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Role of 18F FDG-PET/CT in Recurrent Breast Cancer: Correlation with CA15.3 and Survival Outcomes.

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ABSTRACT:

Background: Breast cancer (BC) is the most frequently diagnosed cancer globally. Following curative treatment of BC, monitoring locoregional and distant recurrence is a major clinical challenge. **Patients and Methods:** Seventy-two female patients with histo pathologically proven BC who were referred for ^{18}F-FDG PET/CT due to a suspicion of recurrence. PET/CT images were analyzed both qualitatively and quantitatively. PET/CT findings and quantitative parameters (SUVmax, SUVpeak, SUVmean, MTV, and TLG) were correlated with the CA15.3 levels and survival outcomes. The gold standard was histopathological examination, radiologic, or clinical follow-up. **Results**: Fifty-eight patients had positive PET/CT findings, while the remainder 14 had negative ones. PET/CT demonstrated an excellent diagnostic performance in detecting recurrent BC (96.6% sensitivity, 92.3% specificity, 98.3% PPV, 85.7% NPV, and 95.8% accuracy). CA15.3 was significantly higher in the patients with positive PET/CT results compared to negative ones (p = 0.044). There was a significant positive correlation (p<0.001) between MTV and TLG of the visceral and the most active recurrent lesions, and CA15.3. TLG of recurrent osseous lesions was highly correlated with CA15.3 (p = 0.025). SUVmax, peak, mean, and MTV were all significant predictors of overall survival (OS) (p = 0.005, 0.005, 0.014, 0.013, respectively).

Conclusions: ^{18}F-FDG-PET/CT is a useful addition to existing monitoring methods for verifying recurrence in BC patients suspected of having relapsed disease and mapping out recurrent sites. It should be considered in patients with suspected BC recurrence but normal CA15.3 levels. OS is significantly shorter in patients with elevated CA15.3 and positive PET/CT than in patients with normal CA15.3 and negative PET/CT recurrence. FDG PET/CT-based volumetric metrics (MTV and TLG) are significantly correlated with CA15.3. In patients with recurrent BC, FDG PET/CT-derived SUVmax, SUVpeak, SUVmean and MTV are significant predictors of survival.

Keywords: breast cancer, CA15.3, 18F-FDG PET/CT, recurrence, survival outcomes.

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INTRODUCTION:

Breast cancer (BC) is the most commonly diagnosed cancer worldwide with an approximately 2.3 million new cases estimated in 2020, and it is the leading cause of cancer mortality among women, making it a serious public health issue. [1] The prognosis of locoregional and distant recurrence following initial BC therapy is poor; however, early detection of the recurrence can enhance survival.[2] BC recurrence may be suspected based on clinical and/or radiological signs, as well as a rise in tumor markers such as cancer antigen 15.3 (CA15.3) and carcinoembryonic antigen (CEA).[3] CA15.3 is a glycoprotein that represents the protein product of the MUC-1 gene. MUC1 appears to have anti-adhesive characteristics, which could facilitate metastatic spread.[4] It is expressed distinctly by various types of epithelial-derived malignancies, e.g., colorectal and lung cancers. However, it is aberrantly overexpressed in 90% of BC patients.[5], [6] CA15.3 is the most often used marker for monitoring therapeutic response of metastatic BC. It could also be used to survey the recurrence of BC after curative treatment of the primary.[7] However, because of a paucity of data demonstrating a survival benefit, the European Society for Medical Oncology and American Society of Clinical Oncology do not advise routine use of CA15.3 in the follow-up of asymptomatic patients following definitive treatment.[8] In clinical practice, it is challenging to manage treatment for BC when serum tumor marker levels increase without any morphological imaging findings, or when morphological imaging findings suggest BC recurrence, but histopathological confirmation is inconvenient. In such cases, ^{18}Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) can be used to evaluate recurrence.[9] Over time, ^{18}FDG-PET/CT has proven to be at the vanguard of diagnosing recurrent BC, particularly in women with advanced local disease or equivocal CT or magnetic resonance imaging (MRI) results.[10] According to the National Comprehensive Cancer Network guidelines, patients with suspected recurrent BC should be evaluated by PET/CT.[11] PET/CT metrics, including the peak and maximum standardized uptake values (SUVpeak and SUVmax, respectively), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), are used to quantify tumor metabolism. [12] The relationship between elevated CA15.3 and ^{18}F-FDG PET/CT can be considered complementary because any notable increase in the CA15.3 levels can signal the presence of disease, while PET/CT will map the tumor sites.[13] Numerous earlier studies showed that using ^{18}F-FDG PET/CT parameters in the initial staging was effective in predicting the survival and prognosis of BC patients.[14],[15],[16] However, only one prior study discussed the predictive value of these parameters in patients with BC recurrence.[12] Furthermore, no previous publications explored the relation between all of the aforementioned PET/CT parameters and CA15.3 levels. So, the goal of our study

was to correlate ^{18}F-FDG PET/CT volumetric parameters with CA15.3 levels and survival outcomes in BC patients with suspected recurrence, as well as to validate the usefulness of ^{18}F-FDG PET/CT in such cases.

PATIENTS and METHODS:

The Institutional Committee of Medical Ethics approved this prospective study, and each patient provided signed informed consent. Between June 2021 and June 2024, a total of 104 women who were primarily treated with a curative intent and subsequently referred for PET/CT imaging because of suspected recurrent BC were initially included in the current study. Patients with missing data (n = 29), incidentally discovered second primary (urinary bladder & ovarian) malignancies on PET/T (n = 2), and those who died before follow-up due to an unrelated cause (n = 1) were excluded, leaving a valid cohort of 72 women to be analyzed in this work. **(Figure 1)**

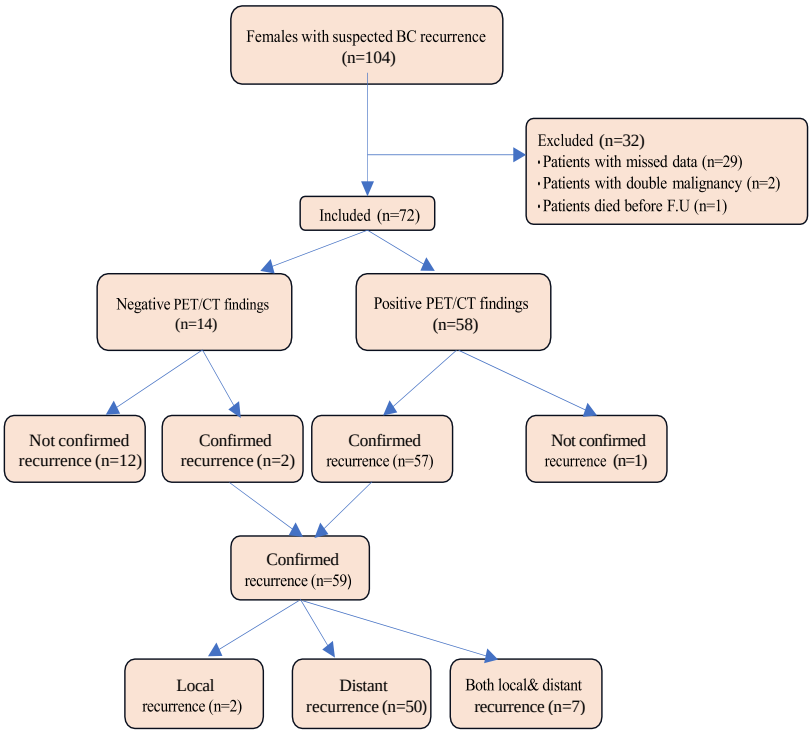

Figure (1): Flow chart of eligible patients and PET/CT findings

^{18}F-FDG PET/CT Imaging:

Imaging was performed within a mean time of 71.9±24.1 minutes after ^{18}F-FDG injection (mean dose =7.6±1.7 mCi) using a high-spatial-resolution, full-ring PET scanner (Biograph Flow, Siemens Healthcare, Erlangen, Germany), combining Lutetium Oxyortho Silicate (LSO)-based PET crystals and 16-slice CT. A low-dose non-contrast CT scan was acquired for attenuation correction and anatomical localization. The imaging field of view extended from the vertex of the skull to the mid-thighs, with the arms held above the head whenever possible. A three- dimensional emission PET scan was then taken over the same anatomical regions, beginning from the mid-thighs to the vertex of the skull. An iterative algorithm was used for image reconstruction, with reoriented tomograms displayed in the transaxial, coronal, and sagittal planes. The manufacturer's workstation (Syngo. via Siemens Healthcare) was used for image analysis.

Image analysis:

PET/CT images were interpreted by two experienced nuclear medicine physicians. **Qualitative assessment:** PET/CT images were visually analyzed, and any increased FDG uptake that did not correspond to the physiological uptake pattern as well as any foci of increased tracer uptake with associated CT abnormalities were considered positive for recurrence. On the other hand, the study was deemed negative when no abnormal FDG uptake was identified throughout the scanned body.

Semi-quantitative assessment: The PET/CT-metabolic parameters (SUVmax, mean, peak, TLG, and MTV) for the suspected locoregional or distant recurrence were obtained by drawing a 3-D VOI over all areas of abnormal uptake in the co-registered PET/CT images.

Conventional imaging modalities (CIMs) were done within three months before PET/CT and included MSCT (n=48), MRI (n=15), mammography (n=3), and bone scintigraphy (n=6).

The CA15.3 concentration was obtained from all patients within 1-2 weeks of PET/CT imaging. Normal levels ranged from 0 - 32 U/ml.

Standard assessment: the reference standard method for verifying the accuracy of imaging results was based on conventional radiological follow-up (n = 41), histopathological examination (n = 14), follow-up PET/CT (n = 7), or clinical follow-up (n = 10) for at least 6 months following the PET/CT scan. PET/CT was defined as true positive (TP) for recurrent BC when the detected lesion(s) were validated by the gold standard and false positive (FP) when the identified lesion(s) were not. PET/CT, on the other hand, was considered true negative (TN) for BC recurrence when the standard method confirmed the absence of recurrence and false negative (FN) when there were no pathological findings indicating recurrence while the gold standard confirmed recurrent disease.

Staging: TNM staging of the primary tumor was conducted according to the AJCC; 8th edition criteria. [17]

Statistical analysis:

The Data was analyzed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Continuous data was reported as means, standard deviations (SD) or medians, range, and inter-quartile range (IQR), whereas qualitative data was presented as frequency and percentages. Chi-square/Fisher's/Monte Carlo Exact tests

were used to compare the difference in frequency distributions among groups. The mean difference between groups was tested using an independent t-test, while the median difference was compared using the Mann Whitney U test. Spearman's correlation was used to test the relationship between CA-15.3 and PET/CT parameters (r = 0.8–1 "very strong", 0.60–0.79 "strong", 0.40–0.59 "moderate", 0.20–0.39 "weak", and 0.01–0.19 "negligible" correlation). Univariate and multivariate Proportional Hazard regression analyses were used to identify independent significant predictors of overall survival (OS). OS is defined as the time between PET/CT and the date of death or last follow-up. Survival probabilities were calculated using Kaplan-Meier analysis and compared using the log-rank test.

Weighted Kappa analysis was used to assess the agreement between PET/CT, CA15.3, and the final diagnosis in the evaluation of BC recurrence. Kappa ≤ 0.00 represents "no" agreement, 0.01 - 0.20 "slight" agreement, 0.21 - 0.40 "fair" agreement, 0.41 - 0.60 "moderate" agreement, 0.61 - 0.80 "substantial" agreement, and 0.81 - 0.99 "almost perfect" agreement. A kappa value of 1 indicates complete agreement. The ROC curve was created to investigate the diagnostic performance of PET/CT and CA15.3 in the assessment of BC recurrence. The validity statistics [sensitivity, specificity, positive and negative predictive values (PPV and NPV)] were computed. A p-value of <0.05 was deemed significant.

RESULTS:

Fifty-eight patients had positive PET/CT findings, while the remainder 14 had negative ones. Twelve of the negative cases showed no recurrence, whereas recurrence was verified in the other two. On the other hand, of the 58 patients with positive PET/CT findings, 57 were confirmed to have recurrence, while the remaining one had no recurring lesions. Out of 59 patients with confirmed recurrence, 2 had local recurrence, 50 had distant recurrence, and 7 had both. **(Figure 1)**

Clinicopathologic characteristics of studied patients:

The current study included 72 female patients with pathologically confirmed BC and suspected recurrent lesions based on CIMs, clinical evaluation, or elevated tumor markers. The mean age was 49.9±12.2 (ranging from 26 to 81 years). The mean period between the PET/CT scan and the last follow-up was 10.47±7.7 months. Most of the primary tumors were invasive ductal carcinoma (IDC) (64, 88.8%), 4 were invasive lobular carcinoma (ILC) (5.6%), while the other 4 were mixed lobular and ducal carcinomas (5.6%). In 56 (77.8%) of the patients, the primary tumor was unifocal, whereas 16 (22.2%) had multifocal lesions. Fifty-four (75%) patients underwent modified radical mastectomy (MRM) and 18 patients (25%) underwent breast conservative surgery. Two (2.8%) patients had grade I, 54 (75%) had grade II, and 16 (22.2%) had grade III BC. Eight (11.1%) cases had stage IA BC, 28 (38.8%) had stage IIA, 9 (12.5%) had stage IIB, 19 (26.4%) had stage IIIA, one (1.4%) case had stage IIIB, and 7 (9.7%) cases had stage IIIC. The molecular

subtypes of BCs of the included patients were as follows: 40 patients (55.5%) had luminal A subtype, 14 (19.4%) had luminal B, 11 (15.2%) had Her2-neu positive subtype, and 7 (9.7%) had triple-negative subtype. CA15.3 concentrations ranged from 4 to 1843 U/mL (median, 38.6 U/mL). Thirty-nine patients exhibited elevated CA15.3, whereas the remaining 33 patients had normal levels. In 19 (26.4%) cases, the Ki-67 level was less than 14%, whereas in 37 (51.4%) cases, it was more than 14%. According to the primary treatment plan, 44 patients underwent chemoradiotherapy, 19 patients received chemotherapy, 6 patients had radiotherapy, and the remaining 3 patients received hormonal therapy. The median OS was 8.5 months, and the median time between primary disease diagnosis and recurrence was 41 months. Forty-eight (66.7%) patients survived and 24 (33.3%) died. The clinicopathologic data is demonstrated in **(Table 1)**.

Table 1: Clinicopathologic characteristics of all studied patients (n=72)

Characteristic	No. (%)
Age at diagnosis (ys), mean±SD (range): 49.9±12.2 (26-81)	
Histologic type: IDC	64 (88.8)
ILC	4 (5.6)
Mixed	4 (5.6)
Primary Tumor Grade: Grade-I	2 (2.8)
Grade-II	54 (75)
Grade-III	16 (22.2)
Primary tumor TNM staging: IA	8 (11.1)
IIA	28 (38.8)
IIB	9 (12.5)
IIIA	19 (26.4)
IIIB	1 (1.4)
IIIC	7 (9.7)
Molecular subtype: Luminal A	40 (55.5)
Luminal B	14 (19.4)
Her2 neu positive	11 (15.2)
Triple-negative	7 (9.7)
CA15.3 level (IU/ml): High	39 (54.2)
Normal	33 (45.8)
Ki-67 level (n=56)**:** ≥14%	37 (51.4)
<14%	19 (26.4)
Line of treatment: Chemo-Radiotherapy	44 (61.1)
Chemotherapy	19 (26.4)
Radiotherapy	6 (8.3)
Hormonal	3 (4.2)
Survival outcome: Survived	48 (66.7)
Died	24 (33.3)

Comparison between positive and negative PET/CT studies:

We found no significant difference between patients with positive and negative PET/CT findings in terms of age at diagnosis (p=0.625), focality (p =0.426), TNM staging (p=0.105), histologic type (p=0.570), primary tumor grade (p=0.285), positive receptors (ER, p = 0.253; PR, p = 0.070; and Her2-neu, p = 0.134), and molecular subtype (p = 0.263). In contrast, the median CA15.3 level was considerably higher in those with positive PET/CT (40.5 vs. 15.4; p=0.044). Ki-67 levels were also significantly higher in positive PET/CT patients (P= 0.041). **(Table 2)** PET/CT revealed BC recurrence in 34 (87.2%) of the 39 patients with elevated CA15.3, as well as 24/33 (72.7%) of those with normal CA15.3 levels.

PET/CT diagnostic performance in detecting recurrent BC:

Our study revealed that PET/CT had a highly significant validity in diagnosing recurrent BC [AUC = 0.945 (95% CI: 0.856 – 1.000), p < 0.001]. The validity criteria were as follows; 96.6% sensitivity, 92.3% specificity, 98.3% PPV, 85.7% NPV, and 95.8% accuracy.

PET/CT had a significant-excellent agreement (weighted kappa=0.863, p<0.001) with the final diagnosis of recurrent BC. It correctly identified recurrent breast lesions in 57/59 patients and excluded recurrence in 12/13 patients. However, it falsely suspected positive recurrence in one patient and negative recurrence in two patients.

Correlation between CA15.3 and PET/CT parameters:

Regarding visceral recurrence, TLG and MTV demonstrated a highly significant (p<0.001) very strong positive correlation (r = 0.886 and 0.822, respectively) with CA15.3. In cases with osseous recurrence, we observed a significant (p=0.025) moderate positive correlation between TLG and CA15.3 (r = 0.456). For the most active (FDG avid) lesions, there was a highly significant (p<0.001) strong positive correlation between TLG, MTV, and CA15.3 (r = 0.617 and 0.642, respectively). Finally, we found no significant correlation between CA15.3 and any of the analyzed PET/CT metrics in the nodal and local recurrence, as shown in **(Table 3)**.

Agreement between CA15.3 and the final diagnosis of recurrent BC:

Using a cut-off value of >30 IU/ml of CA15.3 resulted in a poor agreement (weighted kappa=0.178, p=0.06) between CA15.3 and the final diagnosis of recurrent BC, being agreed in only 44 (61.1%) and differed in the remaining 28 (38.9%) cases. Applying the ROC curve with a cut-off of 30.5 IU/ml revealed a low sensitivity (59.3%) and specificity (69.2%) in predicting disease recurrence, with the AUC of 0.688 **(Figure 2)**.

Table 2: Comparison between positive and negative PET/CT studies

Parameter		PET/CT		*P*
		Positive (n = 58)	Negative (n = 14)	
Age at diagnosis (ys): mean ± SD,range		49.9± 12.1 (26 – 81)	49.3 ± 13.32 (29 – 71)	0.625*
CA15.3 level (IU/ml): median (IQR)		40.5 (69)	15.4 (31)	**0.044****
Ki-67 level: (N=56)	≥ 14%	32 (69.6%)	5 (44.4%)	**0.041*****
	< 14%	14 (30.4%)	5 (55.6%)	
TNM staging:	IA	5 (5.6%)	3 (21.4%)	0.105***
	IIA	21 (36.2%)	7 (50%)	
	IIB	9 (15.5%)	0 (0%)	
	IIIA	16 (27.6%)	3 (21.4%)	
	IIIB	1 (1.7%)	0 (0%)	
	IIIC	6 (10.3%)	1 (7.1%)	
Histological type:	IDC	51 (87.9%)	13 (92.9%)	0.570***
	ILC	4 (6.9%)	0 (0%)	
	Mixed	3 (5.2%)	1 (7.1%)	
Tumor Grade:	Grade-I	2 (3.4%)	0 (0%)	0.285***
	Grade-II	44 (75.9%)	10 (71.4%)	
	Grade-III	12 (20.7%)	4 (28.6%)	
Positive hormonal receptors:	ER	43 (74.1%)	10 (71.4%)	0.253#
	PR	32 (55.2%)	11 (78.6%)	
	Her-2	22 (37.9%)	3 (21.4%)	
Molecular Subtype:	Luminal-A	30 (51.7%)	30 (51.7%)	0.263#
	Luminal-B	13 (22.4 %)	13 (22.4%)	
	Triple Negative	6 (10.3%)	6 (10.3%)	
	Her-2 Neu Positive	9 (15.5%)	9 (15.5%)	

***Independent Sample t-test, **Mann Whitney test, ***The Chi-square test, #Monte Carlo exact test**

Table 3: Spearman's Correlation between PET/CT Parameters and CA15.3

	CA15.3	
	r	***P*-value**
Target recurrent visceral lesion		
• SUVmax	0.180	0.359
• SUVpeak	0.255	0.191
• SUVmean	0.178	0.364
• TLG	**0.886**	**< 0.001**
• MTV	**0.822**	**< 0.001**
Target recurrent osseous lesion		
• SUVmax	0.288	0.172
• SUVpeak	0.330	0.115
• SUVmean	0.192	0.369
• TLG	**0.456**	**0.025**
• MTV	0.387	0.062
Target recurrent nodal lesion		
• SUVmax	0.001	0.997
• SUVpeak	-0.010	0.954
• SUVmean	-0.019	0.917
• TLG	-0.106	0.552
• MTV	-0.125	0.482
Target recurrent local lesion		
• SUVmax	0.095	0.823
• SUVpeak	0.381	0.352
• SUVmean	0.120	0.778
• TLG	0.619	0.102
• MTV	0.405	0.320
Target most active recurrent lesion		
• SUVmax	0.151	0.261
• SUVpeak	0.166	0.218
• SUVmean	0.122	0.366
• TLG	**0.617**	**< 0.001**
• MTV	**0.642**	**< 0.001**

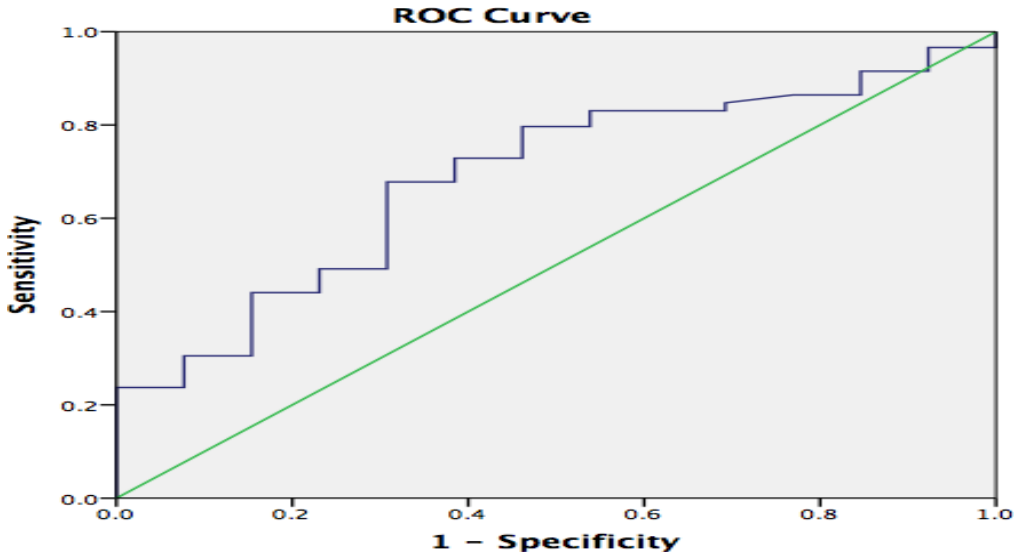

Figure (2): Association between CA15.3 and final diagnosis of recurrent BC

Cox Proportional Hazard Regression Analysis of OS:

Positive PR receptors, SUVmax, SUVpeak, SUVmean, and MTV were all significant predictors of OS in the univariate analyses (p = 0.005; HR = 3.453; 95% CI = 1.454–8.199), (p = 0.005; HR = 1.100; 95% CI = 1.029–1.177), (p = 0.005; HR = 1.137; 95% CI = 1.040–1.243), (p = 0.014, HR=1.149; 95% CI=1.028–1.285), and (p = 0.013, HR=1.005; 95% CI=1.001–1.009), respectively, but none of them remained significant predictors in the multivariate analyses. **(Table 4)**

Table 4: Cox Proportional Hazard Regression Analysis for OS:

Variable	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age at diagnosis (<50)/ys	2.378 (0.980–5.773)	0.056		
ER (positive)	1.687 (0.683–4.170)	0.257		
PR (positive)	3.453 (1.454–8.199)	**0.005**	1.944 (0.673-5.614)	0.219
Her2-neu (positive)	0.674 (0.295–1.540)	0.350		
Ki-67	0.996 (0.969–1.023)	0.754		
CA15.3	1.001 (1.000–1.002)	0.083		
Molecular subtype (non-luminal)	0.544 (0.220–1.343)	0.187		
Multi-focality	0.521 (0.227–1.199)	0.125		
TNM staging (III vs I/II)	0.544 (0.244–1.214)	0.137		
Grading (III vs I/II)	1.287 (0.434–3.820)	0.649		
SUVmax	1.100 (1.029–1.177)	**0.005**	1.620 (0.988–2.692)	0.051
SUVpeak	1.137 (1.040–1.243)	**0.005**	1.252 (0.728-2.155)	0.416
SUVmean	1.149 (1.028–1.285)	**0.014**	0.388 (0.118-1.276)	0.119
MTV	1.005 (1.001–1.009)	**0.013**	0.999 (0.990-1.007)	0.770
TLG	1.035 (0.995-1.075)	0.084		

Association of OS with CA15.3 levels and PET/CT findings

Patients with positive PET/CT findings and high CA15.3 had a substantially shorter OS than those with negative PET/CT and normal CA15.3 (long-rank *p*-value < 0.001). **(Figure 3)**

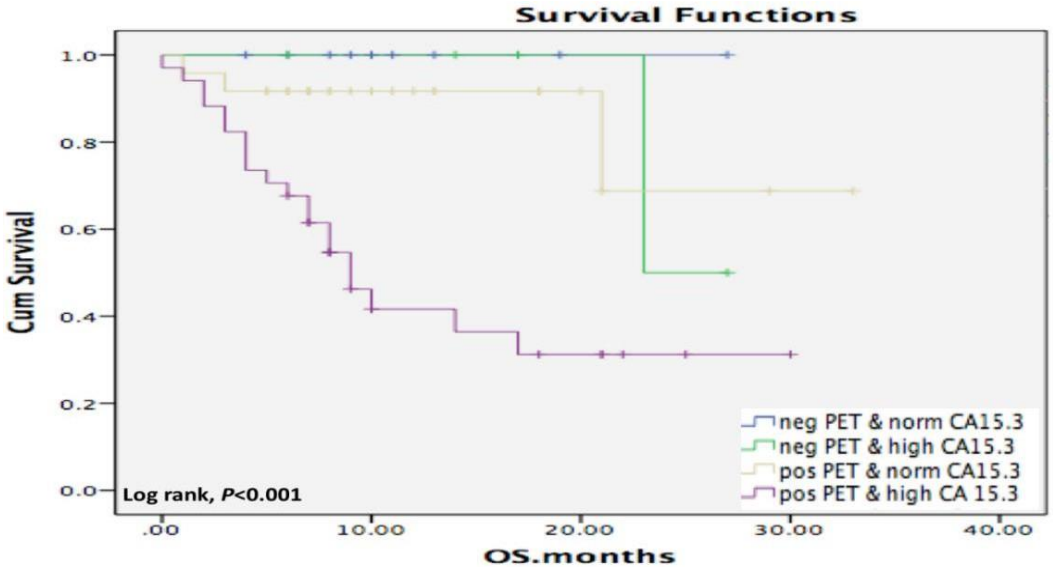

Figure (3): Kaplan-Meier analysis for PET/CT and CA15.3

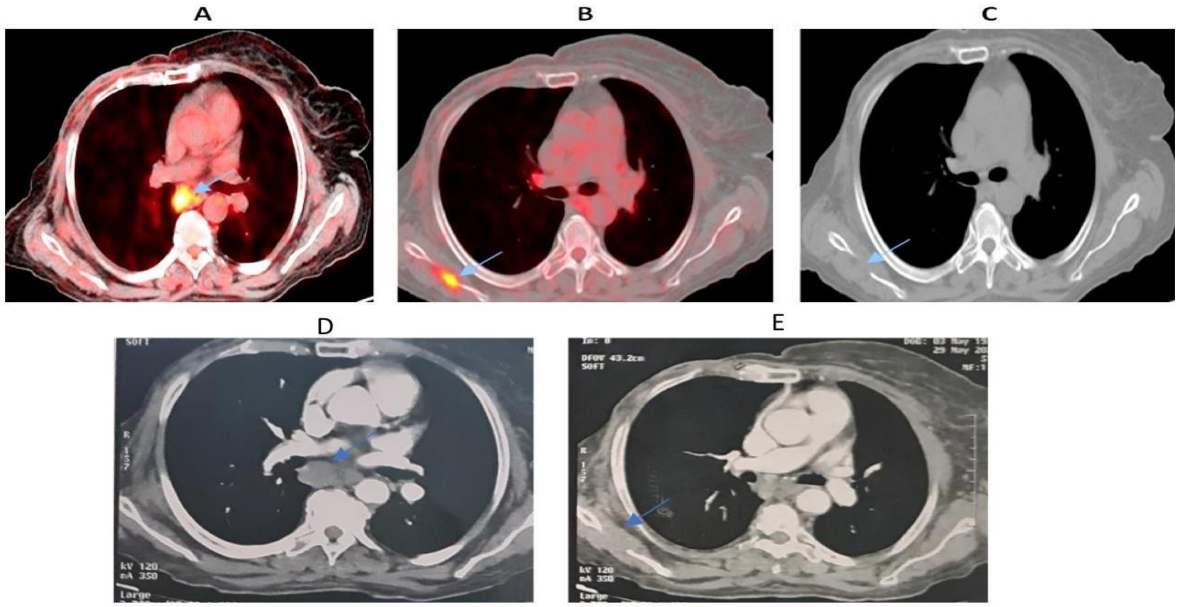

Figure (4): A 64-year old female with right BC who was referred for restaging due to clinical suspicion of recurrence, and her CA15.3 level was within normal range (14 U/ml). The PET/CT images (A&B) showed intense FDG uptake by the mediastinal (para oesophageal) LNs and the right scapula, with a corresponding right scapular lytic lesion in the CT image (C). FU MSCT confirmed both mediastinal and osseous recurrence (D&E).

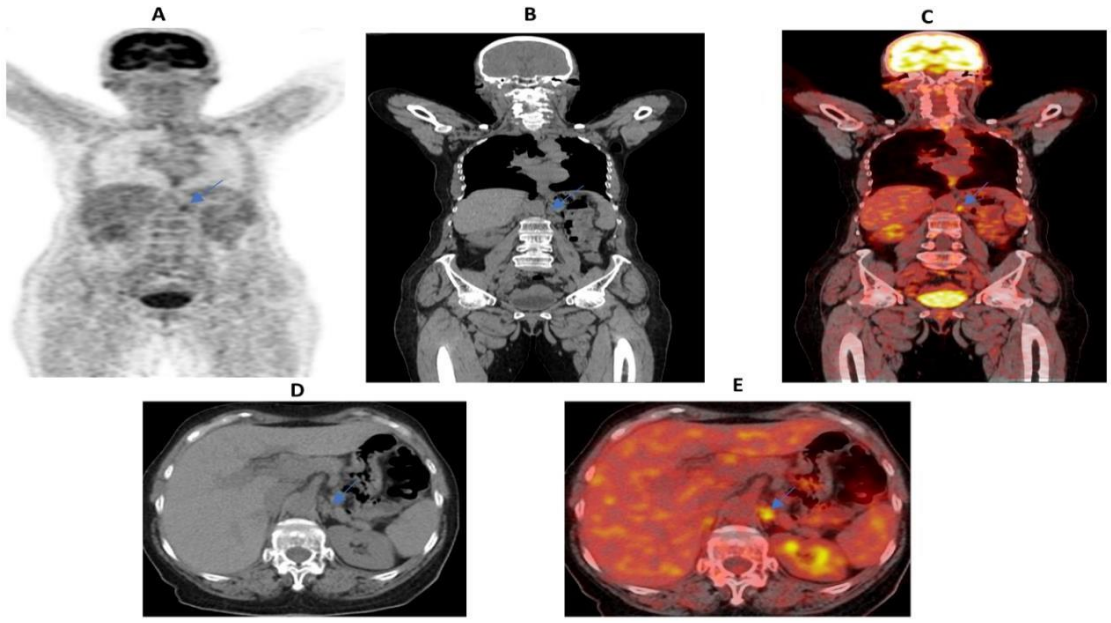

Figure (5): A 62-year-old female with left BC who was referred for restaging due to elevated CA15.3 level (49 U/ml) 20 years after left MRM. PET/CT (C&E) images showed a focal increased FDG uptake by the left adrenal gland, suggesting a recurrent lesion. CT (B&D) images revealed a slightly hypodense lesion in the left adrenal gland. Disease recurrence within the left adrenal gland was confirmed by histopathological and immunohistochemical examinations.

DISCUSSION:

Follow-up of BC patients to rule out recurrence might be challenging. In addition to clinical features, other methods have been applied, such as tumor marker assessment and conventional imaging. Although not being routinely prescribed, the use of ^{18}F-FDG PET/CT scan in the follow-up of these patients is peaking globally.[18] In clinical practice, CA15.3 is the most commonly used tumor marker for BC. However, there have been fluctuations that are inconsistent with the disease's progress.[13]

In our study, we aimed to correlate PET/CT-based parameters with CA15.3 levels and survival outcomes and to verify the significance of ^{18}F-FDG PET/CT in evaluating patients with suspected recurrent BC.

Previous meta-analyses reported that FDG-PET/CT has a sensitivity of 88–95% and a specificity of 69%–93% in diagnosing recurrent BC.[9, 19, 20]. The varied levels of sensitivities and specificities may be explained in part by major quality concerns raised about the reviewed studies. The previous study designs were primarily retrospective and exclusively focused on suspected recurrent BC with elevated tumor markers. Furthermore, there were different methodological issues (e.g., FDG-PET vs. FDG-PET/CT, lesion-based vs. patient-based analysis) and reference standards.

The present prospective study revealed a strong significant correlation (kappa= 0.86, p<0.001) between ^{18}F-FDG PET/CT and the final diagnosis of recurrent BC with a sensitivity, specificity, PPV, NPV, and accuracy of 96.6%, 92.3%, 98.3%, 85.7%, and 95.8%, respectively.

Goktas and Cayvarli reported comparable results (kappa= 0.89, p<0.001), with a sensitivity, specificity, PPV, NPV, and accuracy of 96%, 94%, 98%, 88%, and 96%, respectively, in diagnosing BC recurrence.[21]

Dong et al., evaluated the diagnostic role of ^{18}F-FDG PET/CT in BC recurrence and found that it had a sensitivity of 95% and a specificity of 71.43%. The NPV was 100%, while the PPV was 90.48%. The lower specificity in their study might be related to the different analytical methodology (lesion-based) that yielded high FP results.[22]

We found a FP case that was referred for PET/CT due to elevated tumor marker and demonstrated hypermetabolic contralateral axillary LNs interpreted as suspected nodal recurrence, with no other metabolically active lesions observed elsewhere all over the scanned body. However, histopathological examination revealed reactive lymphoid hyperplasia. Increased metabolic activity in the axillary LNs on PET/CT imaging is frequently associated with inflammatory causes and reactive lymphadenopathy.[23] On the other side, we reported two FN cases; both of them were referred for PET/CT because conventional imaging revealed pulmonary micronodules in each of them, and the second case also had hepatic focal lesions suggesting distant recurrence that were falsely missed on the PET/CT. The recurrent pulmonary and hepatic metastases were confirmed in the follow-up MSCT, which showed morphologic progression of both visceral lesions in the two patients. Furthermore, the patient with pulmonary and hepatic metastases died as her clinical condition deteriorated. Although both patients' primary tumors exhibited a high proliferation index (Ki-67 >14%) and tumor grade (III), which are known to be associated with high FDG uptake [24], the recurrent lesions were non FDG-avid.

Several studies showed a differential expression of immunohistopathological markers between primary and recurrent BC.[25][26] This discordance could be the reason for our FN results.

Interestingly, we observed an isolated metabolically active suprarenal lesion in a patient with a history of left MRM and chemoradiotherapy twenty years ago, which was histopathologically confirmed to be a recurrent metastatic breast lesion. The patient died within one year of the recurrence.

While IDC often metastasizes to various organs, including the lung and pleura, it is extremely uncommon to spread to the adrenal glands. Indeed, suprarenal metastasis of BC tends to occur with ILC and is usually associated with concurrent multi-organ metastases. (27)

The possible explanation for this unusual finding is that our representative patient had both invasive lobular and ductal BCs.

Ciriano Hernández et al. published a case report discussing a solitary recurrent suprarenal metastasis from IDC eleven years following curative therapy of the primary lesion. (28)

This manuscript demonstrated a significant link between CA15.3 levels and positive recurrence on PET/CT in patients being evaluated for suspected recurrent BC; the majority of cases with high CA15.3 levels (34/39) had recurrence on the PET/CT imaging. These findings are consistent with those published by **Mwania et al**, who reported that 27/32 of BC patients with elevated CA15.3 had positive PET/CT findings.(7) This advocates the high diagnostic accuracy of ^{18}F-FDG PET/CT in identifying and mapping out the sites of recurrence in patients with elevated CA15.3 after primary treatment of BC.

On the other hand, we found a considerable number (24/33) of cases with normal CA15.3 levels had BC recurrence on PET/CT. **Gallowitsch et al.** claimed that ^{18}F-FDG PET/CT is a reliable imaging tool for verifying recurrence in BC patients with a clinical suspicion of disease recurrence but normal tumor marker levels.(29) This suggests that ^{18}F-FDG PET/CT has a higher sensitivity in identifying recurrence than CA15.3 in BC patients clinically suspected to have recurrence, and that CA15.3 values within the refence range do not rule out the potential of a positive recurrence on PET/CT.(7)

In several studies, the sensitivity and specificity of CA 15-3 in recurrent BC ranged from 38–80% for sensitivity and 91% for specificity, making it difficult to establish an appropriate cut-off value. (30), (31)

Using a cut-off of >30 U/mL, we found no statistically significant correlation between CA15.3 levels and the final diagnosis of recurrent BC.

Similarly, **Goktas and Cayvarli** could not identify any significant association when they used a cut-off value >25 U/mL.(21)

To the best of our knowledge, this is the first study to investigate the relationship between various PET/CT parameters (SUVs, MTV, and TLG) and CA15.3 in the context of BC recurrence. We noted a highly significant correlation between TLG and MTV of the visceral recurrence and the hottest recurrent lesions ($p<0.001$), as well as TLG of the osseous recurrence ($p=0.025$) and the levels of CA15.3. While no significant correlation was found between CA15.3 and SUVs of the aforementioned lesions or any PET/CT parameters of the nodal recurrence.

Cervino et al. discussed the correlation between SUVmax and CA15.3 values in recurrent BC and found no relation between the two variables with respect to the most active recurrent lesions and visceral/osseous recurrence, which was in accordance with our findings (13).

Similarly, an update study conducted by **Mwania et al**, found no correlation between the SUVmax of the most metabolically active recurrent lesions and CA15.3 levels. (7)

The authors hypothesized that other PET/CT quantitative parameters, such as TLG and MTV, are more accurate than SUVs in assessing glucose metabolism because SUVs don’t reflect the overall disease burden;

additionally, they are frequently subject to various sources of variability, such as reconstruction parameters, regions of interest, patient size, and incubation timing.[7], [13]

We observed that SUVmax, SUVpeak, SUVmean, and MTV of the most metabolically active recurrent lesions were significant predictors of OS.

In the only published study on the relationship between FDG PET/CT-based volumetric metrics (MTV and TLG) and OS in patients with recurrent BC, **Taghipour and colleagues** agreed with us that SUVmax and SUVpeak were significant predictors of OS in BC recurrence, yet they disagreed with our findings by stating that TLG rather than MTV was also a significant predictor. [12] The conflicting results might be explained by relying on MTV and TLG measurements for all recurrent lesions (e.g., MTV_{total} and TLG_{total}), rather than the most active ones in their study.

We found that patients with positive PET/CT results and high CA15.3 have a significantly shorter OS than those with negative PET/CT and normal CA15.3, which is keeping with the findings of **Urso et al**.[32]

limitations of the study: it was a single institution study, which restricted the generalization of findings. Histopathologic confirmation was not available for all patients. A patient-based rather than lesion-based approach was used to assess the diagnostic performance of PET/CT as some patients had numerous recurrent osseous lesions, making the latter approach difficult to apply. In addition, treatment decision is generally based on the confirmation of recurrent disease rather than the number of affected lesions. As a result, the patient-based analysis is clinically more relevant.

CONCLUSIONS:

^{18}F-FDG-PET/CT is an effective supplement to existing surveillance tools for confirming recurrence in BC patients with a suspicion of relapsed disease as well as mapping out recurrent sites. It should be considered in patients with suspected BC recurrence but normal CA15.3 levels. CA15.3 levels are substantially higher in patients with positive PET/CT recurrence, and this group of patients had a significantly shorter OS than patients with normal CA15.3 and negative PET/CT recurrence. Therefore, the values of CA15.3 and PET/CT results are consistently complementary.

FDG PET/CT-based volumetric metrics (MTV and TLG) are significantly correlated with CA15.3 levels.

FDG PET/CT-derived SUVmax, SUVpeak, SUVmean and MTV are significant predictors of survival in patients with suspected recurrent BC.

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