The relationship between CEA and CA 15-3 positivity and metabolic and volumetric 18F-FDG PET/CT parameters in preoperative evaluation of breast cancer

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OBJECTIVE*: We aimed to examine the relationship between tumor marker (Cancer Antigen 15-3 [CA15-3] and Carcinoembryonic Antigen [CEA]) positivity and metabolic (standardized uptake value [SUV]) and volume-based (metabolic tumor volume [MTV] and total lesion glycolysis [TLG]) 18F-Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) parameters of the primary tumor and lymph node.*
MATERIAL AND METHODS*: Our study group consisted of 91 female patients, who underwent PET/CT between January 2018 and December 2019 in our clinic with a diagnosis of breast cancer. These patients had no distant metastasis or supraclavicular and internal mammarian lymph node metastasis. MTV, TLG, and SUVmax values were obtained from the primary breast lesion and axillary lymph nodes.*
RESULTS*: The mean age of the patients, who participated in the study, was 52,19±14,57, and the median values of the primary tumor MTV, TLG, and total MTV values were found to be statistically significantly higher in those who were CEA positive compared to those who were CEA negative.*
The median SUVmax value of the axillary lymph node was found to be statistically significantly higher in those who were CEA positive compared to those who were CEA negative (p: 0.004). There was no statistically significant difference between the other parameters.
CONCLUSION*: There was a statistically significant correlation between CEA positivity in preoperative primary breast cancer and primary tumor volume MTV, TLG, and total MTV values, which are volume-based PET parameters. CEA positivity evaluation may indicate increased tumor load in preoperative.*

KEY WORDS: Breast Cancer, CEA, CA 15-3, MTV, TLG, FDG PET/CT

Introduction

Breast cancer is the second most common cancer worldwide, the most common cancer in women (24.2%), and results in 15% of cancer-related deaths (ranks first) among women [1].

The diagnosis of breast cancer is made by monitoring patients with symptoms, such as pain or mass, through pathological examinations and imaging methods, such as mammography, ultrasonography, and MRI.
Tumor markers are frequently used in the diagnosis and screening, as well as the monitoring of relapses and treatment response. Cancer Antigen 15-3 (CA15-3) and Carcinoembryonic Antigen (CEA) are two tumor markers used in the monitoring of breast cancer and approved by the Food and Drug Administration (FDA) [2,3].
CA 15-3 is a mucin-type glycoprotein produced by the Mucin 1 (MUC-1) gene [4]. MUC-1 is found in almost all epithelial cells, and its overexpression is generally associated with colon, breast, ovarian, lung, and pancreatic
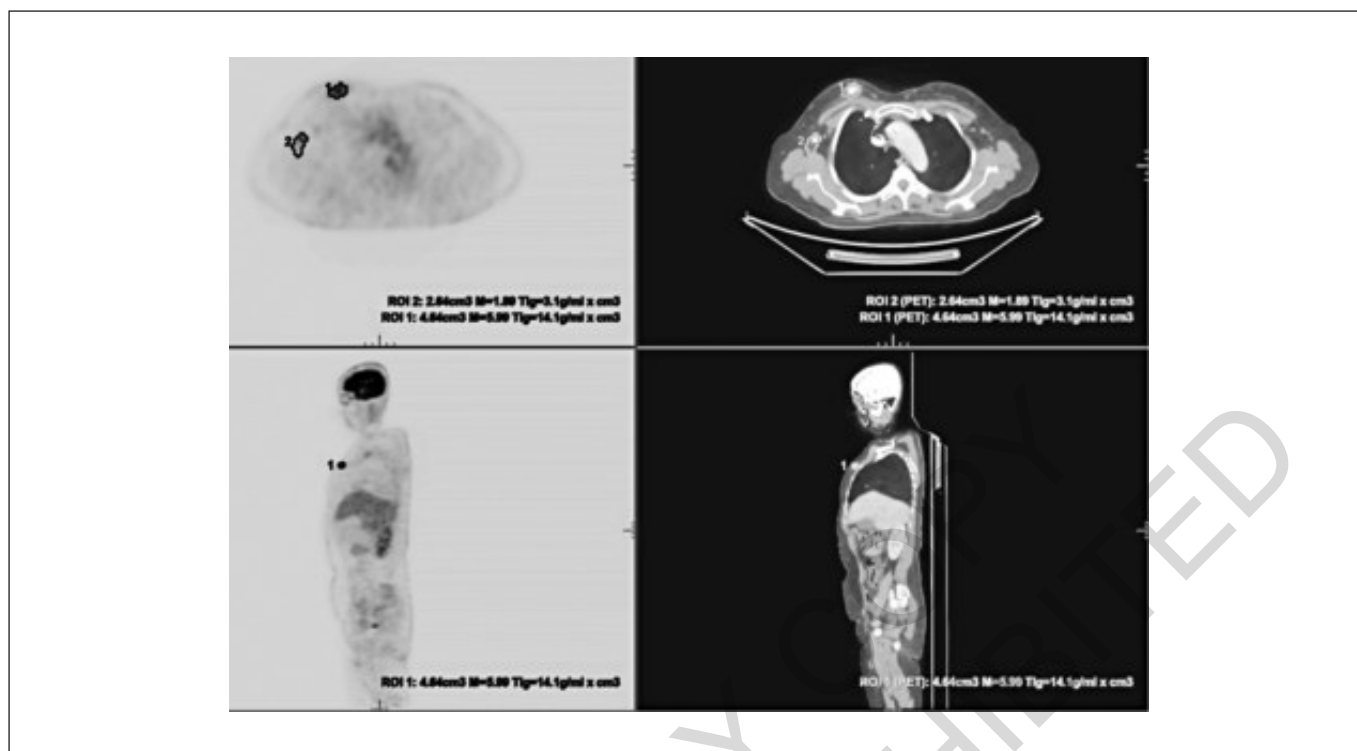
Fig. 1: A 65-year-old patient who has invasive ductal carcinoma and a positive axillary lymph node; breast MTV: 4.64 cm3, breast TLG: 14.1g/ml.cm3, breast SUVmax: 5.99, axillary MTV: 2.64 cm³, axillary TLG: 3.1g/ml.cm³ axillary SUVmax: 1.89, Total MTV: 7.28cm³, total TLG: 17.2g/ml.cm³ CEA: 1.36g/ml CA 15-3: 19.75U/ml

cancers [5]. CEA is a member of the immunoglobulin superfamily. There are 29 genes in the human CEA gene family, including 11 pregnancy-specific glycoprotein genes (4). Increased CA 15-3 and CEA levels have been frequently detected in breast cancer [6].

18F-Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) is used for breast cancer characterization, staging, evaluating treatment response, and detecting recurrence [7,8]. The standardized uptake value (SUV) is the most common semi-quantitative parameter used in FDG PET/CT, providing valuable information in predicting the prognosis [9]. Nowadays, metabolic tumor volume (MTV) and total lesion glycolysis (TLG), which are volume-based PET parameters, are frequently used and found to be particularly associated with a prognosis of breast cancer [10].

In our study, we aimed to examine the relationship between tumor marker positivity in breast cancer and metabolic and volume-based PET/CT parameters of the primary tumor and lymph node.

Material and Methods

Our study group consisted of 91 female patients who underwent PET / CT imaging in our clinic between January 2018 and December 2019 with a pathological-ly proven diagnosis of breast cancer and with simultaneous tumor markers (CEA, CA 15-3). Patients who have not previously undergone surgery or received chemotherapy, independent of axillary lymph node involvement in PET/CT are included in the study. Patients with distant metastases, internal mamarian and supraclavicular lymph node metastases and secondary tumors were excluded. This study was carried out in accordance with local good clinical practice (GCP) guidelines and current laws, and approval for the use of patient data was obtained from our hospital's ethics committee (Permission No: 401/2019).

18F-FDG PET/CT imaging protocol

All patients were asked to stop eating at least 6 hours before and to stop intravenous (IV) glucose intake. Blood glucose values were confirmed to be ≤140 mg/dl by the finger-stick method before FDG injection. One hour after an 18F-FDG injection of 3.5-5.5 MBq/kg, CT images (120 kV, 80 mAs/slice, 700 mm transaxial FOV, no gap, 64xo. 625 mm collimation, pitch 1.4. 0.5s rotation time, 3.3 mm slice thickness, and 512x512 matrix) were taken in the supine position from the vertex to the middle of the thigh, and then PET images (3D FOV 20 cm, ordered subset expectation-maximization algo-
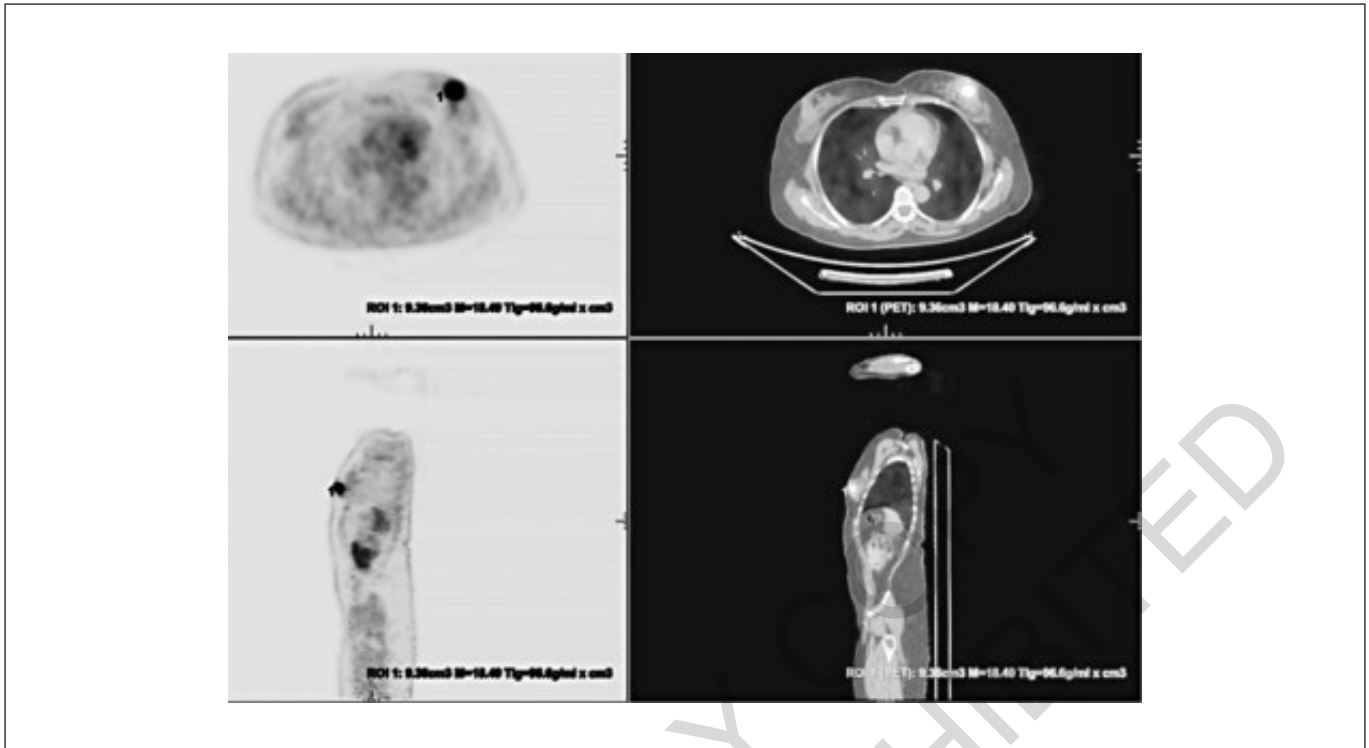
Fig. 2: A 40-year-old patient who has invasive ductal carcinoma and a negative axillary lymph node; primary tumor MTV: 9.36 cm^3, primary tumor TLG:96.6 g/ml.cm^3 CEA: 2ng/ml, Ca15-3: 27.2 U/ml

rithm [OSEM] 5 iterations/12 subsets, full width at half maximum [FWHM] 3 mm) were taken for 2.5 minutes for each bed. A Discovery IQ 4 ring 20 cm axial FOV PET/CT (GE Healthcare, Milwaukee, WI, USA) device was used in both CT and PET imaging.

EVALUATION OF IMAGES

All 18F-FDG PET/CT images were evaluated by experienced (at least ten years) two nuclear medicine specialists using PET Volume Computerized Assisted Reporting (PET-VCAR, GE, USA) (GE Advantage Workstation software version AW 4.7) software. Volumetric regions of interest (ROIs) were drawn manually from the primary breast lesion and axillary lymph nodes to cover the lesion in 3 planes, and automatic MTV, TLG (MTV X SUVmean), and SUVmax values were obtained by the device for each lesion using a 40% SUV threshold. Total MTV and total TLG values were calculated by summing the MTV and TLG values obtained from the primary breast and axilla (Figs. 1,2).

STATISTICAL METHODS

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of variables. In the comparison of two independent groups according to quantitative data, the independent t-test was used with the bootstrap method, while the Mann-Whitney U test was used with the Monte Carlo method. Sensitivity and specificity ratios for the relationship between the classification separated by the cut-off value calculated by the variables and the actual classification were analyzed and expressed by ROC (Receiver Operating Characteristic) curve analysis. In the tables, quantitative variables were shown as mean±SD (standard deviation) and median (Minimum/Maximum), and categorical variables were shown as n (%). Variables were examined at a 95% confidence level, and the p-value was considered significant as it was lower than 0.05.

Results

The mean age of the patients, who participated in the study, was 52,19±14,57; 83 of these patients had invasive ductal carcinoma, and 8 had invasive lobular carcinoma.
The median and mean values of PET parameters and tumor markers are shown in Table I. A CEA level of >5 ng/ml was considered positive, and CEA was positive in 15 (16.4%) patients. A CA 15-3 level of >25

TABLE I - *Mean and median values of patient features, PET parameters and tumor markers*

	N	Mean	Standard Deviation	Median	Minimum	Maximum
Age	91	52,18	14,57	49	21	84
Primary tumor MTV	91	29,72	51,87	49	1	348
Primary tumor TLG	91	110	246,9	38	1,4	1822
Primary tumor SUVmax	91	8,05	8,9	6,8	1,3	7,01
Axillary LAP MTV	57	27,58	60,3	7	0,13	400
Axillary LAP TLG	57	103,72	308	19,1	0,1	2201
Axillary LAP SUVmax	57	6,69	5,87	5,2	1	38
Total TLG	91	47	94,59	20,19	1	748
Total TLG	91	175,07	470,61	63,2	1,4	4023
CEA ng/ml	91	3,79	4,94	2,12	0,43	35,1
CA 15-3 U/ml	91	40,7	84,38	27,08	8,35	677,9

TABLE II - *Relationship between CEA, CA 15-3 positivity and PET Parameters*

	CA 15-3 >25 Positive		P	CEA>5 Positive		P
	- (n=39) Mean±SD. Median (Min/ Max)	+ (n=52) Mean±SD. Median (Min/ Max)		- (n=76) Mean±SD. Median (Min/ Max)	+ (n=15) Mean±SD. Median (Min/ Max)	
Age	52,49±13,91	51,98±15,19	0,868 t	51,67±13,44	54,87±19,73	0,536 t
Primary TM MTV	14 (2 / 291)	13,7 (1 / 348)	0,835 u	13 (1 / 133)	20,5 (7,5 / 348)	0,007 u
Primary TM TLG	47 (2,4 / 1.134)	37,3 (1,4 / 1.822)	0,685 u	37 (1,4 / 1.021)	60,9 (5,3 / 1.822)	0,041 u
Primary TM SUVmax	7,4 (1,4 / 70)	6,1 (1,3 / 41)	0,348 u	6,8 (1,3 / 70)	6,2 (1,7 / 41)	0,714 u
Axillary LAP MTV	4,8 (0,1 / 180)	7,1 (1 / 400)	0,404 u	5,7 (0,1 / 111)	15,9 (1,9 / 400)	0,124 u
Axillary LAP TLG	14,5 (0,1 / 700)	26 (1,9 / 2.201)	0,114 u	20,7 (0,1 / 530)	16,8 (2,3 / 2.201)	0,647 u
Axillary LAP SUVmax	3,8 (1 / 13,9)	6,2 (1,8 / 38)	0,004 u	5,2 (1 / 38)	5,1 (2,1 / 10,8)	0,642 u
Total MTV	18,5 (2 / 471)	22,9 (1 / 748)	0,826 u	19,3 (1 / 181,3)	47,5 (9,4 / 748)	0,024 u
Total TLG	60 (2,4 / 1.834)	64,9 (1,4 / 4.023)	0,793 u	59,6 (1,4 / 1.022,8)	84,4 (5,3 / 4.023)	0,211 u
CEA ng/ml	2,6 (0,4 / 19,8)	2,1 (0,5 / 35,1)	0,186 u	-	-	-
CA 15-3 U/ml	-	-	-	27,4 (8,4 / 677,9)	25,2 (8,9 / 491,7)	0,922 u

t Independent Samples t Test(Bootstrap), u Mann-Whitney U test (Monte Carlo), SD.: Standard Deviation, Min.:Minimum, Max.:Maximum

TABLE III - *Relationship between axillary lymph node positivity and CEA and CA 15-3 positivity*

	Axillary LAP		P
	- (n=34) Mean±SD. Median (Min/ Max)	+ (n=57) Mean±SD. Median (Min/ Max)	
Age	52,56±14,42	51,98±14,80	0,853 t
CEA ng/ml	1,9 (0,5 / 16,1)	2,6 (0,4 / 35,1)	0,222 u
CA 15-3 U/ml	26,7 (8,4 / 84,8)	27,7 (8,4 / 677,9)	0,679 u

t Independent Sample t Test(Bootstrap), u Mann-Whitney U test (Monte Carlo), SD.: Standard Deviation, Min.:Minimum, Max.:Maximum

U/ml was considered positive, and CA 15-3 was positive in 52 (57.1%) patients. Either CEA or CA 15-3 was positive in 59 (64.8%) patients. There was no significant correlation between CEA and CA 15-3 positivity and the age variable The median values of the primary tumor MTV, TLG, and total MTV values were found to be statistically significantly higher in those who were CEA positive compared to those who were CEA negative (p: 0.007, p: 0.041, p: 0.024, respectively) (Table II). The median SUVmax value of the axillary lymph node was found to be statistically significantly higher in those who were CA 15-3 positive compared to those who were CA 15-3 negative (p: 0.004). There was no statistically significant difference between primary tumor MTV, TLG, total MTV, total TLG values and CA 15-3 values (Table II).

TABLE IV - *Relationship between CEA or CA 15-3 positivity and PET Parameters*

	CEA or CA15-3 positivity		P
	- (n=32) Mean±SD. 533±13,33 Median (Min/ Max)	+ (n=59) Mean±SD. 51,75±15,30 Median (Min/ Max)	
Age			0,669 t
Primary TM MTV	13,2 (2 / 133)	13,8 (1 / 348)	0,702 u
Primary TM TLG	38,3 (2,4 / 1.021)	38 (1,4 / 1.822)	0,805 u
Primary TM SUVmax	7,5 (1,4 / 70)	6,1 (1,3 / 41)	0,333 u
Axillary LAP MTV	3,6 (0,1 / 111)	8,7 (1 / 400)	0,079 u
Axillary LAP TLG	13,5 (0,1 / 235,9)	25,3 (1,9 / 2.201)	0,066 u
Axillary LAP SUVmax	4,2 (1 / 13,9)	6,1 (1,8 / 38)	0,011 u
Total MTV	17,2 (2 / 138,8)	25,4 (1 / 748)	0,354 u
Total TLG	55,2 (2,4 / 1.022,8)	66,6 (1,4 / 4.023)	0,472 u
CEA ng/ml	2,2 (0,4 / 4,6)	2,6 (0,5 / 35,1)	0,430 u
CA 15-3 U/ml	16,9 (8,4 / 23,9)	31,9 (8,9 / 677,9)	<0,001 u

t Independent Samples t Test(Bootstrap), u Mann Whitney U test (Monte Carlo), SD.: Standard Deviation, Min.:Minimum, Max.:Maximum

TABLE V - *Evaluation of CEA, CA 15-3, CEA or CA 15-3 positivity and PET parameters with ROC curve analysis*

	Cut off	Sensitivity	Specificity	AUC±SE.	P value
Axillary LAP SUVmax → CEA or CA15-3 positive	> 5,2	60,5%	73,7%	0,708 ± 0,073	0,005
Axillary LAP SUVmax → CA15-3 positive	> 5,2	66,7%	75,0%	0,725 ± 0,067	0,001
Primary TM MTV → CEA Positive	> 7,37	100,0%	35,5%	0,718 ± 0,068	0,001
Primary TM TLG → CEA Positive	> 140	40,0%	88,2%	0,664 ± 0,076	0,031
Total MTV → CEA Positive	> 47,1	53,3%	80,3%	0,682 ± 0,073	<0,001

Roc (Receiver Operating Charcteristic) Curve Analysis (Honley&Mc Nell - Youden index J), AUC: Area under the ROC curve, SE: Standard Error

There was no statistically significant difference between positivity of the axillary lymph node and positivity of CEA and CA 15-3 (p-values p: 0.222, p: 0.667, respectively:) (Table III).

In those who were CEA and CA 15-3 positive, the median SUVmax value of the axillary lymph node was found to be significantly higher compared to those which were negative (p: 0.011) (Table IV).

For the cut-off value (> 7.37 cm³) obtained in primary tumor MTV by ROC curve analysis to detect CEA positivity, the values were as follows: sensitivity 100%, specificity 35.5%, AUC±SE: 0.718±0.068, and p: 0.001; for the primary tumor TLG cut-off (> 140g/ml.cm3) value: sensitivity was 40.0%, specificity 88.2%, AUC±SE: 0.664±0.076, and p: 0.031; for the cut-off value of total tumor MTV (47.1 cm³): sensitivity was 53.3%, specificity 80.3%, AUC±SE: 0.682±0.073, and p:<0.001. These values were statistically significant (Table V).

For the cut-off value (> 5.2) of the SUVmax value of the axillary lymph node in detecting CA 15-3 positivity: sensitivity was 66.7%, specificity 75%, AUC±SE: 0.725±0.067, and p: 0.001); for the cut-off value (> 5.2) in detecting CEA or CA15-3 positivity: sensitivity was 60.5%, specificity 73.7%, AUC±SE: 0.708±0.073, and p: 0.005). These values were statistically significant (Table IV).

Discussion

This study was designed retrospectively to examine the relationship between MTV and TLG, which are metabolic and volume-based parameters obtained from PET CT in breast cancers,

The most important finding of this study is that CEA positivity shows the volume of the primary tumor.

According to a recent meta-analysis of 13 studies, CEA and CA15-3 levels are associated with malignant tumor development in the breast and may also be used in the diagnosis of breast cancer. This meta-analysis also reported that CA 15-3 levels are associated with all stages in breast cancer, have a positive correlation with tumor load, and should be used in the detection and monitoring of tumor load [11].

It was reported that there is no difference between stage I-II tumors and benign tumors in terms of CA 15-3 levels, but there is a statistically significant difference between stage III-IV tumors and benign tumors in terms of CA 15-3 levels [12,13]. It was reported in previous studies that those with high CA 15-3 levels in stage II breast cancer have a worse prognosis than those with normal CA 15-3 levels [14]. Shao et al. showed that as the T and N stages of the primary tumor increased, both CEA and CA 15-3 levels increased statistically [15].

In our study, the primary tumor's MTV, TLG, and total MTV values were found to be higher in those who were CEA positive compared to those who were CEA negative, an indication of the relationship between increased tumor load and CEA positivity, as stated in previous studies. However, in our study, there was no correlation between CA 15-3 positivity and volumetric PET parameters; there was also no correlation between tumor load and CA 15-3 positivity in preoperative breast cancer.

In a study conducted on 355 preoperative breast cancer patients, higher CA 15-3 levels were found in those with N1 and N2 lymph nodes compared to those with N0 lymph nodes [16].. In our current study, there was no significant relationship between positive or negative axillary lymph nodes and CEA and CA 15-3 positivity, but it was found that SUVmax values, which are the metabolic parameters of the axillary lymph node, were statistically higher in patients with positivity for CA 15-3 and one of both tumor markers.

PET/CT has high sensitivity and specificity in staging breast cancer, in evaluating the response to treatment, and in detecting early relapses. The SUVmax, MTV, and TLG values provide information about prognosis, whereas the primary tumor's MTV and TLG values provide prognostic information about lymph node and distant metastases [17,18].

In a study where CEA and CA 15-3 and PET/CT were used together for the detection of recurrence in breast cancer, there was no statistical significance between CA 15-3 positivity (> 25) and recurrence or metastasis in PET/CT. However, when the CA 15-3 cut-off value was taken as >40 U/ml, it showed a significant correlation with PET/CT in detecting recurrence (sensitivity 76%, specificity 64%, PPV 88%, and NPV 44%). In the same study, when the CEA cut-off value was taken as 4.8 ng/ml: sensitivity was 50%, specificity 82%, PPV 90%, and NPV 31% [19].

In a study by Cervino et al., PET/CT and CA 15-3 levels were used to detect recurrent disease in breast cancer, and it was found that mean CA 15-3 levels were higher in the PET-positive group when compared to those in the PET negative group. There was no significant correlation between CA 15-3 levels and SUVmax value. However, higher SUVmax and CA 15-5 levels were reported in the group with visceral metastasis compared to those who did not have visceral metastasis [20]. In their study of CEA and CA 15-3 levels and PET/CT in the detection of breast cancer recurrence and metastases, Dong *et al*. found that there was no statistically significant difference in CEA levels between PET-positive and negative groups. However, CA 15-3 levels were significantly higher in the PET-positive group compared to those in the PET-negative group [21]

Studies regarding PET/CT and tumor markers in breast cancer often focus on the detection of recurrence or metastasis, but there are no studies comparing metabolic and volumetric PET parameters and tumor markers in primary breast tumors. In our study, primary tumor MTV (cut-off> 7.37 cm^3), primary tumor TLG (cut-off> 140g / ml.cm3), and total tumor MTV (cut-off> 47.1cm3) values were statistically significant in determining CEA positivity (p: 0.001, p: 0.031, and p <0.001, respectively).

When the SUVmax cut-off value for the axillary lymph node was taken as>5.2, it was found to be statistically significant in determining the positivity of CA 15-3 (p: 0.001) and the positivities of CEA or CA 15-3 (p: 0.005).

The limitations of our study: it was a retrospective study, the number of patients was low, a comparison with molecular subtypes was not possible due to the low number of patients, and the benign lesions were not compared in tumor marker positivity.

Conclusion

There was a statistically significant correlation between CEA positivity in preoperative primary breast cancer and primary tumor volume MTV, TLG, and total MTV values, which are volume-based PET parameters. CEA positivity evaluation may indicate increased tumor load. in preoperative. Although it was detected more frequently in preoperative primary breast cancer, we found that CA 15-3 positivity was not correlated with tumor load and only correlated with the SUVmax value of the axillary lymph node.

Riassunto

Si è voluto esaminare la relazione tra la positività dei marker tumorali Cancer Antigen 15-3 (CA15-3) e l'Antigene carcinoembrionico [CEA]) e attività metabolica (valore di assorbimento standardizzato [SUV]) e basata sul volume (volume metabolico del tumore [MTV] e glicolisi totale delle lesioni [TLG]) e i dati della tomografia a emissione di positroni (PET)/18F-Fluorodesossiglucosio (18F-FDG) con la tomografia computerizzata (CT) del tumore primario e del linfonodo.

Per lo studio sono state analizzate 91 pazienti di sesso femminile, sottoposte a PET / TC tra gennaio 2018 e dicembre 2019 nella nostra clinica con diagnosi di cancro al seno. Queste pazienti non avevano metastasi a distanza o metastasi dei linfonodi mammari interni e sopraclaveari. I valori MTV, TLG e SUVmax sono stati ottenuti dalla lesione mammaria primaria e dai linfonodi ascellari.

Risultati: l'età media delle pazienti era di 52,19±14,57 anni e i valori mediani di valori di MTV, TLG e i valori MTV totali del tumore primitivo sono risultati statisticamente significativamente più alti in quelle pazienti che erano CEA positive rispetto a quelle che erano CEA negative.

Il valore mediano SUVmax del linfonodo ascellare è risultato essere statisticamente significativamente più alto in coloro che erano CEA positive rispetto a quelle che erano CEA negative (p: 0,004). Non è risultata una differenza statisticamente significativa tra gli altri parametri. La conclusione è che abbiamo riscontrato una correlazione statisticamente significativa tra la positività preoperatoria CEA nel carcinoma mammario primitivo e il volume del tumore primario MTV, TLG e i valori totali di MTV, che sono parametri PET basati sul volume. La valutazione della positività CEA può indicare un aumento del carico tumorale nel preoperatorio.

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