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Original Article

Clinical Effect of Endosonography on Overall Survival in Patients with Radiological N1 Non–Small Cell Lung Cancer

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Purpose It is unclear whether performing endosonography first in non–small cell lung cancer (NSCLC) patients with radiological N1 (rN1) has any advantages over surgery without nodal staging. We aimed to compare surgery without endosonography to performing endosonography first in rN1 on the overall survival (OS) of patients with NSCLC.

Materials and Methods This is a retrospective analysis of patients with rN1 NSCLC between 2013 and 2019. Patients were divided into 'no endosonography' and 'endosonography first' groups. We investigated the effect of nodal staging through endosonography on OS using propensity score matching (PSM) and multivariable Cox proportional hazard regression analysis.

Results In the no endosonography group, pathologic N2 occurred in 23.0% of patients. In the endosonography first group, endosonographic N2 and N3 occurred in 8.6% and 1.6% of patients, respectively. Additionally, 51 patients were pathologic N2 among 249 patients who underwent surgery and mediastinal lymph node dissection (MLND) in endosonography first group. After PSM, the 5-year OSs were 68.1% and 70.6% in the no endosonography and endosonography first groups, respectively. However, the 5-year OS was 80.2% in the subgroup who underwent surgery and MLND of the endosonography first group. Moreover, in patients receiving surgical resection with MLND, the endosonography first group tended to have a better OS than the no endosonography group in adjusted analysis using various models.

Conclusion In rN1 NSCLC, preoperative endosonography shows better OS than surgery without endosonography. For patients with rN1 NSCLC who are candidates for surgery, preoperative endosonography may help improve survival through patient selection.

Key words Endobronchial ultrasound-guided transbronchial needle aspiration, Endoscopic ultrasound with bronchoscope fine needle aspiration, Non–small cell lung carcinoma, Radiological N1, Surgery

Introduction

In patients with non–small cell lung cancer (NSCLC), accurate staging of mediastinal lymph nodes (MLNs) is important for the guidance of appropriate treatment at each stage. Staging of NSCLC is accomplished through various methods including imaging tests, endoscopic procedures, and/or surgery [1,2]. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and/or endoscopic ultrasound with bronchoscope fine needle aspiration (EUS-B-FNA) are minimally invasive techniques that allow nodal staging under real-time ultrasonic guidance [3-5]. According to recent guidelines, endosonography (EBUS-TBNA and/or EUS-B-FNA) is the technique of choice for invasive mediastinal staging in patients with suspicious hilar or MLNs from computed tomography (CT) and/or positron emission tomography integrated with CT (PET-CT) [1,2]. However, recommendations from guidelines have been based on subgroup analysis of trials including patients with clinical stage I to III lung cancer, and the majority of these patients had clinical N2 disease and only a few had clinical N1 disease with a normal mediastinum on imaging.

In previous studies that have analyzed radiological N1 (rN1), the prevalence of occult MLN metastases ranged from approximately 26% to 37% [6-8]. Previous studies have reported that the diagnostic sensitivity of endosonography for detecting occult MLN metastases in rN1 NSCLC patients was approximately 38%-56% [7-10]. The diagnostic performance to confirm occult MLN metastases is lower than expected, it is questionable whether there is any benefit of

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performing endosonography in patients with rN1 NSCLC. In clinical settings, contrary to the recommendations in the guidelines, direct surgery is sometimes performed without preoperative invasive staging in rN1 NSCLC [11-13]. Despite these facts, there has been no comparison of the survival rate between patients who first underwent endosonography and those who underwent surgery without endosonography in rN1 NSCLC.

Therefore, to understand the clinical utility of endosonography in a real clinical setting, we aimed to compare the overall survival (OS) who received surgery without endosonography to those who had endosonography first in rN1 NSCLC patients.

Materials and Methods

1. Study patients

This study was a retrospective analysis of a prospectively collected database compiled from patients with confirmed primary NSCLC with rN1 who underwent endosonography for nodal staging assessment or underwent surgery without endosonography from January 2013 to December 2019 at Samsung Medical Center, a tertiary referral center in the Republic of Korea. Patients with active malignancies of other organs at the time of lung cancer diagnosis were excluded. This study includes 315 study participants from a previous study at our center that analyzed the diagnostic performance of endosonography [8]. In our previous study, we presented information on the prevalence of pN2/N3, the number of lymph nodes (LNs) sampled from N2/N3 stations per patient, and sensitivity in rN1 NSCLC patients undergoing endosonography, comparing it with reports from other institutions [8].

2. Definition of cancer stage

The nodal stage determined by CT and PET-CT was defined as the radiological stage. The rN1 was defined as an enlarged LN on a CT scan (the short axis of nodes > 10 mm) or visual ^{18}F-fluorodeoxyglucose (FDG) uptake on PET-CT scan at N1 station LN. The uptake in the LN was compared with the background of the lung or surrounding mediastinal tissue and reported as positive whenever the FDG uptake was higher than the background uptake [7,14]. The nodal staging determined by endosonography was defined as an endosonographic stage. For staging, the 8th edition of the American Joint Committee on Cancer TNM staging system was used [15]. All LNs were classified according to their station on the International Association for the Study of Lung Cancer (IASLC) lymph node map [16]. A central tumor was defined as the tumor located in the inner one-third of the hemithorax adopted by drawing concentric lines from the midline [17]. The definition of occult mediastinal metastases was the detection of MLN metastases in either MLN dissection (MLND) or endosonographic biopsy in patients with radiologic normal mediastinum [17].

3. Treatment modalities

Whether to perform endosonographic staging first or perform surgery immediately in rN1 NSCLC was decided by the attending physician on a case-by-case basis or through multidisciplinary consultation. We divided patients into two groups: (1) a no endosonography group who underwent definitive surgical lung resection plus MLND without preoperative endosonographic staging and (2) an endosonography first group who underwent endosonography and then planned a treatment method according to the endosonographic stage.

Mediastinoscopic staging was rarely performed during the study period. MLND featured en bloc resection of all visible and palpable LNs in the ipsilateral hilum and mediastinum, irrespective of diameter (stations 10R, 9, 8, 7, 4R, 3, and 2R for right-sided tumors and stations 10L, 9, 8, 7, 6, 5 and 4 L for left-sided tumors) [8,14,18].

EBUS-TBNA/EUS-B-FNA procedures were performed under moderate sedation as previously reported [8,14]. In short, EBUS-TBNA was performed from N3 to N2 and then to N1 (short diameter of LN ≥ 5 mm in sonography) after systematic inspection of mediastinal, hilar, and interlobar LNs. EUS-B-FNA was additionally performed in select cases of LNs where locations could not be examined with EBUS-TBNA [19]. When core tissue was obtained, at least two passes were conducted when possible [5]. During the study period, rapid on-site cytology and elastography were not available.

4. Statistical analyses

All data are reported as the number (%) for categorical variables and as the mean (standard deviation) or median (interquartile range [IQR]) for continuous variables. Data were compared by the Student's t test or Mann-Whitney U test for continuous variables and the chi-squared or Fisher's exact test for categorical variables.

We performed propensity score matching (PSM) to analyze the effect of endosonography on OS in rN1 NSCLC, and cases for analysis were selected with a 1:1 ratio of no endosonography vs. endosonography first. The propensity score was generated using a logistic regression model that included the patient's age, sex, body mass index (BMI), smoking status, underlying pulmonary disease, extra-pulmonary comorbidity, clinical T category, and histologic type. PSM was then performed using nearest neighbor greedy match-

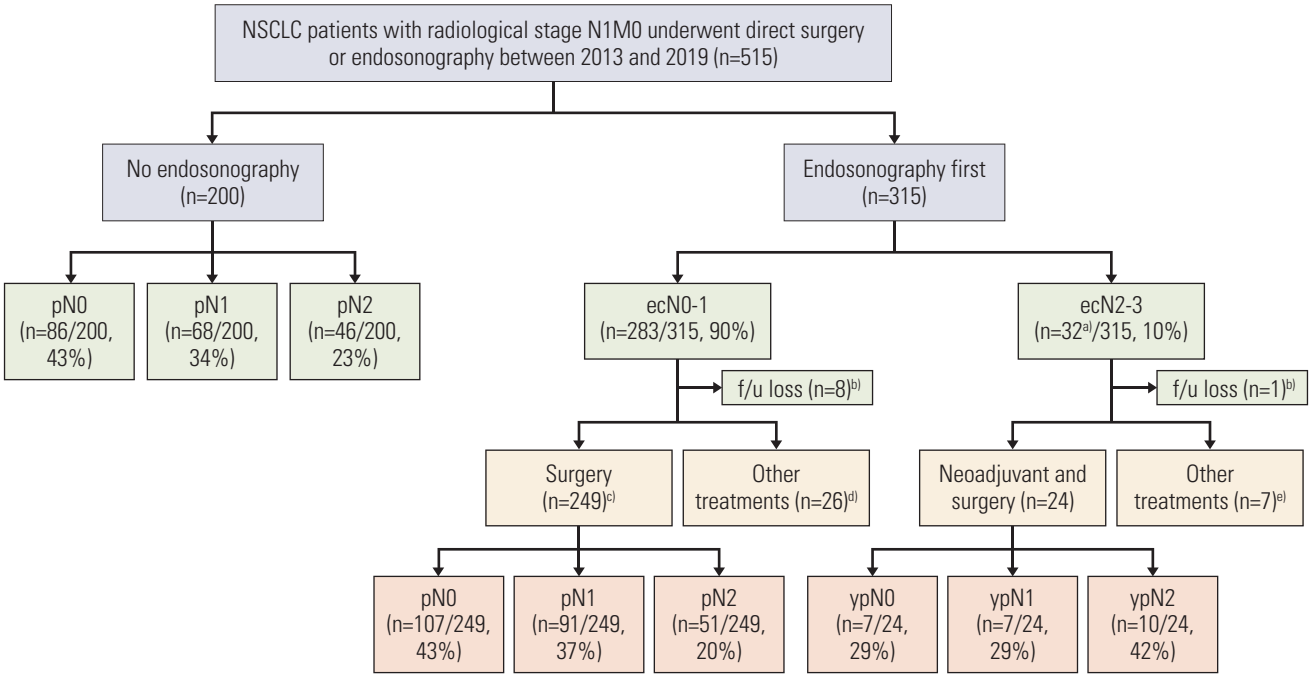

Fig. 1. Flowchart of the study population. eN, endosonographic nodal stage; f/u, follow-up; NSCLC, non–small cell lung cancer; pN, pathologic nodal stage. [a]eN2, n=27; eN3, n=5, [b]Not receiving anti-cancer treatment due to poor general condition (n=5), refusal of anti-cancer treatment by the patient (n=4), [c]Including two patients who were treated with neoadjuvant treatment even though eN0-1 according to clinician's decision, [d]Radiotherapy, n=13; concurrent chemoradiation therapy, n=11; chemotherapy, n=2, [e]Concurrent chemoradiation therapy, n=6; chemotherapy, n=1.

ing with a caliper width of 0.2.

The Kaplan-Meier method was used to estimate the OS in each group. A comparison of OS in groups was performed through the log-rank test. We also presented a hazard ratio (HR) with a 95% confidence interval (CI) for OS using multivariable Cox proportional hazard regression analysis. Three models were constructed: Model 1 was adjusted for age, sex, BMI, smoking status, underlying pulmonary disease, extrapulmonary comorbidity, clinical T category, and histologic type; Model 2 was additionally adjusted for spatial location and tumor attenuation. In patients who underwent surgery and MLND, variables related to surgery such as surgical approach and adjuvant treatment were additionally adjusted in Model 3. p-values < 0.05 were considered to indicate statistical significance. Subgroup analysis was also performed according to treatment method and depending on MLN metastases. All statistical analyses were conducted using SAS ver. 9.4 (SAS Institute Inc., Cary, NC).

Results

1. Baseline characteristics

About 39% (200/515) of NSCLC patients with rN1 received surgery immediately (Fig. 1). The final pathologic nodal stages of the no endosonography group were 43.0%, 34.0%, and 23.0% at pathologic N0 (pN0), pN1, and pN2, respectively. In the endosonography first group, 283/315 (89.8%) were diagnosed with endosonographic N0-1 (eN0-1) and 32/315 (10.2%) were diagnosed with eN2-3. Among these patients, 27 were eN2 and 5 were eN3. The five patients who were eN3 received definitive concurrent chemoradiation therapy (CCRT). One representative case of receiving a definitive CCRP with eN3 is described in the supplementary material (S1 Fig.).

Of the 27 patients diagnosed with eN2, one was lost in follow-up, two received treatment other than surgery, and 24 patients underwent surgery after neoadjuvant therapy. Of the patients diagnosed with eN0-1, eight patients were lost in follow-up, 26 patients received treatments other than surgery, and a final group of 249 patients underwent surgery. Two out of the 249 patients underwent surgery with neoadjuvant therapy after multidisciplinary consultation even

Table 1. Baseline characteristics of NSCLC patients with radiological N1 disease in initial (n=515) and propensity-matched (n=368) cohorts

Variable	Before matching				After matching			
	No endosonography (n=200)	Endosonography first (n=315)	SD	p-value	No endosonography (n=184)	Endosonography first (n=184)	SD	p-value
Age (yr)	65.3±8.7	65.2±10.1	0.003	0.973	65.1±8.9	64.7±10.3	0.037	0.725
Sex								
Female	50 (25.0)	81 (25.7)	–0.016	0.856	48 (26.1)	51 (27.7)	–0.037	0.724
Male	150 (75.0)	234 (74.3)	0.016		136 (73.9)	133 (72.3)	0.037	
BMI	23.9±2.8	24.1±3.0	–0.048	0.602	24.0±2.8	24.0±2.9	0.017	0.875
Smoking status								
Never	54 (27.0)	85 (28.8)	–0.040	0.660	53 (28.8)	51 (27.7)	0.024	0.817
Smoker	146 (73.0)	210 (71.2)	0.040		131 (71.2)	133 (72.3)	–0.024	
Underlying pulmonary disease								
No	96 (48.0)	165 (52.4)	–0.088	0.333	93 (50.5)	95 (51.6)	–0.022	0.835
Yes	104 (52.0)	150 (47.6)	0.088		91 (49.5)	89 (48.4)	0.022	
Extra-pulmonary comorbidity								
No	161 (80.5)	207 (65.7)	0.338	< 0.001	145 (78.8)	141 (76.6)	0.052	0.616
Yes	39 (19.5)	108 (34.3)	–0.338		39 (21.2)	43 (23.4)	–0.052	
Clinical T category								
T1	60 (30.0)	83 (26.4)	0.081	0.124	56 (30.4)	46 (25.0)	0.122	0.450
T2	87 (43.5)	127 (40.3)	0.065		75 (40.8)	81 (44.0)	–0.066	
T3	43 (21.5)	71 (22.5)	–0.025		43 (23.4)	41 (22.3)	0.026	
T4	10 (5.0)	34 (10.8)	–0.216		10 (5.4)	16 (8.7)	–0.128	
Histologic type								
Adenocarcinoma	91 (45.5)	182 (57.8)	–0.248	0.007	91 (49.5)	92 (50.0)	–0.011	0.917
Others	109 (54.5)	133 (42.2)	0.248		93 (50.5)	92 (50.0)	0.011	
Spatial location								
Peripheral	109 (54.5)	147 (46.7)	0.157	0.083	104 (56.5)	76 (41.3)	0.308	0.004
Central location	91 (45.5)	168 (53.3)	–0.157		80 (43.5)	108 (58.7)	–0.308	
Tumor attenuation								
Part-solid	15 (7.5)	26 (8.3)	–0.028	0.758	15 (8.2)	14 (7.6)	0.020	0.847
Solid	185 (92.5)	289 (91.8)	0.028		169 (91.9)	170 (92.4)	–0.020	

Values are presented as mean±standard deviation or number (%). Matched by age, sex, BMI, smoking status, underlying pulmonary disease, underlying extra-pulmonary comorbidities, clinical T category, and histologic type. BMI, body mass index; NSCLC, non–small cell lung cancer; SD, standardized difference.

though they had eN0-1 disease. The final pathologic nodal stages after surgery were 43.0%, 36.5%, and 20.5% at pN0, pN1, and pN2, respectively.

The mean age was around 65 years, and most patients were male in both groups (Table 1). In the initial cohort before matching, there were significantly more patients with extra-pulmonary comorbidity (34.3% vs. 19.5%, $p < 0.001$) and more patients with adenocarcinoma (57.8% vs. 45.5%, p=0.007) in the endosonography first group than in the no endosonography group. There was no significant difference in the pulmonary function test and mutation status between the no endosonography and endosonography first groups (S2 Table). PSM significantly reduced most of the baseline differences between the two groups, however, the proportion of central tumors was significantly higher in the endosonography first group (58.7% vs. 43.5%, p=0.004).

2. Detailed treatment profiles of patients undergoing surgery and MLND

The time interval between the first visit and the surgery was naturally longer in the endosonography first group than in the no endosonography group (32 vs. 23 days, $p < 0.001$)

Table 2. Treatment profile for NSCLC patients with radiological N1 disease who underwent surgery and MLND (n=473)

Variable	Total (n=473)	No endosonography (n=200)	Endosonography first (n=273[a])	p-value
Duration from visit to surgery (day)	28 (20-39)	23 (16-32)	32 (22-48)	< 0.001
Neoadjuvant treatment				
No	447 (94.5)	200 (100)	247 (90.5)	< 0.001
CCRT	26 (5.5)	0	26[b] (9.5)	
Surgical approach				
VATS	160 (33.8)	79 (39.5)	81 (29.7)	0.026
Thoracotomy	313 (66.2)	121 (60.5)	192 (70.3)	
Types of surgical resection				
Sublobar resection	17 (3.6)	10 (5.0)	7 (2.6)	0.562
Lobectomy	376 (79.5)	157 (78.5)	219 (80.2)	
Bilobectomy	45 (9.5)	18 (9.0)	27 (9.9)	
Pneumonectomy	35 (7.4)	15 (7.5)	20 (7.3)	
Pathologic stage				
ypCR	3 (0.6)	0	3 (1.1)	0.572
IA	58 (12.3)	24 (12.0)	34 (12.5)	
IB	49 (10.4)	22 (11.0)	27 (9.9)	
IIA	34 (7.2)	17 (8.5)	17 (6.2)	
IIB	146 (30.9)	58 (29.0)	88 (32.2)	
IIIA	150 (31.7)	62 (31.0)	88 (32.2)	
IIIB	33 (7.0)	17 (8.5)	16 (5.9)	
Post-operative complications[c]	109 (23.0)	47 (23.5)	62 (22.7)	0.840
Pulmonary	82 (17.3)	38 (19.0)	44 (16.1)	0.413
Cardiovascular	40 (8.5)	13 (6.5)	27 (9.9)	0.191
Neurologic	2 (0.4)	0	2 (0.7)	0.511
Bleeding	1 (0.2)	0	1 (0.4)	> 0.999
Adjuvant treatment				
No	194 (41.0)	100 (50.0)	95 (34.8)	0.001
Yes	279 (59.0)	100 (50.0)	178 (65.2)	
CCRT	59 (12.5)	24 (12.0)	35 (12.8)	
Chemotherapy	207 (43.8)	72 (36.0)	134 (49.1)	
Radiotherapy	13 (2.7)	4 (2.0)	9 (3.3)	

Values are presented as number (%) or median (interquartile range). CCRT, concurrent chemoradiation therapy; MLND, mediastinal lymph nodes dissection; NSCLC, non–small cell lung cancer; VATS, video-assisted thoracoscopic surgery. [a]Patients who underwent surgery with MLND in eN0-1 (n=249) and in eN2 (n=24), [b]Including two patients who were treated with neoadjuvant treatment even though eN0-1 according to clinician's decision, [c]Patients might have one or more complications.

(Table 2). Patients who were treated with neoadjuvant therapy took a median of 89 days (IQR, 83 to 100) until surgery. Except for 26 patients who underwent neoadjuvant therapy in the endosonography first group, the time interval between the first visit and the surgery was a median of 30 days (range, 21 to 42 days), and even after excluding patients receiving neoadjuvant therapy, the time interval between the first visit and the surgery was significantly longer in the endosonography first group than in the no endosonography group (p < 0.001). Additionally, there were more cases of thoracotomy in the patients who received endosonography first than in the endosonography group (70.3% vs. 60.5%, p=0.026). There was no significant difference between the two groups in the type of surgical resection, post-operative pathologic stage, and post-operative complications. After surgery, the endosonography first group underwent more adjuvant treatment than the no endosonography group (65.6% vs. 50.0%, p=0.001). In particular, there was a difference in the rate of receiving adjuvant therapy in pathologic stages IIA and IIB (S3 Table). There were 27/54 (50%) in the no endosonography group and 11/41 (27%) in the endosonography first group who did not receive adjuvant therapy for non-medical reasons.

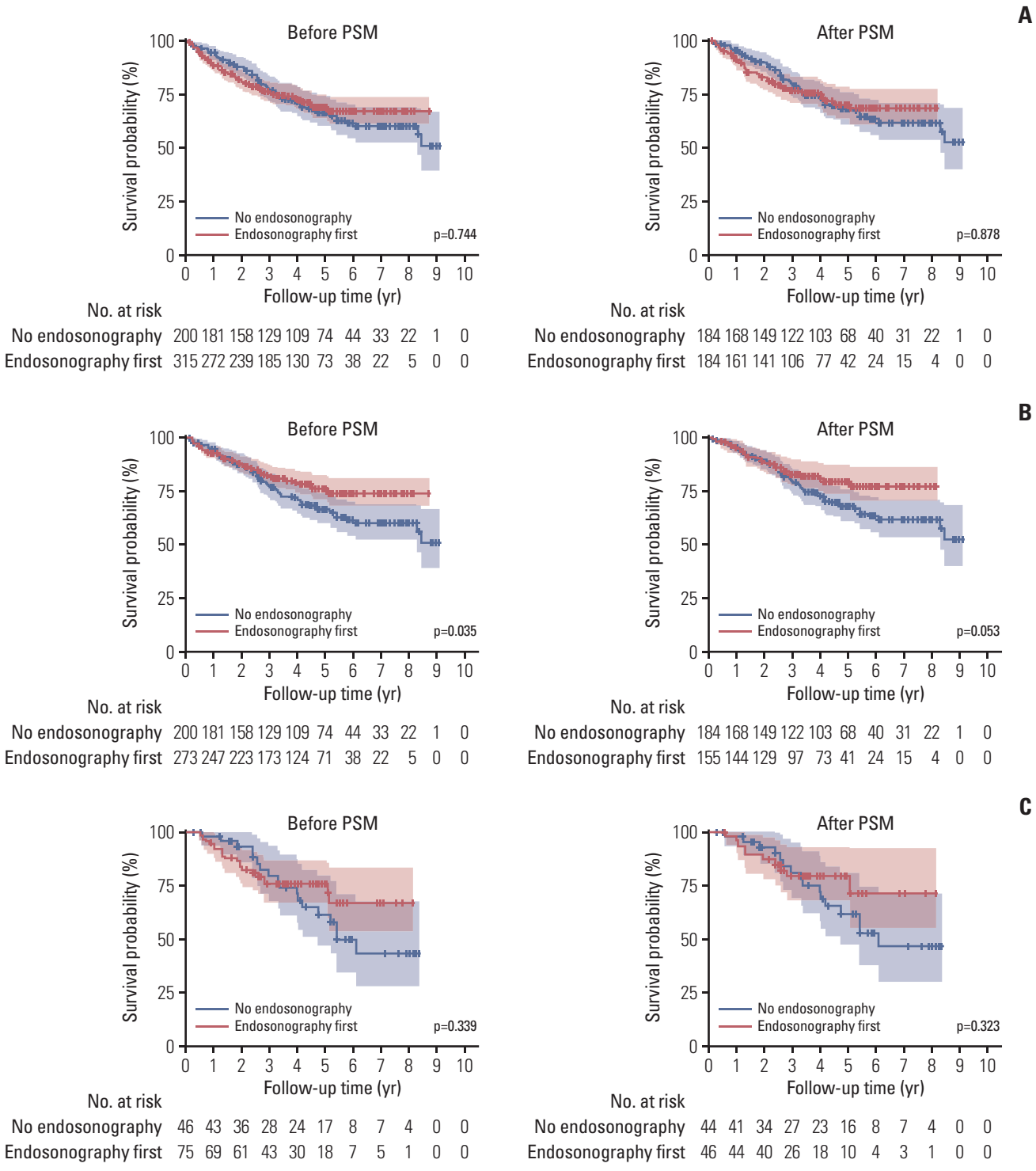

Fig. 2. The overall survival curves before and after propensity score matching in NSCLC with radiological N1. (A) Endosonography first vs. no endosonography group in all patients (before PSM, 315 vs. 200; after PSM, 184 vs. 184). (B) Subgroup who underwent surgery in endosonography first group vs. no endosonography group (before PSM, 273 vs. 200; after PSM, 155 vs. 184). (C) Subgroup with eN2-3 or pN2 in endosonography first group vs. subgroup with pN2 in no endosonography group (before PSM, 75 vs. 46; after PSM, 46 vs. 44). Matching with age, sex, BMI, smoking status, underlying pulmonary disease, underlying extra-pulmonary comorbidities, clinical T category, and histologic type. BMI, body mass index; eN, endosonographic nodal stage; NSCLC, non–small cell lung cancer; pN, pathologic nodal stage; PSM, propensity score matching.

Table 3. Association between overall survival and treatment modalities

Subject	Model	Overall survival		
		HR	95% CI	p-value
All patients				
No endosonography vs. endosonography first	Before PSM (n=200 vs. 315)			
	Unadjusted	0.95	0.68-1.31	0.743
	Adjusted (model 1)[a]	0.98	0.69-1.38	0.886
	Adjusted (model 2)[b]	0.97	0.69-1.38	0.879
	After PSM (n=184 vs. 184)	0.97	0.66-1.43	0.880
Patients who underwent surgery and MLND				
No endosonography vs. subgroup who underwent surgery in endosonography first group	Before PSM (n=200 vs. 273)			
	Unadjusted	0.68	0.47-0.98	0.036
	Adjusted (model 1)[a]	0.69	0.47-1.02	0.061
	Adjusted (model 2)[b]	0.67	0.45-0.99	0.049
	Adjusted (model 3)[c]	0.66	0.44-0.99	0.044
	After PSM (n=184 vs. 155)	0.65	0.41-1.01	0.054
Patients with MLN metastases				
Subgroup with pN2 in the no endosonography group vs. subgroup with eN2-3 or pN2 in endosonography first group	Before PSM (n=46 vs. 75)			
	Unadjusted	0.73	0.38-1.40	0.341
	Adjusted (model 1)[a]	0.65	0.32-1.36	0.255
	Adjusted (model 2)[b]	0.62	0.29-1.33	0.222
	After PSM (n=44 vs. 46)	0.67	0.30-1.49	0.326

Matching with age, sex, BMI, smoking status, underlying pulmonary disease, underlying extra-pulmonary comorbidities, clinical T category, and histologic type. BMI, body mass index; CI, confidence interval; eN, endosonographic nodal stage; HR, hazard ratio; MLN, mediastinal lymph nodes; MLND, mediastinal lymph nodes dissection; pN, pathologic nodal stage; PSM, propensity score matching. [a]Adjusted by age, sex, BMI, smoking status, underlying pulmonary disease, underlying extra-pulmonary comorbidities, clinical T category, and histologic type, [b]Adjusted by age, sex, BMI, smoking status, underlying pulmonary disease, extra-pulmonary comorbidities, clinical T category, histologic type, spatial location, and tumor attenuation, [c]Adjusted by age, sex, BMI, smoking status, underlying pulmonary disease, extra-pulmonary comorbidities, clinical T category, histologic type, spatial location, tumor attenuation, surgical approach, and adjuvant treatment.

3. Effect of nodal staging with endosonography on OS

Patients were followed up for a median of 3.75 years (IQR, 2.21 to 5.20). The 5-year survival rates were 66.9% and 69.3% in the no endosonography and endosonography first groups for all patients (log-rank test, p=0.744), respectively. After PSM, the 5-year survival rates were 68.1% and 70.6% in the no endosonography and endosonography first groups for all patients (p=0.878) (Fig. 2A). Among patients who underwent surgery with MLND, the 5-year survival rates were 66.9% and 76.9% before PSM (p=0.035), and 68.1% and 80.2% after PSM (p=0.052) in no endosonography and endosonography first groups, respectively (Fig. 2B). Among patients with MLN metastases (pN2 in no endosonography vs. eN2-3 or pN2 in endosonography first groups), the 5-year survival rates were 61.3% and 76.1% before PSM (p=0.339), and 61.8% and 79.2% after PSM (p=0.323) in the no endosonography and endosonography first groups, respectively (Fig. 2C).

In an unadjusted model, performing endosonography first did not affect the OS for all patients (HR, 0.95; 95% CI, 0.68 to 1.31; p=0.743) and patients with MLN metastases (HR, 0.73; 95% CI, 0.38 to 1.40; p=0.341) (Table 3). However, in patients who underwent surgery with MLND, nodal staging by endosonography first affected the OS (HR, 0.68; 95% CI, 0.47 to 0.98; p=0.036). After adjustment of numerous clinical variables throughout models, performing endosonography on all patients or patients with MLN metastases did not have a significant effect on the OS. In patients who underwent surgery with MLND, it was not statistically significant in model 1 (HR, 0.69; 95% CI, 0.47 to 1.02; p=0.061). However, in adjusted models 2 and 3, performing endosonography for nodal staging had significant benefits on OS compared with no endosonography group (model 2: HR, 0.67; 95% CI, 0.45 to 0.99; p=0.049; model 3: HR, 0.65; 95% CI, 0.44 to 0.99; p=0.044). The matched-pair analysis shows no significant association between performing endosonography and OS in all groups. However, in patients who underwent surgery and MLND, performing endosonography for nodal staging tended to benefit OS compared with no endosonography

group (HR, 0.65; 95% CI, 0.41 to 1.01; p=0.054).

Subgroup analysis according to histological type, spatial location, and tumor attenuation was performed only in patients who underwent surgery and MLND (S4 Table, S5 Fig.). After PSM, in cases with adenocarcinoma (p=0.036), centrally located tumor (p=0.022), and solid tumor (p=0.043), the OS was significantly better when nodal staging was performed through endosonography than when patients underwent surgery immediately.

Discussion

About 39% of all occult MLN metastases were found through endosonography and used to guide the appropriate treatment for the nodal stage. In particular, eN3 patients were guided to definitive CCRT. More than half of eN2 patients who underwent surgery were down-graded to ypN0-1 due to neoadjuvant therapy. In an adjusted analysis using various models including PSM, patients who underwent surgery in the endosonography first group consistently tended to have a better OS than patients in the no endosonography group.

In our study, about 40% of rN1 NSCLC patients received surgery without endosonography. According to the guidelines, in NSCLC with normal mediastinum at CT or PET-CT, it is recommended that mediastinal nodal staging is performed when enlarged or FDG-PET-avid ipsilateral hilar nodes are present [1,2]. However, in a real clinical setting, patients with rN1 NSCLC sometimes underwent surgery immediately. A systematic review article that summarized studies dealing with occult MLN metastases between 2000 and 2019 reported that the proportion of patients who received invasive mediastinal staging was generally low [20]. Additionally, many other studies on MLN staging reported that invasive mediastinal staging occurred in only about 32%-58% of the study patients, indicating an incompliance with guidelines in real clinical settings [11-13]. For the reason of guideline non-adherence, it is possible to infer differences in treatment preference by doctors, limited experience, or the limited availability of endosonography at the early stage when endosonography was first introduced [11].

Our data showed that nodal staging with endosonography did not significantly affect OS in all patients or when MLN metastases were present, however, OS improved when patients who underwent surgery were targeted. When comparing OS in all patients, the no endosonography group had better survival for the first 3 years in the Kaplan-Meier curve, but the endosonography first group had better survival from a later point in time. This may be because patients who received non-surgical treatment in the endosonography first group showed worse survival due to its higher nodal staging or poorer general condition than those receiving direct surgery, so the no endosonography group seemed to have a better OS in the beginning. However, in the long term, patients who were guided to surgery through endosonographic nodal staging showed better OS due to the benefit received from the correct staging through the procedure (e.g., neoadjuvant therapy). In addition to the benefit of proceeding to surgery after neoadjuvant therapy in eN2, we suspect that the benefit of endosonography was in the detection of N3. Endosonography has identified eN3 and led some patients to staging-appropriate treatment rather than surgery. With direct surgery, there is no way to know if the N3 has metastasized. These facts suggest that, although the proportion of pN2 was similar in the two groups among those who had surgery, the pN2 in the no endosonography group may actually be more likely to have N3 mixed in. We suspect that this difference may have contributed to the divergence in survival curves during long-term follow-up after surgery.

Several studies have attempted to discover the clinical effect of invasive mediastinal staging including mediastinoscopy and endosonography in NSCLC. One study prospectively analyzed patients with negative mediastinal involvement on PET-CT who had tumors larger than 3 cm, central tumors, or rN1 for evaluating the effectiveness of invasive mediastinal staging (EBUS and/or mediastinoscopy). In this study, the median survival in pN2 patients with invasive staging was 11 months longer than in pN2 patients without invasive staging, however, this was not statistically significant (33.6 vs. 22.5 months, p=0.245) [21]. Although it was not limited to rN1, a recent study using a nationwide Dutch cohort reported a trend in invasive nodal staging and the relationship between "unforeseen N2", which meant occult MLN metastases, and the OS of clinical stages IA-IIIB NSCLC [11]. They found an increasing trend in the performance of the endosonography from 2011 to 2017, and invasive mediastinal staging led to improved OS in patients with clinical N1-3 disease [11]. A U.S. study with T1-3N1-3M0 lung cancer patients retrospectively analyzed and compared the practice patterns and clinical outcomes according to guideline-consistent care. In that study, patients with NSCLC who underwent mediastinal staging survived longer than patients who never had mediastinal staging [12].

Conversely, Obiols et al. [22] found that performing surgical exploration of the mediastinum did not affect the OS of pN2 patients (5-year OS after direct surgery vs. performing mediastinal staging, 41% vs. 40%). However, the authors of this study explained that the survival rate of unsuspected pN2 detected by direct surgery was high, possibly due to the lower proportion of unsuspected pN2 (5.5%) compared to other studies, and included a high rate of 80% for single station pN2 and a high rate of 90% for complete resection [22].

The difference in the results of several studies seems to be caused by heterogeneity due to an invasive mediastinal staging method that was not limited to endosonography and the diversity of clinical stages. However, our study showed the clinical usefulness of endosonography in more specific conditions than previous studies by comparing the OS of two groups limited to the rN1 stage.

Endosonography can access not only the hilar, interlobar, and lobar LNs but also the MLNs including N3 station LNs which cannot be accessed by MLND [23,24]. In our study, because of this advantage, some patients with eN3 received definitive CCRT, which could not be confirmed by direct surgery with MLND. In addition, the development of neoadjuvant therapy is likely to further maximize the effect of filtering out some eN2 through endosonography [25]. Considering the results of our study, the advantages of endosonography, and the development of neoadjuvant therapy, we recommend nodal staging by endosonography rather than direct surgery without preoperative endosonographic staging in rN1 NSCLC patients scheduled for surgical resection.

Previous studies have shown that patients with central tumors, adenocarcinomas, and solid tumors had a higher prevalence of occult MLN metastases [8,14,26-28]. Since the prevalence of pN2-3 is high in these conditions, the positive predictive value of eN2-3 by endosonography can be increased and will allow more patients to benefit from proper nodal staging by endosonography. This could explain the improved OS under the higher prevalence of occult MLN metastases in our subgroup analyses (S1 Fig.).

Our study had several limitations. First, this is a retrospective cohort study from one of the referral hospitals that manage many cases of lung cancer nationwide. Therefore, it may limit the generalization to other centers. Also, some variables differed between the two groups because of the retrospective nature of the study. However, we adjusted numerous variables in the analysis as well as the PSM. Second, contrary to recommendations in the guidelines, when a negative result after endosonography was implemented, no additional invasive staging was performed with mediastinoscopy in our institution. However, previous studies have already observed no difference in long-term survival between staging with endosonography and surgical mediastinoscopy [29]. Moreover, one meta-analysis study reported that the rate of "unforeseen N2" after negative endosonography results was similar in patients undergoing immediate surgery to those undergoing confirmatory mediastinoscopy, but the 6.0% rate of complications occurred by mediastinoscopy [30]. Based on this evidence, our center did not perform confirmatory mediastinoscopy after a negative result by endosonography. Third, our analysis tends to be relatively small with a total of 315 in the endosonography group and 200 in the no endosonography group. It is possible that the small study size may have contributed to the lack of statistically significant results. Further studies with larger study populations, controlling for various treatment-related factors, are needed to determine the effectiveness of endosonography in rN1 NSCLC. Finally, our study did not provide information on recurrence-free survival (RFS). Data on survival were finally verified with official mortality records from the Office for National Statistics. However, unlike OS, it was very difficult to assess RFS retrospectively. Some patients wanted to continue follow-up after treatment in their home region rather than at our center, so the exact timing and status of recurrence was not known for all patients.

Despite these limitations, our study is the first to compare the OS in patients with rN1 NSCLC who receive either nodal staging through endosonography or surgery without endosonography. Our research might play an important role in adding evidence to the present guidelines and the need for endosonography in the preoperative staging of rN1 in patients with NSCLC.

In conclusion, our data showed that for patients with rN1 NSCLC who underwent surgery with MLND, preoperative nodal staging through endosonography had better OS compared to surgery without endosonography. We emphasize the importance of the effectiveness of nodal staging with endosonography in rN1 NSCLC surgery candidates by guiding patients to more stage-appropriate treatment.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2022-08-004), and the requirement for informed consent from patients was waived because the study was retrospective.

Author Contributions

Conceived and designed the analysis: Kim BG, Jeong BH, Cho JH.
Collected the data: Kim BG, Cho JH.
Contributed data or analysis tools: Jeong BH, Park G, Kim HK, Shim YM, Shin SH, Lee K, Um SW, Kim H, Cho JH.
Performed the analysis: Kim BG, Park G.
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Conflicts of Interest
Conflict of interest relevant to this article was not reported.

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References

1. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014;45:787-98.
2. Vilmann P, Clementsen PF, Colella S, Siemsen M, De Leyn P, Dumonceau JM, et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Endoscopy. 2015;47:c1.
3. Yasufuku K, Chiyo M, Sekine Y, Chhajed PN, Shibuya K, Iizasa T, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. Chest. 2004;126:122-8.
4. Varela-Lema L, Fernandez-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. Eur Respir J. 2009;33:1156-64.
5. Lee HS, Lee GK, Lee HS, Kim MS, Lee JM, Kim HY, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station? Chest. 2008;134:368-74.
6. Hishida T, Yoshida J, Nishimura M, Nishiwaki Y, Nagai K. Problems in the current diagnostic standards of clinical N1 non-small cell lung cancer. Thorax. 2008;63:526-31.
7. Dooms C, Tournoy KG, Schuurbiers O, Decaluwe H, De Ryck F, Verhagen A, et al. Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: a prospective multicenter study. Chest. 2015;147:209-15.
8. Kim BG, Cho JH, Shin SH, Lee K, Um SW, Kim H, et al. Diagnostic performance of endosonography to detect mediastinal lymph node metastasis in patients with radiological N1 non-small cell lung cancer. Cancer Res Treat. 2023;55:832-40.
9. Sakairi Y, Hoshino H, Fujiwara T, Nakajima T, Yasufuku K, Yoshida S, et al. Validation of EBUS-TBNA-integrated nodal staging in potentially node-positive non-small cell lung cancer. Gen Thorac Cardiovasc Surg. 2013;61:522-7.
10. Naur TM, Konge L, Clementsen PF. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of patients with non-small cell lung cancer without mediastinal involvement at positron emission tomography-computed tomography. Respiration. 2017;94:279-84.
11. Bousema JE, Aarts MJ, Dijkgraaf MG, Annema JT, van den Broek FJ. Trends in mediastinal nodal staging and its impact on unforeseen N2 and survival in lung cancer. Eur Respir J. 2021;57:2001549.
12. Ost DE, Niu J, Zhao H, Grosu HB, Giordano SH. Quality gaps and comparative effectiveness in lung cancer staging and diagnosis. Chest. 2020;157:1322-45.
13. Bousema JE, Heineman DJ, Dijkgraaf MG, Annema JT, van den Broek FJ. Adherence to the mediastinal staging guideline and unforeseen N2 disease in patients with resectable non-small cell lung cancer: Nationwide results from the Dutch Lung Cancer Audit - Surgery. Lung Cancer. 2020;142:51-8.
14. Shin SH, Jeong BH, Jhun BW, Yoo H, Lee K, Kim H, et al. The utility of endosonography for mediastinal staging of non-small cell lung cancer in patients with radiological N0 disease. Lung Cancer. 2020;139:151-6.
15. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016;11:39-51.
16. Giroux DJ, Rami-Porta R, Chansky K, Crowley JJ, Groome PA, Postmus PE, et al. The IASLC Lung Cancer Staging Project: data elements for the prospective project. J Thorac Oncol. 2009;4:679-83.
17. Shin SH, Jeong DY, Lee KS, Cho JH, Choi YS, Lee K, et al. Which definition of a central tumour is more predictive of occult mediastinal metastasis in nonsmall cell lung cancer patients with radiological N0 disease? Eur Respir J. 2019;53:1801508.
18. Kim HK, Choi YS, Kim K, Shim YM, Park K, Ahn YC, et al. Outcomes of mediastinoscopy and surgery with or without neoadjuvant therapy in patients with non-small cell lung cancer who are N2 negative on positron emission tomography and computed tomography. J Thorac Oncol. 2011;6:336-42.
19. Lee KJ, Suh GY, Chung MP, Kim H, Kwon OJ, Han J, et al. Combined endobronchial and transesophageal approach of an ultrasound bronchoscope for mediastinal staging of lung cancer. PLoS One. 2014;9:e91893.
20. MA IJ, Ten Broek RP, Wiering B, Hekma E, de Roos MA. Oncological outcomes of unsuspected pN2 in patients with non-small-cell lung cancer: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2021;32:727-36.

21. Boada M, Sanchez-Lorente D, Libreros A, Lucena CM, Marrades R, Sanchez M, et al. Is invasive mediastinal staging necessary in intermediate risk patients with negative PET/CT? J Thorac Dis. 2020;12:3976-86.
22. Obiols C, Call S, Rami-Porta R, Trujillo-Reyes JC, Saumench R, Iglesias M, et al. Survival of patients with unsuspected pN2 non-small cell lung cancer after an accurate preoperative mediastinal staging. Ann Thorac Surg. 2014;97:957-64.
23. Yasufuku K, Nakajima T, Chiyo M, Sekine Y, Shibuya K, Fujisawa T. Endobronchial ultrasonography: current status and future directions. J Thorac Oncol. 2007;2:970-9.
24. Ernst A, Eberhardt R, Krasnik M, Herth FJ. Efficacy of endobronchial ultrasound-guided transbronchial needle aspiration of hilar lymph nodes for diagnosing and staging cancer. J Thorac Oncol. 2009;4:947-50.
25. Chaft JE, Shyr Y, Sepesi B, Forde PM. Preoperative and postoperative systemic therapy for operable non-small-cell lung cancer. J Clin Oncol. 2022;40:546-55.
26. Cho HJ, Kim SR, Kim HR, Han JO, Kim YH, Kim DK, et al. Modern outcome and risk analysis of surgically resected occult N2 non-small cell lung cancer. Ann Thorac Surg. 2014; 97:1920-5.
27. Bille A, Woo KM, Ahmad U, Rizk NP, Jones DR. Incidence of occult pN2 disease following resection and mediastinal lymph node dissection in clinical stage I lung cancer patients. Eur J Cardiothorac Surg. 2017;51:674-9.
28. Lee PC, Port JL, Korst RJ, Liss Y, Meherally DN, Altorki NK. Risk factors for occult mediastinal metastases in clinical stage I non-small cell lung cancer. Ann Thorac Surg. 2007;84:177-81.
29. Kuijvenhoven JC, Korevaar DA, Tournoy KG, Malfait TL, Dooms C, Rintoul RC, et al. Five-year survival after endosonography vs mediastinoscopy for mediastinal nodal staging of lung cancer. JAMA. 2016;316:1110-2.
30. Bousema JE, van Dorp M, Noyez V, Dijkgraaf MG, Annema JT, van den Broek FJ. Unforeseen N2 disease after negative endosonography findings with or without confirmatory mediastinoscopy in resectable non-small cell lung cancer: a systematic review and meta-analysis. J Thorac Oncol. 2019; 14:979-92.