ULUSLARARASI HEMATOLOJI-ONKOLOJI DERGISI ARTICLE International Journal of Hematology and Oncology

Are Ratio of Lymph Node to Primary Focus SUV-max and PET/CT ^{18}FDG Standard Uptake Value of Lymph Nodes Meaningful in Staging Non-Small Cell Lung Cancer?

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ABSTRACT

Surgical treatment for mediastinal lymph node involvement in non-small cell lung cancer (NSCLC) will not have positive impact on survival. The present study aimed at investigating the role of positron emission tomography/computerized tomography (PET/CT) in staging NSCLC. Ninety-nine patients with maximal standard mediastinal lymph node involvement value (SUVmax) of 2.5 or more on PET/CT scanning were included in this study. All patients underwent invasive staging or pathological staging with direct thoracotomy. Relationship between lymph node SUVmax and lymph node/primary mass SUVmax ratio and presence of lymph node metastasis was investigated. Mean SUVmax ratio was 3.87 in the group with positive mediastinal lymph node on PET/CT but pathologically benign lymph nodes whereas it was 5.69 in those with pathologically malignant lymph nodes. Although there was a numeric difference between two groups, the difference was statistically insignificant (p= 0.65). Lymph node/mass SUVmax ratio was 0.49 in the patients with positive lymph nodes on PET/CT and benign pathology whereas it was 0.65 in those with malignant pathology and the difference between them was found to be not significant (p= 0.61). It was observed, however, that as SUVmax ratio increased, possibility of detecting malignant lymph node raised. Rate of malignancy was 52.38% in the group with SUVmax ratio of 0.1 to 0.3 whereas it was 91.66% in those with SUVmax ratio of 1 or greater. No significant relationship was found between lymph node SUV-max rate and presence of metastatic lymph node. We believe that more multi-center studies are needed with more patients.

Keywords: Non-small cell lung cancer, Staging, ^{18}FDG, PET/CT

ÖZET

Küçük Hücreli Dışı Akciğer Kanseri Evrelemesinde ^{18}FDG PET/BT ile Saptanan Lenf Bezi Standart Tutulum Değeri ve Lenf Bezi / Primer Odak SUVmax Oranı Anlamlı mı?

Küçük hücreli dışı akciğer kanserinde (KHDAK) mediastinal lenf bezi tutulumunda yapılacak cerrahi tedavinin sağkalıma olumlu katkısı olmayacaktır. Çalışmamızda; pozitron emisyon tomografisi/bilgisayarlı tomografinin (PET/BT) KHDAK evrelemesindeki yerini araştırmak hedeflendi. PET/BT'sinde mediastinal lenf bezi maksimum standart tutulum değeri (SUVmax) 2.5 ve üzeri olan 99 hasta çalışmaya alındı. Bütün hastalara invaziv evreleme veya doğrudan torakotomi ile patolojik evreleme uygulandı. Lenf bezi SUVmax ve lenf bezi/primer kitle SUVmax oranı ile lenf bezi metastazı arasındaki ilişki araştırıldı. Mediastinal lenf bezi PET/BT'de pozitif, ancak patolojik olarak benign çıkan hasta grubunda ortalama SUVmax 3,87 iken, patolojide malign çıkanlarda SUVmax ortalama 5,69 olarak bulundu. Aralarında sayısal olarak fark olmasına karşın, istatistiksel olarak anlamlı değildi (p= 0.65). PET/BT pozitif ve patolojisi benign olanlarda lenf bezi/kitle SUVmax oranı 0,49 iken, patolojisi malign olanlarda bu oran 0,65 olarak hesaplandı ve istatistiksel olarak anlamlı ilişki saptanmadı (p= 0.61). Ancak SUVmax ve oranı arttıkça lenf bezinin malign çıkma olasılığının arttığı görüldü. Malignite oranı 0.1- 0.3 grubunda %52.38 iken 1 ve üzeri olduğunda %91.66 idi. Lenf bezi SUVmax'ı ve oranı ile metastatik lenf bezi arasında istatistiksel olarak anlamlı ilişki saptanmadı. Hasta sayısı daha fazla ve çok merkezli çalışmalara ihtiyaç olduğunu düşünüyoruz.

Anahtar Kelimeler: Küçük hücreli dışı akciğer kanseri, Evreleme, 18 FDG, PET/BT

INTRODUCTION

Despite advances in chemotherapy and radiotherapy, the most important treatment modality that might contribute to cure and long-term survival in non-small cell lung cancer (NSCLC) is surgery.[1] However, only minority of the patients have chance of surgical treatment at the time of diagnosis. In the presence of mediastinal lymph node involvement except from the selected cases with microscopic N2 disease and distant metastases, surgical treatment doesn't contribute to survival.[2-4] Thus, the most important issue that should be investigated in the resectable patients without distant metastases is mediastinal lymph node involvement.

Although thoracic computerized tomography (CT) has been used to evaluate mediastinal lymph nodes, its success rate was far from being satisfactory. Recently, positron emission tomography/computerized tomography (PET/CT) has been introduced and it has been reported to be superior to thoracic CT in mediastinal staging of NSCLC.[5,6] The present study aims to investigate the role of PET/CT in lymph node SUVmax and lymph node/primary mass SUVmax ratio in mediastinal staging by comparing clinical stages and post-operative pathological stages of the patients diagnosed with NSCLC.

MATERIAL AND METHODS

Two-hundred and sixty four patients who underwent PET/CT scanning for diagnosis or suspicion of NSCLC in Izmir Dr. Suat Seren Research and Training Hospital of Chest Diseases and Thoracic Surgery and who were operated for purpose of staging and/or treatment were evaluated retrospectively (Approval no. of Scientific Council: 278/2010). A total of 99 patients, 88 male and 11 female, with mean age of 58 ± 16 were included in the study between January 2007 and August 2009. The patients with proven malignant pleural effusion or distant organ metastases were excluded. Mediastinal lymph node SUVmax rate of 2.5 or more on PET/CT scanning was taken as inclusion criterion. Ninety-nine patients with SUVmax rate of 2.5 or more and who were pathologically staged after direct thoracotomy were included in the study.

Tissue samples were taken through "punch" biopsy method under assistance of mediastinoscopy from 2R, 2L, 4R, 4L or 7th stations on which suspicious lymph nodes were located and under assistance of videothoracoscopy from the left hilar and 5th and 6th lymph nodes. During thoracotomy, systematic mediastinal lymph node dissection was made in this study.

The patients underwent PET/CT examination (Siemens Medical Systems, Biograph Duo, Enlargen, Germany) in nuclear medicine department of our hospital. For the diabetic patients, blood glucose levels were regulated first and it was ensured for them to have blood glucose levels below 200 mg/dL. Prior to PET/CT scanning, physical activity was limited and hydration was achieved. Depending on weight of the patients, 370 to 555 MBq of FDG was given intravenously. Sixty minutes after FDG injection, imaging was made between vertex-upper thigh at 7 to 9

bed position depending on length of the patient. SUVmax was estimated considering the focus with the highest involvement relative to adjacent tissues and normal biodistribution. Lesions with SUVmax ratio of 2.5 or more were considered in favour of malignancy.

$$\text{SUVmax} = \frac{\text{Amount of activity on the involved area (mCi/Ml)}}{\text{Injected Dose (mCi)/Body weight (Kg)}}$$

$$\text{SUVmax rate} = \frac{\text{Lymph node SUVmax}}{\text{Primary Focus SUVmax}}$$

All data were analyzed using SPSS software for Windows, v.16.0 (SPSS Inc., Chicago, Illinois, USA). Distribution of variables were examined with Kolmogorov-Simirnov test, evenly distributed numeric data were analysed with Anova and t-test. Chi-square test was used for cathegoric variables. The sensitivity, specifity, positive predictive value, negative predictive value, and accuracy of PET/CT in detecting mediastinal lymph node metastasis were calculated. P values less than 0.05 were considered as statistically significant.

RESULTS

Fifty eight (58.5%) patients with lymph node involvement on any of 2R, 4R or 7th stations on PET/CT underwent mediastinoscopy and 2 patients (2%) underwent videothoracoscopy for presence of tumor on the right lung and hilar lymph node involvement on the left-side (N3?). Eight patients (8.08%) underwent thoracotomy directly for presence of one lymph node involvement on the 5th or 6th stations on the left side. Remaining 31 patients underwent thoracotomy directly because of lack of centrally located tumors, absence of lymph nodes of pathological size on thoracic CT or PET/CT on the mediastinum or presence of lymph node involvement only on the 10th or 11th stations (N1?).

For 27 of 58 patients undergoing mediastinoscopy no additional surgical intervention was made because of detection of metastasis in lymph node and they were referred to neoadjuvant treatment. Thirty one patients in whom no metastasis was found on lymph nodes with mediastinoscopy underwent thoracotomy. Of 70 patients undergoing thoracotomy 50 (71.43%) underwent lobectomy, 15 (21.42%) pneumonectomy, 3 (4.29%) wedge thoracotomy and 2 (2.86%) exploratory thoracotomy. Two patients underwent wedge resection because of respiratory failure and other one because of N2 multi-station involvement.

In regard to histopathological sub-groups of the tumors, 63 patients (57.79%) had squamous cell carcinoma, 32 (32.32%) had adenocarcinoma, 3 (3.04%) had large cell carcinoma and one patient (0.1%) had atypical carcinoid tumor.

When PET/CT results were evaluated in detecting mediastinal lymph nodes, metastatic findings were found clinically in 99 patients whereas lymph node metastasis was found in 73 (73.6%) patients while no metastatic lymph nodes were found in 26 (26.3%) patients on histopathological examinations. The sensitivity of PET/CT in detecting mediastinal lymph node metastasis was found to be 76,84% and specifity was 86,61%, positive predictive value 73,73%, negative predictive value was 86,66% and accuracy rate was found to be 81,81%.

On the histopathological examinations of the lymph nodes without metastasis, diagnoses of reactive hyperplasia in 17 patients, necrotizing granulomatous lymphadenitis (tuberculosis) in 7 patients and anthracosis in 2 patients were made. These 26 patients were divided into two groups as those with and without tuberculosis and statistically evaluated separately and together according to their SUVmax rates. No significant difference was found between them ($p > 0.05$).

When 26 patients (26.3%) with malignant PET/CT findings and benign pathological results were examined, histological type of the tumors were reported to be squamous cell carcinoma in 18 patients, adenocarcinoma in 7 patients and large cell carcinoma in one patient. No statistically significant data was found between incorrect results of PET/CT and histological sub-groups ($p > 0.05$)

Lymph nodes mean SUVmax value was found to be 3.87 in the group of patients with malignant PET/CT findings and in those with pathologically benign findings whereas it was found to be 5.69 in those with malignant pathology. This difference was statistically insignificant ($p = 0.65$).

Table 1. Standardized uptake value (SUVmax) ratio in the patients with positive PET/CT

	(n)	Minimal	Maximal	Average	Std. Deviation
SUVmax ratio	99	0.09	2.21	0.6105	0.34236

Table 2. Averages of standardized uptake value (SUVmax) ratios by histopathological results

	(n)	SUVmax ratio
PET/CT (+) Pathology (-)	26	0.49
PET/CT (+) Pathology (+)	73	0.65

Of the 29 cases whose lymph node size was less than 1 cm, the ones with pathologically malignant (21) had SUV max 6,33 (2,7-8,9) while the benignant ones had SUV max 4,32 (2,6-6,3). As for the cases with lymph node size more than 1 cm, these ratios were respectively 7,88 (2,7-26,0) and 4,0 (2,7-8,9).

In entire group, mean ratio of lymph node to primary focus was found to be 0.61 ± 0.34. Lymph node/primary focus SUVmax ratio was 0.49 in the group with malignant PET/CT findings and benign pathology results where it was found to be 0.65 in those with malignant pathology results. The difference was statistically insignificant (p= 0.61) (Table 1, 2).

When 99 patients who had lymph node SUVmax value of 2.5 or more and thus considered as metastatic according to PET/CT were grouped by SUVmax ratios, pathologically metastatic lymph nodes were found in 11 (52.38%) of 21 patients with ratio of 0.1 to ≤ 0.3, 28 of 39 (71.79%) patients with ratio of 0.3 to ≤ 0.6, 23 (85.18%) of 27 patients with ratio of 0.6 to ≤ 0.9 and 11 (91.66%) of 12 patients with a ratio of 1 or more (Table 3).

DISCUSSION

As the presence of mediastinal lymphatic metastasis in NSCLC is the most important therapeutic inclusion criteria and the most important prognostic predictor in the patients without distant metastasis[7], accurate mediastinal staging is of great importance. Besides preventing the patients who have a chance of operative intervention from losing this chance as a result of an incorrect staging, knowing whether mediastinal lymph node metastasis exists or not helps avoide unnecessary thoracotomies.[8]

Due to the ineffectiveness of anatomic imaging method Thorax CT; PET, which enables metabolical in-

Table 3. Comparison of standardized uptake value (SUVmax) ratios by histopathological results

LAP SUVmax Ratio	Pathology Benign		Pathology Malign		Total (n)
	n	%	n	%	
0.1>- ≤0.3	10	47.62	11	52.38	21
0.3>- ≤ 0.6	11	28.21	28	71.79	39
0.6>- ≤ 0.9	4	15.82	23	85.18	27
1 or more	1	8.34	11	91.66	12

LAP : Lymph adenopathy

formation about the tumor and its methastasis, has been started to be used however, the fact that spatial resolution of this modality was too low has limited its use.[9] Recently, as a consequence of integrating the PET and CT methodologies, integrated PET/CT method has been introduced to clinical practice which is an anatomic-metabolic imaging modality. The optimum time in the discrimination between malignant and benignant lesion was given in the literature as 50-60 minutes after ^{18}FDG injection which is peak for lesion background ratio. In the present study post -injection was monitored in the 60th minute. Some studies reported that PET/CT would reduce unnecessary thoracotomies compared to other conventional methods in staging NSCLC.[10,11]

The most reliable method in investigating the presence of mediastinal lymph node metastasis in patients with potentially accepted resectable NSCLC is still mediastinoscopy. However, approach of applying routine mediastinoscopy to all patients is not widely favored considering its advantages and disadvantages.[12,13] The same studies report that mediastinoscopy is not required in the patients with negative test results because of high specificity and negative predictive values of PET/CT. Several meta-analyses in the mediastinal staging of NSCLC have calculated a mean sensitivity and specificity of 0.79 and 0.91, respectively for PET.[14,15] In the present study the sensitivity of PET/CT in detecting mediastinal lymph node metastasis was found to be 76,84% and specifity was 86,61%, positive predictive value 73.73%, negative predictive value was 86.66% and accuracy rate was found to be 81.81%.

In terms of making the malign/benign discrimination in lymph nodes less than 1 cm in diameter, PET/CT is greater than CT. As the size of the lesion grows, an increase in SUVmax is expected.[16] In our study, we detected malignant lymph note less than 1 cm in diameter in 21 cases.

False positive results at a rate of 16 to 55% might be achieved in the granulomatous and inflammatory diseases.[17,18] In the present study, false positivity rate was 26.3% and reactive hyperplasia was found in 65.54% and tuberculosis in 26.92%. The fact that false positivity rate of PET/CT was high led the investigators to conduct new studies. Studies were first done on SUVmax threshold. Bryant et al.[19] studied 397 patients having undergone PET scanning, 143 of whom had pathologically proven N2. They reported that if SUVmax malignancy threshold was taken as 5.3 instead of 2.5, then sensitivity, specificity and accuracy rate of PET/CT would increase and rate of detecting unexpected N2 disease would decrease. In a similar study by Lee et al.[20], the authors found higher success rate for PET when they took SUVmax threshold as 5.3 instead of 2.5. In the present study, among the group of patients with positive PET/CT results, mean SUVmax ratio was 3.87 in the patients with false positive results whereas it was 5.69 in those with truly positive and the difference was statistically insignificant. The fact that the rate of the patients with diagnosis of tuberculosis was high (27%) in the group with false positive results can be attributed to the fact that our series was containing relatively low number of patients.

Reporting that SUVmax values could vary depending on dose of FDG applied, weight of the patient and the center where the investigation was made. Cerfolio et al.[21] reported that SUVmax ratio that is calculated by dividing lymph node SUVmax value to SUVmax value of the primary focus might be more valuable in evaluating lymph node metastasis. According to that article, mean ratio was 0.40 for those positive with PET but proven to be benign on pathological examination, it was found to be 0.58 in the lymph nodes pathologically proven to be malignant. It was reported that using these ratios would be useful in determining which patients would undergo invasive staging and if invasive staging would be done, which modality was to be chosen. In the present study, the ratio was 0.49 in those with positive PET/CT results and benign pathology and while 0.65 in those with positive PET/CT results but with malignant pathological results and the difference was not found to be statistically significant (p= 0.61). However, it was observed that possibility of being malignant of lymph node raised as SUVmax ratio increased. It was 52.38% in the group of malignancy rate of 0.1 to 0.3 whereas it was 91.66% when malignancy rate was 1 or more.

In conclusion, SUVmax value alone doesn't yield sufficient results in clinical staging. We believe that it would be more useful if it is used together with SUVmax ratio and that studies are needed with higher number of patients.

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