

# Preoperative Risk Factors for Pathologic N2 Metastasis in Positron Emission Tomography-Computed Tomography–Diagnosed N0–1 Non-Small Cell Lung Cancer

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**Background:** Accurate mediastinal lymph node staging is vital for the optimal therapy and prognostication of patients with lung cancer. This study aimed to determine the preoperative risk factors for pN2 disease, as well as its incidence and long-term outcomes, in patients with clinical N0–1 non-small cell lung cancer. **Methods:** We retrospectively analyzed patients who were treated surgically for primary non-small cell lung cancer from November 2005 to December 2014. Patients staged as clinical N0–1 via chest computed tomography (CT) and positron emission tomography (PET)-CT were divided into two groups (pN0–1 and pN2) and compared. **Results:** In a univariate analysis, the significant preoperative risk factors for pN2 included a large tumor size ( $p=0.083$ ), high maximum standard uptake value on PET ( $p<0.001$ ), and central location of the tumor ( $p<0.001$ ). In a multivariate analysis, central location of the tumor ( $p<0.001$ ) remained a significant preoperative risk factor for pN2 status. The 5-year overall survival rates were 75% and 22.9% in the pN0–1 and pN2 groups, respectively, and 50% and 78.2% in the patients with centrally located and peripherally located tumors, respectively. In a Cox proportional hazard model, central location of the tumor increased the risk of death by 3.4-fold ( $p<0.001$ ). **Conclusion:** More invasive procedures should be considered when preoperative risk factors are identified in order to improve the efficacy of diagnostic and therapeutic plans and, consequently, the patient's prognosis.

*Key words:* 1. Non-small-cell lung carcinoma  
2. Lymph nodes  
3. Neoplasm metastasis  
4. Positron emission tomography  
5. Computed tomography

## Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. In 2016, the Korea National Statistical Office announced that malignant neoplasms were the leading cause of death in Korea, while lung

cancer was the leading cause of cancer-related death, accounting for 17,963 deaths. Despite many advances in methods of diagnosing and treating lung cancer over time, little improvement has been observed in survival rates. Therefore, the preoperative accurate staging of non-small cell lung cancer (NSCLC) is an

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increasingly important factor in terms of choosing an optimal therapeutic strategy for long-term survival.

According to the TNM (tumor-node-metastasis) staging system, N2 metastasis may involve the ipsilateral mediastinal lymph node (LN) or the subcarinal LN [2]. Currently, N2 nodal metastasis (stage IIIA) is an indication for neoadjuvant therapy, and affected patients who receive neoadjuvant therapy prior to resection may achieve better survival outcomes than those who receive adjuvant chemotherapy [3]. Therefore, an accurate mediastinal LN assessment may be one of the most important measures in patients with NSCLC. The mediastinal LN status of patients considered suitable for resection should be evaluated using preoperative staging methods such as positron emission tomography/computed tomography (PET-CT), endobronchial ultrasound (EBUS), and mediastinoscopic biopsy. Some centers routinely perform EBUS, endoscopic ultrasound (EUS), and mediastinoscopy before curative resection; although mediastinoscopy is controversial, it is still recognized as the gold-standard method for examining mediastinal LN metastasis [4-6]. However, some centers do not recommend the routine use of these invasive procedures [7,8], as they are not effective for all patients and are associated with disadvantages such as time and financial costs, as well as complications such as bleeding and mediastinitis.

Although PET-CT may lead to misdiagnosis in some cases, with a sensitivity of 79%–85% and specificity of 87%–92% [9], it nonetheless remains the most accurate non-invasive diagnostic tool for assessing nodal metastasis. Accordingly, many surgeons use PET-CT to determine mediastinal LN metastasis status and to inform surgical decisions. However, in patients expected to face a high risk of mediastinal LN metastasis, nodal metastases must be assessed using the more invasive tools mentioned above. In this study, we aimed to determine the risk factors for pN2 disease, as well as its incidence and long-term outcomes, in patients with clinical N0–1 NSCLC as determined using PET-CT.

## Methods

We retrospectively analyzed 305 patients who underwent surgical treatment for primary NSCLC between November 2005 and December 2014. Clinical

staging was determined from PET-CT, conventional chest CT, brain magnetic resonance imaging and, if needed, bronchoscopy findings. Invasive tools (e.g., EBUS, EUS, and mediastinoscopic biopsy) were used for further analysis if PET-CT indicated clinical N2 status or multiple N1 nodes. For patients with a centralized primary tumor that could potentially be resected or a single N1 node, we proceeded with surgery with curative intent and LN dissection without invasive staging. Patients who underwent wedge resection, died in the hospital, and/or underwent induction therapy were excluded from the study, as were patients with carcinoid tumors, small cell carcinoma, and suspected N2 disease on PET-CT. Curative R0 resection and systematic LN dissection were achieved in all patients. Mediastinal LN dissection was performed in at least 2 stations. For right-sided tumors, nodes 2, 4, 7, 8, and 9 were biopsied, while for left-sided tumors, nodes 5–9 were biopsied.

Risk factors for pN2 metastasis were identified by analyzing clinical variables such as age, sex, primary tumor size, primary tumor location, and maximum standard uptake value (SUVmax) on PET-CT. A centrally located tumor was defined as a mass in the inner third of the lung parenchyma on chest CT and a visible mass under bronchoscopic examination, while a peripheral tumor was defined as a mass in the outer two-thirds of the lung parenchyma. Patients were followed postoperatively according to the following schedule: a chest CT examination every 3 months during the first 2 years, every 6 months for 3 additional years, and every year thereafter.

Patients diagnosed with clinical N0–1 disease by PET-CT were divided into pathologic N0–1 and pathologic N2 groups for comparison. All statistical analyses were performed using PASW SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). The Student t-test was used to compare continuous variables, while the chi-square test or Fisher exact test was used to compare categorical variables. Risk factors for pN2 status were analyzed using multivariate logistic regression. Overall survival was analyzed using the Kaplan–Meier method and compared between groups using the log-rank test. The follow-up duration was calculated from the date of surgery until death. All p-values were considered statistically significant at a threshold of <0.05.

This study was reviewed and approved by the in-

Table 1. Characteristics of patients and tumors

Variable	Value
Sex	
Male	106 (63.9)
Female	60 (36.1)
Age (yr)	65.0±9.8 (28.0-85.0)
Tumor size (cm)	3.18±1.3 (1.0-7.5)
Tumor location	
Central	58 (34.9)
Peripheral	108 (65.1)
Maximum standardized uptake value of tumor	6.13±4.5 (0.1-24.3)
Visceral pleural invasion	
Positive	45 (27.1)
Negative	121 (72.9)
Lymphovascular invasion	
+	78 (47.0)
-	88 (53.0)
Lymph node metastasis	
N0	125 (75.3)
N1	19 (11.4)
N2	22 (13.3)
Histologic type	
Adenocarcinoma	101 (60.8)
Squamous cell carcinoma	55 (33.1)
Other types	10 (6.0)
Lobar distribution of tumor	
Right upper lobe	52 (31.3)
Right middle lobe	18 (10.8)
Right lower lobe	27 (16.3)
Left upper lobe	34 (20.5)
Left lower lobe	35 (21.1)
Operative procedure	
Segmentectomy	1 (0.6)
Lobectomy	146 (88.0)
Bilobectomy	7 (4.2)
Pneumonectomy	12 (7.2)

Values are presented as number (%) or mean±standard deviation (range).

stitutional Review Board (IRB approval no., CR-19-064, Daegu Catholic University Medical Center IRB) and informed consent was waived.

## Results

The characteristics of the patients and tumors are shown in Table 1. A total of 166 patients were included; the patients were predominantly men (63.9%), and had an average age of 65±9.8 years.

Table 2. Univariate analysis of factors associated with occult lymph node metastasis

Variable	pN0-1 (n=144)	pN2 (n=22)	p-value
Age (yr)	65.4±9.9	64.1±9.9	0.570
Sex			0.650
Male	91 (63.2)	15 (63.9)	
Female	53 (36.8)	7 (36.1)	
Tumor size (cm)	3.1	3.7	0.038
PET SUVmax	5.8	8.5	0.001
Lobe			0.915
Right upper lobe	29 (20.1)	6 (27.3)	
Right middle lobe	30 (20.8)	4 (18.2)	
Right lower lobe	24 (16.7)	3 (13.6)	
Left upper lobe	15 (10.4)	3 (13.6)	
Left lower lobe	46 (31.9)	6 (27.3)	
Tumor location			<0.001
Central	41 (28.5)	17 (77.3)	
Peripheral	103 (71.5)	5 (22.7)	
Histology			0.272
Squamous cell carcinoma	49 (34.0)	7 (31.8)	
Adenocarcinoma	88 (61.1)	12 (54.5)	
Others	7 (4.9)	3 (13.6)	

Values are presented as mean±standard deviation or number (%), unless otherwise stated.

PET, positron emission tomography; SUVmax, maximum standardized uptake value.

The average tumor size was 3.14±1.3 cm, and peripherally located tumors were more common (65.1%). The mean tumor SUVmax was 6.13±4.5. A majority of patients had no visceral pleural invasion (72.9% versus 27.1% with invasion) or lymphovascular invasion (53% versus 47% with invasion). The most common tumor location was the right upper lobe (31.3%), and lobectomy was the most performed operative technique (88%).

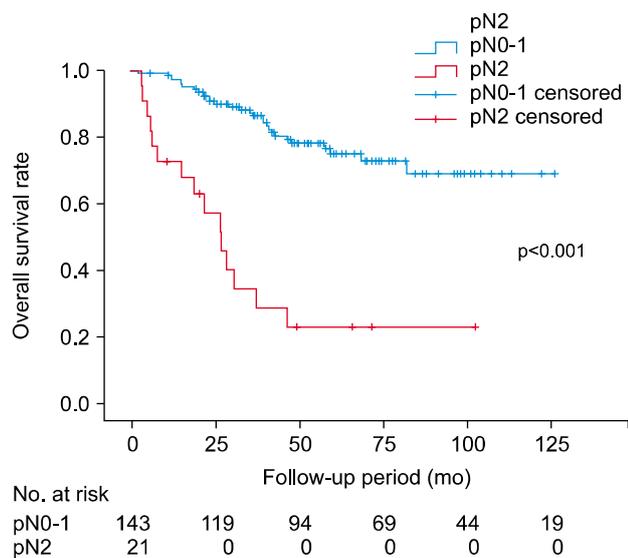
Postoperatively, patients were divided into pN0-1 and pN2 groups for comparison and analysis (Table 2). Our study investigated preoperative risk factors. The mean ages of the 2 groups were 65.4 and 64.1 years, respectively, and both had a male predominance (63.2% and 63.9%, respectively). Although all 166 patients were preoperatively staged as cN0-1, 22 cases (13.2%) were upstaged to pN2 after surgery. We studied the LN sites of these 22 patients, and found skip N2 metastasis in 9 patients. We additionally found that node 7 was the most frequently invaded LN, followed by node 4.

On CT scans, the pN2 group had a significantly

**Table 3. Multivariate analysis of risk factors for occult mediastinal lymph node metastasis**

Variable	Odds ratio (95% confidence interval)	p-value
Central location of tumor	8.541 (2.957–24.673)	< 0.001
Age	0.981 (0.934–1.031)	0.446
Tumor size	1.184 (0.826–1.699)	0.358
SUVmax	0.991 (0.868–1.132)	0.897

SUVmax, maximum standardized uptake value.

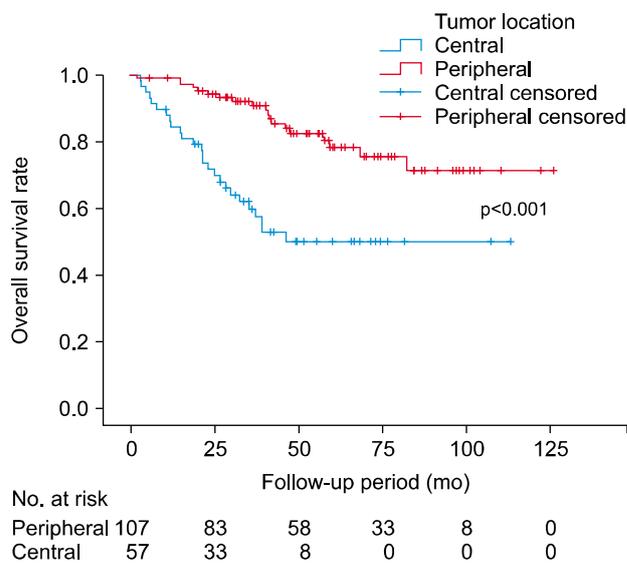


**Fig. 1.** Overall survival rate of in patients with pN0-1 or pN2 status.

larger tumor size (3.7 cm versus 3.1 cm for pN0-1,  $p=0.038$ ), as well as a higher SUVmax (8.5 versus 5.8 for pN0-1,  $p=0.001$ ). However, peripherally located tumors were more common in the pN0-1 group (71.5%,  $p<0.001$ ), while centrally located tumors were more common in the pN2 group (77.3%,  $p<0.001$ ). Adenocarcinoma was the most frequent tumor type in both groups (61.1% versus 54.5%; non-significant difference).

In the multivariate analysis, central location of the tumor was identified as the only significant preoperative risk factor for pN2 status (Table 3).

In a receiver operating characteristic curve analysis, we studied the preoperative risk factors that were statistically significant in the univariate analysis. We identified a tumor size cutoff value of 4.1 cm (area under the curve [AUC]=0.639) and a PET SUVmax cutoff value of 6 (AUC=0.717).



**Fig. 2.** Overall survival rate according to tumor location.

Patients were followed for a mean period of 43 months (range, 2–125 months). Notably, patients in the pN2 group had a significantly lower 5-year overall survival rate (22.9%) than those in the pN0-1 group (75%) (Fig. 1). Furthermore, patients with centrally and peripherally located tumors had 5-year overall survival rates of 50% and 78.2%, respectively (Fig. 2).

Finally, a Cox proportional hazards model showed that the risk of death increased by 3.4-fold (95% confidence interval, 1.81–6.28;  $p<0.001$ ) in patients with a centrally located tumor.

## Discussion

In our study, patients underwent surgery only when preoperative PET-CT showed no mediastinal LN metastasis. However, we identified pN2 metastasis in 22 of the 166 patients (13.3%), consistent with previous studies [10,11]. In a univariate analysis, we identified central tumor location, larger tumor size, and high SUVmax uptake as statistically significant risk factors for pN2 status.

Similarly, Lee et al. [12] and Al-Sarraf et al. [13] reported that the tumor location was a statistically significant risk factor for N2 metastasis. Notably, we observed a significantly higher incidence of pN2 metastasis from centrally located tumors, which may be attributable to their relatively short distance from

the ipsilateral mediastinal and/or subcarinal nodes that define N2 metastasis (compared to the more distant peripheral tumors).

As noted, we also identified tumor size as a risk factor for N2 metastasis and observed a statistically significant difference in the tumor sizes of pN0-1 and pN2 patients. Lee et al. [12] similarly reported that larger clinical tumor sizes were associated with a significant increase in the risk of N2 metastasis, while Kanzaki et al. [14] identified a tumor size >3 cm as a potential risk factor. In contrast, Al-Sarraf et al. [13] concluded that tumor size did not significantly affect the risk of N2 metastasis.

Our identification of the tumor SUVmax as a significant predictor of metastasis is consistent with previous studies [12,14,15]. For example, Kanzaki et al. [14] reported a significant increase in the risk of metastasis in patients with a tumor SUVmax >4. In our study, we determined that the optimal SUVmax cutoff value for predicting N2 metastasis was 6, with mean SUVmax values of 5.8 and 8.5 in the pN0-1 and pN2 groups, respectively. SUVmax is a measure of the uptake of a radiolabeled tracer, such as 18F-fluorodeoxyglucose (FDG), by malignant tissues, and FDG uptake is known to reflect cancer cell viability. Therefore, a high SUVmax suggests a high level of cancer cell activity, which is associated with a high probability of metastasis.

In previous studies, the tumor histologic type was identified as a risk factor for LN metastasis. For example, Kanzaki et al. [14] reported that adenocarcinoma was a risk factor for LN metastasis. In contrast, however, we did not identify histologic type as a risk factor for LN metastasis. Similarly, we did not identify the tumor distribution as a risk factor, in contrast to previous studies [13,14], including the report by Al-Sarraf et al. [13] in which right upper lobe tumors were found to correlate with a higher incidence of pN2 disease.

We further identified central tumor location as a statistically significant preoperative risk factor for LN metastasis in a multivariate analysis.

In our analysis, patients with N2 node-positive disease had a 5-year survival rate of 22.9%, compared to rates of 33.5% in a report by Lee et al. [11] and 35% in a report by Cerfolio and Bryant [16]. Although this discrepancy in survival rates may be attributable to the older age of our patients, we also

must consider other factors. In our stratified analysis, the 5-year survival rates were 50% and 78.2% among patients with centrally and peripherally located tumors, and our Cox proportional hazards model showed that central location of the tumor was associated with a 3.4-fold increase in the risk of death. It is possible that centrally located tumors may require more extensive surgery; additionally, the fact that such tumors are located closer to the mediastinal LN may increase the risk for nodal metastasis, as described above.

Our study had a few limitations of note. First, this was a single-center study based on a relatively small number of patients. Second, the patients underwent operations performed by several surgeons. Third, our conclusions are based on a retrospective analysis of patient data. Accordingly, further research into prognostic factors of survival is warranted.

In conclusion, our findings from this single-center retrospective study suggest that patients with at least one of several preoperative risk factors—including a large tumor size, high SUVmax, and a centrally located tumor—face a higher risk of mediastinal LN metastasis. When the above factors are observed preoperatively, more invasive procedures such as EBUS, EUS, or mediastinoscopy should be considered to improve the efficacy of diagnostic and therapeutic plans and to increase the likelihood of a better prognosis for the patient.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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