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Predictive Values of [18F]FDG PET/CT Metabolic Parameters In The Occurrence of Metastasis In Patients Diagnosed With Triple-Negative Breast Cancer

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Abstract

Introduction: Triple-negative breast cancer (TNBC) accounts for 15-20% of all breast cancers and is associated with a high recurrence rate and poor prognosis. This study aimed to determine the predictive value of [^{18}F]FDG PET/CT metabolic parameters for the occurrence of metastasis in patients diagnosed with triple-negative breast cancer (TNBC).

Materials and Methods: This was a 2-year retrospective descriptive and analytical study. All patients diagnosed with TNBC who underwent [^{18}F]FDG PET/CT as part of the extension workup were included. We sought an association between the occurrence of metastases and various metabolic parameters of PET/CT.

Results: A total of 48 patients were enrolled, with a mean age of 49.8 ± 12.6 years. The tumor was unilateral in 93.7% and multifocal in 8.3% of the patients. The predominant histological type was invasive ductal carcinoma (81.2%). The mean tumor size was 38.5 mm, with a mean SUVmax of 7.4 and a mean MTV of 82.4 cm^3. Over 2 cm³of patients had metastatic disease. The most frequent secondary sites were the bone (16.7%) and lung (10.4%). PET/CT was used to restage all patients after the initial CT scan. Analysis of the influence of specific clinical and metabolic variables on the occurrence of metastases showed that age > 50 years, tumor size ≥ 20 mm, bilateral involvement, presence of multifocal focus, SUVmax ≥ 5, and MTV ≥ 50 cm^3 were associated with the occurrence of metastases in patients.

Conclusion: Triple-negative breast cancer is an aggressive histological subtype that is avid for FDG. Our study showed an association between metabolic parameters on PET/CT and the occurrence of metastases in TNBC patients

Keywords: Breast cancer, metastasis, Positron-Emission Tomography, triple negative

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Introduction

Triple-negative breast cancer (TNBC) is characterized by the absence of estrogen, progesterone, and HER2 receptor expression. It is a histological subtype that frequently occurs in young women (< 50 years of age) (1) and is generally associated with large tumor size, high grade, high mitotic index, and lymph node involvement at diagnosis. TNBC has a higher recurrence rate and poorer prognosis than other histological subtypes of breast cancer. The median survival after diagnosis of metastatic disease is estimated to be 12-18 months (2,3). The absence of a therapeutic target makes therapeutic optimization difficult (4). Immunotherapy, PARP inhibitors, and antibody-drug conjugates (sacituzumab-govitecan) are the mainstay of treatment. Moreover, TNBC presents a paradox: a high response rate to chemotherapy in the neoadjuvant setting (50%) and a high distant recurrence rate (5).

Imaging is essential for breast cancer screening, diagnosis, staging, restaging, and treatment planning (6). Although positron emission tomography (PET) coupled with computed tomography (PET/CT) is not routinely used for the early staging of breast cancer, it is crucial for the staging of high-risk patients (7). Fluorodeoxyglucose ([^{18}F]FDG) is a glucose analog that is taken up by cells in the body. Before radioactive decay, its metabolic degradation is inhibited by substituting an OH bond with fluorine on the second chain of the glucose molecule. Consequently, the distribution of [^{18}F]FDG reflects the distribution of glucose uptake and phosphorylation by cells (8). Thus, [^{18}F]FDG is the most commonly used radiopharmaceutical in oncology and can be used as a metabolic biomarker to assess tumor glycolytic activity (9).

Breast cancer overexpresses glucose transporters (GLUT 1-3), making it sensitive to [^{18}F]FDG PET/CT imaging. However, different breast cancer subtypes show variable avidity for [^{18}F]FDG, reflecting differences in glucose metabolism. Studies have shown that TNBC and HER2-positive cancers show higher FDG uptake, whereas luminal breast cancers, particularly the luminal A subtype, show low uptake (10). Humbert et al. revealed that TNBC showed the highest uptake among the different histological subtypes of breast cancer (11). Mooij CM et al. confirmed that liminal tumors had the lowest uptake value (12).

The high cost and limited availability of [^{18}F]FDG PET/CT, given the high prevalence of breast cancer, presents additional challenges. Despite these limitations, this imaging modality is valuable for the accurate staging of patients with newly diagnosed breast cancer. The detection of unsuspected and distant lymph node metastases can significantly impact staging, treatment planning, and prognosis (13).

Several studies have demonstrated the value of [^{18}F]FDG PET/CT in breast cancer. The unavailability of evidence for [^{18}F]FDG PET/CT in TNBC motivated this study, the aim of which was to determine the predictive values of [^{18}F]FDG PET/CT metabolic parameters in the occurrence of metastases in patients diagnosed with triple-negative breast cancer (TNBC)

Material and Methods

This descriptive and analytical cross-sectional study included forty-eight (48) patients in the nuclear medicine department over 2 years (January 2023 - December 2024).

Patients who received treatment in the nuclear medicine department during the study period were targeted. This study focused on patients diagnosed with breast cancer who met the selection criteria. All patients diagnosed with TNBC who underwent [^{18}F]FDG PET/CT as part of an extension workup were included.

Patients diagnosed with triple-negative breast cancer who received radical, systemic, and local treatment were excluded from the study.

Image acquisition and analysis were performed using a SIEMENS Biograph TruePoint PET CT. The patients fasted (6 h) before the examination. Blood glucose levels were determined and monitored at < 7 mmol/L (< 2 mmol/L in people with diabetes) before the administration of [^{18}F]FDG (3 MBq/kg). The protocol included an initial 6-slice helical CT acquisition (acquisition parameters: peak X-ray tube voltage of 110 kVp, 95 mA, 1.75:1 pitch, slice thickness of 5 mm, and rotation speed of 1.5 seconds per rotation). PET images from the cranial vault to mid-thigh were acquired in three-dimensional non-apnea mode with an acquisition time of 3 min per bed position (for a total of seven bed positions), each covering 15 cm, with an axial sampling thickness of 3 mm per slice. PET/CT images were reconstructed using an iterative attenuation correction reconstruction method derived from CT using subset expectation maximization software (eight subsets, four iterations).

Merged PET, CT, and PET/CT results were interpreted by two higher-education professors who were specialists in nuclear medicine with over ten years (10 years) of experience.

Metabolic parameters, including the maximum standardized uptake value (SUV_{max}) and metabolic tumor volume (MTV), were obtained using the workstation's semi-quantitative software.

SUV_{max} is a semi-quantitative indicator used in PET/CT tumor diagnosis that reflects the highest local FDG metabolic activity of a lesion. MTV is a semi-quantitative indicator used in PET/CT tumor diagnosis that reflects tumor burden.

The analysis did not include total lesion glycolysis (TLG) because it does not represent a truly independent parameter. It is defined as the product of SUVmean and MTV, making it a composite variable derived from two available measurements. This would have introduced a risk of redundancy and statistical collinearity without providing any significant added value in interpretation.

Therefore, we chose to evaluate SUVmax, which reflects the maximum intensity of metabolic activity, and MTV, which

indicates the volumetric tumor burden, separately, considering that this approach allows for a more robust and methodologically consistent analysis. Volumetric segmentation of the lesions was performed semi-automatically by applying a threshold of 40% of the SUVmax, per the commonly adopted recommendations in the literature for defining the metabolically active tumor volume (MTV).

Data were entered using the Kobo Collect application, exported as an Excel file, and analyzed using SPSS version 2.1. The Shapiro-Wilk test was used to assess the normality of the distribution of quantitative variables. Headcounts and percentages were used to describe categorical variables, and means and standard deviations were used for quantitative variables with normal distribution. Medians (quartiles) were used for quantitative variables with skewed distributions. The chi-square test was used to study the association between the occurrence of metastases and PET/CT metabolic parameters (SUV_{max} and MTV) and the specific clinical variables. The significance level was set at $p < 0.05$. The results are presented in tables.

Results

Forty-eight patients were enrolled, with a mean age of 49.8 ± 12.6 years [31-72 years] (Table 1). All patients were women. The tumor was unilateral in 93.7% of patients and multifocal in 8.3% of patients (Table 1). The predominant histological type was invasive ductal carcinoma (81,2%) (Table 1). The mean tumor size was 38.5 mm, with a mean SUV_{max} of 7.4 and mean MTV of 82.4 ± 145.4 cm^3 (Table 2). Over 20% of the patients had metastatic disease. The most frequent secondary sites were the bone (16.7%) and lung (10.4%) (Table 2). PET/CT secondarily restaged all patients after the initial CT (Table 3). Analysis of the influence of specific clinical and metabolic variables on the occurrence of metastases showed that age > 50 years, tumor size ≥ 20 mm, bilateral involvement, presence of multifocal focus, SUVmax ≥ 5, and MTV ≥ 50 cm^3were associated with the occurrence of metastases in patients (Table 4).

Figures 1 and 2. PET images of a patient referred for staging triple-negative breast cancer (TNBC) Maximum Intensity Projection (MIP) image showing heterogeneous [^{18}F]FDG uptake throughout the explored volume (Figure 1). Bilateral [^{18}F]FDG uptake involving both breasts, more pronounced on the right side (A). Bilateral axillary (B), internal mammary, and mediastinal lymphadenopathies (C) and multiple hepatic nodules (D) were consistent with secondary metastatic disease (Figure 2).

Table 1. Distribution of patients according to epidemiological, clinical, and histological characteristics.

	Numbers	Percentages
Ages		
≤ 50 ans	31	64,6
> 50 ans	17	35,4
Mean Age : 42,8 ± 12,6 ans [31-72 ans]		
Involved breast		
Unilateral	45	93,7
Bilateral	3	6,3
Focus		
Uni focal	44	91,7
Multifocal	4	8,3
Histological types		
IDC	39	81,2
ILC	9	18,8

IDC : Invasive ductal carcinoma, ILC : Invasive lobular carcinoma

Table 2. Characteristics of PET/CT patients

	Numbers	Percentages
SUVmax		
≥ 5	39	81,3
< 5	9	18,7
Mean SUVmax : 7,4		
MTV		
≥ 50 cm3	32	66,7
< 50 cm3	16	33,3
Mean MTV: 82,4 ± 145,4 cm^3		
Tumor size		
≥ 20 mm	37	77,1
< 20 mm	11	22,9
Mean Size : 38,5 mm		
Distant metastais		
Oui	10	20,8
Non	38	79,2
Location		
Bone	8	16,7
Lungs	5	10,4
Digestive	2	4,2

SUVmax : maximum standardized uptake value, MTV : Metabolic tumor volume,

Table 3. Distribution of patients according to TNM staging on CT and PET/CT

	TDM (%)	PET/CT [^{18} F] FDG (%)
T1N0M0	10,4	2,1
T1N1M0	25	33,3
T2N2M0	33,3	29,2
T2N3M1	18,7	16,7
T3N3M0	12,5	14,6
T3N3M1	-	4,2
Total	**100**	**100**

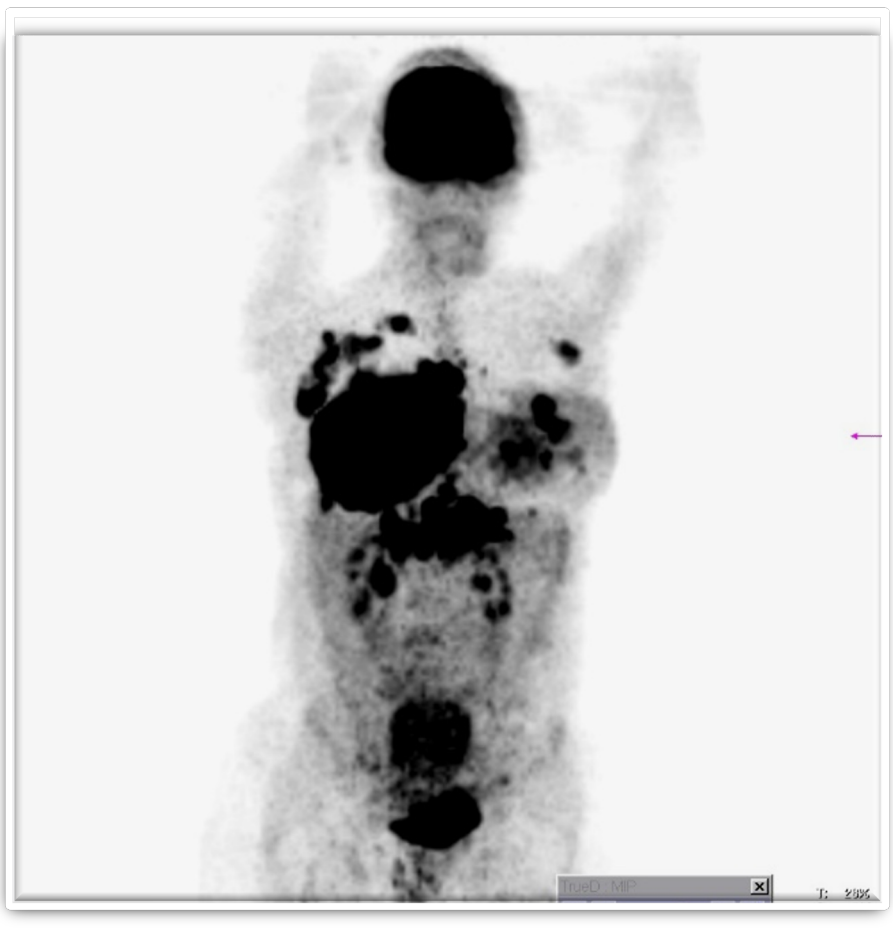

Figure 1. *Maximum Intensity Projection image of a patient with triple-negative breast cancer showing heterogeneous [^{18}F]FDG uptake throughout the explored volume.*

Table 4. Association between patient characteristics and occurrence of metastases

	M+	M-	P value
Age			<0,0001
≤ 50 years	38,5	72,2	
> 50 years	61,5	27,8	
Breast affected			<0,0001
Unilateral	27,8	52,9	
Bilateral	72,2	47,1	
Homes			0,003
Uni focal	43,5	68,4	
Multifocal	56,5	31,6	
Histological types			<0,0001
IDC	76	18,6	
ILC	24	81,4	
SUVmax			0,0006
≥ 5	72,8	22,9	
< 5	27,2	77,1	
MTV			<0,0001
≥ 50 cm3	85,7	33,3	
< 50 cm3	14,3	66,7	
Tumor size			<0,0001
≥ 20 mm	69,5	10,8	
< 20 mm	30,5	89,2	

IDC : Invasive ductal carcinoma, ILC : Invasive lobular carcinoma, SUVmax : maximum standardized uptake value, MTV : Metabolic tumor volume

Figures 1 and 2. PET images of a patient referred for staging triple-negative breast cancer (TNBC) Maximum Intensity Projection (MIP) image showing heterogeneous [^{18}F]FDG uptake throughout the explored volume (Figure 1).

Bilateral [^{18}F]FDG uptake involving both breasts, more pronounced on the right side (A). Bilateral axillary (B), internal mammary, and mediastinal lymphadenopathies (C) and multiple hepatic nodules (D) were consistent with secondary metastatic disease (Figure 2).

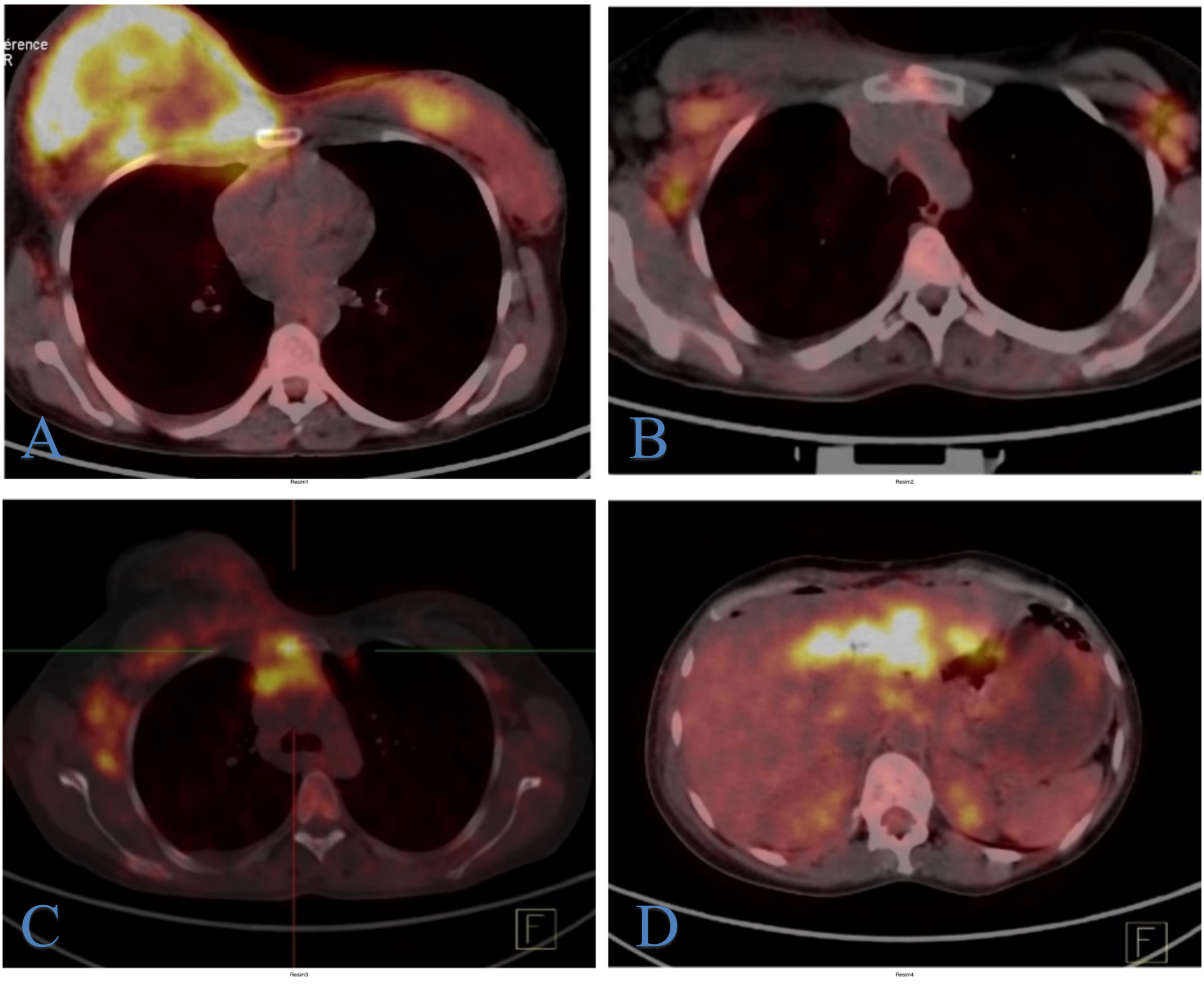

Figure 2. *Axial PET/CT images demonstrate bilateral [^{18}F]FDG uptake involving both breasts, more pronounced on the right side (SUVmax : 8,8 ; MTV : 521cm^3) (A). Bilateral axillary (B), internal mammary and mediastinal lymph node involvement (C), and multiple hepatic nodules (D) were observed, consistent with secondary metastatic disease.*

Discussion

A growing number of studies have investigated whether the metabolic parameters of [18F]FDG PET/CT can predict the prognosis of various types of cancer. Data from the literature suggest that [18F]FDG uptake may correlate with the aggressive behavior of breast tumors (14). Therefore, during the initial work-up of the disease, [18F]FDG PET/CT may significantly modify the staging performed on CT (14). Our study results showed that SUVmax and metabolic tumor volume were associated with the occurrence of metastases in patients diagnosed with TNBC. Several studies have reported similar results (15,16). These results could be explained by the fact that metabolic parameters on PET/CT are closely related to patient prognosis, but also by the fact that these parameters may indirectly reflect the biological behavior of the tumor (17). Moreover, metabolic parameters significantly affect breast cancer prognosis (15,16). One study (17) showed that a high MTV leads to a higher risk of adverse events. The results of Kim et al. contrast with those of our study, supporting the argument that metabolic parameters are not associated with adverse events (19). This difference in results could be influenced by several factors (machine type, acquisition and reconstruction protocol, lesion size, and patient movements).

SUVmax and MTV are the PET parameters most widely used clinically for patient prognosis and follow-up purposes. SUVmax is considered a variable parameter, resulting in the product of metabolic activity normalized to the patient's weight and blood glucose levels. It remains the benchmark for quantitatively characterizing the consequences of PET/CT. A mean SUVmax of 7.4 was reported in our patients. The mean SUVmax found in our

study was lower than that reported by Clermont (15). This difference may be explained by the fact that SUVmax is influenced by numerous factors, which may be machine-related (type of device, type of reconstruction, spatial resolution, poor correction) or patient-related (weight, insulin, and corticosteroid intake). Despite its use and validation, it has limitations and is subject to measurement errors owing to the partial volume effect. It also reflects only the most avid part of the lesion, lacking complete information on the tumor biology.

Pak K. et al (20) showed in their study that patients with high MTV have a higher risk of adverse events. Similar to their research, we found that a high MTV was a predictive factor for the occurrence of metastases in our patients.

Invasive ductal carcinomas generally show higher [^{18}F]FDG uptake and can be assessed using metabolic imaging (20). Invasive ductal carcinoma was the most common histological type in this study. This result aligns with the literature, where this histological type represents over 80% of the histological types of triple-negative breast cancers (20).

This was a single-center retrospective study; therefore, its statistical validity may be biased. Therefore, caution should be exercised when generalizing these results to other populations or regions, as variations in demographics, healthcare systems, and genetic profiles may be present. Larger-scale studies should be conducted in different settings to further validate our research findings. In addition, integrating biological blood parameters with metabolic parameters from [^{18}F]FDG PET/CT could help propose more rigorous predictive methods.

Conclusion

Triple-negative breast cancer is an aggressive FDG-avid histological subtype. Our study showed an association between PET/CT metabolic parameters and the occurrence of metastases in patients with TNBC. It also demonstrated the value of PET/CT in restaging patients compared with CT. PET/CT has prognostic value in predicting the occurrence of metastases in patients diagnosed with TNBC.

Ethical Considerations: Since this was a retrospective study based exclusively on the analysis of existing clinical and imaging data, without any additional intervention on patients or collection of new data, approval from an ethics committee was not required. The data were processed anonymously according to the principles of the Declaration of Helsinki to ensure patient confidentiality and privacy.

Informed Consent: Informed consent was obtained from all the participants included in the study.

Conflict of Interest: The authors declare that there are no conflicts of interest in this study.

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Author Contributions

Abdel Amide Gbadamassi; Conceptualization, Investigation, Data curation, Writing – original draft. **Halima Batani**; Formal analysis, Visualization. **Hafsa Bensimimou**; Formal analysis, Visualization. **Zakaria Ouassafrar**; Methodology, Supervision, Writing – review & editing. **Amal Guensi;** Supervision, Project administration, Validation

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