

Original article

The use of 18F-FDG positron emission tomography to detect mediastinal lymph nodes in metastatic breast cancer

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ABSTRACT

Background: To assess the predictive value of ¹⁸F-fluorodeoxyglucose positron-emission tomography (FDG–PET/CT) in detecting mediastinal lymph node metastasis with histopathologic verification in breast cancer (BC) patients.

Materials and methods: Between February 2012 and October 2019, 37 BC patients who underwent histopathological verification for FDG–PET positive mediastinal lymph nodes were retrospectively analyzed. Nine patients (24%) were screened before beginning treatment, while 27 (76%) were screened at the time of disease progression, an average of 39 months after completion of initial treatment.

Results: The histopathologic diagnosis revealed lymph node metastasis from BC in 15 patients (40%) and benign disease in 22 patients (60%). The standardized uptake value (SUV_{max}) of mediastinal lymph nodes was significantly higher in patients with lymph node metastasis compared to those with benign histology (9.0 ± 3.5 vs. 5.9 ± 2.4 ; $P = 0.007$). The cut-off value of SUV_{max} after the ROC curve analysis for pathological lymph node metastasis was 6.4. Two of the 15 patients with mediastinal SUV_{max} ≤ 6.4 and 13 of the 22 patients with SUV_{max} > 6.4 had lymph node metastasis. Age and pathological findings were prognostic factors for overall survival in univariate analysis. The treatment decision was changed in 19 patients (51%) after mediastinoscopic evaluation of the entire cohort.

Conclusions: This is the first study to support the need for pathologic confirmation of a positive PET/CT result following evaluation of mediastinal lymph nodes for staging BC, either at initial diagnosis or at the time of progression. Treatment decisions were consequently altered for nearly half of the patients.

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1. Introduction

Breast cancer (BC) is the most common malignancy and leading cause of cancer-related deaths in women [1]. Distant metastasis is seen in nearly one-fourth of BC patients, with a 5-year survival rate of 25% [2]. Treatments for BC include surgery, chemotherapy, and radiotherapy (RT), depending on the disease stage. However, patients with metastatic BC have a low likelihood of prolonged remission or cure. Systemic chemotherapy and/or hormone therapy is therefore preferred in most of the metastatic BC patients, and in some cases palliative RT or surgery is recommended. Accurate staging is thus essential for the proper management and treatment

of BC.

Staging and consideration of BC that has spread beyond the breast is typically divided into regional lymph nodes (particularly axillary lymph nodes) and the non-regional lymphatic system or distant organs. Almost all BC patients undergo axillary staging with surgery, while systemic staging is performed radiologically. However, systemic staging is not recommended unless the patient is symptomatic in patients with early-stage disease [3]. Systemic staging is often performed for locally advanced BC, recurrent BC, or BC with known metastases [4,5]. According to the National Comprehensive Cancer Network Practice guidelines, systemic staging is based on conventional imaging modalities, including chest radiography or computed tomography (CT), abdominal ultrasonography or CT, and bone scintigraphy, depending on disease stage [6,7]. However, the systemic staging of patients with conventional imaging is limited by the low sensitivity of these methods. More recently, ¹⁸F-fluorodeoxyglucose positron-emission

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tomography (FDG–PET/CT), with high sensitivity and specificity for detecting lymph node and distant metastases, has proven useful for determining the extent of disease in various cancer types, and in patients with BC [8–13]. Although FDG–PET/CT is recommended for patients with either recurrent or stage IV disease according to guidelines, its use in BC patients for staging increases dramatically [7,10].

The FDG–PET/CT provides functional imaging with higher tumor detection rates, but in some cases it may overstage the disease, increasing the rate of false positivities, because FDG is not a tumor-specific agent and it is also taken up by tissues involved in granulomatous or inflammatory processes [14]. Although mediastinal staging with FDG–PET and histopathologic evaluation in patients with non-small-cell lung cancer (NSCLC) has been well described, its poor sensitivity for small lymph nodes (20% false negative rate) and poor specificity for large lymph nodes (20% false positive rate) still presents a dilemma [15,16]. Histopathological verification is still required to verify PET-positive mediastinal nodes in patients with NSCLC, and the need for surgical evaluation of mediastinal lymph nodes is likely greater for other cancer types [17,18].

Few studies have evaluated the extra-axillary lymphatic spread of BC FDG–PET/CT [19,20] or the histopathologic confirmation of mediastinal FDG–PET positivity of BC [21]. We therefore evaluated the predictive value of FDG–PET/CT in detecting mediastinal lymph node metastasis with histopathologic verification in primary and recurrent BC patients.

2. Materials and methods

2.1. Patient population

This study included 37 BC patients who underwent FDG–PET/CT imaging at Baskent University between February 2012 and October 2019. Nine patients (24%) were screened for initial staging before beginning treatment with chemotherapy and/or RT, and 27 patients (76%) were screened at the time of disease progression. The electronic medical records of patients were reviewed and patients who received systemic therapy or radiation shortly before undergoing FDG–PET/CT imaging were excluded.

All patients were discussed by the institutional tumor board and treatment decisions were made by board members according to the patients' final stage. Patients with systemic metastasis, including mediastinal lymph nodes, were treated with systemic chemotherapy and/or hormone therapy. Patients requiring palliative treatment received RT, while bone-only oligometastatic patients with ≤ 5 metastases during initial diagnosis were treated with curative intent.

2.2. PET/CT technique

Patients were imaged using a dedicated PET/CT system (Discovery-STE 8; General Electric Medical System, Milwaukee, WI, USA). The patients fasted for at least 6 h before administration of intravenous 370–555 MBq (10–15 mCi) FDG. The patients' pre-injection blood glucose levels were measured to ensure that they were below 150 mg/dL. During the distribution phase, the patients lay supine in a quiet room. Combined image acquisition began 60 min after FDG injection. First, an unenhanced CT scan (5-mm slice thickness) from the base of the skull to the inferior border of the pelvis was acquired using a standardized protocol (140 kV and 80 mA). The subsequent PET scan was acquired in 3-dimensional mode from the base of the skull to the inferior border of the pelvis (6–7 bed positions, 3 min per bed position) without repositioning the patient on the table. CT and PET images were acquired with the patient breathing shallowly. Attenuation was corrected

using the CT images. Areas of FDG uptake were categorized as malignant based on location, intensity, shape, size, and visual correlation with CT images to differentiate physiologic uptake from pathologic uptake. A lymph node was considered PET-positive if its FDG uptake was greater than blood pool activity or surrounding background tissues, regardless of lymph node size [22].

2.3. Statistical analysis

Statistical analysis was performed using SPSS for Windows (IBM, Armonk, NY, USA). Descriptive analysis was performed by calculating the mean, standard deviation, range, and median. Time to progression after initial treatment for BC was calculated as the time period between the last day of chemotherapy or RT (whichever was performed) and the diagnosis date of disease progression. The overall survival (OS) rate was calculated using the Kaplan–Meier estimator. The prognostic factors for OS were evaluated using a univariate analysis and the log-rank test. All P values < 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

The median age of patients was 50 years (range, 36–71 years). Of the 37 patients analyzed, mediastinoscopy was performed in 9 (24%) at initial diagnosis; 27 patients (76%) had FDG uptake at the time of disease progression, with an observed median of 39 months (range, 5–146 months) after completion of initial treatment. The FDG–PET/CT was delivered to all patients at a median of 14 days (4–47 days) before mediastinoscopy.

3.2. Mediastinal lymph node evaluation

Hilar lymph nodes were dissected in 16 patients (43%), while in 21 (57%) both hilar and mediastinal lymph nodes were dissected. The histopathologic diagnosis revealed lymph node metastasis from BC in 15 patients (40%) and benign disease in 22 patients (60%). Of 20 patients with benign pathology, 16 (72%) had sarcoidosis, 3 (14%) had tuberculosis, and 3 (14%) had reactive changes.

The median SUV_{max} and size of FDG positive mediastinal lymph nodes were 8 (range, 3.1–20.2) and 2 cm (1.2–3.5 cm), respectively. The SUV_{max} of mediastinal lymph nodes was significantly higher in patients with lymph node metastasis compared to patients with benign histology (9.0 ± 3.5 vs. 5.9 ± 2.4 ; $P = 0.007$). A borderline significant difference in lymph node size was observed in patients with malign and benign pathologies (2.2 ± 0.6 cm vs. 1.9 ± 0.4 cm; $P = 0.15$).

The relationship between lymph node FDG uptake and pathological finding was evaluated based on the cut-off value determined using ROC curve analysis. Fig. 1A shows the ROC curve analysis of the mediastinal lymph node SUV_{max} of with respect to lymph node metastasis. The area under the curve was 0.724 ($P = 0.01$; 95% confidence interval, 0.553–0.858), and the cut-off value of SUV_{max} in the present study was determined to be 6.4. The positive and negative predictive values of FDG–PET/CT for detecting lymph node metastasis were 60% and 87%, respectively (Fig. 1B). Two of the 15 patients with mediastinal $SUV_{max} \leq 6.4$ had lymph node metastasis, while 13 of the 22 patients with $SUV_{max} > 6.4$ had lymph node metastasis (Fig. 2).

3.3. Treatment outcomes

At a median follow-up of 51 months (range, 6–111 months), 28

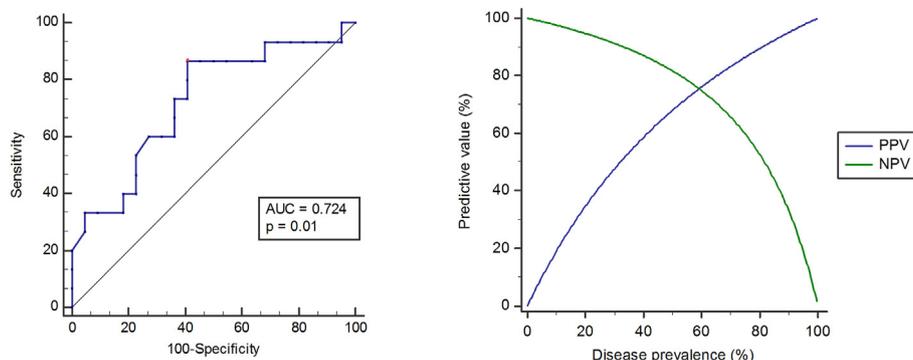


Fig. 1. (A) ROC curve analysis in lymph node metastasis according to the SUV of mediastinal lymph nodes and (B) Graph demonstrating positive (PPV) and negative predictive values (NPV) of FDG-PET/CT for detecting mediastinal lymph node metastasis.

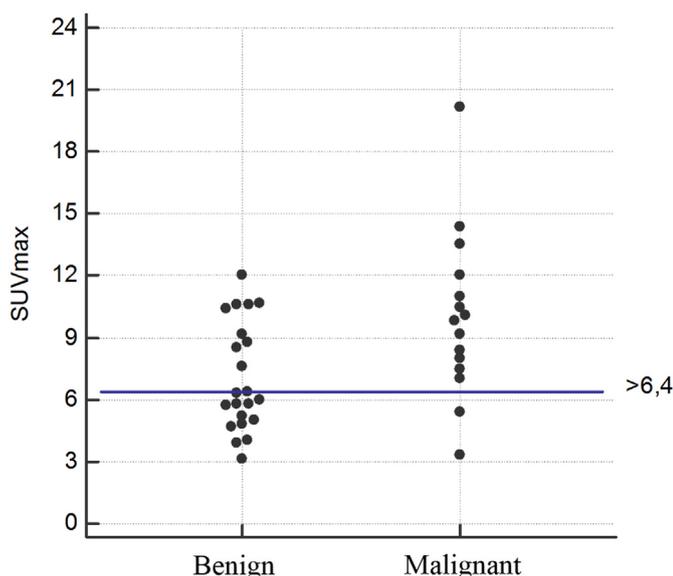


Fig. 2. The distribution of histopathological findings, based on a mediastinal lymph node SUV_{max} cut-off value of 6.4.

patients (76%) were alive (10 [27%] with disease) and 9 (24%) had died (8 [21%] of BC and 1 [3%] of other causes). Eleven patients (30%) had disease progression; of them, 5 had only distant metastasis while 6 had local recurrence at primary tumor site together with distant metastasis. As shown in Fig. 3A, OS ($P = 0.001$) rates were significantly higher in patients with benign histopathology compared to those with malign pathology, while there was a borderline significance ($P = 0.16$) for patients with mediastinal lymph node $SUV_{max} \leq 6.4$ and those with $SUV_{max} > 6.4$ (Fig. 3B). In univariate analysis, age and pathological findings of mediastinal lymph nodes were prognostic factors for OS (Table 1) (see Fig. 4).

3.4. Treatment modifications

Treatment decisions were made according to the pathological findings of suspected mediastinal lymph node metastasis (Fig. 4). The treatment decision was changed in 19 patients (51%) after mediastinoscopic evaluations of the entire cohort.

Mediastinal lymph node evaluation revealed benign lesions in 9 patients, with increased FDG uptake in mediastinal lymph nodes at diagnosis (Table 2). The treatment strategy was consequently changed from palliative to curative intent in all patients (100%). All

patients underwent surgery, 8 patients received adjuvant RT, and 5 received adjuvant chemotherapy. One patient was not treated with RT due to advanced age. All but one patient had invasive ductal carcinoma, and 6 patients had axillary lymph node metastasis. At the time of last visit, all 9 patients were alive with no evidence of disease at a median OS period of 81 months (range, 41–98 months).

Histological evaluation of mediastinal lymph nodes in 15 of the 28 patients (54%) with increased FDG uptake during progression revealed lymph node metastasis. All patients with verified mediastinal lymph node metastasis received systemic chemotherapy and/or hormonotherapy. Of the 13 patients with benign pathology in mediastinal lymph nodes, the cancer metastasized to another organ on only 3 patients; these patients received systemic treatment, while the other 10 patients did not receive any treatment. The treatment strategy for other 10 patients (36%) was changed, with increased FDG uptake in mediastinal lymph nodes observed at the time of disease progression. The median OS in patients with FDG-positive mediastinal lymph node metastasis at the time of disease progression was 42 months (range, 6–111 months), and 10 patients (32%) died during the study period.

4. Discussion

In this study, we evaluated patients with BC and increased FDG uptake in mediastinal lymph nodes at initial diagnosis or during progression, which was verified pathologically. Our results demonstrated that FDG-PET/CT alone is not sufficient to evaluate mediastinal lymph nodes for patients with BC, with a false positive rate of 60%. As a consequence of this histopathological verification, the treatment decision was changed in nearly half of the patients, which highlights the importance of surgical evaluation of mediastinal lymph nodes with increased FDG uptake in BC patients.

Breast cancer is staged surgically, and radiologic images are rarely used. However, FDG-PET/CT has been increasingly used in recent years to detect axillary lymph nodes. The sensitivity and specificity rates of FDG-PET/CT in detecting axillary lymph node metastasis were 60% and 80%, respectively [23]. The detection rate of axillary lymph node depends on tumor size, and the sensitivity of this method has been found to be as low as 20–30% in detecting small tumors [24]. It is therefore not accurate enough to replace axillary dissection or sentinel lymph node biopsy, especially in patients with small primary tumors and without palpable lymph nodes. Extra-axillary lymph node metastases that are not harvested by standard surgical procedures may be seen in 50–60% of patients [25,26]. Previous studies have demonstrated that FDG-PET is superior to conventional imaging modalities in detecting extra-axillary lymph node metastases [21,27,28]. Eubank et al. [21]

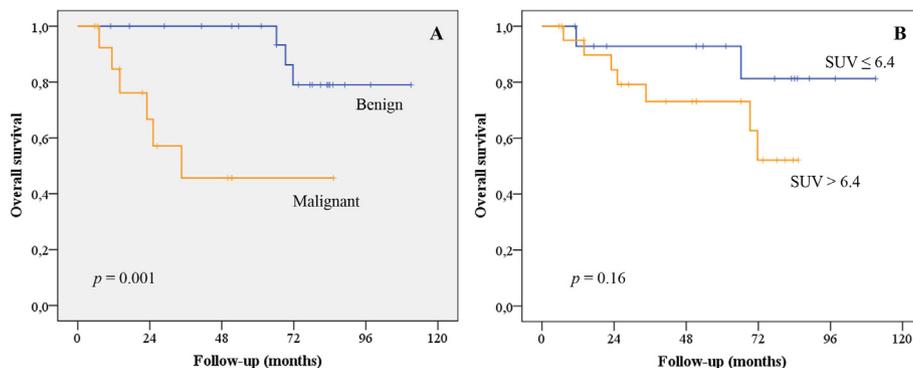


Fig. 3. Overall survival curves of patients with (A) a mediastinal lymph node SUV_{max} of greater than 6.4 and 6.4 or less, and (B) those with or without mediastinal lymph node metastasis detected histopathologically.

Table 1
Univariate analysis of overall survival.

Covariate	Patient number	HR (95% CI)	p
Age			
<50 years	18	1	0.03
≥50 years	19	9.67 (1.21–77.67)	
Lymph node localization			
Hilar	16	1	0.25
Hilar and mediastinal	21	2.53 (0.52–12.23)	
Lymph node size			
<2 cm	18	1	0.42
≥2 cm	19	0.58 (0.15–2.17)	
Pathology			
Benign	22	1	0.004
Malignant	15	9.28 (2.06–41.88)	
SUV_{max} of lymph node			
≤6.4	15	1	0.16
>6.4	22	2.91 (0.60–14.10)	
Organ metastasis			
No	29	1	0.44
Yes	8	1.73 (0.43–6.99)	

found abnormal FDG uptake in mediastinal or internal mammary lymph nodes in 40% of patients, but this was only histopathologically verified in 4 patients. In 60 patients with stage II–III BC, Aukema et al. [28] demonstrated that FDG-PET/CT detected extra-axillary lymph nodes in 28% of the patients, whereas in 17% FDG-PET/CT showed suspicious uptake that was not detected by conventional imaging. In the current study, although all patients had increased FDG uptake in mediastinal lymph nodes only, histopathological evaluation revealed true lymph node metastasis in 40% of cases.

The treatment of choice for metastatic BC patients is systemic agents including chemotherapy, hormonal therapy, and immunotherapy. Although metastatic BC is unlikely to be cured, meaningful improvements in survival have been seen, coincident with the introduction of newer systemic therapies that may extend OS from a few months to many years [29,30]. With FDG-PET/CT a considerable amount of stage change and treatment modifications due to these alterations in stage was previously demonstrated in BC patients [21,28]. In the current study, treatment decisions were changed in 51% of the patients in the entire cohort. All patients with increased FDG uptake at initial diagnosis had negative tumors according to their histopathological examinations, and the treatment intent was changed from palliative to curative intent for all of these patients. Of 28 patients with increased FDG uptake in mediastinal lymph node during the oligoprogression period, treatment was modified for 10 of them (36%). Histopathological verification of

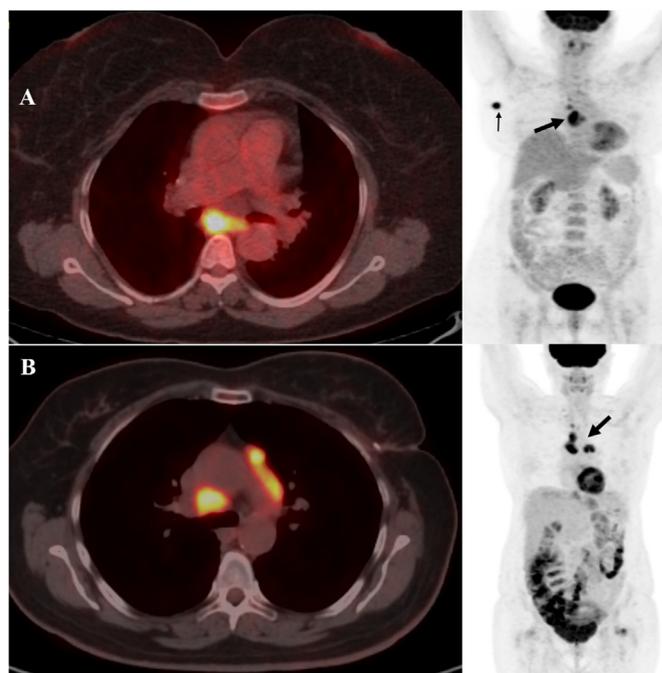


Fig. 4. (A) The FDG-PET/CT images of a representative patients delivered during initial staging. The FDG-PET/CT revealed increased FDG uptake in the upper quadrant of the right breast (SUV_{max} = 12.3) (thin arrow) and increased uptake in the subcarinal lymph node (thick arrow) with SUV_{max} 10.4 and 31 × 14 mm in size, which was biopsied and confirmed a diagnosis of tuberculosis. (B) The FDG-PET/CT images of a representative patients delivered at the time of disease progression revealed increased FDG uptake at subcarinal (SUV_{max} = 10.6) and prevascular lymph nodes (SUV_{max} = 9.8); the histopathological finding was malignant.

increased FDG uptake prevents the delivery of unnecessary treatment to a majority of patients.

Mediastinal lymphatic staging with PET/CT has been well studied in patients with lung cancer, who often develop lymph node metastasis. Although PET/CT has been reported to be highly sensitive and specific in detecting nodal spread, invasive mediastinal staging using mediastinoscopy has been regarded as the gold standard method [31,32]. However, false positive results in nodal staging have been shown in coexistent inflammatory or infectious diseases, so the debate continues over which combination of PET/CT and invasive procedure is most suitable to use for a nodal staging algorithm [33,34]. Bille et al. [33] reported that the false positive rate of PET/CT was 25.7% in 159 patients with lung cancer. Darling et al. [34] reported that 36% of patients with a PET/CT interpreted as

Table 2
Clinical and treatment outcomes of patients who underwent mediastinal lymph node sampling at the time of initial diagnosis.

Patient no	Age	Primary tumor	Primary tumor stage	Increased FDG in mediastinum	Mediastinal SUV _{max}	Mediastinal histology	Treatment	Follow-up	Status
1	44	IDC	T2N0	Right paratracheal ln	3.9	Sarcoidosis	S + RT + KT	51.3	ANED
2	67	IDC	T1N1	Right paratracheal and subcarinal ln	5.0	Tuberculosis	S + RT	97.6	ANED
3	71	Mucinous ca	T1N1	Right paratracheal and subcarinal ln	4.7	Sarcoidosis	S	85.0	ANED
4	56	IDC	T1N1	Right paratracheal ln	7.6	Tuberculosis	S + RT + KT	80.9	ANED
5	51	IDC	T2N1	Right paratracheal and right hilar ln	3.1	Sarcoidosis	S + RT + KT	84.0	ANED
6	47	IDC	T2N0	Right paratracheal and subcarinal ln	4.0	Sarcoidosis	S + RT	89.0	ANED
7	50	IDC	TxN2	Right paratracheal ln	8.5	Sarcoidosis	S + RT + KT	41.3	ANED
8	45	IDC	T1Nmic	Right paratracheal and subcarinal ln	5.7	Sarcoidosis	S + RT	61.2	ANED
9	68	IDC	T1N0	Right paratracheal and subcarinal ln	10.4	Tuberculosis	S + RT + KT	66.2	ANED

Abbreviations: ln = lymph node; IDC = invasive ductal carcinoma; FDG = flouro deoxyglucose; SUV_{max} = maximum standardized uptake value; S = surgery; RT = radiotherapy; CT = chemotherapy; ANED = alive with no evidence of disease.

positive for mediastinal nodes did not have a tumor. In parts of the body often affected by granulomatous disease, the accuracy and specificity of FDG-PET are substantially reduced because of falsely increased FDG uptake in inflammatory nodes [35,36]. In our study, the false positive rate of PET/CT was higher than that identified in previous studies, which may be due to a higher incidence of granulomatous disease in the breast and different primary disease from NSCLC. Another concern regarding mediastinoscopic evaluation is false negativity due to lymph node stations that are not reachable by mediastinoscopy. The PET/CT scans have proven to be less accurate in the subcarinal station, where the highest incidences of both false positive and false negative results were found [37]. The false negativity of mediastinoscopy is 20%, and the success of this technique is surgeon-dependent [38]. In our series, all patients were discussed by a tumor board and only patients suitable for mediastinoscopy were evaluated surgically.

This study is not without limitations. First, the retrospective nature of this single-institution study might have introduced bias. Second, we only evaluated patients who accepted surgical staging, so it is possible that the accuracy and sensitivity of PET/CT in detecting mediastinal lymph node metastasis for BC patients was underestimated. Third, there may be a verification bias due to the surgeons who conducted the lymph node sampling being aware of the inaccuracy of PET/CT scans. As a result, only suspected lymph nodes were removed, and no apparently normal or FDG-avid lymph nodes were dissected, which would introduce bias regarding the false negative rate of PET/CT scans.

5. Conclusions

Our study is the first to support the need for pathologic confirmation of a positive PET/CT result in the evaluation of mediastinal lymph nodes for staging BC, either at initial diagnosis or at the time of progression. Other than NSCLC, mediastinal lymph node metastasis in BC was accepted as stage IV, and the treatment of choice for these patients was changed to palliative intent with worse outcomes. For this reason, although PET/CT is an important tool for lymphatic staging and evaluation of distant metastases, it should be interpreted cautiously in cases of mediastinal involvement in BC patients. The histopathologic evaluation of suspected mediastinal lymph nodes is essential to ensure that treatment decisions are accurate. Because treatment decisions are changed from palliative to curative intent for a substantial number of patients, which may directly affect their survival, surgical evaluation is required for accurate staging and appropriate decisions about treatment to achieve better outcomes in BC patients with increased FDG uptake in mediastinal lymph nodes.

Ethical approval

Ethical approval was not required.

Declaration of competing interest

All authors declare no conflicts of interest related to this article.

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