68GA-PSMA PET-CT IN TRIPLE NEGATIVE METASTATIC BREAST CANCER

PET-CT com PSMA-Ga68 no Câncer de Mama Triplo Negativo Metastático

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ABSTRACT

Objectives: Triple negative breast cancer lacks specific markers and targeted treatments. In this context, the objective of this study is to evaluate, through case studies, the behavior of 68Ga-PSMA PET-CT to detect metastases in patients with triple negative breast cancer. **Methods:** Six patients with metastatic triple-negative breast cancer at initial diagnosis or who presented metastases due to disease progression were selected and evaluated. The participants underwent 68Ga-PSMA PET-CT, and the lesions were classified regarding their anatomical location and in grades ranging from 0 to 5 according to the intensity of tumor uptake. **Results:** As for the distribution of each type of lesion, one patient had local recurrence with grade 3 uptake; one patient had locoregional lymph nodes showing grade 4 uptake; two patients had distant lymph nodes, one with grade 2 uptake and the other with grade 3 uptake; four patients had bone metastases, two of them with grade 2 uptake and two with grade 3 uptake; three patients had lung metastases (one with grade 1 uptake, one with grade 2 uptake and one with grade 3 uptake); one patient had liver metastases with grade 3 uptake. One patient did not have any detectable radiopharmaceutical uptake (grade 0). **Conclusion:** This study demonstrated that 68Ga-PSMA, although originally described as a prostatic marker, is taken up by neoplastic lesions associated with triple negative breast cancer.

Keywords: PSMA, 68Ga-PSMA, triple-negative breast cancer, PET-CT, metastatic cancer.

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INTRODUCTION

Breast cancer is one of the most common malignant neoplasms affecting women all over the world. In Brazil, 74,000 new cases of this neoplasm are estimated for each year of the three-year period comprising 2023-2025[1]. The main challenge for the treatment of the disease is tumor heterogeneity, since even tumors with similar histological types, stages and degrees of differentiation may have different outcomes[2]. Breast neoplasms are divided according to the presence or absence of estrogen, progesterone and HER2

protein receptors. For tumors with positive hormone receptors, hormone therapy is already well established. Likewise, targeted therapies directed against HER2 receptors are used to treat HER2 positive tumors[4-6]. However, one of the most important clinical challenges lies in patients whose tumors do not have hormone or HER2 receptors, the so-called triple negative breast cancer[3]. In these cases, the diagnostic and therapeutic difficulty is due to the lack of cell surface markers that can be used as targets for the diagnosis and treatment of the disease.

Positron Emission Tomography-Computed Tomography (PET-CT) is a hybrid exam that aids diagnosis and treatment in oncology. It consists of a combination of metabolic images (PET), obtained by administering intravenous radiopharmaceuticals with affinity to tumor tissue, with tomographic images (CT), acquired by an X-ray-emitting tomograph. The clinical use of PET-CT has become more widespread with the use of fluorodeoxyglucose F18 (FDG), a glucose analogue radiopharmaceutical that accumulates in sites with high metabolic activity, such as some tumors[7]. Subsequently, the technique evolved by using newer radiopharmaceuticals directed at specific molecular targets for certain types of tumors.

As of 2013, the first studies on 68Ga-PSMA PET-CT were published[8]. 68Ga-PSMA is a radiopharmaceutical marked with the radioisotope gallium 68 that binds to a protein known as prostate-specific membrane antigen (PSMA). This radiopharmaceutical has been increasingly used in prostate cancer[9]. However, despite being known as a prostate-specific antigen, PSMA is not exclusive to the prostate, as it is overexpressed in the neovasculature of several other tumors, including neoplasms of the breast, central nervous system (glioblastomas), mouth (squamous cell carcinoma), salivary glands (cystic adenoid carcinoma), bladder, stomach, large intestine, pancreas and kidneys[10-15].

As for breast tumors, in a study with 315 patients with invasive mammary carcinoma of no special type or invasive lobular carcinoma, 60% of the lesions showed PSMA-positive endothelium, with higher expression in hormone receptor-negative tumors[16]. This finding is interesting, as the growth and progression of breast tumors are accompanied by an increase in neovascularization, a phenomenon that is even more evident and intense in triple-negative tumors[17]. As they do not have surface molecules to act as targets for diagnostic and therapeutic techniques, angiogenesis could be used as a diagnostic and prognostic marker and potentially, as a therapeutic target for these tumors[18]. In this context, 68Ga-PSMA PET-CT could be a useful tool to make this approach feasible, given the avidity of PSMA for the neovasculature of these neoplasms.

Once this clinical use of PSMA is established, possibilities may arise for targeted therapy with another radioisotope, lutetium-177, which, when used as the radiopharmaceutical 177Lu-PSMA, can specifically target tumor cells, destroying them through the emission of beta radiation[18-20]. This strategy follows the so-called teragnostic concept, in which radiopharmaceuticals directed to specific tumor targets are used in image acquisition (e.g. 68Ga-PSMA) to select patients who could benefit from therapies directed towards these same targets (e.g. 177Lu-PSMA)[21]. This technique would therefore be of great value for patients with triple-negative breast cancer, since these tumors lack therapeutic options[18]. Furthermore, it could help in prognostic estimation and minimize treatment side effects[21].

Considering this rationale, this study aims to evaluate the use of 68Ga-PSMA PET-CT in patients with metastatic triple negative breast cancer.

METHODS

This is a descriptive cross-sectional study, which included female patients over 18 years of age with triple-negative breast cancer and metastatic disease, confirmed by conventional radiological imaging (distant lymph nodes affected and/or distant metastases). Six patients undergoing follow-up at Conjunto Hospitalar de Sorocaba or at Santa Casa de Misericórdia de Sorocaba were recruited between 2019 and 2021. They underwent 68Ga-PSMA PET-CT scans at a nuclear medicine center in Sorocaba, Brazil.

In all stages of this study, ethical principles for human studies were respected, according to Resolution 466/2012 of the Brazilian National Health Council (Conselho Nacional de Saúde). The institution Research Ethics Committee approved the study under number 30165820.6.0000.5373.

Image acquisition

A Siemens Biograph™ TruePoint™ PET-CT scanner was used to obtain images from the skull to the root of the thighs one hour after the administration of a mean dose of 3.33±0.2 mCi (123.58 Mbq) of 68Ga-PSMA. Acquisition time was three minutes per bed-position. The scan did not require any preparation.

Image analysis

The images were analyzed by an experienced nuclear medicine physician and a radiologist. Lesions were classified according to their location and intensity of tumor uptake in standardized uptake value (SUV) units.

Lesions were classified in four groups according to anatomical location: 1) local recurrence; 2) localized lymph node lesion (axillary, supraclavicular, internal mammary or more than one locoregional chain); 3) distant lymph node lesion (lymph nodes that do not fit the classification of localized lymph node lesion); 4) metastatic disease (bone metastases and non-bone visceral metastases).

As for intensity of tumor uptake, lesions were classified in five different grades: grade 0 – absent tumor uptake or up to 25% of the mean hepatic SUV; grade 1 – tumor uptake between 25% and 50% of the mean hepatic SUV; grade 2 – tumor uptake between 50% and 100% of the mean hepatic uptake; grade 3 – tumor uptake greater than the mean hepatic uptake but less than the mean splenic uptake; and grade 4 – tumor uptake greater than the mean splenic uptake.

RESULTS

Patients differed according to the extent of metastatic disease. Table 1 presents clinical and demographic data for each patient, as well as their lesions showing 68Ga-PSMA uptake. Thus, four had bone involvement among all patients, three had lung involvement and one had liver involvement. Figure 1 shows the images of lung, liver and bone lesions with 68Ga-PSMA uptake.

TABLE 1 - Clinical and demographic data of patients that underwent 68Ga-PSMA PET-CT, and sites of lesions showing radiopharmaceutical uptake

PATIENT	AGE	PREVIOUS SURGERY	PREVIOUS CHEMOTHERAPY*	PREVIOUS RADIATION THERAPY	LESIONS WITH 68GA-PSMA UPTAKE
1	60	Yes	Yes	No	Bone metastasis
2	47	No	Yes	No	Local recurrence, lung metastasis, locoregional and distant lymph nodes
3	48	Yes	Yes	Yes	Bone and lung metastases, distant lymph nodes
4	66	No	Yes	No	Bone metastasis
5	39	No	Yes	Yes	-
6	50	Yes	Yes	No	Bone, lung, liver and liver metastases

* Patient 1 used Paclitaxel (PCT)/Capecitabine (CB) with Pamidronate, Gemcitabine (GCT) with Pamidronate and CB; patient 2 used vinorelbine (NVB); patient 3 used PCT; patient 4 used PCT/CB; patient 5 used PCT/CB; patient 6 used Doxorubicin + Cyclophosphamide for four Cycles (4XAC) and PCT.

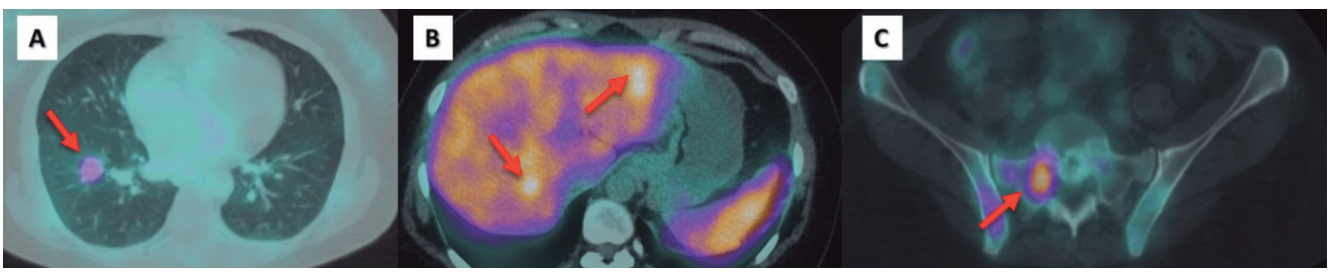

Figure 1. 68Ga-PSMA uptake in metastatic lesions, indicated by the red arrow: lung (Fig.1A), liver (Fig.1B) and bone (Fig.1C) metastases.

The mean SUV for all lesions, regardless of location, was 7.0, with the highest uptake intensity in locoregional lymph nodes (mean SUV = 13.9) and the lowest in bone and lung lesions (mean SUV = 3.0). Table 2 details the mean SUV observed in each type of lesion, as well as the corresponding number of cases.

The mean hepatic SUV used to classify the intensity of tumor uptake, as described in "Methods", was 5.9 (± 0.59), while the mean splenic SUV was 8.9 (±1.7). Only one patient did not have any lesion with 68Ga-PSMA uptake, so her case was classified only according to tumor uptake intensity (as grade 0) rather than regarding anatomical location. The number of cases with lesions in each anatomical location and their intensity of tumor uptake are listed on

TABLE 2 - Mean SUV observed in each type of lesion and corresponding number of cases

LESION TYPE		NUMBER OF CASES (% OF PATIENTS)	MEAN SUV (MINIMUM- MAXIMUM)
Local recurrence		1 (16.7%)	7.1 (7.1 - 7.1)
Locoregional lymph nodes		1 (16.7%)	13.9 (13.9 - 13.9)
Distant lymph nodes		2 (33.3%)	6.2 (3.8 - 8.5)
Distant metastases	Bone	4 (66.6%)	5.35 (3.0 – 7.6)
	Liver	1 (16.7%)	7.6 (7.6- 7.6)
	Lung	3 (50%)	6.36 (3.0 – 8.5)

Note: anatomopathological confirmation of lesions was not performed.

Table 3. Figures 2 and 3 illustrate the aspect of tumor uptake in different patients, compared to liver uptake.

DISCUSSION

Most patients had lesions with high 68Ga-PSMA uptake, including lymph node, lung, bone and liver metastases. Although it was originally described as a marker for prostate cancer, recent studies have reported the presence of the PSMA protein in the neovasculature of other solid tumors[10-15,18]. The avid 68Ga-PSMA uptake by metastatic triple negative breast cancer lesions in this study corroborates previous findings of PSMA overexpression in this type of breast cancer. As angiogenesis is essential in the pathophysiology of many types of metastases[22], especially in triple negative tumors[17], it is believed that the overexpression of PSMA may be a marker of metastatic disease[18].

This is the first study of its kind in Brazil. International literature on the subject is also still scarce. In a systematic review, Bertagna *et al.*[23] identified only 12 papers published on the subject, 11 of which were case reports, and, of these, only eight had breast cancer as a final diagnosis[16,24-30]. Interestingly, two of these cases were incidental findings of synchronous histologically confirmed malignant breast tumors in patients who underwent 68Ga-PSMA PET-CT during workup of prostate cancer[24,25]. The findings of this study, therefore, are in line with the hypothesis that metastatic triple negative breast cancer lesions indeed show positive 68Ga-PSMA uptake.

There are only two published studies that evaluated the performance of 68Ga-PSMA PET-CT in detecting lesions associated with breast cancer. Sathekge *et al.*[31] evaluated 19 women with breast cancer aged between 25 and 66 years, regardless of the type of disease, including cases of locoregional recurrence, metastatic disease, and progesterone receptor positive and negative tumors. The authors reported a detection rate of 84% of all lesions, with no statistically significant difference to the detection rate observed with FDG PET-CT. Another retrospective study by Medina-Ornelas *et al.*[32] compared the detection rates of 68Ga-PSMA PET-CT and FDG PET-CT, reporting a sensitivity of 84% and a specificity of 91.8% for 68Ga-PSMA PET-CT versus a sensitivity of

TABLE 3 - Number of patients presenting each type of lesion according to anatomical location and tumor uptake intensity (in SUV) compared to hepatic and splenic uptake.

	TUMOR UPTAKE INTENSITY IN SUV (LESION/HEPATIC OR SPLENIC)					
ANATOMICAL LOCATION	**GRADE 0 (0 TO UP TO 1.4)**	**GRADE 1 (1.4 – 2.9)**	**GRADE 2 (2.9 – 5.9)**	**GRADE 3 (5.9 – 8.9)**	**GRADE 4 (> 8.9)**	**TOTAL**
Local recurrence	1	-	-	1	-	1
Locoregional lymph nodes	1	-	-	-	1	1
Distant lymph nodes	1	-	1	1	-	2
Bone metastases	1	-	2	2	-	4
Lung metastases	1	1	1	1	-	3
Liver metastases	1	-	-	1	-	1

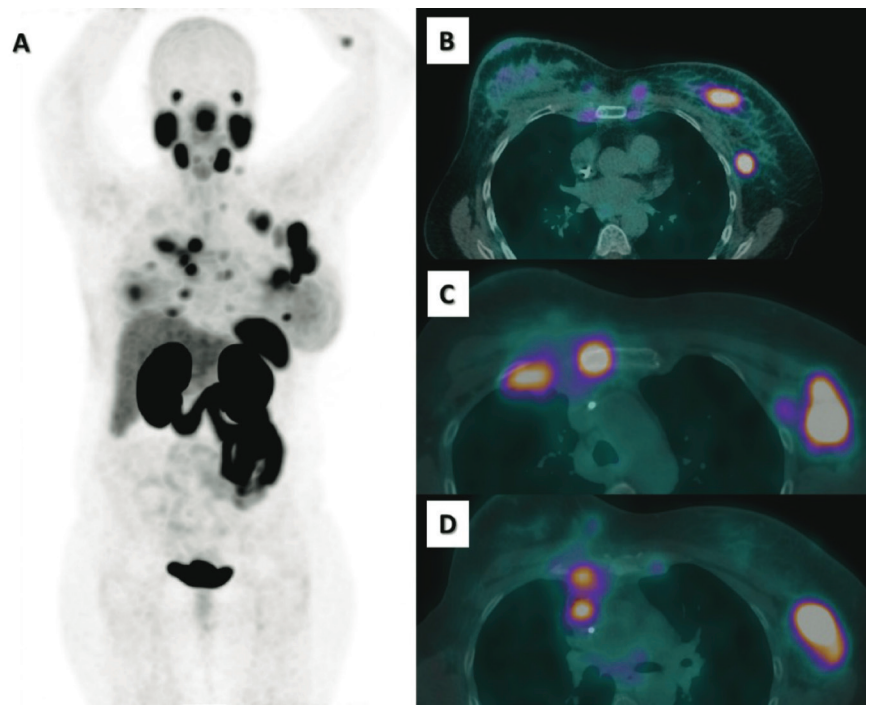

Figure 2. Maximum intensity projection (MIP) full-body images showing lesions with 68Ga-PSMA uptake at higher intensity compared to liver uptake (Fig. 2A). Tracer uptake can be observed in the breast and in axillary lymph nodes (Fig. 2B), in the sternum (Fig. 2C) and in anterior mediastinal lymph nodes (Fig. 2D).

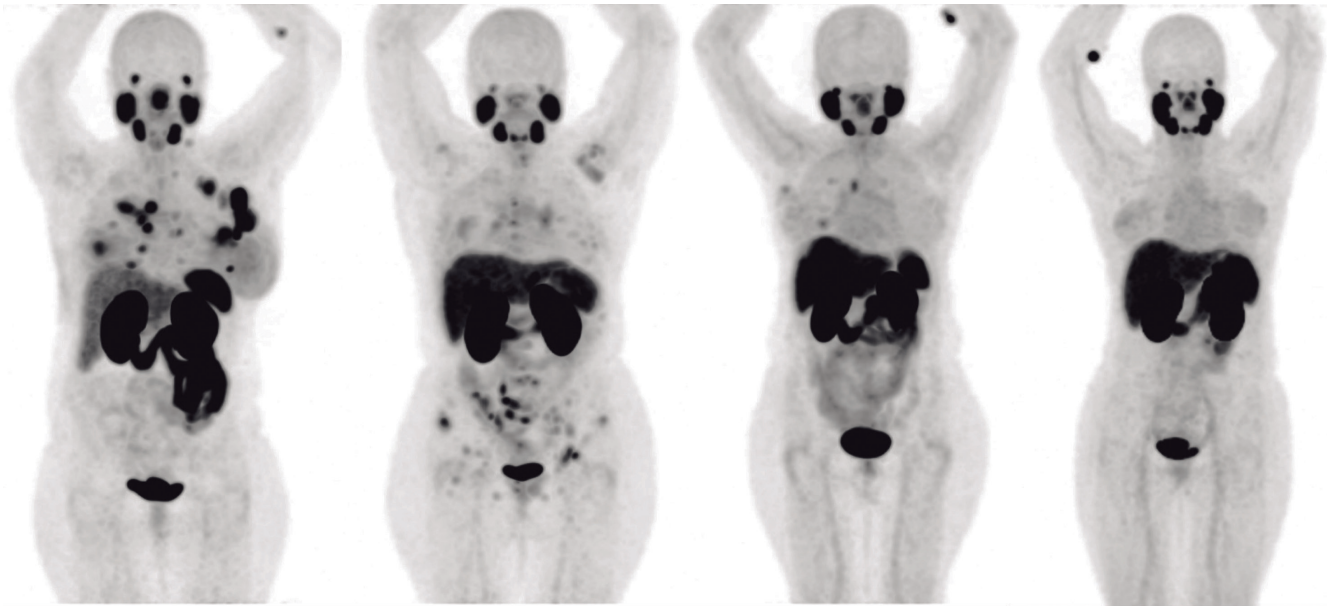

Figure 3. Aspect of 68Ga-PSMA uptake, compared to liver uptake, in MIP images of different patients

99.2% and a specificity of 93.6% for FDG PET-CT. Although that study included patients with different types of breast cancer, it divided them according to the molecular type of the tumor. Interestingly, a statistically significant lower detection rate with 68Ga-PSMA PET-CT compared to FDG PET-CT was observed in patients with luminal A and luminal B HER2 negative subtypes, with no difference for luminal B HER2 positive, HER2 overexpressing, and triple negative subgroups. In addition, all lesions identified by FDG PET-CT in patients with triple negative tumors were identified by 68Ga-PSMA PET-CT. These findings reinforce the importance of approaching breast cancer as a heterogeneous disease, not only from a clinical point of view, but also from a molecular standpoint. Considering such heterogeneity, triple negative breast cancer seems to have a unique profile of PSMA expression, which is up to 4.5 times greater in these tumors than other types of breast cancer[16], possibly due to a more intense angiogenesis.

Another issue that must be discussed is the possible difference in PSMA expression by metastases compared to primary and locoregional lesions. In the study by Sathekge *et al.*[31], the mean SUV found in metastases was significantly higher than the SUV found in primary lesions and in local and lymph node recurrences. This finding is consistent with an immunohistochemical study by Kasoha *et al.*[33], which reported higher PSMA expression in metastatic lesions compared to their respective primary lesions. However, this finding was observed only in the neovasculature of the lesions, but not in tumor cells. This reinforces the hypothesis that PSMA is more relevant for the pathophysiology of metastatic disease than for the primary tumor, possibly due to its role in tumor neoangiogenesis. It is important to consider, however, Medina-Ornelas *et al.*[32] did not observe this finding, possibly due to differences in the study design compared to the work of Sathekge *et al.*[31] Elucidating this issue is crucial for the development of 68Ga-PSMA PET-CT, since it is necessary to correctly identify the patients who could benefit the most from it.

It is also necessary to discuss the possible differences in 68Ga-PSMA uptake among lesions in different organs and tissues. The study by Medina-Ornelas *et al.*[32] did not find differences in the detection rates of bone metastases using 68Ga-PSMA PET-CT compared to FDG PET-CT, regardless of the tumor subtype. Hence, the differences observed in the detection rates of luminal A and luminal B HER2-negative subtypes were no longer found. This finding, however, may have occurred due to the low statistical power of the study, and due to the fact that this was not its main objective. The study by Sathekge *et al.*[31], in turn, did not assess differences in 68Ga-PSMA uptake according to lesion site. Immunohistochemical studies, however, suggest that PSMA expression varies across sites, as reported by Kasoha *et al.*[33], who found a higher expression of PSMA in the neovasculature (but not tumor cells) of brain metastases, compared to bone lesions. Furthermore, an immunohistochemistry study with 92 patients by Wernicke *et al.*[13] also found a PSMA positivity rate of 74% in the neovasculature of breast cancer, which rose to 100% when only brain metastases were evaluated. Our study found a higher uptake of 68Ga-PSMA in liver metastases compared to lungs and bones, which corroborates the previous findings of lower PSMA expression in bone metastases.

Notwithstanding, this study has important limitations. Initially, the sample size was small, although only two other studies in the world analyzed larger samples. Furthermore, no comparison was made between 68Ga-PSMA PET-CT and other imaging techniques, such as FDG PET-CT, which did not allow for sensitivity and specificity analyses. The lack of another confirmatory method also did not allow to control for false-positive results, which have already been described with 68Ga-PSMA PET-CT, including non-malignant breast conditions such as gynecomastia

and pseudoangiomatous stromal hyperplasia[34,35]. Moreover, studies have already reported 68Ga-PSMA uptake by benign lesions, such as granulomas associated with sarcoidosis, Paget's disease of the bone, fibrous dysplasia, healing fractures, senile amyloidosis, among others[36,37].

Despite the limitations, this study indicates that 68Ga-PSMA PET-CT is safe and well-tolerated, showing a good uptake by breast cancer metastatic lesions. This finding, reported for the first time in Brazil, reinforces the possible role of PSMA in the pathophysiology of metastatic breast cancer, especially in patients with triple negative tumors. This study paves the way for future research on the use of PSMA as a target for treatment with radiopharmaceuticals, which can be of great value for patients with triple negative breast cancer, given the limited therapeutic options currently available for these cases[18]. This will only be possible if patients are appropriately selected, given the heterogeneity of the disease, which includes different tumor biology across subtypes, and the role of angiogenesis in disease progression. Once these points are clarified, it will be possible to envisage, according to the concept of theragnostics, the eventual use of Ga68-PSMA PET-CT imaging to select patients eligible for new targeted therapies, such as 177Lu-PSMA, which already demonstrates promising results in the treatment of prostate cancer[20].

DISCLOSURES

The authors declare that they have no conflicts of interest to disclose.

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INFORMATION ABOUT THE ARTICLE

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