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# Increasing the accuracy of $^{18}$F-FDG PET/CT interpretation of "mildly positive" mediastinal nodes in the staging of non-small cell lung cancer

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ABSTRACT

*Introduction:* The aim of this study was to identify radiological factors that may reduce false-positive results and increase diagnostic accuracy when staging the mediastinum of patients with non-small cell lung carcinoma (NSCLC).
*Methods:* This was a retrospective, interdisciplinary, per-node analysis study. We included patients with NSCLC and mediastinal nodes with an SUV max in the range of 2.5–4.0 on PET-CT. We hypothesized that the greatest number of false positive cases would occur in this cohort of patients.
*Results:* A total of 92 mediastinal lymph nodes were analyzed in 44 patients. Mediastinal disease (N2/N3) was histologically confirmed in 15 of 44 patients and in 34 of 92 lymph nodes; positive predictive value of 37% and false positive rate of 63%. Lymph node SUV max, tumor size, ratio of node SUV max to tumor SUV max (*SUVn/SUVp*), and ratio of node SUV max to node size (*SUV n/SADn*) were significantly higher in true positive cases. Using a threshold of 0.3 for SUV *node/tumor* and 3 for SUV *node/size* yielded sensitivities of 91% and 71% and specificities of 71% and 69% respectively for the detection of mediastinal disease. Using both ratios in combination resulted in a sensitivity of 65% and a specificity of 88%. Concurrent benign lung disease was observed significantly more frequently in false-positive cases.
*Conclusion: SUVn/SUVpt* and *SUVn/SADn* may be complimentary to conventional visual interpretation and SUV max measurement in the assessment of mediastinal disease in patients with NSCLC.


## 1. Introduction

Lung cancer is one of the leading causes of death from cancer worldwide. There was an estimated 222,520 new cases of lung cancer (85% non-small cell lung cancer (NSCLC)) in the United States in 2010, with 157,300 deaths [1].

Mediastinal involvement in NSCLC is a highly significant prognostic factor for survival and accurate staging of the mediastinum will correctly identify patients who will benefit the most from surgery [2]. Currently F-18 fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) scanning is recommended for patients with clinical stage 1A to IIIB disease for staging of the mediastinum prior to consideration for surgery [2]. The reported sensitivities of PET-CT for the correct diagnosis of mediastinal lymph node disease range from 69% to 80% with specificities in the range of 82–94% [2–6]. Risk factors for mediastinal disease include adenocarcinoma, tumors located in the upper or middle lobe, tumor size >3 cm, and SUVmax of the primary tumor >4.0 [7].

Traditionally, a maximum standardized uptake value (SUVmax) of 2.5 is used to differentiate benign from malignant lymph nodes [8,9]. Many studies report higher SUV thresholds of 4.4 or 5.3 that resulted in a greater diagnostic accuracy [10,11]. However, high SUV thresholds are associated with high false-negative rates and futile thoracotomies. Therefore a low threshold is used as it leads to a high specificity and negative predictive value for patients with a PET-negative mediastinum obviating the need for invasive staging prior to surgery. Conversely, with a cut-off of 2.5, inflammatory changes in lymph nodes can produce false-positive results with the problem of a low positive predictive value.

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We sought to evaluate the accuracy of $^{18}$F-FDG PET/CT in "mildly positive" lymph nodes with an SUVmax in the range of 2.5–4.0. This is a relatively common clinical scenario and source of diagnostic uncertainty. To the best of our knowledge, no study has examined false-positive or false-negative lymph nodes within this subgroup exclusively.

The aim of this study is to examine radiological and clinicopathological factors in a cohort of patients with NSCLC and mediastinal lymph nodes with an SUVmax in the range of 2.5–4.0. A potential benefit of this study is that this may enable us to identify factors that may reduce false-positive results and increase diagnostic accuracy when staging the mediastinum of patients with NSCLC.

## 2. Material and methods

### 2.1. Patient selection

This study was approved by the institutional clinical research ethics committee. This was a retrospective, interdisciplinary, per-node analysis study. Patients were identified from the lung cancer database of our hospital (a regional tertiary referral hospital for thoracic surgery and for multidisciplinary lung cancer treatment). Patients were deemed eligible for inclusion in the study if they had potentially operable, histologically confirmed or were considered highly likely to have recently developed NSCLC, and underwent combined PET-CT for staging. The study period was from June 2012 to August 2013. Following review of these cases, patients with one or more mediastinal nodes with an SUVmax in the range of 2.5–4.0 were selected for inclusion into the study. Hilar, peribronchial and intrapulmonary lymph nodes (stations 10–14) were not included.

Exclusion criteria were mediastinal nodes with an SUVmax greater than 4, the presence of distant metastatic disease, concurrent malignancy, and previous chemotherapy or mediastinal radiotherapy.

### 2.2. $^{18}$F-FDG integrated PET-CT

The PET-CT was performed in a dedicated PET-CT unit using an integrated PET-CT scanner (GE Discovery VCT, GE Healthcare, Buckinghamshire, United Kingdom). Patients fasted for six hours prior to scanning and were asked to refrain from physical activity for 24 h. Blood glucose levels were verified to be below 8.3 mmol/L. Patients were administered 350 ± 10% megabecquerels (MBq) of $^{18}$F-FDG intravenously and after 60 min of rest, were scanned from the skull base to the mid-thigh level. The scanning time for emission PET was 3 min per bed position. Images were reconstructed using iterative reconstruction.

A non-contrast CT scan of the thorax, abdomen and pelvis, using a standard protocol (120 kV, 80–120 mA, slice thickness of 3.75 mm, pitch of 0.98, and a tube rotation time of 0.5 s per rotation), preceded the PET scan, which was used for diagnostic purposes and for attenuation correction.

FDG positivity in mediastinal lymph nodes (hilar and supraclavicular nodes excluded) was retrospectively evaluated. The maximum standardized uptake value of the primary tumor and any abnormal lymph nodes was determined by drawing a region of interest (ROI) around it and using the maximum SUV recorded within the ROI. The SUV was calculated as the activity per millimeter within a ROI divided by the dose injected in megabecquerels per gram of body weight. The reviewer was blinded to the pathological results from surgery, mediastinoscopy, or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

### 2.3. Staging and surgery

Patients underwent further evaluation of suspicious (>2.5) N2 and N3 lymph nodes with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and/or mediastinoscopy prior to pulmonary resection. Patients with N0, N1 or single-station N2 disease proceeded to surgery while patients with multi-station N2 disease or N3 disease were deemed inoperable and offered chemoradiotherapy.

All patients were staged according to the revised TNM staging system of the International Association for the Study of Lung Cancer [12].

### 2.4. Data collection

The following parameters were evaluated: primary tumor size (maximum length in cm), tumor location by lobe, SUVmax of the primary tumor, SUVmax of each mediastinal node in the range 2.5–4, lymph node size, lymph node shape (ratio short/long axis), ratio of the SUVmax of the node to the SUVmax of the primary tumor (*SUVn/SUVpt*), ratio of the SUVmax of the node to the short axis diameter of the node (*SUVn/SADn*). Lymph node stations were assigned according to the system proposed by the International Association for the Study of Lung Cancer [13]. PET-CT images were also reviewed for radiological evidence of benign pulmonary disease including previous granulomatous disease, emphysema, pneumonia, or fibrotic lung disease.

Pathological data collected from surgery, mediastinoscopy or EBUS-TBNA included pathological subtype of the primary tumor and the grade of differentiation. All lymph nodes sampled were examined by a dedicated pulmonary pathologist for metastatic involvement. Data was collected by the main author and stored in an encrypted central database.

### 2.5. Statistical analysis

Data was collected and stored in Microsoft Excel (Microsoft, Redmond, WA, USA) and was subsequently imported into GraphPad Prism (Graphpad Software, San Diego, CA, USA) for statistical analysis. Distribution of variables was assessed using Shapiro–Wilk normality test. Normally distributed continuous data were analyzed using independent samples *t*-test. Non-Gaussian distributed data were examined using *U* Mann Whitney test. Chi-square or Fischer's exact test were used for categorical data. Receiver operator characteristics (ROC) curves were generated to assess sensitivities and specificities of variables. *P* values <0.05 were considered to be statistically significant.

## 3. Results

44 patients met criteria for inclusion (with a mediastinal node with an SUV 2.5–4) into the study (see Table 1 for patient demographic data). A total of 92 mediastinal lymph nodes were analyzed at stations 2R ($n = 1$), 4L ($n = 17$), 4R ($n = 33$), 5 ($n = 13$), 6 ($n = 1$) 7 ($n = 26$), and 9 ($n = 1$) (Fig. 1).

Metastatic mediastinal disease (N2/N3) was pathologically confirmed in 15 of 44 patients and in 34 of 92 lymph nodes (positive predictive value of 37%). Using an SUVmax of 2.5 as a cut-off value, this yielded a false positive rate of 63%.

The median SUVmax with interquartile range (IQR) was 3.75 (3.58–3.9) in the PET-positive, pathologically positive (true positive) nodes ($n = 34$) and 2.7 (2.6–2.925) in the PET-positive, pathologically negative (false positive) nodes ($n = 58$). The difference was found to be statistically significant ($P < 0.0001$) (Fig. 2).

The *SUVn/SUVpt* was also significantly different between the groups; 0.44 (0.31–0.54) vs 0.22 (0.15–0.33) ($P < 0.0001$) with a