World J Surg (2019) 43:1162–1172
https://doi.org/10.1007/s00268-018-04875-y

ORIGINAL SCIENTIFIC REPORT

Prognostic Factors of Pathological N1 Non-small Cell Lung Cancer After Curative Resection Without Adjuvant Chemotherapy

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Published online: 7 December 2018

Abstract

Background The aim of this study was to evaluate the outcomes of patients with pathological N1 non-small cell lung cancer who did not receive adjuvant chemotherapy. We attempted to identify those patients for whom adjuvant chemotherapy would be indispensable.

Methods Among 132 patients who were diagnosed with pathological N1 lung cancer at a single institution from January 2010 to December 2016 were 32 patients who did not receive adjuvant treatment after curative surgical resection. The surgical and oncological outcomes of these patients were analyzed. Candidate factors for predicting recurrence were analyzed to identify patients at high risk of recurrence.

Results The median follow-up time for all 32 patients was 1044 days. The 5-year recurrence-free survival (RFS) and disease-specific survival rates of the patients without adjuvant therapy were 50.3% and 77.6%, respectively. By multivariate analysis, tumors with a lepidic growth pattern [hazard ratio (HR) 0.119, $p = 0.024$] and extralobar lymph node metastasis (HR 6.848, $p = 0.015$) were significant factors predicting recurrence. The difference between the 5-year RFS rates of patients with tumors with or without a lepidic growth pattern was statistically significant (63.5% vs 40.0%, respectively; $p = 0.050$). The 5-year RFS rates of patients with intralobar lymph node metastasis versus those with extralobar lymph node metastasis were 63.3% and 18.8%, respectively ($p = 0.002$).

Conclusions Patients with tumors without a lepidic growth pattern or with extralobar lymph node metastasis who do not receive adjuvant chemotherapy have a high recurrence rate after surgery. Therefore, these patients should be encouraged to undergo adjuvant chemotherapy if their overall condition is not a contraindication for chemotherapy.

Introduction

The most important prognostic indicator of non-small cell lung cancer (NSCLC) is the tumor, node, metastasis (TNM) stage. Therefore, the treatment plan is established in accordance with the TNM stage [1]. According to the National Comprehensive Cancer Network (NCCN) guidelines for NSCLCs (Version 4, 2018), adjuvant chemotherapy after curative anatomical resection is recommended for patients with pathological N1 NSCLC. The results of many studies have suggested that postoperative adjuvant chemotherapy improves the outcomes of patients with N1 or N2 disease [2, 3]. Furthermore, there have been

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studies showing that adjuvant chemotherapy has helped to prevent local recurrence [4, 5].

NSCLC is composed of various histological types, which often indicate a different prognosis for the same disease stage. In particular, adenocarcinoma is known to have a relatively good prognosis if a lepidic pattern is present in the tumor [6–8]. Meanwhile, some published reports have also revealed that the outcomes of patients with stage II and III lung cancer vary according to metastatic lymph node stations [9, 10]. Some studies have reported that patients with stage II NSCLC intralobar nodal metastasis (lymph node stations #12, #13, or #14) have better outcomes than patients with extralobar metastasis (lymph node stations #10 or #11) [9, 11]. Therefore, the same treatment, namely adjuvant chemotherapy, for every NSCLC patient with N1 disease might not be appropriate.

The administration of adjuvant chemotherapy is usually recommended to occur within 6 weeks after surgery [12, 13]. However, if postoperative complications develop after curative resection, inflammatory diseases such as pneumonia might persist for a long period of time. When adjuvant chemotherapy is administered to a patient with postoperative complications, the patient might have a worse outcome. In addition, chemotherapy after surgery might be refused by the patient. If we could predict what happens when a patient with N1 disease does not receive adjuvant chemotherapy, we could emphasize the importance of chemotherapy to patients who need it but refuse it.

The aim of this study was to evaluate the outcomes of patients with pathological N1 NSCLC who did not receive adjuvant chemotherapy after curative surgery. Therefore, we attempted to distinguish between the patients with better outcomes and those with worse outcomes to identify the patients for whom adjuvant chemotherapy is indispensable. We wanted to distinguish between patients for whom adjuvant chemotherapy is mandatory and those for whom adjuvant chemotherapy can be postponed, based on overall condition.

Patients and methods

Patients

From January 2010 to December 2016, 1337 consecutive patients were diagnosed with and surgically treated for NSCLC at Seoul St. Mary's Hospital at the Catholic University of Korea. Among 132 patients who were diagnosed with pathological N1 lung cancer were 32 patients who did not receive adjuvant treatment after curative surgical resection. None of the study patients received an incomplete resection or received preoperative chemo- or radiotherapy. These 32 consecutive patients were reviewed retrospectively. The surgical and oncological outcomes were analyzed. Predictive factors for recurrence were identified. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital.

Preoperative evaluation and staging

All patients suspected of having lung cancer routinely underwent chest computed tomography (CT), F-18-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT, bronchoscopy, and brain magnetic resonance imaging (MRI) for cancer status. All patients also underwent preoperative pulmonary function testing and echocardiography. Contrast-enhanced chest CT and FDG-PET/CT were used for preoperative lymph node staging. The lymph nodes of patients with stage N1 and N2 disease were considered to be malignant if the short-axis diameter exceeded 10 mm on CT scans and if FDG uptake by the node was greater than that of surrounding mediastinal structures. However, a lymph node with elevated FDG uptake was considered benign if the lymph node contained benign calcifications or if unenhanced CT images showed high attenuation with distinct margins [14, 15]. General symmetrical and equivocal FDG uptake in mediastinal lymph nodes on a PET/CT scan was interpreted as reactive change to inflammation. Patients diagnosed with clinical N0 tumors on chest CT and PET/CT underwent surgery without undergoing invasive preoperative lymph node staging if complete resection was considered feasible.

Surgical procedures and adjuvant therapy

Patients with preoperative clinical N1 NSCLC are considered to be candidates for curative surgery at our institution. All of the patients underwent surgical procedures, which included lobectomy (bilobectomy), and most of them underwent mediastinal lymph node dissection of more than three mediastinal lymph node stations (surgery on the right side included dissection of paratracheal and subcarinal lymph nodes, and surgery on the left side included dissection of subaortic and subcarinal lymph nodes). All of the patients underwent dissection of every visible hilar, peribronchial, and perivascular N1 lymph node. The technique used for lymph node dissection was en bloc resection of the lymph nodes, including adjacent fat tissue.

Most resections were performed by video-assisted thoracoscopic surgery. Our treatment policy after surgery for patients with N1 disease is to administer adjuvant chemotherapy. However, the surgeon sometimes has chosen to omit adjuvant chemotherapy because of the patient's overall condition or patient refusal. Therefore, we reported

the reasons for not performing adjuvant therapy in this study.

Histological evaluation

All clinical specimens were examined by pathologists, whose observations were recorded. Each patient report was reviewed for tumor size, location, tumor differentiation, lymph node status, pleural invasion, lymphatic invasion, and vascular invasion. TNM staging was based on the Seventh Edition of the American Joint Committee on Cancer (AJCC) guidelines. To describe the histomorphological patterns of an adenocarcinoma, the proportion of each component (lepidic, acinar, papillary, micropapillary, and solid) in the total tumor area was measured and recorded semiquantitatively in 5% increments, according to the 2015 WHO classification of lung tumors [16]. In this study, a tumor with lepidic growth pattern was a tumor in which the proportion of lepidic growth pattern was 5% or greater than 5%. The lymph node stations were based on the lymph node map of the International Association for the Study of Lung Cancer (IASCL) [17]. Patients with N1 stations were divided into two groups, according to the location of the lymph node metastasis, as follows: intralobar lymph node (lobar #12, segmental #13) metastasis and extralobar lymph node (hilar #10, interlobar #11) metastasis. We used these factors as variables that were analyzed as predictive factors.

Follow-up evaluation

All patients were followed from the day of surgery. For the first 2 years, they received physical examinations and underwent chest radiography every 3 months, and underwent chest CT that incorporated cervical and abdominal views every 6 months. Thereafter, they received physical examinations and underwent low-dose chest CT every 6 months up to 5 years and thereafter annually.

Statistical analysis

The clinicopathological characteristics of all patients were analyzed. The Kaplan–Meier method was used to analyze data collected from the interval between surgical resection and the time of the final follow-up visit, as well as to estimate recurrence-free survival (RFS) and disease-specific survival (DSS) using the collected data on confirmed recurrences and cancer-related deaths. The Cox proportional hazards model was used in a multivariate analysis to determine the risk of recurrence and cancer-related death for all patients. All variables with a p of <0.1 in the univariate analysis were entered into a multivariate analysis. A p value <0.05 was considered statistically significant. Clinicopathological characteristics were compared by the Student t test, or Wilcoxon rank-sum test for continuous variables and the Chi-square test or Fisher exact test for categorical variables. A p value of <0.05 was considered significant. Statistical analysis was performed using SPSS 19.0 software (IBM Corp, Armonk, NY).

Results

The clinicopathological characteristics of all 32 study patients are shown in Table 1. The mean age was 68.7 ($\pm$10.1) years, and there were more male (56.3%) than female patients. The number of patients with pathological T1a, T1b, T2a, T2b, T3, and T4 disease was as follows: 4 (12.5%), 4 (12.5%), 18 (56.3%), 2 (6.3%), 3 (9.4%), and 1 (3.1%), respectively. Most of the patients had an adenocarcinoma (78.1%), and the others had squamous cell carcinoma (21.9%). Of the adenocarcinoma patients, 15 (46.9%) had tumors with a lepidic growth pattern. Intralobar lymph node metastasis occurred in 23 patients (71.9%), and extralobar lymph node metastasis occurred in nine patients (28.1%).

Table 2 summarizes the reasons why patients did not receive adjuvant therapy. Half of the patients refused chemotherapy after surgery although they had no contraindications, and the other patients did not receive adjuvant therapy because of comorbidities or advanced age.

Survival rates of patients with N1 NSCLC who received adjuvant therapy versus those of patients with N1 NSCLC who did not receive adjuvant therapy after curative surgery

Among all N1 patients, 32 patients did not receive and 100 patients received adjuvant therapy after curative resection. The difference between the RFS rate of patients receiving adjuvant therapy and the rate of those not receiving adjuvant therapy was not significant (52.2% vs 51.9%, respectively; $p = 0.805$). The difference between the respective DSS rates of patients in the two groups was also not significant (72.8% vs 77.6%, $p = 0.786$).

Survival analysis and risk factors for recurrence in patients with N1 NSCLC without adjuvant therapy after curative surgery

The median follow-up time for N1 patients without adjuvant therapy was 1044 days (range 37–2284 days), with recurrence identified in 13 patients (Table 3). Among those 13 patients, locoregional recurrence occurred in eight patients (bronchial stump, one patient; ipsilateral lung, two patients; ipsilateral lymph nodes, three patients; and lung

Table 1 Clinicopathological characteristics of patients with pathological N1 non-small cell lung cancer after curative surgery without adjuvant treatment

Variables	Mean (±SD) or *n* (%)
Age	68.7 (±10.1)
Gender	
Male	18 (56.3%)
Female	14 (43.8%)
Current or former smoker	15 (46.9%)
Serum CEA level (ng/mL)	8.0 (±15.6)
SUVmax	7.5 (±3.0)
TNM stage	
T1aN1M0	4 (12.5%)
T1bN1M0	4 (12.5%)
T2aN1M0	18 (56.3%)
T2bN1M0	2 (6.3%)
T3N1M0	3 (9.4%)
T4N1M0	1 (3.1%)
Unexpected N1 (clinical N0)	20 (62.5%)
Involved lobe	
Right upper	8 (25%)
Right middle	1 (3.1%)
Right lower	8 (25%)
Left upper	7 (21.9%)
Left lower	8 (25%)
Pulmonary function	
FEV1 (%)	93.2 (±20.7)
DLCO (%)	78.8 (±18.7)
Operation	
Lobectomy	30 (93.8%)
Bilobectomy	2 (6.3%)
VATS	28 (87.5%)
Open thoracotomy	4 (12.5%)
Postoperative Complications	9 (28.1%)
Prolonged air leak	7 (21.9%)
Atrial fibrillation	1 (3.1%)
Pneumonia	1 (3.1%)
Operative mortality	0
Tumor size (cm)	3.2 (±1.3)
Metastatic lung nodule (T3 or T4)	3 (9.4%)
Number of dissected lymph nodes	18.3 (±9.8)
Number of dissected N1 lymph nodes	9.8 (±5.5)
Location	
Central	9 (28.1%)
Peripheral	23 (71.9%)
Histology	
Adenocarcinoma	25 (78.1%)
Acinar	17 (53.1%)
Lepidic	2 (6.3%)
Papillary	4 (12.5%)
Solid	2 (6.3%)
Squamous cell carcinoma	7 (21.9%)
Tumor with lepidic growth pattern	15 (46.9%)
Metastatic lymph node stations	
Intralobar lymph node metastasis	23 (71.9%)
Extralobar lymph node metastasis	9 (28.1%)
Pleural invasion	
Visceral pleural invasion	10 (31.3%)
Parietal pleural invasion (T3)	1 (3.1%)
Lymphatic invasion	29 (90.6%)
Vascular invasion	12 (37.5%)

SD standard deviation, *CEA* carcinoembryonic antigen, *FEV1* forced expiratory volume in 1 s, *DLCO* diffusing capacity for carbon monoxide, *VATS* video-assisted thoracoscopic surgery

Intralobar lymph node metastasis = lymph node metastasis in lobar (#12) or segmental (#13) lymph node; extralobar lymph node metastasis = lymph node metastasis in hilar (#10) or interlobar (#11) lymph node

Table 2 Reasons why patients did not receive adjuvant therapy

Cause of no adjuvant chemotherapy	*n* (%)
Old age	4 (12.5%)
Patient refusal (no contraindications for chemotherapy)	16 (50%)
Postoperative complications (pneumonia)	2 (6.3%)
Comorbidities	10 (31.2%)
Other cancers	3
Dementia	1
Renal disease	1
Idiopathic pulmonary fibrosis	1
Cerebrovascular disease	2
Coronary artery disease	1
Decreased pulmonary function	1

Table 3 Summary of recurrence

Overall recurrence	*n* = 13 (40.6%)
Locoregional recurrence	8 (25.0%)
Distant recurrence	0
Both	5 (15.6%)

Locoregional = recurrence within ipsilateral hemithorax including pleura and mediastinal lymph nodes; both = locoregional recurrence + distant recurrence

and lymph nodes, two patients) and locoregional recurrence with distant recurrence occurred in five patients (bilateral lungs, two patients; bilateral lungs and

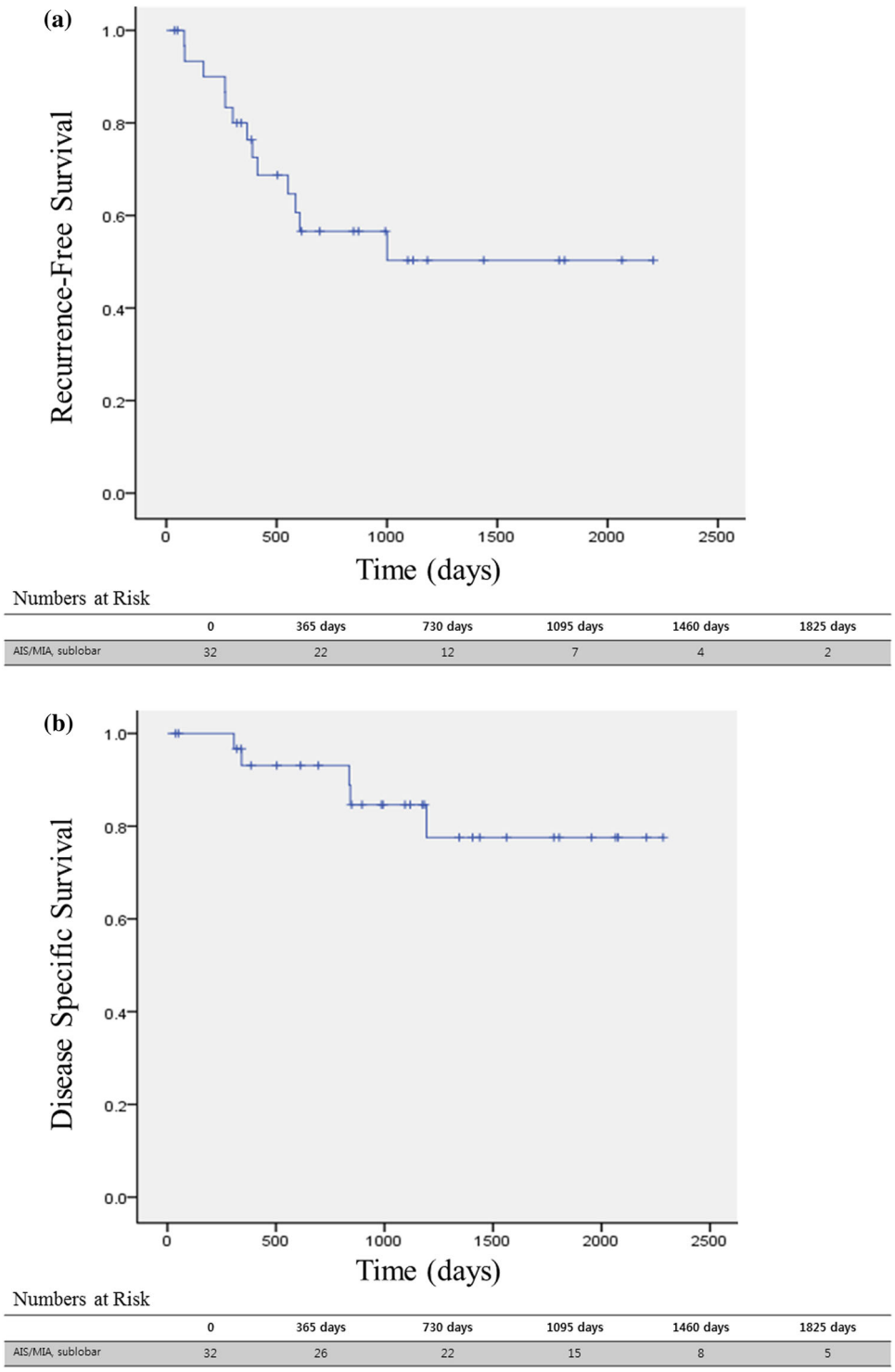


Fig. 1 Recurrence-free survival (**a**) and disease-specific survival (**b**) of patients with pathological N1 non-small cell lung cancer after curative resection without adjuvant chemotherapy

contralateral lymph nodes, one patient; bilateral lungs and ipsilateral supraclavicular lymph nodes, one patient; and ipsilateral lung (with pleura) and brain, one patient). The 5-year RFS and DSS rates were 50.3% and 77.6%, respectively (Fig. 1a, b).

The results of univariate and multivariate analysis are shown in Table 4. Specific variables identified as significant ($p < 0.1$) by univariate analysis included the presence of metastatic lung nodule, tumor with lepidic growth pattern, extralobar lymph node metastasis, and pleural invasion. These variables were entered into the multivariate

Table 4 Univariate analysis and multivariate analysis of risk factors for recurrence in patients with pathological N1 non-small cell lung cancer after curative surgery without adjuvant treatment

Variables	HR	95% CI	*p* value
Univariate analysis			
Age	0.982	0.930–1.037	0.514
Gender (male)	2.350	0.722–7.648	0.156
Smoker	1.175	0.393–3.518	0.773
CEA	0.931	0.829–1.045	0.226
SUVmax	0.975	0.806–1.179	0.791
Unexpected N1 (clinical N0)	0.907	0.295–2.788	0.864
Lobe			0.951
Right upper	1		
Right lower	0.938	0.188–4.683	0.937
Left upper	0.931	0.188–4.617	0.930
Left lower	1.358	0.302–6.111	0.690
FEV1 (%)	0.981	0.956–1.007	0.154
DLCO (%)	0.976	0.945–1.008	0.135
Tumor size (cm)	1.355	0.881–2.083	0.167
Metastatic lung nodule	5.104	1.332–19.558	0.017
Central location	0.719	0.197–2.630	0.618
Histology (adenocarcinoma)	0.444	0.136–1.448	0.178
Tumor with lepidic growth pattern	0.324	0.099–1.057	0.062
Extralobar lymph node metastasis	4.847	1.593–14.753	0.005
Pleural invasion			0.037
Visceral pleural invasion	3.700	1.153–11.870	0.028
Parietal pleural invasion	9.828	1.014–95.280	0.049
Lymphatic invasion	0.429	0.094–1.958	0.274
Vascular invasion	1.723	0.568–5.220	0.336
Multivariate analysis			
Metastatic lung nodule	0.520	0.067–4.056	0.532
Tumor with lepidic growth pattern	0.119	0.019–0.757	0.024
Extralobar lymph node metastasis	6.848	1.458–32.161	0.015
Pleural invasion			0.166
Visceral pleural invasion	4.875	0.939–25.301	0.059
Parietal pleural invasion	1.358	0.094–19.599	0.822

HR hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic antigen, *SUVmax* maximum standardized uptake value, *FEV1* forced expiratory volume in 1 s, *DLCO* diffusing capacity for carbon monoxide

Tumor with lepidic growth pattern = lepidic component ≥5%; extralobar lymph node metastasis = lymph node metastasis in hilar (#10) or interlobar (#11) lymph node

model. Tumors with lepidic growth pattern [hazard ratio (HR) 0.119, $p = 0.024$] and extralobar lymph node metastasis (HR 6.848, $p = 0.015$) were significant predictors of recurrence.

Comparison of clinicopathological characteristics and recurrence-free survival rates among subgroups

We compared the clinicopathological characteristics and RFS rates of patients with tumors with a lepidic growth pattern versus those without a lepidic growth pattern, and of patients with extralobar lymph node metastasis versus those with intralobar lymph node metastasis. Most of the clinicopathological factors of the patients in the subgroups did not differ significantly (Table 5). The difference between the 5-year RFS rates of patients with tumors with or without a lepidic growth pattern was statistically significant (63.5% vs 40.0%, respectively; $p = 0.050$) (Fig. 2a). The 5-year RFS rates of patients with intralobar lymph node metastasis versus those with extralobar lymph node metastasis were 63.3% and 18.8%, respectively ($p = 0.002$) (Fig. 2b).

Discussion

Surgery is the treatment of choice for patients with N1 NSCLC. For patients with N1 disease, anatomical curative resection and lymph node dissection are essential. And most patients are advised to receive adjuvant chemotherapy after surgery. However, because of the toxicity of chemotherapy, treating every patient with N1 disease with adjuvant chemotherapy after surgery is difficult, especially within the recommended 6 weeks after surgery and especially for patients with postoperative complications. Patients may also refuse adjuvant chemotherapy because they feel weak after surgery. For these situations, it is important to determine whether or not adjuvant chemotherapy is mandatory despite the poor overall condition of the patient. The aim of this study was to determine the risk factors of recurrence among patients who did not receive adjuvant chemotherapy after surgery to find out what factors would lead to mandatory chemotherapy. This study found that patients with tumors without a lepidic growth pattern and patients with extralobar lymph node metastasis had poor outcomes. The 5-year RFS was 40.0% in patients with tumors without a lepidic growth pattern and 18.8% in patients with extralobar lymph node metastasis. Therefore, for patients with tumors without a lepidic growth pattern or with extralobar lymph node metastasis, adjuvant chemotherapy is required if possible; otherwise, it may be selected considering the patient's condition.

We investigated the outcomes of all patients with N1 disease who did not receive adjuvant chemotherapy, because the T stage indicated that such patients could be treated by surgery, whereas the N stage was considered to be an important indication for postoperative adjuvant chemotherapy. T3 and T4 lesions were completely resected

Table 5 Comparison of clinicopathological characteristics of patients with tumor with or without lepidic growth pattern and of patients with extralobar versus intralobar lymph node metastasis

Variables	With lepidic growth pattern	Without lepidic growth pattern	*p* value
Age	70.5 (±10.7)	67.0 (±9.7)	0.333
Gender			
Male	5 (33.3%)	13 (76.5%)	0.014
Female	10 (66.7%)	4 (23.5%)	
Current or former smoker	4 (26.7%)	11 (64.7%)	0.031
Serum CEA level	6.1 (±6.9)	9.8 (±20.6)	0.516
SUVmax	7.3 (±3.3)	7.7 (±2.8)	0.736
TNM stage			
T1aN1M0	2 (11.8%)	2 (13.3%)	0.515
T1bN1M0	1 (5.9%)	3 (20.0%)	
T2aN1M0	9 (52.9%)	9 (60.0%)	
T2bN1M0	1 (5.9%)	1 (6.7%)	
T3N1M0	3 (17.6%)	0	
T4N1M0	1 (5.9%)	0	
Involved lobe			
Right upper	5 (29.4%)	3 (20.0%)	0.440
Right middle	1 (5.9%)	0	
Right lower	2 (11.8%)	6 (40.0%)	
Left upper	4 (23.5%)	3 (20.0%)	
Left lower	5 (29.4%)	3 (20.0%)	
Pulmonary function			
FEV1 (%)	94.6 (±23.0)	91.9 (±19.0)	0.722
DLCO (%)	79.9 (±20.7)	77.9 (±17.5)	0.772
Tumor size (cm)	3.2 (±1.2)	3.2 (±1.4)	0.903
Metastatic lung nodule	0	3 (17.6%)	0.229
Location			
Central	3 (20.0%)	6 (35.3%)	0.444
Peripheral	12 (80.0%)	11 (64.7%)	
Pleural invasion			
Visceral pleural invasion	5 (33.3%)	5 (29.4%)	0.629
Parietal pleural invasion	0	1 (5.9%)	
Lymphatic invasion	15 (100%)	14 (82.4%)	0.229
Vascular invasion	8 (53.3%)	4 (23.5%)	0.082
Variables	Extralobar lymph node metastasis	Intralobar lymph node metastasis	*p* value
Age	68.2 (±12.0)	68.8 (±9.6)	0.882
Gender			
Male	7 (77.8%)	11 (47.8%)	0.235
Female	2 (22.2%)	12 (52.2%)	
Current or former smoker	7 (77.8%)	8 (34.8%)	0.049
Serum CEA level	3.1 (±1.5)	10.0 (±18.2)	0.275
SUVmax	7.9 (±2.3)	7.4 (±3.3)	0.692

Table 5 continued

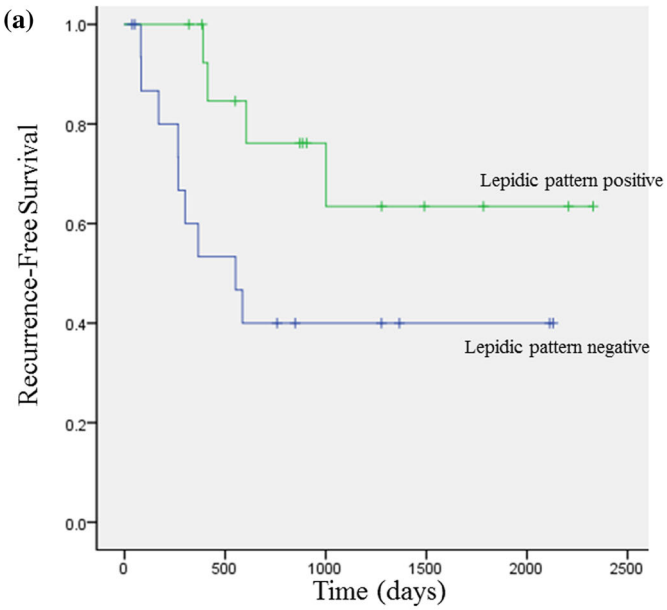
Variables	Extralobar lymph node metastasis	Intralobar lymph node metastasis	*p* value
TNM stage			
T1aN1M0	2 (22.2%)	2 (8.7%)	0.058
T1bN1M0	0	4 (17.4%)	
T2aN1M0	3 (33.3%)	15 (65.2%)	
T2bN1M0	1 (11.1%)	1 (4.3%)	
T3N1M0	2 (22.2%)	1 (4.3%)	
T4N1M0	1 (11.1%)	0	
Involved lobe			
Right upper	4 (44.4%)	4 (17.4%)	0.248
Right middle	0	1 (4.3%)	
Right lower	3 (33.3%)	5 (21.7%)	
Left upper	0	7 (30.4%)	
Left lower	2 (22.2%)	6 (26.1%)	
Pulmonary function			
FEV1 (%)	85.9 (±15.0)	96.0 (±22.1)	0.217
DLCO (%)	79.1 (±20.3)	78.7 (±18.5)	0.958
Tumor size (cm)	3.3 (±1.8)	3.1 (±1.1)	0.704
Metastatic lung nodule	2 (22.2%)	1 (4.3%)	0.184
Location			
Central	1 (11.1%)	8 (34.8%)	0.383
Peripheral	8 (88.9%)	15 (65.2%)	
Pleural invasion			
Visceral pleural invasion	4 (44.4%)	6 (26.1%)	0.128
Parietal pleural invasion	1 (11.1%)	0	
Lymphatic invasion	7 (77.8%)	22 (95.7%)	0.184
Vascular invasion	3 (33.3%)	9 (39.1%)	1.000

CEA carcinoembryonic antigen, *SUVmax* maximum standardized uptake value, *FEV1* forced expiratory volume in 1 s, *DLCO* diffusing capacity for carbon monoxide

Tumor with lepidic growth pattern = lepidic component ≥5%; extralobar lymph node metastasis = lymph node metastasis in hilar (#10) or interlobar (#11) lymph node; intralobar lymph node metastasis = lymph node metastasis in lobar (#12) or segmental (#13) lymph node

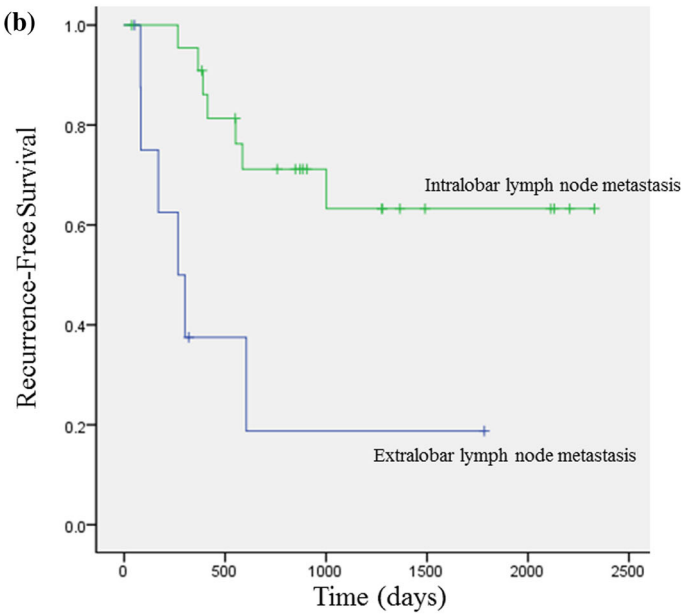
by surgery in this study. Thus, all N1 patients regardless of T stage were analyzed in this study. Multivariate analysis in this study did not find that T factors (tumor size, pleural invasion) were significant factors for recurrence. Therefore, application of the results of this study to all patients with N1 disease who underwent complete surgical resection is feasible.

The differences between the RFS and DSS rates of the patients receiving adjuvant therapy versus those not receiving adjuvant therapy were not significant (5-year RFS 52.2% vs 51.9%, respectively; $p = 0.805$; 5-year DSS 72.8% vs 77.6%, respectively; $p = 0.786$). The reason for the lack of survival benefit from adjuvant therapy was attributed to differences between the clinicopathological characteristics of the patients receiving adjuvant and the patients not receiving adjuvant therapy. However, this study was not performed to compare the survival rates of patients receiving adjuvant chemotherapy with the rates of patients not receiving adjuvant chemotherapy. In addition, we did not think that investigating the efficacy of adjuvant treatment in this study was necessary, because the effectiveness of adjuvant treatment has already been demonstrated in several other studies [2–5, 12, 13]. Most studies that evaluated the outcomes of patients with N1 disease have included patients who have received adjuvant chemotherapy [2, 3, 18, 19]. Outcome studies of patients with N1 lung cancer who did not undergo adjuvant chemotherapy are very rare. Therefore, for patients who have not received adjuvant chemotherapy, identifying the risk of recurrence may be important for selecting those patients who require adjuvant chemotherapy.



Numbers at Risk

	0	365 days	730 days	1095 days	1460 days	1825 days
Lepidic pattern positive	15	14	9	2	2	2
Lepidic pattern negative	17	9	6	2	2	2



Numbers at Risk

	0	365 days	730 days	1095 days	1460 days	1825 days
Intralobar lymph node metastasis	23	21	14	8	5	4
Extralobar lymph node metastasis	9	2	1	1	1	1

Fig. 2 Comparison of recurrence-free survival in patients with tumor with lepidic growth pattern and in patients with tumor without lepidic growth pattern (**a**), and between patients with extralobar lymph node metastasis and patients with intralobar lymph node metastasis (**b**)

The majority of NSCLCs are adenocarcinomas, which show several histological subtypes [16]. We could not compare the outcomes of patients based on histological subtypes because of the low number of study participants. Instead, we divided the patients into two groups according to the presence or absence of a lepidic growth pattern in the tumor. Invasive adenocarcinomas can have a different prognosis depending on the proportion of tumors showing a lepidic growth pattern [7, 20–22]. Furthermore, adenocarcinomas with or without a lepidic growth pattern also have

different tumor biologies [6]. However, most studies on tumors with a lepidic growth pattern have only been focused on stage I lung cancer. In this study, patients with N1 adenocarcinoma with a lepidic growth pattern obtained a better outcome than patients with N1 non-small cell lung cancer without a lepidic growth pattern.

Anatomically, extralobar lymph nodes are located in the hila or fissures. In other words, hilar nodes (station #10) and interlobar nodes (station #11) are not within the pulmonary lobes [17]. Therefore, surgeons usually suspect whether the lymph node was completely resected or not after lobectomy in the case of extralobar lymph node metastasis. In our institution, lymph node dissection is performed by en bloc resection of the lymph nodes, which includes adjacent fat tissue. In addition, a patient in whom a lymph node remained or a lymph node was not completely resected was excluded from this study. Thus, all of the patients included in the study had undergone complete resection of their lung cancer. Nevertheless, the outcome was poor for patients with extralobar lymph node metastasis and N1 disease. In this study, the 5-year RFS rate was 18.8% for extralobar metastatic N1 disease. In addition, the hilar lymph node (station #10) is very close to N2 lymph nodes, so that the boundary between N1 and N2 disease may be ambiguous. We also believe that an extralobar lymph node metastasis should be treated by a strategy that is similar to the treatment strategy used for N2 disease, because N1 disease with extralobar lymph node metastasis has a high recurrence rate that is similar to the rate for N2 disease. Therefore, in the presence of extralobar lymph node metastasis, if assessment shows that the patient could tolerate chemotherapy, a strong recommendation of adjuvant chemotherapy might be advisable, whether or not the patient refuses chemotherapy.

In this study, instead of overall survival, we evaluated RFS, because the aim of adjuvant chemotherapy is to reduce recurrence after curative surgery. Therefore, comparing rates of RFS may be more helpful than evaluating overall survival while deciding on whether to administer adjuvant chemotherapy. Further, RFS is a more accurate measurement of survival, since it reflects the biological behavior of the cancer rather than death from unrelated factors.

This study has a few limitations. First, this was a retrospective review. Second, we obtained data from a single institution, and the sample size was too small to generalize our results. However, this study examined data from surgical patients treated by a relatively standardized protocol at our institution, a tertiary hospital in Korea. Furthermore, a very detailed analysis was possible because of the detailed information stored in the electronic medical records. We used data that described the surgical procedures on lymph node dissection in detail. We excluded data that were considered insufficient descriptions of lymph node dissection. We believe that our data can be used as the basis for future investigations. A larger study should be performed to validate our results. Finally, the follow-up period was relatively short. However, most patients with NSCLC are known to recur within a 2-year postoperative period [23], and early recurrence has been shown to be an accurate reflection of the long-term outcome [24].

In conclusion, patients with tumors without a lepidic growth pattern or with extralobar lymph node metastasis have a high recurrence rate after surgery alone without adjuvant chemotherapy. Therefore, these patients should be encouraged to receive adjuvant chemotherapy if their overall condition is not a major problem. On the other hand, a lepidic growth pattern and intralobar lymph node metastasis are good prognostic factors in patients with N1 NSCLC. Therefore, if adjuvant chemotherapy for patients with N1 NSCLC cannot be performed within the recommended time interval after curative resection, we may choose routine follow-up if the patient's disease has two factors predictive of good outcome. Additional studies that include data from a larger homogenous sample and a longer follow-up period might provide more accurate results.

Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to declare.

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