ORIGINAL ARTICLE

# Is video-assisted thoracoscopy a sufficient approach for mediastinal lymph node dissection to treat lung cancer after neoadjuvant therapy?

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## Abstract

**Background:** The role of video-assisted thoracoscopic surgery (VATS) in mediastinal lymph node dissection (MLND) for non-small cell lung cancer (NSCLC) following neoadjuvant therapy remains controversial. The aim of this study was to demonstrate the sufficiency of VATS by evaluating perioperative and long-term outcomes.

**Methods:** Patients with locally advanced NSCLC and treated with radical surgery after neoadjuvant therapy were identified in our database. The thoroughness of MLND was compared by approach. Multivariable logistic regression analysis was used to evaluate predictors of sufficient MLND. Propensity score matching was performed. Kaplan–Meier and Cox proportional hazard analyses were used to assess long-term survival.

**Results:** Of the 127 enrolled patients, 56 underwent attempted VATS and 71 underwent thoracotomy. Multivariable logistic regression analysis revealed that approach was not a predictor of sufficient MLND (odds ratio 0.81, 95% confidence interval [CI] 0.364–1.803; $P = 0.606$). After matching, 28 pairs of patients were selected from the two groups. There was no significant difference between the numbers of dissected lymph nodes (15 vs. 20; $P = 0.191$) and nodal stations (7 vs. 7; $P = 0.315$). Recurrence-free (log-rank $P = 0.613$) and overall survival (log-rank $P = 0.379$) was similar in both groups. Multivariable Cox proportional hazards model analysis indicated that VATS was not an independent predictor of recurrence-free (hazard ratio 0.955, 95% CI 0.415–2.198; $P = 0.913$) or overall survival (hazard ratio 0.841, 95% CI 0.338–2.093; $P = 0.709$).

**Conclusion:** Compared to thoracotomy, VATS is a sufficient approach for MLND to treat locally advanced NSCLC following neoadjuvant therapy without compromising long-term survival.

## Introduction

Lung cancer is the leading cause of cancer-related death throughout the world, and a considerable proportion of lung cancer is diagnosed in advanced stages.[1,2] Locally advanced-stage non-small cell lung cancer (NSCLC) is defined as stage T3 or T4 tumors, lymph node enlargement (cN1 or cN2), or tumors requiring neoadjuvant therapy.[3] Based on definitive oncological evidence, lobectomy via video-assisted thoracoscopic surgery (VATS) is recommended as a preferred but not universally accepted alternative approach for patients with resectable NSCLC considered appropriate candidates.[4,5] However, thoracoscopic lobectomy is less frequently performed in patients with locally advanced NSCLC who have undergone neoadjuvant therapy. Concerns remain over the feasibility and thoroughness of lymph node dissection accomplished by VATS because of the necessity for tedious dissection through fibrotic planes and to dense adhesions caused by neoadjuvant therapy.[6] With the continuous development of surgical instruments and growing experience, most of these obstacles can now be overcome.[3,7]

Several studies have reported similar long-term outcomes of thoracoscopic lobectomy compared to thoracotomy approaches for patients who have undergone neoadjuvant therapy.[6,8,9] However, the role of VATS in mediastinal lymph node dissection (MLND) for locally advanced lung cancer following neoadjuvant therapy remains controversial. This study analyzed cases in our database to compare patient's perioperative and long-term outcomes between these two approaches and aimed to demonstrate the sufficiency of VATS.

## Methods

### Patient selection

A retrospective analysis was performed of consecutive patients with locally advanced NSCLC who received neoadjuvant chemotherapy or chemoradiotherapy followed by radical pulmonary resection and MLND between 2000 and 2016 at Peking University People's Hospital. Patients with multiple primary tumors and those with tumors other than NSCLC were excluded from the study. Indications for neoadjuvant therapy were biopsy-proven N2 disease, clinical N2 disease, or T3-4N0-1 disease indicated for pneumonectomy. The preoperative choice of therapy between chemotherapy alone or chemoradiotherapy was based on patient conditions and tolerance, and physician recommendation. All patients were treated with platinum-based doublet chemotherapy regimens (gemcitabine/pemetrexed/docetaxel/paclitaxel + cisplatin/carboplatin) for four cycles with or without concurrent thoracic radiotherapy in fractions of 1.8 Gy to a total dose of 45 Gy. Chest computed tomography (CT) and/or positron emission tomography (PET)-CT were taken to evaluate response. Patients without progression who were deemed operable before therapy underwent radical resection.

### Surgical technique

Patients were divided into groups according to the type of surgical approach: thoracotomy and VATS. All thoracotomy surgeries were performed via a standard posterolateral thoracotomy incision. Thoracoscopic surgeries were performed using a two-port or three-port method. The features of our improved thoracoscopic technique (Wang's technique) have been described in previous studies.[7,10] Thoracic surgeons who had overcome the learning curve and achieved proficiency (> 200 lobectomies independently) performed all VATS lobectomies in this study. Our institution began performing thoracoscopic lobectomy in 2006; therefore eligible patients enrolled before 2010 underwent thoracotomy. Radical pulmonary

resection (including lobectomy, bilobectomy, sleeve lobectomy, and pneumonectomy) and routine MLND were performed during surgery. Conversion was defined as surgery that began with thoracoscopic dissection and concluded as a rib-spreading thoracotomy. Patients undergoing conversion were analyzed in the VATS group. If a surgery commenced with thoracoscopic evaluation and then directly converted to thoracotomy before structural dissection, it was assigned to the thoracotomy group. Station 2–11 LNs were identified and dissected by the surgeon during operation, whereas station 12 LNs were identified and removed from specimens in vitro by a pathologist, who also counted the LNs. The thoroughness of LND was evaluated according to the European Society of Thoracic Surgeons[11] and National Comprehensive Cancer Network guidelines. At least three hilar and interlobar LNs and three mediastinal nodes from three stations (right upper and middle lobe: 2R, 4R, and 7; right lower lobe: 4R, 7, 8, and 9; left upper lobe: 5, 6, and 7; left lower lobe: 7, 8, and 9) should be included.[11] If the LND satisfied the abovementioned guideline recommendations, it was defined as sufficient LND.

### Data extraction

Data were collected on patient demographics; smoking history; pulmonary function test; clinical stage prior to neoadjuvant therapy; neoadjuvant therapy modality; pathology results after surgery (histological type, pathological stage, LND conditions); surgical details; postoperative complications; and long-term survival. The 7th edition of the Union for International Cancer Control tumor node metastasis (TNM) staging system was used to determine clinical and pathological stages. The percentage of sufficient MLND, details of the dissected LN stations, and the number of nodes dissected relative to tumor location were recorded.

### Statistical analysis

Baseline characteristics and outcomes were compared between thoracotomy and VATS groups. Categorical variables were expressed as counts and proportions, and comparisons between the groups were conducted using Pearson's $X^2$ or Fisher's exact tests. Continuous variables that exhibited a normal distribution were assessed using the Student's *t*-test, while variables that did not exhibit a normal distribution were assessed using the Mann–Whitney *U* test for two-group comparisons.

The thoroughness of LND between the two groups was assessed according to the proportion of sufficient LNDs using Pearson's $X^2$ test, and the number of LNs or stations was evaluated using nonparametric tests, as stated.

The rates of LND related to tumor location were compared by surgical approach using the $X^2$ test. Univariable and multivariable logistic regression analyses were used to evaluate predictors for sufficient LND.

Propensity score matching was performed for the thoracotomy and VATS groups using a 1:1 nearest matching method with a caliper distance at 0.01. Overall survival (OS) was measured from the date of surgery to the date of death from any cause or the time point of the

last follow-up. Recurrence-free survival (RFS) was measured as the number of months from surgery to recurrence or the time point of the last follow-up. The definition of local recurrence in this study included any recurrence within the ipsilateral lung, bronchial stump, staple line, or the N1–N3 nodal groups. Other circumstances that did not involve local recurrence were considered non-local recurrence.[12] The Kaplan–Meier method was used to calculate the median survival time,

**Table 1** Patient characteristics and treatment modality for all eligible cases and propensity score-matched pairs

| Variables | All included patients | | | Propensity score-matched patients | | |
|---|---|---|---|---|---|---|
| | Thoracotomy group (*n* = 71) | VATS group (*n* = 56) | *P* | Thoracotomy group (*n* = 28) | VATS group (*n* = 28) | *P* |
| Age, mean ± SD | 58.7 ± 8.7 | 56.5 ± 8.7 | 0.156 | 58.1 ± 8.6 | 56.5 ± 8.7 | 0.469 |
| Gender, N (%) | | | **0.001** | | | 1 |
| Male | 65 (91.5) | 39 (69.6) | | 24 (85.7) | 25 (89.3) | |
| Female | 6 (8.5) | 17 (30.4) | | 4 14.3) | 3 (10.7) | |
| Smoking history, N (%) | 53 (74.6) | 35 (62.5) | 0.141 | 19 (67.9) | 22 (78.6) | 0.365 |
| Pulmonary Function | | | | | | |
| FEV1%, mean ± SD | 82.6 ± 20.3 | 87.2 ± 15.9 | 0.198 | 89.3 ± 18.5 | 83.6 ± 15.5 | 0.26 |
| DLCO SB%, mean ± SD | 75.9 ± 18.7 | 80.9 ± 17.8 | 0.175 | 80.0 ± 20.9 | 79.7 ± 16.9 | 0.969 |
| Comorbidity, N (%) | | | | | | |
| Hypertension | 18( 25.4) | 17 (30.4) | 0.531 | 10 (35.7) | 4 (14.3) | 0.064 |
| Diabetes | 5 (7.0) | 5 (10.7) | 0.68 | 4 (14.3) | 2 (7.1) | 0.669 |
| Cardiac disease | 3 (4.2) | 6 (10.7) | 0.286 | 2 (7.1) | 1 (3.6) | 1 |
| COPD | 1 (1.4) | 4 (7.1) | 0.169 | 1 (3.6) | 2 (7.1) | 1 |
| Tumor location, N (%) | | | 0.332 | | | 0.663 |
| Right upper lobe | 24 (33.8) | 20 (35.7) | | 10 (35.7) | 10 (0.35.7) | |
| Right middle lobe | 4 (5.6) | 5 (8.9) | | 2 (7.1) | 1 (3.6) | |
| Right lower lobe | 13 (18.3) | 15 (26.8) | | 6 (21.4) | 7 (25.0) | |
| Left upper lobe | 19 (26.8) | 13 (23.2) | | 6 (21.4) | 9 (32.1) | |
| Left lower lobe | 11 (15.5) | 3 (5.4) | | 4 (14.3) | 1 (3.6) | |
| Clinical TNM stage | | | **0.024** | | | 0.149 |
| T3N0M0 | 10 (14.1) | 4 (7.1) | | 2 (7.1) | 2 (7.1) | |
| T4N0M0 | 4 (5.6) | 2 (3.6) | | 0 | 2 (7.1) | |
| T1N2M0 | 7 (9.9) | 18 (32.1) | | 3 (10.7) | 9 (32.1) | |
| T2N2M0 | 42 (59.2) | 29 (51.8) | | 19 (67.9) | 13 (46.4) | |
| T3N2M0 | 8 (11.3) | 3 (5.4) | | 4 (14.3) | 2 (7.1) | |
| Histology, N (%) | | | **0.006** | | | 0.584 |
| Squamous carcinoma | 49 (69.0) | 24 (42.9) | | 16 (57.1) | 18 (64.3) | |
| Adenocarcinoma | 21 (29.6) | 31 (55.4) | | 12 (42.9) | 10 (35.7) | |
| Large cell | 1 (1.4) | 1 (1.8) | | | | |
| Induction therapy, N (%) | | | 0.487 | | | 0.146 |
| Chemotherapy | 52 (73.2) | 44 (78.6) | | 17 (60.7) | 22 (78.6) | |
| Chemoradiotherapy | 19 (26.8) | 12 (21.4) | | 11 (39.3) | 6 (21.4) | |
| Surgical procedure, N (%) | | | **< 0.001** | | | 1 |
| Lobectomy | 32 (45.1) | 42 (75.0) | | 18 (64.3) | 19 (67.9) | |
| Bilobectomy | 6 (8.5) | 3 (5.4) | | 4 (14.3) | 3 (10.7) | |
| Sleeve lobectomy | 7 (9.9) | 8 (14.3) | | 3 (10.7) | 3 (10.7) | |
| Pneumonectomy | 26 (36.6) | 3 (5.4) | | 3 (10.7) | 3 (10.7) | |
| Conversion, N (%) | — | 6 (10.7) | | — | 3 (10.7) | |

*P* values in bold are statistically significant. COPD, chronic obstructive pulmonary disease; DLCO SB = diffusing capacity of the lung for carbon monoxide, single-breath method; %, its percentage of prediction value; FEV1%, forced expiratory volume in 1 second; %, its percentage of prediction value; SD, standard deviation; TNM, tumor node metastasis; VATS, video-assisted thoracoscopic surgery.

and the log-rank test was used to evaluate differences between the groups. Univariable and multivariable Cox proportional hazards model analyses were used to adjust the effects of chosen variables. A two-sided *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and Stata/SE version 14.0 for Windows (StataCorp, College Station, TX, USA).

# Results

## Patient characteristics and pathology outcomes

A total of 127 patients who met the eligibility criteria were enrolled, including 56 patients who underwent attempted thoracoscopic lobectomy and 71 patients who underwent thoracotomy. In the thoracotomy group, 12 out of the

**Table 2** Patient pathology outcomes after surgery and lymph node dissection situations for all eligible cases and propensity score-matched pairs

| | All included patients | | | Propensity score-matched patients | | |
|---|---|---|---|---|---|---|
| Variables | Thoracotomy group (*n* = 71) | VATS group (*n* = 56) | *P* | Thoracotomy group (*n* = 28) | VATS group (*n* = 28) | *P* |
| Completeness of resection, N (%) | | | **0.033** | | | 0.611 |
| R0 | 61 (85.9) | 55 (98.2) | | 25 (89.3) | 27 (96.4) | |
| R1 | 10 (14.1) | 1 (1.8) | | 3 (10.7) | 1 (3.6) | |
| ypT, N (%) | | | 0.061 | | | 0.422 |
| T1/2 | 56 (78.9) | 51 (91.1) | | 26 (92.9) | 23 (82.1) | |
| T3/4 | 15 (21.1) | 5 (8.9) | | 2 (7.1) | 5 (17.9) | |
| ypN, N (%) | | | 0.189 | | | 0.826 |
| N0 | 13 (18.3) | 17 (30.4) | | 7 (25.0) | 9 (32.1) | |
| N1 | 15 (21.1) | 7 (12.5) | | 5 (17.9) | 5 (17.9) | |
| N2 | 43 (60.6) | 32 (57.1) | | 16 (57.1) | 14 (50.0) | |
| MLND met the guideline | | | 0.692 | | | 0.252 |
| Yes | 27 (47.4) | 24 (43.6) | | 11 (39.3) | 21 (75.0) | |
| No | 30 (52.6) | 31 (56.4) | | 17 (60.7) | 7 (25.0) | |
| LN dissection details, median (25th–75th percentile) | | | | | | |
| LN number | 19 (14–23) | 17 (13–21) | 0.377 | 20 (13.3–23) | 15 (12–20) | 0.191 |
| LN stations | 7 5–8) | 7 (6–8) | 0.464 | 7 (6–8) | 7 (5–7) | 0.315 |
| N1 stations | 3 (2–3) | 3 (2–4) | 0.09 | 3 (2–3) | 3 (2–3) | 0.827 |
| N2 stations | 4 (3–5) | 4 (3–5) | 0.735 | 4 (3–5) | 4 (3–4) | 0.16 |
| N1 LNs | 6 (4–9) | 5 (4–8) | 0.397 | 7 (4–8.5) | 5 (3.3–7) | 0.155 |
| N2 LNs | 10.5 (6.25–14.75) | 10 (7–14) | 0.801 | 11 (5.5–15.5) | 9.5 (7–14.8) | 0.936 |
| Positive N1 stations | 1 (0–2) | 1 (0–1) | 0.082 | 1 (0–2) | 1 (0–1) | 0.402 |
| Positive N2 stations | 1 (0–1.5) | 1 (0–2) | 0.327 | 0.5 (0–2) | 0 (0–2) | 0.645 |

*P* values in bold are statistically significant. MLND, mediastinal lymph node dissection; VATS, video-assisted thoracoscopic surgery.

**Table 3** The rates of lymph node dissection related to tumor location between the two groups

| Nodal station | RUL/RML | | | RLL | | | LUL | | | LLL | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Open (%) | VATS (%) | *P* | Open (%) | VATS (%) | *P* | Open (%) | VATS (%) | *P* | Open (%) | VATS (%) | *P* |
| 2 | 80 | 80 | 1 | 80 | 93 | 0.543 | 18.8 | 0 | 0.232 | 9.1 | 0 | 1 |
| 3 | 55 | 16 | **0.006** | 10 | 26.7 | 0.615 | 25 | 7.7 | 0.343 | | | |
| 4 | 95 | 92 | 1 | 80 | 93.3 | 0.543 | 62.5 | 30.8 | 0.089 | 9.1 | 0 | 1 |
| 5 | | | | | | | 75 | 76.9 | 1 | 72.7 | 100 | 1 |
| 6 | | | | | | | 68.8 | 46.2 | 0.219 | 54.5 | 66.7 | 1 |
| 7 | 90 | 92 | 1 | 90 | 93.3 | 1 | 93.8 | 92.3 | 1 | 100 | 100 | |
| 8 | 35 | 24 | 0.419 | 30 | 33.3 | 1 | 37.5 | 15.4 | 0.238 | 27.3 | 0 | 1 |
| 9 | 25 | 48 | 0.114 | 40 | 53.3 | 0.806 | 75 | 61.5 | 0.688 | 54.5 | 66.7 | 1 |
| 10 | 85 | 76 | 0.708 | 100 | 80 | 0.25 | 68.8 | 100 | **0.048** | 100 | 100 | |
| 11 | 80 | 80 | 1 | 90 | 80 | 0.626 | 56.3 | 92.3 | **0.044** | 72.7 | 100 | 1 |
| 12 | 70 | 68 | 1 | 80 | 80 | 1 | 68.8 | 92.3 | 0.183 | 54.5 | 100 | 0.258 |

*P* values in bold are statistically significant. LUL, left lower lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; VATS, video-assisted thoracoscopic surgery.

71 patients underwent operations that were initiated with thoracoscopic evaluation and subsequently performed via thoracotomy, while the other 59 patients underwent planned thoracotomy. The patients' baseline characteristics are reported in Table 1. The majority of patients were male, but the proportion of male patients was not as high in the VATS group as it was in the thoracotomy group (69.6% vs. 91.5%; $P = 0.001$). Clinical TNM stage ranged from IIB to IIIA, of which stage IIIA-N2 accounted for the majority of patients. The proportion of patients with stage T1N2M0 was higher in the VATS group ($P = 0.024$). Adenocarcinoma was the predominant pathological type in the VATS group, whereas squamous cell carcinoma predominated in the thoracotomy group ($P = 0.006$). Regarding the surgical procedure, the proportion of lobectomies conducted was obviously higher in the VATS group while pneumonectomy was higher in the thoracotomy group ($P < 0.001$). All conversions were proactive. The reasons for conversions included tight adhesions ($n = 3$) and anatomic factors ($n = 3$).

The pathology outcomes after surgery and LND are listed in Table 2. The VATS group achieved more R0 resection than the thoracotomy group (98.2% vs. 85.9%; $P = 0.033$), while the number of dissected LNs and stations was similar between the groups. The rates of sufficient MLND, defined as LND that met the guidelines, were similar in both groups. The rates of LND related to tumor location between the two groups are shown in Table 3. For right upper or middle lobe resections, the rate of station 3 dissection was lower in the VATS group (16% vs. 55%; $P = 0.006$). However, in other circumstances, the VATS group was not inferior to the thoracotomy group. After univariable and multivariable regression, analyses of predictors of sufficient LND were performed (Table 4). Surgery to the upper or middle lobe was found to contribute to sufficient LND compared to surgery to the lower lobe (odds ratio [OR] 3.843, 95% confidence interval [CI] 1.61–9.171; $P = 0.002$). However, approach was not a predictor of sufficient LND (OR 0.81, 95% CI 0.364–1.803; $P = 0.606$).

## Propensity score matching

Propensity score matching was performed for the thoracotomy and VATS groups based on eight variables: age,

**Table 4** Univariable and multivariable regression analyses for predictors of sufficient lymph node dissection

| Variables | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* | OR | 95% CI | *P* |
| Age | 1.035 | 0.99–1.082 | 0.129 | 1.033 | 0.985–1.082 | 0.183 |
| Surgical approach | | | | | | |
|   Thoracotomy | Ref | | | Ref | | |
|   VATS | 0.86 | 0.409–1.811 | 0.692 | 0.81 | 0.364–1.803 | 0.606 |
| Side | | | | | | |
|   Left | Ref | | | Ref | | |
|   Right | 1.519 | 0.696–3.318 | 0.294 | 1.561 | 0.679–3.586 | 0.294 |
| Lobe | | | | | | |
|   Lower | Ref | | | Ref | | |
|   Upper or middle | 3.716 | 1.581–8.733 | **0.003** | 3.843 | 1.61–9.171 | **0.002** |
| Comorbidity | | | | | | |
|   Yes | Ref | | | | | |
|   No | 0.893 | 0.423–1.885 | 0.767 | | | |
| Clinical T stage | | | | | | |
|   T3 or T4 | Ref | | | | | |
|   T1 or T2 | 0.619 | 0.224–1.708 | 0.354 | | | |
| Clinical N stage | | | | | | |
|   N0 | Ref | | | | | |
|   N2 | 0.704 | 0.250–1.983 | 0.507 | | | |
| Histology | | | | | | |
|   Adenocarcinoma | Ref | | | | | |
|   Squamous carcinoma | 1.526 | 0.715–3.258 | 0.274 | | | |
| Induction therapy | | | | | | |
|   Chemotherapy | Ref | | | | | |
|   Chemoradiotherapy | 1.064 | 0.46–2.462 | 0.884 | | | |
| Surgical procedure | | | | | | |
|   Pneumonectomy | Ref | | | | | |
|   Non-pneumonectomy | 1.659 | 0.662–4.158 | 0.28 | | | |

*P* values in bold are statistically significant. CI, confidence interval; OR, odds ratio; VATS, video-assisted thoracoscopic surgery.

gender, tumor histology, comorbidities, neoadjuvant therapy modality, surgical procedure, and pathological T and N stages. These variables were significantly different in the two groups before matching or were identified as factors that may affect long-term survival. After matching, 28 pairs of patients from the two groups were selected for statistical comparison. No differences were identified in patient demographics, clinical characteristics, or treatment modalities between the two groups (Table 1). Three (10.7%) VATS cases were converted to thoracotomy because of tight adhesion of vessels ($n$ = 2) and anatomic factors ($n$ = 1). According to the paraffin pathology outcomes (Table 2), no differences were found in the total number of dissected LNs or stations or the numbers of N1/N2 LNs or stations. Patient perioperative outcomes and morbidities are shown in Table 5. Patients in the VATS group had less bleeding and a shorter postoperative stay than those in the thoracotomy group ($P < 0.001$).

**Table 5** Patient perioperative outcomes for propensity score-matched pairs

| Variables | Propensity score-matched patients | | |
| --- | --- | --- | --- |
| | Thoracotomy group ($n$ = 28) | VATS group ($n$ = 28) | $P$ |
| Surgical duration (minutes), median (25th–75th percentile) | 240 (224–300) | 240 (180–270) | 0.166 |
| Bleeding volume (ml), median (25th–75th percentile) | 200 (300–525) | 100 (30–200) | **< 0.001** |
| Postoperative mortality and morbidity, N (%) | | | |
| 30-day mortality | 1 (3.3) | 0 | 1 |
| Atrial fibrillation | 0 | 1 (3.3) | 1 |
| Acute heart failure | 1 (3.3) | 0 | 1 |
| Prolonged air leak | 4 (13.3) | 3 (10.0) | 1 |
| Atelectasis | 0 | 1 (3.3) | 1 |
| Chylothorax | 0 | 0 | |
| Pneumonia | 4 (13.3) | 0 | 0.112 |
| Pulmonary thromboembolism | 0 | 1 (3.3) | 1 |
| Hoarseness | 0 | 1 (3.3) | 1 |
| No major complications | 21 (70.0) | 23 (76.7) | 0.559 |
| Postoperative tube duration (days), median (25th–75th percentile) | 5 (2–7.5) | 4 (3–5.3) | 0.903 |
| Postoperative stay (days), median (25th–75th percentile) | 8 (7–12) | 6 (5–7) | **< 0.001** |

*P* values in bold are statistically significant. VATS, video-assisted thoracoscopic surgery.

## Survival analysis

No significant differences were observed in RFS between the matched VATS and thoracotomy groups (log-rank $P$ = 0.613), and the median survival times were 16 months (95% CI 8.5–23.5) and 21 months (95% CI 4.5–37.5), respectively (Fig 1a). Furthermore, no significant difference was observed in OS between patients in the VATS and thoracotomy groups (log-rank $P$ = 0.379) (Fig 1b). The multivariable Cox proportional hazards model analyses for RFS and OS are shown in Tables 6 and 7, respectively. VATS was not an independent predictor of RFS (hazard ratio [HR] 0.955, 95% CI 0.415–2.198; $P$ = 0.913) or OS (HR 0.841, 95% CI 0.338–2.093; $P$ = 0.709); however, pathologic N2 stage was associated with worse OS (HR 3.449, 95% CI 1.147–10.37; $P$ = 0.027).

## Discussion

A consensus regarding the adoption of thoracoscopic lobectomy for locally advanced NSCLC following neoadjuvant therapy has not been achieved because of the increased difficulty of complete resection and the risk of pleural dissemination after LND. In addition, the thoroughness of LND via thoracoscopic lobectomy compared to thoracotomy remains uncertain and may affect the oncological efficacy of surgery and patients' long-term survival.

Several previous studies have reported that the number of dissected LNs and stations via VATS or thoracotomy do not differ.[6,9,13–16] D'Amico *et al.* reported that similar numbers of N1/N2 stations were dissected with the two different approaches, supporting the oncologic efficacy of thoracoscopic MLND.[14] Watanabe *et al.* compared LND between VATS and thoracotomy in cN0-pN2 NSCLC patients and reported a similar number of dissected nodes, rate of nodal metastasis, and long-term survival;[15] thus, VATS is a feasible approach for systematic node dissection to treat these patients, without inferior oncologic efficacy compared to thoracotomy. Palade *et al.* conducted a randomized controlled trial and recruited clinical stage I NSCLC patients to compare the outcomes of MLND performed by VATS to those of thoracotomy and concluded that MLND performed via a thoracoscopic approach was as effective as thoracotomy and provided better visualization.[13] These results suggest the efficacy of MLND performed via a thoracoscopic approach in NSCLC patients who have not been administered preoperative chemotherapy or chemoradiotherapy. Kamel *et al.* and Petersen *et al.* compared the outcomes of LND between VATS and thoracotomy following neoadjuvant therapy, and no significant differences were observed.[6,9] However, they did not report additional details regarding the LNs at each nodal station related to the lobe.
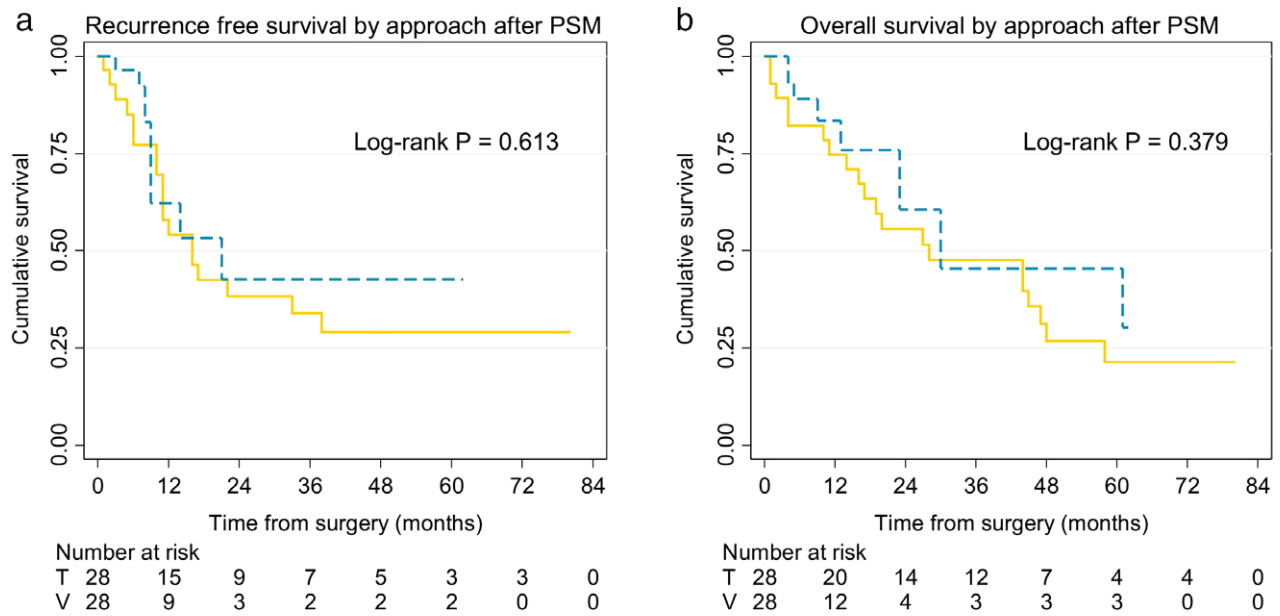
**Figure 1** Kaplan–Meier curve for long-term survival by approach after propensity score matching (PSM). No significant difference in (**a**) recurrence-free survival (log-rank $P = 0.613$) or (**b**) overall survival (log-rank $P = 0.379$) is observed. T, thoracotomy group; V, video-assisted thoracoscopic surgery (VATS) group. (——) Thoracotomy and (------) VATS.

**Table 6** Multivariable Cox proportional hazards model analysis for RFS

| Variables | HR | 95% CI | P |
|---|---|---|---|
| Histology | | | |
|   Adenocarcinoma | Ref | | |
|   Squamous carcinoma | 1.33 | 0.549–3.22 | 0.527 |
| Induction therapy | | | |
|   Chemotherapy | Ref | | |
|   Chemoradiotherapy | 1.307 | 0.526–3.247 | 0.564 |
| Surgical approach | | | |
|   Thoracotomy | Ref | | |
|   VATS | 0.955 | 0.415–2.198 | 0.913 |
| Completeness of resection | | | |
|   R1 | Ref | | |
|   R0 | 0.442 | 0.136–1.435 | 0.174 |
| Pathologic N stage | | | |
|   N0 | Ref | | |
|   N1 | 0.925 | 0.211–4.065 | 0.918 |
|   N2 | 0.442 | 0.136–1.435 | 0.174 |

CI, confidence interval; HR, hazard ratio; RFS, recurrence-free survival; VATS, video-assisted thoracoscopic surgery.

In addition, there is insufficient evidence to recommend VATS as a feasible approach for MLND to treat patients with locally advanced NSCLC following neoadjuvant therapy. Lobe-specific LN stations should be considered;[11] thus, in this study, comparisons of the number of LNs or stations dissected were not definitive.

This study compared the thoroughness of LND between VATS and thoracotomy following neoadjuvant therapy for treating patients with locally advanced NSCLC.

As evaluated by the number of dissected LNs (total number, number of N1 and N2 nodes) and stations (total number, number of N1 and N2 stations), pathological positivity of N1 or N2 LN stations, and rates of nodal station dissection related to tumor location, the results generally indicated that VATS was not inferior to thoracotomy in terms of the efficacy of MLND. In multivariable analysis, tumor location in the upper or middle lobe contributed to more sufficient LND, whereas the surgical approach did not affect the thoroughness of LND. Few studies have discussed whether the choice between preoperative chemotherapy and chemoradiotherapy might affect the thoroughness of MLND. The present study revealed similar rates of sufficient MLND between these two treatment modalities, which is consistent with a previous study.[16] After propensity score matching, the thoroughness of MLND by VATS was similar to that of thoracotomy.

Some studies have also reported that LND by VATS is not as sufficient as by thoracotomy.[17,18] Lee et al. and Denlinger et al. reported that despite similar survival outcomes, LND by thoracotomy was more thorough than by VATS.[17,18] Murakawa et al. reported the same result when comparing the number of LNs and stations, but after propensity score matching no significant difference was observed in LND between the groups.[19] According to these studies, the conflict may be caused by selection bias as a result of patient status and tumor stage; the concept of LND, which has evolved over time; and operative time at the initiation of VATS.

**Table 7** Multivariable Cox proportional hazards model analysis for OS

| Variables | HR | 95% CI | P |
|---|---|---|---|
| Age | 1.028 | 0.975–1.084 | 0.305 |
| Histology, squamous carcinoma/adenocarcinoma | 1.283 | 0.338–2.093 | 0.579 |
| Induction therapy, chemoradiotherapy/chemotherapy | 1.376 | 0.530–3.575 | 0.512 |
| Surgical approach, VATS/thoracotomy | 0.841 | 0.338–2.093 | 0.709 |
| Surgical procedure, lobectomy/pneumonectomy | 0.937 | 0.267–3.283 | 0.919 |
| Pathologic N stage | | | |
| N0 | Ref | | |
| N1 | 2.201 | 0.496–9.776 | 0.3 |
| N2 | 3.449 | 1.147–10.37 | **0.027** |

*P* values in bold are statistically significant. CI, confidence interval; HR, hazard ratio; OS, overall survival; VATS, video-assisted thoracoscopic surgery.

After propensity score matching, the perioperative outcomes showed a low conversion rate (10.7%) similar to other studies (8.3–16.7%), decreased bleeding volume, and shorter length of hospitalization with the use of thoracoscopic surgery after neoadjuvant therapy.[8,9,20] Regarding long-term outcomes, no statistically significant differences were observed in RFS or OS between the two groups. In addition, multivariable Cox proportional hazards model analysis revealed that the surgical approach had no significant influence on patient survival. For locally advanced NSCLC patients who underwent radical surgery after neoadjuvant therapy, VATS achieved oncologic efficacy and long-term survival outcomes similar to thoracotomy. Our findings are consistent with those of previous studies.[9,20,21] Petersen *et al.* reported no difference in the number of dissected LNs and stations between VATS and thoracotomy groups.[9] Park *et al.* reported similar sampled LN stations between minimally invasive surgery and thoracotomy groups.[21] However, these studies did not disclose details of the relationship of the LN stations to pulmonary lobes or further discuss the thoroughness of MLND accomplished by the two approaches. In our study, VATS achieved acceptably thorough MLND, not only in terms of the number of dissected LNs and stations but also in terms of the number of nodal stations related to the tumor location. With respect to long-term survival, VATS was not inferior to thoracotomy.

This study has several limitations. First, although the data were recorded prospectively in our lung cancer database, the analysis was retrospective. In addition, it was a single-center experience, thus the findings may not be generalized to other institutions. Second, as all patients were divided into two groups by approach, the patients in the thoracotomy group were more likely to be male, with a squamous histologic subtype, a higher clinical T descriptor, and will have undergone pneumonectomy. The selection bias caused by the limited sample size and indication for thoracotomy in our center may have affected the distribution of patients. It was difficult to eliminate selection and confounding bias, even with propensity score matching, because of the limited sample size. Patients who underwent surgery via a thoracotomy approach were more likely to undergo pneumonectomy, which may have contributed to more thorough MLND and more R0 resection but poorer pulmonary function reserve than patients who underwent VATS. Third, the follow-up duration was insufficient, which limited the comparisons of long-term survival. Thus, our results should be interpreted with caution.

Compared to thoracotomy, VATS is a qualified and sufficient approach for MLND to treat locally advanced stage NSCLC following neoadjuvant therapy, without compromising long-term survival. Rigorous clinical studies, such as randomized controlled trails, are required to validate the causal effect between surgical approach and oncological efficacy.

## Disclosure

No authors report any conflict of interest.

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