RESEARCH ARTICLE

# Is it possible to achieve more accurate mediastinal nodal radiotherapy planning for NSCLC with PET/CT?

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## Abstract

**Objective:** To assess whether more accurate mediastinal lymph nodes radiotherapy can be performed with fluorodeoxyglucose positron emission tomography / computed tomography.

**Methods:** The retrospective study was conducted at Inonu University Medical Faculty, Malatya, Turkey, and Afyon Kocatepe University Medical Faculty, Afyon, Turkey, and comprised record of patients histopathologically diagnosed with non-small cell lung carcinoma and who underwent fluorodeoxyglucose positron emission tomography / computed tomography between January 2013 and December 2016. Surgery and pathology reports of the patients were reviewed. Histopathologically proven malignant and benign lymph nodes were re-identified with fluorodeoxyglucose positron emission tomography / computed tomography imaging. Anatomical and metabolic parameters of lymph nodes were re-assessed by specialists and compared with histopathology reports. Maximum standardised uptake values were used to assess sensitivity, specificity, positive predictive value, and negative predictive values. SPSS 22 was used for data analysis.

**Results:** The study included 144 mediastinal lymph nodes related to 42 patients who had a mean age of 62.4±9.8 years (range: 41-79 years). In terms of subtypes of the primary squamous cell carcinoma was found in 24(57.2%) patients, adenocarcinoma in 12(27.5%), and other subtypes in 6(15.3%) patients. Of the 144 lymph nodes, 48(33.3%) were metastatic. Sensitivity, specificity, positive predictive value, and negative predictive value were 92.8%, 64.3%, 56.9%, and 94.7%, respectively when maximum standardised uptake value >2.5 was used as the malignancy criterion. When lymph node maximum standardised uptake value / liver standardised uptake value-mean>1.69 was used as the criterion, the sensitivity, specificity, positive predictive value, and negative predictive value were 95.83%, 91.67%, 85.2%, and 97.8%, respectively. When the same values with lymph node >8mm was used as the criterion, the four resultant values were 89.6%, 93.8%, 87.8%, and 94.7%, respectively. When lymph node was replaced with mean attenuation >35 as the criterion, the consequent values were 79.2%, 93.8%, 86.4%, and 90.0%, respectively.

**Conclusion:** Lymph node maximum standardised uptake value / liver standardised uptake value-mean>1.69 was associated with higher negative predictive value and more useful positive predictive value compared to maximum standardised uptake value >2.5. When this parameter was used along with short axis or mean attenuation value, there were no significant increase in positive predictive value, but there was a decrease in negative predictive value.

**Keywords:** Carcinoma, Non-small-cell lung, Radiation therapy, PET scan. (JPMA 70: 29; 2020).
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## Introduction

Early stage non-small cell lung carcinoma (NSCLC) is one of the most commonly diagnosed malignant diseases worldwide.[1,2] Despite the availability of extensive therapeutic approaches in such cases, very high recurrence / relapse rates cannot be avoided. For example,

Pless et al. reported that overall local recurrence (LR) was 60% after surgery and chemo/radiotherapy for NSCLC. It is notable that 30% recurrences occur within the radiotherapy (RT) target region, including mediastinal lymph nodes (MLNs).[3]

The technique of 18-Fluorodeoxyglucose positron emission tomography / computed tomography (18-FDG-PET/CT) is widely used for RT planning. For primary tumour RT planning using FDG-PET/CT, the most important problem is mismatch between PET and CT images, which can be solved by the use of 4D FDG-PET/CT.[4] On the other hand, maximum standardised uptake value (SUVmax) >2.5 is the currently accepted threshold for NSCLC, and the RT target regions are determined as those with SUVmax ≥2.0 in FDG-PET/CT.[5] This is a reasonable practice considering that normal lung tissue has very little FDG uptake. On the contrary, accepting SUVmax >2.5 or higher FDG uptake (in comparing MLNs to the mediastinal blood pool [MBP]) for nodal RT planning, which is currently used, cannot seem suitable due to the much higher basal FDG uptake in the mediastinum. Thus, the threshold set for the primary tumour may not be appropriate for MLNs. Many studies have reported extremely low positive predictive value (PPV) in MLNs with SUVmax >2.5 or higher LN activity compared to the MBP.[6,7] Nevertheless, these criteria are currently used because of their high negative predictive value (NPV). The additional parameter of LN>10mm is commonly included in these parameters.[8,9] However, this approach causes unnecessary beaming of some non-metastatic LNs and lower RT doses to some malignant ones. Occasionally, endobronchial ultrasound needle aspiration (EBUS-NA) has been used along with FDG-PET/CT to resolve this problem, but this has unexpectedly led to a larger RT field and 20% MLN recurrence.[10]

Therefore, we need a new practical FDG-PET/CT parameter for mediastinal nodal RT planning which may achieve increased PPV without a decrease in NPV. Rogash et al. attained a higher PPV using the LN SUVmax/liver SUVmean ratio in NSCLC patients for mediastinal nodal staging.[11] In addition, Fleching et al. reported significant density differences between malignant and benign MLNs.[12] These results lead to the hypothesis that the use of LN SUVmax/liver SUVmean alone or along with size or density may be more helpful in RT planning for MLNs than the currently used parameters.

The current study was planned to assess whether more accurate mediastinal RT planning can be performed with FDG-PET/CT. If more accurate planning can be achieved using a new method, unnecessary irradiation of healthy tissue can be avoided and more effective planning for RT of malignant MLNs can be achieved.

## Materials and Methods

The retrospective study was conducted at Inonu University Medical Faculty, Malatya, Turkey, and Afyon Kocatepe University Medical Faculty, Afyon, Turkey, and comprised record of patients histopathologically diagnosed with NSCLC and who underwent FDG-PET/CT between January 2013 and December 2016.

Those excluded were records of patients with previously diagnosed malignancy, chemotherapy and / or RT before FDG-PET/CT, locally advanced / advanced stage NSCLC per the 8th edition of the tumour, nodes, metastases (TNM) system,[2] or invasive sampling from MLNs before FDG-PET/CT due to possible inflammation.

Surgery and pathology reports of the selected patients were re-examined and histopathologically proven malignant or benign LNs were re-identified carefully in FDG-PET/CT images. Anatomical and metabolic parameters of LNs were assessed by nuclear medicine specialists and MLNs from the patients were evaluated histopathologically. For PET / CT, a 0.1 mCi/kg FDG dose was administered to patients intravenously (IV) after at least six hours of fasting. Subsequently, patients were hydrated with 500ml water orally while they were resting in a quiet, dark room. Between injection and imaging, there was a waiting period of 60±5 minutes. PET/CT scanning was performed using a Siemens Biograph mCTS (20)-3R (Knoxville, TN, USA) or a Siemens Biograph 6 True Point (Knoxville, TN, USA). Following CT imaging from vertex to mid-thigh, PET scanning of the same regions was performed in 7-8 bed positions. An ordered subset expectation maximisation algorithm was used for reconstruction. The regions of interest (ROIs) were drawn manually for primary tumours and MLNs. ROIs for liver SUVmean were also drawn manually for normal liver tissues 2.5 x 2.5cm in size. Non-attenuation-corrected images were used to examine calcified LNs.

In surgical procedure, mediastinal and hilar LN stations were explored based on the clinical stage of the lesion using mediastinoscopy or video-assisted thoracoscopic surgery (VATS) / thoracotomy. All LNs with SUVmax >2.5

and short axis ≥1.0cm or any suspected LNs were removed as much as possible. They were dissected out along with their capsules. EBUS-NA was performed in patients not sampled with the two above-mentioned techniques. Patients in whom EBUS-NA did not provide exact diagnoses, were surgically sampled.

For histopathological examination, formalin-fixed paraffin-embedded tissues were cut into 4-5μm thick sections and kept in 10% formalin for at least 24 hours. The sections were stained with Haematoxylin-and-Eosin (H&E) and examined under a light microscope by pathologists. This evaluation was accepted as the gold standard.

Data was analysed using SPSS 22. Frequencies and percentages, mean±standard deviation (SD), and median and interquartile ranges (IQRs) were determined. Normal distribution of numerical variables was evaluated using Shapiro Wilk normality test and Q-Q graphs. Inter-group comparisons were performed using independent two-sample t-tests for variables in normal distribution and using Mann-Whitney U test for variables in non-normal distribution. Associations between numerical variables were analysed using Spearman correlation analysis. Receiver operating characteristic (ROC) curve analysis was used to evaluate diagnostic tests and to calculate the cut-off values. Associations between categorical variables was calculated using Fisher's exact test. P<0.05 was considered statistically significant.

## Results

Of the 496 records reviewed, 42(8.5%) comprised the study sample. They related to patients who had a mean age of 62.4±9.8 years (range: 41-79 years). In terms of subtypes of the primary squamous cell carcinoma was found in 24(57.2%) patients, adenocarcinoma in 12(27.5%), and other subtypes in 6(15.3%) patients. Of the 144 lymph nodes studied, 48(33.3%) were metastatic LNs. The differences in CT short axis and mean attenuation values between malignant and benign LNs were statistically significant (p<0.05). Mean size and mean attenuation values were 14.9±4.6 mm and 41.8±12.1 respectively in malignant LNs and 8.0±4.2 mm and 35.2±13.5 respectively in benign LNs. When short axis ≥10 mm was used as the malignancy criterion, the sensitivity, specificity, PPV, NPV and accuracy were 84.8%, 81.3%, 65.1%, 92.9% and 82.3%, respectively. ROC analysis showed that the cut-off value for short axis of LNs was >8mm. With this value, sensitivity, specificity, PPV and NPV were 93.8%, 71.9%, 62.5% and 95.8% respectively and area under the ROC curve was 89.4. We found >35 as the cut-off CT mean attenuation value for LNs, with the sensitivity, specificity, PPV and NPV being 81.3%, 55.2%, 47.6% and 85.5% respectively and area under the ROC curve was 66.5. The mean SUVmax values for malignant LNs and benign LNs were 10.9±5.9 and 2.41±1.2, respectively, which were statistically significant (p<0.05). Using SUVmax >2.5, the sensitivity, specificity, PPV and NPV were 92.8%, 64.3%, 56.9% and 94.7% respectively. The cut-off value for LN SUVmax/liver SUVmean was >1.69 and with this cut-off, the sensitivity, specificity, PPV and NPV were 95.8%, 91.7%, 85.2%, and 97.8% respectively (Table 1).

**Table-1:** Diagnostic values of four different parameters.

| Parameters cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| SUVmax >2.5 | 92.8 | 64.3 | 56.9 | 94.7 |
| LN SUVmax/liver SUVmean >1.69 | 95.8 | 91.7 | 85.2 | 97.8 |
| LN size>8 mm | 93.8 | 71.9 | 62.5 | 95.8 |
| Mean LN Att. >35 | 81.3 | 55.2 | 47.6 | 85.5 |

CT: Computerised Tomography; SUV: Standardised Uptake Value; LN: Lymph Node; Att: Attenuation

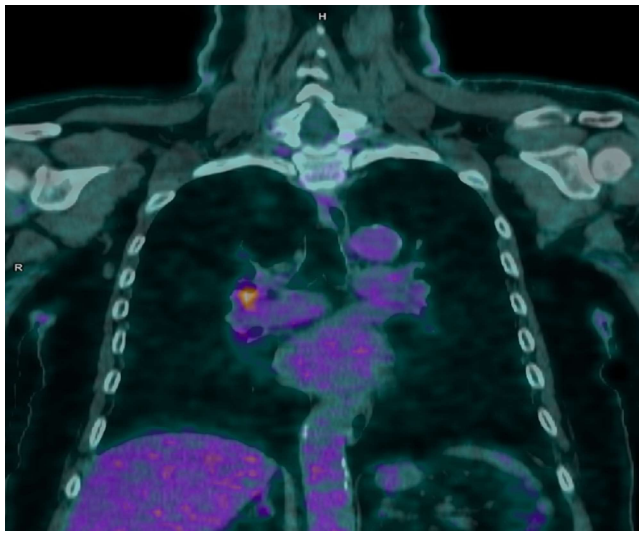

**Figure:** Image of a 65-year-old male. He was diagnosed with squamous cell lung carcinoma. In the FDG-PET/CT imaging there was a hilar lymph node with SUVmax: 3.62; according to SUVmax this node accepted as malignant. But LN SUVmax/liver SUVmean was 1.20 and Histopathological examination of this node showed benignity. If we accept SUVmax >2.5 for nodal radiotherapy unnecessary beaming occurs, however if we select LN SUVmax/liver SUVmean >1.69 we can avoid this problem

*FDG-PT: Fluorodeoxyglucose-positron emission tomography, CT: Computerised Tomography, SUV: Standardised Uptake Value, LN: Lymph Node.*

**Table-2:** LN SUVmax/liver SUVmean with two different CT parameter's Diagnostic Value Separately.

| CT Parameters together with Metabolic Parameters: | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| LN SUVmax/liver SUV mean >1.69 with LN >8 mm | 89.6 | 93.8 | 87.8 | 94.7 |
| LN SUVmax/liver SUV mean >1.69 with LN mean att.>35 | 79.2 | 93.8 | 86.4 | 90.0 |

CT: Computerised tomography; SUV: Standardised Uptake Value; LN: Lymph Node; Att: Attenuation

When the parameter LN SUVmax/liver SUVmean >1.69 was used along with LN >8mm as the malignancy criterion, the sensitivity, specificity, PPV and NPV were 89.6%, 93.8%, 87.8% and 94.7% respectively. When LN SUVmax/liver SUVmean >1.69 along with mean attenuation >35 was used as the malignancy criterion, the sensitivity, specificity, PPV and NPV were 79.2%, 93.8%, 86.4% and 90.0% respectively (Table 2).

## Discussion

To the best of our knowledge, the present study is the first one to focus on the PPV of different parameters, like LN SUVmax/liver SUVmean alone or along with size or density, in RT planning for MLNs.

NSCLC is one of the most commonly diagnosed malignancies worldwide. Although extensive treatment approaches are available, it is the leading cause of cancer-related mortality. Among the therapy options, RT can be used in early, local advanced and advanced stage patients. It has an important role in advanced stage NSCLC in palliative therapy and can also be applied as a part of neoadjuvant / adjuvant therapy in operable cases. In addition, it can be performed in patients who cannot undergo surgery due to medical and / or personal causes.[3-5,8-10]

Despite aggressive therapy during early stages, the recurrence rate of NSCLC is very high. Melloni et al. reported 20-40% recurrence even in stage I patients.[13] Recurrence may occur at distant or local sites. Lou et al. found 26% local recurrence or 30% local recurrence along with distant recurrence in early stage NSCLC patients.[14] In some cases, different RT approaches were used to address the problem, but they were unsuccessful and led to more side effects.[15,16] The main aim in cancer therapy is to preserve normal tissues while eliminating all malignant tissues. This goal has not yet been achieved in NSCLC. RT planning using FDG-PET/CT provided better results compared to CT-based planning in studies over the last decade.[17] However, the results are far from sufficient and have included MLNs recurrences and relapses. Billiet et al. reported approximately 37% local recurrence after postoperative RT planned using FDG-PET/CT with some LN regions showing recurrence rates as high as 22%. An interesting point to address in these reports is whether recurrence was in the mediastinal RT planning region or outside this area.[10] Nygard et al. planned RT based on FDG-PET/CT and found 14% LN recurrences outside the RT region.[18] Both the above recent studies demonstrated no sufficient decrease in nodal recurrence using classical FDG-PET/CT parameters. In planning for RT of primary tumours using FDG-PET/CT, a consensus has emerged regarding the SUVmax cut-off value and a strategy to overcome mismatch between CT and PET.[4,5] On the other hand, no such consensus exists for MLNs. Usefulness of metabolic parameters, suitable cut-off value, and the utility of combined use of tomography and PET parameters remain unclear. Because of this ambiguity, SUVmax >2.5 or increased LN metabolic activity compared to the MBP continues to be used as a positivity criterion due to the high NPV of these parameters. Some studies included the additional parameter of LNs >10mm but this resulted in a widened RT region.[4-6,10,16] The important point is that all the above parameters have a low PPV for MLN evaluation. Mallorie et al. reported 46.8% PPV and 97.7% NPV of the parameter LN activity>MBP activity.[19] Li et al. used SUVmax >2.5 as an indicator of malignancy in mediastinal nodes and found sensitivity, specificity, PPV, NPV and accuracy of 74.2%, 73.2%, 54.4%, 86.8%, and 73.5%, respectively.[20] A meta-analysis yielded values different from the classical criteria; however, the findings were also insufficient.[6] Thus, planning for RT of MLNs is quite challenging for radiation oncologists. Some studies have used EBUS-NA and FDG-PET/CT together. Peeters et al. used visual interpretation of FDG-PET/CT and EBUS-NA together and found that FDG-PET/CT-negative and EBUS-NA-negative LNs can be excluded from the RT region. However, if an LN is EBUS-NA-positive or has higher FDG uptake than the MBP, it should be included except in the case of bilateral symmetrical FDG-PET/CT positivity.[9] This caused widening of the planned target volume in MLNs and probably unnecessary beaming for some nodes due to low PPV of this metabolic parameter. A more helpful metabolic parameter with higher PPV for mediastinal nodal RT planning in NSCLC can enable more

specific beaming, may be leading to decreased mediastinal recurrence / relapse rates and radiation side effects.

To address the problems of low specificity and PPV, some studies used LN SUVmax/liver SUVmean ratios. Rogash et al. found sensitivity, specificity, PPV, NPV and accuracy of 80.6%, 88.2%, 67.4%, 93.8%, and 86.5%, respectively, using LN SUVmax/liver SUVmean >1.7.[11] Nguyen et al. reported sensitivity, specificity and accuracy of 81.6%, 97.6%, and 86.7% respectively using LN SUVmax/liver SUVmean ≥2.31.[21] The current first examined LN SUVmax >2.5, which is a standard semi-quantitative method used by most specialists in mediastinal nodal RT planning. Similar to other studies[10,11] we observed very low PPV (56.9%) and specificity (64.3%), with 92.8% sensitivity and 94.7% NPV. However, when we examined LN SUVmax/liver SUVmean using ROC analysis, the sensitivity, specificity, PPV and NPV were 95.8%, 91.7%, 85.2%, and 97.8%, respectively, with a cut-off >1.69. These were significantly more accurate compared to SUVmax >2.5 (Figure). Interestingly, this value is very similar to that reported by Rogash et al.[11] On the other hand, Nguyen et al. calculated a cut-off value quite different compared to ours, using the same metabolic parameter. Different patient selection criteria and the high number of SCC patients in our study, or the high number of large cell carcinoma patients in the other study[21] may have caused this difference.

Although insufficiency of single CT parameters is known, use of these parameters along with metabolic parameters must be investigated for improving accuracy. It is important to note that in our study, the cut-off value of >8mm for the LN short axis provided more accurate results compared to >10mm, which is used currently, with ROC analysis. In addition, short axis >8mm provided more reliable results compared to SUVmax >2.5. A similar finding was reported by Lee et al.[22] In terms of the use of the short axis in combination with metabolic parameters, studies mostly focused on NPV and sensitivity but not PPV.[6,20] In contrast to most studies, Li et al. investigated specificity in particular and found that if attenuation <70HU and SUVmax >2.5 were accepted as malignancy criteria in non-calcified LNs, the sensitivity was 68% and specificity was 95%. If SUVmax >3.5 was used with the same CT parameter, the sensitivity was only 13% with 94% specificity.[23] Lee at al. reported that if SUVmax >4.0 or SUVmax 2.0-4.0 along with LN mean attenuation values of 25-45 were used, the sensitivity, specificity and accuracy were 88.3%, 82.6%, and 86.0% respectively.[24] We used LN SUVmax/liver SUVmean >1.69 along with LN size >8mm or LN mean attenuation value >35 separately. Using this approach, the former parameter's sensitivity was 6.2% lower and NPV 3.1% lower than that using LN SUVmax/liver SUVmean >1.69 alone, whereas increase in PPV was 2.6%. The latter parameter caused more dramatic decreases (16.6% in sensitivity and 7.8% in specificity), with only a 1.2% increase in PPV compared to LN SUVmax/liver SUVmean >1.69 alone. In the final analysis, use of LN SUVmax/liver SUVmean >1.69 alone appeared more appropriate compared to other parameters in mediastinal nodal RT planning. However, the findings of the current study must be validated through prospective studies with larger patient series.

## Conclusion

LN SUVmax/liver SUVmean >1.69 had a higher NPV than the currently used parameters, and had a more useful PPV as well. Use of this parameter along with short axis or mean attenuation value did not result in a significant increase in PPV, but a decrease in NPV was seen. This parameter may be more beneficial in mediastinal nodal RT planning than the classical ones, enabling more selective RT and providing a strategy to decrease nodal recurrences.

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