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Original Article

Do we need a new SUVmax threshold value for the evaluation of mediastinal lymph nodes?

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ABSTRACT

Background: Mediastinal lymph node involvement is the most important factor determining the treatment and the prognosis with non-small cell lung cancer (NSCLC). In our study, the role of PET-CT was assessed in the evaluation of intrathoracic lymph node involvement in patients with preoperative NSCLC.

Materials and Methods: The study included 510 cases selected according to the criteria identified between January 2009 and July 2011. PET-CT staging and thorax-CT, size of lymph nodes, histological type of tumor, mediastinal lymph nodes taken and the pathological results were assessed.

Results: SUVmax cut-off value was taken as 2.5 for the metastatic analysis of lymph nodes in PET-CT and N1 and N2 lymph node stations were evaluated. Sensitivity for the N2 lymph node stations, was 74.7%, specificity 49.4%, Positive Predictive Value 25.4%, Negative Predictive Value 89,.5% and accuracy 54.1% ($p < 0.001$). Following the statistical analysis, the new SUVmax cut-off value for the N1 lymph node groups was calculated as 3.34, and for N2 lymph node groups 5.6. Based on the new SUVmax cut-off value for N2 lymph node groups, the sensitivity of PET-CT was calculated as 43.2%, specificity 94.4%, PPV 64.1%, NPV 87.8% and accuracy 84.9% ($p < 0.001$).

Conclusions: Calculating a new cut off value of SUVmax all around the world would increase the NPV of PET-CT and so it would reduce to use of invasive methods. PPV of PET-CT is still not at an acceptable level, so positive results of PET-CT for mediastinal lymph node staging should be confirmed with invasive diagnostic techniques.

Keywords: non-small cell lung cancer, lymph node, PET-CT, staging

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Introduction

Lung cancer, with increasing incidence and mortality rates, is one of the most important health problems in the world and almost one third of deaths from cancer are due to lung cancer. Only 15% of the patients can survive for five or more years after being diagnosed [1].

Half of the patients diagnosed with non-small cell lung cancer have mediastinal lymph node involvement and less than 33% are suitable for surgical resection [1]. In order to increase the success rate of surgical treatment, early diagnosis is crucial. For accurate staging of NSCLC, the location and the size of the primary tumor [T factor], regional lymph nodes [N factor] and distant metastasis [M factor] need to be identified. For this aim, Positron Emission Tomography (PET-CT) has started to be used widely in addition to the scanning methods [2].

In patients without distant metastasis, mediastinal lymph node involvement is the most important factor that determines treatment and prognosis. Therefore, accurate evaluation of mediastinal lymphatic metastasis is crucial in the preoperative stage [1,3]. Thorax-CT which is used as the initial method in the identification of metastatic mediastinal lymph node, has limited sensitivity and specificity in showing metastasis in enlarged lymph nodes [4]. On the other hand, mediastinoscopy which is the "gold standard" with excellent sensitivity and specificity rates in mediastinal staging has the disadvantage of being invasive.

The use of PET in patients with NSCLC that shows biological activity of tumor cells has increased in recent years. According to the existing studies, PET-CT is better than thorax-CT in mediastinal staging of NSCLC and it can reduce the use of invasive methods in detecting mediastinal lymph node metastasis. PET-CT is used for diagnosis, staging, restaging and follow up in NSCLC [5-7].

The aim of this study is to determine sensitivity, specificity, negative predictive value, positive predictive value and accuracy rates of PET-CT in the detection of metastatic intrathoracic lymph nodes in patients with NSCLC, through a comparison of PET-CT findings for intrathoracic lymph nodes and histopathological examination results obtained through invasive procedures. It also aims to calculate a new SUVmax cut-off value since SUVmax values in mediastinal lymph nodes increase due to bacterial, granulomas and fungal infections, which are common in Turkey, as well as due to malignancy.

Materials and Methods

The patients who were diagnosed with NSCLC and who underwent thorax-CT and PET-CT, and surgery for treatment and/or staging between January 2009 and July 2011 were prospectively reviewed. The study included all surgical cases that underwent histopathological examination apart from fine needle aspiration biopsy. 28 patients out of 538, who underwent chemoradiotherapy were excluded from the study.

Preoperative assessment of all patients included anamnesis, physical examination, respiratory function tests, electrocardiography, blood biochemistry and hemogram tests, coagulation tests, postero-anterior and lateral lung graphics, thorax-CT and PET-CT. All patients whose tumor size was bigger than 3cm underwent cranial MRI for preoperative staging. Tests and invasive procedures were performed based on TNM staging. Age, gender, preoperative diagnostic tests, location of the mass, enlarged intrathoracic lymph node on thorax-CT (>1cm), SUVmax values of masses and all intrathoracic lymph nodes in PET-CT, operations performed, lymph nodes which were sampled/excised in operation, size of the tumor lesion, histopathological examination results of sampled lymph nodes and tumor type of all patients were recorded in the database.

The areas of FDG accumulation outside normal biodistribution was identified through an evaluation of the F-18 FDG PET-CT scans. The SUVmax values were calculated.

Statistical Analysis

The statistical analysis of the data was conducted with the SPSS for Windows 11.5. Continuous variables were summarized by mean and standard error or by median (smallest-largest) and categorical variables were summarized by frequency and percentage.

Pearson's Chi-Square test and Fisher's exact test were used to assess the significance of thorax-CT results and PET-CT results in detecting metastatic and non-metastatic lymph nodes according to the histopathological results.

Using Pearson's Chi Square or Fisher's Exact tests, thorax-CT results and PET-CT results with SUVmax cut-off of 2.5 were compared for every lymph node station to assess whether they are determinate in differentiating metastatic and non-metastatic lymph nodes according to histopathological results. Sensitivity, specificity, positive and negative predictive values and accuracy rates were calculated to assess the diagnostic indicators.

The areas under the ROC curve were calculated to determine whether PET-CT SUVmax values for every lymph node station produce statistically significant results in predicting metastatic and non-metastatic lymph nodes compared with the histopathological results. Maximum SUVmax values for N1 and N2 lymph node groups were used as a base. When the area under the curve was deemed significant, the best cutoff value was calculated using Youden Index. For each cutoff point, sensitivity, specificity, positive and negative predictive values and accuracy rates were calculated.

Logistic regression analysis was undertaken to assess the role of thorax-CT and PET-CT results in differentiating metastatic and non-metastatic lymph node groups. Odds ratio and 95% confidence intervals were calculated for both examination results. Spearman's correlation test was used to assess the presence of any significant correlation between continuous variables. Kruskal Wallis test was used to assess any significant change in SUVmax values according to the tumor types. When Kruskal Wallis test results revealed significant change, Conover's multiple comparison method was used to identify the causes of the difference. P values less than 0.05 were considered significant.

Results

The study included 510 patients diagnosed with preoperative NSCLC, who underwent thorax-CT and PET-CT, and surgery for staging/treatment between January 2009 and July 2011. 459 of the patients (90%) were male and 51 of them (10%) were female. Their ages ranged between 26 and 87 with a mean age of 59.2 + 9.0.

A diagnosis of NSCLC was made preoperatively for 263 patients (51.5%) by transthoracic fine-needle aspiration biopsy, for 245 patients (48.1%) by bronchoscopic biopsy and for 2 patients (0.4%) by video-assisted thoracoscopic biopsy.

83 patients (16.3%) were diagnosed with diabetes mellitus. Since the presence of DM did not have any significant correlation in evaluation of the PET-CT results, the patients underwent scan according to their pre-scan blood glucose levels. The mean blood glucose level was 103mg/dL (80-150mg/dL).

The patients who underwent neoadjuvant chemoradiotherapy were not included in the study.

Among 510 patients who underwent surgery for staging and/or treatment after diagnosed with NSCLC, lobectomy was performed for 284 patients (55.7%), pneumonectomy for 103 patients (20.2%), wedge resection for 8 patients (1.5%), segmentectomy for 2 patients (0.4%), exploration for 1 case (0.2%), sleeve resection of the left main bronchus for 1 case (0.2%) and mediastinoscopy for 111 patients (21.7%).

In the analysis of tumor localizations, right lung tumor lesion was detected in 286 patients (56%) and left lung tumor lesion was detected in 224 patients (44%). 132 of the right lung tumors (25.8%) were in the upper right lobe, 22 of them (4.3%) were in right middle lobe and 61 (11.9%) were in lower right lobe, and 71 (13.9%) were in the hilar region.

The size of the masses ranged between 0.4 and 20 cm with a mean size of 4 cm. SUVmax value of masses ranged between 0 and 42.8. Mean SUVmax value of the masses was calculated as 12.6.

The distribution of the tumors according to histopathologic type were squamous cell carcinoma in 229 patients (44.9%), adenocarcinoma in 162 patients (31.8%), adenosquamous carcinoma in 36 patients (7.1%), large cell carcinoma in 17 patients (3.3%) and sarcomatoid carcinoma in 12 patients (2.4%). The number of patients, who were not classified into a type, was 54 (10.6%) and these patients only underwent mediastinoscopy.

The role of PET-CT in determining the situation of intrathoracic lymph nodes and mediastinal staging in NSCLC was assessed for every station one by one. In addition, general statistical analysis was conducted for N1 and N2. N1 lymph node stations which were assessed as non-metastatic in PET-CT and histopathologically examined are 191. 160 of these patients had non-metastatic. N1 lymph nodes and 31 of them had metastatic N1 lymph nodes. There were 190 patients assessed as metastatic in PET-CT and examined. Pathological results showed that 120 of these patients had non-metastatic N1 lymph nodes and 70 of them had metastatic N1 lymph nodes. Statistical analysis of the results showed that sensitivity of PET-CT in NSCLC was 69.3%, specificity 57.1%. PPV 36.8% NPV 83.8% and accuracy 60.4% ($p < 0.001$) (Table 1).

Table 1. Diagnostic performance rates for the PET-CT (comparison of PET-CT and pathological results).

Lymph node	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-value
N1	69.3	57.1	36.8	83.8	60.4	< 0.001
N2	74.7	49.4	25.4	89.5	54.1	< 0.001

PPV: Positive Predictive Value NPV: Negative Predictive Value

According to the PET-CT scans of N2 lymph node stations, 228 patients had SUVmax values lower than 2.5 were assessed as non-metastatic and they underwent histopathological examination. According to the pathological results of these patients, lymph nodes were non-metastatic in 204 patients and metastatic in 24 of them. The number of patients, who had metastatic N2 lymph node station in PET-CT and examined was 280. According to the pathological results, lymph nodes in 209 of these patients were non-metastatic and metastatic in 71 patients. Following the assessment of N2 lymph node stations; sensitivity of PET-CT in identifying the situation of lymph nodes was calculated as 74.7%, specificity 49.4%, PPV 25.4%, NPV 89.5% and accuracy as 54.1% ($p < 0.001$) (Table 1).

ROC analysis was conducted and the areas under the ROC curve were calculated in order to assess whether PET-CT SUVmax values for every lymph node station can have statistically significant results in predicting metastatic and non-metastatic lymph node groups compared with the histopathological results. ROC analysis was not conducted for the No 3 lymph node station since it did not have statistically significant results. The maximum SUVmax for the relevant stations were accepted as SUVmax for N1 and N2 respectively. When the area under the curve was deemed significant, the optimal cutoff point was calculated using Youden Index. Following the statistical analyses, a new SUVmax cut-off value was calculated for N1 and N2 lymph node groups for every lymph node station.

By using ROC analysis and Youden Index in N1 and N2 lymph node groups, a new SUVmax cut-off value was calculated which could be interpreted as metastatic involvement in PET-CT. The new SUVmax threshold for N1 lymph node group was 3.34, and for N2 lymph node group was 5.605 (Table 2).

Table 2. The best cut-off value of SUVmax for N1 and N2 lymph node groups.

Lymph node	Area under the ROC Curve	%95 Confidence Internal	P-value	Best Cutoff Value
N1	0.666	0.600-0.732	<0.001	3.34
N2	0.716	0.650-0.781	<0.001	5.605

Following the statistical analysis, sensitivity, specificity, PPV, NPV and accuracy of PET-CT in detecting metastatic and non-metastatic lymph nodes were recalculated according to the new SUVmax cut-off values for N1 and N2 lymph node groups.

The number of patients who had values below the new SUVmax cut-off value of 3.34 for N1 lymph node stations in PET-CT, which were identified as non-metastatic and histopathologically examined were 269. 221 of these patients had non-metastatic N1 lymph nodes and 48 of them had metastatic N1 lymph nodes. There were 112 patients whose SUVmax value in PET-CT was 3.34 or higher and who were identified as metastatic. According to the pathological results, 59 of these patients had non-metastatic N1 lymph nodes and 53 of them had metastatic lymph nodes. Statistical analysis of the results showed that sensitivity, specificity, PPV, NPV and accuracy of PET-CT in assessing N1 lymph node stations in NSCLC patients according to the new SUVmax cut-off value were respectively 52.5%, 78.9%, 47.3%, 82.2% and 71.9% ($p < 0.001$) (Table 3).

Table 3. Diagnostic Performance of the PET-CT based on the new SUVmax cut-off value (comparison of PET-CT and pathological results).

Lymph node	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P-value
N1 (3.340)	52.5	78.9	47.3	82.2	71.9	< 0.001
N2 (5.605)	43.2	94.4	64.1	87.8	84.9	< 0.001

PPV: Positive Predictive Value NPV: Negative Predictive Value

The number of patients, who had values below the new SUVmax cut-off value of 5.605 for N2 lymph node stations in PET-CT and who were identified as non-metastatic and histopathologically examined were 444. According to the pathological results, 390 of these patients had non-metastatic lymph nodes and 54 of them had metastatic lymph nodes. The number of patients who had N2 lymph nodes station with PET-CT SUVmax value of 5.605 or higher, and who were identified as metastatic and histopathologically examined were 64. According to the pathological results, 23 of these patients had non-metastatic lymph nodes and 41 of them had metastatic lymph nodes. Following the evaluation of N2 lymph node stations, sensitivity, specificity, PPV, NPV and accuracy of PET-CT in determining the situation of lymph nodes according to the new SUVmax cut-off value for N2 lymph nodes were respectively, 43.2% 94.4%, 64.1%,87.8% and 84.9% ($p < 0.001$) (Table 3).

Following the analysis of the data for all patients, a new PET-CT SUVmax cut-off value in detecting metastatic intrathoracic lymph nodes was calculated. The new SUVmax cut-off value was 4.5. According to this new value, sensitivity, specificity, PPV, NPV and accuracy of PET-CT in mediastinal staging in NSCLC were respectively 47.9%, 86.7%, 55.7%, 90% and 78.4%.

Diagnostic performance values of PET-CT SUVmax cut-off value of 2.5 and the new SUVmax cut-off value were compared in Table 4.

Table 4. Comparison of PET-CT based on SUVmax cut-off value 2.5 and the new SUVmax cut-off values.

Lymph node	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
PET SUVmax 2'5 N1	69.3	57.1	36.8	83.8	60.4
PET SUVmax new value N1	52.5	78.9	47.3	82.2	71.9
PET SUVmax 2'5 N2	74.7	49.4	25.4	89.5	54.1
PET SUVmax new value N2	43.2	94.4	64.1	87.8	84.9

PPV: Positive Predictive Value NPV: Negative Predictive Value

Discussion

Staging based on TNM staging system is fundamental in planning treatment and predicting prognosis in NSCLC. The most important point is to identify the patients suitable for surgical resection and inoperable patients who could benefit from chemotherapy and/or radiotherapy.

Primary mediastinal lymph node staging can be done with several techniques including imaging techniques, endoscopic techniques and surgical techniques. PET-CT is a special diagnostic tool in diagnosis, staging and follow up of the cancer patients compared to other scanning methods. In the evaluation of mediastinal lymph node metastasis, PET/CT has a higher accuracy rate when compared with thorax-CT and its specificity ranges are between 80-95%, negative predictive value (NPV) is 84-100%, positive predictive value (PPV) is 60-93% [8].

According to the 2003 meta-analysis of Toloza et al. on diagnostic performance of noninvasive mediastinal staging methods based on 20 studies with 3438 patients, sensitivity of thorax-CT in detecting mediastinal lymph nodes metastasis was 57%, specificity 82%, PPV 44% and NPV 17% [7]. In our study, the sensitivity of thorax-CT in detecting metastatic lymph nodes is 75.7%, specificity 41%, PPV 27.3%, NPV 85% and the accuracy 48.4%. While the sensitivity and the NPV of thorax-CT in our study is similar to the other studies, the specificity and the PPV are lower. We believe that this is due to the bigger size lymph nodes caused by infectious and granulomas diseases, which are common in Turkey.

According to the meta-analysis of Toloza et al based on 5687 patients published in 2003, the sensitivity of mediastinoscopy which is considered as gold standard in mediastinal staging was 84%, specificity 100%, PPV 100% and NPV 91% [9]. However, despite these high diagnostic performance rates, the mortality and morbidity rates, albeit low, bring up the necessity of using less invasive or non-invasive staging methods instead of mediastinoscopy due to its disadvantages of being an invasive method and limited number of lymph node sampling.

PET-CT is widely used compared to other non-invasive mediastinal staging methods. There are many studies conducted between 1990 and 2000 comparing the performances of thorax-CT and PET-CT in detecting mediastinal lymph node metastasis and the majority

of these studies concluded that PET-CT is more effective than thorax-CT [7,10,11]. According to the Burry's study published in 1997, the specificity of PET-CT in detecting mediastinal lymph node metastasis is 100%, PPV 100% and NPV 96% [12]. Owing to its high accuracy rates and its being non-invasive, it has been argued that PET-CT could replace mediastinoscopy.

An analysis of these initial studies shows that the number of patients studied are not sufficient, and in some studies mediastinoscopy was not performed for all patients or some patients included in the study were not diagnosed with lung cancer. The studies conducted in the following years did not confirm those initial results. For example, while the sensitivity rate of PET in detecting mediastinal lymph node metastasis was 64%, specificity 77%, PPV 44% and NPV 88% according to the study conducted by Gonzales-Stawinski in 2003 based on 202 patients; according to REED CE's [14] 2003 study based on 302 patients [13] sensitivity was 61%, specificity 84%, PPV 56% and NPV is 87%. On the other hand, Toloza reports that sensitivity of PET in detection of metastatic mediastinal lymph nodes was 84%, specificity 89%, PPV 79% and NPV 93% in his review study published in 2003 based on 1045 patients [7].

Inflammatory diseases are among the reasons for false positive results of PET-CT and FDG accumulation might be seen in regions where there is active inflammation. This activity is caused by macrophage in inflammated regions and increased glucoses uptake in inflammated cells. The reason for low specificity rates, which can be defined as the rate showing lymph nodes in PET-CT are not metastatic, in patients who does not have metastatic intrathoracic lymph nodes in reality is believed to be caused by mediastinal involvement in PET-CT because of benign infectious (tuberculosis, histoplasmosis) and inflammatory diseases. Due to the low PPV rates in the evaluation of mediastinal lymph nodes in PET-CT, there is a need for cell diagnosis to show metastasis. Mediastinoscopy or other invasive mediastinal staging methods can be used. However due to the high NPV rates, if there is no involvement in mediastinal lymph nodes in PET-CT surgical treatment can be planned without invasive staging. Graeter et al. argue that in cases of negative mediastinal lymph nodes in PET-CT in NSCLC patients, mediastinoscopy can be ignored [15].

In our analysis based on SUVmax value 2.5 in detecting N1 disease, the sensitivity of PET-CT was calculated as 69.3%, specificity 57.1%, PPV 36.8% and NPV 83.8% and accuracy 60.4%. In identifying N2 disease, sensitivity, specificity, PPV, NPV and accuracy rates were respectively, 74.7%, 49.4%, 25.4%, 89.5% and 54.1%. In identifying metastatic intrathoracic lymph nodes, sensitivity was calculated as 72%, specificity 53.3%, PPV 31.1%, NPV 86.7% and accuracy 57.3%. In comparison to other studies in the literature, our study had lower specificity and PPV rates and the other diagnostic performance rates were similar.

The new SUVmax cut-off value calculated following the statistical analysis of the patients was 4.5 and sensitivity, specificity, PPV, NPV and accuracy rates based on the new value were respectively 47.9%, 86.7%, 55.7%, 90% and 78.4%. Since the specificity and PPV based on the new SUVmax cut-off value was lower, it might lead to false negative results in evaluation of metastatic lymph nodes that have low involvement. Benjamin et al calculated a new cut-off value in their study and argued that in patients whose SUVmax value is lower than 5.3 and which do not have central tumor and N1 disease, thoracotomy can be performed directly without the need for invasive staging. They also argue that while PET-CT is an important and effective method compared to other non-invasive staging methods, its maximum effectiveness has decreased due to high false positive (infectious and inflammatory diseases) and false negative (micrometastasis) rates [16].

In areas with granulomas diseases, high FDG involvement can be observed in benign lesions. According to the study by Kwan in Taiwan, there is an increased FDG involvement in mediastinum in 28% normal patients [17]. Kang et al. found significant difference between the SUVmax rates of malignant lesions and benign lesions (18). SUVmax cut-off value in lymph nodes which have involvement in mediastinum was calculated as 3.4. In this study, it is argued that FDG involvement is more significant than lymph node size in thorax-CT. Our study showed that when lymph nodes measuring 1cm or more in the short axis in thorax-CT were compared with mediastinal FDG involvement in PET-CT, PET-CT gave more accurate results. It was found that if lymph node size and SUVmax rate are compatible, diagnostic performance is better.

The literature on false positive or false negative results of PET-CT is limited. The study conducted by Takamochi et al. on the basis of patients showed the false positive rate as 14% and false negative rate as 20% [19]. According to our study based on the evaluation of patients, the false positive rate was calculated as 50.6% and false negative rate as 25.3%. The reason for this higher rate of false positivity compared to other reported rates is normal considering the specific circumstances in Turkey. The higher incidence rate of infectious diseases in Turkey is influential in higher rates of false positivity.

To sum up, more studies are being conducted to find the fastest, most accurate and the least invasive methods through a comparative analysis of different mediastinal staging methods. Recent studies focused on showing the role of PET-CT in mediastinal staging. The aim is to determine whether PET-CT could be an alternative to mediastinoscopy in mediastinal staging.

In conclusion, calculating a new cut off value of SUVmax all around the world would increase the NPV of PET-CT and so it would reduce to use of invasive methods. PPV of PET-CT is still not at an acceptable level, so positive results of PET-CT for mediastinal lymph node staging should be confirmed with invasive diagnostic techniques. Invasive staging must be performed in order to verify metastasis in lymph nodes which have pathological involvement in PET-CT. However, rather than deciding on surgery solely based on PET-CT results, more accurate decisions can be taken by taking into account thorax-CT results, localization of tumor masses, cell type, and SUVmax values of the masses.

Declaration of conflicting interests

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