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Investigation of Added Value of Imaging Performed in a Prone Position to Standard ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Imaging for Staging in Patients with Breast Cancer

Meme Kanserli Hastalarda Evreleme için Yapılan Standart ^{18}F-Florodeoksiglukoz Pozitron Emisyon Tomografi/Bilgisayarlı Tomografi Görüntülemesine Yüzüstü Pozisyonda Yapılan Görüntülemenin Katkısının Araştırılması

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Abstract

Objectives: To investigate whether additional imaging in a prone position has any value to the supine whole-body ^{18}fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) images by comparing the visual and quantitative data about a local disease in the breast and axilla for the initial staging of breast cancer (BC).

Methods: In this study, a total of 91 female patients with the BC were studied. Both the supine and prone images were examined based on the axial diameter, number and location of the primary tumor, local invasion signs of the tumor, the number of axillary lymph nodes with a suspected metastasis, metabolic parameters of the primary tumor and axillary lymph nodes, and registration artifacts of the PET and CT images were evaluated individually. These findings were compared with the histopathological data obtained after a surgery.

Results: In the evaluation of a supine and prone imaging, tumor diameter and metabolic tumor volume (MTV) values of the breast lesions were greater in the supine position than in the prone position. However, there was no significant difference found between the other metabolic parameters of a primary tumor and axilla in both positions. In the supine and prone images, accuracy for skin involvement was 84% and 91.3%, respectively.

Conclusion: In our study, we observed that, obtaining additional images in the prone position does not significantly benefit the evaluation of a local disease. The average values of the primary tumor diameter and MTV in the prone position appear to be smaller than the one in the supine position. However, the prone imaging in the patients with a newly diagnosed BC may be beneficial in selected patients and may contribute to preventing the false-positive results especially in patients with a suspected skin involvement.

Keywords: Breast cancer, positron emission tomography/computed tomography (PET/CT), ^{18}F-fluorodeoxyglucose (^{18}F-FDG), prone position

Öz

Amaç: Meme kanserinin ilk evrelendirmesi için yapılan görüntülemede, meme ve aksilladaki lokal hastalık hakkındaki görsel ve niceliksel verileri karşılaştırarak, pron pozisyonda bölgesel görüntülemenin, standart tüm vücut ^{18}flor-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) görüntülerine ek katkısının olup olmadığını araştırmak.

Yöntem: Doksan bir meme kanserli kadın hasta incelendi. Hem supin hem de pron görüntüler; aksiyal çap, primer tümörün sayısı ve yeri, tümörün lokal invazyon bulguları, metastaz şüpheli aksiller lenf nodu sayısı, primer tümör ve aksillar lenf nodlarının metabolik parametreleri ile, PET ve BT görüntülerinin füzyon artefaktları ayrı ayrı değerlendirildi. Bu bulgular ameliyat sonrası elde edilen histopatolojik verilerle karşılaştırıldı.

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Bulgular: Meme lezyonlarının tümör çapı ve metabolik tümör hacmi (MTV) değerleri supin pozisyonda, pron pozisyona göre daha yüksekti. Bununla birlikte, her iki pozisyonda alınan görüntülerde primer tümör ve aksillanın diğer metabolik parametreleri arasında önemli bir fark yoktu. Supin ve pron görüntülerde deri tutulumunun doğruluğu sırasıyla %84 ve %91,3 idi.

Sonuç: Çalışmamızda, pron pozisyonda ek görüntü almanın, lokal hastalık değerlendirmesine anlamlı fayda sağlamadığını gözlemledik. Pron pozisyonda primer tümör çapı ve MTV'nin ortalama değerleri, sırtüstü pozisyondakinden daha küçük bulundu. Bununla birlikte, yeni tanı almış meme kanseri hastalarında, pron görüntüleme, seçilmiş hastalarda faydalı olabilir ve özellikle cilt tutulumu şüphesi olan hastalarda yanlış pozitif sonuçların önlenmesine katkıda bulunabilir.

Anahtar kelimeler: Meme kanseri, pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT), ^{18}F-florodeoksiglukoz (^{18}F-FDG), pron pozisyonu

Introduction

^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT), which is widely used in the several malignancies due to various indications, it has a limited contribution to the primary tumor staging, its role in a nodal staging and detection of the distant metastases has been proven (1,2). Although the role of ^{18}F-FDG PET/CT in the evaluation of a primary tumor and axillary lymph node in staging of breast cancer (BC) is still limited compared with the radiological imaging methods such as: Magnetic resonance imaging (MRI) and ultrasonography, this field is open to developments because of the imaging modalities such as: Positron emission mammography and hybrid PET/MRI systems. Several articles have stated that the ^{18}F-FDG PET/CT imaging in a prone position is more suitable for fusion with a MRI and helps to increase the specificity of the breast MRI (3,4). The standard acquisition protocol in the ^{18}F-FDG PET/CT scan is imaging the area between a vertex and upper thigh in the supine position. It has been speculated that imaging of the breast and axillary region in a prone position in patients with a BC will provide a better diagnostic information because of better differentiation of deep breast tissue structures from the axilla and the chest wall; however, data regarding whether the additional images acquired in a prone position significantly adds value to the evaluation of a local disease in these patients are limited. There are relatively limited number of studies that suggest that the additional imaging in a prone position demonstrates more axillary lymph node involvement (5) and provide evidence that the imaging in a prone position is more successful in both the visualizing metastatic axillary lymph nodes and detecting MF (6,7). Further, ^{18}F-FDG PET/CT does not have a major role for the purpose of local staging such as: MF of the primary tumor, axillary node staging, skin, and nipple invasion, and it is speculated that it may have a decisive role in this field, particularly with a introduction of the hybrid PET/MRI systems (8). Therefore, if additional local imaging in a prone position may provide an important additional diagnostic information in the evaluation of the primary tumor and axillary lymph node, including prone imaging to the ^{18}F-FDG PET/CT protocol for staging in patients with BC will be possible.

Materials and Methods

Patients

The institutional review board approved this retrospective study, and the need for a written informed consent was waived. Ethical permission for the study was given by the Ethics Committee of Bezmialem Vakif University Faculty of Medicine with a letter dated 16 April, 2019, numbered 08/131. The medical records of the patients who underwent ^{18}F-FDG PET/CT imaging for the staging purposes at our clinic between the year 2012 and 2018 were retrospectively reviewed. Ninety-six female patients over the age of 18 years with a histopathologically proven diagnosis of the BC underwent PET/CT after a histopathological diagnosis and before the neoadjuvant chemotherapy, and had an additional image acquired in a prone position along with the standard supine imaging. Five patients with a low ^{18}F-FDG affinity were excluded from the study group, and 91 patients were included in this study. However, because bilateral BC was detected in three of the 91 patients, 94 breast tumors and axilla were evaluated.

^{18}F-FDG PET/CT Image Acquisition

All the patients underwent a ^{18}F-FDG PET/CT imaging using a high-resolution PET scanner fitted with an integrated 16-slice multidetector CT (Biograph 16 PET/CT, Siemens, Chicago, IL, USA). Prior to the ^{18}F-FDG injection, blood glucose levels were measured in the well-hydrated patients who had fasted for at least 4 hrs prior to their scheduled PET/CT sessions. ^{18}F-FDG (296-555 MBq) was intravenously administered to the patients whose blood sugar glucose levels were <200 mg/dL. After the injection, patients were allowed to rest in a quiet comfortable room for 45-60 min to allow a complete ^{18}F-FDG biodistribution. Subsequently, each patient emptied their urinary bladder and was instructed to lie in a supine position on the PET/CT scanner bed. For attenuation correction, and the anatomical localization, low-mAs CT scans from the top of the head to the upper thigh were obtained accordingly. Immediately after the completion of CT scans, PET images of the region from the vertex to the upper thigh were acquired for about 3 min per bed position. Attenuation-corrected PET images were reconstructed using an ordered-subset expectation maximization iterative reconstruction algorithm (18 subsets, 2 iterations). After imaging of the whole-body in a standard supine position, local imaging was performed in the prone position, including both the breast tissue and axilla, immediately after in six patients and as a late imaging for 85 patients (105-120 min after the injection). A custom-made polystyrene breast support device was used during the imaging in a prone position.

Visual and Semi-quantitative Image Analysis

All the images were evaluated by the two experienced nuclear medicine specialists. For all the patients, the diameter of the primary tumor in the axial plane of the breast tissue, the number and distribution of the tumor [unifocality (UF), multifocality (MF), multicentricity (MC)], malignant skin involvement, nipple invasion, pectoral muscle invasion, the number of the potential metastatic lymph nodes in the axilla, presence or absence of the distant metastasis, PET/CT fusion misregistration due to a respiratory or motion artifacts, and the metabolic activity of the primary tumor and axillary lymph nodes were noted in both the supine and prone position images. Metabolic activities of a primary tumor and axillary lymph nodes were evaluated visually by comparison with the background activity as well as by the semi-quantitative measurement [maximum standardized uptake value (SUV_{max})]. If multiple primary tumors were in the breast, the size and metabolic activity of the dominant lesion were evaluated. In addition, among the axillary lymph nodes, the SUV_{max} of the lymph node with a highest metabolic activity was also measured. LIFEx software was used to obtain the metabolic tumor volume (MTV) and total lesion glycolysis [(TLG): MTV × SUV_{mean}], and SUV_{mean} of the primary tumor and axillary lymph nodes (Figure 1) (9). We obtained the MTV and TLG values in both positions using threshold values of SUV_{max} 2.5 for the primary tumor and SUV_{max} of 1.5 for the axilla. Ultimately, we obtained the SUV_{max}, SUV_{mean}, MTV, and TLG values of 92 cases for primary tumor, since remaining two cases were excluded because of their very low ^{18}F-FDG uptake. In addition, 24 axilla were excluded because of a very low or no ^{18}F-FDG uptake in some axillary lymph nodes.

Statistical Analysis

SPSS version 20.0 was used for the statistical analysis. Paired samples t-test was used to evaluate the difference between the mean primary tumor and axilla SUV_{max}, SUV_{mean}, MTV, and TLG values, and the primary tumor size on images obtained in the supine and prone positions, if there was a normal distribution, or the Wilcoxon signed ranked test was used if there was no normal distribution observed. For both the positions, accuracy, sensitivity, specificity, positive predictive value and negative predictive values for the nipple involvement, skin involvement, and pectoral muscle involvement were calculated accordingly. Mann-Whitney U test was used to compare the independent groups with a non-parametric distribution. Pearson correlation analysis was used to evaluate the correlation between Ki-67 proliferation index and the SUV_{max} of a primary tumor and axillary lymph nodes. Variables with the normal distribution were expressed as mean ± standard deviation, and those without a normal distribution were expressed as median (minimum-maximum) values.

Results

The mean age of the 91 female patients with a biopsy-proven BC was 49.6 years (27-80 years). Three patients were diagnosed with a bilateral BC. Accordingly, the total number of the breasts and axilla evaluated were 94. Based on the histopathological evaluation, it was reported that 46 of all the tumors were invasive ductal carcinoma, four were invasive lobular carcinoma, two were invasive papillary carcinoma, one was malignant phyllodes tumor, one was metaplastic invasive breast carcinoma, one was mixed invasive tumor, and the remaining 39 tumors were reported as moderate or highly invasive breast carcinoma without an identified specific histological characteristic. Extra-axillary metastasis was detected in the 19 (20.8%) patients based on the ^{18}F-FDG PET/CT imaging. The distribution of the metastases was as follows: An internal mammary lymph node metastasis in three patients, mediastinal mass in one patient, supraclavicular lymph node metastasis in three patients, liver metastases in two patients, bone metastases in 11 patients, and lung metastases in two patients, and both the bone and soft tissue metastases in four patients.

The mean size of the primary lesions located in the breast was about 30 mm in the supine position, whereas it was 29 mm in the prone position. There was a significant difference in the diameter of the primary tumor (p=0.029); however, there was no patient whose clinical stage changed because of this. The mean SUV_{max}, SUV_{mean}, MTV, and TLG values for the primary tumor and the axillary lymph nodes in a supine and prone position are summarized in the Table 1. A significant difference was found between the MTV values of the primary tumor measured in two different positions (p=0.037). However, there was no significant difference between the MTV value and SUV_{mean} and TLG values of a

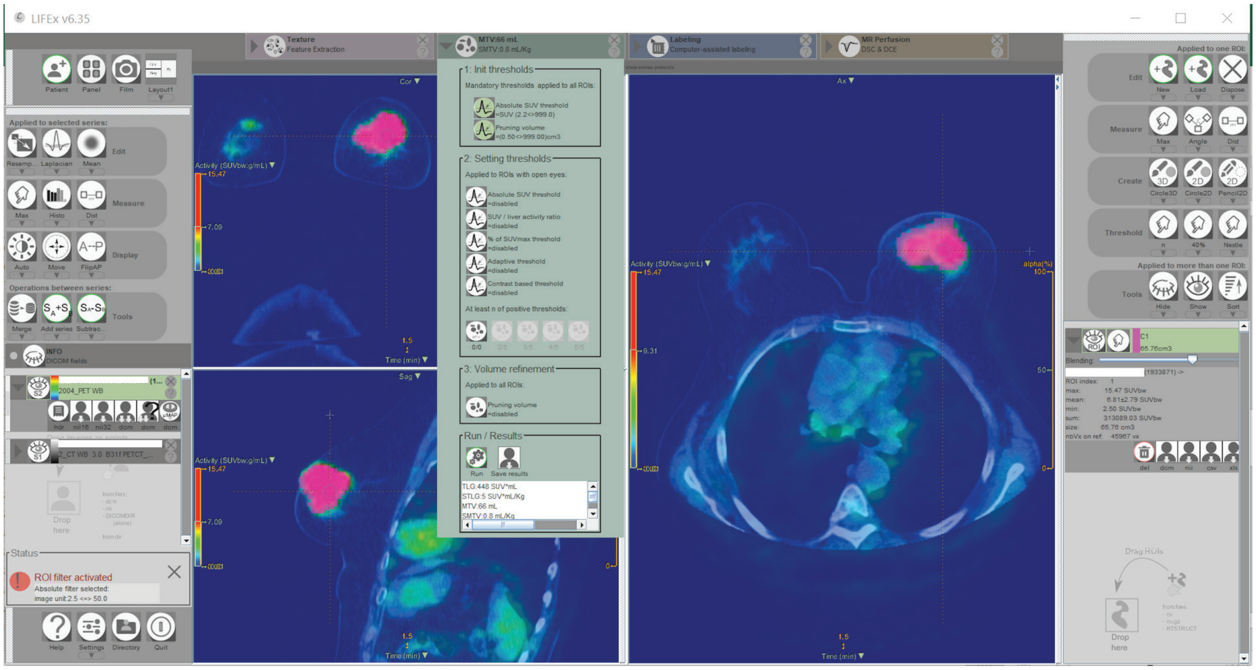

Figure 1. LIFEx software was used to obtain metabolic tumor volume and total lesion glycolysis and SUV average of primary tumor and axillary lymph nodes
SUV: Standardized uptake value

primary tumor and axilla in the both positions.

Primary tumor lesions were grouped based on their distribution like unifocal, multifocal, and multicentric. Accordingly, there was no difference in the tumor localization, and the number between the images acquired in the supine and prone positions. Sixty-three of the tumors were UF, 13 were MF, and 18 were MC.

Lymph nodes with a suspected metastasis on the ^{18}F-FDG PET/CT imaging were classified numerically (1, 2, 3, and multiple). Accordingly, there was no difference in the number of lymph nodes in the 91 axilla (96.8%), except three axillary fossa (3%). One of these patients had four lymph nodes with a suspected metastasis in the supine position, whereas three lymph nodes were observed in the prone images; however, no metastatic lymph node was detected in the axillary dissection performed after the neoadjuvant chemotherapy. Another patient had one lymph node with a suspected metastasis in the supine position and two lymph nodes with a suspected metastasis in the prone position; furthermore, metastasis was detected in three lymph nodes based on the pathological evaluation. The last patient had three lymph nodes in the supine position and one lymph node in the prone position with a suspected metastasis. However, histopathological evaluation did not show any metastatic lymph node.

In the 15 (15.9%) patients, pathological findings in the nipple were identified in at least one of the images in the two different positions. However, in terms of comparison with a histopathological examination, only patients who underwent surgery in their follow-up after PET scan were evaluated. Accordingly, a total of 69 (73%) breast tumors with the available postoperative pathology reports were evaluated in terms of the nipple invasion. Based on this,

Table 1. Primary tumor and axillary lymph node characteristics

		Supine	Prone	p value
Primary tumor	SUV_{max}	8.9±5.1	8.7±5.4	>0.05
	SUV_{mean}	4.3±1.7	4.4±2.1	>0.05
	MTV	24.7±46.8	18.9±42.9	0.037*
	TLG	153.2±439.5	137.3±488.1	>0.05
	Mean diameter (mm)	29.98±14.55	29.04±14.66	0.029*
Axillary lymph node	SUV_{max}	7.3±5.5	7.1±5.4	>0.05
	SUV_{mean}	3.6±1.8	3.5±1.9	>0.05
	MTV	11±18	9.7±15.9	>0.05
	TLG	62±133.2	54.5±122	>0.05

Variables with normal distribution are expressed as mean ± standard deviation. *The significance level is 0.05. SUV_{max}: Maximum standard uptake value, SUV_{mean}: Mean standart uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis in the ^{18}F-FDG PET/CT images, nipple involvement was reported as positive in the eight patients in the supine position and in ten patients in the prone position. In the subsequent histopathological evaluation, it was determined that a total of nine patients had the nipple malignancies. Nipple involvement was confirmed histopathologically in six out of eight patients in the supine position and in seven out of ten patients in the prone position. As a result, false positivity was detected in two patients images obtained in the supine position, and in three patients in the prone position. In addition, in two of nine patients with a histopathologically proven nipple involvement, no involvement was observed in either the supine or prone images, and there was a nipple involvement only in the prone position in one patient, but not in the supine position (Figure 2). Thus, the two patients were considered as false negative in both the positions, and one patient was considered false negative only in the supine position. In a patient with the proven nipple involvement and reported involvement in both the positions, the involvement was more pronounced in the image acquired in the prone position. These results are summarized in the Table 2.

Skin involvement of the primary malignancy was detected in 10 of 69 tumors following a surgery. Skin involvement of the primary malignancy was interpreted based on the presence of thickening, irregularity, and increased ^{18}F-FDG uptake in the skin tissue in the ^{18}F-FDG PET/CT examination.

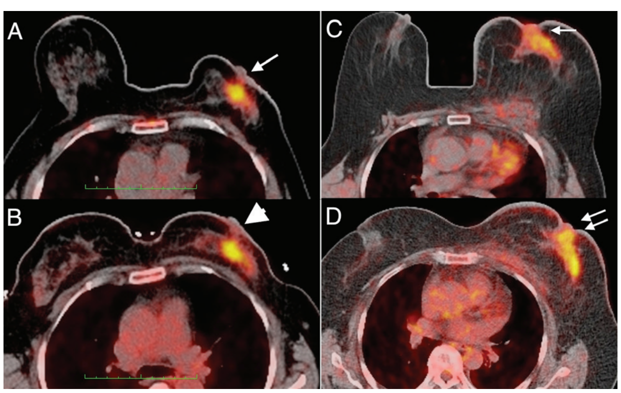

Figure 2. In a 58-year-old patient who underwent ^{18}fluorine-fluorodeoxyglucose positron emission tomography/computed tomography imaging for staging purposes for the diagnosis of unifocal invasive ductal breast carcinoma in the left breast, the nipple retraction in the left breast was more prominent in the prone position (white arrow, A. axial fusion image in prone position) than the images acquired in the supine position (white arrowhead, B. axial fusion image in supine position). However, in another 63-year-old patient, nipple involvement in the left breast was evident in both positions (white arrow, C. axial fusion in prone position and double white arrows, D. axial fusion image in supine position). Malignant tumoral infiltration was detected in the nipple based on the histopathological evaluation performed after surgery in both patients

Accordingly, the skin involvement was identified in the 11 breasts in both positions, and involvement was histopathologically confirmed in seven of them (63%) in both the positions. In addition, suspected skin involvement was identified in the six breasts images obtained in the supine position, whereas skin involvement was ruled out in five of these tumors in the prone position, and only one was considered suspicious, and the skin involvement was confirmed histopathologically in this case (Figure 3). No postoperative involvement was observed in the other five breast tumors with a suspected skin involvement in the supine position. In the two patients whose skin involvement was considered positive in both the positions, the involvement was found to be more pronounced in the prone images. In the two patients with a histopathologically reported skin involvement, no involvement was observed in either of the positions. The patients interpreted as suspicious in terms of the skin involvement in the supine and prone position were also accepted as positive, and the evaluation of the imaging results based on a histopathological data is summarized in the Table 2.

Tumoral invasion signs in the pectoral muscle identified in one patient were not confirmed histopathologically in the ^{18}F-FDG PET/CT images obtained in both the prone and supine positions. In addition, there was suspected tumoral invasion in the two patients in a supine position and in five patients with a prone position, and this involvement was confirmed histopathologically in the two patients classified as suspicious in both the positions. Furthermore, there was no involvement in the images captured in both the positions in two patients whose pectoral muscle invasion was proven after a surgery. Accordingly, results suspected to be positive for pectoral muscle invasion in the supine and prone position were accepted as positive, and the evaluation of the imaging results based on histopathological data is summarized in the Table 2.

When PET/CT fusion images were evaluated in terms of the PET and CT misregistration due to a respiratory or motion artifacts, 12 patients had fusion disagreement only in the prone images and particularly in the axilla, whereas five patients had PET/CT fusion disagreement only in the supine position. Four patients had PET/CT fusion disagreement in both the positions.

There was no significant relationship between the primary tumor SUV_{max}, axillary lymph node SUV_{max}, and primary tumor size values in the supine and prone positions in patients with and without the extra-axillary metastasis,

Table 2. Nipple, skin and pectoral muscle involvement of breast cancer in supine versus prone imaging

		TP	TN	FP	FN	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
Nipple invasion	Supine	6	57	2	3	92.6% (83.7-97.6)	66.7% (29.9-92.5)	96.6% (88.3-99.6)	75% (41.6-92.7)	95% (88.3-97.9)	19.7 (4.7-82.9)	0.35 (0.1-0.8)
	Prone	7	56	3	2	92.6% (83.7-97.6)	77.8% (39.9-97.2)	94.9% (85.8-98.9)	70% (42.3-88.1)	965% (89.2-98.9)	15.3 (4.8-48.6)	0.2 (0.1-0.78)
Skin invasion	Supine	8	50	9	2	84% (73.3-91.7)	80% (44.4-97.5)	84.7% (73.0-92.8)	47% (31.1-63.6)	96.1% (87.8-98.8)	5.2 (2.6-10.3)	0.2 (0.1-0.8)
	Prone	8	55	4	2	91.3% (82-96.7)	80% (44.7-97.5)	93.2% (83.5-98.1)	66.7% (42.5-84.4)	96.5% (88.8-98.9)	11.8 (4.3-31.9)	0.2 (0.1-0.7)
Pectoral muscle invasion	Supine	2	62	1	2	95.5% (87.4-93.2)	50% (6.7-93.2)	98.4% (41.4-99.9)	66.6% (18.4-94.6)	96.8% (92.1-98.8)	31.5 (3.5-277.9)	0.51 (0.2-1.4)
	Prone	2	59	4	2	91% (81.5-96.6)	50% (6.7-93.2)	93.6% (84.5-98.2)	33,3% (11.3-66.1)	96,7% (91.7-98.7)	7.8 (2-30.8)	0.5 (0.2-1.42)

CI: Confidence interval, TP: True positive, TN: True negative, FP: False positive, FN: False negative, PPV: Positive predictive value, NPV: Negative predictive value, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio

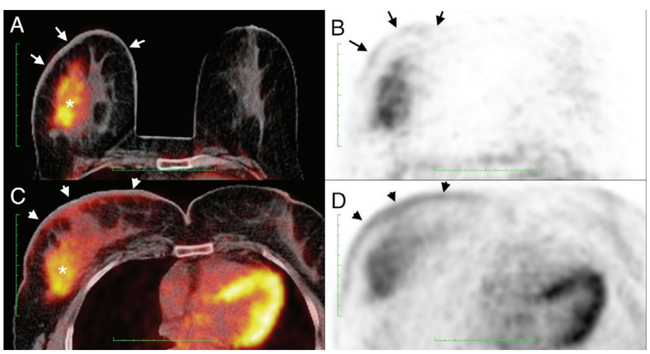

Figure 3. In a 51-year-old female patient with multifocal invasive ductal carcinoma of the right breast, increased thickness with increased ^{18}fluorine-fluorodeoxyglucose uptake in the right breast skin in the supine position (white and black arrowheads, C, D) was decreased in the images taken in the prone position (white and black arrows, A, B). Histopathological examination did not reveal any signs of malignancy in the skin tissue

skin involvement, pectoral muscle invasion, and nipple involvement (p>0.05). The results are summarized in the Table 3.

Based on the correlation analysis between the Ki-67 proliferation index and imaging results, there was a positive correlation between the Ki-67 proliferation index and primary tumor SUV_{max} value in the prone images (p<0.001, r=0.487). However, there was no significant relationship between the primary tumor SUV_{max} value in the supine images. Furthermore, there was a positive correlation between the Ki-67 proliferation index and axillary lymph node SUV_{max} values in both the supine and prone images (p=0.016, r=0.307 vs. p=0.037, r=0.267). There was no significant correlation between the other parameters (Figure 4a, b, c).

Discussion

Khalkhali et al. (10) reported that in technetium-99m scintimammography, imaging in the prone position was a better of a choice than in the supine position because of the differentiation of the deep breast structures in the left breast from the myocardium, and the right breast from the liver and the relaxation of the pectoral muscles. Subsequently, Yutani et al. (11) reported higher SUV_{max} values in the cancerous tissue in the PET imaging performed in the prone position. In the subsequent years, a relatively limited number of the studies showed that additional imaging in the prone position provides more diagnostic information than the images acquired in the supine position (5,6,7).

When axillary lymph nodes were evaluated in the ^{18}F-FDG PET/CT imaging in both the supine and prone positions, there was no difference in the number of the pathological lymph nodes in majority of the patients (96.8%). However, it was predicted that the three lymph nodes with a suspected metastasis in the supine images in three patients may be benign based on the prone imaging, which was subsequently confirmed by the histopathological evaluation, and no metastasis was detected in these lymph nodes. As prone imaging was performed in the late phase rather than immediately after the complete body imaging in these patients, it was believed that the increased ^{18}F-FDG accumulation over a time in the malignant tissue and decreased ^{18}F-FDG accumulation over a time in the benign tissue may have had this dual-phase effect (12). However, Sasada et al. (13) determined that the standard and late SUV_{max} values were equivalent in terms of the diagnostic accuracy in detecting the axillary lymph node metastasis. In addition, Abramson et al. (5) reported that the supine

Table 3. Comparison of SUV_{max} and axial diameter of primary tumor, and SUV_{max} of axillary lymph node measurements derived from supine and prone images with histopathological local involvement results

	Primary tumor SUV_{max}		Axillary lymph node SUV_{max}		Primary tumor size (mm)		
	Supine	Prone	Supine	Prone	Supine	Prone	
M-no	6.8 (2.3-19.8)	6.7 (1.6-17.2)	9.5 (3-12.6)	10 (1.7-13.7)	20 (13-47)	20 (15-50)	
M-yes	7.7 (3.5-103)	7.6 (2.4-17)	5.9 (1.3-27.4)	6.1 (0.0-28)	28 (8-48)	28 (8-46)	
S-no	7 (1.6-22)	6.8 (1-21.4)	6 (1.3-27.4)	5.75 (1-28)	27 (8-73)	25 (3.5-73)	
S-yes	6.9 (3.6-13.5)	6.2 (3.4-18.2)	6.2 (1.3-17)	5.4 (0-17.8)	30 (16-49)	29.5 (15-49)	p>0.05
P-no	7 (1.6-22)	6.8 (1-21.4)	6.7 (1.3-27.4)	6.2 (1-28)	27 (8-73)	25 (3.5-73)	
P-yes	6.7 (4.8-13.5)	5.8 (5.1-18.2)	2.5 (1.3-6.4)	2.55 (0-9.0)	36 (18-61)	38.5 (15-52)	
N-no	7 (1.6-22)	6.8 (1-21.4)	6.7 (1.3-27.4)	6.2 (1-28)	23 (3.5-73)	23 (3.5-73)	
N-yes	6.7 (3.6-13.5)	5.8 (3.4-18.2)	3.3 (1.3-17)	3.2 (0-17.8)	37 (15-52)	37 (15-52)	

Variables without normal distribution are expressed as median (minimum-maximum). SUV_{max}: Maximum standart uptake value, M-no: Group without metastasis, M-yes: Group with metastasis, S-no: Group without skin involvement, S-yes: Group with skin involvement, P-no: Group without pectoral muscle involvement, P-yes: Group with pectoral muscle involvement, N-no: Group without nipple involvement, N-yes: Group with nipple involvement

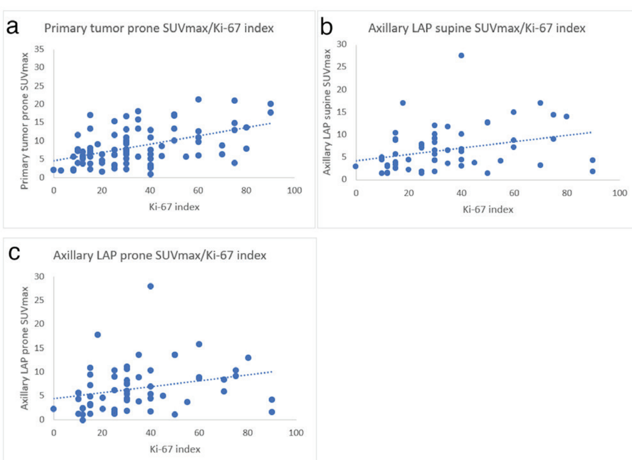

Figure 4. A. Primary tumor SUV_{max} value and Ki-67 proliferation index in the prone position. B. Axillary lymph node SUV_{max} value and Ki-67 proliferation index in the supine position. C. Axillary lymph node SUV_{max} value and Ki-67 proliferation index in the prone position
SUV_{max}: Maximum standardized uptake value

and prone imaging was performed consecutively (the dual-phase effect was negligible) in the evaluation of the axillary lymph nodes and that a higher number of positive lymph nodes was detected in four out of 16 patients in prone imaging. In addition, another study in which the imaging was performed in the prone position followed by the imaging in the supine position reported that a higher number of axillary lymph nodes were detected in the prone position (6).

In the comparison of primary tumor and axillary lymph node SUV_{max} values between the images obtained in the supine and prone positions, in the axillary lymph nodes, there was no significant difference in the SUV_{max} values between the images in the supine position and those in the prone position, whereas primary tumor SUV_{max} values were higher in the supine position than in the prone position. Although the reason for this is not precisely known, it was believed that it may have occurred due to the misregistration artifact or the partial volume effect. Partial volume is particularly affected by how compact the tumor is, as well as the size and shape of the tumor. Measurement results of the SUV_{max} may be higher in the less compact tumors as the tumor tissues in the prone position tend to extend to the edges (14,15). In a retrospective study of the 100 patients designed by Lee et al. (16), they performed prone imaging immediately after a supine position imaging and found higher SUV_{max} values in the supine position, consistent with those obtained in our study. In the same study, the authors also found a higher MTV and the TLG values on images in the supine position (16). In addition, it was presented in our study that there was a significant difference in the images taken in different positions in primary tumor diameters (p=0.029). In this study, in which measurements were made in the axial sections as a standard, it was believed that the reason for the lower tumor diameter in the prone position compared in the supine position was primarily because of the change in the configuration of the tumor. It was believed that the wider spread of the breast parenchyma in the prone position, the tumor mass may have expanded toward the inferior segment, and thus the measurement of its largest diameter may have been lower. In addition, there is a possibility that the tumor diameter may have been measured slightly larger in the supine position because of the surrounding normal breast parenchyma is in a more tightened position in the supine position, especially in the mass lesions with low-moderate ^{18}F-FDG metabolism, which may be one of the reasons why the mean tumor diameter is higher in the supine imaging. Teixeira et al. (6) reported a larger primary tumor volume in a supine imaging, whereas Moon et al. (17) compared the supine ^{18}F-FDG PET/CT with the PET/CT mammography (mammo-PET/CT) in their study and found larger primary tumor size in the mammo-PET/CT in the prone position.

Various studies have shown that the MTV and TLG have a prognostic value in patients with a BC (18,19). In our study, MTV and TLG were also higher in the supine position. Similarly, Arslan et al. (20) found that the tumor size correlated with MTV and TLG. The authors found similar results for the axillary lymph nodes in this study having 139 patients (20). We found the metabolic parameters (SUV_{max}, TLG, MTV) compatible in both the primary tumor and the axilla. All the parameters were numerically higher in the supine position than in the prone position. However, only a significant difference was found in the MTV. Like our study, Lee et al. (16) found that SUV_{max}, MTV, and TLG values were lower in the prone position than in the supine position. They reported that the reason for this may be the partial volume effect. Therefore, they stated that the acquisition position may affect the quantitative PET/CT parameters and the clinical outcomes.

There was no difference between the diagnostic accuracy of both the positions in terms of nipple involvement (92.6%), and sensitivity was higher in the prone images compared with those obtained in the supine position (77.8% and 66.7%, respectively); however, the specificity was slightly higher in the supine images compared with those obtained in the prone position (96.6% and 94.9%, respectively). Positive predictive value for the nipple involvement was higher in the supine images compared with those acquired in the prone position (75% and 70%, respectively), whereas the negative predictive value was slightly higher in the prone images (96.5% and 95%, respectively) compared with those acquired in the supine position. The study by Yoo et al. (21) investigated the importance of the dual-phase prone PET images in terms of nipple-areolar complex involvement in the 21 patients and confirmed that the presence of an increase in the nipple SUV_{max} values in the late phase compared with those in the contralateral breast was an independent variable in terms of the nipple involvement. Although the study design and evaluation criteria were different, we believe that the late prone images were also useful in our study.

Because prone imaging was performed in the late phase, the ^{18}F-FDG uptake in the skin tissue decreased as increasing ^{18}F-FDG uptake in the primary tumor, which facilitated the determination of the patients as negative in terms of the skin involvement. We believed that the ^{18}F-FDG intensity in the skin tissue in a supine position developed secondary to inflammation and that combined evaluation of the images acquired in both the positions and especially dual-phase imaging may be useful. Accordingly, the sensitivity of the supine imaging in terms of a skin involvement was the same as that for the prone imaging (80%), whereas specificity (84.7% and 93.2%, respectively), accuracy (84% and 91.3%, respectively), and the positive predictive value (47.1% and 66.7%, respectively) were lower than those for a prone imaging. The negative predictive value was nearly the same (96%) in both positions. Although the studies have been performed using ^{18}F-FDG PET/CT, and cases showing that the skin involvement affects the prognosis negatively in the literature (22,23) are also available, we could not find a publication that compares the prone and supine images on this subject.

In ^{18}F-FDG PET/CT images acquired in the supine and prone position, one patient had an evidence of tumoral invasion in the pectoral muscle, but it was not confirmed histopathologically. This involvement was also identified in the MRI performed before the treatment, and it was believed that the involvement may not have been detected histopathologically caused by a neoadjuvant chemotherapy performed after the PET/CT scan. In addition, two patients had suspected an involvement in the supine position, and five patients had suspected an involvement in the prone position; involvement was histopathologically confirmed in two patients classified as suspicious in both the positions. In the other three patients who were suspected to be positive only in the prone position and whose histopathological evaluation did not show any signs of a pectoral muscle involvement, only the prone images showed an area of increased density between the malignant mass lesion and the pectoral muscle without the pathological ^{18}F-FDG uptake. This finding was also described in the MRI of the patients who was suspected to have a pectoral muscle invasion. Moreover, all the three patients had multiple fibrocystic structures. The area of increase in density in the prone images was believed to be associated with the fibrocystic-fibro glandular structures described in the last MRI. No involvement was observed in the images acquired in both the positions in two patients with a pectoral muscle invasion after the surgery. Because the breast tissue was very small in one of the patients, muscle invasion could not be differentiated in the images, and prone imaging thus did not enlighten to the differentiation of the tissues. In the other patient, there was no pathological finding in the pectoral muscle tissue, and its vicinity in either of the positions. Accordingly, the accuracy of the supine imaging in predicting the pectoral muscle involvement was slightly higher than that of a prone imaging (95.5% and 91%, respectively), its sensitivity was equal (50%), its specificity was slightly higher than that of a prone imaging (98.4% and 93.6%, respectively), its positive predictive value was significantly higher than that of a prone imaging (66.7% and 33.3%, respectively), and its negative predictive value was nearly equal (96%). Considering that the pectoral muscle involvement does not change the tumor stage, it is believed that it affects the reporting, although it has no clinical significance. While there are studies in the literature regarding the distance of the primary tumor from the pectoral muscle, we were not able to identify a comparative study on a pectoral muscle invasion of the prone and supine imaging in the English literature.

When PET/CT fusion images were evaluated for PET and CT agreement, 12 patients had fusion disagreement only in the prone images especially in the axilla, whereas five patients had it only in the supine position. Four patients had disagreement in both the positions. Although it is known that the imaging in the prone position generally reduces a respiration and movement artifact due to the pressure applied on the chest compared to the supine position (7), in our study, it was suspected that the fusion disagreement in a prone position may be due to less patient comfort in the prone position which results in the higher number of the movement artifacts. It was believed that the arm movement could particularly be the main reason for the incompatibility observed in the axillary lymph nodes in the prone position. In their study on the 198 patients diagnosed with stage II/III BC, Teixeira et al. (6) found a higher disagreement rate in the PET and CT scans in the images acquired in a supine position. This may be due to that the comfort level of the breast positioning device used in a prone position was higher than that of the apparatus used in our study, and/or they performed prone imaging first and then whole-body supine imaging was done. Thus, it may be suggested that the patient compliance is better in the first imaging.

There was no significant relationship between the primary tumor SUV_{max}, axillary lymph node $SUV_{max,}$ and primary tumor size values in the supine and prone position in patients with and without the extra-axillary bone and soft tissue metastasis and patients with and without a skin involvement, pectoral muscle invasion and the nipple involvement (p>0.05). Primary tumor diameter was higher in both positions in the group with a skin involvement, pectoral muscle invasion, and the nipple involvement, whereas a primary tumor and axillary lymph node SUV_{max} values were lower. In addition, the primary tumor SUV_{max} and primary tumor diameter were higher in the group with an extra-axillary metastasis, while the average SUV_{max} in the axillary lymph nodes was lower.

When PET/CT fusion images are evaluated in terms of the PET and CT compatibility, In 12 patients, only prone images and especially axilla fusion mismatch was detected, whereas in five patients only the PET/CT fusion mismatch was observed in the supine position. In four patients, an incompatibility was observed in both the positions.

In the correlation analysis between the Ki-67 proliferation index determined in the histopathological examination performed after a surgery and the imaging results, there was a positive correlation between the Ki-67 proliferation index and a primary tumor SUV_{max} value in the prone images (p<0.001, r=0.487). However, there was no significant relationship between the Ki-67 proliferation index and a primary tumor SUV_{max} value in the supine images. Furthermore, there was a positive correlation between the Ki-67 proliferation index and axillary lymph node SUV_{max} values in both the images taken in the supine and prone positions (p=0.016, r=0.307 and p=0.037, r=0.267, respectively). There was no significant correlation between the other parameters.

Study Limitations

The following were the limitations in our retrospective analysis: (1) The imaging time between the positions was not standardized, (2) the results were likely affected by the dual-phase imaging procedure because prone imaging was done in the late phase in most of the patients, (3) the histopathological data did not have the desired standard because the neoadjuvant chemotherapy protocol was used in most of the patients, and (4) the number of the patients were relatively limited.

Conclusion

Although there are studies which recommend that an additional imaging in the prone position should be included in the evaluation of BC, the advantage of a prone breast PET/CT imaging over the standard supine whole-body imaging has not been clearly determined. The purpose of our study was to make this comparison; however, our result did not indicate any of the imaging positions was significantly more advantageous, and we think that an additional imaging in a prone position may be useful in the selected cases such as, suspicious skin involvement, in the evaluation of a local disease in patients with a BC. In addition, it should be kept in mind that it may change the metabolic and morphological numerical results in images obtained in the different positions.

Ethics

Ethics Committee Approval: Ethical permission for the study was given by the Ethics Committee of Bezmialem

Vakif University Faculty of Medicine with a letter dated 16 April, 2019, numbered 08/131.

Informed Consent: Informed consent was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.B.E., M.A., Design: E.B.E., M.A., Data Collection or Processing: E.B.E., M.A., Analysis or Interpretation: E.B.E., M.A., Literature Search: E.B.E., M.A., Writing: E.B.E., M.A.

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