A prospective comparative study of ultrasonography, contrast-enhanced MRI and ^{18}F-FDG PET/CT for preoperative detection of axillary lymph node metastasis in breast cancer patients.

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A prospective comparative study of ultrasonography, contrast-enhanced MRI and ^{18}F-FDG PET/CT for preoperative detection of axillary lymph node metastasis in breast cancer patients.

AIM: *We aimed to evaluate; (i) the accuracy of ultrasonography (US), contrast-enhanced magnetic resonance imaging (cMRI) and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) for detection of axillary lymph node metastases (ALNMs), (ii) the role of late prone imaging, and (iii) the effect of PET/CT on preoperative staging of breast cancer.*
MATERIAL AND METHODS: *From June 2015 to January 2019, 236 breast cancer patients were preoperatively examined using US, cMRI, and PET/CT and whom underwent pathological evaluations of axillary lymph nodes were analyzed. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) of US, cMRI, and PET/CT for ALNMs were determined.*
RESULTS: *There were 235 female and one male in our study. The mean age was 55,6±11,3 years. Of 158 patients who were histopathologically evaluated, 85 patients (36%) were negative and 73 patients (30.9%) were positive for ALNMs. The remaining 78 patients who were only radiologically evaluated with US and/or cMRI, 24 patients (10.2%) were negative and 54 patients (22.9%) were positive for ALNMs. The sensitivity, specificity, PPV, NPV, and ACC of PET/CT were 80.0%, 92.2%, 92.0%, 80.3%, and 85.7%, respectively. The axillary lymph node, which was suspicious in supine imaging, remained in the suspicious group again in prone imaging in PET/CT.*
CONCLUSIONS: *There is no single absolute modality for detecting ALNMs in breast cancers to replace sentinel lymph node biopsy or axillary lymph node dissection. If ALNM is suspected based on PET/CT, axillary lymph node dissection without sentinel lymph node biopsy might be a better option because it is related to high possibilities of ALNM.*

KEY WORDS: Axillary lymph node metastasis, Magnetic resonance imaging, Ultrasonography, ^{18}F-FDG PET/CT

Introduction

Breast cancer represents the most frequently seen cancer in women in Western countries [1]. The most important prognostic factor is the presence and extent of the locoregional nodal metastasis [2]. Sentinel lymph node biopsy (SLNB) is currently the standard axillary staging procedure in patients with early breast cancer [3,4]. However, the contribution of the SLNB for the detection of metastases in the internal mammary and supraclavicular lymph nodes is not clear. Therefore, if metastatic lymph nodes are detected by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), SLNB is unnecessary and axillary lymph node dissection (ALND) can be performed straightaway [5]. PET/CT has the advantage of identifying not only axillary, internal mammary and mediastinal lymph node

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metastases but also distant metastases. On the other hand, there is also limited data on whether late prone PET/CT provides additional information to supine PET/CT on distribution of locoregional disease in breast cancer. A recent study reported that prone imaging revealed a higher number of visualized lymph nodes presumably due to improved separation of deep structures [6].

The main aim of this study was to assess the accuracy of ultrasonography (US), contrast-enhanced magnetic resonance imaging (cMRI) and PET/CT for detection of axillary lymph node metastases (ALNMs) in preoperative staging of breast cancer patients. Secondly, we aimed to evaluate the role of late prone imaging for visualization of axillary and extra-axillary lymph nodes. Finally, we aimed to evaluate the effect of PET/CT on preoperative staging of breast cancer.

Materials and Methods

Design And Subjects

From June 2015 to January 2019, 236 consecutive biopsy-proven breast cancer patients were included into this prospective study. One patient had bilateral breast cancer. All patients underwent breast and axillary US, cMRI and PET/CT, and were asked to undergo supine and prone positions PET/CT acquisitions after giving informed consent. This study was approved by the Institutional Review Board of our institute (IRB No. 05.06.2015/43/13).

^{18}F-FDG PET/CT Imaging

Whole-body ^{18}F-FDG PET/CT scans were obtained on a Biograph® PET/CT system (Siemens Molecular Imaging, Hoffman Estates, IL, USA). The system consists of a full ring dedicated PET and a 2-slice spiral CT. Patients were required to have fasted during 6 hours before receiving an intravenous application of 10-15 MBq FDG via an antecubital vein contralateral to the affected breast. Patients were kept quiet and comfortable for 60 minutes after the injection. A 1,500 mL of water-based oral contrast agent was applied for bowel marking starting from 6 hours before acquisition. The blood glucose measurements obtained before the scanning were lower than 200 mg/dL. A whole body PET/CT scan was performed in supine position with a low-dose CT scan in normal breathing. Imaging started approximately 60 minutes after intravenous application of FDG covering an area from the skull base to the upper thighs. After resting period of 30 minutes, prone images were obtained from upper thorax including bilateral breast tissue and axillary fossa. During prone imaging both arms were positioned above the head to ensure free hanging of the breasts, thereby avoiding compression and deformation. All images were reconstructed with 5-mm slice thickness and 2.4-mm increment. The PET emission time was adapted to the patient's body weight: <60 kg: 2 min per bed position, 60–80 kg: 2.6 min, >80 kg: 3 min. The administered activity, time of administration, and patient's body weight were used for additional calculation of maximum standardized uptake values (SUVmax).

Image Analysis

Five readers (2 nuclear medicine physician with a minimum 5 years of experience in interpreting PET/CT, and 2 diagnostic radiologists, one is experienced in interpreting MRI and other one in interpreting US images) performed independent reviews of the scans. If there were opposite views from readers with regard to PET/CT evaluation, a consensus was achieved by discussing the findings. Data were analyzed on an image fusion workstation (Symbia; Siemens Healthcare Sector, Erlangen, Germany). Both supine and prone PET/CT scans were evaluated in three orthogonal planes (axial, coronal and sagittal) as well as in 3D projections (maximum intensity projection). The number of separate FDG-avid lesions in the breast and regional lymph node stations was visually assessed after anatomical localization. Any uptake in axilla which could be mapped to a lymph node was considered abnormal and was rated for metastasis. A given PET focus was rated as positive in a small lymph node rather than in a large lymph node, accounting for partial volume effects. Region of interest (ROI) was placed over the most intense area of ^{18}F-FDG accumulation in axillary lymph nodes both for whole body and late prone images. Unsuspected local extra-axillary nodal metastases (internal mammary, mediastinal and infraclavicular) and distant metastases were reported.

Lymphoscintigraphy and Sentinel Lymph Node Procedure

On the day of operation, all patients received a subcutaneous injections of 74 MBq (2 mCi) of Tc99m-nanocolloid in a total volume of 1.2 mL of physiologic saline, given in four equal doses. Both γ-ray detection probe and a peritumoral injection of patent blue dye were intraoperatively used for sentinel lymph node identification.

Gold Standard

Of 236 patients, 73 patients underwent both procedures, SLNB and then ALND, due to positive frozen section analysis of sentinel lymph nodes. Pathological parameters were evaluated including tumor size, lymph node metastasis, hormone receptor status, nuclear grade, HER2 status, and proliferation index was determined using Ki-67 antibody.

Statistical Analysis

We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) for US, cMRI, PET/CT and combinations of the 3 modalities. The level of agreement between the US, cMRI and PET/CT was evaluated using Cohen's kappa. Statistical analysis was carried out using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA). Based on the results of analyses, the p value < 0.05 was considered to be statistically significant.

Results

Clinicopathological Characteristics

There were 235 female and one male. The mean age was 55,6±11,3 years. Of the 223 malignant lesions whose pathological reports were obtained, 197 were ductal carcinoma and 9 were lobular carcinoma. The remaining 17 were mixed type or other pathological types such as mucinous or papillary. The clinicopathological characteristics of 236 patients are shown in Table I.

Table I - *Clinicopathologic characteristics for the 236 patients under study*

Characteristic	**(n) (%)**
Age (year) (SD)	55.6±11,3
Axillary lymph node metastasis (Histopathologically proven)	
Negative	73 (30.9%)
Positive	85 (36.0%)
Distant metastasis	9 (3.8%)
Estrogen receptor	
Negative	43 (20.2%)
Positive	170 (79.8%)
Progesterone receptor	
Negative	71 (33.3%)
Positive	142 (67.7%)
HER-2	
Negative	50 (83.3%)
Positive	10 (16.7%)
C-erb-B2	
Negative	81 (38.0%)
Positive	132 (62.0%)
Histology	
Ductal	197 (88.3%)
Lobular	9 (4.0%)
Mixed	6 (2.7%)
Others	11 (5.0%)
Surgery	
Mastectomy	135 (57.2%)
Breast-conserving surgery	92 (38.9%)
Systemic oncological therapy	9 (3.8%)

SD: Standard Deviation

^{18}F-FDG PET/CT for Detection of Primary Breast Tumor and Axillary Lymph Nodes

Of the 235 patients to whom breast and axillary US performed, 94 patients were positive, 107 were negative, and 34 were suspicious for axillary LNs. Of the 236 patients, cMRI detected axillary LNs as positive in 104 patients, negative in 95 patients, and suspicious in 37 patients. PET/CT detected axillary LNs as positive in 100 patients, negative in 117 patients, and suspicious in 19 patients. We can say that the proportion of suspected cases (19 cases, 8.1%) for PET/CT is statistically significantly less than US and cMRI (34 cases (14.5%) for US, and 37 cases (15.7%) for cMRI) (p=0.028 for PET/CT *versus* US, and p=0.010 for PET/CT *versus* cMRI). Table II summarizes the diagnostic abilities of US, cMRI, and PET/CT on the evaluation of ALNM. When suspicious results were accepted as positive in all imaging modalities; the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of US for determining ALNM were 75.5%, 87.91%, 88.3%, 74.8%, and 81.1%. The sensitivity, specificity, PPV, NPV, and accuracy of cMRI were 84.0%, 83.9%, 85.6%, 82.1%, and 83.9%. The sensitivity, specificity, PPV, NPV, and accuracy of PET/CT were 80.0%, 92.2%, 92.0%, 80.3%, and 85.7%, respectively. PET/CT was both more accurate and less suspicious. In our series, PET/CT could not detect the primary lesion of the breast in 24 (10.1%) of 236 patients.

When the agreement between US, cMRI and PET/CT was examined, there was a moderate agreement between both PET/CT and US (p value: 0.634), and PET/CT and cMRI (p value: 0.605). If suspicious cases were excluded, there was a high degree of agreement between both PET/CT and USG (p value: 0.811), and PET/CT and cMRI (p value: 0.810).

The diagnostic accuracy of PET/CT was different depending on the disease stage. In patients with stage I or II disease, the sensitivity and specificity were 74% and 96%, respectively, which were high compared with stage III and IV patients (92% and 33%, respectively) (Table III). The specificity of PET/CT was found to be low (33%). Because there were small number of patients with negative sentinel lymph node pathology in stage III and IV patient groups (n=6).

Late Prone ^{18}F-FDG PET/CT Imaging

When we examined any contribution of PET/CT imaging in prone position to the detection of ALNMs, none of the lymph nodes reported as suspicious in supine posi-

Table II - *Detection of axillary lymph node metastasis by three imaging modalities*

	US	cMR	PET/CT	1+	2+	3+	US & MRI	US & PET/CT	cMRI & PET/CT	
SLN	+	-	+	-	+	-	+	-	+	-
+	-	+	-	+	-	+	-			
+	100	27	110	17	104	23	113	14	106	
21	95	32	100	27	95	32	101	26		
-	28	81	31	78	15	94	35	74	28	
81	11	98	28	81	11	98	11	98		
Total	128	108	141	95	119	117	148	88	134	
102	106	130	128	108	106	130	112	124		
Sensitivity(%)	78.7	86.6	81.9	89.0	83.5	74.8	78.7	74.8	79.5	
Specificity(%)	74.3	71.6	86.2	67.9	74.3	89.9	74.3	89.9	89.9	
PPV (%)	78.1	78.0	87.4	76.4	79.1	89.6	78.1	89.6	90.2	
NPV (%)	75.0	82.1	80.3	84.1	79.4	75.4	75.0	75.4	79.0	
ACC (%)	76.7	79.7	83.9	79.2	79.2	81.8	76.7	81.8	84.3	

US=ultrasonography; cMRI=contrast-enhanced magnetic resonance imaging; PET/CT=18F-fluorodeoxyglucose positron emission tomography/computed tomography; 1+=axillary lymph node metastasis was suspected based on the results of more than one test; 2+=axillary lymph node metastasis was suspected based on the results of more than two tests; 3+=axillary lymph node metastasis was suspected based on the results of all 3 tests; SLN=sentinel lymph node; PPV=positive predictive value; NPV=negative predictive value; ACC=accuracy.

Table III - *Diagnostic accuracy rates of three imaging modalities according to disease stages.*

	PET/CT		US		cMRI	
	Stage I-II	Stage III-IV	Stage I-II	Stage III-IV	Stage I-II	Stage III-IV
Sensitivity	74%	92%	69%	92%	79%	92%
Specificity	96%	33%	91%	25%	87%	25%
PPV	93%	90%	88%	92%	83%	92%
NPV	82%	40%	77%	25%	84%	25%
Accuracy	86%	84%	81%	85%	83%	85%

US=ultrasonography; cMRI=contrast-enhanced magnetic resonance imaging; PET/CT=18F-fluorodeoxyglucose positron emission tomography/computed tomography; PPV=positive predictive value; NPV=negative predictive value; ACC=accuracy.

tion imaging could be evaluated as absolutely positive or negative. When the SUVmax values of both primary tumor and axillary LNs in PET/CT were examined in both supine and prone positions, no statistically significant difference was found in either SLN positive or negative patients. We observed that the late prone imaging increased both the SUV max values of axillary LNs and the number of visualized axillary LNs (Fig. 1). The mean early lymph node SUVmax value was 6.29±5.55, while the mean late lymph node SUVmax value was 7.84±7.14 (p<0.01). Although this result is statistically significant, this is not clinically effective on any decision-making.

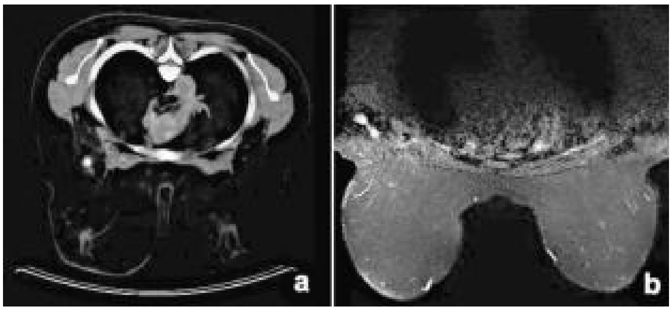

Fig. 1: Case 1: A) 42-year-old woman with left breast cancer. a ^{18}F-FDG PET/CT axial fusion late prone image showing two lymph nodes with high FDG uptake; B) MRI showing two lymph nodes with high contrast uptake.

^{18}F-FDG PET/CT in the Detection of Extra-Axillary Lymph Nodes

Extra-axillary lymph node metastases were detected by PET/CT in 30 patients (12.7%) and the localizations were pectoral (14), internal mammary (10), mediastinal (5) and supraclavicular/subclavicular regions (5), respectively. Of these 30 patients, all of them had also concomitant FDG-avid axillary lymph nodes and US-guided nodal biopsy was performed from the axillary lymph node(s) to confirm metastasis. Pathology confirmed true-positive PET/CT findings in all 30 patients and they were referred to medical oncology for neoadjuvant chemotherapy. Out of these 30 patients with extra-axillary lymph nodes, 28 were not detected by initial conventional imaging.

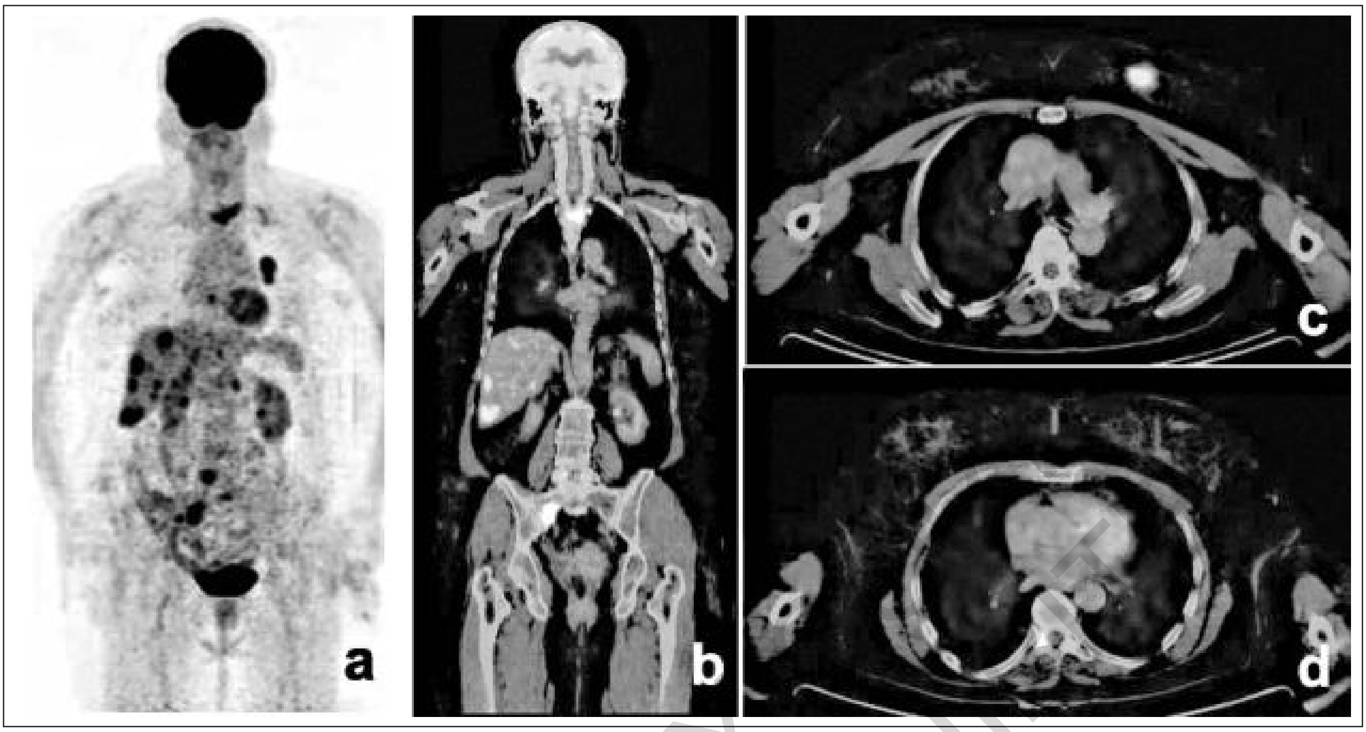

Fig. 2: Case 2: A) 66-year-old woman with right breast cancer. a 18F- FDG PET/CT maximum intensity projection (MIP) image demonstrating liver and bone metastases; B) ^{18}F- FDG PET/CT coronal fusion image demonstrating liver and bone metastases; C) Axial fusion image showing the primary breast lesion with high FDG uptake; D) Axial fusion image showing no axillary lymph node with or without FDG uptake.

^{18}F-FDG PET/CT In The Detection Of Distant Organ Metastasis

Nine patients showed high FDG uptake in distant organs on the initial PET/CT evaluation (Fig. 2). These unsuspected metastases upstaged the patients to stage IV disease. Metastases were confirmed by follow-up imaging in 8 patients. In one patient, liver metastasis was confirmed pathologically by percutaneous liver biopsy. The most common distant metastasis was in the skeletal system and bone metastases were detected in 7 patients. Two patients had lung, 2 had liver, 1 had adrenal and 1 had brain metastasis. One patient had both liver and bone metastases at the same time, and another patient had simultaneous metastases in the bone, brain and adrenal gland. In one of our cases, ALNM was reported as negative in 3 imaging methods, but multiple bone metastases were detected in PET/CT.

Discussion

Although PET/CT has been shown to be helpful in the staging of many malignancies, detecting distant metastases, identifying recurrence and evaluating response to chemotherapy, the value of PET/CT in evaluating loco-regional nodal status for initial staging of breast cancer has not yet been well-defined in clinical practice.

PET/CT is a commonly used imaging modality for staging breast cancer and for detecting distant metastasis. Although the sensitivity of PET/CT is low in the evaluation of axillary lymph nodes, its specificity is quite high. In addition, evaluation of extra-axillary lymph nodes (internal mammary, supraclavicular and infraclavicular) and distant metastases can be performed well with PET/CT [7]. In our study, the most common lymph node involvement after axillary region were detected in pectoral, internal mammary, mediastinal and supraclavicular/subclavicular regions, respectively. The distant metastases were detected in 9 patients and these patients upstaged due to PET/CT findings. Two patients who had distant metastases did not have ALNM.

PET/CT has a high specificity for evaluating both ALNM and internal mammary and mediastinal lymph node metastases [5,8]. In order to increase the sensitivity in the detection of metastatic axillary lymph node by PET/CT, Choi *et al.* showed that late imaging in addition to early imaging in PET/CT did not improve the diagnostic accuracy in 177 patients [9]. In our study, axillary lymph nodes, which were reported as suspicious in the imaging obtained in supine position in 19 patients, could not switch to positive or negative group after imaging in the late prone position, and were interpreted as suspicious again.

PET/CT has been compared with other conventional imaging methods to detect ALNMs in many studies. In a study reviewing data of patients with T1 breast cancer who had undergone preoperative US, cMRI and PET/CT, Hwang *et al*. reported that cMRI afforded the highest sensitivity when used to detect axillary involvement. However, the observed differences in the sensitivity were not significant, and PET/CT afforded the highest specificity, PPV, and ACC [10]. In a more recent study, Ergul *et al.* found that the sensitivity, NPV, and ACC of PET/CT were 67%, 62%, and 75%, respectively, higher than the equivalent values of either cMRI or diffusion-weighted imaging in terms of detection of axillary metastasis. They concluded that PET/CT may guide a surgical decision to proceed or not to SLNB or ALND [11]. In our series, we found that the proportion of suspected cases for PET/CT is statistically significantly less than US and cMRI. PET/CT was both more accurate and less suspicious. In 70 patients with clinical stage IIB and III breast cancers, Segaert *et al*. compared PET/CT and conventional staging methods (biochemistry, lung graphy, liver US, bone scintigraphy) [12]. In this study, PET/CT was superior to detect internal mammary lymphatic chain metastases and distant metastatic disease. However, there was no superiority in axillary staging. When we compared the ACC of US, cMRI and PET/CT modalities in detecting axillary metastases as well as distant metastases, our study found that PET/CT was superior to other methods and that other methods could not identify internal mammary and supraclavicular lymph node metastases. PET/CT showed some advantages in detecting the uncovered extra-axillary nodal metastasis as well as distant organ metastasis.

There were several limitations in our study. Firstly, this was a prospective single-centre study, and the interpreters of the cMRI and PET/CT had knowledge of the US results for the most part. Thus, this knowledge may have affected the results of cMRI and PET/CT. However, cMRI and PET/CT have their own diagnostic criteria for ALNM not related with US findings, so US may not have definitive effects on the results of cMRI and PET/CT. Furthermore, the determination of pathological ALNM mainly depended on SLNBs (66.9%); however, SLNB has a high level of accuracy similar to that of AD [13,14]. Thus, the difference between these two modalities may be small. cMRI and PET/CT are very expensive to implement, so the cost effectiveness of the two tests is questionable. However, as mentioned earlier, cMRI and PET/CT were conducted not only for detection of ALNM but also for various other reasons.

In conclusion, although PET / CT is not used as a substitute for sentinel lymph node sampling, it may be useful in selected cases to avoid unnecessary SLNB / ALND due to its high specificity, similar to the results obtained for scintimammography [15]. ^{18}F-FDG PET/CT can determine candidates for SLNB instead of ALND, even in early breast cancer. The axillary lymph node, which was suspicious in supine imaging, remained in the suspicious group again in prone imaging, causing unnecessary workload and time loss. In primary staging, PET/CT assesses the axillary region to determine if the next step, SLNB, is really needed, as well as detects possible distant organ metastases, which may lead to an upstaging, thereby changing patient management.

Riassunto

Lo scopo di questo studio è quello di valutare: (i) l'accuratezza dell'ecografia (US), della risonanza magnetica potenziata con contrasto (cMRI) e della ^{18}F-fluorodeoxyglucose PET/computed tomography (^{18}F-FDG PET/CT) per l'individuazione di metastasi linfonodali ascellari (ALNM); (ii) il ruolo dell'imaging tardiva in posizione prona e (iii) l'effetto della PET / TC sulla stadiazione preoperatoria del carcinoma mammario.

Sono stati esaminati preoperatoriamente 236 pazienti con carcinoma mammario nell'intervallo tra giugno 2015 e gennaio 2019, utilizzando US, cMRI e PET / CT e quindi al controllo istopatologico dei linfonodi ascellari. Sono stati determinati la sensibilità, la specificità, il valore predittivo positivo (PPV), il valore predittivo negativo (NPV) e l'accuratezza (ACC) di US, cMRI e PET / CT per ALNM.

Lo studio è stato effettuato su 235 donne e un uomo. L'età media era di 55,6±11,3 anni. Dei 158 pazienti valutati istopatologicamente, 85 (36%) erano negativi e 73 (30,9%) positivi per ALNM. I rimanenti 78 pazienti che sono stati valutati solo radiologicamente con US e / o cMRI: 24 pazienti (10,2%) erano negativi e 54 (22,9%) erano positivi per ALNM. La sensibilità, specificità, PPV, NPV e ACC di PET / CT erano rispettivamente 80,0%, 92,2%, 92,0%, 80,3% e 85,7%. Il linfonodo ascellare, che era sospetto nell'imaging supino, rimase di nuovo nel gruppo sospetto nell'imaging PET / CT nella stessa posizione.

Possiamo concludere che non esiste un'unica modalità assoluta per l'individuazione di ALNM nei tumori al seno in sostituzione della biopsia del linfonodo sentinella o della dissezione linfonodale ascellare. Se si sospetta presenza di ALNM sulla base di PET / CT, la dissezione dei linfonodi ascellari senza biopsia del linfonodo sentinella potrebbe essere un'opzione migliore perché è correlata alle elevate possibilità dell'esistenza di ALNM.

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