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Prognostic role of 18F-FDG PET-CT in the prone position in the evaluation of invasive breast carcinoma

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ABSTRACT

Introduction: The objective of this study was to correlate the features of invasive breast carcinoma in 18F-FDG positron emission tomography/computed tomography with histopathological results, findings from other imaging methods, and survival. **Methods:** This observational single-center study included patients who underwent staging 18F-FDG positron emission tomography/computed tomography between September 2012 and April 2019; the results were correlated with the findings of other imaging tests and anatomopathological results. Lesions were evaluated for their maximum standardized uptake value on positron emission tomography/computed tomography performed in the prone position. Tumors were classified into three subtypes (luminal, HER2 and triple-negative) based on immunohistochemical analyses. **Results:** A total of 125 patients with a mean age of 52 years (24–90 years) were analyzed. The primary tumor showed an increased 18F-FDG concentration on positron emission tomography/computed tomography in 122 (97.6%) patients, with a mean maximum standardized uptake value of 7.15 (1.0–32.9 range). The mean maximum standardized uptake value was higher in the triple-negative subtype (11.4; n=24) than in the luminal (6.2; n=89) and HER2 (5.0; n=9) subtypes (p<0.01). Tumors with more aggressive histological and immunohistochemical characteristics showed higher maximum standardized uptake values. Patients with a standardized uptake value greater than 7 in the primary tumor or greater than 6.7 in the axillary lymph nodes had poor overall survival (p=0.03 and p<0.01, respectively). **Conclusions:** Our study suggests that the maximum standardized uptake value obtained on positron emission tomography/computed tomography in the prone position may correlate with the tumor immunophenotype and overall survival regardless of the treatments performed, and can be used as a prognostic biomarker in invasive breast carcinoma patients.

KEYWORDS: breast neoplasms; PET/CT; triple negative breast cancer; survival.

INTRODUCTION

Breast cancer is the most common malignancy in the female population and is the leading cause of cancer-related death in these patients[1]. Breast imaging methods such as mammography, ultrasound and magnetic resonance imaging (MRI) have a fundamental role in diagnosis and locoregional treatment planning[2-4].

Positron emission tomography/computed tomography (PET-CT) with 18F-fluor-deoxi-glucose (18F-FDG) can provide information related to glucose metabolism in different organs and tissues. For patients with breast cancer, this test is generally used to detect distant metastases and recurrences, and evaluate therapeutic responses. However, prior studies have shown that PET-CT can also be used to assess breast tumors. Prone PET-CT with a dedicated protocol for breast evaluation improves the ability to detect and characterize breast cancer, allowing better correlation with conventional breast imaging methods[5-9]. The tumor maximum standardized uptake value (SUVmax) obtained from 18F-FDG PET-CT performed with a specific breast protocol correlates better with tumor aggressiveness and can be used as a prognostic biomarker in patients with invasive breast carcinoma.

The objective of this study was to correlate the features of invasive breast carcinomas in prone 18F-FDG PET-CT scans using a dedicated breast protocol with radiological findings from conventional breast imaging methods (mammography, ultrasound and MRI), as well as histopathological results and overall survival.

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METHODS

This observational, retrospective and single-center study was approved by the institutional review board, and informed consent was waived. We included female patients who had histology-proven invasive breast carcinoma and underwent staging 18F-FDG PET/CT between September 2012 and April 2019, with a dedicated protocol for breast evaluation. From 979 PET/CT exams performed in breast cancer patients during the study period, 631 were excluded because patients did not undergo treatment/follow-up at the institution or had incomplete histological or immunohistochemistry analysis. Additionally, 223 patients were excluded because they underwent some treatment before the PET/CT exam (131 had neoadjuvant chemotherapy and 92 had prior surgical resection), and 125 patients were included in the final analysis.

Pathological analysis

The histopathological diagnosis was performed through analysis of the surgical specimen in 93 patients and percutaneous biopsy in the remaining cases. All biopsies were reviewed by the institution's Department of Pathology. The following histological features were assessed: histological type, presence of an associated *in situ* carcinoma, histological grade, nuclear grade, mitotic index, associated aspects of necrosis, desmoplastic reaction, inflammatory infiltrate, and vascular, perineural and lymphatic invasion.

Breast carcinomas were classified into 3 subtypes based on immunohistochemical expression of hormone receptors and HER2: luminal, positive hormone receptors; HER2-overexpressing, negative hormone receptors and positive HER2; and triple-negative, negative hormone receptors and HER2. Estrogen receptor (ER) and progesterone receptor (PR) were considered positive when => 1% in neoplastic cells, and HER2 was considered positive or overexpressed if immunohistochemistry was 3+ or 2+ with positive gene expression on *in situ* hybridization (ISH)[10,11].

Imaging analysis

Whole-body PET-CT was performed on a dedicated device (PET-CT Gemini TF, Philips) 60–120 minutes after the intravenous administration of 0.154 mCi/kg of weight 18F-FDG in the supine position with capillary blood glucose concentrations below 150 mg/dL. Subsequently, an additional series of images was acquired dedicated for the breast evaluation, with the patient in prone position using an especially made device, which reproduces the coil used in breast MRI. The exam was performed on cephalocaudal acquisition with 2.5 mm-thick contiguous tomographic slices with no use of intravenous or oral contrast agent, followed by the acquisition PET images with 90 seconds acquisition time for each 15 cm bed position. The interpretation of the 18F-FDG PET/CT images was performed by at least two experienced nuclear medicine physicians who considered any areas of increased 18F-FDG uptake in relation to normal breast parenchyma to be positive. SUVmax was calculated in the images acquired in the prone position for each region of interest.

Mammography examinations were performed on a digital device in cranio-caudal and lateral oblique views, with compression between 11 and 18 kg/cm^3 (average 14 kg/cm^3), and with complementary views, if necessary. Ultrasound examinations were performed with a high-frequency transducer from 10–14 mHz, allowing evaluation of the breasts, axillary regions, internal mammary chain and infraclavicular region. MR images were acquired with the patient in the prone position on a 1.5 Tesla device (MAGNETOM Symphony, Siemens; Signa HDxt, GE; or Ingenia, Philips) using a dedicated breast coil before and after injection of the intravenous paramagnetic contrast medium (gadolinium), including T1- and T2-weighted images, dynamic contrast enhancement (DCE) and diffusion-weighted images. According to the BIRADS lexico, mammographic findings were categorized as calcification, asymmetry, architectural distortion or mass[12]. Ultrasound findings were classified as mass or non-mass lesions, and MRI findings were described as mass or non-mass enhancement.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 20.0. Variables are presented using absolute and relative frequencies (qualitative variables) or main summary measures (quantitative variables), such as the mean, standard, median, minimum and maximum deviation. Statistical tests were used, when necessary, to identify correlations between variables. The χ^2 test and Fisher's exact test were used to compare categorical variables; Student's *t* test (or the non-parametric Mann-Whitney test, as indicated) was used to compare quantitative variables between two groups. Kaplan-Meier curves were used to analyze overall survival. To compare the survival curves between different groups, the log-rank test and Cox regression were used to estimate the hazard ratio (HR) with a 95% confidence interval (CI). The level of significance adopted was 5% ($p \leq 0.05$).

RESULTS

This study analyzed 125 patients with a mean age of 52 years (range: 24-90 years), with 38.4% of the patients aged 50 years old or younger at the time of diagnosis. 18F-FDG PET-CT in the prone position was positive in 122 patients (97.6%), with a mean SUVmax of 7.15 (range: 1.00-32.90). Eighty-three patients (66,4%) had multifocal and/or multicentric disease, and 73 patients (58.4%) had suspected axillary lymph nodes on PET-CT, with a mean SUVmax of 5.37 (range: 1.30–26.30). 18F-FDG PET/CT in the prone position had a false-negative result in 3 patients who had luminal subtype; two had a breast MRI examination (one with mass and the other with non-mass enhancement), and one underwent mammography and ultrasound examinations, both of which revealed only an area of architectural distortion.

Sixty-four (51.2%) patients underwent mammography, 81 (64.8%) patients underwent an ultrasound examination, and 101 (80.8%) patients underwent breast MRI (Table 1). There was no statistically significant difference in the SUVmax in relation to the mammography findings (p=0.527). On breast ultrasound and MRI, tumors that presented as a mass showed higher SUVmax values than non-mass lesions (p<0.001 for ultrasound and MRI).

There was a statistically significant correlation between the SUVmax and histological grade, nuclear grade, presence of inflammatory infiltrate, and subtype (Table 2). Tumors with the triple-negative subtype showed a higher SUVmax than those with the luminal and HER2 subtypes.

The mean follow-up period was 82.5 months; 13 patients had distant metastasis, 6 had locoregional recurrence, and 5 died in this period. Patients with an SUVmax in the primary tumor above 7 had worse overall survival than patients with an SUVmax equal to or less than 7 (71.4 x 85.8 months; p=0.030) (Figure 1). Regarding the SUVmax values of the axillary lymph nodes, patients with values above 6.7 had worse overall survival than patients with values less than 6.7 (p<0.001) (Figure 2). There was no correlation between the SUVmax and recurrence pattern.

Table 3 shows the results of Cox regression for overall survival in relation to age, subtype (triple-negative was only compared with Luminal due to the small number of HER2+ patients), SUVmax of the primary tumor, presence of an axillary lymph node with abnormal 18F-FDG uptake, and SUVmax of the axillary lymph nodes. Only the axillary lymph node SUVmax showed a significant correlation with overall survival, with the risk being 15.7% higher for each one-unit increase in the SUV.

Table 1. Findings Described in Conventional Imaging Tests and the Mean maximum standardized uptake values.

Findings	N (%)	Average SUVmax value	p
Mammography (n=64)			
Calcification	9 (7.2)	6.0	0.527
Asymmetry	12 (18.7)	8.0	
Architectural distortion	21 (16.8)	6.4	
Mass	29 (23.2)	6.4	
Ultrasound (n = 81)			
Mass	67 (53.6)	8.8	<0.001
Non-mass lesions	19 (15.2)	5.2	
Breast MRI (n=101)			
Mass	71 (67.3)	8.1	<0.001
Non-mass enhancement	30 (29.7)	4.7	

SUVmax: maximum standardized uptake value.

DISCUSSION

The results of the present study are in agreement with those in the literature, with an accuracy of 97.6% for detecting invasive breast carcinoma, whose lesions had SUVmax values ranging from 1.00–32.90. There is no consensus in the literature on the ideal cutoff SUVmax for the characterization of benign or malignant breast

Table 2. Histological and Immunohistochemical Characteristics of the Lesions and the Mean maximum standardized uptake values.

Features	N (%)	Average value SUVmax (median)	p
Histological grade			
I	12 (9.6)	3.7 (3.2)	0.011
II	39 (31.2)	5.8 (4.5)	
III	41 (32.8)	8.3 (6.8)	
Nuclear grade			
Low	5 (4.0)	3.6 (3.1)	0.016
Intermediate	22 (17.6)	4.5 (4.1)	
High	65 (52.0)	7.6 (6.1)	
Desmoplastic reaction			
Absent	4 (3.2)	9.3 (5.7)	0.224
Discreet	27 (21.6)	7.5 (4.5)	
Moderate	51 (40.8)	6.5 (5.2)	
Accentuated	9 (7.2)	3.6 (3.6)	
Inflammatory infiltrate			
Absent	3 (2.4)	4.6 (4.7)	0.046
Discreet	64 (51.2)	5.3 (4.1)	
Moderate	17 (13.6)	9.3 (6.2)	
Accentuated	7 (5.6)	13.3 (14.3)	
Vascular invasion			
Yes	2 (1.6)	6.7 (7.6)	0.651
No	89 (97.8)	6.7 (5.0)	
Perineural invasion			
Yes	4 (3.2)	3.3 (3.6)	0.199
No	87 (95.6)	6.8 (5.0)	
Lymphatic invasion			
Yes	13 (10.4)	6.1 (5.3)	0.738
No	78 (85.7)	6.1 (5.3)	
Subtype			
Luminal	92 (73.6)	6.2 (4.6)	<0.001
Triple Negative	24 (19.2)	11.4 (9.4)	
Her-2	9 (7.2)	5.0 (4.5)	
Associated DCIS			
Yes	41 (45.0)	6.0 (4.1)	0.228
No	50 (54.5)	7.3 (5.4)	

SUVmax: maximum standardized uptake value.

lesions. In the study by Chae[13] that evaluated 60 breast lesions, 32 of which were malignant and 28 benign, it was concluded that, at a cut-off value of 2.3, the rate of malignancy and specificity of the mean SUVmax for differentiating benign and malignant breast lesions were 61.3% and 76.3%, respectively[13]. Another study that evaluated 172 patients who underwent 18F-FDG PET-CT

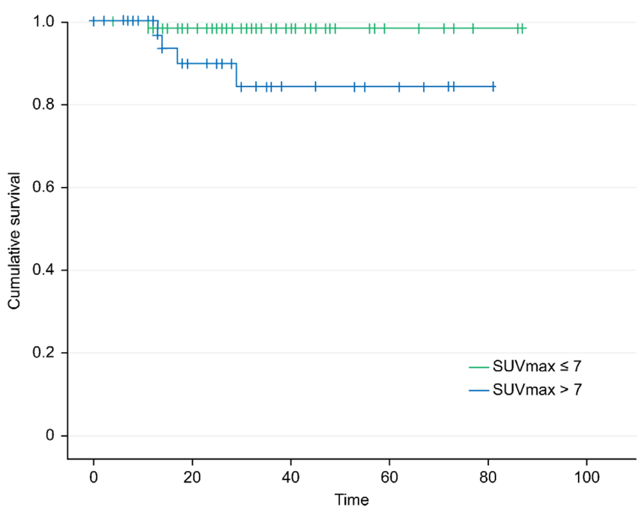

Figure 1. Overall survival of patients evaluated according to the maximum standardized uptake value in the primary tumor.

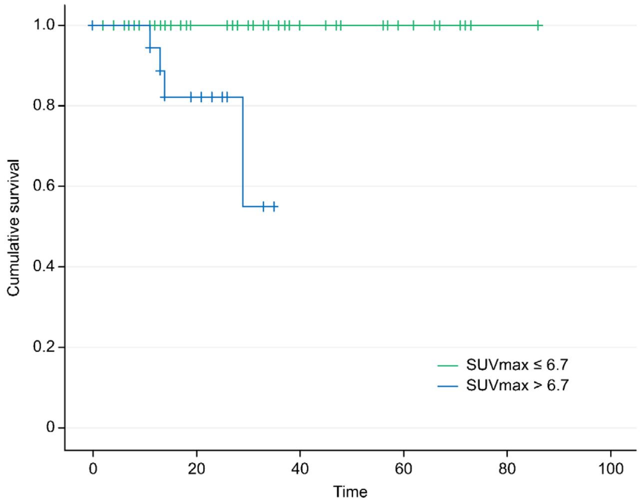

Figure 2. Overall Survival of Patients Assessed according to the maximum standardized uptake value of the Axillary Lymph Nodes.

Table 3. Cox Regression Values for Overall Survival.

Variables	HR	95%CI	p
Age	1.010	0.944–1.082	0.767
Immunophenotype NT	1.184	0.132–10.604	0.880
Primary tumor SUVmax	1.078	0.970–1.197	0.162
Presence of axillary lymph node in the Pet	3.098	0.346–27.735	0.312
SUVmax axillary lymph nodes	1.157	1.046–1.280	0.005

SUVmax: maximum standardized uptake value.

and breast MRI, both in the prone position, also demonstrated that the SUVmax value was not useful in differentiating benign from malignant lesions[7].

Our study showed that tumors with more aggressive histological and immunohistochemical characteristics, such as a high nuclear grade, histological grade III and the triple negative subtype, have higher SUVmax values. The same result was demonstrated in a study by Orsaria[14] that analyzed 50 patients with locally advanced or recurrent breast cancer. These patients underwent 18F-FDG PET-CT for preoperative staging, where it was observed that the average SUV was significantly different between tumor grades 1 (3.3±1.8), 2 (4.5±2.9) and 3 (5.8±3.3) (p=0.05). The authors also concluded that hormone receptor negativity, a high Ki-67 index and the triple-negative subtype were associated with increased 18F-FDG uptake[14]. However, this study was not performed with a dedicated coil for breasts in the prone position. Other reports in the literature have also demonstrated that the triple-negative molecular subtype has a high SUVmax that is proportional to its aggressive biological characteristics, with high sensitivity in FDG PET/CT images[15,16].

Regarding the limitations of this method, Avril[17] analyzed 144 patients with suspicious breast images who underwent FDG PET/CT, and concluded that the method has a high positive predictive value (96.6%) for breast cancer. However, the effects of partial volume and metabolic activity, which depend on the tumor type, are the most significant limitations of the examination[17]. The combination of PET/CT with other imaging methods, such as breast MRI, is promising and may lead to a reduction in the number of unnecessary biopsies[18,19].

The overall survival assessment in this study shows that patients with an SUVmax greater than 7 in the primary tumor and 6.7 in the axillary lymph nodes had poor overall survival. Several authors have investigated the usefulness of 18F-FDG PET/CT in predicting the clinical outcomes of patients with breast cancer, and have proposed cutoff values for the SUVmax. Jo[20] indicated that an SUVmax of 5.95 was the ideal cutoff value for predicting disease-free survival, whereas Ueda[16] indicated that an SUV of 4.0 may be one of the best values for predicting disease prognosis, with a significantly high incidence of mortality after 10 years in patients with an SUV above that cutoff[16]. In the present study, according to the multivariate analysis, only the SUVmax in the axillary lymph nodes showed a statistically significant correlation with overall survival.

The results of this work must be considered in the context of some limitations. This study was retrospective, and the final number of samples analyzed was small because many patients had insufficient data. FDG PET/CT results were included in this study regardless of the size of the lesion, and small tumors might have been underestimated due to the effect of partial volume. For multifocal and multicentric tumors, we only assessed the

SUVmax in the main lesion. We compared PET/CT results with other imaging tests individually, even in patients submitted to different exams. The evaluation of axillary lymph nodes was also limited because we did not investigate the outcome of this finding regarding the performance of biopsy or axillary resection. Conventional imaging information was obtained from radiology reports because images were not available for analysis in many cases. Detailed information on the pattern of metastasis or recurrence was also not available. In addition, this study was performed at a single cancer center.

However, the results presented herein confirm that 18F-FDGPET/CT in the prone position has high sensitivity for the evaluation of invasive breast carcinoma and can be used as an additional and complementary method for the evaluation of these patients, even showing prognostic value, and contribute to more individualized therapeutic decision-making. Currently, 18F-FDG is the most widely used radiopharmaceutical for the evaluation of breast cancer based on the affinity of cells with increased glycolytic metabolism[21]. However, there are other radiopharmaceuticals, such as 18F-fluoroestradiol ([18F] FES), an estrogen analog that shows affinity for nuclear estrogen receptors[22,23], and ERα, an important prognostic biomarker of breast cancer[24]. The hybrid MRI and PET method can also be very promising in the evaluation of breast carcinoma, since it combines the molecular sensitivity of PET with the high-contrast anatomical MR image and its functional resources in a single PET/MRI examination[9].

CONCLUSIONS

FDG PET/CT with a dedicated breast protocol showed high sensitivity for the evaluation of patients with breast carcinoma in our sample, demonstrating a good correlation with other imaging methods, especially breast MRI. Our study suggests that the SUVmax value obtained from PET/CT in the prone position correlates with histological factors associated with tumor aggressiveness, subtype and overall survival and can be used as a prognostic biomarker in patients with breast cancer.

AUTHOR´S CONTRIBUTIONS

CCT: Conceptualization, Methodology, Investigation, Project administration, Data curation, Writing – review & editing. ENPL: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. RABM: Investigation, Validation, Visualization, Writing – review & editing. EFM: Investigation, Validation, Visualization, Writing – review & editing. AGVB: Conceptualization, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – review & editing.

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