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Original Article / Özgün Makale

The role of tumor SUVmax/lymph node SUVmax ratio viewed on PET-CT in the detection of mediastinal metastasis in patients with lung cancer

Akciğer kanserli hastalarda PET-BT'de görüntülenen tümör SUDmax/lenf nodu SUDmax oranlarının mediastinal metastaz tespitindeki yeri

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Background: In this study, we aimed to investigate the lymph node standardized uptake value (SUVmax)/mass SUVmax ratio for the determination of sensitivity of positron emission tomography-computed tomography (PET-CT) in mediastinal lymph node staging in patients with non-small cell lung cancer (NSCLC).

Methods: A total of 31 patients (3 female, 28 males; mean age 61.0±9.2 years; range 35 to 79 years) with pathologically confirmed diagnosis of NSCLC in Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, 9th Chest Diseases Clinic between January 2007 and October 2010 were included. These patients underwent PET-CT and mediastinoscopy for staging. The mass SUVmax/lymphadenomegaly (lymph node) SUVmax ratios were determined by comparing the primary mass SUVmax with the PET-CT SUVmax value of lymph node with mediastinoscopy-confirmed pathological diagnosis. The reliability of these ratios in detecting metastasis was assessed by dividing the ratios into three groups using the 1.5 and 2.5 cut-off values.

Results: No statistically significant difference was found between patients with positive lymph node results and those with negative results with regards to the mass SUVmax levels (p>0.05). The lymph node SUVmax levels of patients with positive lymph node pathology results were found to be statistically significantly higher than in patients with negative pathology results (p<0.01). The relationship of lymph node positive pathology with mass SUVmax/lymph node SUVmax was found to be statistically significant (p<0.01). The rate of the mass SUVmax/lymph node SUVmax ratio between 0 and 1.5 in patients with positive pathology results was found to be higher, whereas the rate of mass SUVmax/lymph node SUVmax ratio to be ≥2.5 in patients with negative pathology results was found to be higher.

Conclusion: Our study results showed that the mass SUVmax/lymph node SUVmax ratio viewed on PET-CT is correlated with mediastinal metastasis in patients with NSCLC. We also demonstrated that the false positivity on PET-CT significantly increased in patients with a cut off ratio value was >2.5.

Key words: Diagnosis of metastasis; mediastinal lymph node standardized uptake value; non-small cell lung cancer; positron emission tomography-computed tomography.

Amaç: Bu çalışmada, küçük hücreli dışı akciğer kanseri (KHDAK) hastalarında mediastinal lenf nodu evrelemesinde pozitron emisyon tomografi-bilgisayarlı tomografinin (PET-BT) duyarlığını saptamada lenf nodu standardize alım değeri (SUDmax)/kitle SUDmax oranı araştırıldı.

Çalışma planı: Çalışmamıza Ocak 2007 - Ekim 2010 tarihleri arasında Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi 9. Göğüs Hastalıkları kliniğinde patolojik olarak kanıtlanmış 31 KHDAK hastası (3 kadın, 28 erkek; ort. yaş 61.0±9.2 yıl; dağılım 35-79 yıl) alındı. Bu hastalar evreleme amacıyla PET-BT çekilmiş ve mediastinoskopi yapılmış hastalar idi. Mediastinoskopi ile patolojik tanısı gösterilen lenfadenomegalilerin (lenf nodu) PET-BT SUDmax değerleri primer kitlenin SUDmax değeri ile karşılaştırılarak, kitle SUDmax/lenf nodu SUDmax oranları saptandı. Bu oranlar 1.5 ve 2.5 kesme değerleri ile üç gruba ayrılarak, metastazı saptamadaki doğrulukları incelendi.

Bulgular: Lenfadenomegali patolojisi sonucu pozitif olan olgular ile negatif olan olguların kitle SUDmax düzeyleri arasında istatistiksel olarak anlamlı bir farklılık bulunmadı (p>0.05). Lenfadenomegali patolojisi sonucu pozitif olan olguların lenf nodu SUDmax düzeyleri, patoloji sonucu negatif olan olgulardan istatistiksel olarak ileri düzeyde anlamlı yüksek idi (p<0.01). Lenfadenomegali patolojisi pozitifliği ile kitle SUDmax/lenf nodu SUDmax arasında istatistiksel olarak ileri düzeyde anlamlı bir ilişki bulunmakta idi (p<0.01). Lenfadenomegali patolojisi pozitif olgularda kitle SUDmax/lenf nodu SUDmax oranının 0 ile 1.5 arasında olma oranı yüksek iken, patolojisi negatif olgularda kitle SUDmax/lenf nodu SUDmax oranının 2.5 ve üzerinde olma oranı yüksek idi.

Sonuç: Araştırmamızın sonucunda KHDAK'li olgularda PET-BT'de kitle SUDmax/lenf nodu SUDmax oranının mediastinal metastaz varlığı ile ilişkili olduğu görüldü. Ayrıca SUDmax oranında 2.5'lik kesme değerinin üstüne çıktığında ileri derecede anlamlı olarak PET-BT'deki yalancı pozitifliğin arttığı sonucuna varıldı.

Anahtar sözcükler: Metastaz tanısı; mediastinal lenf nodu standardize alım değeri; küçük hücreli dışı akciğer kanseri; pozitron emisyon tomografisi-bilgisayarlı tomografi.

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The most important determinant in choosing the best treatment strategy for lung cancer is to correctly identify the tumor stage since treatment regimens vary depending on the preoperative stage of the disease.[1]

Hilar or mediastinal lymph node involvement is observed in 25% of lung cancer patients, whereas 35-45% show demonstrable distant metastasis by the time of diagnosis.[2] The most commonly encountered controversy concerning the treatment modality of lung cancer and cancer prognosis is the presence or absence of metastasis in the mediastinal lymph nodes (N2-N3 disease).[3-5] As a result, the most important preoperative assessment concerns mediastinal lymph node involvement in patients with a resectable tumor without distant metastasis. This may be performed by radiological, bronchoscopic, or surgical procedures. Clinical assessment of the mediastinal lymph node depends mostly on different imaging methods such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), although these methods are not very reliable in and of themselves.[6]

Our primary objective was to perform the most appropriate staging in order to determine the best treatment modality following the diagnosis of lung cancer. Sometimes the patient's clinical condition may not permit invasive interventions. The non-invasive PET-CT examination procedure is currently used as an alternative to mediastinoscopic surgical techniques utilized in the evaluation of mediastinal involvement. These techniques are considered the gold standard. However, PET-CT has been accompanied by controversial issues, for example based on the assessment criteria of the maximum standardized uptake values (SUVmax) due to the presence of false positive and false negative conditions.

A SUVmax value of >2.5-3 reinforces the possibility of malignancy in lung and mediastinal lesions. However, there is no definite diagnostic value for the SUVmax value, and it gives false positive results, particularly with granulomatous diseases. Positron emission tomography is not used instead of mediastinoscopy for mediastinal staging due to the 13-22% false positivity reported in many studies.[7-9] The need for mediastinoscopy in the presence of negative PET is still controversial, and a 5-8% false negative result rate has been obtained during mediastinal staging with PET.[10,11]

Many properties of the PET-CT examination procedure, which is used widely with lung cancer, have been investigated by various clinicians in many studies. In this study, we also investigated the reliability of this procedure which is commonly used in our clinic in cancer patients for the detection of mediastinal metastasis by the SUVmax values of a tumor mass and lymph node.

PATIENTS AND METHODS

Thirty-one patients (3 females, 28 males; mean age 61.0±9.2 years; range 35 to 79 years) who were treated for lung cancer at the ninth chest disease clinics of the Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital between January 2007 and October 2010 were retrospectively examined (Table 1).

Following admission to our clinic, patients underwent a clinical examination along with an assessment of their biochemistry analyses, and posteroanterior (PA) and lateral chest X-rays were taken. Those who were suspected of having lung cancer were scheduled for thorax CT to obtain a detailed assessment of the lesion, while others underwent fiberoptic bronchoscopy and/or transthoracic biopsy for histopathological diagnosis. Those who were diagnosed with non-small cell lung cancer (NSCLC) were assessed using PET-CT to detect distant metastasis and mediastinal involvement.

Positron emission tomography-CT images were obtained at three different centers. The SUVmax values of the primary tumor were calculated in the same manner as any abnormal region in the examined area.

Table 1. Distribution of localization of the mass on PET-CT, the pathology of the mass, and the diagnostic methods of lymph node

	n	%
Localization of the mass on PET-CT		
Upper right	10	32.3
Lower right	6	19.4
Right hilar	2	6.5
Upper left	7	22.6
Lower left	4	12.9
Lower hilar	1	3.2
Subcarinal	1	3.2
Pathology of the tumor		
Squamous	19	61.3
Adenocarcinoma	7	22.6
Non-small cell lung cancer	5	16.1
Diagnostic methods of lymph node		
Mediastinoscopy	22	71.0
Lobectomy	4	12.9
Pneumonectomy	3	9.7
Mediastinotomy	1	3.2
Transtracheal needle biopsy	1	3.2

PET-CT: Positron emission tomography-computed tomography.

Mediastinal lymph node involvement stations with a SUVmax value of more than 2.5 were then considered for further evaluation. Lung cancer patients in our clinic who met the following criteria were included in the study:

- Patients who had a pathologically confirmed diagnosis of lung cancer
- Patients who had been subjected to PET-CT for staging and those who had undergone mediastinoscopy.

Patients with a single fasting plasma glucose level of more than 140 mg/dl were not included in the study since high glucose levels reduce image quality. Patients with distant metastasis, those who were deemed to be clinically inoperable, and those who refused surgery were referred for oncological treatment. The pathological results of patients who had undergone a mediastinoscopic examination were obtained, and the patients were then divided into two groups: those with and those without malignancy. Additional imaging techniques and biopsies were performed on patients with symptoms and signs of distant metastasis. The staging of all patients was done according to the tumor (T), node (N), metastasis (M) staging classification system. The SUVmax values for the sizes and histological types of tumors were compared.

Standard cervical mediastinoscopy was performed under conditions where the SUVmax value was more than 2.5 for superior mediastinal lymph nodes as observed on PET. In contrast, thoracoscopy was performed to evaluate involvement of the inferior mediastinal lymph nodes. Systematic lymph node sampling was performed during a thoracotomy. The decision to perform resections during exploration with a thoracotomy was made according to the localization of the mass and lymph node involvement. Mediastinal lymph node dissection was performed if the presence of a mediastinal metastatic lymph node was confirmed by frozen analysis.

Table 2. Diagnosis and endobronchial distribution on fiberoptic bronchoscopy

	n	%
Diagnosis on FOB		
Present	14	45.2
Absent	17	54.8
Endobronchial distribution on FOB		
Present	14	45.2
Absent	17	54.8

FOB: Fiberoptic bronchoscopy.

The tissue and sections of frozen tissue which were not analyzed during surgery were subjected to standard pathological examination. Sections which were prepared from paraffin blocks were stained with hematoxilen eozin staining.

The Number Cruncher Statistical System (NCSS) 2007 and PASS 2008 statistical software (NCSS, LLC, Kaysville, Utah, USA) programs were used for the statistical analysis of the results obtained during the study. In addition to the definitive statistical methods (mean, standard deviation, frequency) applied for the evaluation of data, Students t-test was used for the comparison of quantitative data between groups for parameters with normal distribution, and the Mann Whitney U-test was used when comparing two groups for parameters without normal distribution., A chi-square test was also employed for comparing qualitative data. A $p<0.05$ value was considered to be statistically significant.

RESULTS

The results of the localization of the masses demonstrated that 32.3% of tumors were in the upper right region, whereas 19.4% of tumor were in the lower right region, 6.5% in the right hilar, 22.6% in the upper left, and 12.9% in the lower left, with one each (3.2%) in the left hilar and subcarinal regions (Table 2).

A fiberoptic bronchoscopy (FOB) revealed the diagnosis in 45.2% of the patients, but the diagnosis for the rest of the patients (54.8%) was made by transthoracic needle biopsy and surgery.

The pathology of the mass was identified as squamous cell in 61.3% of the patients, adenocarcinoma in 22.6%, and NSCLC in 16.1% of the patients (Table 3).

The mean age of patients with positive enlarged mediastinal lymph node pathology was found to be significantly lower than those with negative results (Table 4).

The SUVmax levels of the mass in patients varied between 4 and 41, with a mean of 16.3±9.4 and a median of 16.

The SUVmax levels of enlarged mediastinal lymph node varied between 2.6 and 35, with a mean of 9.1±6.4 and a median of 7.7.

Table 3. Age assessment according to pathology

Pathology	Mean±SD	*p*
Positive	58.6±9.4	0.047*
Negative	65.4±7.0	

SD: Standard deviation; Student's t-test was used; * $p<0.05$.

Table 4. The SUVmax of a cancerous mass, the SUVmax of enlarged mediastinal lymph node, mass SUVmax/lymph node SUVmax and the minimum, maximum, mean, standard deviation, and median values of mass sizes

	Min.-Max.	Mean±SD	Median
Mass SUVmax	4-41	16.3±9.4	16
Lymph node SUVmax	2.6-35	9.1±6.4	7.7
Mass SUVmax/enlarged mediastinal lymph node SUVmax	0.36-7.34	2.3±1.9	2.04
Mass size	1.5-20	5.8±4.6	4

Min.: Minimum; Max.: Maximum; SD: Standard deviation; SUVmax: Standardized uptake values.

The mass SUVmax/enlarged mediastinal lymph node SUVmax levels varied between 0.36 and 7.34, with a mean of 2.3±1.9 and median of 2.04.

Mass size varied between 1.5 cm and 20 cm, with a mean of 5.8±4.5 cm, and a median of 4 cm (Table 5).

No statistically significant difference was found between patients with positive mediastinal lymph node pathology results and those whose results were with regard to the SUVmax levels of the mass ($p>0.05$).

The SUVmax levels of enlarged mediastinal lymph node in patients with positive mediastinal lymph node pathology were significantly higher than those in patients with negative pathology ($p<0.01$).

The mass SUVmax/mediastinal lymph node SUVmax levels of patients with positive mediastinal lymph node pathology were significantly lower when compared with patients who had negative lymph node pathology results ($p<0.01$).

No statistically significant difference was found between patients with positive mediastinal lymph node and those with negative results regarding the size of the mass ($p>0.05$) (Table 6).

There was a statistically significant relationship between the mediastinal lymph node metastasis and the mass SUVmax/lymph node SUVmax ratio ($p<0.01$). The ratio of mass SUVmax/mediastinal lymph node SUVmax between 0 and 1.5 was found to be high in patients with positive lymph node pathology. On the other hand, the ratio of mass SUVmax/lymph node SUVmax ≥2.5 was found to be higher in patients with negative lymph node pathology (Table 7).

Table 5. Evaluation of the mass SUVmax, lymph node SUVmax, lymph node, mass/lymph node SUVmax and mass size according to the pathology

	Pathology				
	Positive		Negative		
	Mean±SD	Median	Mean±SD	Median	*p*
Mass SUVmax	18.3±10.7	16.5	12.8±5.2	13	0.172
Lymph node SUVmax	11.4±6.8	10.6	5.0±2.6	3.8	0.001**
Mass SUVmax/of mediastinal lymph nodes SUVmax	1.7±1.5	1.3	3.5±2.0	2.8	0.004**
Mass size	5.6±4.1	4	6.1±5.2	3.5	0.663

SUVmax: Standardized uptake values; SD: Standard deviation; The Mann-Whitney U-test was used; ** $p<0.01$.

Table 6. Evaluation of mass SUVmax/of mediastinal lymph node SUVmax according to pathology

	Pathology				
	Positive		Negative		
	n	%	n	%	*p*
Mass SUVmax/mediastinal lymph node SUVmax					
0-<1.5	12	60.0	2	18.2	
≥1.5-<2.5	6	30.0	1	9.1	0.002**
≥2.5	2	10.0	8	72.7	

SUVmax: Standardized uptake values; A chi-square test was used; ** $p<0.01$.

Table 7. Evaluation of the stage and mass pathology according to the lymph node pathology

	Pathology				
	Positive		Negative		
	n	%	n	%	*p*
Stage					
Stage II	3	15.0	0	0	
Stage III	11	55.0	10	90.9	0.112
Stage IV	6	30.0	1	9.1	
Mass pathology					
Negative	5	25.0	0	0	
Cell carcinoma	8	40.0	8	72.7	0.224
Adenocarcinoma	2	10.0	1	9.1	
NSCLC (Not otherwise specified)	5	25.0	2	18.2	

NSCLC: non-small cell lung cancer; A chi-square test was used.

No statistically significant difference was found in terms of mediastinal lymph node metastasis with regard to localization of tumor (p>0.05).

DISCUSSION

Various studies have been conducted to compare the role of PET with other conventional imaging methods in the detection of mediastinal metastasis in patients with NSCLC.[12,13]

The sensitivity and specificity along with the positive and negative predictability of PET-CT with 18F-fluorodeoxyglucose (18F-FDG) for mediastinal evaluation in patients with NSCLC has been shown by many studies to be superior to CT alone.[12-14]

In their meta-analytic comparison published in 1999, Dwamena et al.[15] reported that PET was superior to CT in the detection of lymph node metastasis. In that study, PET demonstrated a sensitivity of 79% (62-97%) and a specificity of 91% (79-99%), whereas CT was found to have a sensitivity of 60% (25-89%) and a specificity of 77% (44-95%). The SUV was calculated as follows: [SUV=activity in the region of interest (mCi/ml)/injected dose (mCi)/body weight (kg)].

In the study conducted by Eroğlu et al.[16] in 2007, it was suggested that mediastinoscopy should not be performed in the presence of non-central tumors and under conditions where the primary tumor is squamous cell carcinoma. In these cases, performing a thoracotomy directly might be a good alternative.

Cerfolio et al.[17] demonstrated an 18F-FDG-PET sensitivity of 71%, a specificity of 77%, a positive predictive value of 44%, and a negative predictive value of 91% for N2 lymph nodes. In the same study, these rates were reported as 43%, 75%, 31%, and 84%, according to CT. A significant difference was found between the two methods with regard to sensitivity and positive predictive value, whereas there was no significant difference with reference to specificity and negative predictive value. The same study also demonstrated that PET was superior to CT for mediastinal staging. However, there was a high rate of false positive results, and it could present false N2 positivity at stations 5#, 6# and 7#. On the other hand, there was no statistically significant difference between the rates of false positivity with regard to lymph node localization (p>0.05).

Cansever et al.[18] demonstrated that 18F-FDG-PET has a sensitivity of 100%, a specificity of 75%, a positive predictive value of 55.5%, a negative predictive value of 100%, and an accuracy rate of 80.9% in the assessment of mediastinal lymph node metastases. The authors suggested that 18F-FDG-PET was a safe method for lung cancer surgery and that it had a good negative predictive value for mediastinal staging.

Gonzalez-Stawinski et al.[19] reported a PET sensitivity of 64%, a specificity of 77%, a positive predictive value of 44%, and a negative predictive value of 88%.

Kernstine et al.[20] reported the sensitivity of PET, CT and MRI as 70%, 65% and 86%, respectively along with a specificity of 86%, 79% and 82%. No significant difference was found between the three methods.

Various studies have demonstrated that the FDG uptake for squamous cell carcinoma was higher than that for adenocarcinoma and bronchoalveolar carcinoma, which could be a reason for false negativity.

Kim et al.[21] demonstrated the FDG uptake of squamous cell carcinomas as 10.8±4.4 and 8.8±3.2 in adenocarcinomas. These results show that sensitivity and specificity of PET for squamous cell carcinomas was higher compared with adenocarcinoma. There was no

statistically significant difference in our study between adenocarcinomas and squamous cell carcinomas with regard to false positivity (p>0.05).

The reasons for false positive and false negative have been reported in literature.[19,22,23] Moreover, PET is known to demonstrate false positive results at station 5#, 6# and 7#. As a result, biopsies are required for the confirmation of these stations.[24] No significant difference in false positivity was found in our study regarding the localization of lymph node stations (p>0.05).

In the same study, it was suggested that evaluation of PET together with CT as a suitable non-invasive assessment of mediastinal lymph nodes might reduce the number of invasive interventions. They also suggested that stations suspected of having mediastinal metastasis should be confirmed by a biopsy due to the high rate of false positivity with PET. In addition, invasive mediastinal evaluations should be considered in the patients with other than peripheral T1 tumors due to the high rate of false negativity per patient.[24]

Hiroaki et al.[25] demonstrated in 2007 in their study on 327 patients that the size of the SUVmax value in lung cancer patients with a tumor of more than 3 cm was useful for diagnosis. However, there could be an increase in the diagnostic value of PET-CT when the SUVmax value is combined with the resistive index (RI) value for tumors below 3 cm. In our study, no statistically significant difference was observed between patients with positive lymph node pathology results and those with negative results regarding the size of the mass (p>0.05).

There are many studies which report the use of the SUVmax in the detection of mediastinal lymph nodes and also in the evaluation according to various cutoff values. In the study by Hiroaki et al.[25] a SUVmax value of ≥3.5 was reported with a sensitivity of 80%, a specificity of 99%, and an accuracy of 76%. The RI value was also investigated as an alternative to the SUVmax, and it was calculated as follows:

[RI= (delayed phase SUVmax-early phase SUVmax)/ early phase SUVmax x100)]

Bryan and Cerfolio[26] reported that there was a 24% chance of nodal malignancy under conditions where SUVmax values were between 0-2.5, an 80% chance of malignancy for SUVmax values between 2.6-4.0, and a 96% chance of malignancy for SUVmax values of more than 4.1.

In another study conducted by Bryant et al.[27] a 92% accuracy rate was predicted by this method with a reference SUVmax value of 5.3 for each N2 lymph node station assessed by 18F-FDG-PET. The results of these investigations show that the SUVmax is a predictor for lymph node involvement and that statistically significant SUV differences are observed between malignant and benign lymph nodes.

Standardized uptake values for the primary tumor have been identified by the above studies as independent prognostic factors.[28,29] No fixed SUV value was identified for lymph node metastasis in our study since different PET-CT devices were used at different centers; therefore, they could not be associated with the prognosis. However, the SUVmax values of lymph node in patients in our study with positive pathology results were significantly higher when compared with those with negative pathology results (p<0.01). On the other hand, no statistically significant difference was observed between patients with lymph node metastasis and those without lymph node metastasis (p>0.05).

Furthermore, evaluation of lymph node involvement by non-surgical methods in this study for pathology of the mass in patients who present with NSCLC suggests that better analyses could be performed by using the SUVmax values of lymph nodes in addition to the mass SUVmax/lymph node SUVmax ratio. The rate of false positivity under conditions of lymph node involvement is known to increase independently of the the SUVmax values of lymph node, especially with ratios above 2.5.

The results of our study show that false positivity rate is significantly increased under conditions in which the ratio of tumor SUVmax/lymph node SUVmax was above 2.5 as observed on PET-CT in patients with NSCLC. Our results also demonstrate that the evaluation of the ratio of mass SUVmax/lymph node SUVmax without managing the malignancy of the confirmed mass by using a surgical method may be useful for the detection of whether lymph node involvement was due to metastasis or the result of anthracosis, tuberculosis, and the other granulomatous diseases which are commonly known to lead to false positive results in Turkey.

The SUVmax ratio of lymph node to the mass should be considered instead of the SUVmax ratio of lymph node during the evaluation of lymph nodes in the presence of NSCLC. Considering the fact that the SUV value differs between various centers, it is suggested that an evaluation of the mass SUVmax/lymph node SUVmax ratio in addition to the SUVmax value would reduce the rate of false results caused by the difference in SUVmax values between centers. The evaluation of the tumor SUVmax/lymph node SUVmax ratio, patient age, and the SUVmax value of lymph node in addition to the SUVmax value would also help to administer effective treatment by reducing the rate of

false positive results through the determination of the most suitable preoperative staging.

Our study also demonstrates that the present use of PET-CT should not take the place of tissue biopsy, but it could help in identifying the localization of the biopsy through proper evaluation of the method.

The use of more standardized parameters in conjunction with the SUVmax value during PET-CT assessment and the reduced cost could increase the future safety of PET-CT and facilitate consideration for its use as a routine supplementary method for diagnosis and staging compared with other imaging methods, such as CT, MRI, and scintigraphy, as well as invasive biopsy methods, such as mediastinoscopy and thoracotomies.

Our study clearly demonstrated that the ratio of mass SUVmax/lymph node SUVmax does not have a certain value at diagnosis, but this study may lead to a new approach in the evaluation of PET-CT results.

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