Original Study

Prediction of Unexpected N2 Disease Associated With Clinical T1-2N0-1M0 Non–Small-Cell Lung Cancer

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Abstract

We aimed to identify the predictive criteria of unexpected N2 disease, defined as pathologic N2 disease with clinical N0 or N1, in clinical T1-2N0-1M0 non–small-cell lung cancer. The predictive criteria were defined as tumors with a standardized maximum uptake value of ≥ 3.1 and clinical N1, and showed high diagnostic accuracy in both derivation and validation cohorts.

Background: Despite the recent development of radiologic mediastinal staging modality, unexpected mediastinal lymph node metastasis still occurs. Preoperative accurate nodal staging is important to determine the optimal treatment. Therefore, this study aimed to identify predictors of unexpected N2 disease in non–small-cell lung cancer (NSCLC). **Patients and Methods:** Data from a multicenter database of 2802 patients with clinical T1-2N0-1M0 NSCLC who underwent anatomical segmentectomy or lobectomy were retrospectively analyzed. Unexpected N2 disease was defined as pathologic N2 disease with clinical N0 or N1. The predictive criteria of unexpected N2 disease were established on the basis of the multivariable analysis results of a derivation cohort of 2019 patients, and the criteria were further tested in a validation cohort of 783 patients. **Results:** In multivariable analyses, maximum standardized uptake value (SUV_{max}) of the primary tumor on 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography (odds ratio, 1.072; 95% confidence interval, 1.018–1.129; $P = .008$) and clinical N1 (vs. clinical N0) disease (odds ratio, 5.40; 95% confidence interval, 1.829–15.94; $P = .002$) were independent predictors of unexpected N2 disease. The predictive criteria of unexpected N2 disease was defined as tumors with SUV_{max} of ≥ 3.1, determined by receiver operating characteristic curves, and clinical N1 disease. This criterion showed diagnostic accuracy of 90.6% (sensitivity 32.0%, specificity 94.5%) in the derivation cohort and 91.3% (sensitivity 32.6%, specificity 94.7%) in the validation cohort. **Conclusion:** The predictive criteria of unexpected N2 disease (tumors with SUV_{max} of ≥ 3.1 and clinical N1) can be used to select candidates for preoperative invasive mediastinal staging in patients with clinical T1-2N0-1M0 NSCLC.

Clinical Lung Cancer, Vol. 22, No. 2, 120-6
Keyword: Lymph node metastasis, Mediastinal staging, Non-small cell lung cancer, N2, Thoracic surgery

Introduction

Lung cancer is a one of the leading causes of cancer-related deaths worldwide.[1] Despite the development of various treatment therapies such as immune checkpoint inhibitors (ICI), the prognosis of lung cancer with pathologic mediastinal lymph node (LN) metastasis (N2) remains significantly poor.[2] Furthermore, determining the treatment strategy for patient with N2 disease is sometimes difficult as a result of the disease's heterogeneous characteristics (eg, single or multiple stations, skip or not, bulky or not, and discrete or infiltrative).

Surgery followed by definitive chemoradiotherapy or induction therapy is a standard treatment for patients diagnosed with N2 disease.[3,4] In addition, although a previous study reported the efficacy of initial surgery followed by adjuvant therapy for resectable N2 disease,[5] neoadjuvant therapy is more feasible than adjuvant therapy because the latter may not be performed as a result of complications or poor general condition after the initial surgery.

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Submitted: Oct 10, 2020; Revised: Dec 12, 2020; Accepted: Dec 16, 2020; Epub: Dec 27, 2020

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1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2020.12.010

Therefore, preoperative mediastinal staging is crucial in determining the appropriate treatment strategy for patients with pN2 disease. Nevertheless, some patients have unexpected pathologic ipsilateral mediastinal LN metastasis perioperatively or postoperatively despite improved preoperative imaging modalities, such as high-resolution computed tomography (HRCT) or 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT).[6]

When LN metastasis is suspected, invasive mediastinal staging with endobronchial ultrasound-guided biopsy, endoesophageal ultrasound-guided biopsy, mediastinoscopy, or mediastinotomy are recommended. Meanwhile, a previous study reported that routine mediastinoscopy did not greatly increase the negative predictive value of FDG-PET/CT and routine procedure in all patients, thereby resulting in increased occurrence of complications and higher economic costs.[7,8] Therefore, these invasive procedures should be performed selectively for patients at high risk of N2 disease.

We hypothesized that clinical factors such as imaging findings have a predictive value for unexpected N2 disease. Therefore, preoperative predictive factors for unexpected N2 disease were retrospectively investigated to select optimal candidates for invasive mediastinal staging in clinical T1-2N0-1M0 non–small-cell lung cancer (NSCLC).

Patients and Methods

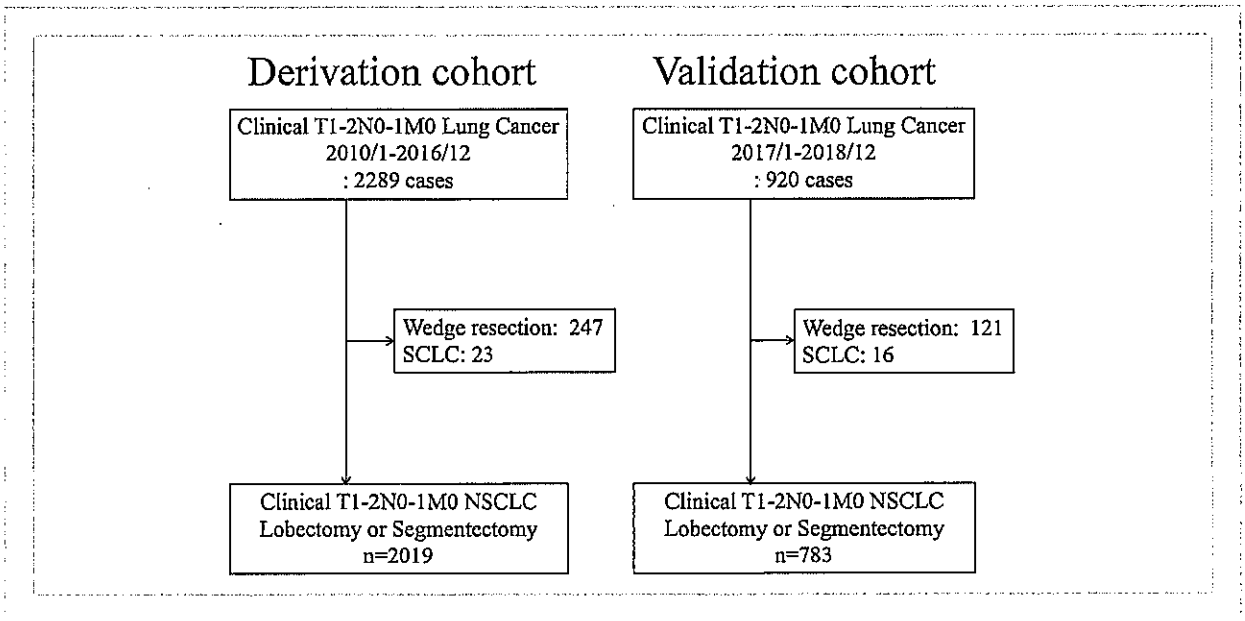
Patient Population

The institutional review boards of participating institutions approved this retrospective review of a prospective database and waived the requirement for informed consent from each patient (Hiroshima University Hospital, approval E-1216; Kanagawa Cancer Center, approval 24-KEN-54; Tokyo Medical University Hospital, approval SH2969). Data from consecutive patients with surgically curative R0 resection of clinical T1-2N0-1M0 lung cancer were initially collected from Hiroshima University Hospital, Kanagawa Cancer Center, and Tokyo Medical University between January 2010 and December 2018. Among them, patients who underwent wedge resection and with pathologic type of small-cell carcinoma were excluded. Predictive factors associated with unexpected N2 metastasis were identified using data from the derivation cohort (n = 2019; from January 2010 to December 2016) and reevaluated using data from the validation cohort (n = 783; from January 2017 to December 2018) (Figure 1). Patients who received any neoadjuvant chemotherapy or radiotherapy were also excluded. Patients included in the derivation cohort were followed for a median of 36.1 months. All tumors were staged according to the 8th edition of the tumor, node, metastasis (TNM) *Classification of Malignant Tumours*.[9] The World Health Organization classification was used for the pathologic diagnosis of patients.[10]

When only comparing patient prognosis according to clinical and pathologic nodal status, 32 patients with clinical T1-2N2M0/pathologic N2 disease who underwent surgical resection without neoadjuvant treatment whose data were collected from the same multicenter database were included. These 32 patients were not included in the analysis to identify predictors of unexpected N2 disease.

In this study, clinical nodal metastasis was defined as an enlarged LN of > 1 cm on HRCT or an SUV_{max} of more than 1.5 in LN on FDG-PET/CT. N1 and N2 stations were determined according to the definition proposed by the International Association for the Study of Lung Cancer.[2] Clinical N0 disease was defined as the absence of these findings on the ipsilateral hilar or mediastinal LN,

Figure 1 Flowchart of Patient Selection. Preoperative Staging was Based on *TNM Classification of Malignant Tumours*, 8th Ed



Abbreviations: NSCLC = non–small-cell lung cancer; SCLC = small-cell lung cancer; TNM = tumor, node, metastasis classification system.

whereas clinical N1 disease was defined as the presence of these findings on ipsilateral hilar without mediastinal LN involvement. Mediastinoscopy or endobronchial ultrasonography was not performed when N2 disease was not suspected on preoperative HRCT and/or FDG-PET/CT.

Classification of N2 Disease

Unexpected N2 disease was defined as pathologic N2 disease with clinical N0 or N1. Patients with skip N2 disease was had mediastinal LN metastases without peribronchial or ipsilateral hilar region LN metastasis, whereas those with single N2 disease had only one station mediastinal LN metastasis. Patients who did not meet these definitions were classified as having multiple N2 disease.

HRCT Imaging

Chest images were acquired using a 16-row multidetector CT. High-resolution images of the tumors were acquired using the following parameters: 120 kVp, 200 mA, section thickness 2 mm, pixel resolution 512 Å—512, scan duration 0.5-1.0 seconds, high spatial reconstruction algorithm with a 20 cm field of view, and mediastinal (40 Hounsfield units [HU]; width, 400,139 HU) and lung (−600 HU; width, 1600 HU) window settings. We defined the size of a solid component as its maximal dimension in the lung window, excluding ground-glass opacity.[11] Radiologists from each participating institution reviewed all CT images and determined tumor sizes.

FDG-PET/CT Imaging

Patients were instructed to fast for > 4 hours before an intravenous injection of 74 to 370 MBq FDG, then to relax for at least 1 hour before FDG-PET/CT scanning. Discovery ST (GE Healthcare, Little Chalfont, UK), Aquiduo (Toshiba Medical Systems, Tochigi, Japan), or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated 3-dimensional PET/CT scanners were used for imaging. Low-dose nonenhanced CT images of 2 to 4 mm section thickness for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient by following a standard protocol. Immediately after CT, PET covered the identical axial field of view for 2 to 4 minutes per table position, depending on the patient's condition and the scanner's performance. An iterative algorithm with CT-derived attenuation correction was used to reconstruct all PET images with a 50 cm field of view. An anthropomorphic body phantom (NEMA NU2-2001; Data Spectrum, Hillsborough, NC) was used to minimize standard uptake value (SUV) variations among institutions. A calibration factor was analyzed by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease interinstitutional SUV inconsistencies; the final SUV used here is referred to as the revised SUV_{max}. Original SUV_{max} values were determined by radiologists from each institution.

Follow-up Evaluation

Postoperative follow-up included physical examination and chest radiography every 3 months, and CT examination every 6 months for the first 2 years. Thereafter, patients were assessed by physical examinations and chest radiography every 6 months and chest CT examination annually. Recurrence was determined on the basis of radiographic features or histologic evidence.

Statistical Analysis

Multiple logistic regression analyses were performed to determine independent variables related to tumor location, solid tumor size, consolidation—tumor ratio (C/T ratio), SUV_{max} of the primary tumor, clinical nodal status, and histologic type in order to predict unexpected N2 disease in the derivation cohort. In addition, receiver operating characteristic (ROC) curves of SUV_{max} were used to determine the optimal cutoff to predict unexpected N2 disease. The diagnostic accuracy, including sensitivity and specificity, of constructed predictive criteria for unexpected N2 disease was assessed in the derivation or validation cohort.

Continuous variables were reported as mean (standard deviation) and compared by the Student t test if normally distributed, and as median (interquartile range) and compared by the Wilcoxon rank sum testing if nonnormally distributed. Categorical variables were compared by the chi-square or Fisher exact test. Recurrence-free survival (RFS) was defined as the time elapsed from surgery to recurrence, death from any cause, or last follow-up. Overall survival (OS) was defined as the time elapsed from surgery to death from any cause or last follow-up. Survival data were calculated by the Kaplan-Meier method and compared by the log-rank test. All data were statistically analyzed by JMP 14 software (SAS Institute, Cary, NC). $P < .05$ was considered statistically significant.

Results

Patient Characteristics

Table 1 summarizes the participants' characteristics in the derivation and validation cohorts. Respectively, median solid tumor size was 18.0 and 20.0 mm, and SUV_{max} was 2.75 and 3.11. The number of patients with clinical N1 was 157 (7.8%) and 54 (6.9%), respectively.

Prognosis of Patients With Clinical T1-2N0-1M0 NSCLC According to Clinical and Pathologic Nodal Status in the Derivation Cohort

Figure 2 shows the prognosis of patients with clinical T1-2N0-1M0 NSCLC according to nodal status, including 32 patients with clinical N2/pathologic N2 disease who underwent surgical resection without neoadjuvant treatment. Characteristics of clinical N2/pathologic N2 disease are listed in Supplemental Table 1 in the online version. RFS and OS were significantly lower in patients with unexpected pN2 disease (cN0-1/pN2) (n = 125; 5-year RFS, 30.9%; 95% confidence interval [CI], 21.7-41.9 and 5-year OS, 71.0%; 95% CI, 59.9-80.1) compared to those without pN2 disease (cN0-1/pN0-1) (n = 1894; 5-year RFS, 83.0%; 95% CI, 80.7-85.1 and 5-year OS, 89.1%; 95% CI, 87.0-90.9; $P < .001$ and $< .001$, respectively). Conversely, the difference in RFS and OS was not significant between patients with unexpected N2 disease (cN0-1/pN2) and those with clinical N2/pathologic N2 disease (cN2/pN2) (n = 32; 5-year RFS, 18.2%; 95% CI, 7.0-39.8 and 5-year OS, 58.2%; 95% CI, 32.9-78.0; $P = .106$ and .179, respectively).

Prognosis of Unexpected Pathologic N2 Disease With or Without Adjuvant Therapy in the Derivation Cohort

Among patients with unexpected pN2 disease, the difference in RFS and OS was found to be significant between patients receiving adjuvant therapy (n = 82; 5-year RFS, 32.5%; 95% CI, 20.6-47.2

Table 1 Patient Characteristics

Characteristic	Derivation Cohort (N = 2019)	Validation Cohort (N = 783)
Age (years), median (IQR)	69.0 (63.0-75.0)	71.0 (64.0-76.0)
Sex		
Male	1097 (54.3)	458 (58.5)
Female	922 (45.7)	325 (41.5)
Nodule location		
Right upper lobe	662 (32.8)	255 (32.6)
Right middle lobe	137 (6.8)	49 (6.3)
Right lower lobe	447 (22.1)	153 (19.5)
Left upper lobe	475 (23.5)	196 (25.0)
Left lower lobe	298 (14.8)	130 (16.6)
Nodule diameter on CT (mm), median (IQR)	23.0 (17.0-31.0)	24.0 (17.0-32.0)
C/T ratio, median (IQR)	0.9 (0.6-1.0)	1.0 (0.7-1.0)
Solid tumor size on CT (mm), median (IQR)	18.0 (11.0-27.0)	20.0 (13.0-28.0)
SUV_{max}, median (IQR)	2.75 (1.31-6.64)	3.11 (1.49-7.12)
Clinical T factor		
T1mi	143 (7.1)	47 (6.0)
T1a	278 (13.8)	96 (12.3)
T1b	732 (36.3)	261 (33.3)
T1c	487 (24.1)	183 (23.4)
T2a	267 (13.2)	149 (19.0)
T2b	112 (5.5)	47 (6.0)
Clinical N factor		
N0	1862 (92.2)	729 (93.1)
N1	157 (7.8)	54 (6.9)
Surgical procedure		
Segmentectomy	361 (17.9)	190 (24.3)
Lobectomy	1658 (82.1)	593 (75.7)
Histologic type		
Adenocarcinoma	1651 (81.8)	627 (80.1)
Squamous-cell carcinoma	238 (11.8)	103 (13.2)
Other	130 (6.4)	53 (6.8)
Invasion		
Pleural	406 (20.1)	156 (19.9)
Vascular	637 (31.6)	251 (32.1)
Lymphatic	472 (23.4)	168 (21.5)

Categorical data are presented as n (%) and continuous data as median (IQR).
Abbreviations: C/T ratio = consolidation/tumor ratio; CT = computed tomography; IQR = interquartile range; SUV_{max} = maximum standardized uptake value.

and 5-year OS, 81.2%; 95% CI, 67.6-90.0) and those who did not (n = 43; 5-year RFS, 25.6%; 95% CI, 14.1-42.0 and 5-year OS, 56.8%; 95% CI, 31.0-67.5; $P = .0061$ and $< .0001$, respectively) (Supplemental Figure 1 in the online version).

Identification of Predictive Criteria for Unexpected N2 Disease

Possible predictors of unexpected N2 metastasis are shown in Table 2. Multivariable analysis showed that the SUV_{max} (odds ratio [OR], 1.072; 95% CI, 1.018–1.129; $P = .008$) and clinical N1 (OR, 5.400; 95% CI, 1.829–15.94; $P = .002$) were independent prognostic factors for unexpected N2 disease. ROC curve analysis showed that the optimal cutoff value of SUV_{max} was 3.1 (sensitivity 89.6%, specificity 56.6%; Supplemental Figure 2 in the online version). Predictive criteria of unexpected N2 disease were defined as clinical N1 and SUV_{max} of ≥ 3.1. The patient population was then stratified on the basis of these predictive criteria.

Impact of Predictive Criteria in Derivation Cohort

The predictive criteria of unexpected N2 disease showed a diagnostic accuracy of 90.6% (sensitivity 32.0%, specificity 94.5%) in the derivation cohort. Table 3 shows the number of patients who met the criteria in the derivation cohort. Among these patients, unexpected N2 disease was found in 40 (27.6%) of 145 patients who met the criteria; meanwhile, 85 (4.5%) of 1874 patients who did not meet the criteria did not (OR, 8.02; 95% CI, 5.25-12.25; $P < .001$). Significant differences on the frequency of single pN2 (15.2% vs. 1.7%; $P < .001$, respectively) and multiple pN2 (8.3% vs. 1.3%; $P < .001$, respectively) were observed between patients who met the criteria and those who did not (Table 4). The frequency of pN0, pN1, and unexpected N2 disease based on clinical T status, clinical N status, C/T ratio, SUV_{max}, nodule location, and histologic type is shown in Supplemental Table 2 in the online version.

Impact of Predictive Criteria in Validation Cohort

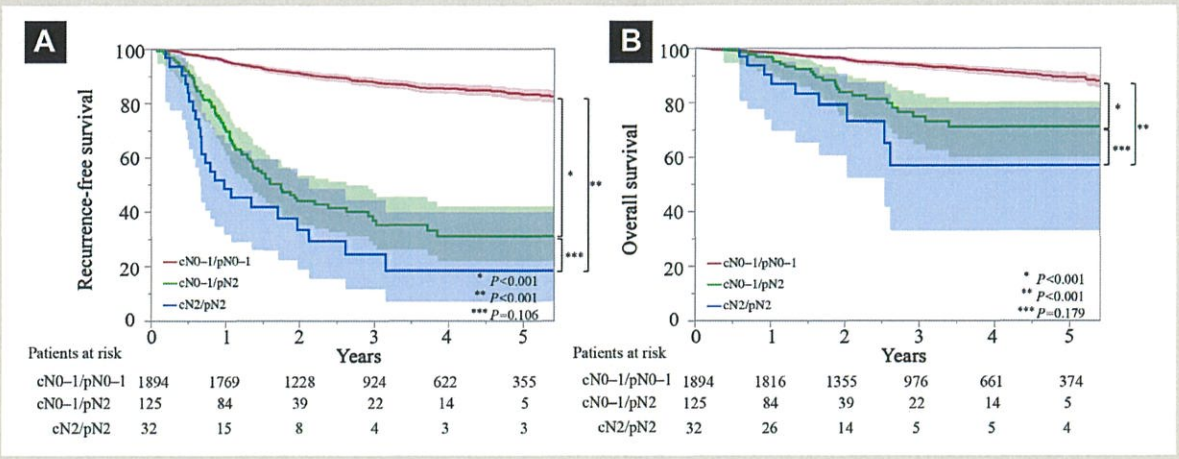
The predictive criteria of unexpected N2 disease showed diagnostic accuracy of 91.3% (sensitivity 32.6%, specificity 94.7%) in the validation cohort. Table 4 shows the number of patients who met the criteria in the validation cohort. Among these patients, unexpected pN2 disease was found in 14 (26.4%) of 43 patients who met the criteria; meanwhile, the disease of 29 (4.0%) of 740 patients did not (OR, 8.68; 95% CI, 4.25-17.73; $P < .001$). Significant differences of the frequency of single pN2 (7.6% vs. 1.4%; $P = .011$, respectively) and multiple pN2 (15.1% vs. 1.2%; $P < .001$) were observed between patients who met the criteria and those who did not (Table 4).

Discussion

The predictive criteria of unexpected N2 disease was defined as tumors with a SUV_{max} of ≥ 3.1 and clinical N1, and showed high diagnostic accuracy in both the derivation and validation cohorts. Preoperative LN biopsy by endobronchial ultrasound or mediastinoscopy should be performed in patients who meet these criteria, and preoperative therapy is recommended if mediastinal LN metastasis is found. The results of this multicenter study with a large number of patients support previous findings that the SUV_{max} of primary tumor is an independent risk factor for unexpected N2 disease.[12] The frequency of unexpected N2 was reported in approximately 2.0% to 18.5% of patients.[12-16] Unexpected N2 disease in 6.2% of patients in this study is within the range of these results.

Generally, the presence of mediastinal nodal metastasis is associated with poor outcomes in patients with NSCLC.[2] A previous study reported that patients with unexpected N2 disease had a 5-year survival of 35.8% versus 62.5% without pN2 disease.[16]

Figure 2 RFS and OS in Patients With Non–Small-Cell Lung Cancer According to Clinical and Pathologic Nodal Status. (A) Five-year RFS Rates Were 83.0%, 30.9%, and 18.2% in Patients With cN0-1/pN0-1, cN0-1/pN2, and cN2/pN2 Disease, Respectively. (B) Five-year OS Rates Were 89.1%, 71.0%, and 58.2% in Patients With cN0-1/pN0-1, cN0-1/pN2, and cN2/pN2 Disease, Respectively



Abbreviations: OS = overall survival; RFS = recurrence-free survival.

Similarly, in this study, patients with unexpected N2 disease had significantly worse prognosis than those without unexpected N2 disease (cN0-1/pN0-1). Although a previous study reported that unexpected N2 disease is a better prognostic factor compared to expected pN2 disease,[3] unexpected N2 disease is also associated with poor outcomes.

Although surgery is a highly effective treatment procedure for local disease, multidisciplinary therapy is necessary for advanced lung cancer. The efficacy of neoadjuvant therapy for patients with resectable N2 disease has been identified; the current standard treatment for clinical N2 NSCLC is definitive chemoradiotherapy or neoadjuvant therapy followed by surgery.[4,17] The disadvantages of preoperative therapy include increased risk of postoperative complications; advantages include decreased tumor volume (downstaging), eradication of clinically undetected micrometastases in the whole body, and better tolerance and compliance than with adjuvant therapy.[18,19] If surgery is performed without information regarding mediastinal LN metastasis, then systemic treatment such as adjuvant chemotherapy may be delayed or cannot be performed as a result of the patient's deterioration in general condition after the initial surgery. In fact, approximately 1 of 3 of patients with unexpected N2 disease in this study did not initiate adjuvant chemotherapy for some reason and had poor prognosis. Although previous studies reported that patients with unexpected N2 disease who underwent initial surgery followed by adjuvant chemotherapy have a good survival rate,[15] neoadjuvant therapy could be associated with better prognosis in patients with resectable N2 disease.

In recent years, several randomized trials have revealed the efficacy of ICI for the treatment of patients with lung cancer. Especially for patients with stage IV lung cancer, randomized clinical trials have demonstrated a survival benefit with ICIs; thus, it has become a new standardized treatment therapy. On the basis of these results, several randomized trials are evaluating the efficacy of ICIs (eg, nivolumab, pembrolizumab, atezolizumab, durvalumab, ipilimumab) as a neoadjuvant treatment for patients with stage I to IIIB resectable lung cancer.[20] Although these studies are ongoing, some of them have shown showed the efficacy and safety of neoadjuvant ICIs.[20,21] Moreover, ICIs provided in the neoadjuvant setting could

Table 2 Multivariable Analysis of Possible Predictors of Unexpected N2 Disease

Characteristic	Univariable		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Location, right vs. left	1.342 (0.930-1.976)	.137		
Solid tumor size on CT (cm)	1.723 (1.478-2.008)	<.0001	1.177 (0.757-1.830)	.470
C/T ratio, 1 vs. <1	3.790 (2.478-5.798)	<.0001	1.108 (0.394-3.118)	.845
SUV_{max}	1.106 (1.080-1.133)	<.0001	1.072 (1.018-1.129)	.008
Disease, clinical N1 vs. 0	7.481 (4.926-11.36)	<.0001	5.400 (1.829-15.94)	.002
Histologic type, AD vs. non-AD	0.885 (0.562-1.392)	.596		

Abbreviations: AD = adenocarcinoma; C/T ratio = consolidation/tumor ratio; CI = confidence interval; CT = computed tomography; OR = odds ratio; SUV_{max} = maximum standardized uptake value.

Table 3 Diagnostic Accuracy, Sensitivity, and Specificity in Detecting Unexpected N2 Disease

Predictive Criteria[a]	Unexpected N2 Disease	
	Present	Absent
Derivation cohort[b]		
Positive, n	40	105
Negative, n	85	1789
Validation cohort[c]		
Positive, n	14	39
Negative, n	29	701

[a]Predictive criteria of unexpected stage N2 disease were defined as tumor with maximum standardized uptake value of ≥ 3.1 and clinical stage N1.
[b]Accuracy, 90.6%; sensitivity, 32.0%; specificity, 94.5%.
[c]Accuracy, 91.3%; sensitivity, 32.6%; specificity, 94.7%.

be superior than in an adjuvant setting because it is associated with the expansion of tumor-specific T cells in the tumor before surgery.[22] This could be a standardized treatment strategy in the near future; hence, accurate preoperative mediastinal staging is needed as a diverse treatment for lung cancer.

This study has several limitations. First, this was a retrospective analysis of prospectively collected patient data. Second, no information existed on tumor location (central or peripheral) or FDG uptake of hilar/mediastinal LN on FDG-PET/CT, although these were reported as risk factors for unexpected N2 disease.[23,24] Third, the assessment of clinical N1 disease may vary from one institution to another because of the absence of an international standard. Fourth, although the survival of patients with clinical N2/pathologic N2 disease was evaluated, why preoperative therapy was not introduced for these patients remains unclear. Similarly, although we compared survival between patients who did and did not receive adjuvant therapy in unexpected N2 disease, why adjuvant therapy was not introduced remains unclear. Adjuvant therapy is often not available for patients with a poor general condition; however, there are no data on the number of patients who could not receive adjuvant therapy as a result of poor general condition, which led to selection bias.

Conclusion

Predictive criteria based on clinical LN status and FDG-PET/CT are useful for the prediction of pN2 disease in patients with clinical T1-2N0-1M0 NSCLC. The predictive criteria may help select the optimal candidate for preoperative invasive mediastinal staging. This could lead to a more accurate preoperative diagnosis of pN2 lung cancer and provide a wider choice of treatments.

Clinical Practice Points

- Despite the recent development of radiologic mediastinal staging modality such as high-resolution computed tomography or 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography, some patients had unexpected mediastinal lymph node metastases perioperatively or postoperatively.
- In this study, data from a multicenter database of 2802 patients with clinical T1-2N0-1M0 non–small-cell lung cancer were retrospectively analyzed to identify predictors of unexpected N2 disease. The predictive criteria of unexpected N2 disease were defined as tumors with a maximum standardized uptake value of ≥ 3.1 and clinical N1 disease on the basis of the multivariable analysis results of a derivation cohort. This predictive criteria

Table 4 Comparison of Frequency of Unexpected N2 Disease Between Patients Who Met the Predictive Criteria and Those Who Did Not

Characteristic	All Tumors	Predictive Criteria	Other	*P*
Derivation cohort				
N	2019	145	1874	
Unexpected pN2	125 (6.2)	40 (27.6)	85 (4.5)	<.001
Skip pN2	28 (1.4)	4 (2.8)	24 (1.3)	.137
Single pN2	54 (2.7)	22 (15.2)	32 (1.7)	<.001
Multiple N2	36 (1.8)	12 (8.3)	24 (1.3)	< .001
Unknown	7 (0.3)	2 (1.4)	5 (0.3)	
pN0	1728 (85.6)	48 (33.1)	168 (89.7)	<.001
pN1	166 (8.2)	57 (39.3)	109 (5.8)	<.001
Validation cohort				
N	783	53	730	
Unexpected pN2	43 (5.5)	14 (26.4)	29 (4.0)	<.001
Skip pN2	9 (1.2)	0	9 (1.2)	<.001
Single pN2	14 (1.8)	4 (7.6)	10 (1.4)	.011
Multiple N2	17 (2.2)	8 (15.1)	9 (1.2)	<.001
Unknown	3 (0.4)	2 (4.7)	1 (0.1)	
pN0	660 (84.3)	16 (30.2)	644 (88.2)	<.001
pN1	80 (10.2)	23 (43.4)	57 (7.8)	<.001

Data are presented as n (%). Predictive criteria of unexpected N2 disease were defined as tumor with maximum standardized uptake value of ≥ 3.1 and clinical N1.

showed high diagnostic accuracy of 90.6% (sensitivity 32.0%, specificity 94.5%) in the derivation cohort (n = 2019) and 91.3% (sensitivity 32.6%, specificity 94.7%) in the validation cohort (n = 783).

- This predictive criteria of unexpected N2 disease may help clinicians select the optimal candidate for preoperative invasive mediastinal staging and may lead to a more accurate preoperative diagnosis of pN2 lung cancer and the provision of various treatment choices to patients with clinical T1-2N0-1M0 non–small-cell lung cancer.

Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2020.12.010.

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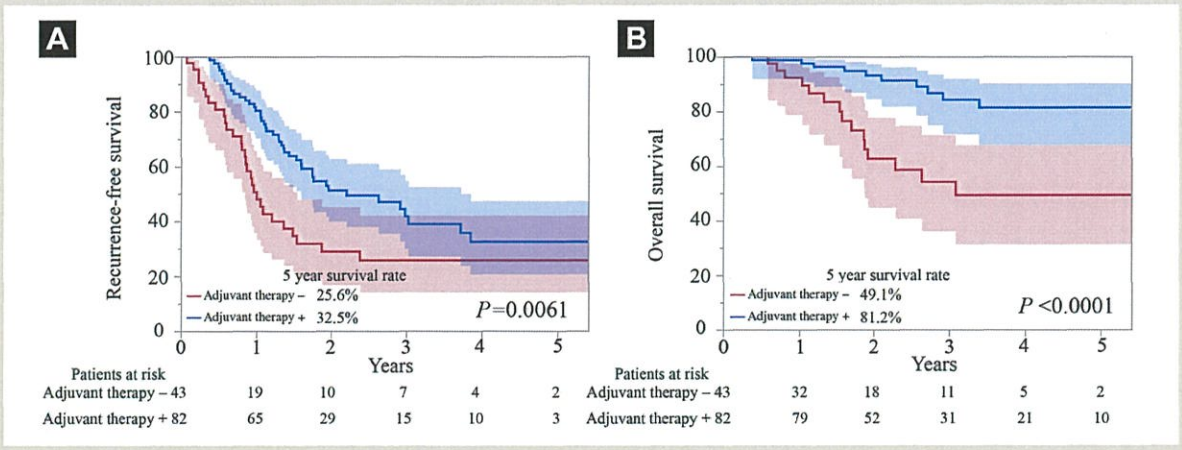
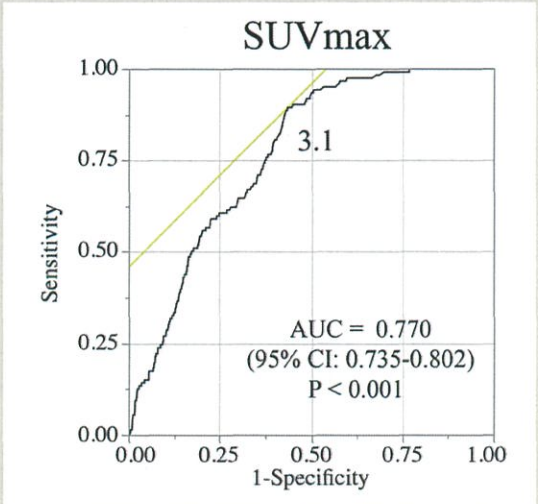
Supplemental Data

Supplemental Figure 1 **RFS and OS in Patients With Unexpected N2 Non–Small-Cell Lung Cancer With or Without Adjuvant Therapy (A) Five-year RFS Rates Were 32.5% and 25.6% in Patients With and Without Adjuvant Therapy, Respectively. (B) Five-year OS Rates Were 81.2% and 49.1% in Patients With and Without Adjuvant Therapy, Respectively**



Abbreviations: OS = overall survival; RFS = recurrence-free survival.

Supplemental Figure 2 **ROC to Detect Unexpected N2 Disease Receiver Operating Characteristic (ROC) Area Under the Curve to Detect Unexpected N2 Disease For Standardized Maximum Uptake Value in Patients With Clinical T1-2N0-1M0 Non–small-cell Lung Cancer**



Supplemental Table 1 Characteristics of 32 Patients With Clinical N2/Pathologic N2 Disease

Variable	Value
Age (years), median (IQR)	73.5 (69.0-76.8)
Sex	
Male	24 (75.0)
Female	8 (25.0)
Nodule location	
Right upper lobe	7 (21.9)
Right middle lobe	1 (3.1)
Right lower lobe	6 (18.8)
Left upper lobe	13 (40.6)
Left lower lobe	5 (15.6)
Nodule diameter on CT (mm), median (IQR)	30.5 (23.3-39.0)
C/T ratio (%), median (IQR)	100 (94-100)
Solid tumor size on CT (mm), median (IQR)	30.5 (23.0-39.0)
SUV_{max}, median (IQR)	9.12 (5.9-14.6)
Clinical T factor	
T1mi	0
T1a	1 (3.1)
T1b	5 (15.6)
T1c	10 (31.3)
T2a	10 (31.3)
T2b	6 (18.8)
Surgical procedure	
Segmentectomy	2 (6.3)
Lobectomy	30 (93.7)
Histologic type	
Adenocarcinoma	21 (65.6)
Squamous-cell carcinoma	8 (25.0)
Other	3 (9.4)
Invasion	
Pleural	13 (40.6)
Vascular	27 (84.4)
Lymphatic	21 (65.6)
pN2 status	
Skip N2	1 (3.1)
Single N2	7 (21.9)
Multiple N2	20 (62.5)
Unknown	4 (12.5)
Adjuvant therapy	15 (46.9)

Categorical data are shown as n (%) and continuous data as median (IQR).
Abbreviations: C/T ratio = consolidation/tumor ratio; CT = computed tomography; IQR = interquartile range; SUV_{max} = standardized maximum uptake value.

Supplemental Table 2 Frequency of pN0, pN1, and Unexpected N2 Disease by Cohort

Characteristic	Unexpected pN2 Disease		pN0		pN1	
	Derivation Cohort	Validation Cohort	Derivation Cohort	Validation Cohort	Derivation Cohort	Validation Cohort
Clinical T status						
T1mi	0 (0/142)	0 (0/47)	99.3 (141/142)	100 (47/47)	0.7 (1/142)	0 (0/47)
T1a	1.4 (4/279)	0 (0/96)	98.2 (274/279)	99.0 (95/96)	0.4 (1/279)	1.0 (1/96)
T1b	3.7 (27/732)	2.7 (7/261)	90.3 (661/732)	93.1 (243/261)	6.0 (44/732)	4.2 (11/261)
T1c	10.9 (53/487)	6.6 (12/183)	78.2 (381/487)	79.2 (145/183)	10.9 (53/487)	14.2 (26/183)
T2a	11.2 (30/267)	8.7 (12/149)	71.5 (191/267)	70.5 (105/149)	17.2 (46/267)	21.5 (32/149)
T2b	9.8 (11/112)	25.5 (12/47)	71.4 (80/112)	53.2 (25/47)	18.8 (21/112)	21.3 (10/47)
Clinical N status						
N0	4.5 (84/1862)	3.0 (29/729)	89.9 (1673/1862)	88.2 (643/729)	5.6 (105/1862)	7.8 (57/729)
N1	26.1 (41/157)	25.3 (14/54)	35.0 (55/157)	31.5 (17/54)	38.9 (61/157)	42.6 (23/54)
C/T ratio						
1	9.8 (96/979)	8.2 (40/489)	76.8 (752/979)	77.1 (377/489)	13.4 (131/979)	14.7 (72/489)
<1	2.8 (29/1040)	1.0 (3/294)	93.9 (976/1040)	96.3 (283/294)	3.4 (35/1040)	2.7 (8/294)
SUV_{max}						
≥3.1	11.9 (112/939)	9.6 (38/394)	72.6 (682/939)	71.1 (280/394)	15.4 (145/939)	19.3 (76/394)
<3.1	1.2 (13/1080)	1.3 (5/389)	96.9 (1046/1080)	97.7 (380/389)	1.9 (21/1080)	1.0 (4/389)
Nodule location						
Right upper lobe	6.5 (43/662)	2.8 (7/255)	87.5 (579/662)	87.4 (224/255)	6.0 (40/662)	9.4 (24/255)
Right middle lobe	4.4 (6/137)	6.1 (3/49)	90.5 (124/137)	79.6 (39/49)	5.1 (7/137)	14.3 (7/49)
Right lower lobe	8.1 (36/447)	8.5 (13/153)	83.0 (371/447)	83.7 (128/153)	9.0 (40/447)	7.8 (12/153)
Left upper lobe	5.1 (24/475)	5.6 (11/196)	85.1 (404/475)	86.7 (170/196)	9.9 (47/475)	7.7 (15/196)
Left lower lobe	5.4 (16/298)	6.9 (9/130)	83.9 (250/298)	76.2 (99/130)	10.8 (32/298)	16.9 (22/130)
Histologic type						
Adenocarcinoma	6.1 (100/1651)	5.3 (33/627)	87.5 (1445/1651)	86.1 (540/627)	6.4 (106/1651)	8.6 (54/627)
Squamous-cell carcinoma	5.5 (13/238)	5.8 (6/103)	77.7 (185/238)	76.7 (79/103)	16.8 (40/238)	17.5 (18/103)

Data are presented as % (n/N).
Abbreviations: C/T ratio = consolidation/tumor ratio; SUV_{max} = standardized maximum uptake value.