

Outcomes of Pulmonary Resection and Mediastinal Node Dissection by Video-Assisted Thoracoscopic Surgery Following Neoadjuvant Chemoradiation Therapy for Stage IIIA N2 Non-Small Cell Lung Cancer

Yeong Jeong Jeon, M.D.¹, Yong Soo Choi, M.D.¹, Kyung Jong Lee, M.D.²,
Se Hoon Lee, M.D.³, Hongryull Pyo, M.D.⁴, Joon Young Choi, M.D.⁵

¹Department of Thoracic and Cardiovascular Surgery, Divisions of ²Pulmonary and Critical Care Medicine and ³Hematology-Oncology, Department of Medicine, Departments of ⁴Radiation Oncology and ⁵Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine

Background: We evaluated the feasibility and outcomes of pulmonary resection and mediastinal node dissection (MND) by video-assisted thoracoscopic surgery (VATS) following neoadjuvant therapy for stage IIIA N2 non-small cell lung cancer (NSCLC). **Methods:** From November 2009 to December 2013, a total of 35 consecutive patients with pathologically or radiologically confirmed stage IIIA N2 lung cancer underwent pulmonary resection and MND, performed by a single surgeon, following neoadjuvant chemoradiation. Preoperative patient characteristics, surgical outcomes, postoperative drainage, postoperative complications, and mortality were retrospectively analyzed. **Results:** VATS was completed in 17 patients. Thoracotomy was performed in 18 patients, with 13 planned thoracotomies and 5 conversions from the VATS approach. The median age was 62.7±7.9 years in the VATS group and 60±8.7 years in the thoracotomy group. The patients in the VATS group tended to have a lower diffusing capacity for carbon monoxide ($p=0.077$). There were no differences between the 2 groups in the method of diagnosing the N stage, tumor response and size after induction, tumor location, or histologic type. Complete resection was achieved in all patients. More total and mediastinal nodes were dissected in the VATS group than in the thoracotomy group ($p<0.05$). The median chest tube duration was 5.3 days (range, 1 to 33 days) for the VATS group and 7.2 days (range, 2 to 28 days) for the thoracotomy group. The median follow-up duration was 36.3 months. The 5-year survival rates were 76% in the VATS group and 57.8% in the thoracotomy group ($p=0.39$). The 5-year disease-free survival rates were 40.3% and 38.9% in the VATS and thoracotomy groups, respectively ($p=0.8$). **Conclusion:** The VATS approach following neoadjuvant treatment was safe and feasible in selected patients for the treatment of stage IIIA N2 NSCLC, with no compromise of oncologic efficacy.

Key words: 1. Non-small-cell lung carcinoma
2. Neoadjuvant therapy
3. Video-assisted thoracoscopic surgery
4. Lobectomy

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Corresponding author: Yong Soo Choi, Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
(Tel) 82-2-3410-6542 (Fax) 82-2-3410-6986 (E-mail) ysooyah.choi@samsung.com

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Introduction

Lung resection by video-assisted thoracoscopic surgery (VATS) was first reported in 1992 [1]. Subsequently, VATS has been increasingly performed worldwide for early-stage non-small cell lung cancer (NSCLC). Multiple studies have demonstrated that VATS lobectomy may reduce postoperative pain, the length of hospitalization, and the incidence of complications [2,3]. However, the application of VATS in patients with stage IIIA N2 NSCLC who have undergone neoadjuvant therapy remains controversial. Concerns have been articulated regarding the technical difficulty of mediastinal node dissection (MND), which could compromise the oncologic outcomes [4]. However, as experience with VATS has increased, surgeons have successfully performed VATS lung resection and MND with comparable outcomes [5-7]. We evaluated the feasibility of lobectomy and MND by VATS following neoadjuvant therapy for stage IIIA N2 NSCLC.

Methods

1) Patient selection

A retrospective analysis of 35 consecutive patients with stage IIIA N2 NSCLC was performed. Patients who underwent pulmonary resection and MND, which were performed by a single surgeon, following neoadjuvant chemoradiation at Samsung Medical Center between November 2009 and December 2013 were eligible. All cases had pathologically or radiologically confirmed T and N staging. The histologic evaluation of mediastinal nodes was conducted by mediastinoscopy or endobronchial ultrasound. The imaging studies included computed tomography and positron emission tomography. The TNM (tumor-node-metastasis) staging was based on the seventh edition of the American Joint Committee on Cancer lung cancer staging guidelines. All patients completed preoperative concurrent chemoradiotherapy (CCRT) and underwent anatomic resection and MND. The operative technique was chosen by the surgeon.

2) Statistical analysis

Preoperative patient characteristics, surgical outcome, postoperative drainage, postoperative complications, recurrence rate, and mortality were compared

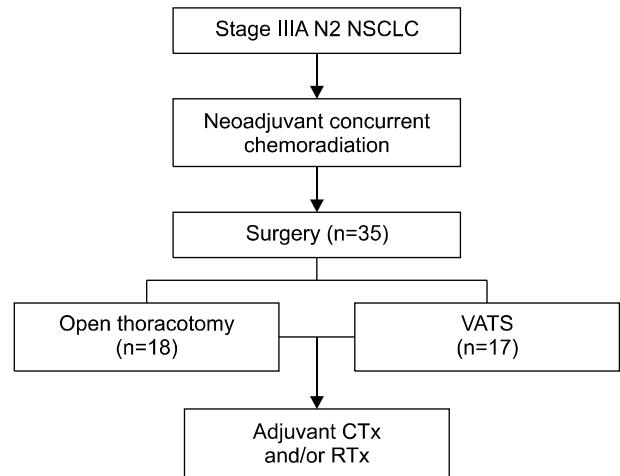


Fig. 1. Study design. NSCLC, non-small cell lung cancer; VATS, video-assisted thoracoscopic surgery; CTx, chemotherapy; RTx, radiotherapy.

between the VATS and thoracotomy groups. Measurements are presented as mean±standard deviation for continuous variables or number of patients and percentages for categorical variables. Intergroup comparisons were made with the Mann-Whitney test for continuous variables or the Pearson chi-square and Fisher exact tests for categorical variables. The 5-year survival rate was analyzed with the Kaplan-Meier method, and statistical significance was calculated using the log-rank test. All p-values <0.05 were considered to indicate statistical significance. All analyses were performed on an intent-to-treat basis using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA).

Results

Between November 2009 and December 2013, a total of 35 patients with stage III N2 NSCLC underwent pulmonary resection after induction therapy. Pulmonary resection and MND by VATS were attempted in 22 patients, while 13 patients underwent the same procedure through an open thoracotomy. Five patients were converted to a thoracotomy due to anthracofibrotic nodes (4 patients) or tight adhesions (1 patient); these patients were included in the thoracotomy group. As a result, 17 patients were included in the VATS group and 18 in the thoracotomy group. All patients underwent neoadjuvant CCRT (Fig. 1). The patients received cisplatin/paclitaxel (TP) or

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Table 1. Baseline characteristics

Baseline characteristic	Video-assisted thoracoscopic surgery (n=17)	Thoracotomy (n=18)	p-value
Sex (male)	14 (82)	17 (95)	0.34
Age (yr)	62.7±7.9	60±8.7	0.98
Pulmonary function tests			
Forced expiratory volume in 1 second (% predicted)	86.8±15.8	89.7±17.9	0.766
Diffusing capacity for carbon monoxide (% predicted)	80.5±18.9	90.1±18.6	0.077
Body mass index >25 kg/m ²	9 (53)	3 (17)	<0.05
Method for diagnosis of N stage			
Mediastinoscopy	5 (29.4)	9 (50)	0.214
Endobronchial ultrasound or imaging	12 (70.6)	9 (50)	
Tumor response after induction			
Complete response	0	1 (5.6)	1.0
Partial response	10 (58.8)	10 (55.6)	
Stable disease	7 (41.2)	7 (38.9)	
Tumor size after induction (mm)	26.3±12.9	40.6±31.9	0.228
Tumor location			
Peripheral	9 (53)	7 (39)	0.404
Central	8 (47)	11 (61)	
Histologic type			
Adenocarcinoma	12 (70.6)	8 (44.4)	0.182
Squamous cell carcinoma	5 (29.4)	8 (44.4)	
Mixed		2 (11.1)	
Positive nodal station reported			
2R	4 (23.5)	2 (11.1)	0.402
4R	8 (47)	9 (50)	0.862
4L	2 (11.7)	3 (16.7)	1.0
7	6 (35.2)	8 (44.4)	0.826
Single	11 (64.7)	16 (88.9)	0.096
Multiple	6 (35.3)	2 (11.1)	
Maximum size of node on imaging (mm)	7.5±8.1	12.7±7.1	0.191

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

cisplatin/docetaxel (DP) for 5 weeks and a total dose of 44 Gy with 2.0 Gy/fraction of radiation, concurrently. The median age was 62.7±7.9 years in the VATS group and 60±8.7 years in the thoracotomy group. The patients in the VATS group tended to have a lower diffusing capacity for carbon monoxide (DLCO) (p=0.077). More patients in the VATS group had a body mass index (BMI) >25 kg/m² (53% versus 17%, p<0.05). The method of the preoperative diagnosis of the N stage, tumor response and size after induction, tumor location, histologic type, maximum size of the node, and number of perioperative positive nodal stations reported were not significantly different between the 2 groups (Table 1).

Most patients underwent lobectomy (88.2% in the VATS group and 77.8% in the thoracotomy group)

(Table 2). Two patients in the VATS group and 2 patients in the thoracotomy group underwent bilobectomy, and 2 patients in the thoracotomy group underwent sleeve lobectomy. There were no differences in the anatomic distribution of the resected lobes, and all patients underwent complete resection. The patients in the VATS group had significantly more total (24±8.1 versus 13.5±9.4, p<0.05) and mediastinal nodes dissected (13±6.5 versus 6±6.2, p<0.05). There was no difference in mediastinal clearance (nodal downstaging to ypN0 and ypN1) between the 2 groups.

In terms of postoperative complications, the median chest tube duration was 5.3 days (range, 1 to 33 days) in the VATS group and 7.2 days (range, 2 to 28 days) in the thoracotomy group (Table 3). The duration of hospitalization was 8.4 days (range, 5 to

Table 2. Surgical outcomes

Surgical outcome	Video-assisted thoracoscopic surgery (n=17)	Thoracotomy (n=18)	p-value
Surgical procedure			
Lobectomy	15 (88.2)	14 (77.8)	
Bilobectomy	2 (11.8)	2 (11.1)	
Sleeve lobectomy		2 (11.1)	
Resected lobe			
Left upper lobe	3 (17.6)	3 (16.7)	1.0
Left lower lobe	2 (11.8)	2 (11.1)	1.0
Right upper lobe	7 (41.2)	8 (44.4)	0.845
Right lower lobe	3 (17.6)	3 (16.7)	1.0
Right middle/lower lobe	2 (11.8)	2 (11.1)	1.0
Resection margin (R0)	17 (100)	18 (100)	
No. of nodes dissected			
Total	24±8.1	13.5±9.4	0.004
Mediastinal	13±6.5	6±6.2	0.04
Mediastinal clearance (yes)	8 (47.1)	12 (66.7)	0.241
Extracapsular extension of node (present)	6 (35.3)	8 (44.4)	0.581

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

Table 3. Perioperative outcomes and complications

Variable	Video-assisted thoracoscopic surgery (n=17)	Thoracotomy (n=18)	p-value
Mortality at 30 days	0	1 (5.6)	
Chest tube duration (day)	5.3 (1-33)	7.2 (2-28)	0.281
Length of hospitalization (day)	8.4 (5-49)	11 (4-829)	0.465
Complications			
Prolonged air leak	2 (11.8)	4 (22.2)	1.0
Pneumonia	1 (5.9)	1 (5.6)	1.0
Acute respiratory distress syndrome	1 (5.9)	1 (5.6)	1.0
Atrial fibrillation	3 (17.6)	4 (22.2)	0.68
Vocal cord palsy	1 (5.9)	0	1.0
Pulmonary thromboembolism	2 (11.8)	0	1.0
Wound infection	0	2 (11.1)	0.131
Interval between surgery and adjuvant treatment (median day)	27	28	0.820
Completeness of adjuvant treatment (%)			
Chemotherapy	62.5	50	0.851
Radiotherapy	25	62.5	0.073

Values are presented as number (%) or median (range).

49 days) and 11 days (range, 4 to 829 days) in the VATS and thoracotomy groups, respectively. No significant differences were noted with regard to post-operative complications, including prolonged air leak, pneumonia, acute respiratory distress syndrome (ARDS), atrial fibrillation, or wound infection. There was no significant difference between the groups in the time interval between surgery and initiation of

chemotherapy.

The median follow-up duration was 36.3 months. The 5-year survival rate was 76% in the VATS group and 57.8% in the thoracotomy group (p=0.39). The 5-year disease-free survival rate was 40.3% in the VATS group and 38.9% in the thoracotomy group (p=0.8) (Fig. 2).

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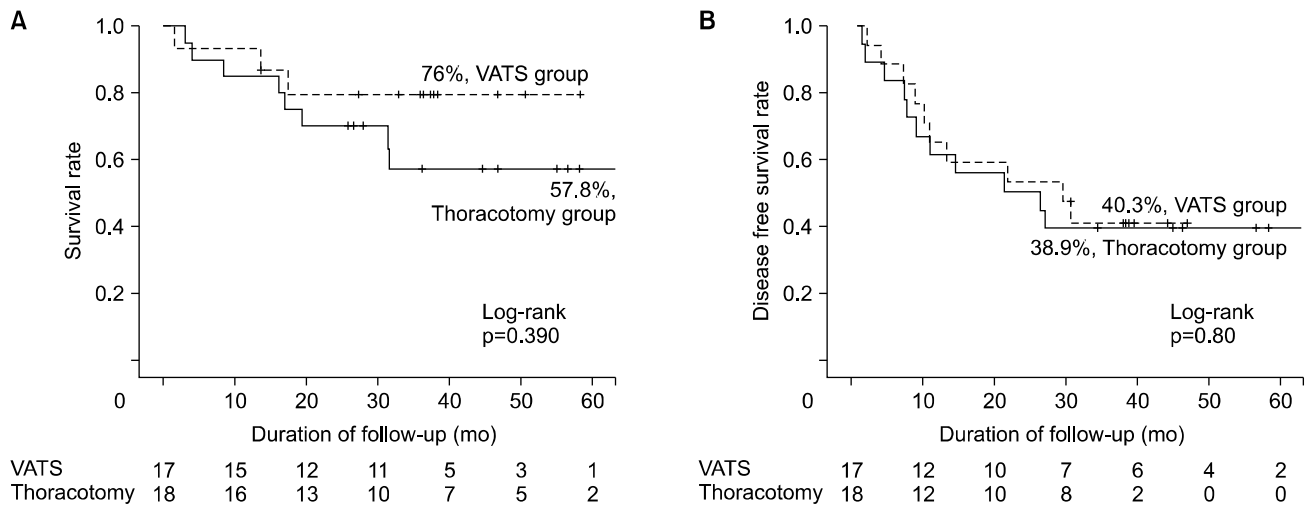


Fig. 2. (A, B) Kaplan-Meier analysis of overall survival after surgery. VATS, video-assisted thoracoscopic surgery.

Discussion

In recent years, VATS lung resection has been widely performed for patients with early-stage NSCLC. Studies have demonstrated the advantages of VATS compared with thoracotomy, including reduced post-operative pain, preserved pulmonary function, and shorter length of hospitalization and chest tube duration [2,8]. However, concerns have been raised regarding VATS for patients with locally advanced lung cancer following induction therapy due to the presence of tissue adhesions, an indistinct plane of dissection, and fragile blood vessels. Nonetheless, several studies have demonstrated the successful application of VATS in patients with locally advanced NSCLC following induction therapy without complications [6,7].

At our institution, patients with stage IIIA N2 NSCLC received CCRT with weekly DP or TP and 4,400 cGy in 5 cycles before surgery. The operative technique was chosen by the surgeon. After surgery, patients underwent adjuvant chemotherapy, radiotherapy, or both (Fig. 1).

The present study evaluated the feasibility and safety of lobectomy and MND by VATS following neoadjuvant therapy for stage IIIA N2 NSCLC. Since November 2009, we have performed this procedure by VATS in selected patients who have undergone neoadjuvant chemoradiotherapy. In cases where concerns arose regarding the technical difficulty or oncologically compromised outcomes during VATS, we

converted to conventional thoracotomy. In the present study, 5 (22.7%) of the 22 patients in whom VATS was attempted were converted to open thoracotomy, due to anthracofibrotic nodes (4 patients) or tight adhesions (1 patient). No bleeding problems occurred.

Upon retrospective review, VATS was preferred for patients with a lower DLCO or a higher BMI. No preference in surgical approach was noted in terms of the method of diagnosis of N2 disease, tumor location or size, the resected lobe, the station of positive nodes, or the presence of multiple positive nodal stations.

Although concerns have been raised regarding satisfactory MND by VATS, only a few surgeons have reported the efficacy of thoracoscopic MND [9,10]. They demonstrated that MND by VATS was not inferior to MND by open thoracotomy [11,12]. Of note, we found that the VATS group was associated with larger numbers of total and mediastinal nodes dissected. This may be attributed to the high percentage of patients who underwent preoperative video-assisted mediastinoscopic dissection in the thoracotomy group.

The length of hospitalization and chest tube duration in the VATS group were shorter than in the thoracotomy group, although not to a statistically significant extent. There were no differences between the 2 groups in early mortality (within 30 days) or postoperative complications, including prolonged air leak, pneumonia, ARDS, atrial fibrillation, or wound

infection. The survival analysis identified no differences in the 5-year overall and disease-free survival rates between the groups.

This study has several limitations. It was a retrospective study of a single experienced surgeon with a relatively small number of patients. The duration of follow-up was relatively short, with a median follow-up time of 3 years. The conversion rate to thoracotomy was relatively high, at 22.7%.

In conclusion, the VATS approach following neoadjuvant treatment was a feasible surgical approach for the treatment of stage IIIA N2 NSCLC with acceptable mid-term outcomes in selected patients, with no compromise of oncologic efficacy. Large and randomly assigned prospective analyses of long-term outcomes for locally advanced lung cancer following induction treatment need to be performed to validate the oncologic efficacy of VATS.

Conflict of interest

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

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