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ORIGINAL PAPER

[^{68}Ga]Ga-PSMA-11 PET-CT: Local preliminary experience in prostate cancer biochemical recurrence patients

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Summary ***Objectives: Clinical approach of prostate cancer (PCa) biochemical recurrence (BCR) is an ever-changing topic. Prostate-specific membrane antigen positron emission tomography ([^{68}Ga]Ga-PSMA-11 PET-CT-PSMA PET-CT) has shown good potential in this field.***
The aim is to evaluate PSMA PET-CT detection rate in PCa BCR and assess its impact on clinical outcome.
Material and methods: Out of 319 patients with PCa who underwent PSMA PET-CT between October 2015 and June 2019, 70 had developed BCR after treatment with curative intent. Two groups were created: one with BCR after surgery (RP group) (N: 48; 68.6%) and other with BCR after radiotherapy (RT group) (N: 22; 31.4%). Clinical, analytical, pathological and PSMA PET-CT results were evaluated.
Results: Initial age was different between groups (p = 0.008). RP patients were mainly at intermediate risk (85.1% vs 42.9%, p = 0.001) while RT patients were at low risk of recurrence (8.5% vs 47.6%, p = 0.001). In RP and RT groups, PSMA PET-CT detected, respectively, pelvic relapse in 31.3% and 63.6%, and extrapelvic relapse in 18.8% and 31.8%. Salvage treatment was performed in 61.9% (n = 26) of RP patients and in 15% (n = 3) of RT patients, p < 0.001. Of RP patients submitted to salvage treatment, 59.1% achieved complete remission. Concerning these patients, local radiotherapy led to complete remission in 68.4% (n = 13). Of RT patients submitted to salvage treatment, two had complete remission and one had partial remission.Concerning detection rate, PSMA PET-CT was positive for pelvic relapse when pre-PET PSA ≥ 0.8 ng/mL (RP) or ≥ 2.3 ng/mL (RT) and for extrapelvic relapse when PSA ≥ 0.4 ng/mL (RP) or ≥ 3.5 ng/mL (RT), p > 0.05.
Conclusions: Biochemical persistence rate after salvage therapy was similar (30-40%). The cut-off PSA values for pelvic relapse detected on PSMA PET-CT were ≥ 0.8 ng/mL (RP) and ≥ 2.3 ng/mL (RT).

KEY WORDS: Biochemical recurrence; PSMA PET-CT; Salvage treatment; Prostate cancer.

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INTRODUCTION

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men, with an estimated 1.1 million new cases worldwide in 2012, accounting for 15% of all cancers diagnosed (1). Radical prostatectomy and radiotherapy are among the treatments of choice for localized PCa. However, between 27% and 53% of all patients develop a rising PSA and experience *biochemical recurrence* (BCR) (2). PSA elevation is highly predictive of clinical recurrence but not all patients with BCR after treatment with curative intent have local relapse. Therefore, it is very important to distinguish the ones that may benefit from local salvage treatment from those that don't. BCR is defined as 2 consecutive PSA values equal or superior to 0.2 ng/mL after radical prostatectomy, or a PSA increase equal or superior to 2 ng/mL above the nadir after radiotherapy (3, 4). However, the indication for further treatments should not be based solely on a pre-determined PSA threshold but should be decided on the individualized risk of progression (5).
In BCR, conventional imaging, such as *computed tomography* (CT), *magnetic resonance imaging* (MRI) and bone scintigraphy, has limited accuracy for the detection of recurrence sites (local, regional or systemic), especially at low PSA levels, while it is known that the optimal therapeutic window for salvage treatment in BCR is below 0.5-1 ng/mL (6). On the one hand, *salvage radiotherapy* (SRT) is considered the treatment of choice for PCa patients with BCR after radical prostatectomy. Its efficacy depends on early detection of disease limited to the prostatic fossa. On the other hand, distant metastases require systemic therapies, such as hormonal therapy or chemotherapy (7), whereas local treatment may lead to unnecessary side effects (8).
Therefore, to achieve the best possible results while avoiding unjustified therapies and side effects, treatment must be individualized for each patient. In this field, molecular imaging techniques offer a great potential. In 2011, the Heidelberg group introduced [^{68}Ga] Ga-PSMA-11 (also known as HBED-CC, Glu-urea- Lys(Ahx)-HBED-CC and PSMA-HBED-CC) in Germany for clinical imaging of PCa. *Prostate specific membrane antigen* (PSMA) is a membrane glycoprotein codified by the PSMA gene (FOLH1) located on the short arm of chromosome 11. Despite the name "*specific*", PSMA is also expressed in other tissues such as the brain, salivary glands, liver, kidney, small intestine, ganglia and neovasculature of some solid tumors, but in very lower levels. Concerning prostate, PSMA is expressed in normal, benign and malignant prostatic epithelium but its expres-

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sion in PCa is 100-1000-fold of what is observed in normal cells (9, 10). The localization of the catalytic site of PSMA in the extracellular domain allows the development of small specific inhibitors that are internalized after ligand binding (11). Over the last years, many articles concerning the use of [^{68}Ga] Ga-PSMA-11 PET/CT (PSMA PET-CT) in this scenario have been published and the results appear to be promising (12-17), leading to treatment plan changes in up to 87.1% of patients (6).
A meta-analysis revealed detection rates of 48% at PSA levels of 0.2 ng/mL, increasing to 56% and 70% at levels of 0.5 and 1.0 ng/mL, respectively. These results were quite superior to those observed with conventional imaging techniques and even [18F] Choline PET/CT (18).
This study aims to evaluate PSMA PET-CT detection rate in prostate cancer patients with BCR after treatment with curative intent and assess its impact on clinical outcome.

Material and methods

This study followed the rules of the local ethics committee and were in accordance with the Helsinki Declaration. It was a preliminary cross-sectional study of prostate cancer patients with BCR after treatment with curative intent at our institution. Within a total of 319 PCa patients who underwent PSMA PET-CT between October 2015 and June 2019, 70 developed BCR after treatment with curative intent. [^{68}Ga]Ga-PSMA-11 was synthesized locally, at ICNAS (*Instituto de Ciências Nucleares Aplicadas à Saúde*). ^{68}Ga-PSMA-HBEDCC (Glu-NH-CO-NH-Lys-(Ahx)-[[^{68}Ga]Ga(N,N'-bis-[2-hydroxy-5 (carboxyethyl)benzyl]ethylenediamine-N,N'-diacetic-acid]) (^{68}Ga-PSMA-11) was prepared in a similar procedure as described by *Eder et al.* (19). All patients underwent a whole-body PET-CT acquisition (*Siemens Biograph, Siemens Healthcare, Gemini GXL Philips, Philips*) 60 minutes after intravenous injection of 2 MBq/Kg of [^{68}Ga]Ga-PSMA-11. PSMA PET-CT scans were acquired in three-dimensional mode with 4 minutes per bed position. Patients were well hydrated and voided immediately before the scan. No adverse effects were reported. PSMA PET-CT images were independently interpreted by two nuclear medicine physicians. In case of disagreement, the final diagnosis was reached by requesting a third opinion. The main criteria of positivity for PSMA PET-CT scans were: any area of focal uptake of the radiotracer (single or multiple), higher than the surrounding background, that did not correlate with physiologic tracer uptake. PSMA PET-CT positive lesions were classified as "*pelvic relapse*" [prostate/prostate bed relapse and/or pelvic lymph nodes, excluding common iliac nodes (LNs)] or "*extrapelvic relapse*" (inguinal LNs and/or above common iliac bifurcation LNs and/or bone lesions and/or other visceral lesions). PSMA PET-CT negative scans were considered false negative by definition.
Two groups were created: patients submitted to surgery (RP group) (N: 48; 68.6%) and patients treated with radiotherapy (RT group) (N: 22; 31.4%). Clinical, analytical, pathological and PSMA PET-CT results were evaluated. All continuous variables were reported as mean and standard deviation. Categorical variables were described according to their frequency and percentage. Descriptive analysis of demographic and clinical variables was performed. Chi-square test was used for categorical variables. Continuous variables were compared using the T student. The detection rate of PSMA PET-CT was assessed. All tests performed were 2-sided. Statistical significance was taken at a p value of less than 0.05. All data were analysed using the *Statistical Package for the Social Sciences* (SPSS) 23.0 (*IBM SPSSS Statistics Corp.; Armonk, New York, USA*).

Results

Demographic and clinical data (Table 1) showed that RT patients were older than RP patients (66 ± 6.5 *vs* 69 ± 6.2 years, p = 0.008), but PSA was similar between groups (8.7 ± 5.7 *vs* 7.5 ± 5.8 ng/mL, p = 0.4). Patients were divided according to the *European Association of Urology* (EAU) risk group classification for BCR of localised PCa: Low-risk were defined by PSA < 10 ng/mL and Gleason score < 7 (ISUP grade 1) and cT1-2a; Intermediate-risk was defined by PSA 10-20 ng/mL or Gleason score 7 (ISUP grade 2/3) or cT2b and High-risk was defined by PSA > 20 ng/mL or Gleason score > 7 (ISUP grade 4/5) or cT2c (12).
Most patients in RP group were in the intermediate-risk category (85.1%), while in the RT group the low-risk cat-

Table 1.
Demographic and clinical data.

Data	RP group (n: 48)	RT group (n: 22)	p
Age at PCa diagnosis (years)	66 ± 6.5	69 ± 6.2	0.008
Initial PSA (ng/mL)	8.7 ± 5.7	7.5 ± 5.8	0.4
EAU risk groups for BCR of localised PCa			0.001
- Low-risk	8.5%	47.6%	
- Intermediate-risk	85.1%	42.9%	
- High-risk	6.4%	9.5%	
Time between initial treatment and BCR (months)	23.5 ± 42.7	44.5 ± 42.5	0.09

RP group: group previously submitted to surgery; RT group: group previously submitted to radiotherapy; PCa: prostate cancer; EAU: European Association Urology; BCR: biochemical recurrence.

Table 2.
Relapse pattern between groups.

Data	RP group (n: 48)	RT group (n: 22)	p
Pelvic relapse	15 (31.3%)	14 (63.6%)	0.001
Extrapelvic relapse	9 (18.8%)	7 (31.8%)	
No disease	24 (50%)	1 (4.5%)	
Global SUVmax	8.4 ± 5.7 [3.3-16.7]	5.6 ± 3.9 [2.7-17.4]	0.3

RP group: group previously submitted to surgery; RT group: group previously submitted to radiotherapy; SUVmax: maximum standardized uptake values of [^{68}Ga]Ga-PSMA-11.

Table 3.
PSA value in pelvic and extrapelvic relapse between groups if positive PSMA PET-CT.

Data	PSA value in pelvic relapse (ng/mL)	PSA value in extrapelvic relapse (ng/mL)	p
RP group + positive PSMA PET-CT	0.99 ± 0.9	1.0 ± 13.2	0.6
RT group + positive PSMA PET-CT	3.0 ± 2.1	4.5 ± 5.4	0.2

RP group: group previously submitted to surgery; RT group: group previously submitted to radiotherapy.

Table 4.
Detection rate of PSMA PET-CT for pelvic relapse in RP patients.

Sensibility and specificity of PSMA PET-CT for pelvic relapse in RP patients			
PSA value (ng/mL)	Sensibility	Specificity	p
0.2	93.3%	3%	0.06
0.3	80%	18.2%	
0.4	73.3%	33.3%	
0.5	73.3%	60.6%	
0.6	73.3%	63.6%	
0.7	73.3%	66.6%	
0.8	73.3%	72.7%	
0.9	66.7%	78.8%	
1.0	46.7%	78.8%	

RP group: group previously submitted to surgery.

Table 5.
Detection rate of PSMA PET-CT for pelvic relapse in RT patients.

Sensibility and specificity of PSMA PET-CT for pelvic relapse in RT patients			
PSA value (ng/mL)	Sensibility	Specificity	p
0.9	92.9%	12.5%	0.5
1.8	85.7%	25%	
2.0	71.4%	25%	
2.3	71.4%	37.5%	
3.0	50%	37.5%	
3.5	42.9%	50%	

RT: group previously submitted to radiotherapy.

egory was the most prevalent (47.6%), with this difference being statistically significant (p = 0.001). The time interval between initial treatment and BCR was similar between groups (Table 1).
In RP patients, final pathology revealed pT2a in six (13.4%), pT2c in 16 (33.3%), pT3a in 14 (28.9%) and pT3b in 12 cases (24.4%). N status was N0 in 29 (60.4%), N1 in 13 (27.1%) and Nx in six cases (12.5%). R status revealed R0 in 41 (85.4%) and R1 in seven cases (14.6%). In RP and RT groups, PSMA PET-CT detected pelvic relapse in 31.3% and 63.6% of patients and extrapelvic relapse in 18.8% and 31.8%, respectively. PSMA PET-CT was negative in 24 (50%) of RP group and in one case (4.5%) of RT group. The maximum standardized uptake value (SUV_{max}) of the lesion with the highest [^{68}Ga]Ga-PSMA-11 uptake per patient was also analysed, and no statistical significant difference was found between groups (Table 2). In positive PSMA PET-CT, PSA values were not able to distinguish between pelvic and extrapelvic disease in either groups (Table 3). Salvage treatment was performed in 61.9% (n = 26) of RP group (local radiotherapy in 54.7%, radiotherapy to a single bone metastasis in 2.4% and lymphadenectomy in 4.8%) and in 15% (n = 3) of RT group(radical prostatectomy with bilateral pelvic lymphadenectomy in two and high-dose brachytherapy in one case), p < 0.001. Out of all RP patients submitted to salvage treatment, 59.1% achieved complete remission. Concerning these patients, local radiotherapy led to complete remission in 13 cases (68.4%). Neither extended lymphadenectomy nor radiotherapy to the single bone metastasis led to complete

Table 6.
Detection rate of PSMA PET-CT for extrapelvic relapse in RP patients.

Sensibility and specificity of PSMA PET-CT for extrapelvic relapse in RP patients			
PSA value (ng/mL)	Sensibility	Specificity	p
0.2	88.9%	2.6%	0.9
0.3	77.8%	17.9%	
0.4	66.7%	30.8%	
0.5	55.6%	41%	
0.6	44.4%	51.3%	
0.7	44.4%	53.8%	
0.8	44.4%	59%	
0.9	44.4%	66.7%	
1.0	44.4%	74.4%	

RP group: group previously submitted to surgery.

Table 7.
Detection rate of PSMA PET-CT for extrapelvic relapse in RT patients.

Sensibility and specificity of PSMA PET-CT for extrapelvic relapse in RT patients			
PSA value (ng/mL)	Sensibility	Specificity	p
0.9	100%	13.3%	0.2
1.8	85.7%	20%	
2.0	85.7%	33.3%	
2.3	71.4%	33.3%	
3.0	71.4%	53.3%	
3.5	71.4%	60%	
4.0	57.1%	80%	
4.5	42.9%	80%	

RT: group previously submitted to radiotherapy.

remission. In fact, none of the removed nodes harboured tumour cells. Out of the three RT patients submitted to salvage treatment, two had complete remission (both submitted to radical prostatectomy with bilateral pelvic lymphadenectomy) and one had partial remission (targeted high-dose brachytherapy). Pathology obtained from salvage radical prostatectomy revealed ISUP grade 2 pT3bN1M0R0 and ISUP grade 2 pT3bN0M0R0. In both cases, the initial biopsy specimens firstly done before radiotherapy revealed an ISUP grade 1.
Concerning detection rate, PSMA PET-CT was positive for pelvic relapse when pre-PSMA PET-CT PSA ≥ 0.8 ng/mL (RP) or ≥ 2.3 ng/mL (RT) (Tables 4, 5) and for extrapelvic relapse when PSA ≥ 0.4 ng/mL (RP) or ≥ 3.5 ng/mL (RT), p > 0.05 (Tables 6, 7).

Discussion

This study showed the preliminary experience of PSMA PET-CT in real-world PCa patients that experienced BCR after treatment with curative intention. In BCR patients, 68-Ga PSMA avidity in the pelvic region was higher in the radiotherapy than in prostatectomy cohort (63.6% *vs* 31.3%), in line with other studies that showed a proportion of 52% *vs* 22% (14). The negativity of PSMA PET-CT was almost exclusive of RP patients (50% *versus* 4.5%). Gallium 68-PSMA, similarly to most other PSMA based agents, has a significant urinary tracer excretion with high activity often seen in the bladder. This could

interfere with the evaluation of the postprostatectomy bed/seminal vesicle bed regions as well as lower pelvic lymph nodes.

Salvage treatment in patients previously submitted to radiotherapy was done only after re-biopsy and confirmation of tumour persistence. In our limited experience, radical prostatectomy could portend better results than high-dose brachytherapy. The final pathological upgrading compared to the pre-radiotherapy biopsy has to be seen with caution, given the difficulties in evaluating the Gleason score after radiotherapy. Concerning RP patients, radiotherapy was the only effective salvation treatment. Other attempts to reach complete remission were not succeeded, even extended lymphadenectomy did not reveal ganglia metastases. In fact, according to *Budaus et al.*, the comparison between preoperative PSMA PET-CT lymph nodes findings with histologic work-up after radical prostatectomy performed for high risk prostate cancer only detected 33.3% of the patients as being true positive for lymph node metastasis, and 66.7% of the patients as a false negative. Our population had a reduced incidence of high-risk patients, so we must presume that our results were following the low sensitivity (33.3%) and high specificity (100%) rate of PSMA PET-CT for detection of lymph node metastasis in this work (15).

The SUVmax value in our population was low, in line with the findings of *Demerci et al.* (16). They showed that SUV max values correlated significantly with grade groups of primary tumours. The EAU risk groups for BCR of localised PCa in RP and RT were predominantly intermediate and low-risk respectively. This explained the lower SUVmax detected in RT patients compared with RP patients.

The optimal cut-off PSA values for pelvic relapse detected on PSMA PET-CT were ≥ 0.8 ng/mL (RP) and ≥ 2.3 ng/mL (RT). The optimal cut-off values for extrapelvic relapse detected on PSMA PET-CT were ≥ 0.4 ng/mL (RP) and ≥ 3.4 ng/mL (RT). Sanli et al concluded that a PSA value of 0.83 ng/ml was the optimal cut-off value for distinguishing between positive and negative PSMA PET-CT in general (17).

EAU Guidelines (5) include a weak recommendation for offering PSMA PET-CT scan to men with a persistent PSA > 0.2 ng/mL to exclude metastatic disease. According to our results, this cut-off seems too low. However, it was a preliminary study with few patients and we hope to increase our experience in this setting to see if this cut-off is applied to our population. It has also been reported that patient's prognosis was improved when salvage therapy was initiated before the PSA level exceeds 0.5 ng/mL (20).

In our population, the cut-off of 0.5 ng/mL for RP patients was associated with a sensibility of 73.3% and specificity of 72.7% in pelvic relapse and with a sensibility of 55.6% and specificity of 30.8%. Literature showed that these cut-off values can differ from 17.5% to 61.5% (6).

In other studies, the detection sensitivity of PSMA PET-CT is dependent on the PSA at the time of imaging, with detection sensitivities in the range of 50-60% when the PSA is as low as 0.2 to 0.5 ng/mL (21, 22). However, the cut-off value for PSA performing PSMA PET-CT has yet to be defined, and thus prospective studies are required to recommend PSMA PET-CT for patients with BCR.

With increasing use of PSMA PET-CT scan, its value must be balanced critically with cost and clinical benefit. Given the high costs and limited availability of PSMA PET-CT scan, choline PET-CT is still widely used in patients with prostate cancer relapse, despite its low sensibility for low PSA levels. A meta-analysis by *Han et al.* (23) showed that PSMA PET-CT altered the management in 54% of patients. They reported that the use of PSMA PET-CT imaging lead to an increase in the proportion of patients receiving radiotherapy (from 56% to 61%), surgery (from 1% to 7%), focal therapy (from 1% to 2%), and multimodal treatment (from 2% to 6%), and to a decrease in patients receiving systemic treatment (from 26% to 12%) and no treatment (from 14% to 11%).

The evidence for introducing management changes as a result of PSMA PET-CT findings is low, and prospective studies are required. The risk of early treatments causing more harm than good, as well as the long-term effects on progression-free and overall survival rates are still unclear (24). An interesting potential benefit of PSMA PET-CT could be to select, with higher accuracy, patients to high-dose radiotherapy for oligometastatic disease. In our study, there was one patient who underwent radiotherapy to a single bone metastasis, yet no complete remission was achieved. Whether this approach improves patient outcomes remains unclear, the impact of potentially avoiding androgen deprivation therapy and its toxicity would definitely be important.

Some limitations must be also elicited as they could influence results and conclusions. The small number of patients, different size groups and the monocentric nature of the study could limit the applicability of these results. Population studied was heterogeneous: patients submitted previously to radiotherapy were fewer, older and belonged to a lower risk group for BCR instead of patients submitted previously to radical prostatectomy were almost the double and belonged to an intermediate-risk group.

The lack of PSA kinetics and the lack of comparison with standard conventional imaging could introduce a bias: the majority of patients did not have a simultaneous approach with conventional imaging. However, the available literature supports PSMA PET-CT superiority over conventional imaging in this setting (13).

Conclusions

PSMA PET-CT has shown good potential for using in patients with BCR, but most studies are limited by their retrospective design. Despite the limited information in major guidelines, it could be standard in patients with recurrent PCa, mainly with low PSA. PSA level is associated with the positivity rate of PSMA PET-CT. The cut-off PSA values for pelvic relapse detected on PSMA PET-CT were ≥ 0.8 ng/mL (RP) and ≥ 2.3 ng/mL (RT). However, PSA levels could not discriminate between PSMA PET-CT positivity for pelvic or extrapelvic relapse.

Biochemical persistence rate after salvage therapy was similar between groups (30-40%).

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