

68Ga-PSMA PET/CT imaging in recurrent prostate cancer: Where are we now?

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Introduction Prostate cancer (PCa) is a major health concern worldwide with up to 60% of patients experiencing biochemical relapse after radical treatment. Early diagnosis of PCa recurrence is of high importance for successful salvage therapy. The need for accurate imaging has prompted the introduction of prostate-specific membrane antigen (PSMA)-based radiotracers for positron emission tomography (PET).

Material and methods In this review we summarized and discussed the results of the studies analyzing the utility of 68Ga-PSMA PET/CT in patients who experienced a biochemical relapse of prostate cancer.

Results PSMA-based PET scans have been proved to provide a superior diagnostic performance over other modalities for localization of the site of early PCa recurrence. 68Ga-PSMA has been also shown to have a higher sensitivity and specificity than other established PET radiotracers such as radiocholines.

Conclusions The early studies show promising results and support the use of 68Ga-PSMA for PCa restaging. However, the number of studies concerning the utility of 68Ga-PSMA PET in the context of secondary PCa staging is limited and there is still a considerable scope for further research in this field.

Key Words: recurrent prostate cancer ↔ biochemical relapse ↔ prostate-specific membrane antigen ↔ 68Ga-PSMA PET/CT

INTRODUCTION

Prostate cancer (PCa) is the second most frequent cancer and the fifth leading cause of cancer death in males worldwide [1]. In Europe, there are 340 000 new cases and over 70 000 prostate cancer-related deaths reported annually. When detected early, in a prostate gland-localized stage of the disease, the 5-year survival is nearly 100% [2, 3]. However, PCa recurrence after primary treatment is quite common. Biochemical relapse, defined as a PSA value >0.2 ng/ml in patients after radical prostatectomy and a PSA level >2 ng/ml above the nadir PSA in patients after radiation therapy, occurs in 20–30% of patients after surgical treatment and in up to 60% of patients after primary external-beam therapy [3, 4].

The European Association of Urology (EAU) recommends a transrectal ultrasound (TRUS), computed tomography (CT), magnetic resonance imaging

(MRI) and bone scintigraphy (BS) for the detection of recurrence sites [3]. However, these conventional imaging modalities are not always effective for an early and reliable detection of PCa relapse. BS and CT are of no additional diagnostic value (detection rate <5%) when the PSA levels are <20 ng/ml or the PSA velocity is <2 ng/ml/y. Endorectal coil imaging shows utility in local recurrence detection, but only in patients with PSA levels >2 ng/ml [5]. Moreover, morphologic imaging (TRUS and CT) sensitivity in detecting local PCa relapse remains relatively low (25–54%) and is only moderately improved by functional MRI techniques. CT and MRI sensitivity for the detection of lymph node metastases is reported to be 30–80% [6].

The early differentiation between local and metastatic PCa is of high importance for patient management [2]. According to the 2013 EAU Guidelines on Prostate Cancer, patients with PCa recurrence

who would benefit the most from salvage radiation therapy (SRT) are those with PSA levels ≤ 0.5 ng/ml. The 6-year biochemical recurrence-free survival in these men is 48%, whereas it is only 40%, 28% and 18% in men with PSA levels of 0.51–1 ng/ml, 1.01–1.5 ng/ml, and >1.5 ng/ml, respectively [5]. Siegmann et al. found that patients with a PSA level <0.28 ng/ml before SRT had a better outcome than those with higher PSA levels and that they may have a chance of a long-term durable response without further treatment [7]. Finally, at PSA levels >2 ng/ml, SRT is almost ineffective. Thus, new molecular imaging modalities with improved specificity and sensitivity for imaging of recurrent PCa, especially at low PSA levels are of particular clinical interest.

In recent years radiocholine positron emission tomography (PET)/CT has been widely studied and used for PCa restaging. Compared with ^{18}F -choline, ^{11}C -choline allows for a better evaluation of the pelvic region, because of a lower urinary excretion (although a greater bowel elimination). ^{18}F -choline, on the other hand, has the advantage of being available in centers without a cyclotron (its half-life is significantly longer than that of ^{11}C -choline, 110 vs. 20 minutes) and shows a slightly higher sensitivity for bone metastases. Nonetheless, both radiotracers show similar diagnostic accuracy. Many studies have clearly demonstrated that radiocholine PET/CT results can lead to change in treatment [8]. However, radiocholine PET sensitivity strongly depends on PSA level and its kinetics. Its value for the detection of recurrent PCa is limited in patients with PSA levels <2.5 ng/ml [9, 10]. In patients with PSA <1.0 ng/ml the probability of positive radiocholine PET scan is only 19% and may be as low as 12.5% when PSA <0.5 ng/dl. Hence, some authors recommend radiocholine PET imaging in patients with PCa biochemical relapse only when the PSA level is higher than 1.5 ng/ml, PSA velocity exceeds 0.75 ng/ml/y, or PSA doubling time is shorter than 6 months [8, 10]. Since biochemical relapse is already suspected when PSA level exceeds 0.2 ng/ml, there is a high demand for more sensitive PET radiotracers.

Radiotracers targeting markers of PCa cells show huge promise in the field and prostate-specific membrane antigen (PSMA) seems to be receiving the greatest attention.

Prostate-specific membrane antigen

PSMA is a type II, 750-amino-acid integral membrane glycoprotein (100–120 kDa), with a 19-amino-acid N-terminal cytoplasmic tail, a 24-amino-acid helical intramembrane segment, and a large 707-amino-acid extracellular C-terminus [12, 13]. The extracel-

lular domain of the PSMA has an enzymatic activity of glutamate-carboxypeptidase/folate hydrolase and is only active as a dimer [12]. Following substrate binding, PSMA-bound ligands are internalized via clathrin-coated pits, endocytosed and transported into the cell [14]. PSMA was first cloned in 1993 [15]. Its gene (FOLH1) is located on the short arm of chromosome 11 [16].

Despite its name, PSMA is not specific to the prostate gland and is expressed in other normal tissues such as the salivary and lacrimal glands, kidney (proximal tubules), liver, spleen, nervous system glia (astrocytes and Schwann cells), duodenum (brush border) and the colon (neuroendocrine cells of the crypts). At the jejunal border PSMA, called folate hydrolase 1, assists in the folate absorption [16–19]. In the nervous system, PSMA has been termed NAALADase and is responsible for hydrolyzing N-acetyl aspartyl-glutamate (NAAG), the third-most-prevalent peptide neurotransmitter in the mammalian nervous system [20]. Although PSMA had been first discovered in the prostate in 1987, its role in the gland is still not well-defined [21]. Yet it seems PSMA may be involved in releasing folates into the seminal fluid [13].

In the normal human prostate PSMA is present in the cytoplasm and expressed on the apical side of the epithelium surrounding the prostatic ducts. Dysplastic changes in the prostate result in the expression of PSMA on the luminal surface of prostatic ducts [22, 23]. Its expression has been also shown to increase from benign prostatic hyperplasia to high-grade prostatic intraepithelial neoplasia to prostatic adenocarcinoma, where it reaches 100–1000-fold of what is observed in the normal prostate cells [24, 25]. It has been reported that nearly all prostate adenocarcinomas (primary tumors as well as metastatic lesions) show PSMA expression. According to the study by Mannweiler et al. less than 10% of primary or metastatic prostate tumors are not expressing PSMA [26]. Sweat et al. reported only 2% PSMA-negative lymph node metastases of PCa [27]. It was also found that the higher the Gleason score of the primary lesion, the higher the PSMA expression [28, 29, 30]. High PSMA expression is also associated with propensity to metastasize, androgen independence and disease progression [29, 31, 32].

Apart from prostate cancer, the PSMA presence has been also confirmed in kidney and bladder cancer as well as numerous non-genitourinary cancers, such as breast and colon cancer [33–39].

The favorable characteristics of PSMA (overexpression in PCa cells and ligand-enzyme complex internalization after ligand binding) have led to the development of molecular imaging agents targeting the enzyme. First were the radiolabeled monoclonal an-

tibodies targeting the intracellular domain of PSMA. However, they showed disappointing results due to the low image contrast, low sensitivity, and high background signal [37]. More recently, new PSMA-targeted agents such as small-molecule inhibitors (targeting the extracellular domain of PSMA) have been developed and extensively studied [38, 39]. They have been labeled with many radionuclides including ^{111}In , ^{18}F , ^{89}Zr , ^{64}Cu , ^{86}Y , and ^{68}Ga . However, it is ^{68}Ga -PSMA (Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga (HBED-CC)]) that receives the greatest attention [8]. In this agent HBED-CC moiety chelates the ^{68}Ga radiometal and is conjugated through a linker with a urea that binds in the active site of PSMA. ^{68}Ga is produced by a tabletop $^{68}\text{Ge}/^{68}\text{Ga}$ generator which makes it an attractive radionuclide, especially for PET centers that do not operate a cyclotron.

68Ga-PSMA PET imaging in recurrent prostate cancer

Biochemical recurrence following local therapy has been the most extensively studied application of PSMA-based imaging. The two largest reported studies were by Afshar-Oromieh et al. and Eiber et al. Afshar-Oromieh et al. retrospectively assessed ^{68}Ga -PSMA PET/CT results of patients with suspected PCa progression after radical treatment and found at least one lesion indicative of PCa in 82.8% of cases. Lesion detection rate correlated positively with PSA level (sensitivity for PSA values ≤ 0.5 ng/ml was 48.1% and for values > 20.0 ng/ml it reached 100.0%) and ADT. However, it was not correlated with primary tumor Gleason score and PSA_{dt}. In a subset of lesions for which histology was available, the true sensitivity was 76.6% with a specificity of 100.0% [40]. In other study by Afshar-Oromieh et al. ^{68}Ga PSMA PET-positivity was also correlated with PSA levels – the authors showed a detection rate of 60% at PSA < 2.2 ng/ml and 100% at PSA > 2.2 ng/ml [19]. Correspondingly, in a retrospective study by Demirkol et al. none of the ^{68}Ga -PSMA PET/CT scans revealed negative results in patients with PSA levels above 2 ng/ml [41].

In a retrospective study by Eiber et al. patients with PCa biochemical recurrence after radical prostatectomy were assessed. Similarly to Afshar-Oromieh et al., detection rate was 89.5% and it correlated positively with serum PSA levels rising from 57.9% in patients with PSA < 0.5 ng/ml to 96.8% in patients with PSA ≥ 2.0 ng/ml. No significant association was found for PSA_{dt}, yet PSA velocity did increase the detection rate. Opposite to Afshar-Oromieh et al., Eiber et al. found that primary lesion Gleason score (≤ 7 vs. ≥ 8) significantly increased detection rate. The

authors did not observe significant differences in detection rate with regard to ADT (lesions were detected in 95.7% of patients with ADT vs. 87.1% without ADT). Eiber et al. also reported that 33% of lesions were observed in PET only (not suspicious in CT) and that in 25% of cases PET revealed more lesions than CT [6].

Ceci et al. have evaluated 70 patients after RP or RT with curative intent and biochemical relapse or persisting high PSA levels after primary treatment. Correspondingly to Afshar-Oromieh et al. and Eiber et al. the authors found that the detection rate was associated with PSA level. PSA_{dt} was also showed to have a significant impact on ^{68}Ga -PSMA PET/CT sensitivity. PSA level, ongoing ADT, patient's age, GS, time from primary therapy and PCa TNM staging, on the other hand, were not associated with PET/CT positivity. ROC analysis showed that PSA_{dt} of 6.5 months (AUC 0.868) and PSA level of 0.83 ng/ml (AUC 0.764) were optimal cut-off values for predicting with high probability of a positive or negative PET/CT scan result [4].

The overall percentage of positive ^{68}Ga -PSMA PET among patients with biochemical recurrence in a systematic review and meta-analysis by Perera et al. (16 articles involving 1309 patients analysed) was 76%. ^{68}Ga -PSMA PET detection rate increased with pre-PET PSA and was higher the higher the PSA levels (0–0.2 ng/ml: 42%, 0.2–1 ng/ml: 58%, 1–2 ng/ml: 76%, > 2 ng/ml: 95%). ^{68}Ga -PSMA PET positivity increased with shorter PSA_{dt} and for PSA_{dt} ≥ 6 months and < 6 months equalled 64% and 92%, respectively. ^{68}Ga -PSMA sensitivity and specificity in per-patient analysis were both 86%. Per-lesion analysis showed a sensitivity of 80% and a specificity of 97% [42].

The results of the above studies support the application of ^{68}Ga -PSMA PET/CT in the diagnosis of PCa biochemical recurrence. Yet it must be emphasized that the majority of gathered data was derived from small, retrospective studies with heterogenous patient cohorts (Table 1).

68Ga-PSMA vs. radiocholines

Several groups have directly compared ^{68}Ga -PSMA to radiocholines in the detection of biochemically recurrent PCa.

Afshar-Oromieh et al. have evaluated patients suspected of progressive disease following conventional treatment. The authors found a higher detection rate for PCa lesions with ^{68}Ga -PSMA than ^{18}F -fluoromethylcholine (86.5% vs. 70.3%). ^{68}Ga -PSMA proved superior to ^{18}F -fluoromethylcholine PET/CT especially at low PSA levels – for PSA levels ≤ 2.82 ng/ml

the sensitivity was 68.8% vs. 43.8%, respectively (Table 2). 68Ga-PSMA was also reported to show superior radiotracer uptake and tumor-to-background ratio [43].

In a prospective study by Morigi et al. 18F-fluoromethylcholine and 68Ga-PSMA PET/CT was performed in patients after curative therapy who developed a post-therapy PSA rise. Similarly to Afshar-Oromieh et al., PSMA-targeted radio-

tracer showed higher PCa lesion detection rates than 18F-fluoromethylcholine and its superiority was demonstrated across all PSA values – detection rate varied from 50% vs. 12.5% for PSA levels <0.5 ng/ml and to 88% vs. 63% for PSA levels >2.0 ng/ml (Table 2). Additionally, 68Ga-PSMA-based scans detected more lesions and showed higher tumor-to-background ratio. Correspondingly to previous studies, the authors found that the most

Table 1. Characteristics of the studies investigating the utility of 68Ga-PSMA PET/CT in recurrent prostate cancer

Author	Study type (year)	Study group number	Inclusion criteria	Median GS (range)	Median PSA ng/ml, (range)	68Ga-PSMA detection rate	Factors correlated with PET positivity	Factors not correlated with PET positivity
Asfhar-Oromieh [40]	retrospective (2015)	319	BCR (n=292), primary staging (n=27)	7 (5-10)	4.59 (0.01-41395)	82.8%	PSA level ADT	GS PSAdt
Ceci [4]	retrospective (2015)	70	BCR	7 (5-9)	1.7 (0.2-32.2)	74.2%	PSA level PSAdt	PSAvel ADT age GS time from PT TNM
Demirkol [41]	retrospective (2015)	14	BCR or disease progression	n/a	2.5 (0.2-191.5)	100%	PSA level	n/a
Eiber [6]	retrospective (2015)	248	BCR	7 (6-10)	2.0 (0.2-59.4)	89.5%	PSA level PSAvel GS	PSAdt ADT

ADT – androgen deprivation therapy; BCR – biochemical recurrence; GS – Gleason score; PSAdt – PSA doubling time; PSAvel – PSA velocity; PT – primary therapy; TNM – tumour-node-metastasis

Table 2. Characteristics of the comparative studies included in this section

Author	Compared radiotracers	Study type (year)	Study group number	Inclusion criteria	PSA level, mean (±SD)	Time window between PET/CT scans	Detection rate
Schwenck [46]	68Ga-PSMA vs. 11C-choline	retrospective (2016)	103	BCR	2.7 (median)	24 hours	lymph nodes: 94% vs. 71% bones: 98% vs. 64% overall: 83% vs. 79%
Bluemel [44]	68Ga-PSMA vs. 18F-choline	retrospective (2016)	125	BCR	5.4 (±12.73)	51 days	18F-choline: 74.4% 68Ga-PSMA in 18F-choline(-) scans: 43.8% overall: 85.6%
Pfister [45]	68Ga-PSMA vs. 18F-choline	retrospective (2016)	66	BCR	2.7 and 2.35 (median)	n/a	per-patient analysis: PPV: 78.9% vs. 82.1% per-lesion analysis: PPV: 67.3% vs. 75.7% NPV: 88.8% vs. 96.6% ACC: 82.5% vs. 91.9%
Morigi [11]	68Ga-PSMA vs. 18F-choline	prospective (2015)	38	BCR	1.72 (±2.54)	30 days	PSA level <0.5: 50% vs. 12.5% PSA level 0.5-2.0: 71% vs. 36% PSA level >2.0: 88% vs. 63% overall: 66% vs. 32%
Afshar-Oromieh [43]	68Ga-PSMA vs. 18F-choline	retrospective (2014)	37	BCR	11.1 (±24.1)	30 days	PSA level ≤2.82: 68.8% vs. 43.5% PSA level >2.82: 100% vs. 90.5% overall: 86.5% vs. 70.3%

ACC – accuracy; BCR – biochemical recurrence; NPV – negative predictive value; PPV – positive predictive value
All PSA levels are given in ng/ml

significant predictor for positive PET result for both 18F-fluoromethylcholine and 68Ga-PSMA was PSA level at the time of imaging. Morigi et al. reported that 68Ga-PSMA PET/CT impact on patients management was exceptionally high, especially when the scan was performed at low absolute PSA levels [11].

Blumel et al. reported that 68Ga-PSMA PET/CT detects disease in 43.8% of patients with biochemical PCa recurrence, but negative 18F-choline scans. Sequential imaging (performing 68Ga-PSMA PET/CT after negative choline scans) increased detection rate by 11.2% (from 74.4% to 85.6%) (Table 2). 68Ga-PSMA PET/CT detection rates were 28.6%, 45.5% and 71.4% for PSA levels of ≥ 0.2 to < 1 ng/ml, 1-2 ng/ml and > 2 ng/ml, respectively [44].

Similarly, in a retrospective study Pfister et al. demonstrated superior performance for 68Ga-PSMA PET compared to 18F-fluoroethylcholine PET among patients with biochemical recurrence. Sensitivity and specificity for 68Ga-PSMA and 18F-fluoroethylcholine were 86.9% vs. 71.2% and 93.1% vs. 86.9%, respectively [45] (Table 2).

Schwenck et al. have assessed the utility of 68Ga-PSMA and 11C-choline PET/CT in patients with PCa biochemical relapse. Compared to choline radiotracer, 68Ga-PSMA showed higher detection rate for both lymph node (71% vs. 94%) and bone metastases (64% vs. 98%). The overall detection rate was 83% in 68Ga-PSMA and 79% in 11C-choline PET (Table 2). Additionally, pathologic lesions showed a significantly higher radiotracer uptake in 68Ga-PSMA PET than in 11C-choline PET. PSMA-based radiotracer superiority was more marked in patients with low PSA levels (< 1 ng/ml) [46]. To our knowledge, the study by Schwenck et al. is the only direct comparison of 68Ga-PSMA and 11C-choline PET performed so far.

The results of the studies comparing radiocholines and 68Ga-PSMA PET/CT for the diagnosis of recurrent PCa are very promising for the latter one. PSMA-based scans show higher sensitivity and specificity, especially at low PSA levels. Tumour lesions also show higher 68Ga-PSMA uptake and higher tumour-to-background ratio. However, the number of studies comparing 68Ga-PSMA and radiocholines is limited and the majority of data comes from retrospective analyses.

CONCLUSIONS

The growing need for accurate imaging of early PCa recurrence has prompted the introduction of 68Ga-PSMA PET. Although a limited number of studies is available, the results support the use of 68Ga-PSMA PET in the context of secondary PCa staging. Moreover, PSMA-based PET scans have so far been proven to provide superior diagnostic performance than any other modality (including radiocholine PET/CT) for localisation of the site of early PCa recurrence.

However, owing to its limited history robust sensitivity and specificity, data are not available for 68Ga-PSMA PET/CT scans. Also, most PSMA-assessing research were small, retrospective, single-institutional studies with heterogenous patient cohorts. Only few studies compared 68Ga-PSMA performance with established radiotracers such as radiocholines. Large, multidisciplinary, well-thought-out prospective trials are needed to definitely uncover the true utility of PSMA-based PET in PCa recurrence diagnosis. Despite significant advances, there is a considerable scope for further research in PSMA PET.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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