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Clinical implications of uncertain resection in scenarios of metastasis of the highest or most distant mediastinal lymph node station following surgical treatment of non-small-cell lung cancer

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ABSTRACT

Objectives: The positive highest nodal station after operation is one of the definitions of "uncertain resection" proposed by the International Association for the Study of Lung Cancer. This study was performed to determine the prognostic value of positive highest or the most distant nodal station in patients with N2 non-small-cell lung cancer (NSCLC).

Materials and Methods: Three hundred thirty-nine patients who underwent complete anatomical resection and mediastinal lymph node (LN) dissection for N2 NSCLC between 2000 and 2015 were reviewed. Cases of operative mortality, extracapsular invasion of LN and incomplete resection were excluded from analysis.

Results: The mean age was 61.58 ± 9.43 years, and 235(69.3%) patients were male. The numbers of total dissected LNs and positive LNs were 29.90 ± 11.92 and 5.49 ± 5.90, respectively. The subcategory of N stage was divided as follows: N2a1, 91(26.8%); N2a2, 132(38.9%); and N2b, 116(34.2%). One hundred forty-two (41.9%) patients showed highest LN metastasis, and 162(47.8%) patients showed most distant LN metastasis. Kaplan–Meier analysis revealed no differences between distant LN negative and positive patients regarding 5-year overall survival (43.1% vs. 39.2%; p = 0.428) and between highest LN negative and positive patients regarding 5-year overall survival (42.1% vs. 40.0%; p = 0.539). On multivariable analysis, metastasis to the most distant mediastinal LN (hazard ratio (HR): 1.050; p = 0.755) and metastasis to the highest mediastinal LN (HR: 1.015; p = 0.924) were not related to overall survival.

Conclusion: The current definition of uncertain resection based on metastasis of the highest or most distant LNs did not show survival differences in completely resected N2 NSCLC.

1. Introduction

Knowing a patient's resection status after cancer surgery is important because this characteristic may be a strong predictor of prognosis and can influence further treatment planning [1]. Traditionally, tumor status following treatment has been indicated according to residual tumor (R) classification, as follows: R0, no residual tumor; R1, microscopic residual tumor; and R2, macroscopic residual tumor [1]. However, the resection status in various cancers cannot be described uniformly by R factors alone. For non-small-cell lung cancer (NSCLC), the International Association for the Study of Lung Cancer (IASLC) has classified resection status into three categories: complete resection, incomplete resection, and uncertain resection. Uncertain resection is defined when there are no definite residual cancer cells in the thoracic cavity, but complete resection cannot be confirmed [2].

The definition of uncertain resection proposed by the IASLC includes four criteria. More specifically, uncertain resection is defined when the resection margins are free of disease microscopically but when one of the following also applies: 1) intraoperative lymph node evaluation has been less rigorous than systematic nodal dissection or lobe-specific systematic nodal dissection as described above, 2) the highest mediastinal node removed is positive, 3) the bronchial margin

Abbreviations: NSCLC, non-small-cell lung cancer; IASLC, the International Association for the Study of Lung Cancer; CT, Chest computed tomography; PET, positron-emission tomography; AJCC, American Joint Committee on Cancer; LN, lymph node; SEPAR, Spanish Society of Pneumology and Thoracic Surgery

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shows carcinoma in situ, and 4) pleural lavage cytology is positive (R1 cy+). Gagliasso et al. reported that patients with uncertain resection showed worse survival than did those suggested to have complete resection [3]. Many researchers have studied the clinical implications of specific criteria such as mediastinal lymph node dissection, carcinoma in situ on resection margin or pleural cytology, but few previous studies investigated about the clinical implications of metastasis at the highest mediastinal lymph nodes [4,5]. Therefore, this retrospective study was performed to elucidate the clinical implications and their impacts on patient survival in the context of uncertain resection according to metastasis of the highest or most distant mediastinal lymph nodes after an attempt to achieve complete resection of NSCLC.

2. Material and methods

2.1. Patients

This retrospective study was approved by the institutional review board (IRB no. 2019-1385-001) of our institution. Between 2000–2015, 468 patients underwent surgery for N2 NSCLC. The exclusion criteria for analysis were operative mortality, extracapsular invasion of metastatic lymph nodes, incomplete resection (R1 or R2) at the resection margin, and sublobar resection techniques such as segmentectomy or wedge resection. Finally, 339 patients who underwent complete resection were analyzed (Fig. 1). All patients underwent complete mediastinal lymph node dissection, and no patient received mediastinal lymph node sampling or lobe-specific lymph node dissection. Chest computed tomography (CT), bronchoscopy and pulmonary function testing were performed preoperatively in all patients. However, the other diagnostic modalities have been changed during the study periods. Before 2011, we usually performed mediastinoscopic biopsy if N2 metastasis was suspected. EBUS has been started since 2015. positron-emission tomography (PET), has been done since 2005. Postoperatively, chest CT and PET-CT scans were obtained at six-month intervals for the first two years after surgery and then annually thereafter to detect recurrence.

2.2. Definition of "uncertain resection"

The stage was calculated based on the eighth edition of the American Joint Committee on Cancer (AJCC) criteria [6]. All mediastinal lymph nodes were defined based on the IASLC lymph node map [7]. Even though the IASLC defined metastasis at the highest mediastinal lymph node station as uncertain resection [2], the other guidelines defined the most distant mediastinal lymph node station as uncertain resection [8], so we evaluated the clinical implications of metastasis at both the "highest mediastinal lymph node" and "most distant mediastinal lymph node." We defined the highest and lowest mediastinal lymph nodes, respectively, as the most distant mediastinal lymph node stations. For right-side lung cancer, 2R (upper paratracheal lymph node) was defined as the highest mediastinal lymph node station, and 9 (intrapulmonary ligament lymph node) was defined as the lowest mediastinal lymph node station. For left-side lung cancer, 6 (para-aortic lymph node) and 4 L (left paratracheal lymph node) were defined as the highest mediastinal lymph node stations, and 9 (intrapulmonary ligament lymph node) was defined as the lowest mediastinal lymph node station. Based on final pathologic reports, patients were divided into two categories: metastasis to the highest mediastinal lymph node station (highest LN [lymph node] positive patients vs. highest LN negative patients) and both the highest and lowest mediastinal lymph node stations (distant LN positive patients vs. distant LN negative patients).

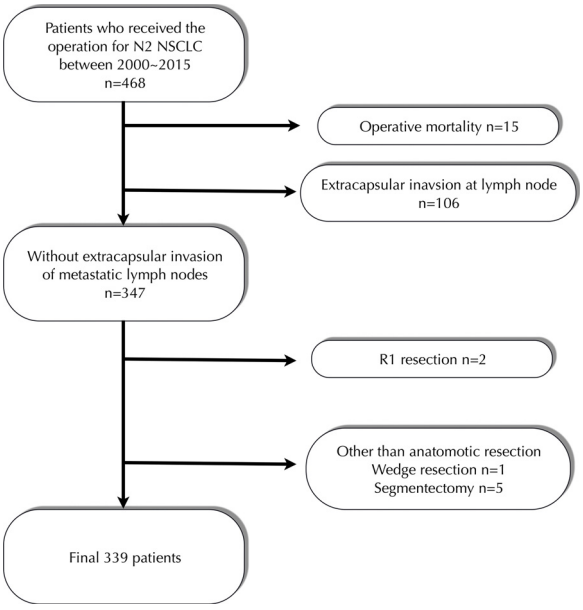

Fig. 1. Patient selection.

2.3. Statistical analysis

The clinical and pathologic characteristics were described as mean ± standard deviation for all continuous variables and absolute number (percentage) for all categorical variables. Overall survival was defined from the date of operation to death or last follow-up, and disease-free survival was defined from the date of operation to recurrence or last follow-up. The Kaplan-Meier method and log-rank test were used to perform univariate survival analysis, and the Cox proportional hazard model was used to identify independent prognostic factors. Variables with p-value < 0.05 were considered statistically significant. All statistical procedures were performed using R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Basic characteristics and patterns of lymph node metastasis

Study participant characteristics are summarized in Table 1. The mean age was 61.58 ± 9.43 years, and 235 (69.3%) patients were male. The numbers of total dissected lymph nodes and positive lymph nodes were 29.90 ± 11.92 and 5.49 ± 5.90, respectively. Among 339 patients, 189 (55.7%) patients were diagnosed as clinical N0-1. The patients in each subcategory of N stage were as follows: N2a1, 91 (26.8%); N2a2, 132 (38.9%); and N2b, 116 (34.2%). Two-hundred eighty-seven (84.6%) patients received the adjuvant therapy; 174 (51.3%) patients received the adjuvant chemotherapy and 113 (33.3%) patients received the adjuvant chemoradiation therapy.

Two hundred twenty-four (66.7%) patients had right-side lung cancer. Among these, 96 (42.8%) showed metastasis at the right upper paratracheal lymph node (station 2R), and 16 (7.1%) showed metastasis at the right intrapulmonary ligament lymph node (station 9). Separately, 115 (33.3%) patients had left-side lung cancer, with 46 (40%) showing metastasis at the left paratracheal lymph node (station 4 L) and para-aortic lymph node (station 6), whereas 15 (13.0%) showed metastasis at the left intrapulmonary ligament lymph node (station 9). One hundred forty-two (41.9%) patients presented with metastasis at the highest LN and 197 (58.1%) patients showed no metastasis at highest LN. One hundred sixty-two (47.8%) patients presented with metastasis at the most distant LN and 177 (52.8%) patients showed no metastasis at the most distant LN. The eleven (3.2%) patients showed both highest and lowers LN metastasis.

Table 1
Basic characteristics of patients.

Variables	Mean, n (%)
Age (years)	61.58 ± 9.43
Male	235 (69.3%)
Preoperative diagnostic modalities	
Mediastinoscopy	111 (32.7%)
PET/CT	179 (52.8%)
EBUS	25 (7.3%)
Pathology	
Adenocarcinoma	186 (54.9%)
Squamous cell carcinoma	123 (36.3%)
Other	30 (8.8%)
cT stage	
T1 / T2 / T3 / T4	105 (30.9%) / 173 (51.2%) / 46 (13.5%) / 15 (4.4%)
cN stage	
N0 / N1 / N2	148 (43.6%) / 41 (12.1%) / 150 (44.3%)
pT stage	
T1 / T2	77 (22.7%) / 144 (42.4%)
T3 / T4	77 (22.7%) / 41 (12.2%)
Tumor size (cm)	3.82 ± 1.99
Neoadjuvant therapy	54 (15.9%)
Type of operation	
Lobectomy or bilobectomy	269 (79.3%)
Pneumonectomy	70 (20.7%)
Number of total dissected lymph nodes	29.90 ± 11.92
Number of positive lymph nodes	5.49 ± 5.90
pN subtype	
N2a1	91 (26.8%)
N2a2	132 (38.9%)
N2b	116 (34.2%)
Metastasis to the most distant nodal station	162 (47.8%)
Metastasis to the highest nodal station	142 (41.9%)
Adjuvant therapy	287 (84.6%)
Chemotherapy	174 (51.3%)
Chemoradiation therapy	113 (33.3%)

PET/CT; Positron emission tomography/computed tomography, EBUS; Endobronchial ultrasound.

3.2. Survival analysis

The median follow-up period was 36.9 months. One hundred forty-two (41.8%) patients showed recurrences; 42 (12.4%) local recurrences and 100 (29.4%) distant metastases. Among all patients, the five-year overall survival and disease-free survival rates were 41.2% and 31.1%, respectively (Fig. 2A and B). Kaplan–Meier analysis revealed no differences between most distant LN negative and positive patients on overall survival (43.1% vs. 39.2%; p = 0.428; Fig. 3A) and disease-free survival (33.4% vs. 28.6%; p = 0.631; Fig. 3B). Also, there were no differences between highest LN negative and positive patients on overall survival (42.1% vs. 40.0%; p = 0.539; Fig. 3C) and disease-free survival (31.8% vs. 30.1%; p = 0.999; Fig. 3D).

For multivariable analysis, two models were established using the Cox model (Table 2). In model 1 with the most distant LN status, metastasis to the most distant mediastinal lymph node was not related to overall survival (HR:1.050; p = 0.755), whereas neoadjuvant therapy and pathologic T and N subcategories were related to overall survival. Separately, in model 2 with the highest LN status, metastasis to the highest mediastinal lymph node was not related to overall survival (HR: 1.015; p = 0.924).

4. Discussion

In addition to complete and incomplete resection, the IASLC previously proposed the definition of uncertain resection [2]. Even though it has been well-established that incomplete resection is related to disease recurrence and poor patient survival after lung cancer surgery, the clinical implications of uncertain resection have been investigated only in a few studies [3]. Gagliasso et al. reported that the patients who received an uncertain resection showed worse survival than did those who were received the complete resection, but their research analyzed all four criteria of uncertain resection together [3]. Among the four criteria of uncertain resection, the clinical and prognostic implications of other criteria have been studied extensively. There are many clinical trials on systematic lymphadenectomy versus sampling of ipsilateral mediastinal lymph nodes during lobectomy for NSCLC, but one meta-analysis suggested that clinical trials on mediastinal lymph node dissection showed many biases, indicating controversies between systematic lymphadenectomy and sampling [9]. Also, while many papers have analyzed the effects on survival of carcinoma in situ lesions at the bronchial resection margin, conflicts remain [10]. According to a recent meta-analysis on pleural cytology, 5.8% of patients showed malignant cells following saline lavage pleural cytology during lung cancer surgery, and positive cytology was related to poor survival [11]. However, lymph node metastasis at the highest or most distant mediastinal stations has not been widely studied.

Regarding metastasis at the highest mediastinal lymph node as a suitable criterion for uncertain resection is based on the lymphatic drainage patterns of mediastinum. Drainage from the superior mediastinum continues to transfer cephalad to the scalene lymph nodes in the neck, while the lymphatic drainage from the lower regions of the mediastinum may convey caudad to the para-aortic lymph nodes below the diaphragm [12]. Therefore, metastasis at the distant mediastinal lymph nodes can imply metastasis to the N3 node (scalene lymph node; 1R or 1 L in the IASLC lymph node map) or distant metastasis (M1; abdominal para-aortic lymph nodes). Therefore, we can assume that patients with metastasis at the distant mediastinal lymph nodes might show poorer survival than patients with no metastasis at the distant mediastinal lymph node stations. Based on these considerations, Mountain proposed that, within each lymphatic drainage region, the most distant lymph node must be microscopically proven to be free of

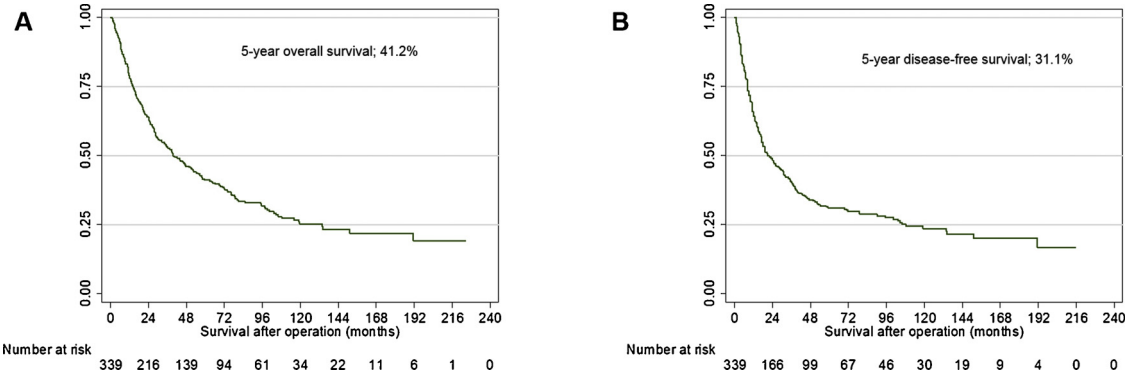

Fig. 2. Survival curves. A. Overall survival in all patients. B. Disease-free survival in all patients.

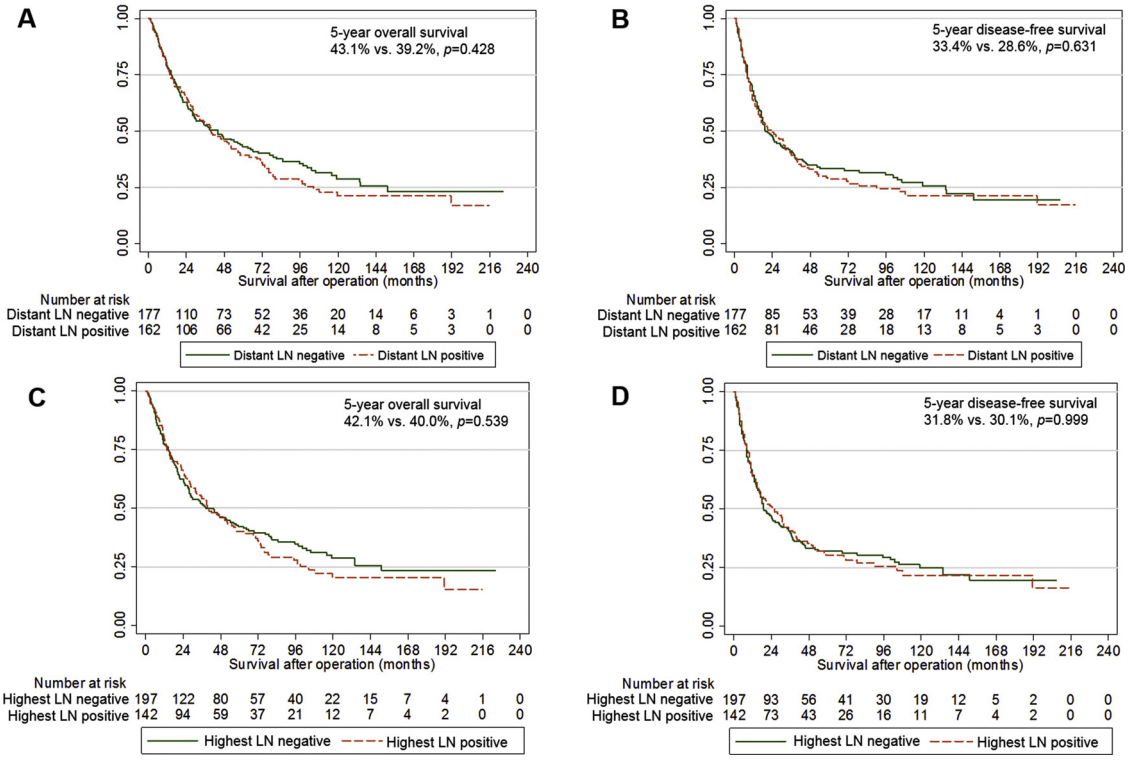

Fig. 3. Survival curves. A. Overall survival according most distant LN metastasis. B. Disease-free survival according most distant LN metastasis. C. Overall survival according to highest LN metastasis. D. Disease-free survival according to highest LN metastasis.

Table 2
Univariable and multivariable analyses for overall survival in surgically treated N2 NSCLC patients.

	Univariable model		Multivariable model 1		Multivariable model 2	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age	1.018 (1.003–1.032)	0.018	1.019 (1.003–1.034)	0.017	1.019 (1.009–1.034)	0.018
Female (vs. male)	0.675 (0.504–0.904)	0.008	0.817 (0.592–1.128)	0.220	0.817 (0.592–1.129)	0.221
Pathology (Adeno vs. non-adeno)	0.730 (0.563–0.947)	0.018	0.835 (0.622–1.121)	0.229	0.839 (0.626–1.125)	0.241
Neoadjuvant therapy	1.875 (1.341–2.620)	< 0.001	1.874 (1.321–2.658)	< 0.001	1.867 (1.317–2.647)	< 0.001
Pathologic T stage (AJCC 8th edition)						
T2 (vs. T1)	2.135 (1.459–3.126)	< 0.001	2.281 (1.5416–3.368)	0.001	2.278 (1.543–3.3.63)	< 0.001
T3 (vs. T1)	3.521 (2.297–5.397)	< 0.001	3.319 (2.150–5.122)	< 0.001	3.324 (2.153–5.132)	< 0.001
T4 (vs. T1)	3.108 (1.734–5.572)	< 0.001	3.431 (1.883–6.253)	< 0.001	3.442 (1.887–6.278)	< 0.001
N2 category						
N2a2 (vs. N2a1)	1.170 (0.832–1.646)	0.366	1.080 (0.762–1.531)	0.666	1.075 (0.759–1.523)	0.684
N2b (vs. N2a1)	1.562 (1.111–2.195)	0.010	1.771 (1.226–2.559)	0.002	1.794 (1.244–2.588)	0.002
Adjuvant therapy	1.035 (0.695–1.542)	0.864	1.171 (0.777–1.765)	0.450	1.170 (0.777–1.763)	0.456
Highest LN metastasis	1.085 (0.836–1.408)	0.539	…	…	1.015 (0.751–1.371)	0.924
Distant LN metastasis	1.110 (0.857–1.437)	0.429	1.050 (0.775–1.423)	0.755	…	…

tumor to indicate complete resection [13]. The Spanish Society of Pneumology and Thoracic Surgery (SEPAR) also proposed that the most distant nodal stations (the highest in the superior paratracheal and the lowest in the pulmonary ligament) must be metastasis-negative for a designation of complete resection [8]. Separately, the IASLC proposed that, if the highest mediastinal node removed is positive, the case can be regarded as uncertain resection. Even though the IASLC defined uncertain resection based on metastasis positivity of the highest mediastinal lymph node, we investigated both the highest and most distant mediastinal lymph nodes based on the characteristics of lymphatic drainage of the mediastinum and the suggestions of Mountain and the SEPAR. However, in contrast with the assumption, our results showed that metastasis at the most distant mediastinal lymph node or highest mediastinal lymph node sites was not related to survival.

In our dataset, a subcategory of N2 status proposed as part of the AJCC's eighth edition staging system was related to survival [14]. Though not considered in this analysis, the number of metastatic lymph nodes and the ratio between metastatic lymph nodes and dissected lymph nodes have been reported as risk factors for poor survival in N2 patients [15]. This indicates that the tumor burden of metastatic mediastinal lymph nodes is related to survival of N2 patients. Elsewhere, the American College of Chest Physicians suggested subsets of stage IIIA (N2), as follows: $IIIA_1$, incidental nodal metastases on final pathology of the resection specimen; $IIIA_2$, nodal metastases (single or multiple stations) recognized before thoracotomy; $IIIA_3$, nodal (single station) metastases recognized at intraoperative staging (mediastinoscopy, other nodal biopsy, or PET scan); and $IIIA_4$, bulky or fixed multistation N2 disease [16]. These subsets also focused on the tumor burdens of the mediastinum. Usually, N2 NSCLC has been regarded as both locoregional and systemic disease, so understanding the systemic tumor burden might be important for determining patient prognosis. Even though there may be the possibility of N3 or M1 metastasis if the

highest or most distant mediastinal lymph nodes are positive, metastasis to the highest or most distant mediastinal lymph nodes seems not to be related to survival. In addition, it seems that, in the era of targeted therapy and immunotherapy, the biologic characteristics of lung cancer might be more important than the extent of metastasis for patient survival.

This study has several limitations. First, we did not perform pleural cytology routinely. Though several investigations have reported that positive pleural cytology is related to poor survival [11], pleural cytology is not recommended in a routine fashion. Second, the definition of highest mediastinal lymph node in left-side NSCLC is vague. Based on previous reports that described lymphatic drainages in the mediastinum [12], we defined both the 4 L and 6 stations as the highest mediastinal lymph nodes because these lymph node stations both potentially drain into the neck lymph nodes. In addition, during the long period of study, the diagnostic polices have been changed. Also, the long period itself could result in the selection bias. These limitations have to be fully considered when analyzing the results of this study. Despite these limitations, this study also has several advantages. First, we analyzed a consistent group of patients, in that all patients underwent anatomic resection and complete mediastinal lymph node dissection. Also, we excluded patients with extracapsular invasion and R1 resection, which have been proposed as cases of incomplete resection [17], because we focused on metastasis to the highest or distant mediastinal lymph node stations. Most importantly, the previous studies analyzed small numbers of patients (53 patients) [4] or showed relatively low yields of mediastinal lymph nodes (mean 12.6 ± 6.4 lymph nodes) [5], but our study analyzed the higher numbers of patients with higher numbers of mediastinal lymph nodes.

5. Conclusion

In conclusion, the current definition of uncertain resection based on metastasis of highest or most distant mediastinal lymph nodes did not show survival differences in completely resected N2 NSCLC. The subcategories of N2 and T stage were more highly associated with overall survival rather than metastasis at the highest and most distant mediastinal lymph nodes.

Author contributions

(I) Conception and design: Seong Yong Park
(II) Administrative support: Kyoung Young Chung, Seong Yong Park
(III) Provision of study materials or patients: All authors
(IV) Collection and assembly of data: Go Eun Byun, Seong Yong Park
(V) Data analysis and interpretation: Seong Yong Park
(VI) Manuscript writing: Seong Yong Park
(VII) Final approval of manuscript: All authors

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Declaration of Competing Interest

None

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