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Review

^{68}Ga-PSMA-PET/CT Has a Role in Detecting Prostate Cancer Lesions in Patients with Recurrent Disease

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Abstract. *Background/Aim: Early detection of recurrent πrostate cancer (PCa) lesions is paramount to allow patients to avail of localised salvage therapy options. The most significant reason for failure of salvage therapy is undetected metastatic disease. This demonstrates the need for a more accurate monitoring tool. The prostate-specific membrane antigen (PSMA) is increasingly investigated as a novel tracer for gallium 68 PET/CT to detect PCa lesions in patients with recurrent disease. Materials and Methods: The Embase, Pubmed and the Cochrane databases were searched to identify studies investigating the accuracy of ^{68}Ga-PSMA-PET/CT in detecting PCa lesions. Studies were analysed with regards to image analysis, sensitivity, specificity and detection rates; compared to conventional methods and with the effects of contributing characteristics.Results: 24 studies were analysed. ^{68}Ga-PSMA-PET/CT was associated with sensitivity and specificity values of 33-93%, and >99% respectively. The tracer produced excellent contrast 1 h post injection. Probability of detection increases with increasing prostate-specific antigen (PSA), and at low PSA levels, is greater than that of current choline tracers. Early detection of lesions by the tracer allows alterations in follow up treatment. However, detectability may be affected by tracer trapping, androgen deprivation therapy and levels of PSMA expression. Conclusion: ^{68}Ga-PSMA PET/CT shows promise as a tool for the detection of PCa lesions in patients with suspected recurrence. However further studies with more reports on sensitivity and specificity with longer follow-up times are needed.*

Prostate cancer (PCa) is the second most common cancer in males, and the sixth cause of mortality among men worldwide (1). Radical prostatectomy (RP) and radiotherapy (RT) are the main methods of treatment used (1, 2). Both methods provide a good chance of overall survival. A percentage of 68-83% of patients have a 10-year progression-free survival after RP (2). Despite this, up to 40% of patients may incur a rise in PSA above 0.2 ng/mL, a state referred to as biochemical failure or Biochemical recurrence (BCR), after RP (2-4). Patients with locally advanced disease treated with external beam radiotherapy and long term hormone therapy experience excellent overall survival (5). However BCR reported in patients who received RT (PSA >2 ng/ml (3)), with and without Androgen Deprivation Therapy (ADT) was 12-26% (6).

Currently, salvage RT is associated with the best outcomes for patients, with PSA <0.5 ng/ml, that are treated with RP (7). Treatments available to patients previously treated with RT, with PSA <10 ng/ml, include salvage RP, cryotherapy, High-intensity focused ultrasound (HIFU), and interstitial RT (8-12). The most significant reason for failure of salvage therapy is undetected metastatic disease (13). Due to poor sensitivity of currently used imaging modalities, novel biomarkers are under investigation to improve PCa detection, within the therapeutic window for salvage therapy options, using PET (14). Choline-based tracers (^{18}F and ^{11}C) are most commonly used to target PCa (15, 16), but suffer from low sensitivity and specificity at low PSA levels, identifying the need for a new imaging agent (16, 17).

Prostate specific membrane antigen (PSMA) is a membrane bound glycoprotein overexpressed in PCa (18). which, coupled with Gallium 68 (^{68}Ga), is showing particular promise in the detection of PCa. Afshar-Orimiech was the first to obtain images with ^{68}Ga-PSMA-PET/CT, from a 67-year-old male previously treated with RT, who presented with

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a rising PSA. Images suggested the tracer had a strong ability to detect PCa relapse (19). This review discusses the potential for ^{68}Ga-PSMA-PET/CT to improve our ability to detect local, lymph and metastatic PCa lesions in patients with recurrent disease after primary therapy, with high detection rates, even at low PSA.

Materials and Methods

Search strategy for identification of studies. A literature search of electronic databases Pubmed, Embase and The Cochrane library were carried out, using 'PSMA', 'Prostate Specific Membrane Antigen', 'PET/CT' and a Subject Mesh search was also used. The bibliographies of selected studies were checked for relevant studies. The last search was conducted on 30th of January 2017.

Type of studies. Clinical trials, and retrospective analyses from the last five years were selected which tested the use of the 68Ga-PSMA-PET/CT. Studies with sample sizes ≥10, and studies comparing 68Ga-PSMA-PET/CT to other tracers or imaging modalities were included. Non-English studies and abstracts were excluded.

Type of participants. PCa patients previously treated with RT and/or RP with BCR, or suspected progressive disease indicated on other imaging modalities. Patients with primary disease, who were imaged to rule out metastasis before RP. Patients of all ages, PSA levels, and Gleason score (GS), and patients receiving/not receiving ADT were included. Patients being evaluated for possible treatment with 177Lu-PSMA were included. Chemotherapy patients were excluded.

Type of interventions. ^{68}Ga radiolabelled HBED-CC, which is the conjugate of PSMA, used with PET/CT is the intervention.

Outcome measures. Sensitivity, specificity, and detection rates of the imaging modality at different PSA levels were analysed. The number of patients with local, lymph node metastasis (LNM) and distant metastasis was recorded, as were the follow up treatments prescribed to patients following positive imaging results. The effects of PSA, GS and ADT, on the results were noted.

Results

This review aimed to investigate whether ^{68}Ga radiolabelled PSMA, with PET/CT, is an appropriate imaging tool for early detection of PCa lesions in recurrent PCa patients. A total of 24 studies were reviewed, accounting for a total of 2,408 patients with sample sizes ranging from 14-532. PSMA is a cell surface protein overexpressed in PCa (18). This strategy to target PSMA to identify prostate cancer emerged after preliminary reporting of the detection of high contrast in lesions targeted with ^{68}Ga-PSMA-PET/CT (19). These efforts are being made with the assumption that all PCa express PSMA (20, 21). This review highlights the benefits of the tracer; reporting high specificity, and detection rates, particularly at low PSA levels. Included comparative studies show superiority of ^{68}Ga-PSMA over choline based tracers. However the standardisation of its use for staging recurrent PCa patients remains challenging. These included false negatives, possibility of PSMA negative PCa, tracer trapping, and potentially improved sensitivity with 18[F]DCFPyl and PET/MR imaging. An argument in favour of ^{68}Ga is its ability to be extracted from a ^{68}Ge/^{68}Ga radionuclide generator. In contrast, choline tracers need to be extracted from a cyclotron using isotopes, proving cost intensive.

^{68}Ga-PSMA-PET/CT is a promising imaging technique for detecting PCa lesions in patients with recurrent disease. The most challenging prerequisite for currently used imaging modalities which detect recurrent PCa, is their sensitivity and specificity, especially in patients with early BCR (22-27). 68Ga-PSMA-PET/CT is associated with excellent specificity (>99%), but variable sensitivity (33-94%) (28-32). Detection rates are reported to improve with increasing PSA levels, from approximately 50% for PSA <0.5 ng/ml to close to 95% for PSA >2 ng/ml (33, 34). In instances were pelvic lymph node involvement was detected with ^{68}Ga-PSMA, subsequent nodes detected at pelvic lymph node dissection gave rise to a >90% sensitivity. One explanation for such high specificity is the strong evidence for excellent contrast produced 1hr post imaging (p.i). The maximum standard uptake value (SUVmax) of positive lesions was higher with ^{68}GaPSMA than Choline based PET/CT tracers. Furthermore the tracer uptake in background tissue was significantly lower with ^{68}Ga PSMA than with choline tracers, improving the detectability of lesions (35, 36). Further explanation for high specificity, and reports of good sensitivity, are the improved images produced with the combination of morphological CT imaging, and physiological PET information. For example, when CT and MR imaging is used alone for diagnosing LNM, lymph nodes are assessed based on shape and size (37). A threshold of 8-10 mm is generally used to identify nodes suspicious of PCa. This has resulted in low sensitivity of 34-40% (28-30). Giesel *et al*. reported that a further 57% of patients were identified with lesions after PET and CT images were combined (38). PET compensates for the limitations of CT, making cancer positive nodes that would have otherwise been suspected as inflammatory, reactive or non-existent, more easily identifiable (35). Where low sensitivity was reported (39), it is hypothesized that the presence of the untreated prostate cancer could be the underlying cause for an observed increased uptake of the tracer and depletion of tracer concentration in the blood pool. Restricted perfusion of the tracer in the lymph due to poor vascularisation thresholds could also account for the limited (4/12) number of patients with LN involvement detected by ^{68}Ga-PSMA-PET/CT.

The strength of the tracer is questioned when faced with more clinically challenging cases of recurrent PCa. Earlier studies report better detection ratio than later studies. This

may be because more challenging cases of PCa, with negative alternative imaging, were being referred for imaging with ^{68}Ga-PSMA-PET/CT, as it became more popularly used. The tracer is based on the theory that all prostate cancers express PSMA (35), however the authors cannot exclude the possibility of PSMA negative PCa, or the heterogeneity of PSMA expression, like in Neuroendocrine PCa (40-42). Decreased PSMA expression in advanced disease, caused by tumour differentiation (21), and the effect of previous therapies on PSMA expression are other possible factors (40, 43). This may explain false negative findings, and why in certain studies, 18F-choline had greater tracer uptake than ^{68}Ga (36, 44), as choline does not target PSMA. Choline is internalised into the cell membrane by increased activity of choline kinase and fatty acid synthases (45, 46). The superiority of 68-Ga-PSMA over 18F-fluoroethylcholine PET/CT has been demonstrated in the detection of locoregional recurrent and/or metastatic lesions prior to salvage lymphadenectomy (47). Similarly, 68Ga-PMSA-PET/CT identified sites of recurrent disease in 43.8% of patients with negative 18F-Choline PET/CT scans (48). When ^{68}Ga-labelled PSMA-11 was compared to 11C-Choline PET/CT to identify metastasis for patients with primary and recurrent disease, ^{68}Ga-PSMA-11 achieved higher detection rates for lymph nodes and bone lesions. However 11C-Choline still identified 37 lesions that were not detected using ^{68}Ga-PSMA. Hence this study suggests that both methodologies could lead to differences in tumour, nodes and metastases (TNM) classification of patients (49).

False negative findings could also be attributed to the low injection activity of ^{68}Ga. Variation in injected tracer amount was due to the short half-life of ^{68}Ga/Ge (50, 51). A higher radioactivity could result in higher detection rates by providing higher statistics, adding to the imaging quality (32). This suggestion however can be argued as statistically invariable to have caused adverse molecular interactions as all injections contained 2 nmol of the PSMA ligand. Alternatively, the presence of androgens stimulate the production of prostate cancer cells containing PSMA, the use of ADT could potentially alter imaging results (52, 53). The aim of ADT is to reduce PSA and tumour size, however results indicate a trend towards higher detection for patients treated with ADT. This could be due to the fact that more patients with more advanced disease are referred for ADT (31, 44, 54). However other studies report prolonged ADT appears to down regulate PSMA (55, 56). The effects of ADT on imaging results needs to be evaluated further, considering the large number of patients referred for ADT.

Tracer trapping is an area of concern in relation to the tracer, due to reports of normal tissue expressing PSMA (22). Poor follow up in the studies means unknown side effects associated with tracer trapping (57) could have a knock-on effect on radiolabelled PSMA treatments (44, 50, 58-60). When looking specifically at tracer uptake in the lymph nodes, radiologists must have caution regarding the celiac ganglia, located at the level of the superior mesenteric arteries, which have shown sufficient tracer uptake mimicking LNM (61). The recommendation to exploit the high contrast produced by early imaging (<1h p.i) also avoids needing urinary catheterization or hydration requirements (60).

Further evidence suggests detection rates may be improved by combining MRI and PET. PET/MRI produces images with improved lesion contrast, due to improved soft tissue resolution. Visualisation of local infiltration and the tumours relationship to adjacent organs (62, 63), allows for more precise tumour delineation. A study comparing PET/MRI to PET CT (despite using FDG) reported improved detection of lymphadenopathy and bone metastases with PET/MRI (64). PET/MR images were taken 3h p.i in the study comparing MRI to CT (59). This meant high contrast could have been due to greater internalization of PSMA into PCa cells. Manufacturers are currently looking into eliminating the Halo artefact produced with PET/MRI around the bladder, which was its most pronounced limitation. It caused reduced visualisation of the tumour, leading to inaccurate standard uptake values (SUV) readings. Hydration, catheterization and voiding the bladder before imaging are advised by manufacturers, to reduce bladder artefact, however results of such measures are insufficient. They conclude that if manufacturers can find a means of improving the halo artefact, PET/MRI would be a superior imaging modality with reduced radiation exposure (59), questioning why our efforts are not focused on this techniques over PET/CT.

Alternatively, higher sensitivity was also demonstrated through the use of a PSMA labelled 18F radionuclide (18[F]DCFPyl) in place of ^{68}Ga (44). [18F]DCFPyl is a novel PSMA ligand that has the potential to detect suspected sites of prostate cancer potentially missed by conventional imaging modalities (65). When compared to ^{68}Ga-labelled PSMA, ^{18}[F]DCFPyl detected metastases in three extra patients, with comparable tumour to background ratios. This may be the result of the higher injection dose used with ^{18}[F]DCFPyl, allowing later acquisition times and improving the signal to noise ratio. Another advantage of ^{18}[F]DCFPyl is that six patients can be scanned with a single preparation, compared to 2-4 patients with ^{68}Ga-PSMA.

^{68}Ga-PSMA-PET/CT can improve follow up therapy for patients with recurrent disease after radiotherapy/prostatectomy. PSA only testing, has its limitations, and alone cannot stage patients (66). Information about the location and number of lesions is needed to determine the most appropriate follow up. Despite the literature proving the diagnostic ability of C-choline and F-choline, these tracers have poor sensitivity at low PSA, which limit their use in routine follow up of PCa (45, 46, 52). Hence, research to find

an imaging tool with such capabilities is necessary. The argument prompting the investigations of ^{68}Ga-PSMA is its unique ability to determine the exact location and size of lesions, particularly at low PSA levels, impacting treatment follow up (38, 67).

The European guidelines outline the benefits associated with treating at low PSA,(7) reducing the risk of BCR. However to achieve this, we need to identify a diagnostic test which is accurate at low PSA. ^{68}Ga-PSMA PET/CT was proposed to surpass all other imaging modalities for PSA values >1 ng/ml (51). However for patients previously treated with RP, the European Association of urology dictates that the cut off PSA value for salvage RT is <0.5 ng/ml (7). Though there is a decline in detection rate with decreasing PSA, the tracer is clearly superior at detecting lesions in patients with PSA<0.5 ng/ml, than 18F-choline. We have to consider a logical explanation for decreasing detection rate at low PSA levels, that PSMA expression is reduced in small, low grade tumours (68, 69). With improved detection at low PSA, patients whose cancers may have went undetected, until PSA levels exceeded eligibility for salvage RT, can now avail of salvage RT (70).

^{68}Ga-PSMA-PET/CT has demonstrated the ability to optimize the clinical management of - PCa patients. Currently, salvage RT after RP following BCR is prescribed without significant imaging results. Therefore when PSA progresses after salvage RT, it suggests that lesions occur outside of the treated area (70-72). Morigi et al demonstrated that ^{68}Ga-PSMA was capable of identifying 75% of lesions outside of the prostate bed, in patients with BCR who would have been eligible for salvage RT (73). Analysis of ^{68}Ga-PMSA PET/CT scans of 70 patients with BCR after radical prostatectomy referred for salvage radiation therapy identified 34 patients with pathological ^{68}Ga-PSMA uptake in the prostatic fossa, the pelvic nodes or both (74). Similarly, the presence of recurrent PCa in patients with increasing PSA and positive ^{68}Ga-PMSA-PET-CT was confirmed on subsequent biopsy in 57% of the 46 cases studied, even in those patients with very low (<0.2 ng/ml) PSA levels (75). Furthermore, at least one lesion suspicious for prostate cancer in 98/131 (75%) patients tested was detected by ^{68}Ga-PSMA PET/CT in Dewa *et al*.'s investigations (76). This evidence highlights the potential for positive ^{68}Ga-PMSA PET-CT to modify the course of treatment for these patients. In the case of radiotherapy, this change can be seen in the documented use of a radiotherapy boost to PET-positive lesions (74, 76-79). For instance, Bluemel *et al*. reported that the introduction of ^{68}Ga-PSMA PET/CT imaging results into the final treatment decision of patients with persisting PSA and/or BCR following radical prostatectomy modified treatment plan in 42.2% of the 45 patients tested (78). On the basis of the number of metastatic lesions detected with PET, salvage radiotherapy was either extended to metastases, dose escalated or replaced by systemic ADT therapy (2/19). The study, furthermore, identified that 13.3% of patients had in fact presented with extra pelvic disease and thus would not have benefited from radiation to the prostate bed and a general extension to pelvic lymph nodes (78).

Improved tumour visualisation with 68Ga-PSMA allows for more accurate tumour delineation. This means physicians can consider more targeted, conformal radiotherapy techniques. One such option is dose escalation, achieved with intensity modulated radiotherapy. Customized radiotherapy options such as simultaneous integrated boost (SIB), focal therapy or HIFU, are currently under investigation (80). SIB can be used in combination with whole pelvis RT, and delivers the boost to the whole gland or prostate bed. Alternatively the boost can target intraprostatic lesions as opposed to entire gland, reducing side effects whilst maintaining a higher dose to the tumour (81, 82). ^{68}Ga-PSMA could potentially aid in such planning techniques.

For patients that can no longer avail of salvage therapy options, the tracer can identify patients who are eligible for theranostics. Theranostics is a treatment technique where therapeutic (or diagnostic) drugs are attached to radionuclides which target specific proteins expressed by cancerous cells (PSMA) (83). It can be hypothesised that using the same substance, for both diagnosing and therapy, will improve accuracy and precision of targeted therapy (50). Once prostate cancer metastasizes, it becomes one of the most aggressive tumours types, specifically, Metastatic castration-resistant PCa (mCRPR). No curative treatment exists for mCRPC, and current treatments are associated with severe side effects (84). This demonstrates the significant need for more targeted treatments for these patients. A significant number of patients in the studies were subsequently referred for theranostics, post imaging, including radium-223, and PSMA labelled ligands Iodine-131 Lithium-177, and Yttrium-90. These are attracting greater clinical interest as a treatment approach for mCRPR (57, 85, 86).

^{68}Ga-PSMA-PET/CT images did not require multiple investigations to clarify unclear findings. The SUV values suggest uptake is high in local, lymph, and bone metastasis (31, 60). In comparison, Technetium-99m (99mTC) is currently the standard technique for identifying bone metastases in high risk patients (87-89). However it has significantly low specificity, because of poor anatomical precision and uptake in benign lesions, leading to false positives, thus, additional imaging is needed. When compared to ^{68}Ga, only 1/12 patients with suspected PCa was detected with 99mTC (60).

One argument against using this technique alone to determine follow up treatment is the tracer's unclear role in identifying LNM. Despite promising results the standardisation of pelvic lymph node dissections for nodal metastasis identified with ^{68}Ga-PSMA-PET/CT,(32) resulted in a high number of

false negative LN discovered, and so extended pelvic lymph node dissections should remain the standard of care with RP until larger similar studies are done (39).

The lack of histopathological findings restricts the impact of these findings. Only 160 patients out of 2,408 patients scanned, were biopsied. Nonetheless, despite the small number of patients biopsied, it was reported that when patients were referred for follow up treatment, based on imaging results, their PSA decreased (35). This indicates their treatment worked, having successfully treated all of the disease with no undetected disease elsewhere. Therefore, despite not being pathologically proven, the imaging results were true positives.

Conclusion

This review reports high specificity, and high detection rates of ^{68}Ga-PSMA-PET for the identification of patients with recurrent PCa, specifically at low PSA levels. This allows patients to avail of local treatment options and delay systemic therapy and associated side effects. The combination of physiological information from ^{68}Ga-PSMA-PET, and morphological CT imaging, allows for improved tumour visualisation and delineation, playing to the advantage of targeted therapies. However further investigation of the approach in combination with PET MRI or the 18[F]DCFPyl ligand may further advance its clinical potential. Ultimately, additional evidence focusing on the longer term clinical benefit of ^{68}Ga-PSMA-PET in the management of prostate cancer patients are warranted.

Conflicts of Interest

All Authors declare no conflict of interest.

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