous positivity on PET/MRI (33%). When the equivocal MRI lesions were classified as positive, there was a total of 20 patients who had positive osseous lesions on mpMRI. 60% (12 of the 20) had overlap between osseous lesions seen on MRI and those seen on PET/MRI. When the equivocal lesions were classified as negative lesions, there was an 86% overlap between the MRI and PET, supporting the decision to interpret equivocal lesions as negative lesions.

**True positive rate of PSMA PET/MRI and MRI when stratified by PSA value**

We established that PSMA PET/MRI was more likely to detect a

| BCR (n = 108) | Mean (Range) |
|--------------|--------------|
| Age          | 69 +/- 9.1 (41 – 87) |
| PSA          | 5.56 +/- 11.1 (0.06-70.35) |

| Primary Treatment (n = 109) | Radiation therapy only | Radical Prostatectomy and Radiation therapy | Radical Prostatectomy only |
|-----------------------------|------------------------|------------------------------------------|---------------------------|
| Radiation therapy only      | 12 (11.0%)             | 13 (11.9%)                               | 84 (77.1%)                |
| Radical Prostatectomy only  | 13 (11.9%)             | 13 (11.9%)                               | 84 (77.1%)                |

| Androgen Deprivation Therapy last received (n = 113) | < 2 weeks (Currently Using) | < 6 months | < 6 months (Currently Using) | > 6 months | Unknown |
|----------------------------------------------------|-----------------------------|-----------|-----------------------------|-----------|--------|
|< 2 weeks (Currently Using)                        | 1 (0.9%)                    | 4 (3.54%)| 12 (10.3%)                  | 82 (72.6%)| 14 (12.4%) |
|< 6 months                                         | 4 (3.54%)                   |           | 12 (10.3%)                  |           |        |
|< 6 months (Currently Using)                       |                             |           |                             |           |        |
|> 6 months                                         |                             |           |                             |           |        |
|Unknown                                            |                             |           |                             |           |        |

Table 1: Demographics of patients with biochemical recurrence included in this study.
pathological lesion than MRI in BCR. However, the question subsequently arose regarding the location of these pathological lesions relative to PSA levels. Sub-cohort analysis reviewed strata of PSA ranges in biochemical recurrence. PSMA PET/MRI was more likely to have a positive read than MRI at all PSA levels (Fig. 1). In patients with serum PSA levels < 0.2 ng/mL, PSMA PET/MRI was positive in detecting a suspicious lesion within the chest, abdomen, and pelvis in 32% of patients while MRI was positive in only 9% of patients. These detection percentages increased as the PSA levels increased (Fig. 1).

PSMA PET/MRI detected N1 and N2 nodes and osseous lesions more frequently than MRI at all PSA levels (Table 3). mpMRI detected more lesions in the prostatic bed at lower PSA levels than the PSMA PET/MRI alone. However, PSMA PET/MRI detected more lesions in the prostatic bed than mpMRI at higher PSA levels.

True positive rate of PSMA PET/MRI and MRI when stratified by primary treatment modality and ADT use

Assuming primary treatment modality may play a role in detection rates, positive reads were compared with the treatment modality for BCR patients (Table 4). PSMA PET/MRI was more likely to detect abnormal lesions in patients who were post radical prostatectomy ($p = 0.001$). There were no significant differences in performance of PSMA PET/MRI and MRI in evaluating biochemical recurrence in patients who were post radiation therapy or post radical prostatectomy and radiation therapy.

When reviewing the number of positive scans relative to androgen deprivation therapy in patients with biochemical recurrence, PSMA PET/MRI was superior to MRI regardless of when the patient received the last dose of hormone therapy (Table 5).

Sensitivity of PSMA PET/MRI and MRI in patients with available reference standard

A total of 43 patients had a histopathological biopsy report or PSA trend which could be used as reference for sensitivity analysis. 8 (19%) osseous lesions, 12 (28%) lymph nodes, 1 (2%) lung lesion, 1 (2%) pelvic mass, 5 (12%) prostate lesions, and 2 (5%) prostatic bed lesions were biopsied among these patients.

### Table 3
PSMA PET/MRI detected more abnormalities in N1, N2, and Osseous lesions in biochemical recurrent patients than MRI but was less likely to detect abnormalities in the prostate or prostate bed in PSA levels as low as 0.5.

|          | 0-0.2 ng/mL | 0.2–< 0.5 ng/mL | 0.5–2.0 ng/mL | >2.0 ng/mL |
|----------|-------------|----------------|--------------|-----------|
| N1       | 4 (13.8%)   | 9 (25.0%)      | 8 (23.5%)    | 13 (20.0%)|
| PSMA PET/MRI | 0 (0%)     | 3 (12.0%)      | 3 (8.82%)    | 5 (7.69%) |
| MRI      | 3 (10.3%)   | 3 (8.33%)      | 5 (14.7%)    | 9 (13.8%) |
| N2       | 3 (10.3%)   | 4 (11.1%)      | 1 (2.94%)    | 2 (3.08%) |
| PSMA PET/MRI | 0 (0%)     | 6 (16.7%)      | 10 (29.4%)   | 6 (9.23%) |
| MRI      | 2 (6.89%)   | 6 (16.7%)      | 10 (29.4%)   | 6 (9.23%) |
| Osseous  | PSMA PET/MRI | 3 (10.3%)     | 3 (8.33%)    | 1 (2.94%) |
| MRI      | 0 (0%)      | 4 (11.1%)      | 1 (2.94%)    | 2 (3.08%) |
| Prostate | PSMA PET/MRI | 1 (3.45%)     | 0 (0%)       | 0 (0%)    |
| MRI      | 0 (0%)      | 1 (2.78%)      | 2 (5.89%)    | 4 (6.15%) |
| Prostatic Bed | PSMA PET/MRI | 0 (0%)     | 3 (8.33%)    | 1 (2.94%) |
| MRI      | 0 (0%)      | 6 (16.7%)      | 0 (0%)       | 1 (0.02%) |
| Other    | PSMA PET/MRI | 0 (0%)     | 1 (2.78%)    | 1 (2.94%) |
| MRI      | 0 (0%)      | 1 (2.78%)      | 0 (0%)       | 0 (0%)    |

### Table 4
PSMA PET/MRI was more likely to detect abnormal lesions in patients who were post radical prostatectomy.

|          | Radical Prostatectomy | Radiation Therapy | Radical Prostatectomy + Radiation Therapy |
|----------|-----------------------|-------------------|------------------------------------------|
| n        | 84                    | 12                | 13                                        |
| Positive | Positive PET/MRI | 42 (50%)          | 11 (92%)                                  |
| MRI      | Positive MRI          | 21 (25%)          | 12 (100%)                                 |
|          |                       | 8 (62%)           | 4 (31%)                                   |

Fig. 1. The detection rate of pathological lesions in biochemical recurrence was always greater with PSMA PET/MRI than MRI, regardless of PSA level.
Table 5
PSMA PET was more likely to have a positive read than MRI regardless of when the patient received his last dose of androgen deprivation therapy.

| Androgen deprivation therapy | n | Positive PET/MRI | Positive MRI |
|-----------------------------|---|------------------|--------------|
| <2 weeks (Currently Using)  | 1 | 0 (0%)           | 0 (0%)       |
| <6 months                   | 4 | 2 (50%)          | 1 (25%)      |
| <6 months (Currently Using) | 12| 8 (67%)          | 3 (25%)      |
| >6 months                   | 82| 50 (61%)         | 34 (41%)     |
| Unknown                     | 14| 4 (29%)          | 1 (7.1%)     |

7 patients had a negative reference test while 36 had a positive reference test. This resulted in a sensitivity of 95.5%, positive predictive values of 87.5%, and a detection rate of 82.4% for PSMA PET/MRI. MRI had a sensitivity of 63.6%, positive predictive value of 84.9%, and a detection rate of 54.9%. Out of the 7 patients with a negative reference test, 3 (43%) patients received radiation therapy as the primary treatment while 3 (43%) were post radical prostatectomy and 1 (14%) received both as primary treatment. Due to the highly biased sample population, this study has a reduced number of negative reference tests which could be utilized for specificity analysis and negative predictive value. Therefore, these analyses were not performed.

Discussion

Our study showed PSMA PET/MRI had a higher accuracy, sensitivity, and positive predictive value than MRI when evaluating patients with biochemical recurrence. This same pattern was consistent when performing sub-analysis using PSA levels, primary treatment modality, and time since androgen deprivation therapy. A limitation in our analysis was the small number of cases available for specificity analysis (n = 7), resultant from the large selection bias in this cohort as individuals who were evaluated by the gold standard (ie biopsy) were already diagnosed with biochemical recurrence by their PSA levels, resulting in a negligible sample size of patients who had a true negative reference.

In prior studies, the sensitivity and specificity of PSMA PET/MRI has persistently been reported to be >80% in BCR, as demonstrated in the recently performed OSPREY [16,17] and proPSMA [18,19] trials. However, no study to the author’s knowledge has compared the utility of PSMA PET/MRI with mpMRI in detection of biochemical recurrence in patients who received radiation therapy as primary treatment. Future studies should evaluate the role of PSMA PET/MRI with MRI in the detection of biochemical recurrence after radiation therapy in a larger cohort.

MRI is well recognized for its ability to identify local recurrence after prostatectomy, even at low PSA levels [20–22]. In our study, abnormalities in the prostate and the prostatic bed were better characterized on MRI at lower PSA levels while PSMA PET/MR detected more abnormal lesions at higher PSA levels, suggesting that combined utility with PSMA PET/MRI would be a better option for restaging in biochemical recurrence. This reiterates the findings of Guberina et al. [23] where PSMA PET/MRI detected recurrence in more patients than PSMA PET/CT and had a greater diagnostic confidence for the identification of local recurrent disease. The combined modality also has improved utility in guiding treatment planning, such as salvage lymphadenectomy [24] and precision radiotherapy [25].

Historically, there has been concern that androgen receptor therapy can influence the detection rate in recurrent disease, especially in patients who are post radical prostatectomy [26]. We show above that despite the potential for physiologic inhibition and/or lack of receptor binding potential, PSMA PET/MRI was still superior to MRI in detecting abnormal lesions regardless of when the last dose of androgen deprivation therapy was administered.

Finally, our findings suggest that recurrence is more likely to be detected in lymph nodes than in the bone. It is important to note that bone metastases have a high washout rate with PSMA in comparison to lymph nodes [27]. Internalization rates in bone metastases were also low when compared to other soft tissue and lymph node lesions. Clinically, osseous lesions are more likely to be seen in higher PSA levels [28], thereby allowing the clinician to determine the likelihood of recurrence in the axial and appendicular skeleton.

Another limitation of this study is that multiple patients sought care at other institutions either prior to the PET/MRI scan or after. As a result, information was not complete for several patients enrolled in this trial. Only a small number of the subjects had 2-year follow-up or underwent confirmatory biopsy, which introduces the possibility of selection bias for this subset.

Conclusions

We conclude that PSMA PET/MRI is a robust imaging modality with higher sensitivity than multiparametric MRI alone for the detection of biochemical recurrence. Together, this combined imaging modality is a powerful tool which can aid in not only the detection of the abnormal lesion, but also guide in treatment planning. In patients who are being evaluated for biochemical recurrence and require imaging, PSMA PET/MRI should be recommended for restaging and treatment planning.

CRediT authorship contribution statement

Juana Martinez: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. Kritika Subramanian: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. Daniel Margolis: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – review & editing. Elisabeth O’Dwyer: Data curation, Investigation, Methodology, Writing – review & editing. Joseph Osborne: Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. Yuliya Jhanwar: Data curation, Writing – review & editing. Himanshu Nagar: Writing – review & editing. Nicholas Williams: Formal analysis, Arindam RoyChoudhury: Formal analysis, Writing – review & editing. Gabriela Madera: Formal analysis, Project administration. John Babich: Conceptualization, Funding acquisition, Writing – review & editing. Sandra Hui-cochea Castellanos: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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