

 Mehmet Agar¹,  İlham Gulceker²,  Muhammed Kalkan³,
 Hakki Ulutas⁴,  Muhammet Reha Celik⁵

¹Firat University, Faculty of Medicine, Department of Thoracic Surgery, Elazığ, Türkiye

²Sanko University Hospital, Department of Thoracic Surgery, Gaziantep, Türkiye

³Malatya Training and Research Hospital, Department of Thoracic Surgery, Malatya, Türkiye

⁴İzmir Economics University, Faculty of Medicine, Department of Thoracic Surgery, İzmir, Türkiye

⁵Atılım University, Faculty of Medicine, Department of Thoracic Surgery, Ankara, Türkiye

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Corresponding Author: Mehmet Agar, Firat University, Faculty of Medicine, Department of Thoracic Surgery, Elazığ, Türkiye
Email: md.mehmetagar@gmail.com

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INTRODUCTION

PET/CT is an imaging method that combines anatomical details with functional metabolic data in the staging of non-small cell lung cancer (NSCLC) (1). It provides higher sensitivity and accuracy than computed tomography, which focuses only on anatomical size, particularly in the evaluation of mediastinal lymph node involvement. However, in clinical practice, the success of PET/CT depends on the level of agreement between metabolic imaging and histopathological results, that is, the

PET/CT nodal pitfalls: The reality of false positivity and negativity in non-small cell lung cancer

Abstract

Aim: To evaluate the diagnostic accuracy of preoperative 18F-FDG PET/CT for mediastinal and hilar lymph node staging in non-small cell lung cancer (NSCLC), using postoperative histopathology as the reference standard.

Materials and Methods: This retrospective single-center study included 37 NSCLC patients who underwent anatomical lung resection and systematic lymph node dissection between 2015 and 2020. PET/CT findings were compared with histopathology to calculate sensitivity, specificity, positive and negative predictive values, and accuracy. True-positive (TP) and false-positive (FP) cases were compared using Mann–Whitney U and Fisher exact tests. Firth penalized logistic regression assessed predictors of TP nodal metastasis.

Results: Of 37 patients, 89.2% were male, and mean age was 60.9 ± 7.7 years. Mean tumor diameter was 4.11 ± 2.02 cm, and mean SUVmax was 16.8 ± 7.5 . PET/CT indicated nodal involvement in 33 patients (89.2%), while histopathology confirmed metastasis in 19 (51.4%). Sensitivity was 89.5%, specificity 11.1%, positive predictive value 51.5%, negative predictive value 50.0%, and accuracy 51.4%. Among PET-positive patients, TP cases had higher primary tumor SUVmax and larger tumors, with more frequent extracapsular extension (ECE) and pathological stage III disease. Firth regression identified tumor diameter (OR 1.74), ECE (OR 2.96), and stage III (OR 3.21) as independent predictors of TP status. FP findings clustered in stations 4 and 10, whereas false-negative findings occurred most often in stations 7 and 11.

Conclusion: PET/CT alone was insufficient for definitive nodal staging because of substantial false positivity and clinically relevant false negativity. Histopathological confirmation of PET-positive nodes, when indicated, may prevent mis-staging and inappropriate treatment selection while preserving curative surgical opportunities.

Keywords: Carcinoma, non-small-cell lung; positron emission tomography computed tomography; lymphatic metastasis; false positive reactions; false negative reactions

distinction between true-positive and false-positive (FP) findings (2).

True-positive results refer to situations in which the high 18F-FDG uptake observed in a lymph node is confirmed to be malignant metastasis on pathological examination performed after surgery or biopsy (3). Studies have shown that PET/CT exhibits a high sensitivity in this area, with rates reported to be between 74% and 94%. An SUVmax value exceeding 2.5 or 3.0 is typically regarded as a strong indicator of metastasis (4).

In contrast, false-positive findings occur when a lymph node reported as metastatic on PET/CT is found to be pathologically negative (pN0), which is one of the most important limitations of the method (3). FDG uptake is not specific to cancer. Glucose metabolism is also intensely utilized by activated macrophages, neutrophils, and lymphocytes involved in the inflammatory response. Granulomatous diseases such as tuberculosis, sarcoidosis, pneumoconiosis, and anthracosis, as well as conditions such as pneumonia and reactive hyperplasia, may cause intense uptake that mimics malignancy on PET/CT and lead to incorrect staging.

False-positive rates are higher, especially in regions where tuberculosis is endemic, and may lead to the patient unjustly losing the chance of surgical treatment (5). Therefore, current guidelines require histopathological confirmation using methods such as EBUS-TBNA or mediastinoscopy in patients with PET-positive lymph nodes, especially when this result will change the treatment strategy (6).

MATERIALS AND METHODS

Study Design and Patient Population

This retrospective, single-center study aimed to evaluate the accuracy of intraoperative and pathological detection of lymph node involvement using preoperative PET/CT in patients with NSCLC who underwent surgical resection. The study included 37 patients who underwent anatomical lung resection and systematic lymph node dissection at our clinic between 2015 and 2020, underwent preoperative PET/CT scans, and completed pathological lymph node assessments. Patients with small cell lung cancer, those who received neoadjuvant therapy, and those without complete pathological lymph node data were excluded.

This study was conducted in accordance with the Ethics Committee of the Firat University Scientific Research and Publication Ethics Board (2026/02-30) (approval date: 05 February 2026).

PET/CT Evaluation

All patients underwent 18F-FDG PET/CT before surgery. Cases in which FDG uptake was detected in mediastinal or hilar lymph nodes on PET/CT were classified as “PET lymph node positive,” whereas those with no pathological uptake were classified as “PET lymph node negative.” The SUVmax of lymph nodes exhibiting uptake on PET/CT and the specific areas of uptake were recorded. No specific cutoff value was calculated for PET/CT SUVmax measurements. Regardless of any predefined numerical threshold, any lymph node demonstrating FDG uptake on PET/CT was accepted as “PET lymph node positive” based on the value provided by the imaging system.

Surgical and Pathological Evaluation

During the surgical procedure, all patients underwent systematic dissection of the mediastinal and hilar lymph nodes. In all

patients, at least three mediastinal stations, together with hilar/interlobar stations, were sampled or dissected. The lymph nodes removed intraoperatively were sent for histopathological examination, and the presence of metastasis was evaluated. Cases with pathologically detected metastasis were defined as “pathological lymph node positive (pN+),” whereas those without metastasis were defined as “pathological lymph node negative (pN-).” In addition, the presence of lymphovascular invasion (LVI), perineural invasion (PNI), pleural involvement, and extracapsular extension (ECE) were recorded from pathology reports.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25. Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), and categorical variables are presented as counts and percentages. A 2 $\times$ 2 diagnostic accuracy table was created to evaluate the relationship between PET/CT findings and pathological lymph node stations, which facilitated the calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy of PET/CT. To investigate the differences between true-positive and false-positive cases, the Mann-Whitney U test was applied to continuous variables, whereas categorical variables were examined using either the chi-square test or Fisher’s exact test. Due to the limited sample size, Firth penalized logistic regression analysis was utilized to identify independent predictors of pathological confirmation of lymph node positivity on PET/CT. The final multivariable model included the primary tumor SUVmax value, tumor diameter measured on PET/CT, histological subtype, lymphovascular invasion, perineural invasion, pleural involvement, extracapsular extension, and pathological stage III disease. Statistical significance was set at $p < 0.05$.

RESULTS

The study included 37 patients, comprising 33 men (89.2%) and 4 women (10.8%). The mean age of the group was 60.9 ± 7.7 years. The mean age of male patients was 60.5 years, whereas that of female patients was 64.8 years. Preoperative PET/CT assessments indicated that the mean tumor diameter was 4.11 ± 2.02 cm, with an average tumor SUVmax value of 16.8 ± 7.5 . Utilizing the TNM 8th staging system, 40.5% of the patients were identified as Stage I, 37.8% as Stage II, and 21.7% as Stage III. Table 1 presents a detailed account of the patients’ demographic, clinical, surgical, and pathological features.

Among the 33 patients with lymph node positivity on PET/CT, metastasis was pathologically confirmed in 17 patients (51.5%) (true positive), whereas metastasis was not detected histopathologically in 16 patients (48.5%) (false positive) (reactive lymph nodes, 90%; granulomatous lymphadenitis, 8%; anthracosis, 2%). Pathological metastasis was detected in two of the four patients who showed no SUVmax uptake in any lymph

node station on PET/CT (false-negative), whereas the remaining two patients had pathologically negative lymph nodes (true-negative). According to these data, the sensitivity of PET/CT

in detecting lymph node metastasis was 89.5%, specificity was 11.1%, PPV was 51.5%, NPV was 50%, and overall diagnostic accuracy was 51.4%.

Table 1. Demographic, clinical, surgical, and pathological characteristics of the patients (n = 37)

Variable		Value
Sex, n (%)	Male	33 (89.2)
	Female	4 (10.8)
Age, years	Mean $\pm$ SD	60.9 $\pm$ 7.7
	Male (mean)	60.5
	Female (mean)	64.8
Surgical approach, n (%)	Thoracotomy	25 (67.6)
	VATS	12 (32.4)
Side of surgery, n (%)	Right	20 (54.1)
	Left	17 (45.9)
Anatomical resection, n (%)	Upper lobectomy	18 (48.6)
	Lower lobectomy	7 (18.9)
	Bilobectomy	2 (5.4)
	Pneumonectomy	10 (27.1)
Primary tumor PET characteristics	PET tumor diameter (cm), mean $\pm$ SD	4.11 $\pm$ 2.02
	PET SUVmax, mean $\pm$ SD	16.8 $\pm$ 7.5
Histological diagnosis, n (%)	Squamous cell carcinoma	24 (64.9)
	Adenocarcinoma	12 (32.4)
	Giant cell carcinoma	1 (2.7)
Lymphovascular invasion, n (%)	Present	11 (29.7)
	Absent	26 (70.3)
Perineural invasion, n (%)	Present	9 (24.3)
	Absent	28 (75.7)
Pleural involvement, n (%)	Present	8 (21.6)
	Absent	29 (78.4)
Surgical margin, n (%)	Negative	36 (97.3)
	Positive	1 (2.7)
Extracapsular extension, n (%)	Present	5 (13.5)
	Absent	32 (86.5)
Pathological stage (TNM-8), n (%)	Stage I	15 (40.5)
	Stage II	14 (37.8)
	Stage III	8 (21.7)

Abbreviations: n, number of patients; PET, positron emission tomography; SD, standard deviation; TNM, tumor, node, metastasis; VATS, video-assisted thoracoscopic surgery.

In the analysis of clinicopathological features, the SUVmax values of the primary tumor were notably higher in the TP group than in the FP group ($p = 0.03$). Additionally, the diameter of the primary tumor, as measured on PET/CT, was significantly larger in the TP group ($p = 0.02$) (Table

2). When examining aggressive pathological characteristics, extracapsular extension was more prevalent in the TP group than in the false-positive group ($p = 0.01$). Consequently, Stage III disease was significantly more common in the TP group ($p = 0.02$) (Table 2).

Table 2. Comparison of true-positive and false-positive lymph node findings in PET-positive patients

Variable	True positive (TP) (n = 17)	False positive (FP) (n = 16)	p-value
Primary tumor SUVmax	Higher	Lower	0.03
Tumor diameter on PET (cm)	Larger	Smaller	0.02
Histology (Squamous), n (%)	More frequent	Less frequent	0.18
Lymphovascular invasion, n (%)	Similar	Similar	0.11
Perineural invasion, n (%)	More frequent	Less frequent	0.03
Pleural involvement, n (%)	More frequent	Less frequent	0.09
Extracapsular extension, n (%)	Markedly higher	Very rare	0.01
Pathological Stage III, n (%)	Higher proportion	Lower proportion	0.02

Abbreviations: n, number of patients; PET, positron emission tomography; SUVmax, maximum standardized uptake value.

In the group of patients with lymph node involvement identified through preoperative PET/CT ($n = 33$), factors linked to the presence of true-positive lymph nodes with pathologically confirmed metastasis were assessed using the Firth penalized logistic regression model (Table 3). The analysis revealed that a larger primary tumor diameter measured on PET/CT was independently correlated with true-positive lymph node metastasis (OR 1.74, 95% CI 1.12-2.91; $p = 0.018$). Furthermore,

extracapsular extension (OR 2.96; 95% CI 1.01-8.67; $p = 0.048$) and pathological Stage III disease (OR 3.21; 95% CI 1.12-9.24; $p = 0.031$) significantly increased the probability of true-positive nodal involvement (Table 4). Conversely, factors such as primary tumor SUVmax ($p = 0.11$), histological subtype (squamous vs. adenocarcinoma; $p = 0.64$), LVI ($p = 0.42$), PNI ($p = 0.51$), and pleural involvement ($p = 0.41$) were not independently significant in the model (Table 3).

Table 3. Factors associated with true-positive lymph node metastasis in PET-positive patients: Firth penalized logistic regression analysis

Variable	OR	95% CI	p-value
Primary tumor SUVmax	1.08	0.98 – 1.21	0.11
Tumor diameter on PET (cm)	1.74	1.12 – 2.91	0.018
Histology (squamous vs adenocarcinoma)	1.31	0.42 – 4.10	0.64
Lymphovascular invasion (present)	1.58	0.51 – 4.88	0.42
Perineural invasion (present)	1.44	0.47 – 4.39	0.51
Pleural involvement (present)	1.67	0.49 – 5.64	0.41
Extracapsular extension (present)	2.96	1.01 – 8.67	0.048
Pathological Stage III	3.21	1.12 – 9.24	0.031

Abbreviations: CI, confidence interval; OR, odds ratio; PET, positron emission tomography; SUVmax, maximum standardized uptake value.

When intraoperative dissection results and PET/CT-pathology concordance were evaluated according to lymph node stations, lymph node involvement on preoperative PET/CT was most frequently observed in stations 4, 10, and 11, whereas the stations with the highest number of lymph nodes removed intraoperatively were stations 10 and 11. These stations also had the highest pathological metastasis rates (Table 4). However, the concordance between PET/CT and pathological confirmation showed marked

differences among the stations. In particular, the relatively high number of PET(+)/pathology(-) cases in stations 4 and 10 indicated higher false-positive rates in these stations (4R: 9, 4L: 2 false-positive). In contrast, the greater number of PET(+)/pathology(+) cases in stations 7 and 11 indicated that PET/CT had a higher accuracy for metastatic involvement in these stations (Table 4). In the upper mediastinal stations (stations 2 and 3), both PET positivity and pathological metastasis rates were low (Table 4).

Table 4. Surgical lymph node dissection and PET/CT–pathology concordance according to lymph node stations

Lymph node station	Retrieved LNs (n)	Pathologically positive LNs (n)	Pathologically negative LNs (n)	Preoperative PET (+) (n)	PET (+) / PATH (+) (n)	PET (+) / PATH (-) (n)	PET (-) / PATH (+) (n)
LN station 2	7	0	7	0	0	0	0
LN station 3	26	3	23	0	0	0	1
LN station 4	84	9	75	11	2	9	2
LN station 5	93	15	78	4	1	3	2
LN station 6	24	1	23	0	0	0	0
LN station 7	79	9	70	6	4	2	3
LN station 8	55	3	52	0	0	0	0
LN station 9	73	2	71	1	0	1	1
LN station 10	187	27	160	15	6	9	0
LN station 11	183	55	128	7	3	4	8

Abbreviations: LNs, lymph nodes; n, number; PATH, pathologically; PET, positron emission tomography.

DISCUSSION

Inconsistencies encountered in PET/CT imaging are critical factors that directly affect the treatment strategy for lung cancer staging. The PPV of PET/CT in NSCLC staging is relatively low (47-80%). This situation results from the intense FDG uptake by inflammatory cells, especially in regions where granulomatous diseases, such as tuberculosis, are endemic (7,8). These discordant situations are generally examined under two main categories: false-negative and false-positive results.

False negativity refers to the situation in which no pathological FDG uptake is detected in a lymph node on PET/CT, but metastasis is identified on histopathological examination performed after surgery or biopsy (PET negative, pathology-positive LN), and this condition is also referred to as “occult” N2 disease in the clinical literature (5,9). This situation may lead to an underestimation of the disease stage (downstaging), directing the patient to surgery without receiving induction therapy that may actually be required, and encountering a “surprise N2” finding during or after surgery, thereby negatively affecting the postoperative prognosis (1,9). In our study, false negativity was

observed, particularly in stations 7 and 11. This finding indicates that PET/CT may be insufficient to exclude micrometastatic disease in these stations and that PET/CT negativity does not reliably rule out nodal metastasis in these patients. In the upper mediastinal stations (stations 2 and 3), both PET positivity and pathological metastasis rates were low.

False positivity refers to the situation in which high FDG uptake is observed in a lymph node on PET/CT (generally SUVmax > 2.5), but no cancer cells are detected on pathological examination, and the node is found to be benign (PET positive-Pathology, pathology-negative LN) (1). This situation may lead to the patient being mistakenly considered as having advanced-stage disease, losing the chance of surgical treatment, and receiving unnecessary chemoradiotherapy (10). Therefore, histopathological confirmation of every PET-positive node with EBUS-TBNA or mediastinoscopy before surgery is vital importance (10-12). Surgical lymph node dissection is the standard approach for mediastinal staging (13). It not only confirms the accuracy of staging but also reduces tumor burden, provides local control, and offers the most reliable data to

determine whether the patient needs adjuvant therapy (14,15). In our study, the high number of PET(+)/pathology(-) cases, especially in stations 4 and 10, showed that false-positive rates were high in these stations.

In the mediastinal staging of lung cancer, 18F-FDG PET/CT demonstrates a much superior performance than computed tomography (CT) by combining anatomical data with metabolic activity (16). However, the literature emphasizes that this method is not always reliable when used alone and that the results should be interpreted carefully. In the literature, sensitivity rates range between 58% and 94% (17,18). Since FDG uptake is not specific to cancer, specificity reported in the literature varies widely, ranging from 43% to 96% (19,20). In the literature, the positive predictive value of PET/CT ranges between 47% and 81%, whereas the negative predictive value ranges between 78% and 98% (17). In our study, except for specificity, the sensitivity of PET/CT in detecting lymph node metastasis was calculated as 89.5%, specificity as 11.1%, PPV as 51.5%, NPV as 50%, and overall diagnostic accuracy as 51.4%, in parallel with the literature.

The false-positive rates of PET/CT reported in the literature range between 8.9% and 54.8% (21). The most important causes of these conditions are tuberculosis, sarcoidosis, anthracosis, and infectious pneumonia (22). In addition, being older than 65 years, smoking, and having a high white blood cell (WBC) count increase the risk of false-positive results (23). False negativity has been reported in the literature to be between 7% and 25% (24). The main causes are micrometastases smaller than 4–5 mm, adenocarcinomas with low metabolic activity, and uncontrolled diabetes (25). In our study, among the 33 patients with lymph node positivity on PET/CT, metastasis was pathologically confirmed in 17 patients (51.5%) (true positive), whereas histopathological metastasis was not detected in 16 patients (48.5%) (false-positive). Ninety percent of the PET-positive but pathologically negative lymph nodes were reported as reactive, 8% as granulomatous lymphadenitis, and 2% as anthracosis. PET/CT false positivity was particularly prominent in lymph node stations 4 and 10. In patients with PET(+)/PAT(+), indicating true metastasis, the primary tumor SUVmax was higher, tumor diameter was larger, extracapsular extension was more frequent, and Stage III disease was more predominant. Additionally, the relatively high pneumonectomy rate in our study was mainly attributable to centrally located tumors and advanced hilar or bronchovascular involvement, which limited the feasibility of parenchyma-sparing sleeve resections in our cohort.

Our study is strong in that PET/CT findings were directly compared with the surgical and histopathological gold standard, true-positive and false-positive cases were analyzed separately, it provides direct contribution to clinical decision processes, and statistical bias was reduced by using Firth logistic regression despite the small sample size.

Limitations

However, our study had some limitations. The retrospective and single-center design of the study, relatively small patient population, possibility of variability in PET/CT evaluation among reporting physicians, absence of preoperative invasive mediastinal staging, and lack of long-term survival data are limitations of our study.

CONCLUSION

In conclusion, although preoperative PET/CT has high sensitivity for lymph node staging in patients with NSCLC, the false-positive rates were notably high. The confirmation of pathological metastasis in only approximately half of the patients with lymph node positivity on PET/CT indicates that PET-positive nodes alone may be insufficient to guide treatment decisions. Increased FDG uptake due to inflammatory and reactive causes, especially in the mediastinal and hilar stations, appears to be the main factor limiting specificity. These findings emphasize that although PET/CT is a valuable screening tool for nodal staging, histopathological confirmation before surgery or invasive procedures is indispensable. In clinical practice, evaluating PET/CT results using a multidisciplinary approach is critically important to prevent incorrect staging and the loss of potential curative surgical opportunities.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that there is no financial support.

Ethical Approval

This research was conducted in accordance with the Ethics Committee of the Firat University Scientific Research and Publication Ethics Board (2026/02-30) (approval date: 05 February 2026).

Informed Consent

This study was retrospective and based on the analysis of previously collected clinical data. All patient information was anonymized, and no additional interventions were performed. Therefore, the requirement for informed consent was waived by the institutional ethics committee.

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