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Improving diagnostic performance of ^{18}F-FDG-PET/CT for assessment of regional nodal involvement in non-small cell lung cancer

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AIM: To assess the diagnostic performance of combined 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron-emission tomography (PET)/computed tomography (CT) mediastinal blood pool (MBP) activity cut-off for staging nodal involvement, and to examine other variables that may improve the diagnostic performance of PET/CT in non-small cell lung cancer (NSCLC).

MATERIALS AND METHODS: All patients diagnosed with NSCLC who underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and ^{18}F-FDG-PET/CT between June 2016 and August 2018 were included. Nodal station and nodal staging-based analyses were performed, comparing the MBP cut-off and five other PET/CT parameters (node maximum standardised uptake value [SUV_{max}], node/MBP SUV_{max} ratio, node/tumour SUV_{max} ratio, node short axis diameter, and node SUV_{max}/node short axis diameter ratio) with histopathology results. The optimal cut-off value for each PET/CT parameter was determined using receiver operating characteristic curve analysis.

RESULTS: One hundred and thirteen patients with a total of 321 nodes with pathological sampling were included. Nodal activity above MBP on PET/CT demonstrated 97.4% sensitivity, 35.8% specificity, 32.8% positive predictive value, and 97.8% negative predictive value. Of the five other PET/CT parameters examined, the two most promising were node SUV_{max} and node/MBP SUV_{max}. The node SUV_{max} cut-off of 3.9 demonstrated 90.9% sensitivity and 61.9% specificity, and the node/MBP SUV_{max} cut-off of 1.7 demonstrated 90.9% sensitivity and 60.7% specificity.

CONCLUSION: Compared to the MBP cut-off, use of a higher node/MBP SUV_{max} ratio cut-off and use of other PET/CT variables can improve the diagnostic performance of PET/CT for NSCLC nodal staging. In particular, specificity for detecting malignant nodal involvement is improved while maintaining high sensitivity.

Introduction

Lung cancer is one of the leading causes of death worldwide, the most common cause of death from cancer in the UK, and the second most common cause of years of life

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lost in the UK.[1–3] The staging of non-small cell lung cancer (NSCLC) using the TNM classification is a powerful predictor of prognosis and survival, with regional lymph node involvement being one of the major elements included in the classification.[4,5] Surgical resection is the principal potentially curative treatment considered for patients without mediastinal lymph node involvement or distant metastasis, and may be considered for a proportion of patients with nodal N2 disease depending on the extent of mediastinal involvement[6,7]; however, advanced nodal metastatic disease is a general contraindication to surgical resection. Accurate nodal staging is thus crucial for guiding best management.

Combined 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET)/computed tomography (CT) is a test that is now in routine use in the UK for NSCLC staging as it enables non-invasive evaluation of both the mediastinum and distant metastases[8,9]; however, difficulties remain in clinical practice around the interpretation of PET/CT for nodal staging due to the variety of inflammatory and reactive conditions that can cause increased nodal FDG avidity and appearances similar to malignancy. Small-volume nodal involvement may lead to false-negative PET/CT findings. Guidelines from the National Institute for Health and Care Excellence (NICE), European Society of Thoracic Surgeons (ESTS) and European Respiratory Society (ERS) recommend that tissue confirmation is indicated in all cases of PET-positive or enlarged hilar or mediastinal lymph nodes before consideration of radical treatment, with the minimally invasive techniques of endobronchial ultrasonography (EBUS) with transbronchial needle aspiration (TBNA) or oesophageal ultrasonography (EUS) with fine-needle aspiration (FNA) being the first choices for tissue sampling.[10–12]

Diagnostic accuracy of PET/CT and the appropriate selection of patients for tissue sampling are thus affected by the definition of a positive test. For ^{18}F-FDG-PET/CT, parameters that have been shown to be significantly different between benign and malignant nodes are size of lymph node, conventionally measured as short axis diameter, and maximum standardised uptake value (SUV_{max}).[13] Numerous activity thresholds for lymph node positivity have been explored in the literature, including use of SUV_{max} 2.5 as the cut-off, and comparison of nodal activity with liver background, mediastinal blood pool (MBP), and tumour SUV_{max}.[14–17] In a previous retrospective study, nodal activity greater than MBP had the highest sensitivity among the different thresholds explored.[18] Based on this finding and the desirability of high sensitivity and low number of false negatives for PET/CT as an initial staging test, MBP has become the standard cut-off used at the Royal Free London NHS Foundation Trust to guide assessment of nodal involvement. All patients with suspected nodal metastasis using this cut-off are recommended for EBUS-TBNA for thorough assessment of nodal stations.

The objective of the present study was to evaluate the diagnostic performance of ^{18}F-FDG-PET/CT for the assessment of nodal involvement in NSCLC using MBP as a cut-off, 2 years following the authors' retrospective study.[18] In addition, other variables and cut-offs that could serve to increase the diagnostic performance of PET/CT for nodal assessment were assessed.

Materials and methods

Patient population

Consecutive patients who underwent EBUS-TBNA at Royal Free London NHS Foundation Trust between June 2016 and August 2018 for suspected lung cancer were identified. Patients were eligible if they underwent ^{18}F-FDG-PET/CT and received a histopathologically confirmed diagnosis of primary NSCLC from percutaneous CT-guided biopsy, EBUS-TBNA, or surgery. Both PET/CT and EBUS were performed before the start of any treatment, including surgery. Patients were excluded if they had synchronous cancer other than NSCLC. This study was registered with the Quality Governance Department at Royal Free London NHS Foundation Trust. All procedures performed in this retrospective study were in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Specific research ethics approval and informed consent for this study were not required according to NHS Health Research Authority guidance and the institutional Research and Development department.

^{18}F-FDG-PET/CT image acquisition

Patients underwent ^{18}F-FDG-PET/CT using a Biograph mCT PET/CT system (Siemens, Munich, Germany) following intravenous administration of ^{18}F-FDG and a 60 minute uptake period. The activity of FDG was calculated using a weight-based formula according to departmental policy, up to a maximum of 400 MBq. Before ^{18}F-FDG administration, patients fasted for at least 6 hours, with blood glucose verified to be $\leq$11 mmol/l. Unenhanced CT imaging was performed in line with standard protocols from skull base or skull vertex to mid-thigh using automatic exposure control (Siemens CARE Dose4D and CARE kV) with a reference of 65 mAs and 120 kV. PET imaging was performed over the same area at 2–4 minutes per bed position, depending on activity injected and body mass index (BMI), with a bed position overlap of 42%. Reconstruction methods included time of flight and point spread function, with two iterations, 21 subsets, and a Gaussian 2 mm full-width half-maximum filter.

Pathology sample acquisition

EBUS-TBNA was performed on an outpatient basis under conscious sedation using a combination of intravenous fentanyl and midazolam, in addition to local anaesthesia using 10% lidocaine to the oropharynx and 1% lidocaine to the tracheobronchial tree. Linear EBUS (EB-530US; Aquilant Endoscopy, Basingstoke, UK) was performed to systematically assess the hilar and mediastinal lymph nodes, followed by sampling of targeted lymph nodes with a 22 or 25

G needle (ECHO-HD-22-EBUS-O-C, ECHO-HD-25-EBUS-O-C; Cook Medical, Limerick, Ireland) and applied suction under direct ultrasound visualisation. The site and number of lymph nodes punctured and the number of passes per node were at the operator's discretion. Samples were transferred to formalin for cell block processing.

The decision to proceed to surgery was made on the basis of a multidisciplinary team consensus opinion. Patients deemed suitable underwent lung resection surgery with systematic lymph node dissection at one of two regional tertiary cardiothoracic centres. Pathology used standard techniques and confirmation by immunohistochemistry was performed.

Data collection

Variables selected for evaluation in this study were SUV_{max} of MBP (MBP-SUV_{max}), SUV_{max} of lymph node (N-SUV_{max}), SUV_{max} of primary tumour (T-SUV_{max}), N-SUV_{max}/MBP-SUV_{max} ratio, N-SUV_{max}/T-SUV_{max} ratio, short axis diameter of lymph node (N-SAD) in mm, and N-SUV_{max}/N-SAD ratio. N-SUV_{max} and T-SUV_{max} were measured by placing a region of interest (ROI) over the relevant areas. If there was more than one lesion in the lung, the lesion with the highest SUV_{max} was considered to be the primary lung tumour. Similarly, if there was more than one avid lymph node within a nodal station, the lymph node with the highest SUV_{max} was recorded for each nodal station. The N-SAD of avid nodes was measured manually. MBP-SUV_{max} was measured by placing a ROI within the lumen of the aortic arch. The reviewing nuclear medicine physician was blinded to the pathology results.

Histopathology results were collected for all nodal stations with sampling from EBUS-TBNA and/or surgery. Nodes that were not sampled by the operator during EBUS because morphological appearances were normal were included with a result of "no malignancy". Nodes that were not sampled during EBUS because of technical challenges and safety concerns were excluded from analysis. EBUS-TBNA samples that were reported by the pathologist as inadequate or indeterminate were included in analysis as "no malignancy", due to the lack of objective criteria for defining inadequacy. Lymph node stations were classified according to the International Association for the Study of Lung Cancer (IASLC) lymph node map.[19] Nodal stations 10–11 were considered hilar for the purpose of comparison of involved hilar nodes between PET/CT and EBUS/surgery-sampled nodes.

Data and statistical analysis

Analysis was performed of individual nodal stations, comparing PET/CT with histopathology results, and analysis of nodal staging, comparing PET/CT nodal staging with histopathology nodal staging on a per patient basis. For the nodal staging-based analysis, a true-positive result was considered N2/3 disease on both PET/CT and pathology, a false-positive was N2/3 on PET/CT and N0/1 on pathology, a false-negative was N0/1 on PET/CT and N2/3 on histopathology, and a true-negative was N0/1 on both PET/CT and histopathology. For both analyses, surgical histopathology results were used as the reference standard where available, and EBUS-TBNA histopathology results were used where surgical histopathology was not available.

Receiver operating characteristic (ROC) curve analysis was used to assess and compare diagnostic performance of the selected PET/CT variables. Cut-offs for these variables were identified after interrogation of the ROC curves, and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of these cut-offs were determined. Cut-off values producing maximal combined sensitivity and specificity were determined from calculation of Youden's index. Statistical analysis was carried out using SPSS Statistics software (IBM SPSS Statistics, Version 20). p-Values <0.05 were considered statistically significant.

Results

One hundred and thirteen patients met inclusion criteria, with a total of 321 nodal stations with pathological sampling. Two hundred and thirty-four nodal stations were sampled by EBUS-TBNA and 123 nodal stations were sampled surgically, with 36 nodal stations sampled using both techniques. Thirty-five patients underwent EBUS-TBNA followed by surgical resection, while 78 patients underwent only EBUS. Seventy-four patients underwent PET/CT before EBUS-TBNA (range 1–90 days) and 39 patients underwent PET/CT after EBUS (range −56 to 0 days), with a median time interval of 10 days between PET/CT and subsequent EBUS-TBNA. Patient characteristics are described in Table 1. The prevalence of metastatic NSCLC involvement of nodal stations was 70/234 (29.9%) from EBUS-TBNA and 15/123 (12.2%) from surgery. EBUS-TBNA yielded non-diagnostic results for 27/234 (11.5%) nodal stations. The

Table 1
Patient characteristics (N=113).

	n (%)
Sex	
Male	66 (58.4)
Female	47 (41.6)
Age (years)	
Mean ± standard deviation	71.1 ± 11.0
Range	42–90
NSCLC histology subtype	
Adenocarcinoma	66 (58.4)
Squamous cell carcinoma	39 (34.5)
Adenosquamous carcinoma	5 (4.4)
Non-small cell lung cancer unspecified	3 (2.6)
Lymph node stations sampled	
Left upper paratracheal (2L)	3 (0.9)
Right upper paratracheal (2R)	13 (4.1)
Left lower paratracheal (4L)	24 (7.5)
Right lower paratracheal (4R)	53 (16.5)
Subaortic (5)	12 (3.7)
Para-aortic (6)	8 (2.5)
Subcarinal (7)	84 (26.2)
Inferior mediastinal (8, 9)	26 (8.1)
Left hilar (10L, 11L)	45 (14.0)
Right hilar (10R, 11R)	53 (16.5)

prevalence of N2/N3 disease on a per patient basis was 35/113 (31%) from EBUS-TBNA staging and 5/35 (14.3%) from surgical staging; a total of 38/113 (33.6%) patients had N2/N3 disease from either EBUS-TBNA or surgical staging.

In both nodal station and nodal staging-based analyses (Table 2), nodal activity above MBP on PET/CT demonstrated high sensitivity and negative predictive value (NPV) for metastatic nodal involvement, but low specificity and positive predictive value (PPV). The proportion of false positives was 156/321 (48.6%). Left lower paratracheal (station 4L) and left hilar nodes had the highest proportions of false positives (15/24 (62.5%) and 26/45 (57.8%), respectively). Two of 321 false negatives were identified, both involving the subcarinal nodal station (station 7).

ROC curve analysis was carried out for selected variables for all individual nodal stations compared with pathological diagnosis (Fig 1, Table 3). The ROC curves for N-SUV_{max} and N-SUV_{max}/T-SUV_{max} had the largest and smallest areas under the curve (AUCs), respectively, with significant difference between the two. Youden's index and cut-offs aiming for ≥90% sensitivity were determined for each variable from interrogation of the ROC curves (Table 3).

Table 4 shows the results of nodal station and nodal staging-based analyses carried out for the individual cut-offs in Table 3 that maintained high sensitivities (≥90%). All cut-offs had higher specificities than the MBP cut-off. N-SUV_{max} ≥3.9 and N-SUV_{max}/MBP-SUV_{max} ≥1.7 had the highest specificities and the lowest proportions of false positives (93/321 (29%) and 96/321 (29.9%), respectively), resulting in a reduction of the proportion of false positives by up to 40% compared with MBP.

Discussion

In this study, following on from previous work on ^{18}F-FDG-PET/CT for the assessment of nodal staging in NSCLC, it was confirmed that using MBP as a cut-off had high sensitivity and NPV for differentiating between histopathologically confirmed benign and malignant nodes. These characteristics are desirable with PET/CT, as current guidance recommends that certain NSCLC tumours with non-enlarged PET-negative nodes may be considered directly for surgical resection, without further mediastinal staging.[11] A low rate of PET false negatives would thus decrease the risk of futile surgeries being performed on PET-negative patients who actually have N2/3 disease; however, the low rate of false negatives using the MBP cut-off was found to be accompanied by a high rate of false positives, similar to findings from previous studies.[20,21] The specificity of MBP on nodal station-based analysis (35.8%) in this study was lower than the specificity obtained in our previous study (72.1%).[18] This may be attributed to the fact that MBP was not a standard cut-off used for the cohort in the previous study, compared to the current study where all patients who had hilar or mediastinal nodal activity greater than MBP were recommended for EBUS. The latter methodology can be expected to produce a more accurate analysis of the diagnostic performance of the MBP cut-off.

The diagnostic performance of five PET/CT parameters that are already conventionally measured in clinical practice or easy to derive from these conventional measurements was examined: N-SUV_{max}, N-SUV_{max}/MBP-SUV_{max}, N-SUV_{max}/T-SUV_{max}, N-SAD, and N-SUV_{max}/N-SAD. All five variables were found to have good diagnostic performance individually for differentiating between benign and malignant lymph nodes in the present cohort, with all except N-SUV_{max}/T-SUV_{max} having AUC ≥0.80 on ROC curve analysis. Thus, the accuracy of the N-SUV_{max}/MBP-SUV_{max} ratio variable could be improved by using a higher cut-off than MBP (or N-SUV_{max}/MBP-SUV_{max} ≥1). The MBP cut-off specificity of 35.8% could be improved by using thresholds such as N-SUV_{max} ≥3.9, N-SUV_{max}/MBP-SUV_{max} ≥1.7, N-SUV_{max}/T-SUV_{max} ≥0.20, N-SAD ≥7.0 mm, and N-SUV_{max}/N-SAD ≥0.35, while maintaining sensitivities of ≥90%, with use of the N-SUV_{max} ≥3.9 cut-off reducing the proportion of false positives by up to 40%. Clinical reporting of PET/CT may thus be aided by use of these cut-off values when measuring and comparing N-SUV_{max} with MBP, T-SUV_{max}, and N-SAD.

Although specific cut-offs may not be directly comparable between studies due to differences in PET/CT manufacturers, FDG dose and prevalence of NSCLC subtypes in the region,[17] previous studies, which have individually examined these variables, have similarly found good diagnostic performance.[16,18,20,22–24] Notably, an N-SUV_{max}/T-SUV_{max} ratio of 0.20 was found, which had similar sensitivity and specificity values to those of Koksal *et al.*, who found this cut-off to have sensitivity of 92.8% and specificity of 47%.[22] An N-SUV_{max} cut-off of about 4.0 has similarly been proposed by Evison *et al.*, although they obtained higher specificity (89.6%) with this cut-off.[21] Moloney *et al.* proposed using an N-SUV_{max}/N-SAD cut-off of 0.3, similar to our cut-off of 0.35, but with a lower sensitivity (71%) and higher specificity (69%).[20]

Current guidance recommends that all patients with suspected NSCLC and an abnormal mediastinum on PET/CT should have EBUS-TBNA and/or EUS-FNA initially for pathological staging, followed by surgical staging if EBUS or EUS are negative for mediastinal involvement.[11,12,25] In following this pathway, it must be acknowledged that the selection of patients for pathological staging should not depend only on objective PET/CT parameters, but also on other parameters known to correlate with malignancy, such as patient characteristics and clinical history, and visual assessment of the pattern or symmetry of nodal uptake on PET/CT.[26] After taking all of this evidence into account, it is

Table 2
Diagnostic performance of mediastinal blood pool cut-off.

	Nodal station-based analysis	Nodal staging-based analysis
Sensitivity (%, 95% CI)	97.4 (91.0–99.7)	100.0 (90.5–100.0)
Specificity (%, 95% CI)	35.8 (29.8–42.2)	20.8 (12.4–31.5)
Positive predictive value (%, 95% CI)	32.8 (26.8–39.2)	37.8 (28.2–48.1)
Negative predictive value (%, 95% CI)	97.8 (92.1–99.7)	100.0 (79.4–100.0)

CI, confidence interval.

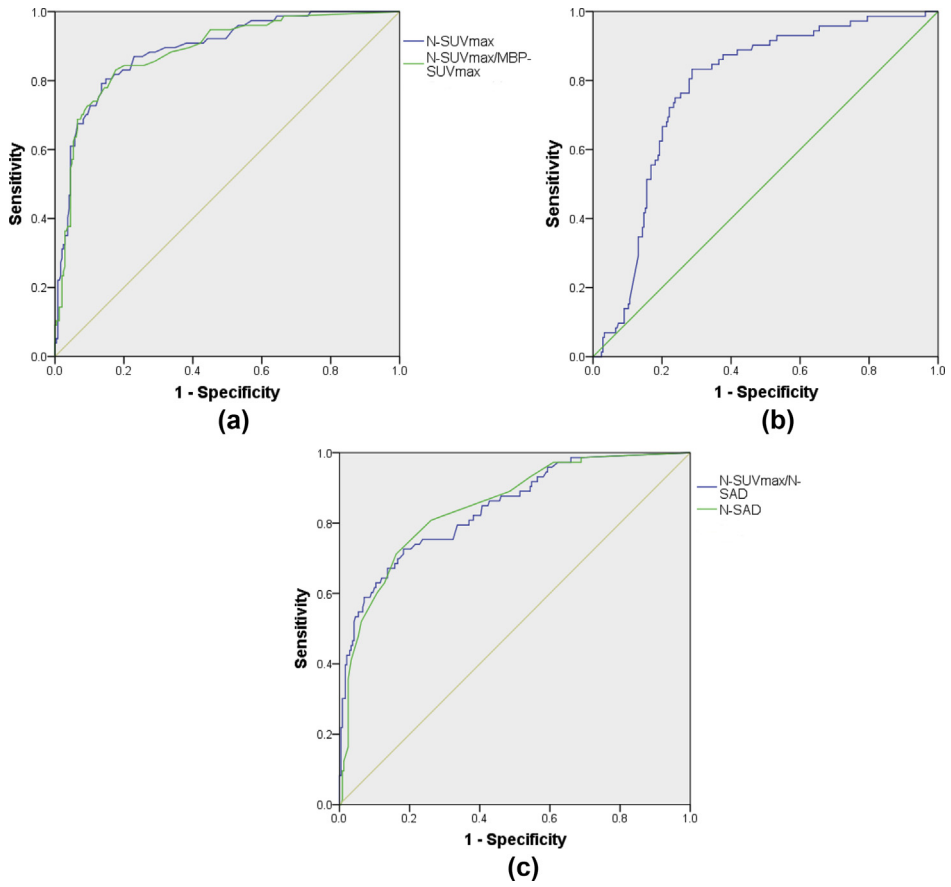

Figure 1 ROC curve analysis comparing diagnostic performance of selected variables against pathological diagnosis. (a) N-SUV_{max} and N-SUV_{max}/MBP-SUV_{max}. (b) N-SUV_{max}/T-SUV_{max}. (c) N-SAD and N-SUV_{max}/N-SAD.

important to proceed only with investigations that will yield the most useful information for staging and guiding management, with least risk to the patient.[10] Minimally invasive tissue sampling techniques are recommended as the initial choice for pathological sampling because they have good safety profiles and are generally well-tolerated by patients, but there are still risks associated with EBUS-TBNA requiring deep sedation, including hypoxaemia, bleeding, infection, and very rarely pneumothorax,[27,28] as well as a short delay to first treatment. Technical challenges of EBUS-TBNA must also be considered: diagnostic yield is increased with systematic sampling of all visible nodes in at least three mediastinal stations, which is often not feasible if nodes are too small or narrow to be amenable to sampling, the nodes are in difficult anatomical locations, or the patient cannot tolerate the procedure.[11,29] Thus, decreasing the number of false positives referred for pathological staging would be helpful, and we have shown that one way this might be achieved is with the aid of measurable PET/CT diagnostic variables with higher specificity than the MBP cut-off. Of course, improving specificity of PET/CT and decreasing the number of false positives is likely to incur a higher false negative rate, and further work is required to evaluate whether this higher false negative rate would be acceptable in clinical practice; however, in this study, all diagnostic variables examined had higher sensitivity on

Table 3
Comparison of ROC curves and cut-offs for selected PET/CT variables for nodal staging.

	N-SUV_{max}	N-SUV_{max}/MBP-SUV_{max}	N-SUV_{max}/T-SUV_{max}	N-SAD (mm)	N-SUV_{max}/N-SAD
ROC AUC (95% CI)	0.89 (0.85–0.93)*	0.88 (0.84–0.93)*	0.78 (0.72–0.83)*	0.85 (0.80–0.90)*	0.84 (0.79–0.90)*
Youden's index	5.7	2.4	0.40	10.5	0.60
Sensitivity (%)	80.5	83.1	83.3	71.2	72.6
Specificity (%)	85.2	82.4	71.3	83.8	81.7
Cut-off with sensitivity ≥90%	3.9	1.7	0.20	7.0	0.35

* indicates p-value <0.0005.
ROC, receiver operating characteristic; AUC, area under the ROC curve; PET/CT, 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron-emission tomography (PET)/computed tomography (CT); SUV_{max}, maximum standardised uptake value (SUV_{max} of lymph node [N-SUV_{max}], SUV_{max} of primary tumour [T-SUV_{max}], N-SUV_{max}/MBP-SUV_{max} ratio, N-SUV_{max}/T-SUV_{max} ratio); MBP, mediastinal blood pool; N-SAD, short axis diameter of lymph node.

Table 4
Diagnostic performance of alternative cut-offs identified.

	N-SUV_{max} ≥3.9	N-SUV_{max}/ MBP-SUV_{max} ≥1.7	N-SUV_{max}/ T-SUV_{max} ≥0.20	N-SAD ≥7.0 mm	N-SUV_{max}/ N-SAD ≥0.35
Nodal station-based analysis					
Sensitivity (%, 95% CI)	90.9 (82.2–96.3)	90.9 (82.2–96.3)	91.7 (82.7–96.9)	93.2 (84.7–97.7)	91.8 (83.0–96.9)
Specificity (%, 95% CI)	61.9 (55.5–68.0)	60.7 (54.2–66.8)	53.3 (46.8–59.7)	45.8 (39.4–52.4)	44.8 (38.4–51.3)
Positive predictive value (%, 95% CI)	42.9 (35.2–50.9)	42.2 (34.6–50.1)	36.7 (29.6–44.2)	34.3 (27.8–41.4)	33.5 (27.0–40.5)
Negative predictive value (%, 95% CI)	95.6 (91.1–98.2)	95.5 (90.9–98.2)	95.6 (90.6–98.4)	95.7 (90.1–98.6)	94.7 (88.9–98.0)
Nodal staging-based analysis					
Sensitivity (%, 95% CI)	94.6 (81.8–99.3)	94.6 (81.8–99.3)	94.3 (80.8–99.3)	100.0 (90.0–100.0)	94.3 (80.8–99.3)
Specificity (%, 95% CI)	53.2 (41.5–64.7)	53.2 (41.5–64.7)	44.2 (32.8–55.9)	26.3 (16.9–37.7)	31.6 (21.4–43.4)
Positive predictive value (%, 95% CI)	49.3 (37.2–61.4)	49.3 (37.2–61.4)	43.4 (32.1–55.3)	38.5 (28.4–49.2)	38.8 (28.4–50.0)
Negative predictive value (%, 95% CI)	95.3 (84.2–99.4)	95.3 (84.2–99.4)	94.4 (81.3–99.3)	100.0 (83.2–100.0)	92.3 (74.9–99.1)

SUV_{max}, maximum standardised uptake value (SUV_{max} of lymph node [N-SUV_{max}], SUV_{max} of primary tumour [T-SUV_{max}], N-SUV_{max}/MBP-SUV_{max} ratio, N-SUV_{max}/T-SUV_{max} ratio); MBP, mediastinal blood pool; N-SAD, short axis diameter of lymph node; CI, confidence interval.

nodal staging-based analysis compared with nodal station-based analysis, suggesting that there may not be significant false downgrading of N2/3 disease on PET/CT using these new cut-offs.

The strengths of this study include the large sample size of lymph nodes, with pathological confirmation of each included node. A detailed assessment of the diagnostic performance of multiple easily measurable PET/CT variables has been carried out, which to the authors' knowledge have not been assessed in combination before. Furthermore, the focus was on the very clinically relevant question of how to decrease the number of false positives on PET/CT, while maintaining high sensitivity and NPV. A limitation of this study is that while all cases of lymphadenopathy with activity greater than MBP were referred for EBUS-TBNA, there were cases where positive nodes were not sampled, often due to technical challenges. Cases in which systematic mediastinal sampling was difficult often result in sampling only of those lymph nodes most likely to be positive, potentially introducing bias in this study. Furthermore, surgical pathology was not obtained for all PET-positive nodes, and EBUS-TBNA carries a small risk of false negatives. Nonetheless, EBUS-TBNA has been well-evidenced to have high sensitivity and NPV, and thus was deemed a suitable reference standard to compare PET/CT to in this study, being reflective of clinical practice as well.[25,29] Finally, if multiple nodes exist in a nodal station, there may have been a discrepancy if the node sampled for pathology using EBUS-TBNA or surgery was different from the most avid node identified on PET/CT and included in analysis.

In conclusion, this study highlights some of the challenges of PET/CT interpretation in trying to achieve accurate nodal staging of patients with NSCLC. Although the MBP activity cut-off had low specificity, the N-SUV_{max}/MBP-SUV_{max} ratio, as well as N-SUV_{max}, N-SUV_{max}/T-SUV_{max}, N-SAD, and N-SUV_{max}/N-SAD, were PET/CT parameters with improved diagnostic performance for differentiating between benign and malignant lymph nodes if different cut-offs are selected. Histopathological confirmation remains of paramount importance in any case with suspicion of nodal involvement, but use of these variables may aid clinical reporting and multidisciplinary team decision-making for patients being staged for NSCLC, particularly in equivocal cases.

Conflict of interest

The authors declare no conflict of interest.

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