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The Impact of Pretreatment ^{18}F-FDG (PET/CT) Maximum Standardized Uptake Value and Neutrophil/Lymphocyte Ratio (NLR) in Predicting Prognosis in Surgically Treated Oligometastatic Breast Cancer Patients

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Abstract

Purpose: To evaluate baseline PET/CT SUVmax value and Neutrophil/lymphocyte ratio (NLR), as prognostic indicators of progression free survival (PFS) and overall survival (OS) in surgically treated oligmetastatic breast cancer (OMBC) patients.

Materials and Methods: The pretreatment ^{18}FDG-PET-CT SUVmax and NLR in surgically treated OMBC patients were compared with clinicopathological parameters. The prognostic value of pretreatment SUVmax and NLR for PFS and OS were assessed using Log rank and Cox regression.

Results: Overall, 87 OMBC were included, mastectomy and axillary clearance was performed in 72 patients (83%) who responded to preoperative systemic. The receiver operator curve (ROC) demonstrated that SUV_{max} of 4.4 and 6.5 to be the cut off value for predicting PFS in patients with oligometastasis to bones and visceral organs respectively. Additionally, baseline NLR cut off value of 2.7 predicted PFS in all studied patients. In surgically treated 46 OMBC patients (64%) to bones SUV_{max} of >4.4 had a significantly shorter OS [Hazard ratio (HR 2.9)] <4.4 (P<0.01), whereas patients with SUV_{max} of ≤4.4 had significantly longer PFS compared with those with SUV_{max} >4.4 (P=0.02). Similarly, 26 OMBC patients (36%) to visceral organs with SUV_{max} ≤6.5 had significant improvement in OS compared to those with SUV_{max} >6.5 (HR 2.3)]. Moreover, patients with NLR ≥2.7 showed significantly lower PFS (HR, 2., P<0.001) and overall survival rate (HR,1.9, P=0.02) than patients with NLR<2.7. Cox regression multivariate for OS revealed that higher baseline SUV max and NLR along with visceral metastasis were independently correlated with poor prognosis, with HR 3.04, 8.83 and 9.21 respectively.

Conclusion: The pretreatment PET-CT SUV_{max} and NLR showed a significant association with different clinicopathological prognostic factors in OMBC patients. Additionally, the may be considered as potential independent prognostic indicators of clinical outcomes in surgically treated OMBC patients.

Keywords: ^{18}FDG PET/CT SUV_{max}; NLR Oligometastatic breast cancer

Introduction

Breast cancer is considered the most common cancer in women in developed world, only a minority of patients <10% has metastatic disease (stage IV) at diagnosis [1]. Additionally, distant metastatic relapse will develop in 20-30% of patients with early BC [2]. Survival of stage IV patients is constantly improving due to advances in available multimodality therapies and a better understanding of tumor biology [3-5]. Oligometastatic breast cancer (OMBC) is a subset of metastatic breast cancer (MBC) with limited number (usually ≤5) and sites of metastasis and constitutes as high as 20% of all MBCs [6]. Prolonged disease control is possible in patients with OMBC when treated with aggressive multidisciplinary management including primary tumor extirpation [7,8]. In a metaanalysis of 10 studies that included 28,693 with stage IV breast cancer, women undergoing a resection of the primary breast cancer were more likely to survive three years compared with women not undergoing a primary cancer resection (40 versus 22 percent, odds ratio [OR] 2.32, 95% CI 2.08-2.6, p<0.01). Moreover, surgical resection was performed more likely in patients who had metastatic disease confined at one site only (63 versus 44 percent) [9]. Main limitations of this analysis were its retrospective nature and patient selection bias. In addition, data on HER2+ patients are missing in most studies, limiting the applicability of these results in all disease subgroups and in the modern era of HER2-targeted therapies.

However, five randomized, controlled trials in the US/India/Austria/Netherlands/Turkey address the role of primary tumor excision in MBC. The results of the Indian and Turkish trials were recently presented and showed no statistically significant difference in survival between patients undergoing surgery versus those receiving systemic

therapy [10,11]. Long term survival in OMBC is either due to selection of patients whose tumors have indolent disease biology or to effects of therapy. The sparse data, heterogeneity of disease biology and absence of randomized trials make treatment recommendations less evidence based. Moreover, metastasis is a sequence of complex interactions between the tumor cells, microenvironment and host. Genetic, epigenetic and host immune processes contribute to the equilibrium that is permissive of metastasis [12].

Increasing detection of oligometastatic disease is dependent on recent improvements in sensitivity and sophistication of imaging technology. Positron emission tomography/computed tomography (PET/CT) is a widely used diagnostic tool that combines anatomic with functional imaging using [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG), a biomarker of cellular metabolism. It can detect enhanced glycolysis of cancer cells and has proven valuable in diagnosing, staging, detecting recurrences, and assessing response to therapy in a multitude of malignant disorders [13]. The standardized uptake value (SUV) of PET/CT is a semiquantitative simplified measurement of the tissue FDG accumulation rate, and studies of the head and neck, lung, esophageal, endometrial, cervical and renal cell cancer have explored the prognostic significance of the maximum standardized uptake value (SUVmax) [14-19]. Moreover, the improved diagnostic performance of PET/CT imaging over conventional imaging has been investigated in the staging of high-risk patients with early breast cancer and the detection of bone metastases in patients with metastatic breast cancer [20,21]. Recently, several studies reported the correlation between maxSUV of breast cancer and several clinicopathologic or immune-histochemical features [22-25]. Limitations in published series include small numbers, lack of histologic correlates, and the intra individual variation in SUV by body site and motion artifact. On the other hand, an important continuing challenge in diagnosing OMBC is to discover prognostic biomarkers that predict the patient outcome and individualize patient management based on obvious therapeutic implications. Several biomarkers such as neutrophils, lymphocytes, neutrophil to- lymphocyte ratio (NLR), mean platelet volume, red cell distribution width, circulating tumor cells and gamma-glutamyl transferase have been considered as potential prognostic factors for cancer [26-30]. There is accumulating evidence for the association of NLR with survival of patients with many kinds of cancers, including breast cancer [31-38]. However, the published results are inconsistent. Some studies reported that NLR was significantly associated with shorter DFS and OS in breast cancer patients, while others showed that NLR could not be considered as an independent prognostic factor for breast cancer [39-41]. Consequently, in the current retrospective, single-institution study, we examined both baseline FDG avidity on PET/CT images assessed by the maximum SUV (SUV_{max}) and NLR, as prognostic indicator of progression free survival (PFS) and overall survival (OS) in surgically treated oligmetastatic breast cancer patients. Furthermore, identifying reliable prognostic markers would be of ultimate importance to individualize the management of patients with OMBC.

Material and Method

Retrospective review of breast cancer patients treated or referred to King Fahad Specialist Hospital-Dammam during the period between January 2010 and December 2013 after obtaining IRB approval. All patients signed informed consent. Electronic medical records were reviewed to determine known prognostic variables including: age, histology, grade, tumor phenotype (ER, PR, and HER2 expression), Ki 67 index, neutrophil/lymphocyte ratio (NLR) and first-line treatment administered. NLR was taken as the baseline sample immediately after breast cancer diagnosis was confirmed and before the initiation of any treatment modality (pretreatment NLR). NLR is calculated as neutrophil count divided by lymphocyte count. Progression-free survival (PFS) was defined as the length of time from the date of the diagnosis to disease progression. Overall survival (OS) was defined as the interval between the date diagnosis and the date of death from any cause. We defined HR-positive, HER2-negative and Ki67 index <14% as luminal A, HR positive and HER2-positive (or HER2-negative with Ki67 index ≥14%) as luminal B. Her-2/Neu status was defined positive when over-expressed with 3 plus staining in IHC or amplified with a ratio >2.2 by fluorescence in situ hybridization (FISH). Ki67 was visually scored for percentage of tumor cell nuclei with positive immune staining above the background level by two pathologists. Oligometastatic breast cancer patients were treated with anthracycline based chemotherapy (CT) ± Herceptin or hormonal therapy. Those who had objective tumor response after 6 cycles of CT were offered mastectomy and axillary lymph nodes dissection. On the other hand, patient who develop progressive disease after systemic treatment were not offered surgery. Palliative radiation was offered to bone lesions as necessitated by symptoms. Hormonal therapy as well as targeted therapies were also offered. Locoregional radiation was left to physician discretion.

Inclusion criteria

Female gender, 18 to70 years of age, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, life expectancy of >3 months, adequate bone marrow reserve, adequate liver and renal function, with no systemic or locoregional therapy in the metastatic setting. Biopsy proven invasive breast cancer by tru-cut biopsy, base line PET/CT as a part of staging work up, patients should have evidence of >1 FDG avid lesion at any of the following common metastatic breast cancer sites: bone, liver, lungs and non-regional lymph nodes.

Exclusion criteria

Patients who had excisional biopsy were excluded from the study because of higher incidence of inflammatory complications that may interfere with tumor imaging with PET/CT. In addition to patients who had received neoadjuvant chemotherapy or radiation therapy before undergoing PET/CT, brain metastasis at presentation, pregnancy or breast-feeding, history of diabetes mellitus, diagnosis of second primary malignancy, and active or uncontrolled infection.

Pretreatment ^{18}F-FDG-PET-CT scan

The FDG-PET/CT scans were carried out using a Gemini XL PET/CT that combines a germanium oxyorthosilicate-based PET scanner and a 16-slice Brilliance CT scanner (Philips). All patients fasted for at least 6 hours before PET scans and had serum glucose levels 7.8 mmol/L. Before and after injection, patients were kept lying comfortably in a quiet, dimly lit room. There was no significant difference in blood glucose levels measured at the time of the pre- and post-^{18}F-FDG studies. CT data were acquired first (120 kV, 100 mAs, no contrast enhancement). PET emission data were acquired in a 3-dimensional mode, with 3-5 min per bed position, and reconstructed using a 3-dimensional row-action maximum-likelihood algorithm. The attenuation-corrected images were normalized for injected dose and body weight and converted into standardized uptake values (SUVs).

The SUV was defined as (tracer concentration [kBq/mL])/(injected activity [kBq]/patient body weight [g]). Image acquisition was started 1 h ± 10 min after intravenous administration of FDG (7.4 MBq/kg body weight). PET studies were acquired at 3-5 min per bed position, depending upon the patient's weight and body habitus, for a total of six or seven bed positions. As per our protocol, low dose CT images were obtained with oral contrast only for attenuation correction. Interpretation of the dual PET-CT images was carried out by a nuclear medicine physician/radiologist trained in PET-CT. Lesions with standardized uptake value (SUV) of >2.5 were considered malignant. A region of interest was drawn at each pathologic site of tracer uptake, and the SUVs were calculated automatically by the computer using the body weight method: SUV_decay-corrected activity (kBq)/tissue (ml) injected FDG dose (kBq)/body weight (g). Maximum SUV was measured at every site of metastases, at the primary tumor (if present), and at each of the respective regional and distant nodal groups. For patients who had multiple metastatic sites, the singlelesion with the highest SUV_{max} was used for calculation. Tumor size had to be a minimum of 1 cm to minimize partial volume averaging effects in FDG-PET interpretation. For visual analysis, abnormal FDG uptake was defined as substantially greater activity in the tissue than in the aortic blood on attenuation-corrected images. When abnormal FDG uptake was present in bone, the exact anatomic location of the abnormal uptake was identified on the CT images.

Statistical consideration

The impact of different clinical parameters on Baseline SUV_{max} was evaluated by Mann-Whitney U test (between 2 groups) or Kruskal-Wallis test (≥3 groups). Receiver operator characteristic (ROC) curves were used to identify potential SUV cutoffs values in patients with multiple and oligometastatic disease. An area under the curve of 1.0 would indicate a perfect test, whereas 0.5 would represent a noninformative test. Kaplan-Meier method was accessed for survival analysis. The SUV_{max} values are presented as medians and interquartile ranges (IQRs), because data were not normally distributed. Prognostic variables identified by univariate analysis, with P<0.1, were analyzed in the multivariate Cox model. All reported P-values were two-sided. Statistical significance levels were set at P<0.05. Disease free survival (DFS) and overall survival (OS) were calculated using the Kaplan Meier analysis. Log-rank test and Cox regression analysis were performed to correlate the various clinical and pathological parameters to treatment outcomes. All analyses were performed using SPSS 16.0 package program, (SPSS, Chicago, IL).

Results

The final analysis included 87 patients (median age, 48 years; range, 28-70years) who initially presented with oligometastatic breast cancer who underwent pretreatment PET/CT imaging to exclude multiple metastatic sites. Other baseline characteristics including pretreatment neutrophil/lymphocyte ratios are provided in Table 1. The median time from diagnosis of MBC to disease progression was 20 months (range, 12–38 months). The majority of patients (n=74; 85%) initially had a clinically advanced stage breast cancer (stage III and IV) while the remaining 13 patients (15%) presented with stage II disease and all patients were subsequently found to harbor metastatic disease. Invasive ductal carcinoma was encountered in the vast majority of patients (n=78; 90%). With regards to tumor phenotype luminal A, B (ER/PR-positive) constituted the largest subgroup (n=49; 57%) whereas luminal B like, Her2neu positive and triple negative was encountered in 17%, 15% and 11% of the studied patient population, respectively. Seventy patients (80%) received chemotherapy, and 17 patients (20%) received targeted therapy, possibly combined with chemotherapy or endocrine therapy. With regards to indications of PET/CT scanning as reported in patients files were: to further characterize nature of suspicious lesions detected on other radiologic studies in 70 patients (80%) and to assess patients presenting with either locally advanced breast cancer or with symptoms in (12%) of patients (Table 2). Overall, 46 patients (53%) had evidence of oligo metastatic disease to bones only whereas 41 patients (47%) had visceral either to lung in 25 patients (61%), liver in 12 patients (29%) or lymph nodes in 4 patients (10%) on PET/CT images respectively). In total, 80 patients (92%) had at least 1 biopsy result that confirmed the MBC diagnosis. Among the patients with FDG-avid lesions, according to anatomic site, the numbers with positive biopsies were as follows: bones, 30 of 46 patients (65%); liver, 18 of 25 patients (72%); and lung, 7 of 12 patients (58%) and all metastatic LNs were biopsied. The median SUV_{max} of the studied 87 patients was 10.2 ± 5.1 (range, 2.8-18.3). Median SUV_{max} was also significantly different among different tumor grade groups (P<0.01) and was increased by increases in the tumor grade. The SUV_{max} was significantly higher in triple negative tumors (P=0.01) and Her2neu positive tumors (P=0.02), compared to luminal A, B tumors respectively (Table 3). Moreover, median NLR was significantly higher in patients with Her2neu positive tumors (P=0.04) and in patients presenting with visceral metastasis (P=0.05) respectively (Table 3). Moreover, the median value of baseline neutrophil/lymphocyte ratio (NLR) was 1.97 (range, 0.83-8.9). The receiver operating curve (ROC) demonstrated a baseline NLR of 2.7 cut off for predicting PFS (area under the curve: 0.759; standard error: 0.0678 with a sensitivity of 75.7% and a specificity of 80% for predicting the PFS (Figure 1).

In total 87 patients, 50 patients had NLR less than 2.7, and 37 patients had NLR equal to or higher than 2.7. It is worth mentioning that on multiple regression analysis baseline NLR is found to be the single clinicopathological factor significantly related to baseline SUV max (P=0.04).

In patient presented with breast cancer metastasizing to bone only, the receiver operator curve (ROC) demonstrated a SUVmax of 4.4 to be the optimal cutoff for predicting PFS (area under the curve: 0.698; standard error: 0.0683). A SUVmax of 4.4 yielded a sensitivity of 67.3% and a specificity of 76.2% for predicting the PFS (Figure 2). Similarly, patient presented with multiple metastatic disease, the receiver operator curve (ROC) demonstrated a SUV_{max} of 6.5 to be the optimal cutoff for predicting PFS (area under the curve: 0.843; standard error: 0.068). A SUV_{max} of 6.5 yielded a sensitivity of 87% and a specificity of 81.2% for predicting the PFS (Figure 3).

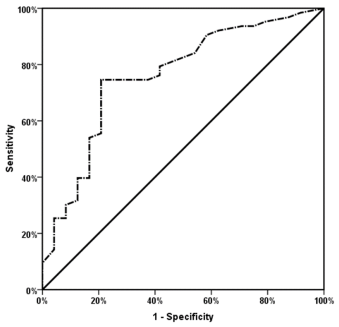

Figure 1: The receiver operator curve (ROC) of baseline neutrophil/ Lymphocyte ratio (NLR) in oligometastatic breast cancer patients.

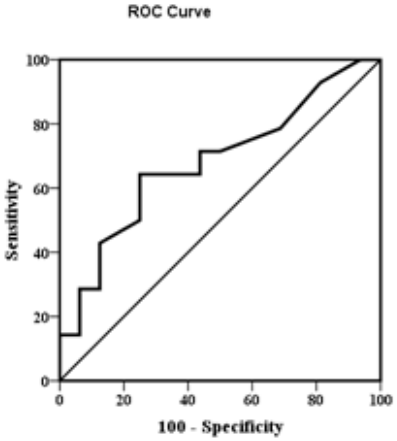

Figure 2: The receiver operator curve (ROC) of baseline PET-CT SUV_{max} in oligometastatic breast cancer metastasizing to bone only.

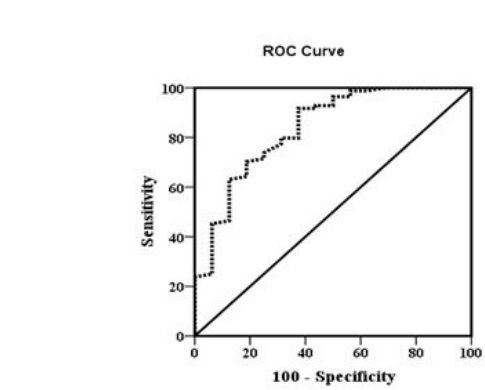

Figure 3: The receiver operator curve (ROC) of baseline PET-CT SUV_{max} in oligometastatic breast cancer metastasizing to visceral organs.

Baseline Characteristic	**No. of Patients**	**%**
Age		
≤50	50	57
>50	37	43
Tumor phenotype		
Luminal A	25	29
Luminal B	24	28
Luminal B like	15	17
Her2 neu positive	13	15
Triple negative	10	11
Histology		

Ductal	78	90
Lobular	6	7
Other	3	3
Grade		
1	0	
2	7	8
3	80	92
Proliferation index		
Ki 67% ≤ 14%	17	20
Ki 67% ≥ 14%	70	80
Stage at initial breast cancer diagnosis		
Stage I	0	
Stage II	13	15
Stage III	50	57
Sage IV	24	28
Indications for PET/CT		
Other abnormal radiology	70	80
Locally advanced breast cancer & Symptoms	10	12
& Symptoms		
Indication not determined	7	8
First therapy for MBC		
Endocrine therapy	12	14
Targeted with or without endocrine therapy	5	6
Chemotherapy	70	80
Baseline NLR		
<2.7	50	57
≥2.7	37	43

Table 1: Baseline characteristics of the studied group of patients.

Disease Site	Baseline SUV_{max} Values	Baseline NLR
Bone N=46		
Median	4	1.8
Range	5.2(2.8-8)	3.1(0.83-3.9)
Low quartile	3	0.98
High quartile	5	3
Liver N=12		

Median	9.4	1.8
Range	10.5(3.5-14)	7.7(1.2-8.9)
Low quartile	6.7	2.2
High quartile	12.5	4.8
Lung N=25		
Median	7.8	2
Range	10.3(3.2-13.5)	7.3(1.6-8.9)
Low quartile	5.7	1.9
High quartile	10.4	5.3
Lymph node N=4		
Median	6.5	1.8
Range	9.8(3-12.8)	2.6(1.2-3.8)
Low quartile	5	1.3
High quartile	9.4	3.2

Table 2: Baseline SUV max and NLR by Disease Site.

Baseline Characteristic	**No. of Patients**	**%**	**Baseline SUV_{max}**		**Baseline NLR**	
			Median	**Pvalue**	**Median**	**Pvalue**
Age						
≤50	50	57	6.3	0.456	1.9	0.646
>50	37	43	6.9		1.8	
Tumor phenotype						
Luminal A	25	29	4.3	0.332	1.9	0.432
Luminal B	24	28	4.9	0.344	1.8	0.478
Luminal B like	15	17	5.4	0.235	2	0.368
Her2 neu positive	13	15	9.1	0.02	3.8	0.0416
Triple negative	10	1	10.8	0.01	2.3	0.07
Histology						
Ductal	78	90	6.2		1.8	0.345
Lobular	6	7	5.7	0.443	1.9	
Other	3	3	7.1		2	
Grade						
1	0					0.332
2	7	8	7		1.9	
3	80	92	9.8	0. 01	2.8	
Proliferation index						

Ki 67% ≤ 14%	17	20	3.7		1.98	0.654
Ki 67% ≥ 14%	70	80	8.3	0. 01	2.6	
Metastatic sites						
Visceral	41	47	9.8	0.005	3.8	0.05
Bone only	46	53	3.8		0.93	

Table 3: Baseline SUV_{max} and NLR comparison between and among groups.

Standard prognostic variables

Mastectomy and axillary clearance was performed in 72 patients constituting 83% of the studied patient population, while 15 patients did not have surgery to breast cancer primary as they progressed during preoperative systemic treatment. We first examined known prognostic variables (intrinsic phenotype, metastatic disease site, first line treatment, age, tumor grade, histology and baseline neutrophil/lymphocyte ratio) in surgically treated patients and demonstrated the inferior OS of patients with triple-negative disease (negative for ER, PR, and HER2; HR, 3.1) compared with luminal A, B (ER/PR-positive and HER2-negative disease) (P<0.01) (Figure 4). Similarly, patients who had visceral metastases (N=41) had inferior survival (HR, 1.7; P=0.03) compared with patients who had oligo- metastasis to bones. Patients who received targeted therapy (including with endocrine therapy or chemotherapy) or chemotherapy alone in the first-line setting had significantly decreased survival (P=0.001; HR, 1.6 and 3.7, respectively) compared with patients who received endocrine therapy. It is noteworthy that grade (P=0.07), age (P=0.68), and histologic subtype (P=0.66) had no significant effect on prognosis.

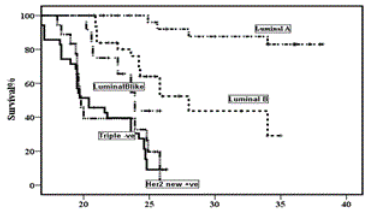

Figure 4: Overall Survival of different phenotypes.

Maximum standard uptake value and NLR as prognostic variables

Among 72 surgically treated patients, a strong correlation between the SUV_{max} cut off value 4.4 in bone and OS was observed in the survival analysis using the Kaplan-Meier method. As the surgically treated 46 OMBC patients to bones (64%) with a SUV_{max} of more than 4.4 had a significantly shorter OS (HR, 2.9) than patients with less than 4.4 (P<0.01) (Figure 5). Furthermore, patients with bone metastasis having SUV max of 4.4 or less median progression free was not reached, consequently they had significantly longer progression free survival compared to patients with more than 4.4 in their bone metastasis (P<0.02) (Figure 6). Additionally, it was observed that surgically treated 26 OMBC patient (36%) presenting with visceral metastasis with SUV max cut off ≤6.5 had significant improvement in OS (HR, 2.3) and PFS (HR, 2.7) compared to those patients with SUV max cut off value >6.5 (Figure 7). Moreover, patients with NLR equal to or higher than 2.7 showed significantly lower PFS (HR, 2.1, P<0.001) and overall survival rate (HR, 1.9, P=0.02) than patients with NLR lower than 2.7 (Figure 8).

In surgically treated patients, Cox regression multivariate for overall survival revealed that higher baseline SUV max and NLR along with visceral metastasis status were independently correlated with poor prognosis, with hazard ratio 3.04 (95% confidence interval [CI], 1.41-9.14), 8.83 (95% CI, 2.41-14.13), and 9.21 (95% CI, 3.24-17.73), respectively.

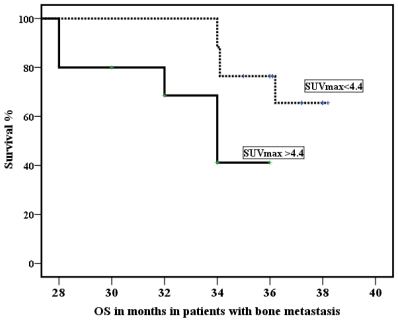

Figure 5: Overall Survival for patients with bone metastasis.

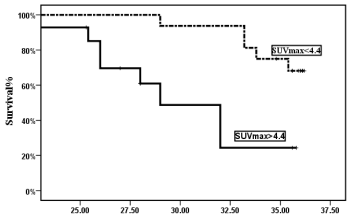

Figure 6: Progression Free Survival for patients with bone metastasis.

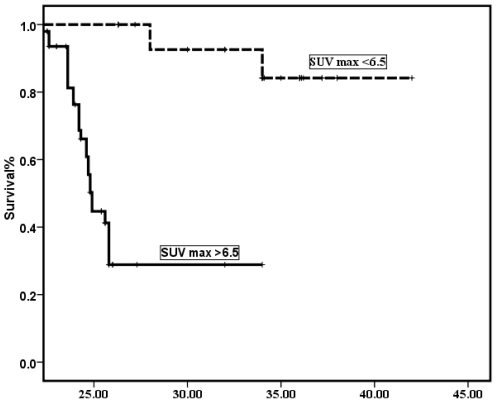

Figure 7: Overall Survival for oligometastatic patients to visceral organs.

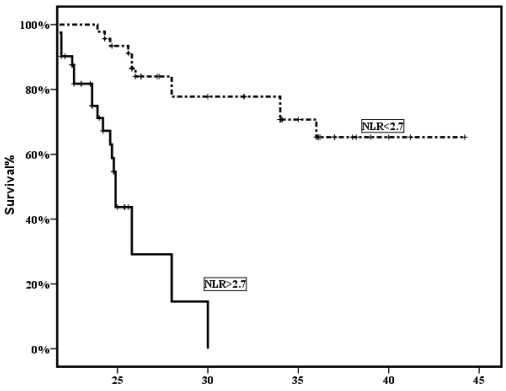

Figure 8: Overall Survival for oligometastatic patients to visceral organs.

Discussion

The oligometastatic breast cancer constitutes a distinguishing subgroup of metastatic breast cancer characterized by single/few detectable metastatic lesions (usually ≤5). Some tumor cell characteristics (altered cell adhesion, intravasation, and bloodstream survival) seem to favour the metastatic spread, while others such as tumor dormancy could result in limited dissemination [12,42]. The oligometastatic phenotypes have also been recently identified from various tumor types and metastatic sites, showing different genetic signatures between patients with few or many metastases. Recently published studies demonstrated a biological basis for oligometastases and a potential for using MicroRNA-200c enhancement to identify patients most likely to develop polymetastatic progression after metastasis-directed treatment [43]. A meta analysis confirmed that multimodal approach is endorsed for these selected patients including resection of the primary breast cancer as it resulted in prolonged disease control and improved survival [9]. Main limitations of this analysis were its retrospective nature and patient selection bias. In addition, data on HER2+ patients are missing in most studies, limiting the applicability of these results in all disease subgroups and in the modern era of HER2-targeted therapies.

The role of primary tumor excision in MBC was also recently addressed in five randomized, controlled trials in the US/India/Austria/Netherlands/Turkey. In the Indian study, patients were randomized after 6 months of anthracyline/taxane-based chemotherapy. Surgery consisted of BCS or modified radical mastectomy + axillary dissection. The lack of survival benefit among subgroups following primary tumor excision [30]. In the Turkish trial, patients were randomized upfront, no stratification was planned. A trend in improved survival was shown in patients with bone-only disease, limited metastatic burden, and favorable histology [31]. The discrepancy in results between retrospective and randomized studies emphasizes on the fundamental demand for improving risk stratification of patients harboring limited burden metastatic disease based on potential clinicopathogoical and molecular prognostic factors. Accordingly, the rationale of our study was to evaluate the impact of different clinicopathological prognostic indicators including baseline NLR and PET-CT SUV max on patients outcome. However, the identification of patients with truly oligometastatic disease is challenging. The improved diagnostic performance of PET/CT imaging over conventional imaging has been investigated in the staging of high-risk patients with early breast cancer and the detection of bone metastases in patients with metastatic breast cancer [20,21]. Moreover, F-18FDG PET can provide quantitative information about tumor glucose metabolism, which represents the aggressiveness of the malignant lesion. FDG uptake can be evaluated noninvasively and be measured with good inter-test reproducibility [22,25].

The combined index, using neutrophil and lymphocyte counts in the form of a neutrophil to lymphocyte ratio (NLR), has been used as a cost-effective and simple parameter of systemic inflammation or stress. The combined index may also be related to prognosis in many types of cancer, including breast cancer [38].

Our study included 87 OMBC who had baseline FDG-PET-CT done prior to any treatment. Visceral metastasis were encountered in 41 patients (47%) had evidence of visceral metastases with or without non regional lymph node involvement. While oligometastatsis to bones only, were observed in 46 patients (53%). In total, 80 patients (92%) had at least 1 biopsy result that confirmed the metastatic breast cancer diagnosis. The SUVmax was significantly higher in triple negative tumors (P=0.01) and Her2 neu positive tumors (P=0.02) compared to luminal A and B tumors respectively. Kim et al. also reported that triple negative tumors had a significantly higher maxSUV than non-triple negative tumors (p=0.016) [44]. Correspondingly, Basu et al. observed that triple negative breast tumors were associated with enhanced FDG uptake commensurate with their aggressive biology [22]. Moreover, median NLR was significantly higher in patients with Her2neu positive disease (P=0.04) and in patients presenting with visceral metastasis (P=0.05) respectively. Similarly, Noh et al. reported that patients with NLR equal to or higher than 2.5 were associated with increased T stage, younger age, positive HER2 status, and higher disease-specific mortality [38].

In surgically treated OMB patients, univariate analysis demonstrated inferior OS of patients with triple-negative disease (negative for ER, PR, and HER2; HR, 3.1) compared with luminal A,B

(ER/PR-positive and HER2-negative disease) (P<0.01). Similarly, patients who had visceral metastases (N=41) had inferior survival (HR, 1.7; P=0.03) compared with patients who had oligo- metastasis to bones. Zhang et al. also reported that the presence of visceral metastasis (P=0.035), number of metastatic sites (P=0.002), chemotherapy as the first-line therapy after PET/CT (P=0.037) were significantly associated with shorter PFS and OS [45]. It is noteworthy that grade (P=0.07), age (P=0.68), and histologic subtype (P=0.66) had no significant effect on prognosis. Morris et al reported comparable results, as grade (P=0.09), age (P=0.45), histologic subtype (P=0.95) were found to have no significant impact on survival [46].

To the best of our knowledge, this retrospective study represents the first series that succeeded to find out cut off values of baseline 18 F PET-CT FDG SUV_{max} uptake for surgically treated breast cancer patients presenting with oligometastasis to visceral organs or to bones (6.5, 4.4) respectively. More importantly, our study demonstrated that baseline NLR cut off value of 2.7 predicted PFS with a sensitivity of 75.7% and a specificity of 80% in OMBC patients. It is worth mentioning that on multiple regression analysis baseline NLR was found to be the single cliniccopathological factor significantly related to baseline SUV max (P=0.04).

In the current study, surgically treated OMBC patients presenting with visceral metastasis with SUV max cut off ≤6.5 had significant improvement in OS (HR, 2.3) and PFS (HR, 2.7) compared to those patients with SUV max cut off value >6.5. Additionally, SUV_{max} of 6.5 yielded a sensitivity of 87% and a specificity of 81.2% for predicting the PFS. This finding was also confirmed previously in other trials [47,48]. Bong et al. reported a cut off value of 6.6 for the SUV_{max} for the whole group without segregation of patients according to the site of metastasis (visceral or bone) and he also demonstrated longer survival in patients with a lower SUV [47]. With regards to, OMBC patients presenting with bone metastasis SUV_{max} of 4.4 or less median progression free was not reached, consequently they had significantly longer progression free survival compared to patients with more than 4.4 in their bone metastasis (P<0. 02). Moreover, SUV_{max} of 4.4 in OMBC to bones yielded a sensitivity of 67.3% and a specificity of 76.2% for predicting the PFS. Correspondingly, Morris et al observed a strong correlation between the SUV_{max} in bone and OS (P<0.001). By using the tertile with the lowest SUV_{max} as the reference group (median, 4.7; range, 2.1-5.8), patients in the highest tertile of SUV_{max} (median, 11.2, range, 9.3-29.6) had the shortest survival (HR, 3.13) [46].

More importantly, our study demonstrated that baseline NLR cut off value of 2.7 predicted PFS with a sensitivity of 68.7% and a specificity of 78.5% in OMBC patients. It is worth mentioning that on multiple regression analysis baseline NLR was found to be the single cliniccopathological factor significantly related to baseline SUV max (P=0.04). Moreover, patients with NLR equal to or higher than 2.7 showed significantly lower progression -free and overall survival rate than patients with NLR lower than 2.7. Correspondingly, Noh et al. reported that patients with NLR equal to or higher than 2.5 were associated higher disease-specific mortality [38]. In surgically treated patients, Cox regression multivariate for overall survival revealed that higher baseline SUV max and NLR along with visceral metastasis status were independently correlated with poor prognosis, with hazard ratio 3.04 (95% confidence interval [CI], 1.41-9.14), 8.83 (95% CI, 2.41-14.13), and 9.21 (95% CI, 3.24-17.73), respectively. Likewise, Noh et al reported Cox proportional multivariate hazard model for disease-specific mortality revealed that higher NLR along with negative ER status and positive nodal status were correlated with poor prognosis, with hazard ratio 4.08 (95% confidence interval [CI], 1.62-10.28), 9.93 (95% CI, 3.51-28.13), and 11.23 (95% CI, 3.34-37.83), respectively [38].

The current study has several strengths

First: it included a broad representation of various intrinsic subgroups of surgically treated OMBC either to visceral organs or to bones only which permitted studying prognostic outcome in each disease subset separately.

Second: 80 patients (92%) had at least 1 biopsy result that confirmed the MBC diagnosis (the gold standard), which contrasts to some other series in which the diagnostic performance of PET/CT imaging was compared with other imaging modalities.

Third: we correlated baseline FDG uptake (SUV_{max}) and NLR with OS, which is a clean endpoint, as this considers both variable tumor biology and treatment administered. Moreover, multiple regression analysis baselines NLR was found to be the single cliniccopathological factor significantly related to baseline SUV_{max}. Consequently, these two baseline prognostic indicators can be used to individualize treatment in OMBC patients such as excluding poor prognosis patients from risk of resection of primary breast cancer.

There are limitations to the current study: it was retrospective, it did not assess tumor: background ratios, it included a heterogeneous population both in terms of variable follow up imaging (timing and modality) and treatment regimens administered. Although 92% of patients underwent a biopsy of at least 1 site, we cannot be absolutely sure that all of the FDG-avid lesions observed on PET/CT images truly represented MBC. Furthermore, we examined PET/CT imaging from only 1 time-point and thus are unable to comment on the prognostic effect of PET/CT imaging (with regard to treatment effect). Finally, because this was a retrospective study, the cost-effectiveness of PET/CT imaging could not be assessed.

Conclusion

This study demonstrates that the pretreatment ^{18}FDG-PET-CT SUV_{max} and NLR showed a statistically significant association with different clinicopathological prognostic factors. In addition, they may be considered as a potential independent prognostic indicator of clinical outcomes in surgically treated OMBC patients. Ultimately prospective studies will be needed to further validate the prognostic potential of pretreatment ^{18}FDG-PET-CT SUV_{max} and NLR in OMBC patients.

Conflict of Interest

All authors confirm that there is no conflict of interest and they all agree to the manuscript. No financial support nor grants were offered to this research.

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