Turk Gogus Kalp Dama 2016;24(2):333-339
doi: 10.5606/tgkdc.dergisi.2016.10982

Original Article / Özgün Makale

Importance of SUV_{max} threshold in positron emission tomography-computed tomography assessment of mediastinal and hilar lymph nodes in non-small cell lung cancer

Küçük hücreli dışı akciğer kanserinde mediastinal ve hiler lenf nodlarının pozitron emisyon tomografi-bilgisayarlı tomografi ile değerlendirilmesinde SUV_{max} eşiğinin önemi

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ABSTRACT

Background: This study aims to determine a new cut-off value for standardized uptake value in positron emission tomography-computed tomography evaluation of mediastinal lymph nodes in non-small cell lung cancer in Turkey.

Methods: A total of 207 patients with non-small cell lung cancer who were performed positron emission tomography-computed tomography between November 2006 and February 2010 were prospectively analyzed. Of these patients, 143 patients (125 males, 18 females; mean age 62.1 years; range 39 to 85 years) whose invasive staging was performed after positron emission tomography were included in the study. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rates of positron emission tomography were calculated and compared using a maximum standardized uptake value cut-off value of ≥2.5 and the newly determined maximum standardized uptake value cut-off value.

Results: The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rates were 45.3%, 78.9%, 55.8%, 71%, and 66.4%, respectively, when the maximum standardized uptake value cut-off value was considered 2.5 in mediastinal lymph nodes. The new maximum standardized uptake value cut-off value was determined to be 4.8 in metastatic lymph nodes. These values were 39.6%, 91.1%, 72.4%, 71.9% and 72%, respectively, according to the new maximum standardized uptake value cut-off value of 4.8. There was a significant difference only between specificity rates when the two different maximum standardized uptake value cut-off values were used (p=0.022).

Conclusion: In this study, the sensitivity of positron emission tomography in the evaluation of mediastinal lymph nodes was lower than those reported in the literature. This situation may be associated with the frequently observed granulomatous infections such as tuberculosis in our country. Results of positron emission tomography should be evaluated according to countries and a new maximum standardized uptake value cut-off value should be calculated particularly for mediastinal lymph node metastasis in multicenter studies in our country.

Keywords: Lymph node; non-small cell lung cancer; positron emission tomography.

ÖZ

Amaç: Bu çalışmada Türkiye'de küçük hücreli dışı akciğer kanserinde mediastinal lenf nodlarının pozitron emisyon tomografi-bilgisayarlı tomografi değerlendirmesinde standardize tutulum değeri için yeni bir eşik değeri belirlendi.

Çalışma planı: Kasım 2006 - Şubat 2010 tarihleri arasında pozitron emisyon tomografi-bilgisayarlı tomografi uygulanan küçük hücreli dışı akciğer kanserli toplam 207 hasta prospektif olarak incelendi. Bu hastalardan pozitron emisyon tomografi sonrası invaziv evrelemesi yapılan 143 hasta (125 erkek, 18 kadın; ort. yaş 62.1 yıl; dağılım 39-85 yıl) çalışmaya alındı. Pozitron emisyon tomografinin duyarlılığı, seçiciliği, pozitif prediktif değeri, negatif prediktif değeri ve doğruluk oranları ≥2.5'lik bir maksimum standardize tutulum değeri eşik değeri ve yeni saptanan maksimum standardize tutulum değeri eşik değeri kullanılarak hesaplandı ve karşılaştırıldı.

Bulgular: Mediastinal lenf nodlarında maksimum standardize tutulum değeri eşik değeri 2.5 olarak kabul edildiğinde; duyarlılık, seçicilik, pozitif prediktif değer, negatif prediktif değer ve doğruluk oranları sırasıyla %45.3, %78.9, %55.8, %71 ve %66.4 idi. Metastatik lenf nodlarında yeni maksimum standardize tutulum değeri eşik değeri 4.8 olarak belirlendi. Yeni maksimum standardize tutulum değeri eşik değeri 4.8'e göre bu değerler sırasıyla; %39.6, %91.1, %72.4, %71.9 ve %72 idi. İki farklı maksimum standardize tutulum değeri eşik değeri kullanıldığında, sadece seçicilik oranları arasında anlamlı farklılık vardı (p=0.022).

Sonuç: Bu çalışmada mediastinal lenf nodlarının değerlendirilmesinde pozitron emisyon tomografinin duyarlılığı literatürde bildirilenlerden daha düşük idi. Bu durum ülkemizde tüberküloz gibi granülomatöz enfeksiyonların sık görülmesine bağlı olabilir. Pozitron emisyon tomografi sonuçları ülkelere göre değerlendirilmeli ve ülkemizde yapılacak çok merkezli çalışmalar ile özellikle mediastinal lenf nodu metastazı için yeni bir maksimum standardize tutulum değeri eşik değeri hesaplanmalıdır.

Anahtar sözcükler: Lenf nodu; küçük hücreli dışı akciğer kanseri; pozitron emisyon tomografi.

Available online at
www.tgkdc.dergisi.org
doi: 10.5606/tgkdc.dergisi.2016.10982
QR (Quick Response) Code

Received: March 09, 2015 *Accepted:* June 24, 2015

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Lung cancer ranks first among cancer-related deaths, accounting for 12% to 16% of all cancers and 17.8% to 28% of all cancer-related deaths. Despite advanced treatment applications, only 10% to 15% of the patients with lung cancer could survive more than five years after diagnosis.[1] For this reason, early diagnosis and establishment of new methods for the prevention of the disease are of utmost importance. Recently, positron emission tomography (PET) has become a very important imaging method in diagnosis, staging and monitoring of cancer patients, as well as for treatment planning. Since PET in clinical applications can display metabolic changes in cancer cells, it is an important auxiliary imaging technique in diagnosis of malignancy. Although there are many agents that can be used in PET imaging, glucose analogues targeting the increased glucose metabolism such as 18F-fluoro-deoxy-D-glucose (FDG) that are frequently radiolabeled in the images are used in many thoracic malignancies. Generally, a lesion with a standardized uptake value (SUV) of >2.5 is accepted as malign.[2]

Studies performed for non-small cell lung cancer (NSCLC), the most frequent cause of death due to malignancy, have revealed that mediastinal lymph node (MLN) metastasis is the most important prognostic factor while also the most important factor in defining the treatment for patients without distant metastasis.[3] Detection of MLN on thorax computed tomography (CT) provides anatomical information; however, thorax CT has limited sensitivity and specificity to detect the presence or absence of metastasis.[4] Computed tomography has a sensitivity of 57% and a specificity of approximately 82% in mediastinal staging. On the other hand, PET has higher accuracy, having sensitivity of 74.9% to 91%, specificity of 80% to 95%, negative predictive value (NPV) of 84% to 100%, and positive predictive value (PPV) of 60% to 93% in the assessment of MLN metastasis.[5]

In this study, we aimed to determine a new cut-off value for maximum standardized uptake value (SUV_{max}) in PET-CT evaluation of MLN in NSCLC in Turkey.

PATIENTS AND METHODS

Two-hundred and seven patients who were examined by PET-CT due to the diagnosis of NSCLC between November 2006 and February 2010 in the Department of Thoracic Surgery of Medical Faculty of Ankara University were evaluated prospectively. Of these patients, 143 (125 males, 18 females; mean age 62.1 years; range 39 to 85 years) were included in the study whose lymph node sampling was performed by transbronchial needle aspiration (TBNA), mediastinoscopy, and thoracotomy. The study protocol was approved by the Medical Faculty of Ankara University Ethics Committee. Written informed consent was obtained from each patient, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

All tests and invasive interventions were performed according to the 1997 tumor node metastasis (TNM) staging. Age, sex, fasting blood glucose level, and histories of diabetes mellitus, tuberculosis, chemotherapy and/or radiotherapy were evaluated. In addition, location of the mass, SUV_{max} of the mass and MLN, dimensions of MLN, cell type, and pathology results of the lymph node sampling were also analyzed.

Before PET-CT scan, patients were asked to fast for eight hours; thus, the blood glucose level of each patient was below 150 mg/dL (78-148 mg/dL) before the procedure. In each patient, images were obtained from the skull base to the upper thigh. After the measurements of the blood glucose level and blood pressure, 18F-FDG dose, which was calculated according to the body weight of the patients (0.15 mCi/kg), was administered intravenously for PET-CT scan. Following the injection, which was performed in the half-roll position in armchairs located in the waiting room, the images of the patients, who took a rest at an appropriate room temperature, were obtained after bladder emptying. For the thorax images, a PET-CT device (Discovery-STE 8, General Electric Medical System, Waukesha, WI, USA) that is a combination of a tomography unit with helical octagonal slice and a PET unit including bismuth germanate block detector was used.

Statistical analysis

Data were analyzed using the SPSS for Windows version 15.0 software (SPSS, Inc., Chicago, IL, USA). Categorical variables were expressed as number and percentages, whereas numerical variables were expressed as mean ± standard deviation. The differences between the groups were evaluated using the chi-square test, t test or one-way analysis of variance according to the types of the variables. Receiver operating characteristics (ROC) analysis was used to determine the most appropriate cut-off value for SUV_{max} level. In the comparison of diagnostic methods, the sensitivity, specificity, PPV, NPV, and accuracy measures were used. A p value of <0.05 was considered statistically significant.

Table 1. General characteristics of patients (n=143)

	n	%	Mean	Min-Max	SUV_{max} average
Gender					
Female	18	12.6			
Male	125	87.4			
Age (years)			62.08	39-85	
Chemotherapy/radiotherapy history					
Chemotherapy	10	92.8			
No chemotherapy	128	7.2			
No information	5				
Cell type*					
Adenocarcinoma	52	36.3			
Squamous cell carcinoma	78	54.5			
SUV_{max}					
Squamous cell carcinoma			15.04	2.6-54	
Adenocarcinoma			10.92	1.71-28	
Differentiation					
Well	11	9.6			5.95
Moderate	59	54.8			13.13
Poor	50	35.7			14.8
No information	33				
Lymph node staging method					
Resection	132	92.3			
Transbronchial needle aspiration	8	5.5			
Mediastinoscopy	3	2.1			

Min: Minimum; Max: Maximum; SUV_{max}: Maximum standardized uptake value; * p=0.02.

RESULTS

General characteristics of the patients are given in Table 1. According to the radiological evaluation of patients; TBNA, mediastinoscopy or surgical resection was performed. Of the patients, 132 (92.7%) underwent an operation. In the remaining non-operated 11 patients (8%), mediastinoscopy was performed on three patients and TBNA was performed on eight patients. In these patients, N_2 was determined and treatment plan was changed from operation to adjuvant or neoadjuvant treatment. The preliminary case (6.9%) was operated after ruling out the lymph node metastasis by TBNA or mediastinoscopy in compliance with the preoperative findings. In preoperative staging, lymph node metastasis was observed in four patients after resection in pathologic examination of lymph node involvement. In these four patients, three had hilar lymph nodes adjacent to the mass on TBNA, and the right lower lobe tumors were paraesophageal lymph nodes in one patient. Location of the lymph nodes may have an effect on false negative. In these patients with false negative lymph nodes, the nodes were close to the mass.

Lymph node metastasis was found in eight of the 14 patients with SUV_{max} of >2.5 and in 29 of the 92 patients with SUV_{max} of <2.5. Fifty patients (35%) had centrally located tumor and N_1 was determined in 21 (42%) of these. In 21 (42%) of the centrally located tumors, no involvement was determined in PET-CT; however, pathological examination revealed metastasis in 17 (40.5%). Non-central tumor was present in 93 patients (65%); while no involvement was determined in PET-CT in 12 (15.4%), metastasis was determined in hilar lymph node in pathological examination. The accuracy rate in determining hilar lymph node metastasis in PET-CT in centrally located tumors was significantly lower than in non-central tumors (p=0.005).

In the present study; sensitivity, specificity, PPV, NPV and accuracy of PET-CT were evaluated with SUV_{max} of 2.5 as the cut-off in N_1 and N_2 and a new SUV_{max} cut-off value was calculated by ROC analysis (Figure 1). In this analysis, the dependent variable with the SUV_{max} in the metastasis of lymph nodes and independent variable with the SUV_{max} in all lymph glands were used and the new cut-off value was calculated. The new SUV_{max} cut-off value was determined to be 5.7 for N_1 lymph nodes and 4.08 for

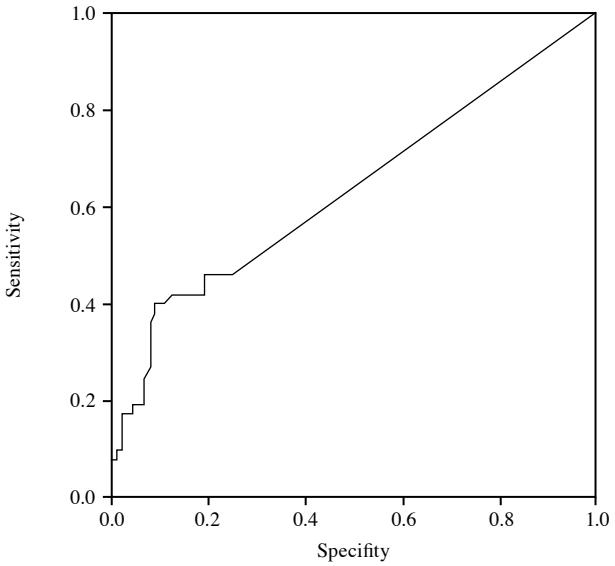

Figure 1. Receiver operating characteristic curve for new maximum standardized uptake value cut-off value (4.8) in N_1 and N_2 lymph node stations.

N_2 lymph nodes. When N_2 and N_1 lymph nodes were evaluated together, the new SUV_{max} cut-off value was determined to be 4.8. The sensitivity, specificity, PPV, NPV, and accuracy of PET-CT in determining lymph node metastasis with SUV_{max} of 5.7, 4.08, and 4.8, as well as comparison of these values with those calculated for SUV_{max} of 2.5 are presented in Tables 2 and 3.

The MLN metastasis rates in adenocarcinoma and squamous cell carcinoma were 41.7% and 36.4%, respectively. In the present study, cell type had no significant effect on MLN metastasis (p=0.686). Evaluation of the mass in terms of SUV_{max} and the possibility of lymph node metastasis revealed that the mean SUV_{max} of the mass with lymph node metastasis was 14.3±9.0, whereas the mean SUV_{max} of the mass without lymph node metastasis was 12.0±6.4, and the difference was not significant (p=0.08). Statistical evaluation of the SUV_{max} of the lymph node and the SUV_{max} of the primary mass in terms of risk for lymph node metastasis revealed that if the ratio of MLN SUV_{max} to the primary tumor SUV_{max} (lymph node SUV_{max}/primary mass SUV_{max}) was >0.29, the rate of metastatic possibility was determined to be high, and the sensitivity, specificity, PPV, NPV, and accuracy in this level were calculated to be 91%, 45%, 64.5%, 81.8%, and 69%, respectively.

DISCUSSION

The use of TNM staging system is essential in malignant diseases in order to plan the treatment and predict the prognosis. In the treatment planning of patients with NSCLC, distinguishing patients suitable or unsuitable for surgical resection but who may benefit from chemotherapy and/or radiotherapy is of importance. Mediastinal lymph node involvement has been reported in 26% of newly diagnosed lung cancer patients, of whom extrathoracic metastasis has been determined in 49%.[3]

Studies on NSCLC, the most frequent cause of death due to malignancy, have demonstrated that MLN metastasis is the most important prognostic factor and also the most important factor in defining the treatment for patients without distant metastasis.[6] Tumor localization within the thorax, tumor size, tumor respectability, and its relationship with the surrounding anatomic structures can be determined using thorax CT. Presence of MLN can also be shown anatomically by thorax CT; however, it has limited sensitivity and specificity to show the presence or absence of metastasis. In MLN staging, the sensitivity and specificity of CT are approximately 57% and 82%, respectively.[4] Positron emission tomography-CT has become a very important imaging tool in planning the diagnosis, as well as in staging and monitoring of cancer patients. In the evaluation of MLN metastasis, the accuracy of

Table 2. Sensitivity, specificity, positive and negative predictive values, and accuracy of positron emission tomography-computed tomography in determining N_1 with maximum standardized uptake value of 2.5, 5.7, and 4.08

N_1	SUV_{max}= 2.5	SUV_{max}= 5.7	*p*	N_2SUV_{max}= 2.5	SUV_{max}= 4.08	*p*
Sensitivity (%)	21.6	16.2	0.553	57.9	57.8	1.000
Specificity (%)	86.8	99.0	0.001	84.7	88.7	0.354
Positive predictive value (%)	36.4	85.7	0.023	36.7	44.0	0.582
Negative predictive value (%)	76.0	77.2	0.821	92.9	93.2	0.929
Accuracy (%)	69.9	77.6	0.139	81.1	84.6	0.432

SUV_{max}: Maximum standardized uptake value.

Table 3. Sensitivity, specificity, positive and negative predictive values, and accuracy of positron emission tomography-computed tomography in determining N_1 and N_2 with maximum standardized uptake value of 2.5 and 4.8

N_1 and N_2	SUV_{max}= 2.5	SUV_{max}= 4.8	*p*
Sensitivity (%)	45.3	39.6	0.553
Specificity (%)	78.9	91.1	0.022
Positive predictive value (%)	55.8	72.4	0.154
Negative predictive value (%)	71.0	71.9	0.884
Accuracy (%)	66.4	72.0	0.305

SUV_{max}: Maximum standardized uptake value.

PET-CT is higher than CT, with sensitivity of 74.9% to 91%, specificity of 80% to 95%, NPV of 84% to 100%, and PPV of 60% to 93%.[5]

Evaluation of NSCLC through non-invasive tests has demonstrated that the lymph nodes having the possibility to become metastatic should be verified by cytopathology. Transbronchial needle aspiration, endobronchial ultrasound-fine needle aspiration, endoscopic ultrasound, and transthoracic needle aspiration are newly developed minimally invasive techniques providing cytopathological diagnosis. While the specificity of these techniques is high, their NPV is low. These can be defined by minimal invasive surgical techniques (Table 4).[6] Mediastinoscopy is still the gold standard in the assessment of MLN.[7]

In previous studies, while the specificity of PET-CT has been reported to be high in detecting metastatic lymph nodes, its sensitivity has been reported to be low.[6] In our study, when the mediastinal and hilar lymph nodes were evaluated together with SUV_{max} cut-off value as 2.5, the sensitivity and PPV were found to be lower as compared to those reported in other studies. In the study by Shin et al.[8] performed on 184 cases, the sensitivity and specificity of PET-CT was reported to be 43% and 95%, respectively, for detecting N_2 disease in stage T_1 NSCLC. In the meta-analysis by Gould et al.[9] including 28 studies, the sensitivity was 61% and the specificity was 79%. In their study, Taşçı et al.[10] reported sensitivity, specificity, NPV, PPV, and accuracy of PET-CT in detecting N_2 disease to be 72%, 94.4%, 97.7%, 49.2%, and 92.7%, respectively. In our study, the sensitivity and PPV were determined to be low. In the study by Liu et al.,[11] the sensitivity and PPV were determined as 65% and 78.5%, respectively. Furthermore, in their study, Andrea et al.[12] investigated the accuracy rate of PET-CT in intrathoracic lymph node staging and determined the sensitivity, specificity, PPV, NPV and accuracy as 54.2%, 91.9%, 82.3%, 74.3%, and 80.5%, respectively. In the present study, the sensitivity was lower than and the specificity was similar to those reported in previous studies. Presence of inflammatory diseases is known to be the reason leading to false positive results on PET-CT and FDG uptake may be observed in the regions where active inflammation is present. It was considered that mediastinal involvement might be observed on PET-CT due to the presence of lower involvement, benign infections (tuberculosis, histoplasmosis) and inflammatory diseases. In the assessment of MLN by PET-CT, the cell diagnosis is required to prove the metastasis due to the lack of PPV. Before deciding on surgery, invasive/minimally invasive staging should be performed. However, since NPV was determined to be high, the treatment may

Table 4. Accuracy rate of different techniques in staging of mediastinal lymph nodes

	Sensitivity	Specificity	NPV	PPV	Prevalence
	%	%	%	%	%
Computed tomography	57	82	83	56	28
Positron emission tomography	84	89	93	79	32
Transbronchial needle aspiration	76	96	71	100	70
Endoscopic ultrasound-fine needle aspiration	88	91	77	98	69
Mediastinoscopy	81	100	91	100	37

PPV: Positive predictive value; NPV: Negative predictive value.

be planned before staging if no involvement was determined in the MLN on PET-CT.

In the present study population, the SUV_{max} cut-off value was determined to be 4.8. With the use of this cut-off value, the sensitivity and PPV were determined to be low at a rate of 39.6% and 72.4%, respectively, which can lead to false negative results in the assessment of lymph nodes; i.e. metastasis. In their study, Lee et al.[13] determined a new cut-off value and suggested that despite its importance and efficacy in non-invasive staging, the efficacy of PET-CT was low due to the false-positive (infection, inflammatory diseases) and false negative (micro-metastasis) results.

In regions where prevalence of granulomatous diseases is high, high FDG uptake may be monitored in benign lesions. In a study by Kwan et al.[14] conducted on healthy subjects in Taiwan, FDG uptake was monitored in the mediastina of 28% of the subjects. In their study, Kang et al.[15] determined a significant difference between the SUV_{max} of benign and malignant lesions.

In the present study, it was found that if the ratio of SUV_{max} of the MLN to the SUV_{max} of the primary tumor was >0.29, the rate of metastatic possibility was high at a rate of 91%; it was also detected that the lymph node could be malignant. In their study, Cerfolio et al.[16] investigated the possibility of metastasis according to the ratio of the SUV_{max} of the lymph node to that of the MLN on PET-CT, and determined in the pathologically proven cases that if the ratio of SUV_{max} of the primary tumor to that of MLN was >0.56, the lymph node could be malignant at a rate of 94%.

The SUV_{max} values were found to be significantly higher in the squamous cell carcinoma than in adenocarcinoma (p=0.02). Kim et al.[17] determined the SUV_{max} to be 10.8±4.4 for squamous cell carcinoma, and 8.8±3.2 for adenocarcinoma. The accuracy rate in determining hilar lymph node metastasis in PET-CT in centrally located tumors was significantly lower than in non-central tumors (p=0.005). It is difficult to detect the metastasis in lymph node that is adjacent to the primary tumor in PET-CT. N_1 lymph nodes are very close to primary tumors; thus, it may be overlooked because of FDG uptake of primary tumor. In the study by Al-Sarraf et al.,[18] the distinction of lymph node invasion was determined to be challenging in the tumors located in the hilum.

In their study, Lee et al.[19] investigated risk factors for occult mediastinal metastasis in NSCLC and showed that central location, larger tumor size, high SUV_{max} of PET-CT, and adenocarcinoma cell type were the risk factors. In the present study, in terms of lymph node metastasis, the N_1 risk was higher only in the centrally located tumors (p=0.005).

When the results of the present study were compared with those conducted in other developing countries, the accuracy rates were found to be lower. This might be due to the frequency of tuberculosis, fungal and other infections in Turkey. Positron emission tomography-CT results should be evaluated separately for each country and new SUV_{max} cut-off value should be determined considering our country's realities in future multi-center studies for MLN, in particular.

Positron emission tomography-CT, a noninvasive staging method, has higher accuracy than other methods in the mediastinal lymph node staging; however, sufficient results have not been achieved. Although PET-CT is an appropriate technique, it is not as reliable as biopsy as the final diagnosis may be established by pathologic examination in the staging of mediastinal lymph node in lung cancer.

In conclusion, distinguishing patients suitable or unsuitable for surgical resection but who might benefit from chemotherapy and/or radiotherapy is important in non-small cell lung cancer. Recently, positron emission tomography-computed tomography is frequently used in lung cancer staging. However, decisions should be based on not only positron emission tomography-computed tomography findings but also on tumor location, cell type, and computed tomography findings interpreted by an experienced radiologist. As the rate of hilar lymph node metastasis is high particularly in the centrally located tumors, these tumors should be evaluated in detail.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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