ORIGINAL ARTICLE

Comparison of serum NEDD-9, CA 15-3, and CEA levels and PET metabolic parameters in breast cancer patients with 18 F-FDG PET / CT

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SUMMARY

OBJECTIVE: *Analyze the over expression of neural precursor cell expressed developmentally down-regulated protein 9 (NEDD-9) deregulated associated with a poor prognosis in various carcinomas. Our objective was to investigate the relationship between the levels of NEDD-9, CA 15-3, and CEA and PET (SUVmax, MTV40, TLG40) with the clinical parameters of patients with breast cancer (BC).*

METHODS: *One hundred and eleven patients (82 BC patients who underwent 18F-FDG PET/CT and 29 healthy controls) were evaluated. SUVmax, MTV, and TLG of the primary tumor were compared with the molecular and histopathological subtypes. 18F-FDG, MTV, and TLG were evaluated based on the clinical data, i.e., nodal involvement, distant metastasis, ER and PR status, Ki-67, serum levels of NEDD-9, CA15-3, and CEA. We compared the NEDD-9 in the BC and healthy control groups.*

RESULTS: *The mean ± SD of SUVmax in the 82 patients was 13.0 ± 8.6. A statistically significant relationship (p = 0.022) was found between the molecular subtypes and 18F-FDG uptake. The relationship between 18F-FDG uptake and TLG measured in patients <50 years, ER-PR negativity, and HER2 positivity were statistically significant (p=0.015, 0.007, 0.046, and 0.001, respectively). MTV40, TLG40, and CA 15-3 in metastatic patients were statistically significant (p=0.004, 0.005, and 0.003, respectively). NEDD-9 in the BC group was significantly higher than in the healthy group (p=0.017). There was a positive correlation between SUVmax and Ki67 and CA 15-3; MTV40 and CEA; CA 15-3, CEA, SUVmax, and MTV40; a negative correlation was found between CEA, TLG40, and age.*

CONCLUSION: *The use of SUVmax, MTV40, and TLG40 parameters with NEDD-9 and tumor markers has been shown to provide a high diagnostic, predictive, and prognostic value for the management of BC. This is considered to be the basis of interventions focused on the treatment objectives related to NEDD-9.*

KEYWORDS: *Breast neoplasms. Fluorodeoxyglucose F18. Adaptor proteins, signal-transducing. Carcinoembryonic antigen.*

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INTRODUCTION

The Cas protein family plays a role in the management of cell survival, proliferation, and migration.[1] The "Neural precursor cell expressed developmental downregulated 9" (NEDD-9) initiates a process resulting in differentiation, proliferation, and migration by revealing the potential tumorigenesis of cells.[2] NEDD-9 overexpression is associated with poor prognosis, shortened survival in breast carcinomas (BC) and many other types of cancer. NEDD-9 overexpression has been reported to be strongly correlated with cancer metastasis due to its regulatory property on cell migration.[3-5]

Carcinoembryonic antigens (CEA) and carbohydrate antigens 15-3 (CA 15-3) are used in BC follow-up; however, their prognostic value is limited regarding its sensitivity and specificity.[6] The American Society of Clinical Oncology does not recommend them for the diagnosis, screening, staging, and treatment follow-up of BC.[7] ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is recommended for the staging, prognosis, and follow-up of BC.[8] In several studies, the maximum standardized uptake (SUVmax) levels, tumor characteristics and total metabolic tumor volume (MTV), lesion glycolysis (TLG) have demonstrated potential prognostic value.[9,10]

We aim to investigate the potential predictive, diagnostic, prognostic, and clinical value of NEDD-9, CA15-3, and CEA, along with PET parameters (SUVmax, MTV, TLG) in BC.

METHODS

Patients

We included eighty-two BC patients who underwent ^{18}F-FDG PET/CT and 29 healthy subjects, with a total 111 subjects enrolled in this study. For our prospective study, the local ethics committee approval has obtained (2018/1380). Verbal and written informed consent was obtained from patients.

Histological Analysis

BC histopathological analysis was performed on tissue samples prior to ^{18}F-FDG PET/CT or breast-conserving surgery following ^{18}F-FDG PET/CT. The Scarff Bloom Richardson (SBR) classification system was used for staging. Receptors found positive for ER and PR showed 10% or more in immunohistochemical staining in positive tumor cells.

Scoring for HER2;

- Score 0: negative immunostaining,
- Score 1: poor staining/staining lesser than 30%,
- Score 2: Uniform/complete membranous staining, even if weak staining,
- Score 3: Uniform staining of at least 30%.

Cut-off value Ki-67 determined at 15% by using immunohistochemical and gene expression profiling methods for the differentiation of Luminal subtypes in routine practice and <15% was considered low, and ≥ 15% high.[11]

Molecular subgroups;

1. Luminal A: ER (+) and/or PR (+), HER2 (-) & Low Ki-67 (<15%),
2. Luminal B: ER (+) and/or PR (+), HER2 (+), or HER2 (-) & High Ki-67 (≥15%),
3. Triple negative/basal: ER (-), PR (-), HER2 (-),
4. HER2 Type: ER (-), PR (-), HER2 (+).

18F-FDG PET/CT Imaging

Glucose levels lower than 150 mg/dl at least six hours of fasting were admitted. 3.7-5.3 MBq/kg ^{18}F-FDG IV injection was administered. After 45 to 60 minutes after IV injection, imaging was obtained from the vertex-mid thigh (mCT 20 ultra HD LSO PET/CT, Siemens Molecular Imaging, Hoffmann Estates, Illinois, USA).

Maximum standard uptake (SUVmax) was calculated by "volume-of-interest (VOI)" on the most active-looking slice of ^{18}F-FDG positive lesions. SUVmax was calculated according to the formula: Maximum activity inside the ROI (MBq/gr), injected ^{18}F-FDG dosage (MBq/kg body mass). Metabolic tumor volume (MTV40) and tumor lesion glucose (TLG40) was calculated by the standard methods.

Based on the PET/CT parameters, histopathological-molecular characteristics, receptor properties, nodal involvement and distant metastasis, NEDD-9 was evaluated and reported along with CA15-3 and CEA. The NEDD-9 expression was compared between the BC and healthy control groups.

Biochemical analysis

CEA and CA 15-3 measured by electrochemiluminescence, Roche, Cobas 6000 model (Tokyo, Japan) immunological autoanalyzer system with chemiluminescent test kits. NEDD-9 expression obtained by enzyme-linked immunosorbent assay anti-NEDD-9 antibodies (INOVA, San Diego, Calif., USA).

Statistical analysis

Data were analyzed by SPSS software (v21.0; IBM, Armonk, NY, USA). The normalization of data distribution was evaluated by the Kolmogorov-Smirnov test. The Mann Whitney and Kruskal Wallis tests were used for comparing the variables; the correlation analysis was evaluated by the Pearson test. The Chi-Square test was used to evaluate categorizable variables. Results were considered statistically significant when P <0.05.

RESULTS

The Mean±SD age was 55.0±12.5 years in the BC group, and 50.3±11.3 years in the control group (p = 0.078). A total of 51.2% in the BC group and 44.8% in the control group were in the menopause period (p = 0.554). ^{18}F-FDG uptake was observed in all tumors (n = 82). The mean SUVmax was 13.0 ± 8.6 (median= 11.6, range=2.1-48.4). The molecular subtype classification was as follows: 13 (15.9%) identified luminal A; 50 (61.0%) luminal B; 10 (12.2%) triple-negative; and 9 (11.0%) HER2 type. The relationship between ^{18}F-FDG uptake and molecular subtype classification was evaluated; the mean SUVmax in luminal A was 9.4±6.5, 12.1±6.9 in luminal B, 16.7±12.9 in triple-negative, and 19.2 ± 10.4 in the HER2 type. A statistically significant relationship was found between the molecular subtypes and SUVmax (p = 0.022).

Invasive ductal carcinoma was in found 73.2% (n = 60), invasive lobular carcinoma in 9.8% (n = 8), mucinous in 6.1% (n = 5), apocrine in 4.9% (n = 4), micropapillary in 3.7% (n = 3), neuroendocrine in 1.2% (n = 1), and mixed type in 1.2% (n= 1). No statistically significant difference was found between histopathological types and ^{18}F-FDG uptake.

The clinical features of patients were evaluated according to 18F-FDG uptake, MTV40, and TLG40. The mean±SD of TLG40 (244.1 ± 444.3) in the group below 50 years (n = 32) was not found to be significantly higher than the mean±SD of TLG40 (122.3±276.5) in those older than 50 years (n = 50) (p = 0.015). A total of 76.8% (n = 63) of tumors were ER(+), 61.0% (n = 50) were PR(+), and 20.7% (n=17) were HER2(+). 18F-FDG uptake was associated with negative ER-PR and positive HER2; the association was statistically significant (p = 0.007, 0.046, and 0.001, respectively). Ki-67 expression was high (≥ 15%) in 70 cases (85.4%) and low (<15%) in 12 cases (14.6%). SUVmax, MTV, and TLG40 did not show any statistically significant difference compared to Ki-67 (Table 1).

A total of 65.9% of patients (n= 54) presented LN involvement but there was no correlation with

TABLE 1. MEAN±SD SUVMAX, MTV40, TLG40, NEDD-9, CA 15-3 AND CEA VALUES CHANGE ACCORDING TO THE CLINICAL AND HISTOPATHOLOGICAL CHARACTERISTICS OF THE PATIENTS

	n (%)	SUVmax (Mean±SD)	p-value	MTV40 (Mean±SD)	p-value	TLG40 (Mean±SD)	p-value	NEDD-9 (ng/ml) (Mean±SD)	p-value	CA 15-3 (U/ml) (Mean±SD)	p-value	CEA (ng/ml) (Mean±SD)	p-value
Age													
< 50 ≥ 50	32 (39.0%) 50 (61.0%)	14.4±8.7 12.2±8.4	0.201	37.6±67.9 14.7±17.8	0.126	244.1±444.3 122.3±276.5	0.015*	1.8±1.3 2.2±1.9	0.467	22.6±35.9 22.1±23.2	0.618	13.28±36.06 5.18±16.22	0.768
ER													
Negative Positive	19 (23.2%) 63 (76.8%)	17.9±11.6 11.6±6.9	0.007*	22.2±37.3 24.0±48.1	0.725	247.1±532.8 146.6±281.1	0.054	2.3±1.7 2.0±1.7	0.323	26.3±29.7 21.1±28.4	0.302	1.8±1.2 10.3±29.3	0.031*
PR													
Negative Positive	32 (39.0%) 50 (61.0%)	15.5±10.4 11.5±6.8	0.046*	19.2±30.2 26.5±53.4	0.736	183.6±416.0 161.1±312.4	0.151	2.3±2.1 1.9±1.4	0.714	23.2±23.8 21.7±31.5	0.172	5.8±20.1 9.9±29.2	0.084
HER2													
Negative Positive	65 (79.3%) 17 (20.7%)	11.7±8.2 18.0±8.4	0.001*	25.2±49.9 17.5±23.4	0.868	166.0±383.2 184.8±217.2	0.124	2.1±1.8 1.8±1.3	0.762	20.5±21. 0 29.3±48.0	0.331	5.5±15.1 19.2±48.3	0.556
Ki-67													
< 15% ≥ 15%	12 (14.6%) 70 (85.4%)	9.7±7.2 13.6±8.7	0.117	18.6±19.2 24.5±48.8	0.641	135.2±163.4 175.8±377.7	0.582	1.6±1.3 2.1±1.7	0.265	25.3±25.0 21.8±29.3	0.491	15.1±33.4 7.2±24.5	0.546
Nodal involvement													
Absent Present	28 (34.1%) 54 (65.9%)	11.3±5.5 14.0±9.7	0.423	14.9±14.6 28.1±54.9	0.766	112.6±121.5 199.5±426.0	0.571	2.3±2.0 1.9±1.5	0.363	20.3±18.9 23.3±32.6	0.938	4.2±7.5 10.5±31.4	0.880
Organ metastasis													
Absent Present	55 (67.1%) 14 (17.1%)	12.8±8.8 16.3±9.7	0.148	18.1±40.7 53.2±69.7	0.004*	100.5±125.1 504.1±749.6	0.005*	2.2±1.8 1.5±1.3	0.152	17.9±17.7 41.3±54.1	0.003*	3.3±5.6 25.5±52.2	0.052*

*= p<0.05 statistically significant.

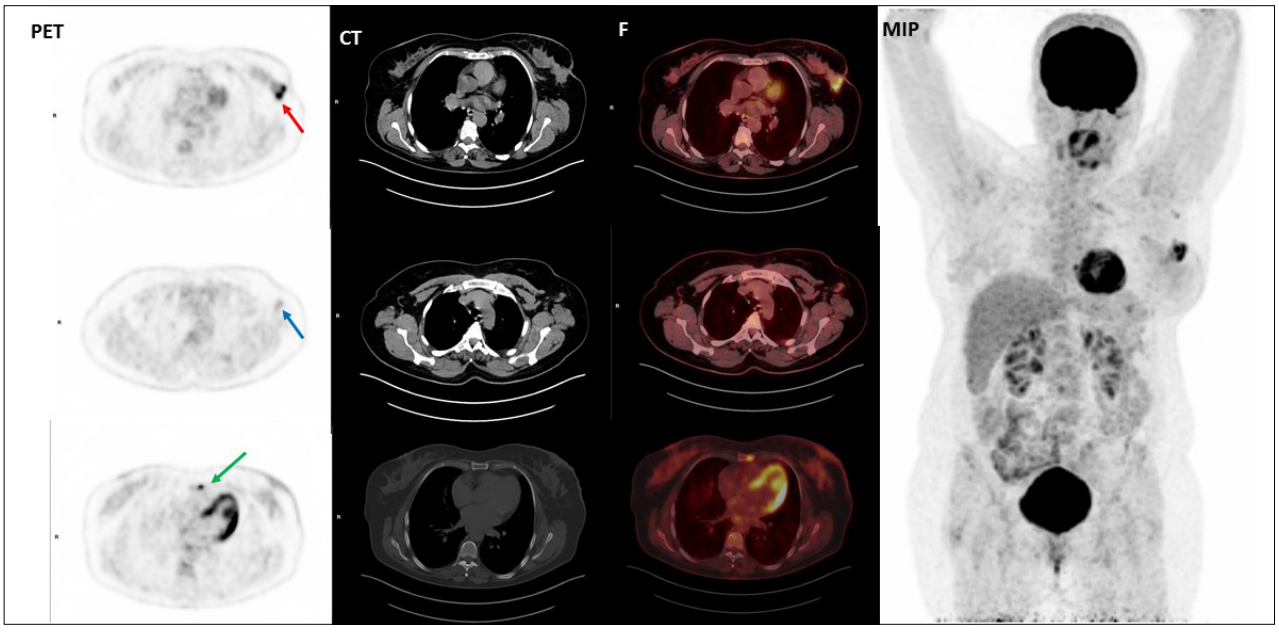
SUVmax, MTV40, and TLG40 (Table 1). Distant metastasis detected in 14 cases (17%). In 13.4% (n= 11) there was bone-bone marrow metastasis (Figure 1), in 1.2% (n= 1) multiple variable metastasis, in 1.2% (n= 1) liver, and in 1.2% (n = 1) lung. No statistically significant difference was found (p= 0.148) in SUVmax between groups with/without distant metastasis; MTV40 and TLG40 in patients with distant metastasis were significantly higher than in those without it (p-values= 0.004 and 0.005, respectively) (Table1). The mean serum NEDD-9 was 2.05 ± 1.69 ng/ml in BC and 1.44 ± 0.88 ng/ml in healthy controls. NEDD-9 was significantly higher in BC compared to the healthy controls (p= 0.017). The clinical features of BC were evaluated according to the NEDD-9, CA 15-3, and CEA values; no statistically significant relationship between NEDD-9 and receptor status (ER, PR, HER2), Ki67, LN, or distant metastasis was found (p> 0.05). CA 15-3 in metastatic BC was found to be statistically significantly higher than in those without organ metastasis (p = 0.003) (Table 1).

The correlations between SUVmax, MTV40, and TLG40 and NEDD-9, CA 15-3, and CEA are presented in Table 2. There was a statistically significant correlation between SUVmax and Ki-67, CA 15-3, and a negative correlation between SUVmax and CEA. A statistically significant correlation was found between MTV40 and CEA. A statistically significant negative correlation was found between TLG40 and mean age, and a positive correlation between CA 15-3, CEA, SUVmax, and MTV.

DISCUSSION

The oncogenic characteristics associated with NEDD-9 have been highlighted in many studies. The metastatic inducing effect of NEDD-9 is present in many cancers, including BC.[12,13] ^{18}F-FDG PET/CT has been shown to provide useful BC staging and follow-up. In BC, there are limited data regarding the combination of NEDD-9, PET/CT parameters for combined diagnostic and prognostic potentials. Ueda et al.[14] evaluated 152 BC cases preoperatively with ^{18}F-FDG PET/CT; they analyzed high SUVmax with tumor size, grade, nuclear type, LN metastasis, histopathological subtype, negative ER - PR and positive HER2 expression and their statistically significant correlation with poor prognosis in BC. Studies have shown ^{18}F-FDG uptake in BC might be statistically different according to the histopathological subtype, molecular grading, ER - PR receptor expression, LN involvement, and distant metastasis. ^{18}F-FDG PET/CT provides insufficient benefits, especially in LN and distant organ metastasis.[8,15] A meta-analysis of 23 studies

FIGURE 1. 53 YEARS OLD F, LEFT BREAST LOCALISED ER(-),PR(-),HER2(-) TRIPLE NEGATIVE (LUMINAL C) INVASIVE DUCTAL TYPE CARCINOMA (PET: POSITRON EMISSION TOMOGRAPHY, CT: COMPUTED TOMOGRAPHY, F: FUSION, MIP: MAXIMUM INTENSITY PROJECTION), KI 67: 50%, PRIMARY TUMOR AXIAL DIAMETER: 2.61 cm, PRIMARY TUMOR SUV MAX: 9.24, PRIMARY TUMOR SUVMEAN: 5.41, PRIMARY TUMOR MTV40(%): 6.62, TLG40: 35.8, AXILLARY LN METASTASIS(+),BONE METASTASIS(+), SERUM NEDD 9 LEVEL: 6.954 ng/ml,SERUM CA15.3 LEVEL:69.8 (U/ml), SERUM CEA LEVEL:2.59 (ng/ml).



published by Liu et al.[15] concluded that the ^{18}F-FDG PET/CT method has low metastatic sensitivity but high specificity, whereas conventional methods such as MRI were more effective in detecting metastasis. Robertson et al.[16] emphasized that 18F-FDG uptake has very low sensitivity for LN detection.

In our study, statistically significant differences were found between the molecular subtypes and SUVmax, and ER - PR negativity, HER2 positivity, and increased 18F-FDG uptake were significantly correlated. However, we did not find statistical significance in SUVmax between non-metastatic and LN involvement/distant metastatic BC.

MTV and TLG parameters from ^{18}F-FDG PET/CT provide information not only on the severity of 18F-FDG uptake but the volume and metabolic activity of the tumor. Son et al.[17] concluded that MTV is a useful prognostic factor for metastatic BC. Marinelli et al.[18] found the MTV of 47 triple-negative BC (TNBC) patients, MTV is a strong prognostic factor for TNBC. Based on the study of 135 IDC patients, Yoo et al.[19] concluded that TLG is predictive of ALN metastasis. Based on 85 BC patients, Koizumi et al.[20] reported that TLG is predictive of bone metastasis detection. In our study, we did not find any statistical correlation between SUVmax and distant organ metastasis; but the MTV40 and TLG40 calculated in distant metastatic patients were significantly higher than those without metastasis.

NEDD-9 overexpression revealed a complex signaling mechanism that provides a basis for migration, invasion, morphological transformation and proliferation, number of aggressive tumor characteristics, and metastasis-related studies in different tumors.[3,4] Kong et al.[5] noted that NEDD-9 expression was increased in TNBC patients. Štajduhar et al.[21] showed, based on 40 non-metastatic tissue samples and 40 metastatic samples from BC, increased NEDD-9 expression in ALN metastasis. Hata et al.[22] reported a high NEDD-9 expression in bone metastatic BC. Loskutov et al.[23] noted that NEDD-9 inhibition significantly reduced tumor growth and metastasis in BC xenograft models. In a meta-analysis of 13 studies, 1179 cases and 493 controls, Fu and Li[24] concluded that CA15-3 and CEA are potential markers for BC and can be used for tumor staging and follow-up. In many published data, these were reported to be beneficial in poor prognosis, metastasis, and treatment follow-up.[25] In our study, NEDD-9 was found to be statistically significantly higher in BC compared to healthy controls. The CA 15-3 of a distant metastatic group was significantly higher than in one without metastasis. A statistically significant positive correlation was found between SUVmax and CA 15-3; a negative correlation was found between CEA and SUVmax. A statistically significant correlation was found between MTV and CEA. A statistically significant correlation was found between TLG and CA 15-3, CEA, SUVmax, and MTV.

TABLE 2. CORRELATION ANALYSIS AMONG WITH CLINICAL, PATHOLOGICAL, BIOCHEMICAL FEATURES AND PET PARAMETERS IN PATIENTS GROUP

	SUVmax	MTV40	TLG40			
	r	p	R	p	R	P
Age						
	- 0.169	0.128	- 0.120	0.282	- 0.227	0.040*
LN diameter						
	0.059	0.676	0.140	0.317	0.185	0.185
Ki-67						
	0.285	0.010*	- 0.009	0.937	0.154	0.168
NEDD-9						
	- 0.020	0.859	- 0.127	0.255	- 0.141	0.206
CA 15-3						
	0.299	0.006*	0.200	0.071	0.321	0.003*
CEA						
	- 0.021	0.849	0.301	0.006*	0.281	0.010*
SUVmax						
	-	-	0.128	0.250	0.512	0.000*
MTV40						
	-	-	-	-	0.853	0.000*

*= p<0.05 statistically significant.

Increases in NEDD-9 expression in BC and SUVmax are due to significant changes in molecular subtypes and receptor status; the relationship between metastasis and MTV40 and TLG40, using NEDD-9 and ^{18}F-FDG PET/CT metabolic parameters together, can contribute to BC staging. The correlation of CA 15-3 and CEA with ^{18}F-FDG PET/CT metabolic parameters may provide diagnostic, predictive, and prognostic value. We conclude that the use of SUVmax, MTV40, and TLG40 in combination with NEDD-9 and tumor markers will enhance BC management and provide a basis for NEDD-9-related treatment and target-oriented interventions.

Conflicts of interest

None.

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None.

Author contribution form

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Idea/concept	40%	20%	10%	5%	5%	5%	5%	10%
Design	30%	30%	10%	5%	5%	5%	5%	10%
Check	20%	20%	20%	5%	5%	5%	5%	20%
Source and fund providing	30%	30%	10%	5%	5%	5%	5%	10%
Data collecting and/or processing	30%	20%	20%	5%	5%	5%	5%	10%
Analysis-comment	30%	30%	10%	5%	5%	5%	5%	10%
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RESUMO

OBJETIVO: *Analisar a associação da superrexpressão das células NEDD-9 ao prognóstico negativo em vários tipos de carcinoma. Nosso objetivo foi investigar a relação entre os níveis de NEDD-9, CA 15-3 e CEA e PET (SUVmax, MTV40, TLG) e os parâmetros clínicos em pacientes com câncer de mama (CM).*

MÉTODOS: *Cento e onze pacientes (82 pacientes de CM submetidos a 18F-FDG PET/TC e 29 controles saudáveis) foram avaliados. SUVmax, MTV, e TLG do tumor primário foram comparados nos subtipos molecular e histopatológico. A captação de 18F-FDG, MTV, e TLG foi avaliada com base em dados clínicos (envolvimento nodal, metástase distante, status de ER e PR, Ki-67, níveis séricos de NEDD-9, CA15-3 e CEA). Foi comparada a NEDD-9 do grupo de CM e o controle saudável.*

RESULTADOS: *A média ± DP de SUVmax de 82 pacientes foi de 13,0 ± 8,6. Uma relação estatisticamente significativa (p=0,022) foi encontrada entre subtipos moleculares e captação de 18F-FDG. A relação entre captação de 18F-FDG e TLG medida em pacientes com idade <50 anos, ER-PR negativo e HER2 positivo foi estatisticamente significativa (p=0,015; 0,007; 0,046; e 0,001, respectivamente). MTV40, TLG40 e CA 15-3 em pacientes metastáticos foram estatisticamente significantes (p=0,004, 0,005 e 0,003, respectivamente). NEDD-9 no grupo BC foi significativamente maior do que no grupo saudável (p=0,017). Uma correlação positiva foi encontrada entre SUVmax e Ki67 e CA 15-3; MTV40 e CEA; CA 15-3, CEA, SUVmax e MTV40; uma correlação negativa foi encontrada entre CEA, TLG40 e idade.*

CONCLUSÃO: *O uso dos parâmetros SUVmax, MTV40 e TLG40 com NEDD-9 e marcadores tumorais demonstrou um alto valor diagnóstico, preditivo e prognóstico para o manejo do CM. Isso é considerado a base para intervenções focadas nos objetivos de tratamento relacionados às NEDD9.*

KEYWORDS: *Neoplasias da mama. Fluorodesoxiglicose F18. Proteínas adaptadoras, transdutoras de sinal. Antígeno carcinoembrionário.*

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