Original Article

Is FDG-PET/CT Used Correctly in the Combined Approach for Nodal Staging in NSCLC Patients?

FS Simsek, A Comak[1], M Asik[2], D Kuslu[3], TA Balci[4], H Ulutas[5], R Koroglu[2], E Kekilli[1], A Akatli[6], F Elmali[7], NC Yalcin[8], H Akyol[9]

Department of Nuclear Medicine, Pamukkale University, Faculty of Medicine, Denizli, Departments of [1]Nuclear Medicine, [5]Thoracic Surgery and [6]Pathology, Inonu University, Faculty of Medicine, Malatya, [2]Department of Nuclear Medicine, Afyon Kocatepe University, Faculty of Medicine, Afyon, Departments of [3]Nuclear Medicine and [8]Thoracic Surgery, Medical Sciences University, Antalya Education and Research Hospital, Antalya, [4]Department of Nuclear Medicine, Firat University, Faculty of Medicine, Elazig, [7]Department of Biostatistics, Izmir Katip Celebi University, Faculty of Medicine, İzmir, [9]Department of Pathology, Medical Sciences University, Elazig State Hospital, Elazig, Turkey

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ABSTRACT

Background: The most widely accepted approach nowadays in nodal staging of non–small cell lung cancer (NSCLC) is the combined use of 18-Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) and endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA). However, this approach may not be sufficient, especially for early stages. **Aims:** Our aim was to assess whether more satisfactory results can be obtained with standardized uptake value maximum lymph node/standardized uptake value mean mediastinal blood pool (SUVmax LN/SUVmean MBP), SUVmax LN/Primary tumor, or a novel cut-off value to SUVmax in this special group. **Subjects and Methods:** Patients with diagnosed NSCLC and underwent FDG-PET/CT were reviewed retrospectively. 168 LNs of 52 early stage NSCLC patients were evaluated. The LNs identified in surgery/pathology reports were found in the FDG-PET/CT images. Anatomic and metabolic parameters were measured. Statistical analysis was performed by using of MedCalc Statistical Software. **Results:** Regardless of LNs size; sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of SUVmax >2.5 were 91.5%, 65.9%, 58.2%, and 95.1%, respectively. Optimum cut-off value of SUVmax was >4.0. Sensitivity, specificity, PPV, and NPV were found as 81.0%, 90.0%, 81.0%, and 90.0% respectively. Optimum cut-off value of SUVmax LN/SUVmean MBP was >1.71. Sensitivity, specificity, PPV, and NPV were found as 94.7%, 80.0%, 71.1%, and 96.7%, respectively. Optimum cut-off value of SUVmax LN/Primary tumor was >0.28. Sensitivity, specificity, PPV, and NPV were found as 81.1%, 85.1%, 72.9% and 90.1%, respectively. **Conclusion:** SUVmax LN/SUVmean MBP >1.71 has higher PPV than currently used, with similar NPV and sensitivity. This can provide increase in the accuracy of combined approach. In this way, faster nodal staging/treatment decisions, cost savings for healthcare system and time saving of medical professionals can be obtained.

Keywords: *EBUS-TBNA, FDG-PET/CT, NSCLC, staging*

Introduction

Lung cancer is one of the most common malignancies in the world. Approximately 85% of cases are non-small cell lung cancer (NSCLC). Its staging generally performed

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Address for correspondence: Dr. FS Simsek, Department of Nuclear Medicine, Pamukkale University, Faculty of Medicine, Denizli, Turkey.
E-mail: fselcuksimsek@gmail.com

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with the tumor node metastasis (TNM) system.[1-3] Chest computed tomography (CT) and/or 18-Fluoro-deoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) provide reliable results for T staging, and FDG-PET/CT provides reliable results for M staging. However, N staging has remained challenging without invasive diagnostic techniques. CT, diffusion weighted-magnetic resonance imaging (DW-MRI) or FDG-PET/CT have insufficient for N staging.[1-6] The most widely accepted approach nowadays in N staging is the combined use of FDG-PET/CT and endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA). In this approach, all lymph nodes (LNs) with SUVmax >2.5, or higher FDG uptake than mediastinal blood pool (MBP) activity is sampled with EBUS-TBNA as much as possible. Often, short axis >10 mm LNs are added to these metabolic parameters.[7,8] However, a novel study reported that, this approach may not be sufficient, especially for the early stage NSCLC.[9] As a result, for EBUS-TBNA, which has low NPV, we apply LN/patient selection criteria with parameters which have low PPV. Thus, lots of patients undergo more invasive procedures for N staging.[10-12] This causes delaying of N staging/initial therapy, additional costs for healthcare system and consuming time for medical staffs. To avoid the above-mentioned problems, it is clear that, we need a novel LN/patient selection criterion for the combined approach of EBUS-TBNA, and FDG-PET/CT. Recent studies reported that more reliable results could be achieved with SUVmax LN/SUVmean MBP or SUVmax Lymph Node/Primary (SUVmax LN/Pr Tm) for characterization of mediastinal LNs.[13,14]

Our aim was to assess whether more satisfactory results can be obtained with SUVmax LN/SUVmean MBP, SUVmax LN/Pr Tm or a novel cut-off value to SUVmax for selection of LNs/patients in EBUS-TBNA in early stage NSCLC patients. This may increase the accuracy of combined approach. In conclusion, faster nodal staging and treatment decisions can be achieved. In addition, it can provide cost savings for the healthcare system and save the time of medical professionals.

Materials and Methods

Patients with diagnosed NSCLC and underwent FDG-PET/CT were reviewed retrospectively. Inclusion and exclusion criteria were determined as follows.

Inclusion Criteria:

a. Patients with diagnosed early stage NSCLC according to 8th edition of TNM system[3]
b. Pathological evaluation after FDG-PET/CT
c. Fasting plasma glucose <200 mg/dL before imaging

Exclusion Criteria:

a. Presence of another predetermined malignancy
b. Patients with a history of surgery, chemotherapy, and/or radiotherapy anamnesis before the FDG-PET/CT
c. Sampling before FDG-PET/CT due to the possibility of inflammation

As a result, 52 patients were included in the study. Surgery/pathology reports were evaluated thoroughly. The LNs identified in the reports were found in the FDG-PET/CT images. Anatomic and metabolic parameters were measured by nuclear medicine specialists. As a result, 168 LNs were evaluated in 52 patients. In our surgical departments, SUVmax >2.5 and/or short axis >10 mm criteria were used for LN sampling. If any LN was suspected to be malignant during surgery even if they did not meet criteria, these LNs were excised, and histopathologically examined. The approval of the Ethical Committee was obtained before the study.

PET/CT protocol

Following a minimum six hours of fasting, 0.1 mCi/kg FDG was administered intravenously. Imaging was initiated at the 60th (±6) minute of post injection. CT and PET scanning were performed from vertex to mid-thigh and the Ordered Subset Expectation Maximization algorithm was used for reconstruction. For SUVmean MBP, 1.5 × 1.5 cm region of interest was drawn manually in the non-calcify arcus aorta.

Surgery

Specific number 33 patients underwent video-assisted thoracic surgery or thoracotomy. Eleven patients underwent mediastinoscopy and eight patients underwent EBUS-TBNA. Four EBUS-TBNA negative patients underwent mediastinoscopy procedure. Thus, the total number of the patients who performed mediastinoscopy was 15. If LNs had positive EBUS-TBNA results, it is accepted as malignant. For other LNs, histopathological examination was accepted as gold standard.

Statistical analysis

Statistical analysis was performed by using of MedCalc Statistical Software version 18.9 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Association between categorical variables was calculated using Fisher's exact test and $P < 0.05$ was accepted as statistically significant. Receiver operating characteristic (ROC) curve analysis was used for evaluating the diagnostic tests and calculating the cut-off values.

Results

Patient characteristics

Twenty-eight (53.8%) cases were classified as squamous cell carcinoma (SCC), 17 (32.7%) were adenocarcinoma and 7 (13.5%) were classified as other subtypes. Eighteen (34.6%) patients were diagnosed as stage I and 34 (65.4%) patients were

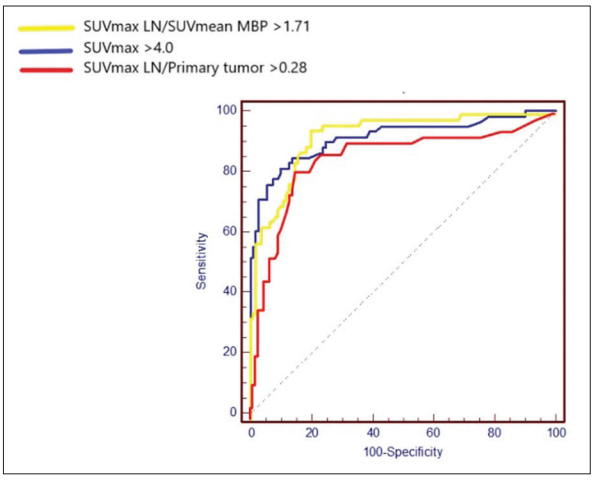

Figure 1: The Receiver Operating Characteristic Curve Analysis of Metabolic Parameters

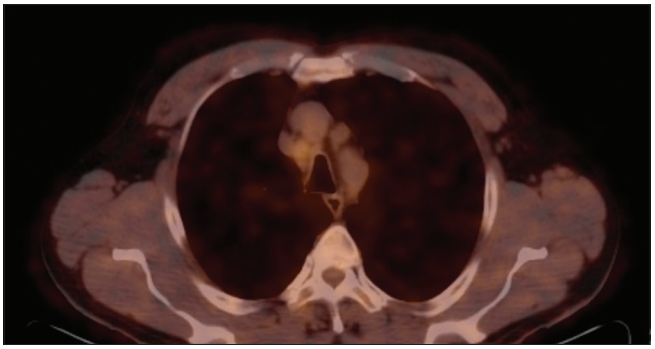

Figure 2: An 55-year-old male patient diagnosed with squamous cell carcinoma and had not detected distant metastasis in FDG-PET/CT scanning. Right paratracheal LNs short axis was 9 mm; SUVmax was 4.03; SUVmax LN/SUVmean MBP was 1.32 and SUVmax LN/primary tumor was 0.37. This node diagnosed as non-malignant after the histopathological examination. Only SUVmax LN/SUVmean MBP > 1.71 could characterized accurately this node

Table 1: Patients Characteristics

Variables	*n* (%)	
Age mean±SD (min-max)	61.7 (range: 41-79)	
Gender	Male	50 (96.2)
	Female	2 (3.8)
Fasting Blood Pool Level mean±SD (min-max)	107.3 mg/dl (range: 79-195)	
Histopathological Type	SCC	28 (53.8)
	Adenocarcinoma	17 (32.7)
	Others	7 (13.4)
Stages	I	18 (34.6)
	II	34 (65.4)
LN Pathology Results	Malign	58 (34.5)
	Benign	110 (65.5)

Table 2: Comparison of the Metabolic Parameters Between Malign and Benign LNs

	Benign (min-max)	Malignant (min-max)	*P*
SUVmax LN	2.2 (0.82-7.91)	8.58 (1.45-23.75)	<0.05
SUVmax LN/SUVmean MBP	1.1 (0.4-5.55)	3.6 (0.94-22.41)	<0.05
SUVmax LN/Pr.tm	0.14 (0.02-1.03)	0.47 (0.04-1.09)	<0.05

(SUVmax LN=Standardized uptake value maximum of lymph node; SUVmax LN/SUVmean MBP=Standardized uptake value maximum of lymph node/Standardized uptake value mean of Mediastinal Blood Pool; SUVmax LN/Pr.Tm. = Standardized uptake value maximum of lymph node/Primary tumor)

Table 3: Different Metabolic Parameters' Optimum Cut-off Values and Their Diagnostic Results

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Area Under the ROC Curve	Standard Error (±)	CI (95%)
SUVmax LN >4	81.0	90.0	81.0	90.0	0.91	0.02	0.86-0.95
SUVmax LN/SUVmean MBP >1.71	94.7	80.0	71.1	96.7	0.93	0.02	0.88-0.96
SUVmax LN/Pr.Tm. >0.28	81.1	85.1	72.9	90.1	0.85	0.04	0.79-0.90

(CI: Confidence interval; PPV=Positive Predictive Value; NPV=Negative Predictive Value; SUVmax LN=Standardized uptake value maximum of lymph node; SUVmax LN/SUVmean MBP=Standardized uptake value maximum of lymph node/Standardized uptake value mean of Mediastinal Blood Pool; SUVmax LN/Pr.Tm. = Standardized uptake value maximum of lymph node/Primary tumor)

diagnosed as Stage II. Tumor SUVmax median value was 16.65 (5.8–45.3). Total 103 mediastinal, 65 hilar LNs were examined, and 58 (34.5%) of them were malignant. The results and demographic parameters were summarized in Table 1.

LN Parameters

Mean SUVmax, SUVmax LN/SUVmean MBP, and SUVmax LN/Pr.Tm values of malignant and benign LNs were calculated separately. Differences between malignant and benign lesions were found statistically significant as shown in Table 2.

Cut-off values and comparisons of metabolic parameters

Regardless of LN size; the sensitivity, specificity, PPV, and NPV of SUVmax >2.5 were calculated as 91.5%, 65.9%, 58.2%, and 95.1%, respectively. The optimum cut-off value of SUVmax was >4.0. The sensitivity, specificity, PPV, and NPV were found as 81.0%, 90.0%, 81.0%, and 90.0%, respectively. Optimum cut-off value of SUVmax LN/SUVmean MBP was >1.71. The sensitivity, specificity, PPV, and NPV were found as 94.7%, 80.0%, 71.1%, and 96.7%, respectively. Optimum cut-off value of SUVmax LN/Pr Tm was >0.28. The sensitivity, specificity, PPV, and NPV were found as 81.1%, 85.1%, 72.9% and 90.1%, respectively. Results were shown in Table 3, Figures 1 and 2.

Discussion

Nodal staging is one of the most important parts of the TNM system. However, anatomical imaging techniques such as chest CT or DW-MRI are inadequate for this purpose. Although FDG-PET/CT is reliable for T and M staging, it is insufficient for N staging due to low PPV.[5,6,15] The most widely accepted approach nowadays in N staging is the combined use of FDG-PET/CT and EBUS-TBNA. In this approach, all metabolically positive and short axis >10 mm LNs are sampled with EBUS-TBNA as much as possible.[7,8] Metabolic positivity is considered as, higher FDG uptake than MBP, or SUVmax >2.5. However, these parameters have low PPV alone or together. Hwangbo *et al*. accepted the SUVmax >2.5 as a malignity criterion for LNs. Authors found only 40% PPV.[16] Köksal *et al*. conducted a study comparing the FDG activity of LN with the MBP. The authors reported that only 14% of LNs with higher FDG uptake than MBP were malignant.[17] However, these parameters are still used for the selection of LNs/patients to EBUS-TBNA because of their high NPV. Mostly, short axes of LNs are added to above parameters, but this approach can complicate the situation.[18] If this approach is used to select LNs/patients for EBUS-TBNA, the sensitivity is unexpectedly low, especially in early stage patients.[9] A recent study reported that, if LN >10 mm was accepted as the selection criterion, EBUS-TBNA's sensitivity, specificity, PPV, and NPV were 90%, 100%, 100%, and 75%, respectively.[19] Guarize *et al*. accepted the higher FDG uptake than MBP or >10 mm, as the criterion of selection. The authors found that 20% of the EBUS-TBNA negative LNs were metastatic.[20] Liu *et al*. used the same method and found 66.7% accuracy for some LN sites. Moreover, the accuracy of six out of the eight LN sites was less than 78%.[10] In addition, they could not sample four lymph node regions due to EBUS-TBNA limitations. Vial *et al*. found only 40% sensitivity in patients with early stage NSCLC, by using the above-mentioned method in 2018.[9] Thus, it is clear that, we need a novel, practical, and more accurate parameter for the combined use of EBUS-TBNA and FDG-PET/CT in early stage NSCLC patients. This parameter can increase the accuracy of combined approach. This would provide faster staging/initial therapy in some cases. In addition, decreased costs for the healthcare system and decreased consuming of time for medical professionals can be achieved.

In a recent study, >4.0 was determined as a cut-off value instead of SUVmax >2.5. The sensitivity, specificity, PPV, NPV, and accuracy were found as 70.4%, 94.5%, 95.0%, 68.2% and 80.1%, respectively (13). The authors have achieved very useful PPV with this approach; however, decreasing of the NPV was dramatic. In another study, cut-off value for SUVmax was determined as >3.25. The sensitivity was 94%, specificity was 86%, but this approach also led to low NPV.[21] Shinya *et al*. reported >3.6 as a cut-off value, and they calculated 87% sensitivity with 88% specificity.[22] In a study published in 2017, although different cut-off values were examined for SUVmax, none of them have enough accuracy.[14] We determined SUVmax >4.0 as an optimum cut-off value. The sensitivity, specificity, PPV and NPV were 81.0%, 90.0%, 81.0% and 90%, respectively. Our cut-off value was the same as Lee and his friends. Using this value, we achieved a more acceptable NPV and a more useful PPV than its work. However, SUVmax >4.0 did not have sufficient sensitivity and NPV compared to SUVmax >2.5. Therefore, we think using SUVmax >4.0 for LN/patient selection in EBUS-TBNA is an inappropriate approach in patients with early stage NSCLC.

Due to insufficient results with SUVmax, we studied different parameters. One of them was SUVmax LN/SUVmean MBP. However, in the literature, some studies examined SUVmax LN/SUVmax MBP, others SUVmax LN/SUVmean MBP.[23,24] Based on our clinical experience, we consider that SUVmax LN/SUVmean MBP reflect blood pool activity much

better. Lee *et al*. examined SUVmax LN/SUVmean MBP and calculated ≥1.4 as a cut-off. With this value, authors found 69.4% sensitivity and 64.7% specificity.[24] Mallorie *et al*. calculated the sensitivity and NPV as 95% and 96.2%, respectively, with SUVmax LN/SUVmean MBP. However, with this parameter, specificity was only 61% and PPV was only 56.8%.[14] Nguyen *et al*. determined SUVmax LN/MBP ≥2.15 as a cut-off value. They found the sensitivity, specificity, and correctly classified LN ratio as 87.4%, 92.5%, and 89.0%, respectively.[23] Another study determined 1.8 as a cut-off value for the same parameter, and the sensitivity, specificity, PPV, NPV, and accuracy were found as 86.1%, 87.4%, 67.4%, 95.4%, and 87.1%, respectively.[25] We calculated >1.71 as optimal cut-off value with ROC analysis. Its sensitivity, specificity, PPV, and NPV were 94.7%, 80.0%, 71.1%, and 96.7%, respectively. When SUVmax LN/SUVmean MBP >1.71 was compared to SUVmax >2.5, both had similar NPV and sensitivity. On the other hand, SUVmax LN/SUVmean MBP >1.71 had significantly higher specificity and PPV (80.0% vs 65.9%, and 71.1% vs 58.2%). Therefore, we think that the use of SUVmax LN/SUVmean MBP >1.71 instead of SUVmax >2.5 for EBUS-TBNA patients may be more accurate in patients with early stage NSCLC. SUVmax LN/Pr. Tm rate was the other parameter to study in this research. Primary tumors FDG uptake reflects its aggressiveness. Because of that, SUVmax LN/Pr tm rate can be another useful parameter for the selection of LNs/patients to EBUS-TBNA. According to Cerfolio *et al*., if the SUVmax LN/Pr.Tm value was higher than 0.56, this LN was malignant with 94% likelihood.[26] Maloney *et al*. calculated a >0.3 cut-off value for the same parameter and they found 71% specificity with 91% sensitivity.[21] In a recent study determined >0.4 as a cut-off value. The sensitivity, specificity, PPV, NPV, and accuracy were found as 81.5%, 79.2%, 86.3% 72.7%, and 78.2%, respectively.[13] However, some other studies reported that this parameter could not be an appropriate approach for mediastinal LNs.[17,27] We determined >0.28 as an optimal cut-off value for SUVmax LN/Pr. Tm regardless of size. The sensitivity, specificity, PPV, and NPV were calculated as 81.1%, 85.1%, 72.9%, and 90.1%, respectively. The sensitivity and NPV of this parameter were lower than SUVmax >2.5. Therefore, we believe it is not a suitable approach to use this parameter instead of SUVmax >2.5 for the selection of LNs/patients to EBUS-TBNA.

Our study had some limitations. Firstly, it was a retrospective study and inherently had limitations. Secondly, the number of patients was not very high. However, we had also some advantages. Firstly, histopathological results were obtained from 92.3% of the patients after FDG-PET/CT. Remaining 7.3% patients had positive EBUS-TBNA results for malignity. In addition, our patient population were only consisting of early stages and more homogenous than most other studies, because of that, we think our results could reliable for this special group.

Conclusion

SUVmax LN/SUVmean MBP >1.71 has higher PPV than currently used, with similar NPV and sensitivity. Because of that, maybe it is more suitable for the selection of LNs/patients to EBUS-TBNA in patients with early stage NSCLC. This can provide increasing of the accuracy of combined approach. In this way, faster nodal staging, and treatment decisions can be obtained. In addition, it can provide cost savings for the healthcare system and save the time of medical professionals.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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