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Lung: Short Report

Utility of PET for Nodal Staging in Subsolid Clinical Stage IA (T1 N0) Lung Adenocarcinoma

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ABSTRACT

BACKGROUND Positron emission tomography (PET) is the standard of care for non-small cell lung cancer (NSCLC) clinical staging, but it may have limited utility in evaluating subsolid lung adenocarcinomas that can have relatively indolent behavior without hypermetabolic activity.

METHODS The sensitivity and specificity of PET for determining pathologic lymph node status and disease-free survival were assessed in patients operated on for cT1 N0 subsolid lung adenocarcinoma from January 2006 to June 2022 (at Stanford University School of Medicine, Stanford, CA). Patients with clinical or pathologic tumor size >30 mm, hilar or mediastinal lymph node size >1cm, and purely solid tumors were excluded.

RESULTS PET was available in 498 of 534 (93.2%) patients and more often was used in older patients with larger and more solid tumors. The overall pathologic lymph node–positive rate was 8.4% (45 of 534). PET specificity was 95.1%, but sensitivity was only 20.0%. A tumor diameter of 18.5 mm and a solid component percentage of 62.5% had the maximum predictive accuracy for pathologic lymph node positivity, with a 0% and 1.5% rate of pathologic and PET lymph node positivity, respectively, for tumors with values lower than those thresholds. There was no significant difference in 5-year disease-free survival between individuals who did and did not undergo PET scanning (76.6% vs 96.8%; $P = .07$). Conversely, 134 (26.9%) patients who underwent PET scanning had 171 incidentally detected hypermetabolic lesions unrelated to lung cancer, with only 13 of 134 (9.7%) patients identified as having non-NSCLC premalignant or malignant conditions requiring further therapy.

CONCLUSIONS PET scan use for subsolid lung adenocarcinoma has high specificity but limited sensitivity for predicting pathologic lymph node positivity. PET also has no association with disease-free survival and often detects clinically unimportant findings rather than changing lung cancer management, particularly for patients with smaller and less solid tumors.

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Accurate clinical staging is critically important in directing management of non-small cell lung cancer (NSCLC). An integral component of noninvasive NSCLC clinical staging is 18-fluorine fluorodeoxyglucose (FDG) positron emission tomography (PET) combined with computed tomography (CT), which has demonstrated a 20% reduction in "futile thoracotomies"

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Abbreviations and Acronyms

CT = computed tomography
DFS = disease-free survival
FDG = fluorodeoxyglucose
IQR = interquartile range
LN = lymph node
LUAD = lung adenocarcinoma
MTD = maximum tumor diameter
NSCLC = non-small cell lung cancer
PET = positron emission tomography

IN SHORT

- FDG PET imaging in subsolid LUADs demonstrates high specificity but poor sensitivity for nodal staging, with no impact on DFS.
- Patients with subsolid nodules ≤18.5 mm and with a ≤62.5% solid component have minimal risk of LN involvement, a finding suggesting that FDG PET may potentially be deferred in these cases.
- FDG PET frequently detects clinically insignificant distant lesions, leading to unnecessary interventions and health care costs.

among patients with potentially resectable NSCLCs vs the use of CT alone.[1] Consequently, integrated PET with CT is currently the standard of care for clinical staging of NSCLCs.[2] However, PET use may not provide similar benefits across the entire spectrum of patients with NSCLC. Notably, the 20% rate of reduction in futile thoracotomies was observed in studies that included resectable stage IA to IIIA tumors, in contrast to studies limited to patients with stage IA tumors that observed only a 7.4% reduction.[3] In addition, routine PET use has potential limitations regarding the financial and psychological burden associated with detection of false positive lesions.

The utility of PET in directing care may also vary with tumor histologic type because NSCLC encompasses several pathologic types and subtypes. Specifically, the impact of using PET for lung adenocarcinomas (LUADs) that are pure ground-glass nodules or have a partly solid imaging appearance is unclear. These LUADs often have a lepidic-type histologic component and behave less aggressively than other adenocarcinomas and NSCLC subtypes.[4] Although both National Comprehensive Cancer Network and Fleischner guidelines recognize that PET may be unnecessary if there is not a significant solid component in LUADs with a partly solid imaging appearance, studies exploring the utility of PET for nodal staging of patients with subsolid nodules[4-7] are limited, and therefore data on diagnostic performance of PET for nodal staging of subsolid nodules are relatively scarce. This study was undertaken to examine the diagnostic performance of PET in nodal staging of cT1 N0 subsolid nodules suspected to be on the adenocarcinoma spectrum and determine whether PET use provides a disease-free survival (DFS) benefit.

PATIENTS AND METHODS

PATIENTS AND DATA. After obtaining Stanford University Institutional Review Board approval (IRB-70048), which waived the need for patient consent because the study involved only retrospective chart reviews, 1101 consecutive patients who underwent surgical resection of subsolid lung nodules between January 2006 and May 2022 at Stanford University School of Medicine (Stanford, CA) were retrospectively reviewed. Only patients aged ≥18 years and confirmed histopathologically as having LUAD were included. Patients with clinical and pathologic maximum tumor diameter (MTD) >30 mm, with distant metastases, and who received neoadjuvant chemoradiotherapy were excluded. Patients with subsolid nodules with >90% solid component or nonavailability of CT scans for calculating the percentage of solid component in nodules were also excluded from this study. The percentage of solid component represents the solid area within the entire tumor cross-section. Patients with hilar or mediastinal lymph nodes (LNs) >1 cm (ie, LN positive [≥N1] according to standard CT guidelines) were also excluded from this study.

Retrospective data on demographic, clinical, radiologic/or PET, and pathologic characteristics were collected from the electronic health records. The general practice for LN assessment for all lung cancer resections over the study period was multinodal station dissection, with LN sampling that included frozen section assessment used in selective fashion. The extent of resection necessary for each patient was determined by the surgeon's assessment of whether a sublobar resection could achieve an adequate margin on the basis of the size and location of the nodule. There was a trend over the study period away from lobectomy for all patients with early-stage NSCLC on the basis of accumulating evidence that sublobar resection did not compromise outcomes in certain conditions, including for small and partly solid nodules.

PRIMARY AND SECONDARY OUTCOMES. The primary outcome of the study was the diagnostic performance (sensitivity, specificity, and accuracy) of

PET in detection of LN metastases of subsolid lung nodules.

Additional methods can be found in the Supplemental Materials.

RESULTS

BASELINE PATIENT CHARACTERISTICS AND OUTCOMES STRATIFIED BY PET USE. Overall, 534 patients met study criteria, and 498 (93.2%) of these patients received a PET scan for clinical staging at a median of 28 days (interquartile range [IQR],14-55 days) before surgery. The patients who received a PET scan were significantly older (68.8 years [IQR, 62.7-74.9 years] vs 65.5 years [IQR, 53.0-69.6 years]; $P = .002$), had a higher pathologic MTD (17.0 mm [IQR, 12.0-22.0 mm] vs 10.0 mm [IQR, 8.0-13.7 mm]; $P < .001$), and had a higher solid component percentage (70.0% [IQR, 25.0%-85.0%] vs 22.5% [IQR, 10.0%-67.5%]; $P < .001$) (Supplemental Table 1).

Of these 534 patients, 45 (8.4%) had pathologically positive LN involvement (26 [4.9%], pN1; 19 [3.6%], pN2). None of the patients who did not have a PET scan had pathologically positive LNs, whereas 9% patients (45 of 498) of the patients who had a PET scan had a positive pathologic NL. There was no significant difference in the 5-year DFS (76.6% [72.1%-81.3%] vs 96.8% [90.7%-100%];, $P = .07$) and 5-year overall survival (88.7% [85.4%-92.2%] vs 96.8% [90.7%-100%];, $P = .52$) between individuals who received a PET scan and those who did not (Supplemental Figure 1).

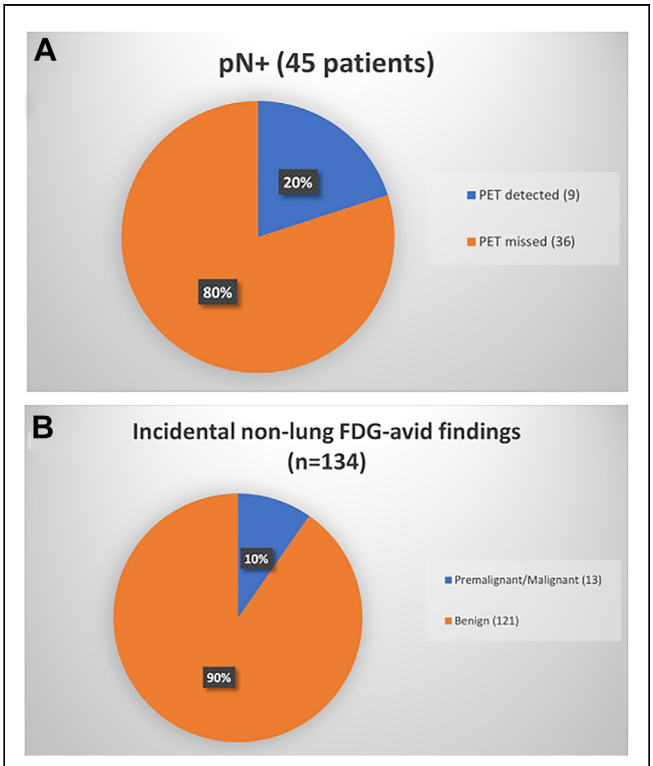

FIGURE Pie charts depicting that (A) 80% of patients with pathologic lymph node–positive (pN+) disease were missed by fluorodeoxyglucose (FDG) positron emission tomography (PET) and (B) >90% of patients with incidentally detected FDG-avid distant lesions had benign disease.

DIAGNOSTIC PERFORMANCE OF PET FOR NODAL STAGING AND PREDICTORS OF PATHOLOGIC LYMPH NODE INVOLVEMENT. The incidence of PET-positive LNs was 6.2% (31 of 498). Supplemental Table 2 shows the baseline characteristics of patients who received PET stratified by PET LN status. Older age, larger tumor size, and increased solid component were independent predictors of LN positivity on PET (Supplemental Table 3). The 5-year DFS (77.6% [73.1%-82.5%] vs 60.7% [42.8%-86.2%]; $P = .03$) and 5-year overall survival (89.8% [86.4%-93.3%] vs 72.7% [55.6%-95.2%]; $P < .001$) were significantly higher in the patients who were identified as PET negative for LN involvement compared with those identified as LN positive (Supplemental Figure 2).

The specificity of PET in detecting pathologic LN involvement was 95.1%, but sensitivity was only 20.0% (Figure A). The positive predictive value, negative predictive value, and accuracy are presented in Table 1. PET LN positivity was not an independent predictor of pathologic LN involvement (Supplemental Table 4). Moreover, the area under the receiver operating curve (with 95% CI) of PET LN positivity demonstrated poor accuracy (0.56% [0.47%-0.67%];, $P = .20$) for predicting pathologic LN involvement, whereas MTD, percentage of solid component, and primary tumor maximum standardized uptake value demonstrated moderate accuracy (Supplemental Figure 3).

The receiver operating curve analysis using the Youden Index identified optimal values for MTD (18.5 mm) and percentage of solid component (62.5%), with the highest accuracy for predicting both PET and pathologic LN positivity. In patients with MTD <18.5 mm and a solid component percentage of <62.5%, there was a 0% rate of pathologic LN positivity and a 1.5% rate of PET LN positivity (Table 2).

DETECTION OF INCIDENTAL LESIONS. There were 171 incidentally detected FDG-avid distant lesions unrelated to lung cancer in 134 of 498 (26.9%) of patients who underwent PET scanning. The most frequent sites of the detected 171 distant

TABLE 1 The Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy of Positron Emission Tomography for Lymph Nodal Staging in Patients With Subsolid cT1 N0 Lung Adenocarcinoma

PET Status	Pathologic LN-positive	Pathologic LN-negative	
PET-positive	9	22	PPV = 9/31 (29.0%)
PET-negative	36	431	NPV = 431/467 (92.3%)
	Sensitivity = 9/45 (20.0%)	Specificity = 431/453 (95.1%)	Accuracy = 440/498 (88.3%)

LN, lymph node; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value.

lesions were LNs (cervical, axillary, or inguinal: 30 [17.5%]), thyroid (27 [15.8%]), bone (20 [11.7%]), oronasopharynx (15 [9.0%]), spine or vertebra (13 [7.6%]), adrenal (12 [7%]), and lower (11 [6.4%]) and upper (10 [5.8%]) gastrointestinal tract. Only 9.7% (13 of 134) of these patients were confirmed to have other non-NSCLC premalignant or malignant conditions (Figure B). An invasive biopsy was performed in 34 of 134 (25.4%) patients, whereas 82 of 134 (61.2%) were evaluated with follow-up imaging and 18 of 134 (13.4%) were clinically determined to have insignificant findings requiring no further follow-up.

COMMENT

Use of PET to stage and direct therapy of patients with resectable NSCLC accurately is well accepted, but its utility for subsolid adenocarcinomas is less clear. Our study shows that PET scans for patients who underwent resection of small subsolid adenocarcinomas has high specificity but poor sensitivity for LN involvement, by failing to detect 80% of the LN metastases and, notably, none of 19 mediastinal LN metastases while also not affecting DFS. Conversely, PET frequently detected non-NSCLC distant lesions that sometimes resulted in invasive biopsies but were predominantly clinically insignificant.

Previous studies also demonstrated PET to have low sensitivity of 0% to 44% for nodal staging of subsolid adenocarcinomas,[4-7] substantially lower than that observed in NSCLCs overall (~75%). The low positive predictive value may reflect the low rate of LN metastases (8.4%), in line with 2.3% to 10.5% rate in other studies of subsolid nodules,[5,7] but less than the 10% to 25% rate of nodal upstaging for stage I lung cancer with unsuspected LN metastases.[8] Consistent with these data, a realist synthesis analysis of major randomized controlled trials of PET for NSCLCs showed that the role of PET in staging NSCLCs was only in those findings with a moderate or high degree of suspicion for detecting LN and distant metastases.[9]

One finding of this study was that patients with MTD <18.5 mm and a solid component percentage of <62.5% had an extremely low rate of pathologic and PET LN positivity. Current National Comprehensive Cancer Network guidelines recommend the use of PET for stage I to IV NSCLC, although they make an exception for pure ground-glass nodules and partly solid nodules with a solid component <6 mm. Our results support an even more selective approach that incorporates an MTD of 18.5 mm and a solid component percentage of 62.5%, given their high accuracy in predicting PET and pathologic LN positivity and the extremely low rate of PET and pathologic LN positivity at values lower than these thresholds.

Despite the high specificity of PET for nodal staging, as in other studies of subsolid nodules (81.5%-98%),[4,6,7] PET for NSCLCs often results in false upstaging to M1.[10] Much the same, our study also showed that PET frequently detects distant lesions that are most often benign.

TABLE 2 The Rate of Positron Emission Tomography and Pathologic Lymph Node Positivity on the Basis of the Optimal Thresholds of Maximum Tumor Diameter and Percentage of Solid Component

		Pathologic LN Positivity		PET LN Positivity	
Optimal Thresholds		Yes	No	Yes	No
MTD <18.5 mm *and* solid component percentage <62.5%	Yes	0/159 (0%)	159/159 (100%)	2/134 (1.5%)	132/134 (98.5%)
	No	45/375 (12%)	330/375 (88%)	29/364 (8%)	335/364 (92%)

LN, lymph node; MTD, maximum tumor diameter; PET, positron emission tomography.

Detection of such lesions not only lacks an impact on lung cancer treatment, but also results in invasive biopsies, delay in definitive management, and increased health care costs. Although these incidental findings did not alter lung cancer management, it is possible that some patients may have been falsely assumed to have metastatic disease on the basis of an incidental PET finding, and they never received potentially curative care of their early-stage disease.

The study findings should be interpreted considering the following limitations. First, this was a single-institution study with a limited sample size. Therefore, further validation using larger, multiinstitutional data sets is necessary. Second, there was a selection bias given the inclusion of only patients who underwent surgery rather than those prescribed to undergo PET or CT. Some patients with small subsolid nodules may have had a PET scan that revealed more extensive disease such that treatment was appropriately adjusted away from primary surgery. Third, the criteria used in reporting LN status on PET precludes determination of the exact maximum standardized-uptake value threshold and characteristics used for determining LN positivity. Finally, the already somewhat selective use of PET by surgeons in this study suggests that PET may occasionally be used to investigate a specific clinical suspicion that ultimately influenced the decision to proceed with surgery, and PET may therefore have had some unmeasured utility. However, a strength of the study is the inclusion of a relatively large group of patients whose specific PET and pathologic data are available for analysis.

In conclusion, our study demonstrates that PET use for subsolid adenocarcinomas has high specificity but limited sensitivity for nodal staging and is not associated with DFS. Furthermore, in patients with subsolid nodules $\leq$18.5 mm and with a $\leq$62.5% solid component, PET is unlikely to detect LN metastases because of their low prevalence. PET scans for these cancers detect clinically unimportant findings more often than they change lung cancer management, particularly for smaller and less solid tumors. Although current guidelines recognize the limited utility of PET in some cases of partly solid LUADs, our study provides more specific criteria for when PET use can likely be deferred.

The Supplemental Material can be viewed in the online version of this article [https://doi.org/10.1016/j.atssr.2024.07.007] on http://www.annalsthoracicsurgery.org.

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