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Original Article

Impact of PSMA PET/CT on the therapeutic decision of Prostate Carcinoma Biochemical Recurrence

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Abstract

Background: Prostate Cancer (PCa) is the most common malignant tumor in males and Biochemical Relapse (BCR) consists of a challenging scenario compared to primary staging due to small volume of disease and low PSA levels. Prostate-Specific Membrane Antigen (PSMA), Positron Emission Tomography (PET) presents superior performance and strongly affects therapeutic choice.

Objective: The objective of this study was to evaluate the impact of PSMA PET, compared to conventional imaging methods, on BCR therapeutic approach in patients treated at the public Brazilian health system.

Methods: 128 patients diagnosed with BCR were evaluated using PSMA after conventional imaging. Disease extension defined by PET was compared with conventional imaging; staging / extension changes and therapeutic management impact were then determined. PET comparison with conventional imaging and decision-making changes were analyzed using descriptive statistics and statistical tests.

Results: Disease detection rate was 60% and 41% using PSMA and conventional exams, respectively. PET detection rates and sensitivity increased proportionally to the increase in PSA levels and no statistically significant difference was observed in the rate of disease detection between patients with and without androgen blockade. After disclosure of PET findings and the results of the confrontation with conventional imaging, the board changed the management decision in 36% of the patients with and locoregional treatment indication was predominant

Conclusions: The impact of PSMA on BCR therapeutic management, when compared to conventional exams, is significant, favoring the indication of locoregional salvage treatments and PSMA cost-effectiveness over traditional investigation has been demonstrated in other countries.

Keywords: PSMA, PET/CT; Prostate Cancer; Biochemical Relapse

Introduction

Prostate Cancer (PCa) is the most common malignant tumor in men, after non-melanoma skin cancer, representing 30% of diagnoses of the disease in the country. Data from the National Cancer Institute (INCA) estimates 72.000 new cases/yearly of PCa for the 2023-2025 triennium[1]. About 10 years after a curative proposal treatment, approximately 30-50% of the men who underwent Radiotherapy (RT) and 20-40% who were primarily treated with Radical Prostatectomy (RP) may experience an increase in Prostate-Specific Antigen (PSA) without detectable disease by conventional imaging exams[2].This condition is well-known as Biochemical Recurrence (BCR) and it is defined by the European and American Urological Associations (EUA and AUA, respectively) as a confirmed serum PSA value of ≥0.2ng/mL after PR and as a ≥2ng/mL increase above the nadir PSA, with or without hormonal therapy after RT. For high-risk cases, it is recommended not to wait for a ≥2 ng/ml increase above nadir if patients are fit for salvage therapy and if relapse is confirmed by positive biopsy[3,4].

BCR consists of a challenging scenario compared to the primary staging of PCa since there is usually a small disease volume, the location of the relapsing lesions is unknown and there are acknowledged limitations of the traditional imaging exams, such as Computerized Tomography (CT), Bone Scintigraphy (BS) and even Magnetic Resonance (MRI). Lymph node micrometastases identification by CT, the detection of bone impairment by BS, and bone marrow lesions by both methods are limited, especially when related to a slight increase in PSA levels [5,6]. Likewise, the MRI evaluation of the prostate gland after RT may be intricate due to changes and an inflammatory process radiation related [7].

Anyhow, accurate location and extension determination of the disease is paramount to deciding and individualizing the treatment of the patient with BCR of the PCa, since there might be still eligibility for salvage targeted treatments with curative intent in localized or oligometastatic recurrences [8].

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BCR detection has been improving since the publication of the first positron emission tracers studies [9] and molecular information provided by PET/CT was incorporated in the investigation guidelines, such as NCCN [10], regardless of the radiopharmaceutical, but mostly by Prostate Specific Membrane Antigen (PSMA) ligands which is the focus of this work.

Objective

The objective of this study was to evaluate the impact of PSMA PET, compared to conventional imaging methods, on the therapeutic approach in BCR scenario in patients with PCa treated at the public Brazilian health system.

Materials and Methods

Ethics approval

This retrospective analysis was approved by the research ethics committee of Santa Casa de Misericórdia de São Paulo Hospital (SCMSP). All participants signed an informed consent form authorizing the use of their clinical and imaging data under proper confidentiality. Patient data were stored on the REDCap platform.

Patients

From March 2019 to August 2020, 128 patients (mean age 67,15 ± 6,41 years old) diagnosed with BCR of PCa were referred to the Specialty Medical Outpatient Center (Ambulatório Médico de Especialidades - AME Barradas) from urology departments of 10 different institutions in order to undergo PSMA PET/CT. All patients presented with recent PSA results (at most 30 days) on the day PET was performed.

The patients were divided into two groups according to the primary treatment: RP (n=116 – 91%) and RT (n=12 – 9%). Most of the participants underwent exclusively RP or RT, but some of them had undergone another therapy modality with a salvage / adjuvant aim. Table 1 shows the patients' classification according to the previous and current treatment modalities.

Table 1: Patient's classification according to the previous and current treatment modalities.

Primary Treatment		Salvage / Adjuvance		
RP (91%)	n=116	RP	57,8%	n=67
		RP + RT	13,8%	n=16
		RP + RT + previous ADT	5,2%	n=6
		RP + RT + current ADT	5,2%	n=6
		RP + previous ADT	8,5%	n=10
		RP + current ADT	9,5%	n=11
RT (9%)	n=12	RT	41,7%	n=5
		RT + previous ADT	25%	n=3
		RT + current ADT	33,3%	n=4

The patients in current ADT were not classified as resistant to castration, as the hormonal blockade had been prescribed after the detection of increased PSA levels, before ordering a PET-CT, and this deprivation was maintained while the medical team waited for its realization.

Conventional primary assessment

Clinical and imaging data were obtained not only on the day PSMA PET was performed but also from patients' charts. BCR investigation provided clinical information such as PSA curve and doubling time, when available, MMR and/or total abdominal CT scan, and BS reports.

^{68}Ga-PSMA PET/CT protocol

PET imaging was performed from the proximal femora to the skull base on a GE Discovery 600 PET/CT scanner 60 minutes after intravenous injection of 1.85MBq/Kg (0,05mCi/Kg) of 68Ga-HBED-CC-PSMA (or ^{68}Ga-PSMA-11). Fifteen minutes after the tracer injection, 500mL of saline hydration and 20mg of furosemide were administered to avoid excessive urinary activity, especially focal retention on the ureters and to expand the bladder [11]. Kidney failure was not a concern because intravenous iodinated CT contrast was not part of the protocol.

PET/CT imaging reports were written by nuclear medicine physicians with experience in prostate cancer PET imaging and the level of tracer uptake, SUVmax, location, and morphological appearance of the lesions were mentioned.

Imaging comparison

Conventional imaging reports, such as BS, CT and MRI, were compared with PET findings and classified into groups regarding unidentified disease by PSMA PET, confirmation of conventional imaging findings, exclusion of lesions, and detection of additional lesions.

For the comparison of the extent of the disease determined by the 2 methods, the findings were categorized according to the TNM system [12] and descriptively as Local Disease (LD), i.e., prostate bed and/or seminal vesicle remnant involvement and prostat e gland after RT, Pelvic Nodal Involvement (PNI), Distant Nodal Involvement (DNI) and metastatic disease. After that, we analyzed whether the result of this comparison implied changes in the extent definition of the recurrent disease.

Decision-making deliberation

The cases were discussed at the urology department of Santa Casa based on the clinical features and conventional imaging reports, and then a therapeutic management proposal was made. After that, the PSMA findings were revealed, and an additional debate decided whether the former proposal would remain. Although the patients were referred from urology departments of 10 different institutions, we decided to centralize the discussion at Santa Casa based on NCCN PCa guidelines [10] to avoid bias regarding probable differences and background knowledge among services.

Results

BCR detection rate

The overall detection rate was 60% (75 PETs from 125 patients), considering only positive results (excluding indeterminate results). Three patients had equivocal results (2% - 3 of 128) and 50 negative PETs, i.e., undetected disease (39%). For the analysis of the PSMA PET results, according to the primary therapy employed, indeterminate results were excluded, and no significant difference was observed (p=0.359 – Fisher's exact test) between patients treated with RP and RT.

PSMA PET findings and PSA levels

Equivocal results were also excluded from the analysis of the PSMA PET detection rate according to PSA levels, leaving n=125.

PET detection rates increased proportionally to the increase in PSA levels (table 2) and the sensitivity values calculated for arbitrarily chosen serum PSA values were 64.5% for 0.2ng/mL, 78.8% for 0.4 ng/mL, 91.2% for 1.0 ng/mL and 92.7% for 2.0ng/mL. We chose not to calculate the specificity and prediction values (positive and negative predictive values) since all individuals in the series were considered ill according to the BCR criteria, so there would be no false negative results. There was no significant difference (Chi-square test p=0.435) in the rate of disease detection by PSMA PET between patients with and without androgen blockade.

Table 2: PSMA detection rate according to the range of the total PSA level.

Range	Nº Positive Pets	Nº Patients / Range	Detection Rate
<0,2ng/mL	4	15	26.67%
0,21-1,0ng/mL	19	53	35.85%
1,1-2,0ng/mL	14	16	87.50%
>2,0ngmL	38	41	92.68%
Total	75	125	60%

Confrontation to conventional imaging

The detection of lesions only by PSMA PET was observed in 28% (n=36) of the patients, exclusion of lesions in 10% (n=13), identification of additional lesions in 8% (n=10), exclusion and detection of additional lesions combined in 16% (n=20), suspicious lesions using conventional imaging methods without a correlated increase in PSMA molecular expression in 2% (n=3), PET and conventional exams both negative in 30% (n=38) and concordance between the methods with detection of lesions in 6% (n=8).

There was a predominance of exclusion of bone lesions determined as suspicious and/or indeterminate by BS in the RP group and equivalent to the exclusion of suspicious lymph nodes in the RT group. Regarding the sites of additional lesions, prostate bed and lymph nodes in patients treated with RP and prostate and lymph nodes in those treated with RT stood out.

The mean dimension measured in the smallest transverse axis of the lymph nodes was 0.6cm, with the smallest identified lymph node measuring 0.3cm. Bone lesions were not measured, considering that tomography is not the most accurate method for such measurement and because bone marrow lesions do not usually show alterations correlated to CT.

The time gap between conventional examinations and PET PSMA was <1 month in 10.94% of the cases, between 1 and 3 months in 29.7%, between 3 and 6 months in 21.09%, and over 6 months in 38.27% of cases.

Staging and extension disease changes

The sites of recurrence were identified in 53 patients (41%) by the conventional imaging investigation, whereas PSMA PET identified the relapsed disease in 75 patients (60%) (figure 1).

An increase in the volume of disease was detected with no change in staging in 10 patients whom 6 (60%) had already been classified as metastatic by conventional methods and 4 (40%) as locoregional disease.

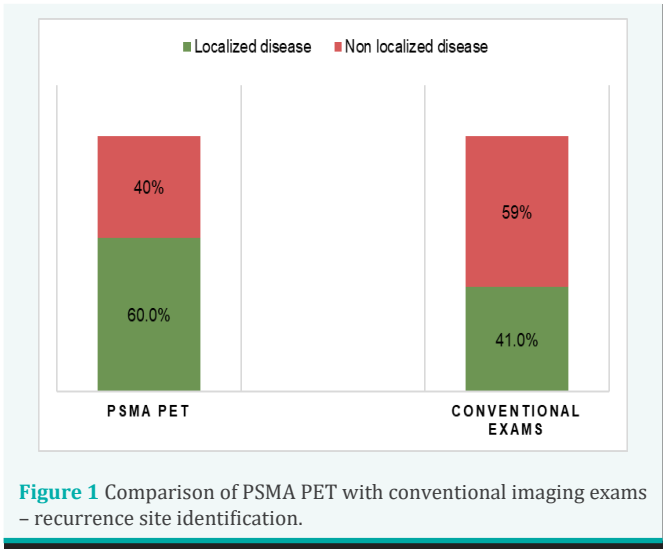

Figure 1 Comparison of PSMA PET with conventional imaging exams – recurrence site identification.

Therapeutic management impact

After the disclosure of PSMA PET findings and the results of the confrontation with conventional imaging, the board changed the management decision in 36% (n=46) of the patients with biochemical recurrence, 35% (n=41) of the patients treated with RP, and 42% (n=5) of the patients treated with RT.

In the group primarily treated with RP, regardless of other salvage / adjuvant modalities, there was a locoregional treatment (75% n=30) predominance, either due to contraindication of

systemic treatment due to downstaging (37.5% n=15) or to changes in the modality of locoregional treatment (37.5% n=15), such as alteration in the extension of the RT field or indication of lymphadenectomy. The locoregional treatment changed to systemic in 2 patients (5%) for upstaging and in 8 (20%) there was a change in the systemic treatment modality from ADT to chemotherapy or the addition of medication for ADT owing to the increase in the disease volume detected by PET. Lastly, in 1 patient follow-up was chosen instead of ADT, due to the negative PET and low serum PSA levels. Table 3 shows the changes in management decisions according to the previous and current treatment modalities.

Regarding the negative imaging results, besides the low PSA levels, we must know that the baseline status of PSMA molecular expression of these patients is unknown, once they did not undergo a primary staging PET/CT. It is known that 5 to 8% of PCa patients might not overexpress PSMA for unknown reasons [16]. This fact may explain the 3 patients with suspicious lesions on conventional imaging methods without a correlated increase in PSMA molecular expression. There is another condition that we must consider in the face of a negative or equivocal PET: after RP, benign prostatic glandular tissue is frequently found on the surgical margins of the apex and bladder base.

Table 3: **Therapeutic management impact according to treatment modalities.**

Treatment Modality	% Changing	Therapeutic Decision Change
RP	44,8% (n=30)	ST → LRT (n=13) LRT modality change (n=13) ADT → ADT + Chemo (n=3) LRT → ST (n=1)
RP + RT	6,25% (n=1)	ST → Follow up (n=1)
RP + previous ADT	50% (n=5)	ADT → ADT + Chemo (n=2) LRT → ST (n=1)\ ST → LRT (n=1) LRT modality change (n=1)
RP + current ADT	36,4% (n=4)	ADT → ADT + Chemo (n=2) ST → LRT (n=1) LRT modality change (n=1)
RP + RT + previous ADT	16,7% (n=1)	ADT → ADT + Chemo (n=1)
RP + RT + current ADT	n = 0	0
RT	42% (n=5)	Salvage RP possibility (n=5)

Discussion

The imaging evaluation of the patients with BCR of PCa may be challenging, so the nuclear physician and the radiologist must know the clinical features of the patients such as previous primary treatment, risk classification, and PSA levels (initial and current). Furthermore, it is important to bear in mind the most probable sites of recurrence, drainage lymph node chains, basic technical principles of surgery, and the main causes of pitfalls, false positive and false negative results.

Another particularity of the BCR imaging evaluation is that PSA values can be low, and it is already known that the detection rate of disease by PSMA PET is directly proportional to the values of this marker [13,14]. The results of this study were consistent with this relationship, observing an increase in the detection rate, sensitivity, and positive predictive value of the test with the increase in PSA levels, as observed in the literature [13-15].

Albeit there is evidence that an increase in PSA levels after RP may be related to production by the residual benign gland, studies indicate that this event is uncommon, has no prognostic relevance, and should not be associated with postoperative PSA recurrence [17-19]. Also, this residual prostatic gland tends to reveal no uptake or low-grade uptake on postoperative PSMA PET [20]. In the face of this evidence, we conclude that an increase in PSA after RP with a negative PET is most likely related to a small volume disease undetected by the method or to a disease with no PSMA overexpression, especially if associated with conventional imaging findings. Moderate to high-grade focal uptake on the prostate bed should be reported and the nuclear physician must be aware of the exam protocol in order to prevent interference from the urinary bladder.

Concerning the PSMA performed during ADT, we found no difference in the rates of disease detection by PET in patients

with and without hormone blockade. Although some studies indicate that the molecular expression of PSMA is increased in the presence of ADT and in patients resistant to castration, since the transcription of the RNA of this molecule is androgen-suppressed [21,22], there is still not enough data to state that the PET performance is superior in patients undergoing hormone blockade. The NCCN guideline [10], for example, recommends performing PET before the beginning of deprivation, but studies that evaluated the effect of short or long-term ADT on PSMA uptake by PCa lesions have not yet shown evidence of unequivocal negative or positive impact on PET parameters that discourage the investigation of patients who have already started the blockade [23-25].It is likely that the response evaluation scenario, with promising results which are still in validation, will be more affected, but it was not the aim of this analysis.

The confrontation between methods showed that the BCR investigation with only traditional exams, would have detected the disease in less than half (41%) of the casuistry. Among patients without any suspicious lesions on conventional imaging studies, the detection of locoregional recurrence was predominant over metastatic disease, with emphasis on the prostatic surgical bed, notably next to the vesicourethral anastomosis, nodal involvement, and previously irradiated glandular parenchyma.

Slightly more than half of the patients had a change in staging/extent and upstaging was the predominant status, with identification of the disease in patients without suspicious lesions in the conventional investigation responsible for most of the cases, followed by the detection of systemic and regional impairment of lymph nodes, respectively. In the case of downstaging, the exclusion of bone metastases accounted for the highest number of cases.

The initial therapeutic proposal was modified after the disclosure of the PET findings in 36% of the patients, with a preponderance of choice for locoregional therapies. With regard to the analysis of the changes in the management decision according to the subcategories of previously performed and/or current treatments, it is evident that the impact will naturally be of greater magnitude in patients who have only undergone the primary treatment, whether surgical or radiotherapy. The presence of previous irradiation of the prostate bed/pelvis, for example, limits the options for locoregional treatment modalities. This fact is confirmed among the patients who did not change their therapeutic strategy despite the change in staging, including upstaging, since most of them had already undergone radiotherapy. Nevertheless, PET PSMA played an important role in excluding locoregional and systemic diseases in patients who would already be submitted to prostate bed radiotherapy, for example, even confirming the programming of the field to be irradiated, as well as the bone disease volume definition, maintaining the indication of ADT and ruling out, at first, the need for chemotherapy.

The main limitations of this study are the heterogeneous casuistry due to the presence of current or previous salvage / adjuvant treatment modalities and its retrospective nature. Also, the time gap between conventional examinations and PET PSMA was considerable, often over 6 months due to reasons related to the Brazilian National Public Health System and the coronavirus disease 2019 (COVID-19) pandemic. This fact does not seem to disproof our findings whereas, regardless of the upstaging predominance after confrontation to conventional exams, the majority of the patients were still eligible for locoregional therapies and, compared with recent meta-analyses, the impact on decision-making does not seem to be overestimated [26-29].

The impact of PET PSMA on the therapeutic management of prostate cancer, when compared to conventional exams, is significant, favoring the indication of locoregional salvage treatments in the evaluation of biochemical recurrence. The cost-effectiveness of PSMA over traditional exams on the PCa biochemical relapse investigation has been demonstrated in other countries [30-32]. It is paramount to analyze the incorporation of this method in the Brazilian public health service.

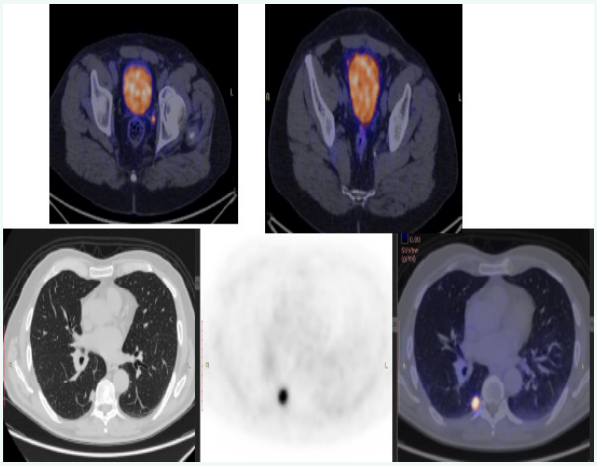

Figure 2 A). 70-years-old, PCa Gleason 9(5+4), treated with RP. BCR investigation showed PSA of 0.86ng/mL, abdominal CT with node adjacent to the bladder, and BS without suspicious lesions. PSMA PET identified small lymph nodes near the bladder (SUVmax = 3.7 – 0.6cm) and additional ones on the left obturator (SUVmax = 6.1 – 0.7cm) and mesorectal chains (SUVmax = 5.6 – 0.4cm); B). 76-years-old, PCa Gleason 7(3+4), treated with RP and salvage RT. BCR investigation showed PSA of 9.26ng/mL, abdominal CT, and BS without suspicious lesions. PSMA PET did not detect abdominal lesions. PSMA hyper concentration was identified on a pulmonary nodule (green arrow) in the right lower lobe (1.5cm and SUVmax = 27.8) and on lymph nodes in the mediastinum and left cervical level VI (SUVmax = 6.6). Anatomopathological report with immunohistochemical analysis after CT-guided biopsy confirmed pulmonary metastasis from PCa.

Patient Summary

In this study, we compared PSMA PET and conventional exams performance in the BCR investigation of PCa. PSMA PET provides valuable information which may increase therapeutic strategy options and reliably permit the indication of salvage treatments.

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Authors' Contributions

Conception of the study: Anna C. B. Silva. Analysis: Anna C. B. Silva, Luís, G. M. Toledo, Roni de C. Fernandes. Interpretation of data: Anna C. B. Silva, Alan R. Ziroldo, Roni de C. Fernandes. Draft and revision of the work: Guilherme V. Sawczyn, Shirlene T. Alarcon, Fábio Lewin. All authors have read and approved the revised manuscript.

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