Diagnostic accuracy of ^{68}Ga-PSMA PET hybrid imaging in evaluating treatment response to ^{177}Lu-PSMA radioactive ligand therapy in patients with advanced metastatic prostate cancer: a systematic review and meta-analysis

Timothy James O. Lam, MD, Arrene Joy B. Baldonado, MD, Dominic N. Velasco, MD

Department of Radiological Sciences, Section of Nuclear Medicine and PET-CT center, Cardinal Santos Medical Center, San Juan City, Philippines
E-mail address: timothyjameslam@yahoo.com

ABSTRACT

Introduction:

^{68}Ga-PSMA PET is an effective imaging modality in the evaluation of prostate cancer. However, there is limited data on its use in the evaluation of therapeutic response, particularly in radioligand therapy. .

Objective:

Our aim is to investigate the diagnostic accuracy of ^{68}Ga-PSMA PET hybrid imaging in evaluating response to ^{177}Lu-PSMA therapy in patients with mCRPC compared with the standard use of serum PSA.

Methodology:

A systematic review was done according to the Cochrane diagnostic accuracy reviews guidelines and the PRISMA checklist of literature from January 2015 to August 2020. Literature search, study selection, and data extraction were conducted by 2 reviewers. Statistical analysis of data was done using Meta-DiSc v1.4

Results:

A total of 5 studies were included following screening. A total of 128 patients were included in the review. Using PSA response as the reference standard, the pooled sensitivity and specificity of ^{68}Ga-PSMA PET hybrid imaging to evaluate treatment response to ^{177}Lu-PSMA therapy was 85% (CI: 74 to 92%) and 74% (CI: 62 to 84%), respectively. The computed diagnostic accuracy was 79.7%.

Conclusion:

^{68}Ga-PSMA PET hybrid imaging is an effective diagnostic procedure in evaluating treatment response to ^{177}Lu-PSMA therapy ligand therapy with good sensitivity, specificity, and diagnostic accuracy.

Keywords*: PET, PSMA, Gallium, Lutetium, Treatment response, Prostate cancer*

INTRODUCTION

Prostatic malignancy is the second most common form of cancer in men and the fifth most common cancer-related death in men worldwide [1]. In the Philippines, prostate cancer (PC) has shown a significant increase in incidence and mortality with an average annual change of 4.5% and 11.4%, respectively [2]. Upon diagnosis, about 10-20% of these patients present with advanced disease and more than 40% of them will subsequently develop metastatic castration-resistant prostate cancer (mCRPC) [3]. The standard treatment for mCRPC usually involves the use of systemic chemotherapy, immunotherapy, and hormonal therapy but despite our current knowledge, the treatment of mCRPC largely remains a significant challenge [4, 5].

A relatively new approach to the management of mCRPC is the use of radioactive ligands that selectively target the antigen expressed on prostate cancer cells. Prostate-specific membrane antigen (PSMA), a type II cell surface-bound glycoprotein, is highly expressed by the prostate gland but significantly more so in prostate cancer cells [6]. Of the known PSMA radioligands currently available, the most broadly recognized are ^{68}Ga-PSMA and ^{177}Lu-PSMA used in diagnosis and treatment of prostate cancer, respectively.

Targeted therapy using ^{177}Lu-PSMA has revealed promising results in its use as a life-prolonging treatment option for mCRPC [7]. However, not all patients with mCRPC will have a good treatment response to ^{177}Lu-PSMA and up to a third of them would show progressive disease [8]. Considering this data, including the adverse effects associated with radioactivity and relatively high cost of treatment, it is crucial to have an optimal measure of response that allows us to periodically reevaluate the cost-effectiveness of therapy. A study on the clinical impact of PSMA-PET in patient management found a change in the treatment plan for 76% of patients [9].

Response to systemic therapy for PC is largely assessed clinically and biochemically (i.e., serum PSA), and with the advent of imaging, we have gained a more visual approach to evaluation. ^{68}Ga-PSMA PET has been proven to be an effective imaging modality primarily in the detection of primary, metastatic, and recurrent prostate cancer [10]. However, limited data are available on the use of modern imaging in the evaluation of therapeutic response [11].

OBJECTIVE

Our aim is to investigate the diagnostic accuracy of ^{68}Ga-PSMA PET sub-analyzed specifically to ^{177}Lu-PSMA therapy response in patients with mCRPC compared with the conventional use of serum prostate specific antigen (PSA).

METHODOLOGY

Search Strategy

This systematic review was performed in accordance with the Cochrane diagnostic accuracy reviews guidelines and the Preferred Reporting Items for systematic reviews and meta-analysis (PRISMA) checklist. A comprehensive literature search was performed using databases from Google scholar, Cochrane library and pub-med/Medline spanning the period of January 2015 to August 2020. An amalgamation of the search terms PSMA, PET, and treatment response were used including synonyms namely prostate specific membrane antigen and positron emission tomography. These were combined with Boolean operator (AND) to narrow the search. Pearling was done to add studies that may have been missed in the initial database search.

Study Selection

In the initial search, study titles that were obviously unrelated were omitted, along with duplicated articles. Abstracts of selected studies were further analyzed, excluding those that are again found to be irrelevant or did not fit the inclusion criteria. The reviewers independently identified all studies that complied with inclusion criteria. Disagreement between the two reviewers (T.L. and A.B) were resolved by a consensus. For studies where a consensus between the two reviewers could not be reached, a third reviewer (D.V.) was consulted for arbitration and definitive consensus with regards to the concerned studies.

Inclusion and exclusion criteria

The included studies involved the evaluation of treatment response to ^{177}Lu-PSMA therapy by use of ^{68}Ga-PSMA PET hybrid imaging with either computed tomography (CT) or magnetic resonance imaging (MRI) which were categorized. The studies evaluated treatment responses based on either the PET Response Criteria in Solid Tumors (PERCIST) or the European

Organization for Research and Treatment of Cancer (EORTC) criteria, and were categorized as complete response, partial response, stable disease, or disease progression. Studies limited to the English language were included as well as non-English studies that have been translated to English. Where data were not extractable, the study was excluded. Any study that did not use serum PSA for biochemical response evaluation was likewise excluded.

Biochemical response as the reference standard

The reference standard for this study is the use of serum PSA as a biochemical marker for response to therapy. The studies evaluated biochemical responses according to the percent change in serum PSA levels (e.g., decrease of >50%) and may be additionally categorized into complete response, partial response, stable disease, or progressive disease.

Data extraction

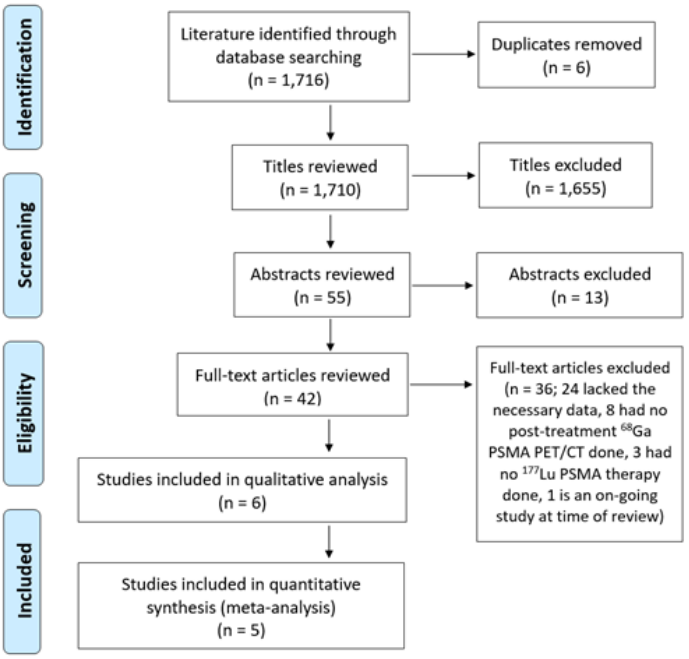
The following variables were extracted from each eligible study: first author, year published, study demographics, number of patients, characteristics of patients, details of ^{68}Ga-PSMA PET/CT imaging, 177Lu-PSMA treatment regimen, and serum PSA. Diagnostic accuracy figures, specifically true positive (TP), true negative (TN), false positive (FP), false negative (FN) were extracted from the data provided in each study, where positive was defined as “treatment response” and negative as “no treatment response”.

Statistical analysis

Sensitivity, specificity, pooled diagnostic accuracy, and Spearman’s correlation coefficient between the logit of sensitivity and the logit of (1-specificity) was calculated. The Summary receiver operating characteristic (SROC) curves were constructed using the random effects Der-Simonian-Laird model. Meta-DiSc v1.4 program was used for all statistical analysis including the generation of Forest and SROC plots.

RESULTS

Initial search of the literature yielded 1,716 studies. Review of these titles excluded 1,655 studies as they were obviously not relevant to the research question. Review of the abstracts of the remaining studies led to exclusion of 13 studies that did not comply with the set inclusion criteria. Finally, 42 relevant papers were identified for full text review. Of these, six studies from the literature search were found to fit our inclusion criteria. Flow chart shown in PRISMA flow diagram is shown in figure 1.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/

FIGURE 1. PRISMA flow chart

Quality assessment

Complete manuscripts of the selected studies were assessed for bias and appraised for applicability of methodology utilized using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) 2 tool. These assessments were done by two reviewers. See Table 1 for summary. The study results were reported in accordance with the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guideline [12].

After quality assessment of the included studies, one was omitted as it was deemed to have a high and unclear risk of bias for the index test and reference standard, respectively. A total of five studies were included in the final analysis.

TABLE 1. QUADAS 2 appraisal of studies

	Risk of Bias				Applicability		
STUDIES [Reference]	Patient Selection	Index Test	Reference Std.	Flow And Timing	Patient Selection	Index Test	Reference Std.
Acar [13]	+	+	+	+	+	+	+
Ahmadzadehfar [14]	+	+	+	+	+	+	+
Grubmüller [15]	+	+	+	+	+	+	+
Gupta [16]	+	+	+	+	+	+	+
Maffey-Steffan [17]	+	+	+	+	+	+	+
Scarpa [18]	+	-	?	+	+	+	+
+ *low risk* ? *unclear* - *high risk*							

Characteristics of the included studies

Of the final five included studies, three were published in 2019, one in 2018, and one in 2016. Four studies were retrospective, and one was prospective in their approach. Studies originated from Turkey, Germany, Austria, and India. They included a total of 128 patients. All patients were diagnosed cases of metastatic prostate cancer that were refractory to chemotherapy and/or hormonal therapy. All studies evaluated treatment response to ^{177}Lu-PSMA radioactive ligand therapy with the use of ^{68}Ga-PSMA PET hybrid imaging and serum PSA. One study used either PET/MRI or PET/CT depending on the contraindication (e.g., metal implants) while the rest of the studies used PET/CT only. Summary of study characteristics are shown in Table 2. The studies had pre-defined criteria for treatment response according to serum PSA changes and molecular imaging changes as described in the subsequent sections.

Reference biochemical responses

Two studies generally categorized PSA responses into a decrease of >50% and other % changes, while the rest have categorized responses into complete response, partial response, stable disease, or progressive disease. Three studies had favorable PSA responses in more than half of their patients ranging from 57.8% to 75.0%, while the other two studies had fewer desirable responses with as low as 13.0% of patients.

PET hybrid imaging responses

Four studies utilized the PERCIST for evaluation of response by imaging. Of these studies, one included the use of the EORTC criteria for molecular response and another included a Visual and Semiquantitative PET Score. These additional response criteria showed good agreement with the PERCIST criteria. One study used a pre-defined category of responses based on SUV changes that is similar to the PERCIST criteria. Similarly with the biochemical responses, three studies had favorable PET responses ranging from 63.1% to 80.0%, and two studies with less promising responses, as low as 21.7% of patients.

Pooled diagnostic accuracy

The computed sensitivity from these studies ranged from 67 to 100% (Figure 2) with a pooled sensitivity of 85% (CI: 74 to 92%). The specificity ranged from 44 to 100% (Figure 3) with a pooled specificity of 74% (CI: 62 to 84%). The corresponding receiver operating characteristic (ROC) plane and curve shown in Figure 4 and 5, respectively, assesses the accuracy of ^{68}Ga-PSMA PET for treatment response to ^{177}Lu-PSMA therapy.

The area under the ROC curve (AUC) was computed to be 0.8. The calculated diagnostic effectiveness (accuracy) was 79.7%.

TABLE 2. Baseline characteristics of the included studies

Author **Year [Ref]**	**Acar** **2019 [13]**	**Ahmadzadehfar** **2016 [14]**	**Grubmüller** **2018 [15]**	**Gupta** **2019 [16]**	**Maffey-Steffan** **2019 [17]**
Country	Turkey	Germany	Austria	India	Austria
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Prospective
Total (N)	19	20	38	23	28
Age (years), mean (range), median (IQR), or mean ± SD	66 ± 8 Mean ± SD	75.2 (64–82) Mean (Range)	71.5 (67.3, 77.3) Median (IQR)	75.5 (57-81) Mean (Range)	71.4 (50-91) Mean (Range)
Patient characteristics	Metastatic PC with refractory to chemotherapy, hormonal therapy, or surgery	Metastatic PC refractory to chemotherapy and/or hormonal therapy	Metastatic PC refractory to hormonal therapy and/or chemotherapy	Metastatic PC refractory to chemotherapy, radiotherapy, hormonal therapy, or surgery	Metastatic PC refractory to chemotherapy, monoclonal antibody therapy, and/or hormonal therapy
^{177}Lu-PSMA treatment regimen	200 mCi (7.4 Gbq) of Lu-177 PSMA I&T, 3 to 8 cycles in 8 to 10-week intervals	Mean 162.1 mCi (6.0 GBq), range 110.8-191.9 (4.1-7.1) of Lu-177 PSMA, average 2 cycles	200 (7.4 GBq) of Lu-177 PSMA 617, 3 cycles in 4-week intervals	Mean 195.9 mCi (7.25 GBq), median 198.6 (7.35), range 178.4-205.4 (6.6–7.6) of Lu177-PSMA-617, (# of cycles not mentioned)	222 mCi (6 GBq) of Lu-177 PSMA-617, 3-4 cycles in 6-week inter-vals
^{68}Ga-PSMA PET imaging protocol	PET/CT 3.1 mCi (115 MBq) of Ga-68 PSMA I&T 10–12 bed positions from vertex to feet, 1.5-min emission per bed position	PET/CT 0.05 mCi (2 MBq)/ kg BW of ^{68}Ga PSMA (Image acquisition protocol not mentioned)	PET/MRI 0.05 mCi (2 MBq)/kg BW of ^{68}Ga PSMAHBED-CC conjugate 11 4 bed positions from skull base to thighs, 5 min sinogram mode PET/CT 0.05 mCi (2 MBq)/kg BW of ^{68}Ga PSMAHBED-CC conjugate 11 4 min per bed position, vertex to upper thighs	PET/CT 0.05 mCi (2 MBq)/kg BW of ^{68}Ga PSMA-11, 4 min per bed position in 3D mode	PET/CT 4.0 mCi (150 MBq), range 3.2-4.3 (120–160 MBq) of ^{68}Ga PSMA-11 Skull to midthighs, 2 min emission with an axial field-of-view of 15.6 cm per bed position in 3D mode
PET response criteria	PERCIST	PR: ↓ >30% SUV, PD: ↑>30% or new lesions, SD: ↓<30% SUV	Modified PERCIST	PERCIST 1.0 EORTC criteria for molecular response	PERCIST Visual PET Score Semiquantitative PET Score
PSA response classification / criteria	↓>50%, others	↓>50%, ↓>30%, any ↓, any ↑	CR: 0 ng/ml, PR: ↓≥50%, PD: ↑≥25%, SD: between −50% & +25%	PR: ↓≥50%, SD: between ↓<50 and ↑<25, PD: ↑≥25%	↓>50%, any ↓, Classified into TR, SD, and PD

IQR interquartile range, ADT androgen deprivation therapy, BW body weight, ↓ decrease, ↑ increase, CR complete response, PR, partial response, TR treatment response, SD stable disease, PD progressive disease

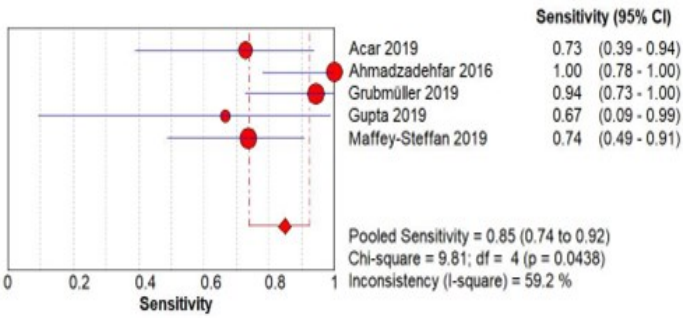


FIGURE 2. Forest plots of the sensitivity of ^{68}Ga-PSMA PET for treatment response to ^{177}Lu-PSMA therapy

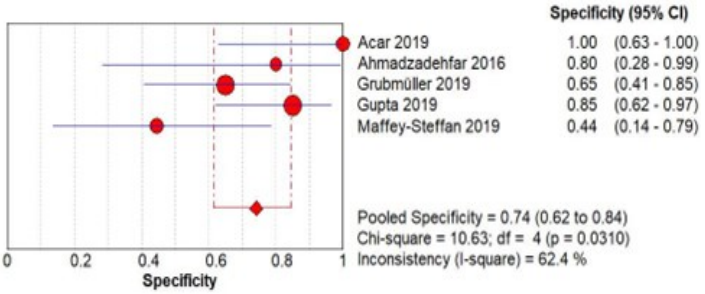


FIGURE 3. Forest plots of the specificity of ^{68}Ga-PSMA PET for treatment response to ^{177}Lu-PSMA therapy

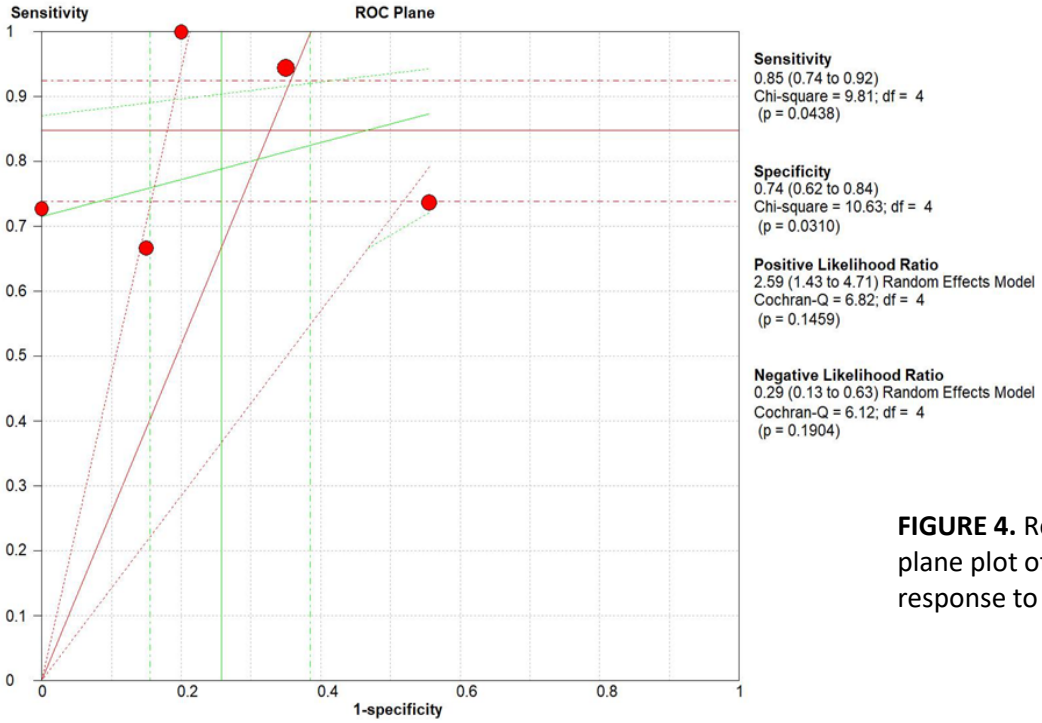


FIGURE 4. Receiver operating characteristic plane plot of ^{68}Ga-PSMA PET for treatment response to ^{177}Lu-PSMA therapy

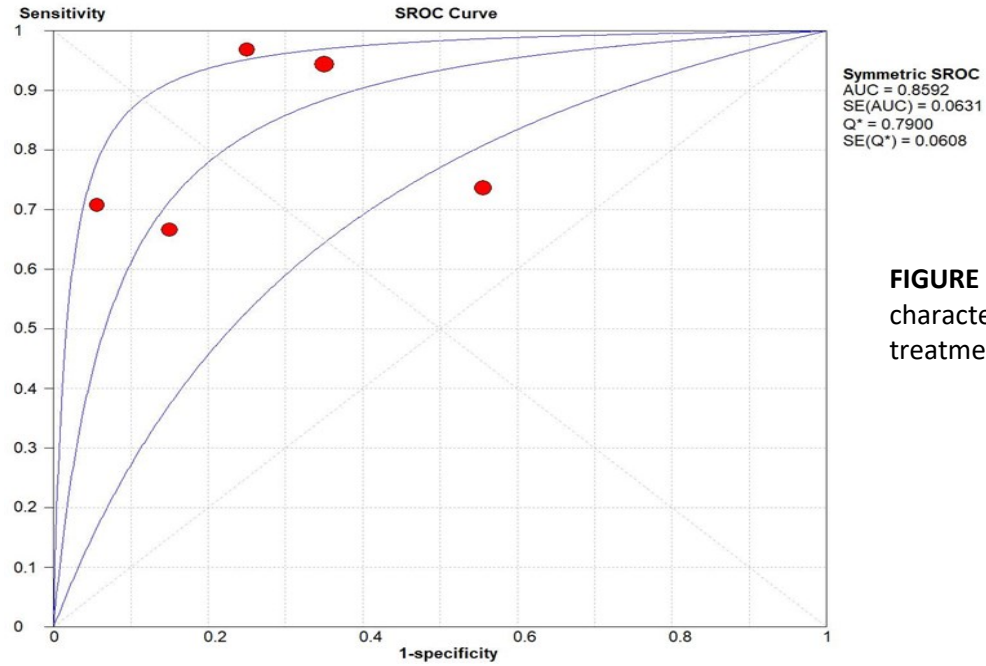


FIGURE 5. Summary receiver operating characteristic curves plot ^{68}Ga-PSMA PET for treatment response to ^{177}Lu-PSMA therapy

DISCUSSION

^{177}Lu PSMA radioligand therapy has shown encouraging outcomes through a great proportion of treated men demonstrating significant responses with reductions in serum PSA levels of more than 50%, ranging from 30% to 70%. These results parallel PSA responses attained by the chemotherapy agents, Cabazitaxel and Docetaxel, used in mCRPC [8, 19]. Consistent with the Prostate Cancer Working Group (PCWG) 1 criteria [20], PSA responses of the included studies similarly defined partial response as a decline of >50%. Unlike the higher ratio of PSA responders in aforementioned literature, our study showed that only 66 of the 128 patients (51.2%) had favorable decline in PSA levels. Although these are biochemical responses alone. With the updated PCWG 2 and 3 criteria, it is now discouraged to use PSA response exclusively in the decision-making process on whether to alter the patient's treatment regimen. These new criteria give emphasis on imaging rather than blood biomarkers in the evaluation of disease progression [20, 21]. Given the availability of various medical arsenal provided by modern science, the measurement of disease burden from prostate cancer should indeed not be restricted to a single parameter.

There are several imaging modalities available in the assessment of prostate cancer and although radionuclide bone imaging is broadly used in the PCWG 3 criteria to evaluate treatment response, it has considerable limitation given the recent technological advances [22]. The rapidly developing and expanding role of modern imaging has led to a more optimal assessment of treatment response giving rise to a trend to include hybrid imaging as a mainstay in therapy monitoring. In the theragnostic framework, ^{68}Ga-PSMA PET is the logical imaging modality of choice for evaluating treatment response [23], as it provides a more targeted detection of prostate cancer cells at a molecular level .

PET hybrid imaging provides the advantage of using both molecular and morphologic assessment of a disease. Although visual appraisal of images is the mainstay of disease evaluation, certain imaging criteria may aid in drawing a clearer diagnostic conclusion. In fact, molecular criteria have been found to perform better than morphologic criteria in assessing the response to treatment in patients with metastatic prostate cancer and an increased PSA level [24]. Given its potential contribution in the management of prostate cancer, its precision must be established to support its use. As such, the measure of diagnostic accuracy is not limited to effectively detecting the presence of a certain disease condition, but more precisely allows us to discriminate between two certain conditions of interest [25]. This study concisely discerned two conditions after treatment with ^{177}Lu-PSMA, specifically "with treatment response" (i.e., complete response and partial response) and "no treatment response" (i.e., stable disease and progressive disease).

Although there has been limited data comparing ^{68}Ga-PSMA PET hybrid imaging with biochemical parameters, there have been anecdotal findings on their concordance in some studies. In a single-center study that evaluated their initial experience with ^{177}Lu-PSMA therapy, it was interestingly noted that there was a clear parallel between changes in PSA level and imaging among those who underwent ^{68}Ga-PSMA PET/CT [26]. A retrospective study by Gafita et al. involving 124 patients treated with ^{177}Lu-PSMA reported that patients who had a decline of PSA also showed a reduced risk of PSMA-targeted PET/CT-based progression compared with those who had stable disease [27]. Plouznikoff et al. reported that ^{68}Ga-PSMA PET findings may even precede changes in serum PSA potentially allowing us to detect early relapse and low-volume oligoprogressive disease prior to biochemical changes [28]. As these studies demonstrate, the utility of ^{68}Ga-PSMA PET hybrid imaging may play an important role in the evaluation of radioligand therapy.

The utility of ^{68}Ga-PSMA PET hybrid imaging has also been studied in evaluating responses from other treatment modalities for prostate cancer. In a study by Kallur et al., no significant correlation was found between ^{68}Ga-PSMA response with biochemical response of 51 evaluable pre- and post-therapy cases in which treatment involved mostly hormone therapy [29]. In contrast, all included literature in this study reported concordance of PET and PSA responses in most of their population, in line with the computed diagnostic accuracy parameters. A possible explanation for this deviance involving hormonal therapy is that inhibition of the androgen receptor by androgen deprivation therapy can markedly increase PSMA expression limiting the accuracy of ^{68}Ga-PSMA PET in this demographic [30]. Therefore, careful consideration in choosing the modality for follow-up evaluation should be observed.

One importance of ^{68}Ga-PSMA PET hybrid imaging lies in its influence on clinical decision making in the treatment of prostate cancer. Kuten et al. found that imaging data from ^{68}Ga-PSMA PET/CT guided further therapeutic management in 73.3% of their patients and had a major added value in monitoring response by allowing lesion -

based and not only patient-based analysis [31]. Aside from the benefit of evaluating response, Kurshid et al. also found that baseline PSMA PET-CT scan has the potential for predicting treatment response [32]. As pre-treatment ^{68}Ga-PSMA PET is a prerequisite to gauge eligibility for ^{177}Lu-PSMA therapy, it is arguably rational to use the same imaging modality to assess responses comparing baseline to ensuing follow-up in this form of treatment.

Strengths and limitations of this study

This study presents a review of the existing literature based on Cochrane and STARD guidelines. This review gives an overview of the diagnostic accuracy of ^{68}Ga-PSMA PET hybrid imaging sub-analyzed to ^{177}Lu-PSMA therapy response. Limitations of this study include moderate statistical heterogeneity found among the studies (see Figures 2 and 3). There was also marked variation in the ^{177}Lu-PSMA treatment regimen and differences in imaging protocol and doses of ^{68}Ga-PSMA PET used across the studies. One study included the use of PET/MRI whereas most studies utilized PET/CT. These dissimilarities preclude this review from recommending a specific ^{68}Ga-PSMA hybrid imaging protocol.

CONCLUSION

There ^{68}Ga-PSMA PET hybrid imaging demonstrated good sensitivity, specificity, and diagnostic accuracy, compared with the standard biochemical parameter using serum PSA in the evaluation of treatment response to ^{177}Lu-PSMA radioligand therapy in patients with advanced metastatic prostate cancer. Although these data are generally supportive of its use, significant heterogeneity precludes constructing definitive recommendations. There is a need for further studies on its impact in the clinical setting.

ACKNOWLEDGEMENT

The authors express their utmost gratitude to Ms. Ma. Kristine Joy S. Calvario and Dr. Candice Genuino-Montaño for their guidance in the construction of the protocol up to finalization of this manuscript.

FUNDING

Not applicable.

DISCLOSURE

The authors declare no conflicts of interest relevant to the preparation of this study .

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.
2. Wong MCS, Goggins WB, Wang HHX, et al. Global incidence and mortality for prostate cancer: Analysis of temporal patterns and trends in 36 countries. European Urology.2016;70(5):862-874. doi:10.1016/j.eururo.2016.05.043.
3. Yap TA, Zivi A, Omlin A, de Bono JS. The changing therapeutic landscape of castration-resistant prostate cancer. Nat Rev Clin Oncol. 2011;8(10):597-610. doi:10.1038/nrclinonc.2011.117.
4. Frieling JS, Basanta D, Lynch CC. Current and emerging therapies for bone metastatic castration-resistant prostate cancer. Cancer Control. 2015;22(1):109-120. doi:10.1177/107327481502200114.
5. Heck MM, Retz M, D'Alessandria C, et al. Systemic Radioligand Therapy with (177)Lu Labeled Prostate Specific Membrane Antigen Ligand for Imaging and Therapy in Patients with Metastatic Castration Resistant Prostate Cancer. J Urol. 2016;196(2):382-391. doi:10.1016/j.juro.2016.02.2969.
6. Wright GL Jr, Haley C, Beckett ML, Schellhammer PF. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol Oncol. 1995;1(1):18-28.
7. Hofman MS, Emmett L, Violet J, et al. TheraP: A randomized phase 2 trial of 177Lu-PSMA-617 theranostic treatment vs Cabazitaxel in progressive metastatic castration-resistant prostate cancer (clinical trial protocol ANZUP 1603). BJU International. 2019;124:5-13. doi:10.1111/bju.14876.
8. Emmett L, Willowson K, Violet J, Shin J, Blanksby A, Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci. 2017 Mar;64(1):52-60. doi: 10.1002/jmrs.227. PMID: 28303694; PMCID: PMC5355374.
9. Albisinni S, Artigas C, Aoun F, Biaou I,Grosman J,Gil T, et al. Clinical impact of 68Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in patients with prostate cancer with rising prostate-specific antigen after treatment with curative intent: preliminary analysis of a multidisciplinary approach. BJU Int.2017;120:197–203. doi: 10.1111/ bju.13739.
10. Oliveira JM, Gomes C, Faria DB, et al. 68Ga-prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography for Prostate Cancer Imaging: A Narrative Literature Review. World J Nucl Med. 2017;16(1):3-7.
11. Turpin A, Girard E, Baillet C, et al. Imaging for metastasis in prostate cancer: A review of the literature. Frontiers in

Oncology. 2020;10. doi:10.3389/fonc.2020.00055.

12. Bossuyt PM, Reitsma JB, Bruns DE, et al. Stard 2015: An updated list of essential items for Reporting Diagnostic Accuracy Studies. BMJ. 2015. doi:10.1136/bmj.h5527.
13. Acar E, Özdogan Ö, Aksu A, Derebek E, Bekis R, Çapa Kaya G. The use of molecular volumetric parameters for the evaluation of Lu-177 PSMA I&T therapy response and survival. Ann Nucl Med. 2019;33(9):681-688. doi:10.1007/s12149-019-01376-3.
14. Ahmadzadehfar H, Eppard E, Kürpig S, et al. Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. Oncotarget. 2016;7(11):12477-12488. doi:10.18632/oncotarget.7245.
15. Grubmüller B, Senn D, Kramer G, et al. Response assessment using 68GA-PSMA ligand pet in patients undergoing 177LU-PSMA radioligand therapy for metastatic castration resistant prostate cancer. European Urology Supplements. 2019;18(1). doi:10.1016/s1569-9056(19)30513-5.
16. Gupta M, Choudhury PS, Rawal S, Goel HC, Rao SA. Evaluation of response in patients of metastatic castration resistant prostate cancer undergoing systemic radiotherapy with lutetium177-prostate-specific membrane antigen: A comparison between response evaluation criteria in solid tumors, positron-emission tomography response criteria in solid tumors, European organization for research and treatment of cancer, and MDA criteria assessed by gallium 68-prostate-specific membrane antigen positron-emission tomography-computed tomography. Urol Ann. 2019;11(2):155-162. doi:10.4103/UA.UA_111_18.
17. Maffey-Steffan J, Scarpa L, Svirydenka A, et al. The 68ga/177LU-theragnostic concept in PSMA-targeting of metastatic castration–resistant prostate cancer: Impact of post-therapeutic whole-body scintigraphy in the follow-up. European Journal of Nuclear Medicine and Molecular Imaging. 2019;47(3):695-712. doi:10.1007/s00259-019-04583-2.
18. Scarpa L, Buxbaum S, Kendler D, et al. The 68Ga/177Lu theragnostic concept in PSMA targeting of castration-resistant prostate cancer: correlation of SUVmax values and absorbed dose estimates. Eur J Nucl Med Mol Imaging. 2017;44(5):788?800. doi:10.1007/s00259-016-3609-9.
19. Oudard S. TROPIC: Phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. Future Oncol. 2011 Apr;7(4):497-506. doi: 10.2217/fon.11.23. PMID: 21463139.
20. Scher, H. I., Halabi, S., Tannock, I., Morris, M., Sternberg, C. N., Carducci, M. A., … Hussain, M. (2008). Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. Journal of Clinical Oncology, 26(7), 1148–1159. doi:10.1200/jco.2007.12.4487.
21. Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-1418. doi:10.1200/JCO.2015.64.2702.
22. Perez-Lopez R, Tunariu N, Padhani AR, et al. Imaging diagnosis and follow-up of Advanced Prostate Cancer: Clinical Perspectives and state of the art. Radiology. 2019;292(2):273-286. doi:10.1148/radiol.2019181931.
23. Heinzel A, Boghos D, Mottaghy FM, et al. 68ga-PSMA PET/CT for monitoring response to 177LU-PSMA-617 radioligand therapy in patients with metastatic castration-resistant prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2019;46(5):1054-1062. doi:10.1007/s00259-019-4258-6.
24. Osmany S, Zaheer S, Bartel TB, et al. Gallium-68–labeled prostate-specific membrane antigen–11 PET/CT of prostate and Nonprostate Cancers. American Journal of Roentgenology.2019;213(2):286-299. doi:10.2214/ajr.19.21084.
25. Šimundić AM. Measures of Diagnostic Accuracy: Basic Definitions. EJIFCC. 2009;19(4):203-211. Published 2009 Jan 20.
26. McBean R, O'Kane B, Parsons R, Wong D. LU177-PSMA therapy for men with advanced prostate cancer: Initial 18 months experience at a single Australian Tertiary Institution. Journal of Medical Imaging and Radiation Oncology. 2019;63(4):538-545. doi:10.1111/1754-9485.12891.
27. Gafita A, Heck MM, Rauscher I, et al. Early prostate-specific antigen changes and clinical outcome after 177LU-PSMA radionuclide treatment in patients with metastatic castration-resistant prostate cancer. Journal of Nuclear Medicine. 2020;61(10):1476-1483. doi:10.2967/jnumed.119.240242.
28. Plouznikoff N, Artigas C, Sideris S, Gil T, Flamen P. Early Detection of Metastatic Prostate Cancer Relapse on 68Ga-PSMA-11 PET/CT in a Patient Still Exhibiting Biochemical Response. Clin Nucl Med. 2020;45(1):81-82. doi:10.1097/RLU.0000000000002799.
29. Kallur KG, Ramachandra PG, Rajkumar K, et al. Clinical Utility of Gallium-68 PSMA PET/CT Scan for Prostate Cancer. Indian J Nucl Med. 2017;32(2):110-117. doi:10.4103/0972-3919.202255.
30. Hope TA, Truillet C, Ehman EC, et al. 68Ga-PSMA-11 PET imaging of response to androgen receptor inhibition: first human experience. J Nucl Med 2017;58(1):81–84.
31. Kuten J, Sarid D, Yossepowitch O, Mabjeesh NJ, Even-Sapir E. [68ga]ga-PSMA-11 PET/CT for monitoring response to treatment in metastatic prostate cancer: Is there any added value over standard follow-up? EJNMMI Research. 2019;9(1). doi:10.1186/s13550-019-0554-1
32. Khurshid Z, Ahmadzadehfar H, Gaertner FC, et al. Role of textural heterogeneity parameters in patient selection for 177LU-PSMA therapy via response prediction. Oncotarget.2018;9(70):33312-33321. doi:10.18632/oncotarget.26051