European Radiology (2019) 29:5288–5297
https://doi.org/10.1007/s00330-019-06128-5

NUCLEAR MEDICINE

Comparison of prognostic values of primary tumor and nodal ^{18}F-fluorodeoxyglucose uptake in non-small cell lung cancer with N1 disease

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Received: 29 November 2018 / Revised: 23 January 2019 / Accepted: 25 February 2019 / Published online: 21 March 2019

Abstract

Introduction We hypothesized that, in non-small cell lung cancer (NSCLC) with N1 metastasis, N1 nodal ^{18}F-fluorodeoxyglucose (FDG) status offers independent and incremental prognostic value.

Methods We enrolled 106 NSCLC patients with pathology-confirmed N1 metastasis. N1 node FDG positivity, primary tumor maximum standard uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were measured. Kaplan-Meier method and Cox regression analyses were performed for cancer-specific survival (CSS) and disease-free survival (DFS).

Results Subjects were 67 males and 39 females (61.9 ± 9.4 years). Eighty-one (76.4%) and 25 (23.6%) had pathologic stage IIB and IIIA NSCLC, respectively. All underwent complete tumor resection. FDG-positive N1 nodes were larger and had higher primary tumor SUV_{max}. During a follow-up of 42 months, there were 56 recurrences and 31 cancer deaths. Significant univariate predictors were stage, no adjuvant therapy, and FDG-positive nodes for DFS, and stage, no adjuvant therapy, node size, tumor MTV, TLG, and SUV_{max}, and FDG-positive nodes for CSS. Independent predictors on multivariate analyses were FDG-positive nodes (HR = 3.071, $p = 0.003$), greater tumor TLG (HR = 3.224, $p = 0.002$), and no adjuvant therapy (HR = 3.631, $p < 0.001$) for poor CSS, and FDG-positive nodes (HR = 1.771, $p = 0.040$) and no adjuvant therapy (HR = 2.666, $p = 0.002$) for poor DFS. Harrell's concordance and net reclassification improvement tests showed that CSS prediction was significantly improved by the addition of N1 FDG status to a model containing tumor TLG.

Conclusion N1 node FDG status can be useful for predicting the outcome of NSCLC patients with N1 metastasis beyond that provided by other prognostic variables.

Key Points

- *In NSCLC with N1 disease, N1 node FDG status is useful as a prognostic predictor.*
- *FDG-positive N1 nodes provide additional prognostic value beyond TLG of primary tumor.*
- *Combining TLG of primary tumor and N1 node uptake can stratify the survival of patients.*

Keywords Lung cancer · Positron emission tomography · Fluorodeoxyglucose F18 · Lymph nodes

Abbreviations

C-index	Concordance index
CSS	Cancer-specific survival
DFS	Disease-free survival
ECOG	Eastern Cooperative Group
FDG	^{18}F-Fluorodeoxyglucose
LNs	Lymph nodes
MTV	Metabolic tumor volume
NRI	Net reclassification improvement
NSCLC	Non-small cell lung cancer
PET/CT	Positron emission tomography/computed tomography
ROC	Receiver operating characteristics
SUV_{max}	Maximum standard uptake value
TLG	Total lesion glycolysis

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Introduction

In non-small cell lung cancer (NSCLC), involvement of draining lymph nodes (LNs) results in a more advanced stage of disease that adversely affects patient outcome [1]. However, N1 disease in NSCLC is associated with a relatively wide range of 5-year survival between 34 and 54% [2]. This is affected by several factors including histologic cell type, T stage, number of involved nodes, and nodal involvement through direct invasion or distinct metastasis [3–10].

^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has become an important modality for evaluating cancer disease, and measuring tumor FDG uptake as the maximum standard uptake value (SUV_{max}) can help assess patient prognosis. In lung cancer, several recent studies report that metabolic tumor volume (MTV) and total lesion glycolysis (TLG) may be superior to SUV_{max} for predicting patient outcome [11–13].

Some researchers have suggested that the metabolic tumor burden of the whole body including all primary and metastatic lesions might have greater prognostic value than measurements of primary lung tumor FDG uptake alone [14]. Furthermore, NSCLC patients with confirmed N1 metastasis have shown poorer outcomes when the N1 nodes are FDG positive versus FDG negative [15]. These findings imply a potential prognostic role for metastatic N1 node FDG status in patients with NSCLC. However, researchers have not proven that nodal FDG positivity offers prognostic value independent of and incremental to other variables including magnitude of primary tumor FDG uptake.

In this study, we thus investigated NSCLC patients with pathologic N1 disease and compared the preoperative PET/CT values of primary tumor FDG uptake level and N1 node FDG status for predicting survival following curative surgery.

Materials and methods

Study population

We retrospectively reviewed a total of 3153 consecutive patients who underwent FDG PET/CT for newly diagnosed NSCLC at our institution between 2008 and 2013. Among them, 254 patients with pathology-confirmed N1 disease but no evidence of distant metastasis (M1 disease) as determined by FDG PET/CT, bone scintigraphy, brain MRI, or contrast-enhanced CT were included. All of these subjects underwent complete tumor resection with systematic lymphadenectomy. During operation, mediastinal staging was performed by mediastinal LN dissection. This consisted of en bloc resection of all nodes at stations 2R, 4R, 7, 8, 9, and 10R for right-sided tumors and nodes at stations 4L, 5, 6, 7, 8, 9, and 10L for left-sided tumors [15]. Based on this information, we included subjects who had N1 disease but did not have N2 involvement.

Exclusion criteria were N1 involvement through direct extension of primary tumor ($n = 115$), neo-adjuvant treatment ($n = 25$), and history of or concurrent second malignancy ($n = 8$). Consequently, a total of 106 NSCLC patients with N1 disease separate from the primary tumor were included for analysis. This retrospective observational study was approved by the Institutional Review Board of Samsung Medical Center with exemption for written consent from study subjects.

FDG PET/CT imaging

All patients fasted for at least 6 h and had blood glucose level < 150 mg at the time of PET/CT. Imaging was performed 60 min after injection of 5 MBq/kg FDG without intravenous or oral contrast on a Discovery LS (GE Healthcare, $n = 35$) or a Discovery STe PET/CT scanner (GE Healthcare, $n = 71$). Continuous spiral CT was performed with an 8-slice helical CT (140 keV; 40–120 mA; Discovery LS) or 16-slice helical CT (140 keV; 30–170 mA; Discovery STe). An emission scan was then obtained from head to thigh or foot for 4 min per frame in 2D mode with reconstruction of attenuation-corrected PET images (4.3 × 4.3 × 3.9 mm). Reconstruction was conducted using an ordered subset expectation maximization algorithm (28 subsets, 2 iterations; Discovery LS). Alternatively, 2.5 min per frame in 3D mode with reconstruction of attenuation-corrected PET images (3.9 × 3.9 × 3.3 mm) was used with a 3D ordered subset expectation maximization algorithm (20 subsets, 2 iterations; Discovery STe).

Review of PET images and analysis of FDG uptake

The image interpretation and measurement of tumor uptake were performed by two nuclear medicine physicians with more than 5 years of experience (C.H.L and S.H.H), who were blinded to the patients' clinical outcomes. Primary tumor SUV_{max}, MTV, and TLG were measured using volume viewer software on a GE Advantage Workstation version 4.4. This software allows automatic determination of volumes of interest using an SUV-based isocontour threshold method. After a volume of interest was placed over the primary lung cancer, the software measured SUV_{max}, average SUV (SUV_{avg}), and MTV of the entire primary tumor. MTV was defined as the tumor volume with FDG uptake segmented above a threshold SUV of 2.5. TLG was calculated as the product of MTV and SUV_{avg}.

The metastatic N1 LN on the pathologic report was evaluated for FDG uptake according to the International Association for the Study of Lung Cancer (IASLC). C.H.L and S.H.H independently visually assessed whether N1 nodes had increased FDG uptake that was discernable from

background activity. Disagreements were resolved by discussion to reach a consensus.

To minimize false positive results, we used a stringent criterion for N1 node FDG positivity that required the absence of high attenuation (> 70 HU) or gross calcification of the nodes, and no fibrotic or calcified lung lesions on CT. We also repeated analysis applying a less stringent criterion that considered any N1 node with focal uptake greater than background activity ($SUV_{max} \geq 2.5$) as positive, irrespective of CT findings.

Medical record review

Clinical information, tumor characteristics, and survival data were obtained from medical records. Patient characteristics comprised age, sex, Eastern Cooperative Group (ECOG) performance, smoking history, method of surgery, and employment of adjuvant treatment. Tumor characteristics included histologic type, pathologic stage, pathologic size, and number of involved N1 LNs. TNM stage was based on the eighth edition of the TNM Lung Cancer Staging System. Primary endpoints of interest were cancer-specific survival (CSS) and disease-free survival (DFS). CSS was defined as the time from surgery to death attributed to lung cancer. In the analysis of CSS, patients who died of other causes or were alive at the last follow-up were counted as censored observations. DFS was defined as the time from surgery to date of tumor recurrence. In the analysis of DFS, patients who were alive at the last follow-up were counted as censored observations.

Statistical analyses

The significance of differences in variables between groups was assessed by Student's *t* tests, Pearson chi-square tests, or Fisher's exact tests. Receiver operating characteristic (ROC) analysis determined the optimal cut-off values of variables for predicting patient survival. Univariate analysis for significant prognostic factors was performed by the Kaplan-Meier method with log-rank tests. Significant univariate variables ($p < 0.05$) were included for multivariate analysis using the Cox proportional hazards regression model. The incremental value of significant variables for improving predictive accuracy was compared by the 5-year Harrell concordance index (C-index) [16] and the net reclassification improvement (NRI) index [17] using R packages "compareC" and "survIDINRI," respectively. All statistical tests were two-sided with a significance level set at 0.05 and were performed with SPSS 23.0 (SPSS Inc.), MedCalc 15.5 (MedCalc), or R 3.4.3 software (Institute for Statistics and Mathematics).

Results

Clinical and pathological features

Subjects for this study were 67 males and 39 females with a mean age of 61.9 ± 9.4 years. There were 69 smokers (65.1%), and five patients (4.7%) had poor performance status (ECOG 2–3). Other clinical characteristics and PET parameters are summarized in Table 1. Eighty-one patients (76.4%) had pathologic stage IIB disease (34 had T1 and 47 had T2 stage tumors), while 25 (23.6%) had IIIA NSCLC (T3–4). The histologic type was adenocarcinoma in 52 cases (49.1%) and non- adenocarcinoma in 54 cases (50.9%); squamous cell carcinoma was diagnosed in 39 cases. After complete tumor resection, adjuvant treatment was given in 83 cases (78.3%) and was refused in the remaining 23 cases. Adjuvant treatment comprised chemotherapy ($n = 76$), concurrent chemoradiation therapy (CCRT; $n = 5$), and radiotherapy ($n = 1$). Median surgical follow-up was 42 months (range 2–91 months). During this interval, 56 recurrences (52.8%; 31 local and 25 distant) and 32 deaths (30.2%) occurred. All deaths were NSCLC-related except for a single patient who died from acute cholecystitis with gall bladder perforation.

N1 nodal FDG status

Quantitative measurements showed that a total of 46 subjects had N1 nodal $SUV_{max} \geq 2.5$. Visual assessment for discernable N1 node FDG uptake by two nuclear medicine physicians showed high inter-observer agreement. There were only two cases of disagreement (both cases with nodal SUV_{max} of 2.3) that later reached consensus as being FDG negative. Comparison demonstrated a perfect concordance between SUV_{max}-based and visual identification of N1 nodes that had significant FDG uptake.

In order to minimize the influence of inflammatory lesions, we used a stringent criterion of excluding cases ($n = 5$; 10.9%) with high nodal attenuation or calcified lung lesions from the nodal FDG-positive group. Hence, using this criterion, 41 N1 nodes were finally categorized as FDG positive. We also performed additional analysis using a less stringent criterion of including all 46 cases with N1 nodal $SUV_{max} \geq 2.5$ as FDG positive.

Comparison of clinical variables according to nodal FDG uptake

Clinical characteristics of the total study population and subjects divided into N1 node FDG-positive and FDG-negative groups are summarized in Table 1. No difference in number of involved N1 nodes or TNM stage between groups was identified. However, FDG-positive nodes were significantly larger ($p = 0.002$) and were more often linked with non-

Table 1 Clinical characteristics and PET parameters according to N1 node FDG uptake

	Total (%)	Node uptake + ($n = 41$)	Node uptake − ($n = 65$)	p value
Histology				*0.041*†
Adenocarcinoma	52 (49.1%)	15 (36.6%)	37 (56.9%)	
Non-adenocarcinoma	54 (50.9%)	26 (63.4%)	28 (43.1%)	
N1 nodal size (mm)	6.3 ± 4.9	8.2 ± 5.4	5.0 ± 4.1	*0.002**
Number of involved nodes				0.228†
Single	67 (63.2%)	23 (56.1%)	44 (67.7%)	
Multiple	39 (36.8%)	18 (43.9%)	21 (32.3%)	
TNM stage (8th)				0.532†
Stage IIB (T1–2)	81 (76.4%)	30 (73.2%)	51 (78.5%)	
Stage IIIA (T3–4)	25 (23.6%)	11 (26.8%)	14 (21.5%)	
Primary tumor MTV (cm^3)	15.5 (4.0–38.1)	18.3 (5.5–44.2)	8.9 (3.6–28.8)	0.277*
Primary tumor SUV_{max}	9.4 (6.4–12.6)	10.6 (7.8–14.1)	7.9 (6.1–11.2)	*0.017**
Primary tumor TLG	62.5 (16.9–192.4)	110.9 (22.7–323.1)	34.3 (14.7–161.3)	0.402*
Cancer-specific deaths	31 (29.2%)	20 (48.8%)	11 (16.9%)	*< 0.001*†
Recurrences	56 (52.8%)	26 (63.4%)	30 (46.2%)	0.083†

MTV, metabolic tumor volume; *TLG*, total lesion glycolysis; *SUV*, standard uptake value. Data are numbers of patients (proportion) or median values (interquartile range). † Pearson's chi-square; *Student's t tests. Italic numbers indicate p values < 0.05

adenocarcinoma histology ($p = 0.041$) and greater primary tumor SUV_{max} ($p = 0.017$). Furthermore, patients with FDG-positive nodes were significantly more likely to have cancer-specific death ($p < 0.001$) and showed a tendency for greater tumor recurrence ($p = 0.083$), although not to a statistically significant degree.

When the less stringent criteria were applied for nodal FDG positivity, positive N1 nodes were larger ($p = 0.006$) and more often linked with greater primary tumor SUV_{max} ($p = 0.009$). Patients with FDG-positive N1 nodes according to the less stringent criteria were significantly more likely to have tumor recurrence ($p = 0.025$) and cancer-specific death ($p = 0.005$; data not shown).

Associations of variables with cancer-specific death and disease recurrence

Correlations of clinical variables with cancer-specific death and disease recurrence are shown in Table 2. ROC analyses showed that the optimal cutoff values for predicting cancer-specific death were 64 years for age, 7 mm for N1 node size, 10.7 for primary tumor SUV_{max}, 25.2 cm^3 for primary tumor MTV, and 222 for primary tumor TLG.

Using these cutoff values, patients with older age, male gender, poor performance status (ECOG 2–3), smoking history, larger nodal size, higher TNM stage (IIIA), higher primary tumor MTV, TLG, and SUV_{max}, and positive N1 node FDG uptake had significantly greater rates of cancer-specific death and shorter mean survival. Those with higher TNM stage and positive nodal FDG uptake had significantly greater rates of recurrence and shorter mean disease-free survival. Conversely, patients who received adjuvant treatment had significantly lower rates of cancer-specific death and recurrence and longer mean survivals.

Univariate and multivariate predictors of cancer-specific and disease-free survival

The p values of log-rank tests obtained from Kaplan-Meier survival analyses are shown in Table 2. Significant univariate predictors of decreased DFS were greater TNM stage ($p = 0.024$), no adjuvant therapy ($p < 0.001$), and positive nodal FDG uptake ($p = 0.008$). For decreased CSS, significant univariate predictors were greater TNM stage ($p < 0.001$), no adjuvant therapy ($p < 0.001$), older age ($p < 0.001$), male gender ($p = 0.002$), poor ECOG performance status ($p = 0.009$), smoking ($p < 0.001$), larger node size ($p = 0.007$), higher primary tumor MTV, TLG, and SUV_{max} (all $p < 0.001$), and positive nodal FDG uptake ($p < 0.001$). Significant associations of positive N1 node FDG uptake with decreased CSS and DFS were maintained when the less stringent criteria for nodal FDG positivity were used ($p = 0.002$ and 0.004, respectively). Kaplan-Meier survival curves according to primary tumor TLG and nodal FDG status are shown in Fig. 1. Representative patients with negative nodal FDG uptake and favorable outcome and with positive nodal FDG uptake and poor outcome are illustrated in Fig. 2.

On multivariate analyses, FDG-positive N1 nodes (HR = 3.071, $p = 0.003$), greater primary tumor TLG (HR = 3.224, $p = 0.002$), and no adjuvant therapy (HR = 3.631, $p < 0.001$)

Table 2 Correlation of clinicopathologic variables with cancer-specific and disease-free survival

	Variables	Cancer-specific survival			Disease-free survival		
		Deaths (%)	Survival (months)	*p*	Recurrences (%)	Survival (months)	*p*
Age[a]	≤ 64	8/58 (13.8)	74.3 ± 3.2	*< 0.001*	28/58 (48.3)	51.2 ± 4.3	0.067
	> 64	23/48 (47.9)	53.1 ± 5.5		28/48 (58.3)	42.0 ± 5.6	
Sex	Female	5/39 (12.8)	81.5 ± 4.0	*0.002*	22/39 (56.4)	48.3 ± 5.0	0.690
	Male	26/67 (38.8)	58.9 ± 4.6		34/67 (50.8)	46.5 ± 8.8	
ECOG	0–1	28/101 (27.7)	69.4 ± 3.4	*0.009*	52/101 (51.5)	46.6 ± 3.5	0.362
	2–3	3/5 (60.0)	33.3 ± 16.0		4/5 (80.0)	31.0 ± 19.3	
Smoking	−	3/37 (8.1)	85.0 ± 3.3	*< 0.001*	21/37 (56.8)	49.0 ± 4.9	0.545
	+	28/69 (40.6)	56.3 ± 4.5		35/69 (50.7)	46.5 ± 4.9	
Adjuvant therapy	+	17/83 (20.5)	75.6 ± 3.3	*< 0.001*	40/83 (48.2)	50.8 ± 3.7	*< 0.001*
	−	14/23 (60.9)	36.7 ± 7.5		16/23 (69.6)	28.2 ± 7.9	
Histologic type	Non-ADC	19/54 (35.2)	62.3 ± 5.0	0.118	24/54 (44.4)	52.3 ± 5.4	0.155
	ADC	12/52 (23.1)	73.1 ± 4.5		32/52 (61.5)	42.0 ± 4.6	
Nodal size[a]	≤ 7	15/70 (21.4)	74.2 ± 3.8	*0.007*	37/70 (52.9)	48.5 ± 4.3	0.493
	> 7	16/36 (44.4)	55.1 ± 6.4		19/36 (52.8)	40.7 ± 5.5	
Node involve no.	Single	19/67 (28.4)	67.3 ± 4.3	0.947	33/67 (49.3)	46.6 ± 4.4	0.824
	Multiple	12/39 (30.8)	68.0 ± 5.5		23/39 (59.0)	46.6 ± 5.9	
TNM stage (8th)	IIB (T1–2)	16/81 (19.8)	75.0 ± 3.6	*< 0.001*	39/81 (48.2)	50.8 ± 4.2	*0.024*
	IIIA (T3–4)	15/25 (60.0)	45.6 ± 6.8		17/25 (68.0)	34.4 ± 6.6	
Primary MTV[a]	≤ 25.2	13/71 (18.3)	76.2 ± 3.7	*< 0.001*	37/71 (52.1)	50.2 ± 4.3	0.202
	> 25.2	18/35 (51.4)	45.5 ± 3.4		19/35 (54.3)	38.5 ± 5.6	
Primary TLG[a]	≤ 222	16/81 (19.8)	75.6 ± 3.4	*< 0.001*	41/81 (50.6)	50.5 ± 4.1	0.057
	> 222	15/25 (60.0)	38.3 ± 5.9		15/25 (60.0)	33.1 ± 6.3	
Primary SUV_{max}[a]	≤ 10.7	12/68 (17.7)	77.3 ± 3.5	*< 0.001*	35/68 (51.5)	49.2 ± 4.0	0.178
	> 10.7	19/38 (50.0)	49.0 ± 6.0		21/38 (55.3)	42.6 ± 6.6	
Nodal FDG uptake	−	11/65 (16.9)	78.0 ± 3.5	*< 0.001*	30/65 (46.2)	52.6 ± 4.1	*0.008*
	+	20/41 (48.8)	50.9 ± 5.8		26/41 (63.4)	36.4 ± 6.0	
Nodal FDG uptake*	−	11/60 (18.3)	77.0 ± 3.8	*0.002*	26/60 (43.3)	54.2 ± 4.3	*0.004*
	+	20/46 (43.5)	54.6 ± 5.5		30/46 (65.2)	36.4 ± 5.4	

p values are from log-rank tests (italic indicates < 0.05). [a] Thresholds from ROC analysis. *ADC*, adenocarcinoma; *MTV*, metabolic tumor volume; *TLG*, total lesion glycolysis; *SUV*, standard uptake value. *Less stringent criteria. Data are patients (%) or mean ± SD in months

were independent predictors of decreased CSS. FDG-positive N1 nodes (HR = 1.771, $p = 0.040$) and no adjuvant therapy (HR = 2.666, $p = 0.002$) were independent predictors for decreased DFS (Table 3). Similar results were obtained with the less stringent criteria for positive nodal FDG uptake (Table 3).

Survival analysis excluding ultracentral primary tumors with no discernable N1 node

Among our study population, seven cases had an ultracentral primary tumor with no discernable N1 node by PET/CT or contrast-enhanced CT. All were male patients with squamous cell carcinoma. In order to eliminate possible bias by the presence of these cases, we performed additional survival analysis excluding these seven cases. The results of multivariate analyses showed that N1 node FDG positivity (HR = 3.648, $p = 0.005$), greater primary tumor TLG (HR = 2.539, $p = 0.027$), and no adjuvant therapy (HR = 4.431, $p < 0.001$) were independent predictors of reduced CSS. N1 node FDG positivity (HR = 1.856, $p = 0.033$) and no adjuvant therapy (HR = 2.799, $p = 0.002$) were independent predictors for reduced DFS (Table 4). Furthermore, similar results were obtained when using the less stringent criteria for positive nodal FDG uptake (Table 4).

Prognostic value of nodal FDG uptake in subjects stratified according to cancer stage

Patients with stage IIIA disease had a significantly shorter 3-year CSS of 48.2% compared to the 80.8% for those with stage IIB disease ($p < 0.001$). In order to exclude the influence of cancer stage, we performed additional

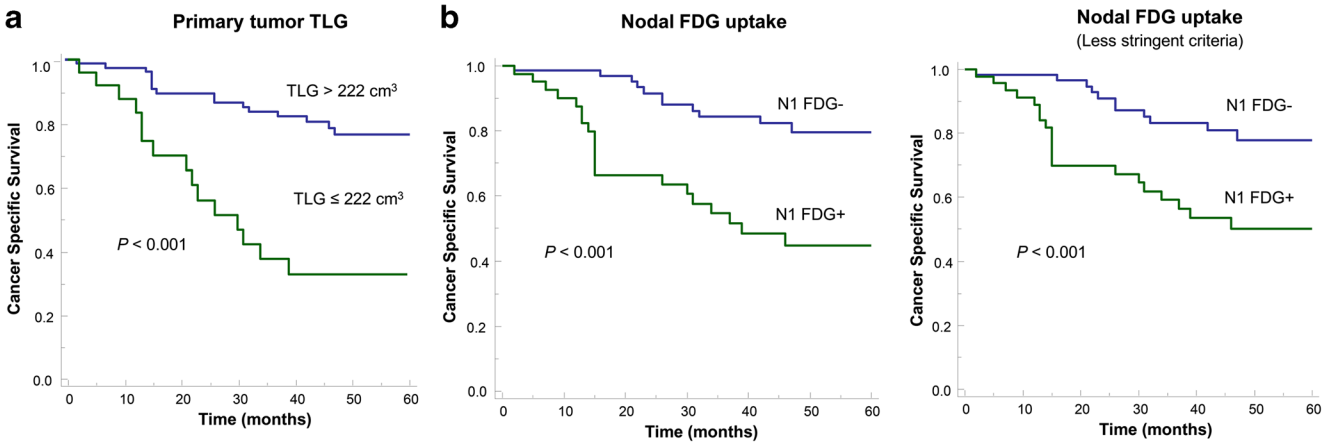

Fig. 1 **a** Kaplan-Meier curves for cancer-specific survival according to primary tumor TLG and (**b**) N1 node FDG status

survival analysis after patients were stratified into stage IIB and stage IIIA groups. The results showed that nodal FDG positivity was associated with significantly worse survival compared to nodal FDG negativity in patients with stage IIB disease (3-year CSS, 68.4% vs. 90.2%; $p = 0.003$). It also showed a tendency for association with worse survival in patients with stage IIIA disease (3-year CSS, 31.2% vs. 61.5%; $p = 0.074$), although not to a statistically significant degree. Kaplan-Meier survival curves of patients stratified according to tumor stage and N1 nodal FDG status are shown in Fig. 3.

Comparison of performance of predictive models including FDG parameters

We next compared the performance of predictive models for CSS that included one or more of the FDG parameters that showed prognostic value. As a result, Harrell's C-index for FDG-positive nodes (0.676; 95% CI, 0.589–0.763) was not significantly different from that for high primary tumor TLG (0.668; 95% CI, 0.596–0.739; $p = 0.873$). The C-index for FDG-positive nodes using the less stringent criteria was also similar at 0.650 (95% CI, 0.561–0.740; $p = 0.756$). Incorporation of nodal FDG uptake information into a Cox model that contained primary tumor TLG significantly increased the C-index to 0.741 (95% CI, 0.646–0.837; $p = 0.006$), and this was also shown using the less stringent criteria for nodal FDG positivity (C-index = 0.729; 95% CI, 0.631–0.826; $p = 0.023$).

NRI tests for predicting CSS showed that a model containing nodal FDG positivity significantly outperformed a model without this information with an NRI score of 0.419 (95% CI, 0.073–0.649; $p = 0.020$). This result indicates that 41.9% of patients who suffered cancer-specific death or survived were correctly reclassified by a model with nodal FDG information added. The use of the less stringent criteria for nodal FDG positivity showed similar results with an NRI score of 0.314 (95% CI, 0.000–0.591; $p = 0.041$).

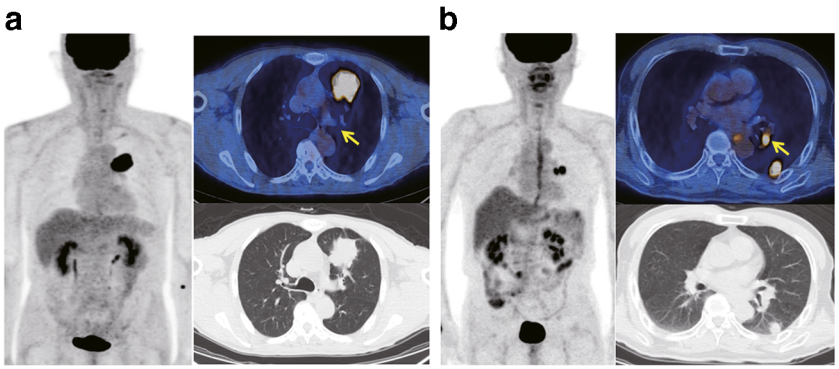

Fig. 2 Representative PET/CT images of N1 nodes with negative and positive FDG uptakes. **a** Maximum intensity projection (left), transaxial fusion PET/CT (right top), and CT (right bottom) images of a 69-year-old male with stage IIA squamous cell carcinoma in the left upper lung that showed a high primary tumor TLG of 240.1. The metastatic N1 node did not show significant FDG uptake (arrow), and the patient was free of disease for 76 months after curative resection. **b** Maximum intensity projection (left), transaxial fusion PET/CT (right top), and CT (right bottom) images of a 65-year-old male with stage IIA adenocarcinoma in the left lower lung showing a low primary tumor TLG of 16.7. The metastatic N1 node was positive for FDG uptake (arrow), and the patient died of recurrent disease at 15 months after curative resection

Table 3 Multivariate analyses of survival using Cox proportional hazards models

Variable	Cancer-specific survival		Disease-free survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Adjuvant therapy	3.631 (1.706–7.726)	*< 0.001*	2.666 (1.447–4.914)	*0.002*
Primary TLG	3.224 (1.519–6.846)	*0.002*	–	
Nodal FDG uptake	3.071 (1.450–6.501)	*0.003*	1.771 (1.027–3.053)	*0.040*
Less stringent criteria				
Adjuvant therapy	3.797 (1.781–8.093)	*< 0.001*	2.659 (1.446–4.889)	*0.002*
Primary TLG	3.402 (1.601–7.229)	*0.002*	–	
Nodal FDG uptake	2.687 (1.275–5.661)	*0.009*	1.917 (1.116–3.295)	*0.019*

HR, hazards ratio; *CI*, confidence interval; *TLG*, total lesion glycolysis. Italic numbers indicate *p* values < 0.05

Prognostic stratification using primary tumor TLG and FDG-positive N1 disease

Given the major prognostic roles of primary tumor TLG and nodal FDG status, we compared Kaplan-Meier subject survival curves stratified into four subgroups. The results showed that patients with high primary tumor TLG and positive nodal FDG uptake had significantly worse CSS than all other subgroups. Furthermore, patients with low primary tumor TLG and negative nodal FDG uptake had significantly better CSS than all other subgroups (Fig. 4). The latter finding was also observed using the less stringent criteria for nodal FDG positivity (Fig. 4).

Discussion

The principal finding of this study of NSCLC patients with pathology-proven N1 metastasis is that FDG uptake in the N1 nodes is associated with significantly worse outcome following curative surgery.

The relatively wide range of survival for NSCLC patients with N1 disease is inadequately accounted for by differences in tumor size, which stratifies patients into only two different TNM stages [18]. Hence, effort is ongoing to identify prognostic information residing within metastatic N1 nodes. However, reports to date have shown that number, size, and type (direct versus separate involvement) of involved LNs have limited usefulness for stratifying prognosis of patients with N1 disease.

PET/CT is widely used for evaluating patients with NSCLC, and FDG uptake of lung tumors has been shown to correlate with aggressive tumor behavior [19]. Furthermore, tumor SUV_{max}, MTV, and TLG are recognized as significant prognostic factors in patients with lung cancer [11–13, 20–22]. However, most previous studies regarding the prognostic value of tumor FDG uptake have focused on NSCLC patients without metastatic disease. When lung cancer has spread, PET/CT features of the metastatic lesions rather than the primary tumor are likely to provide important prognostic information. Indeed, researchers have proposed that, in advanced NSCLC, total metabolic tumor burden that includes metastatic as well as primary tumors offers improved prognostic information [23–25]. However, summing the metabolic volume with that of the primary tumor would dilute any distinct prognostic information contained in metastatic LNs. Moreover, the relatively small size of LNs compared to the primary tumor would result in only a minor contribution of LN metabolic state to the summed metabolic volume. For these reasons, we treated N1 node FDG status as a separate

Table 4 Multivariate survival analyses after excluding subjects with ultracentral tumors

Variable	Cancer-specific survival		Disease-free survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Adjuvant therapy	4.431 (1.991–9.859)	*< 0.001*	2.799 (1.478–5.302)	*0.002*
Primary TLG	2.539 (1.112–5.795)	*0.027*	–	
Nodal FDG uptake	3.648 (1.484–8.969)	*0.005*	1.856 (1.051–3.278)	*0.033*
Less stringent criteria				
Adjuvant therapy	4.720 (2.120–10.512)	*< 0.001*	2.772 (1.468–5.236)	*0.002*
Primary TLG	2.756 (1.211–6.269)	*0.016*	–	
Nodal FDG uptake	3.066 (1.260–7.457)	*0.014*	2.053 (1.159–3.636)	*0.014*

HR, hazards ratio; *CI*, confidence interval; *TLG*, total lesion glycolysis. Italic numbers indicate *p* values < 0.05

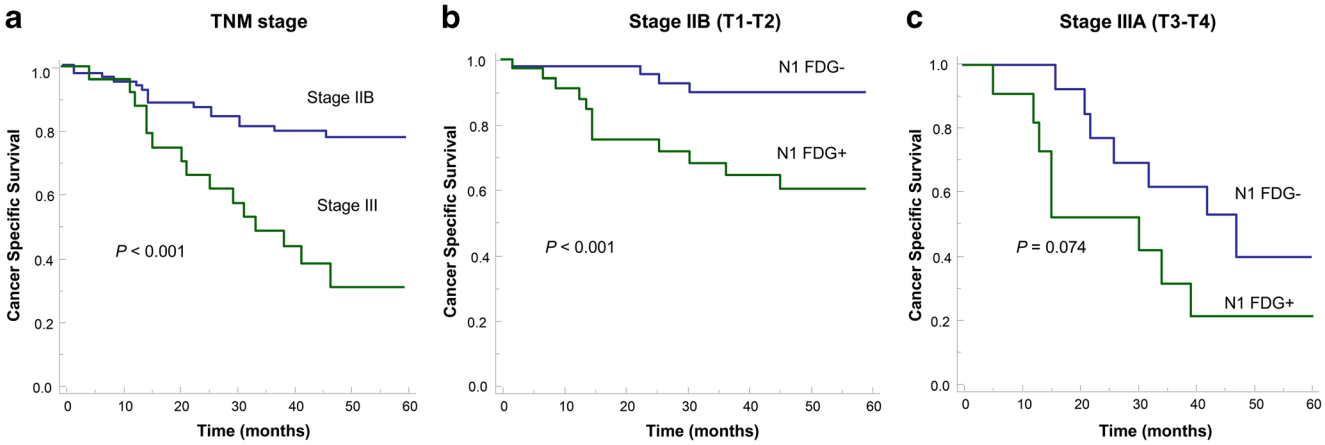

Fig. 3 **a** Kaplan-Meier curves for cancer-specific survival according to TNM stage and (**b**) in the stratified stage according to N1 node FDG status

variable to be analyzed for prognostic value with other known predictors of survival.

While this study focused on NSCLC patients with N1 metastasis, patients with N1 disease caused by direct extension of the primary cancer were excluded because their survival could differ from cases with N1 metastasis distinct from the primary tumor [3, 4]. Furthermore, FDG uptake of lymph nodes with direct extension from primary lung cancer is difficult to measure accurately due to influence by the adjacent primary tumor. Consistent with previous reports, positive nodal FDG uptake was also associated with higher primary tumor SUV_{max} [26].

Kaplan-Meier survival analyses showed that N1 node FDG positivity was associated with worse DFS and CSS compared to FDG negativity. A SUV_{max} threshold of 2.5 was used to identify N1 nodes with significant FDG uptake, and this cutoff offered perfect concordance with visually discernable FDG uptake. In lung cancer, a SUV_{max} of 2.5 is widely used as cutoff for identifying mediastinal LN metastasis [26–29] and is also used as the threshold to define MTV. FDG uptake caused by inflammation can be mistaken as caused by malignant cells, but this can be minimized by interpreting uptake in LNs with high attenuation or gross calcification as benign [30, 31]. FDG positivity categorized using a stringent criterion to exclude such nodes demonstrated significant independent prognostic value, as did that using a less stringent criterion that considered all nodes with increased SUV_{max} as FDG positive.

ROC analysis of surgically removed metastatic N1 node measurements revealed that a longest diameter of 7 mm was the best cutoff for predicting patient outcome. Although this measurement showed significant correlation with N1 nodal FDG positivity, it did not demonstrate independent prognostic value as the latter did. This finding underlines the greater importance of metabolic state compared to anatomic size of metastatic LNs on tumor cell aggressiveness and invasiveness

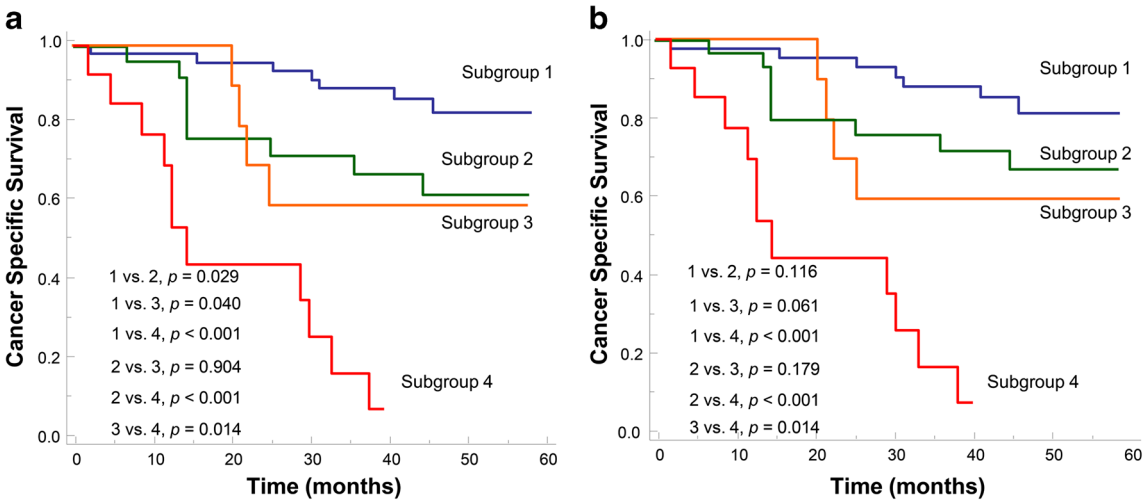

Fig. 4 Kaplan-Meier curves for cancer-specific survival in 4 subgroups categorized according to primary tumor TLG and N1 node FDG status. Subgroup 1 had low tumor TLG and negative nodal FDG uptake; subgroup 2 had high tumor TLG and negative nodal FDG uptake; subgroup 3 had low tumor TLG and positive nodal FDG uptake; subgroup 4 had high tumor TLG and positive nodal FDG uptake

[32–34]. However, since diameter measurements of surgically removed specimen are likely significantly different from in vivo measurements, it should be interesting to explore in the future, whether a certain nodal diameter cutoff measured by CT has independent prognostic value in lung cancer patients with N1 disease.

For primary lung tumors that were located ultracentrally, it was difficult to discriminate N1 node FDG status due to limited imaging resolution. However, N1 node FDG status remained an independent predictor of patient outcome on additional survival analysis performed after excluding these cases.

In our study subjects, greater tumor stage was also significantly associated with worse outcome. We thus performed additional survival analysis after stratifying subjects according to cancer stage, and the results supported the prognostic value of N1 node FDG status independent of cancer stage.

Given the major independent prognostic values of tumor TLG and nodal FDG status, we additionally compared the performance of predictive models for CSS that incorporated one or both PET parameters. Of the statistics used, the Harrell C-index can be interpreted as the probability that a subject with an outcome is given a higher probability of the outcome than a randomly chosen subject without the outcome [16]. The NRI is the net proportion of events reclassified correctly plus the net proportion of nonevents reclassified correctly for a pre-specified set of cutoff points [17]. In our results, C-index and NRI analyses showed that inclusion of nodal FDG status in addition to tumor TLG led to a predictive model with significantly improved discriminatory power regarding CSS. Finally, combining these two variables stratified a subgroup of patients with high tumor TLG and positive nodal FDG uptake who had the worst prognosis, as well as a subgroup of patients with low tumor TLG and negative nodal FDG uptake who had the best prognosis.

The current standard treatment for NSCLC patients with N1 disease following complete resection is cisplatin-based adjuvant chemotherapy [35]. In such patients, identification of imaging biomarkers that can better stratify prognosis might help employ more appropriate risk-adapted therapies. The findings of this study indicate that incorporating both primary tumor and N1 node FDG positivity can help stratify outcomes of NSCLC patients with N1 disease. Future investigations are therefore warranted to clarify whether these PET parameters might help discern patients who need aggressive adjuvant therapy following surgery from those who do not.

Major limitations of this study are its retrospective design and a rather modest number of subjects. The relatively uneven distribution of surgical and adjuvant treatment modes could also have influenced the results. Therefore, a prospective study with a larger number of subjects will be required to validate the conclusions of this study.

Conclusion

In NSCLC patients with pathologic N1 metastasis, FDG positivity of the N1 node and high primary tumor TLG were independent predictors of poor survival. Furthermore, incorporating N1 node FDG information into a predictive model containing tumor TLG significantly improved the model's power to discriminate CSS.

Funding This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (# 2016R1C1B2013411).

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Kyung-Han Lee.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry This work was supported by Kyunga Kim, Biostatics, Samsung Medical Center.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Diagnostic or prognostic study
- Performed at one institution

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