Original Paper, PET/CT.

The Relationship between ^{18}F-FDG PET/CT Volumetric Parameters and Pathological Factors in Metastatic Breast Cancer.

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ABSTRACT:

Objective: Assess correlation between the ^{18}F-FDG PET/CT volumetric parameters and clinico-pathological prognostic factors in metastatic breast cancer. **Methods:** In this prospective study we included 52 patients who underwent ^{18}F-FDG PET/CT with metastases to loco/regional lymph nodes, distant metastases were detected in 22 of them. The association of maximum standardized uptake value (SUVmax), mean standardized uptake value (SUV mean), metabolic tumor volume (MTV), tumor/liver uptake ratio (TLR) and total lesion glycolysis (TLG) of the loco/regional lymph nodes and distant metastases with clinico-pathological prognostic factors were assessed. **Results:** There were significant correlations between regional lymph nodes metastases SUVmax and SUV mean and tumor grade & N stage, while no significant correlation was found regarding the other parameters including focality of the primary tumor, histology, ER, PR, HER2, KI67, molecular subtype and M stage. On the other hand, regional lymph nodes metastases MTV, TLG and TLR, correlation was found regarding N stage only and no significant correlation was found regarding the other parameters. No significant correlations between volumetric parameters of bone metastases and clinic-pathological risk factors could be elicited.

Conclusion: Volumetric parameters of the metastatic loco-regional lymph nodes in breast cancer can reflect aggressiveness of the tumor, therefore can help in therapy planes, while this not found regarding bone metastases.

Key Words: Metastatic breast cancer, PET/CT, Pathological risk factors.

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INTRODUCTION:

Breast cancer prognosis refer to the probability of many important clinical outcomes as overall survival, disease free interval and quality of life over a determined period of time based on both clinico-pathological, molecular and genetic factors [(1)]. One of the strong prognostic factors in breast cancer is the axillary lymph node involvement [(2)].

The development of distant metastases from breast cancer is one of the primary reasons for mortality [(3)]. Larger tumor size and poor histo-pathological differentiation are considered prognostic markers of the metastatic potential of breast cancer [(4-5)].

Many studies stated that ^{18}F-FDG PET/CT volumetric parameters had an important role in staging, prognosis and predictive value in breast cancer patients [(6-7)].

We aim to study relationship between PET CT metabolic parameters for the metastatic regional lymph nodes & bones and the prognostic & predictive clinico-pathological variables so that it may be added as additional prognostic factors or as predictive factor that may be used in tailoring treatment plan.

PATIENTS AND METHODS:

This prospective analytical cross section study was performed in Nuclear Medicine unit at Kasr Al-Ainy Hospital (NEMROCK), Cairo University, enrolled 52 patients with pathologically proven breast carcinoma who had loco-regional lymph nodes metastases, addition distant metastases were found in 22 of them. The study protocol was approved by the Research Ethics Committee.

Patient eligibility criteria included female patients above 18 years old who have breast cancer. Exclusion criteria include patients less than 18 years old, patients who received neoadjuvant chemotherapy or radiotherapy, patients who received GM-CSF, patients with large FDG extravasation at the injection site, pregnancy, double malignancy, breast feeding and patients with chronic renal disease

Patients' medical records were reviewed to collect data on age, sex, weight, height, previous chemotherapy, radiotherapy or surgical interventions, diabetes status, use of medications (e.g. insulin) and serum creatinine level.

The injected ^{18}F-FDG dose and the time in between injection and subsequent imaging was also recorded. Patients' preparation was done according to the EANM procedure guidelines for FDG PET/CT tumor imaging: version 2.0 [8].

Patients were instructed to fast for at least 4 hours, minimize their physical activity on the day of the study, kept relaxed and warm and avoid talking and chewing too much to reduce accumulation of tracer into muscles of mastication and the larynx. Blood glucose level was checked (< 200 mg/dl).

The Scanner used was LYSO-based PET component with a 64-channel CT component. Imaging was performed at 45 to 65 min (mean 55 min) following intravenous injection of 4.62 MBq/kg (0.125 mCi/kg) ^{18}F-FDG. All patients underwent imaging in the arms-up position from the skull to the upper thigh's region. Patients were instructed to breathe shallowly during imaging.

Two trained nuclear medicine physicians interpreted the FDG PET/CT images.

For the visual and qualitative interpretation, it was considered as a positive result of visual analysis when focal FDG activity was found to be higher intensity than that of the surrounding tissues, which could not be related to benign or physiologic uptake.

Semi-quantitative and quantitate analysis using ROIs, the size of the ROIs was based roughly on the PET Response Criteria in Solid Tumors (PERCIST) criteria, which defines the background FDG activity through a 3-cm diameter spherical ROI in the right hepatic lobe. ROIs in the other organs were defined to be 1.2 cm in order to produce a 1 cm3-volume spherical ROI, based on the proposed size criteria for measuring pathologic lesions [9]. Maximum SUV (SUVmax), mean SUV (SUV mean), Tumor liver Ratio (TLR), Total lesion glycolysis (TLG (and Metabolic Tumor Volume (MTV) were calculated for the regional nodal deposits and distant metastases and normalized by total body weight.

Statistical analysis: Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparing categorical data, Chi square (□2)
test was performed.

Exact test was used instead when the expected frequency is less than 5. Correlations between quantitative variables were done using Spearman correlation coefficient. P-values less than 0.05 were considered as statistically significant.

RESULTS:

The overall study population included 52 female patients with breast cancer. Mean age was 49.05±9.23 with age range from 30 to 74 years who had loco-regional lymph nodes metastases, 32 (61.5%) patients in N1, 15 (28.9 %) in N2 and 5 (9.6 %) patients in N3. Distant metastases were found in 22 patients (42.3%) as follows: bone (25%), liver (9.6%), lung (5.8%) and others (1.9%) as summarized in ***Table (1)***. According to histo-pathological characteristics, most of the patients (49 of them) had IDC and 3 patients had lobular carcinoma. According to pathological grade, 41 were grade II, 11 were grade III. Other histopathological factors are provided in details in ***Table (1)***.

Table (1): Clinical characteristics of the patients and histo-pathological factors.

Age	**Mean±SD (49.05±9.23)**	**Range (30-74) years**	
		Number	**%**
Focality (Breast Tumor)	**Uni-focal**	27	51.9%
	Multifocal	25	48.1%
Distant Metastases	**Bone**	13	25%
	Liver	5	9.6%
	Lung	3	5.8%
	Others	1	1.9%
N stage	**1**	32	61.5%
	2	15	28.9%
	3	5	9.6%
AJCC staging	**2**	10	36.5%
	3	20	28.6%
	4	22	34.9%
Histology	**IDC**	49	94.2%
	Lobular	3	5.8%
Grade	**II**	41	79.7%
	III	11	20.3%
ER	**Negative**	9	17.9%
	Positive	43	82.1%
PR	**Negative**	15	28.6%
	Positive	37	71.4%

The volumetric parameters of ^{18}F-FDG PET/CT (SUVmax, SUV mean, MTV, TLG and TLR) for regional lymph node and distant metastases are illustrated in ***(Table 2)***.

Table (2): Parameters of F18 FDG PET CT for regional lymph nodes and distant metastases.

	Mean	Standard Deviation	Median	Minimum	Maximum
Loco-regional lymph nodes metastases					
SUVmax	8.53	5.74	5.80	1.02	25.50
SUV mean	4.46	2.80	3.40	0.07	12.15
MTV (Cm3)	7.54	14.58	3.19	0.61	68.74
TLG	43.33	114.58	13.65	0.06	691.53
TLR	3.44	2.24	2.94	0.60	8.95
Size of Largest (mm)	20.41	9.45	19.03	8.00	50.00
Bone metastases					
SUVmax	10.56	6.70	9.54	2.79	30.00
SUVmean	5.15	2.06	5.35	1.48	7.96
MTV (Cm3)	4.99	4.07	3.42	0.00	14.13
TLG	22.70	19.99	20.55	0.04	80.52
TLR	4.42	3.31	3.57	1.24	13.32
Other metastases					
SUVmax	10.43	6.78	9.14	2.30	21.70
SUVmean	5.37	3.02	4.46	1.70	12.04
MTV (Cm3)	93.35	298.66	4.68	0.02	1041.03
TLG	778.55	2552.38	19.58	0.05	8880.02
TLR	3.67	2.25	3.36	1.05	7.61
Size (mm)	35.32	39.88	26.00	1.20	156.00

Analysis of loco-regional lymph nodes:

There were significant correlations between SUVmax of loco-regional lymph nodes and tumor grade (p=0.011) where grade II had mean SUVmax of 7.25±5.7 compared to 11.38±5.06 in grade III. Also, high statistical correlation between SUVmax and N stage (p< 0.001) was found ***(Table 3)***.

No significant correlation was found regarding the other parameters including focality of the primary tumor (P value 0.985), histology (P value0.633), ER (P value 0.303), PR (P value 0.747), HER2 (P value 0.619), KI67 (P value 0.642), molecular subtype (P value 0.686) and M stage (P value 0.218). The same was found with SUV mean of the lymph nodes where significant correlations were found regarding tumor grade with mean SUV mean of 3.95±2.74 in grade II compared to 5.97±2.53 in grade III (p=0.009) and high statistical correlation between it and N stage.

Again, highest mean SUV mean value was found in N2 (p=0.002) ***(Table 3)***.

No significant correlation was found regarding the other parameters including focality of the primary tumor (P value 0.985), histology (P value 0.697), ER (P value 0.262), PR (P value 0.693), HER2 (P value 0.597), KI67 (P value 0.828), molecular subtype (P value 0.511) and M stage (P value 0.104).

The only positive correlation was that between MTV of loco-regional lymph nodes and N state with mean values of 3.37±3.28, 15.96±24.21 and 8.98±13 for stages N1, N2 and N3, respectively (p value= 0.04) ***(Table 3)***, while no significant correlation regarding the other parameters including focality of the primary tumor (P value 0.510) , histology (P value 0.436), grading (P value 0.583) ER(P value 0.282), PR(P value 0.349) , HER2 (P value 0.203), KI67(P value 0.514) , molecular subtype (P value 0.275), and M stage (P value 0.163) was found.

Similarly, a highly significant correlation between TLG of loco-regional lymph nodes and N stage was found (p= 0.001) ***(Table 3)*** as well as between TLR of loco-regional lymph nodes and N stage (p< 0.001) only ***(Table 3)***. No significant correlation was found regarding the other parameters including focality of the primary tumor (P value 0.658 and 0.751), histology (P value 0.798 and 0.826), grading (P value 0.076 and 0.266) ER(P value 1 and 0.371) , PR(P value 0.387 and 0.774), HER2 (P value 0.191 and 0.597), KI67(P value 0.555 and 0.877), molecular subtype (P value 0.330 and 0.389) and M stage (P value 0.115 and 0.183) and TLG & TLR of loco-regional lymph nodes respectively.

There were highly significant positive correlations between SUVmax, SUV mean, MTV, TLG and TLR of the regional lymph nodes with size of the largest lymph node (P value <0.001). However, no significant correlation could be detected between them and age of the patient

Table 3: The significant correlates between different volumetric parameters of loco-regional lymph nodes and clinico-pathological risk factors.

		SUVmax (regional LN metastases)					
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	**P value**
Grade	**II**	7.58	5.70	5.13	1.02	25.50	0.011
	III	11.38	5.06	12.43	4.42	19.07	
N stage	**1**	6.09	4.34	4.75	1.02	19.07	< 0.001
	2	13.07	5.76	13.09	2.60	25.50	
	3	10.52	5.31	11.42	4.80	17.52	
		SUVmean (regional LN metastases)					
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	**P value**
Grade	**II**	3.95	2.74	2.77	0.07	12.15	0.009
	III	5.97	2.53	5.86	2.51	10.35	
N stage	**1**	3.47	2.53	2.58	0.07	10.35	0.002
	2	6.37	2.59	5.54	2.20	12.15	
	3	5.02	2.33	5.12	2.59	7.54	
		MTV (regional LN metastases)					
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	**P value**
N stage	**1**	3.37	3.28	2.43	0.65	17.86	0.046
	2	15.96	24.21	5.12	0.61	68.74	
	3	8.98	13.00	4.22	0.98	32.08	
		TLG (regional LN metastases)					**p value**
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	
N stage	**1**	11.19	10.56	9.42	0.06	45.00	0.001
	2	110.87	197.62	31.79	1.33	691.53	
	3	46.38	66.74	19.99	2.55	164.24	
		TLR= (SUVmax LN/SUV mean liver)					**p value**
		Mean	**SD**	**Median**	**Minimum**	**Maximum**	
N stage	**1**	2.34	1.29	2.12	0.60	6.58	< 0.001
	2	5.31	2.00	5.04	1.18	8.95	
	3	5.08	3.30	3.14	2.04	8.78	

Analysis of distant metastases:

Distant metastases were found in 22 patients (42.3%) as follows: bone metastases in 13 patients, liver metastases in 5 patients, lung metastases in 3 patients and one patient with metastases to infra-clavicular muscle. None of the patients with bone metastasis had ILC, ki-67 <20% or were ER negative.

There were no significant correlations between volumetric parameters of bone metastases in breast cancer and clinic-pathological risk factors (P value > 0.05%) as follow: focality of the primary tumor (P value 0.727), grading (P value 0.390), PR (P value 0.056), HER2 (P value 0.667), molecular subtype (P value 0.439) and M stage (P value 0.238) ***(Figure 1, 2)***.

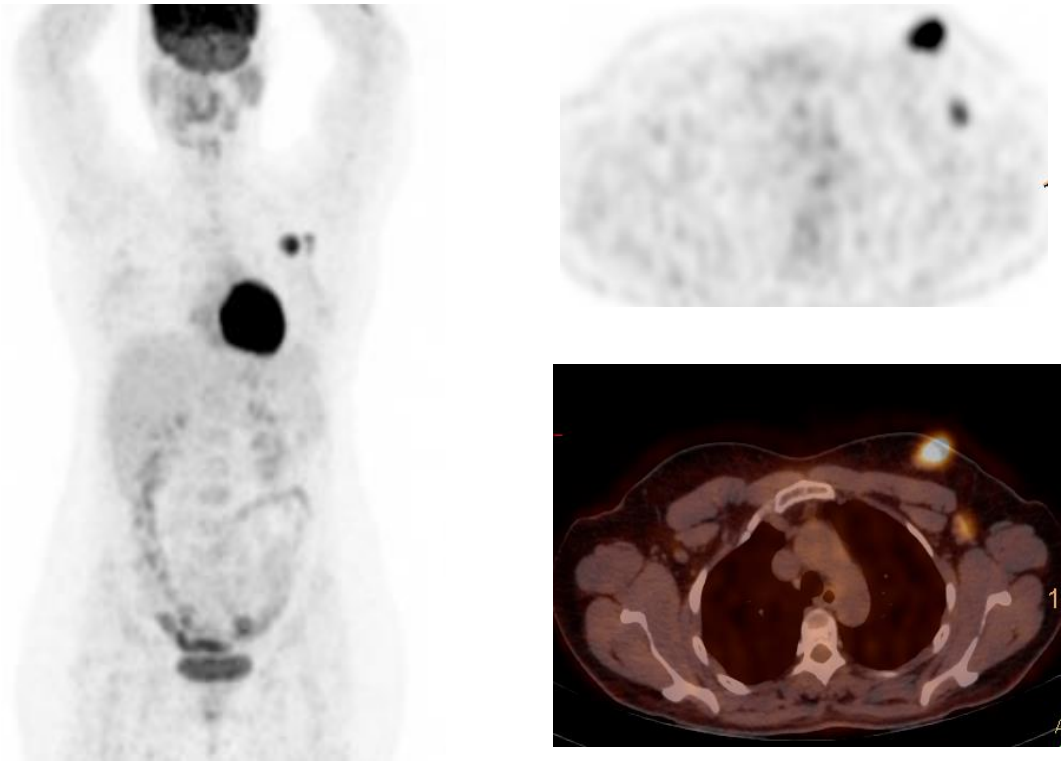

Figure (1): PET/CT for a 42-year-old female patient with hypermetabolic left uni-focal upper outer quadrant breast lesion pathologically proven infiltrative duct carcinoma, grade II with hypermetabolic left axillary lymph nodes. Clinical Staging: T1N1M0 Stage 2, ER negative, PR positive. PET/CT metabolic parameters for primary neoplasm (SUV max8.9, SUVmean5.2, MTV6, TLG31.3, TLR5.7 and size 2.2 cm). PET/CT metabolic parameters for metastatic lymph nodes (SUVmax4.8, SUVmean2.7, MTV4.2, TLG 11.8, TLR 3.1 and size of the largest lesion 1.3 cm.

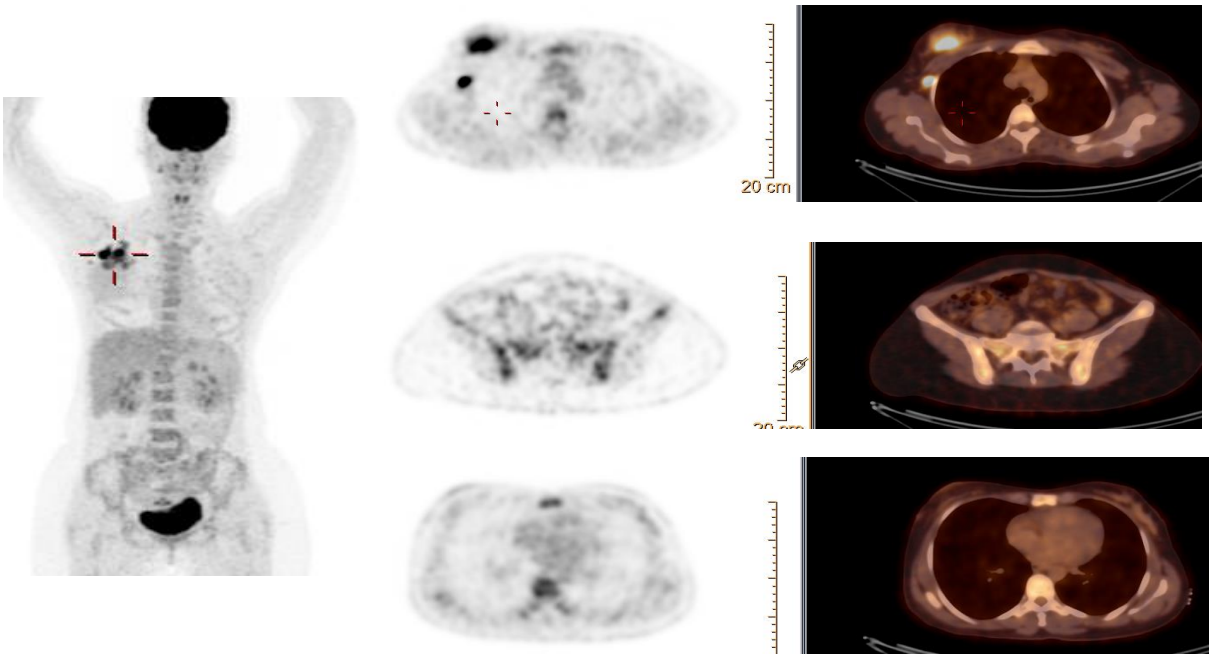

Figure (2): PET/CT for a 37-year-old female patient had hypermetabolic right multifocal breast lesions pathologically proven infiltrative duct carcinoma grade II with hypermetabolic right axillary lymph nodes and multiple bone metastases. Clinical Staging: T2N2M1 Stage 4, ER positive, PR negative. PET/CT metabolic parameters for primary neoplasm (SUVmax11.9, SUVmean6.1, MTV10, TLG32, TLR6, size of the largest lesion 3.2 cm). PET/CT metabolic parameters for metastatic axillary lymph nodes (SUVmax15.8, SUVmean7.5, MTV4.2, TLG31.7, TLR 7.2 and size of the largest lesion 5 cm. PET/CT metabolic parameters for the most active bone deposit at left iliac bone (SUVmax5.3, SUVmean2.8, MTV1.2, TLG 3.3 and TLR 2.4.

DISCUSSION:

^{18}F-FDG PET/CT has an important role regarding diagnosis, staging and prognosis prediction in breast cancer patients **(10)**.

The prognostic and predictive factors are important to evaluate prognosis and to be able to choose the best possible treatment plan. The most significant prognostic factor in breast cancer is the state of lymph nodal metastases that sometimes coupled with a worse prognosis, and therefore the patients always require chemotherapy and more extensive radiotherapy **(11)**.

In the current study in metastatic breast cancer patients to loco/regional lymph nodes, 32 (61.5%) patients in the N1 group, 15 (28.9%) in the N2 group and 5 (9.6%) patients in the N3 group.

Chiacchio et al,. reported different distribution for the metastatic lymph nodes where 18 (25%) in the N1group, 21 (29%) in the N2 group and 24 (33%) patients in the N3 group [(12)].

In contrast Chang et al., reported that 8 patients in N1 (22.9%), 5 patients in N2 (14.3%) and 5 patients in N3 (14.3%) [(13)]. This difference may be due to difference of sample size included in the studies or different screening programs. In the current study distant metastases (M1) were found in 22 patients (42.3%).

SUVmax is the most commonly used parameter, different quantitative measurements such as MTV and TLG are better in assessment of the volume, shape, and heterogeneity of the tumor [(14)].

The mediastinal vessels and normal liver tissue are the most commonly used parameters for individual background activity [(15)].

Paquet et al,. reported that SUV liver is relatively constant regardless of which correction method was used. In the current study, we used the SUV liver to represent individual normal uptake [(16)]. Normalization of the SUVmax value using normal liver uptake may reduce the effect of individual bias. The use of TLR as an alternative approach to evaluate the prognosis and treatment response has been reported in several studies [(17-18)].

PET indices for lymph nodes metastases seem to be useful in evaluate prognosis as shown in ***Yong-il Kim, et al,.*** study who found that lymph nodes metabolic & volumetric parameters have significant predictors of disease recurrence in triple-negative breast cancer patients and considered to be useful parameters for evaluating prognosis where a significant differences between patients with and without recurrence (with lymph nodes SUVmax, SUV mean, MTV, and TLG; all $P < 0.001$) has been found [(19)].

In addition, ***Jahae Kim et al,.*** reported that high lymph nodes SUV (P=0.011 and 0.035) and MTV (P =0.011 and 0.035) as well as high histological grade (P=0.008 and 0.012), negative ER (P=0.045 and 0.009) were associated with shorter disease-free survival and overall survival respectively [(20)]. Similarly, ***Clément Bouron et al,.*** found in the multivariate analysis that lymph node involvement was associated with lower disease-free survival [(21)].

The TLR value reported to be associated with lymph node involvement and distant metastases [(22)], however in our study; we found no correlation between TLR, lymph node involvement and distant metastases.

Regarding the correlation between volumetric parameters for loco-regional lymph nodes and different clinic-pathological factors, ***Chang et al,.*** reported a non-significant correlation between the SUVs of the axillary lymph nodes and the tumor grade, ER, PR and HER2 index [(13)]. We found similar results regarding receptors index but in contrast we found significant correlation between the metabolic volumetric parameters with N stage and SUVs of the axillary lymph nodes with tumor grade.

There were significant correlations between SUVmax & SUV mean of loco-regional lymph nodes and tumor grade & N stage in our study and this is in agreement with another one showed lymph nodes metastases SUVmax was positively and significantly correlated with the N status, they also found significant correlation with M status [(13)]. However, in the current study no significant correlation was found between SUVmax & SUV mean of loco-regional lymph nodes and M status as well as the whole other parameters

Positive significant correlation was found in our study between MTV, TLG and TLR of loco-regional lymph nodes and N state only with no significant correlation regarding the other clinoco-pathological parameters.

To our knowledge, no study has been examined the relationship between volumetric parameters of bone metastases in breast cancer and clinico-pathological risk factors. In the current study there were no significant correlations between volumetric parameters of bone metastases and clinico-pathological risk factors. Further assessment in a larger group of patients is recommended.

CONCLUSIONS:

In metastatic breast cancer patients, volumetric parameters of the metastatic loco-regional lymph nodes can reflect aggressiveness of the tumor; therefore they can be added as additional prognostic factors or as predictive factor which may help in therapy planning. On the other hand, this association was not found regarding bone metastases.

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