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# Thoracoscopic Versus Open Lobectomy After Induction Therapy for Nonsmall Cell Lung Cancer: New Study Results and Meta-Analysis

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## ABSTRACT

**Introduction:** The use of video-assisted thoracoscopic surgery (VATS) lobectomy has become a mainstay of modern thoracic surgery practice and the technique of choice for resection of early-stage lung cancers. However, the benefits of VATS following induction therapy are yet to be clarified. This study aims to assess whether VATS lobectomy achieves similar perioperative and oncologic outcomes compared to thoracotomy for nonsmall cell lung cancer after induction therapy.

**Methods:** We retrospectively reviewed the outcomes of 72 patients who underwent lung lobectomy after induction therapy in our institution from January 2017 to January 2020. Subsequently, we carried out a comprehensive literature search and pooled our results with available data from previously published studies to perform a meta-analysis.

**Results:** VATS was associated with reduced intraoperative blood loss ( $P = 0.05$ ) and less perioperative complications ( $P = 0.04$ ) in our local institution. The meta-analysis comprised nine studies. A total of 943 patients underwent VATS and 2827 patients underwent open lobectomy. VATS was associated with significant shorter surgery duration ( $P < 0.0001$ ), shorter chest-tube drainage duration ( $P < 0.0001$ ), and shorter hospital stays ( $P < 0.0001$ ). Furthermore, there was significantly less perioperative complications ( $P = 0.006$ ) and less intraoperative blood loss ( $P = 0.036$ ) in the VATS group. However, there were no significant differences in 3-y overall survival and 3-y disease-free survival rates.

**Conclusions:** In some selected patients undergoing induction therapy, VATS lobectomy could achieve equivalent perioperative outcomes to thoracotomy but evidence is lacking on oncologic outcomes. Further trials with a focus on oncologic outcomes and longer follow-up are required.

### Keywords:

Induction therapy

Lobectomy

Non-small cell lung cancer

Thoracotomy

Video-assisted thoracoscopic surgery

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## Introduction

Recent trials indicate that neoadjuvant therapy can improve the completeness of resection and survival in patients with locally advanced nonsmall cell lung cancer (NSCLC).<sup>1-3</sup> However, tissue adhesions and increased vascular fragility after neoadjuvant therapy can increase the surgical risk, post-operative complication rate, and mortality.<sup>4,5</sup> Despite the advantages of thoracoscopic surgery for patients without induction therapy, including shorter postoperative hospital stays, decreased chest drainage times, and reduced post-operative complication rates,<sup>6,7</sup> video-assisted thoracoscopic surgery (VATS) resection after induction therapy has remained relatively contraindicated with respect to the technical difficulty of the thoracoscopic approach.<sup>8</sup> Nevertheless, with advances in both the equipment and technique, and the experience gained, the use of VATS in more technically challenging operations has expanded.<sup>9,10</sup> Indeed, several studies have reported the feasibility of VATS lobectomy for locally advanced NSCLC following induction therapy.<sup>11-13</sup> However, the evidence regarding its safety and oncologic outcomes still remains weak. In this report, we retrospectively reviewed the perioperative outcomes of patients with NSCLC who received induction therapy followed by lobectomy in our institution from January 2017 to January 2020. We then collected all current evidence comparing VATS lobectomy *versus* open thoracotomy in the treatment of NSCLC following neoadjuvant therapy to perform a meta-analysis of all published data.

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## Methods

### *Individual patient data from Arnaud De Villeneuve (ADV) thoracic and vascular surgery department (ADV center)*

#### *Preoperative management*

A single-center experience of consecutive VATS and thoracotomy lobectomy for the management of NSCLC requiring neoadjuvant therapy (chemotherapy with or without radiotherapy) at Arnaud De Villeneuve (ADV) University Hospital Center was reviewed during a three-year period from January 2017 to January 2020. The histological diagnosis was confirmed either by fibrobronchoscopy, endobronchial ultrasonography (EBUS), or computed tomography (CT)-guided percutaneous biopsy. Preoperative clinical staging was assessed by CT scan, positron emission tomography (PET)/CTFDG, and magnetic resonance imaging (MRI) of the brain. EBUS was used for invasive nodal staging prior to induction therapy in case of N2 or N3 clinical stages with a mediastinal uptake on PET/CTFDG. Repeat EBUS was performed in patients with N2 disease after induction therapy. Patients with persistent N2 disease were excluded. Tumor, nodes, and metastases (TNM) staging of malignant tumors was based on the eighth edition of the American Joint Committee on Cancer (AJCC) lung cancer staging guidelines. All cases were discussed in a multidisciplinary tumor board meeting and scheduled for surgery 4-6 wk after completion of induction

therapy. The surgical approach was three-port VATS for the VATS lobectomy group and posterolateral thoracotomy for the thoracotomy group. Patients with tumors of more than 7 cm and those with central airway and/or vascular invasion were not eligible for the VATS approach. Data were obtained from patient case notes and electronic patient records and then entered into a dedicated database. Data included demographics, comorbidities, clinical stage, histology, pathological stage, perioperative outcomes, surgery duration, intraoperative blood loss, conversion rate, perioperative complications, chest-tube drainage duration, length of hospital stay, 30-d mortality, and final pathology report (lymph node number [LNN], lymph node station number [LNSN], and R0-resection margins). Follow-up data were collected from patient clinical notes and from direct patient and physician contact. The final follow-up evaluation was in February 2021. Overall survival (OS) was defined as the time period between surgery and death or last follow-up evaluation. Disease-free survival (DFS) was defined as the time period between surgery and recurrence or death. The study was approved by the local institutional review board with a waiver of individual patient consent.

#### *Statistical analysis*

Statistical analyses were performed using SAS Enterprise Guide, version 7.3 (SAS Institute, USA). Continuous parametric data are presented as means  $\pm$  standard deviation (SD) and categorical variables as numbers and percentages. We used the  $\chi^2$  test for categorical variables and Mann-Whitney or student's t-test for quantitative variables, as per the normality of the distribution, assessed with the Shapiro-Wilk test. The Kaplan-Meier analysis method was used for a survival analysis and the comparison of two survival curves was performed using the log-rank test. Statistical significance was defined as a P value <0.05.

#### *Meta-analysis*

A meta-analysis was performed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Fig. 1).<sup>14</sup>

#### *Search strategy*

A literature search was undertaken to identify published studies comparing VATS *versus* thoracotomy lobectomy following induction therapy. Candidate studies in English were sought for up to February 2021 via a computerized search of PubMed, Embase, Cochrane CENTRAL, Web of Science, and Google Scholar databases. Keywords and meSH terms entered in the search were 'lung cancer,' 'thoracotomy,' 'video-assisted thoracoscopic surgery,' 'induction therapy,' 'neoadjuvant therapy,' and 'comparative study'. The reference lists of all the relevant retrieved articles were evaluated manually for further relevant studies.

#### *Study selection*

Studies were considered for inclusion and further analysis on the basis of the following criteria:

1. Patients diagnosed with NSCLC who received neoadjuvant therapy by chemotherapy either alone or in combination with radiotherapy.
2. Randomized controlled trials or observational studies (cohort and case-control studies).
3. Studies comparing the effects of VATS lobectomy with open thoracotomy.
4. Studies providing sufficient perioperative and oncologic outcome data.

Studies having enrolled patients undergoing robot-assisted lobectomy were excluded. Also, studies with inextractable data, review articles, editorials, comments, letters, case reports, and animal experimentation were excluded from the analysis.

#### Clinical end points

The study outcomes analyzed included surgery duration, intraoperative blood loss, conversion rate, chest-tube drainage duration, perioperative complication rate, length of hospital stay, 30-d mortality, LNN, LNSN, R0-resection margins, OS, and DFS.

#### Data extraction and quality assessment

Two independent analysts (K.H. and L.C.) identified the publications based on the title and abstract as per the above-mentioned eligibility criteria. Any disagreement was resolved by a third analyst (P.A.). Thereafter, the full texts of potentially relevant studies were reassessed to determine their conformity with the criteria. Relevant data from included articles were extracted and entered into a standardized data form. The following data were extracted from each included study: first author, publication year, geographical area, study design, enrollment date, number of patients in each group, demographic data, clinical characteristics including clinical stage, histology, pathological stage, type of induction therapy, and follow-up. We additionally collected perioperative outcomes and long-term survival outcomes consisting of 3-y OS rates and 3-y DFS rates. Survival data were extracted directly from the text or indirectly after calculation from the Kaplan–Meier survival curves.

The quality of included studies was rated as per the Newcastle–Ottawa Scale (NOS). This evaluates the quality of nonrandomized studies by analyzing the following three criteria: selection of study groups, comparability of the groups, and ascertainment of either the exposure or outcome of interest for case-control or cohort studies. The scale assigns a maximum of nine stars to each study.<sup>15</sup> For our analysis, studies were graded as good quality with 8-9, fair with 5-7, and poor with <5 stars. Any disagreement was resolved by a third analyst (P.A.). More details about the NOS quality assessment can be found in [Supplementary Data \(S1\)](#).

#### Statistical analyses

Statistical analyses were performed with the R statistical software ([www.r-project.org](http://www.r-project.org), version 4.0.2) using the ‘meta’ (v.4.13-0) package. The mean difference (MD) was used as a summary statistic for continuous variables including surgery duration, intraoperative blood loss, conversion rate, chest-tube drainage duration, length of hospital stay, LNN, and

LNSN. A pooled relative risk (RR) was used to estimate the RR of perioperative complications, perioperative mortality, and R0-resection margins after VATS compared with open thoracotomy. Hazard ratios (HRs) were obtained for OS and DFS. Heterogeneity between studies was measured using the  $I^2$  index from Higgins *et al.*<sup>16</sup> which describes the percentage variation across studies that is a result of heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity with increasing values indicating increasing heterogeneity: 25%-49% indicating low, 50%-74% indicating moderate, and  $\geq 75\%$  indicating high heterogeneity. For  $I^2 \geq 50\%$ , the interstudy heterogeneity was considered as significant and meta-analyses were conducted using a random-effects model. Otherwise, for  $I^2 < 50\%$  the heterogeneity was classed as acceptable and a fixed-effects model was applied. Random-effects models were used with the inverse variance method for high levels of heterogeneity and variations in measurements. We also calculated the Q-statistic but only reported whether this was significant or not. For OS and DFS analysis, if HRs could not be extracted from the included studies, the data were calculated from Kaplan–Meier curves as per the method provided by Tierney *et al.*<sup>17</sup> Funnel plots were used to test for publication bias. Egger’s test of the intercept was used to test for funnel plot asymmetry.<sup>18</sup> All analyses were two-tailed and a  $P$  value  $< 0.05$  was considered statistically significant.

## Results

### Results from local data (ADV center)

The patient’s baseline characteristics are reported in [Table 1](#). Thirty three patients underwent VATS lobectomy and 39 patients underwent thoracotomy lobectomy. There were no significant differences in age, gender, pulmonary function tests (FEV1, DLCO), smoking history, tumor histology, clinical stage, and induction treatment between the two groups. However, patients in the thoracotomy group were more likely to have hypertension ( $P = 0.022$ ). The mean tumor size was smaller in the VATS group than in the thoracotomy group ( $P = 0.014$ ). IIIA disease was the predominant stage and adenocarcinoma was the predominant pathological type.

[Table 2](#) reports perioperative outcomes for the two groups. There was no difference between the two groups in terms of surgery duration ( $191.52 \pm 69.5$  versus  $186.6 \pm 64.5$  min,  $P = 0.36$ ), chest-tube drainage duration ( $3.11 \pm 4.21$  versus  $3.28 \pm 2.25$  d,  $P = 0.41$ ), and length of hospital stay ( $7.35 \pm 4.13$  versus  $7.61 \pm 4.17$  d,  $P = 0.44$ ) in the VATS group versus the thoracotomy group, respectively. In addition, no difference was found for LNN ( $13.05 \pm 5.78$  versus  $14.52 \pm 7.85$ ,  $P = 0.18$ ) or LNSN ( $5.55 \pm 1.56$  versus  $5.53 \pm 1.96$ ,  $P = 0.65$ ) between the VATS group versus the thoracotomy group, respectively.

VATS achieved greater R0-resection margins than thoracotomy ( $96.9\%$  versus  $84.6\%$ ,  $P = 0.025$ ). There was a trend for an increased intraoperative blood loss in the thoracotomy group ( $188.52 \pm 163.59$  mL versus  $277.43 \pm 290.04$ ,  $P = 0.05$ ) that did not quite reach statistical significance. Perioperative complications however were higher in the thoracotomy group ( $27.3\%$  versus  $33.3\%$ ,  $P = 0.04$ ).

**Table 1 – Patient’s baseline characteristics (ADV center study).**

Variables	Thoracotomy	VATS	P value
Age, y ± SD	63.17 ± 8.1	60.54 ± 7.9	0.171
Female gender, n (%)	22 (56.4)	13 (39.4)	0.121
FEV1%, mean ± SD	88.9 ± 15.2	86.5 ± 18.3	0.552
DLCO%, mean ± SD	66.66 ± 14.4	66.24 ± 14.7	0.891
Comorbidities, n (%)			
Hypertension	15 (38.4)	5 (15.1)	<b>0.022</b>
Diabetes	8 (20.5)	4 (12.1)	0.247
Cardiac disease	9 (23.1)	2 (6.1)	0.052
COPD	9 (23.1)	11 (33.3)	0.337
Smoking history, n (%)	35	29	0.802
cTm size, cm ± SD	48.38 ± 27.2	33.29 ± 19.5	<b>0.014</b>
cTNM, n (%)			0.521
IIB	3 (7.7)	5 (15.1)	
IIIA	21 (53.8)	18 (54.5)	
IIIB	4 (10.2)	1 (3.1)	
IV	11 (28.3)	9 (27.3)	
Histology, n (%)			0.407
Adenocarcinoma	25 (64.1)	18 (54.5)	
Squamous cell	13 (33.3)	15 (45.5)	
Other	1 (2.6)	0	
Induction therapy, n (%)			0.569
Chemotherapy	32 (82.1)	25 (75.7)	
Chemoradiotherapy	7 (17.9)	8 (24.3)	
Tumor location, n (%)			0.531
Right upper	15 (38.5)	15 (45.4)	
Right middle	2 (5.1)	2 (6.1)	
Right lower	5 (12.9)	7 (21.2)	
Left upper	10 (25.6)	7 (21.2)	
Left lower	7 (17.9)	2 (6.1)	

P values inferior to 0.05 are highlighted in bold.

VATS = video-assisted thoracoscopic surgery; SD = standard deviation; FEV1 = forced expiratory volume in 1 s; DLCO = diffusing capacity of carbon monoxide; COPD = chronic obstructive pulmonary diseases.

The conversion rate was 9%. Thirty-day mortality was 2.59% in the thoracotomy group but no patients died in the VATS group ( $P = 0.29$ ).

The mean follow-up time was 33 mo. Three-y OS and 3-y DFS was 95.5% and 52.9% in the VATS group and 96.8% and 48.7% in the thoracotomy group, respectively. There was no significant difference in 3-y OS (log-rank test,  $P = 0.655$ ) and 3-y DFS (log-rank test,  $P = 0.331$ ) between both groups (Fig. 2).

## Meta-analysis results

### Study description and baseline characteristics

The initial literature search yielded 553 articles. After screening of titles and abstracts, and additional searches in accordance with the inclusion criteria, we included a total of eight published retrospective studies.<sup>12,13,19-24</sup> The study evaluation process is presented in Figure 1. After the addition of new, local data from our institution (ADV center), meta-analyses were thus performed using data from nine cohort

studies comparing VATS and thoracotomy lobectomy following neoadjuvant therapy. A total of 3770 patients were included of which 53% were male with a median age of 61.5 (56-68) y. A total of 943 patients underwent VATS and 2827 patients underwent thoracotomy. All studies provided data on age, gender, and histology. Six published studies<sup>13,19-21,23</sup> and ADV Montpellier provided explicit clinical stage data involving 672 patients, of whom 73% had clinical stage IIIA-IIIB tumors. Based on the available data from all studies except one,<sup>12,13,19-23</sup> and ADV Montpellier, platinum-based doublet chemotherapy was the most common induction treatment. The mean follow-up time for all patients was 28.5 mo. The study descriptions are summarized in Table 3.

### Surgery duration

Five studies provided data on surgery duration and these studies involved 169 patients in the VATS group and 310 patients in the thoracotomy group. No heterogeneity was identified among these studies ( $I^2 = 0.0\%$ ,  $P = 0.43$ ). The meta-analysis



**Table 2 – Perioperative outcomes (ADV center study).**

Perioperative outcomes	Thoracotomy	VATS	P value
Any complication, n (%)	13 (33.3)	9 (27.3)	<b>0.04</b>
Air leak >5 d	5 (12.8)	4 (12.1)	
Atrial arrhythmia	4 (10.25)	1 (3.03)	
Pneumonia	2 (5.1)	2 (6.1)	
ARDS, n (%)	1 (2.6)	0 (0)	
Bronchopleural fistula	1 (2.6)	0 (0)	
Pleural effusion	2 (5.1)	0 (0)	
Surgery duration, median min	186.6 ± 64.5	191.52 ± 69.5	0.36
Blood loss, median ml	277.43 ± 290.04	188.52 ± 163.59	<b>0.05</b>
Chest tube duration, median days	3.28 ± 2.25	3.11 ± 4.21	0.41
Length of stay, median days	7.61 ± 4.17	7.35 ± 4.13	0.44
30 d mortality, n (%)	1 (2.59)	0	0.29

Data are presented as mean ± standard deviation.

P values inferior to 0.05 are highlighted in bold.

VATS = video-assisted thoracoscopic surgery; ARDS = acute respiratory distress syndrome.

demonstrated that patients undergoing VATS lobectomy had significantly shorter surgery durations (fixed-effects MD = -16.4; 95% CI = [-19.37, -13.45];  $P < 0.0001$ ) (Fig. 3).

#### Intraoperative blood loss

Intraoperative blood loss was evaluated in five studies, thus including 169 patients in the VATS group and 310 patients in the thoracotomy group. Compared to thoracotomy, intraoperative blood loss was significantly reduced with VATS (random-effects MD = -97.76; 95% CI = [189.55, -5.97];  $P = 0.036$ ) with evidence of interstudy heterogeneity ( $I^2 = 99%$ ,  $P < 0.001$ ) (Fig. 3).

#### Chest-tube drainage duration

Eight articles reported on data for chest-tube drainage duration. These studies involved 267 patients in the VATS group and 616 patients in the thoracotomy group. The meta-analysis demonstrated that patients undergoing lobectomy via VATS had significantly shorter chest-tube drainage times compared to those via thoracotomy (random-effects MD = -1.42, 95% CI = [-1.87, -0.97],  $P < 0.0001$ ). Heterogeneity was observed among included studies ( $I^2 = 95.5%$ ,  $P < 0.001$ ) (Fig. 3).

#### Length of hospital stay

The meta-analysis of all included studies revealed that length of hospital stay was significantly reduced by 2.45 d for patients in the VATS group compared to those in the thoracotomy group (random-effects MD = -2.45, 95% CI [-3.10, -1.79],  $P < 0.0001$ ). However, heterogeneity was observed among studies ( $I^2 = 99%$ ,  $P < 0.01$ ) (Fig. 4).

#### Perioperative complication rate

A perioperative complication rate analysis was based on eight studies, involving 267 patients in the VATS group and 616 patients in the thoracotomy group. Perioperative complications were significantly reduced in the VATS group compared with thoracotomy (fixed-effect RR = 0.73, 95% CI = [0.59; 0.91],  $P = 0.006$ ). The heterogeneity among the studies was not significant ( $I^2 = 16%$ ,  $P = 0.31$ ) (Fig. 4).

#### Thirty-day mortality

All included studies provided data on 30-d mortality. Compared to conventional thoracotomy, thoracoscopic surgery did not have an effect on 30-d mortality rate (fixed-effects RR = 0.64, 95% CI = [0.38; 1.09]  $P = 0.10$ ). No heterogeneity was identified among the studies ( $I^2 = 0.0%$ ;  $P = 0.8$ ) (Fig. 4).

#### Conversion rate

All included studies reported the rate of conversion to thoracotomy. The random-effects model was used to estimate the proportion of conversion, given there was a nonsignificant trend for heterogeneity between studies ( $I^2 = 50%$ ,  $P = 0.06$ ). The conversion proportion was 0.14 (95% CI = [0.09; 0.20]). None of these conversions led to perioperative deaths in eight studies; the remaining study did not provide data on this topic.<sup>24</sup>

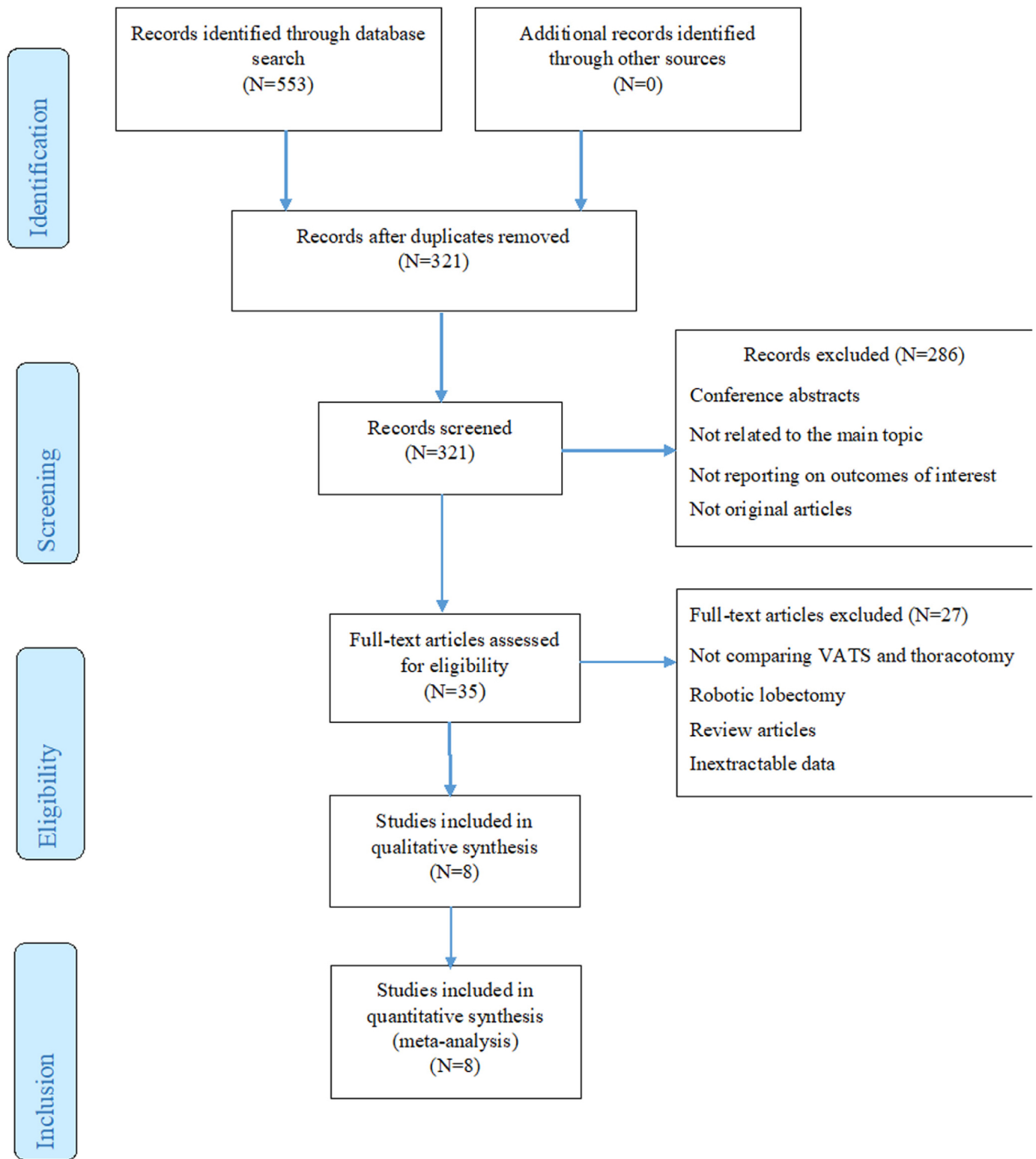
#### Lymph node number (LNN) and lymph node station number (LNSN)

Eight studies reported data on the total number of lymph nodes dissected, thus involving 874 patients in the VATS group and 2624 patients in the thoracotomy group. There was a trend for a better performance of VATS in lymph node dissection compared with thoracotomy; however, the difference did not reach statistical significance (random-effects MD = -0.67, 95% CI = [-2.74; 1.40],  $P = 0.52$ ). There was significant heterogeneity between studies ( $I^2 = 97.4%$ ,  $P < 0.0001$ ) (Fig. 5).

Six studies provided data regarding the number of lymph node stations dissected, involving 172 patients in the VATS group and 354 patients in the thoracotomy group. The number of lymph node stations dissected did not significantly differ between VATS and thoracotomy (random-effects MD = 0.06, 95% CI = [-0.22; 0.34],  $P = 0.67$ ), with evidence of heterogeneity between studies ( $I^2 = 77.7%$ ,  $P = 0.0004$ ) (Fig. 5).

#### R0-resection margins

All included studies reported data on resection margins. The fixed-effects model was used for this analysis because there



**Fig. 1 – PRISMA flow chart of the study selection process.**

was no significant heterogeneity between studies ( $I^2 = 28.2\%$ ,  $P = 0.19$ ). VATS achieved equal quality in R0-resection to thoracotomy (fixed-effects  $RR = 1.01$ , 95%  $CI = [0.99; 1.02]$ ,  $P = 0.07$ ) (Fig. 5).

*Overall survival and disease-free survival*  
OS was defined as the time period between surgery and death or last follow-up evaluation. The 3-y weighted mean OS was 64.37% in the VATS group and 64.35% in the thoracotomy

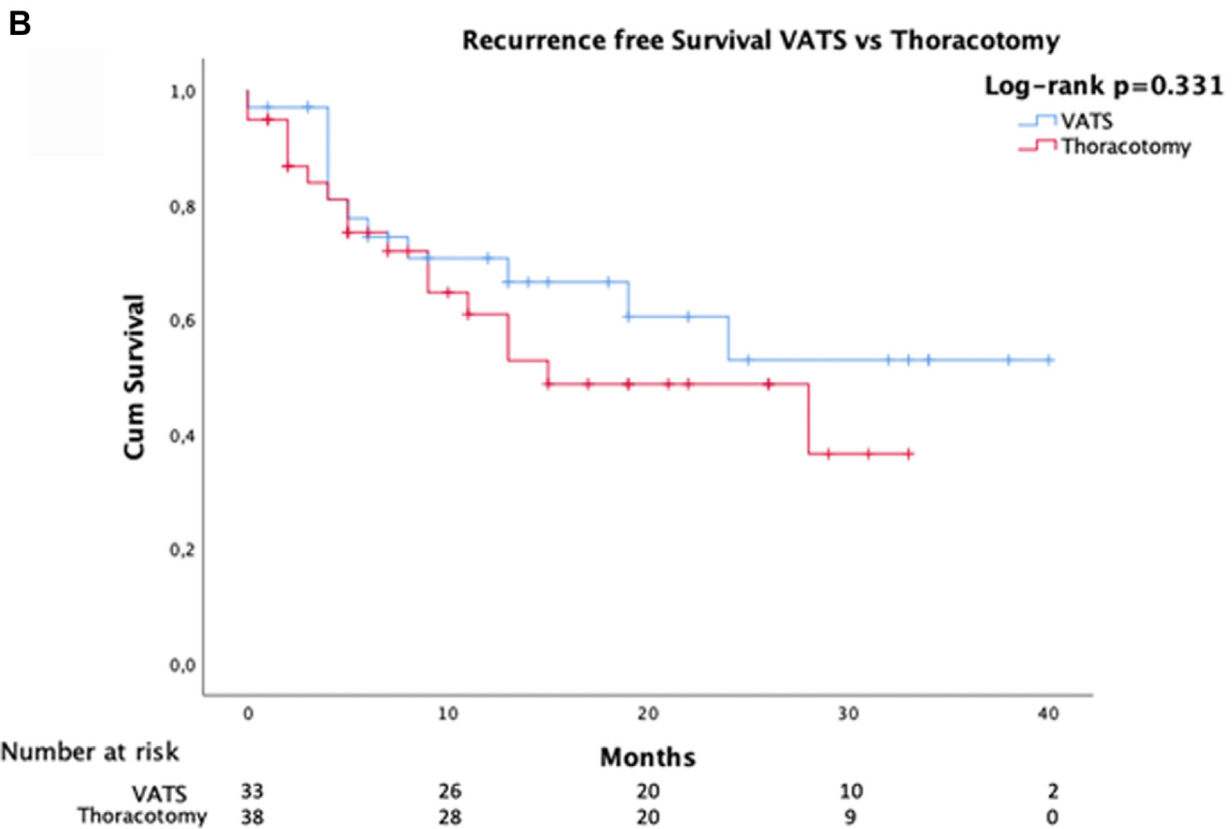
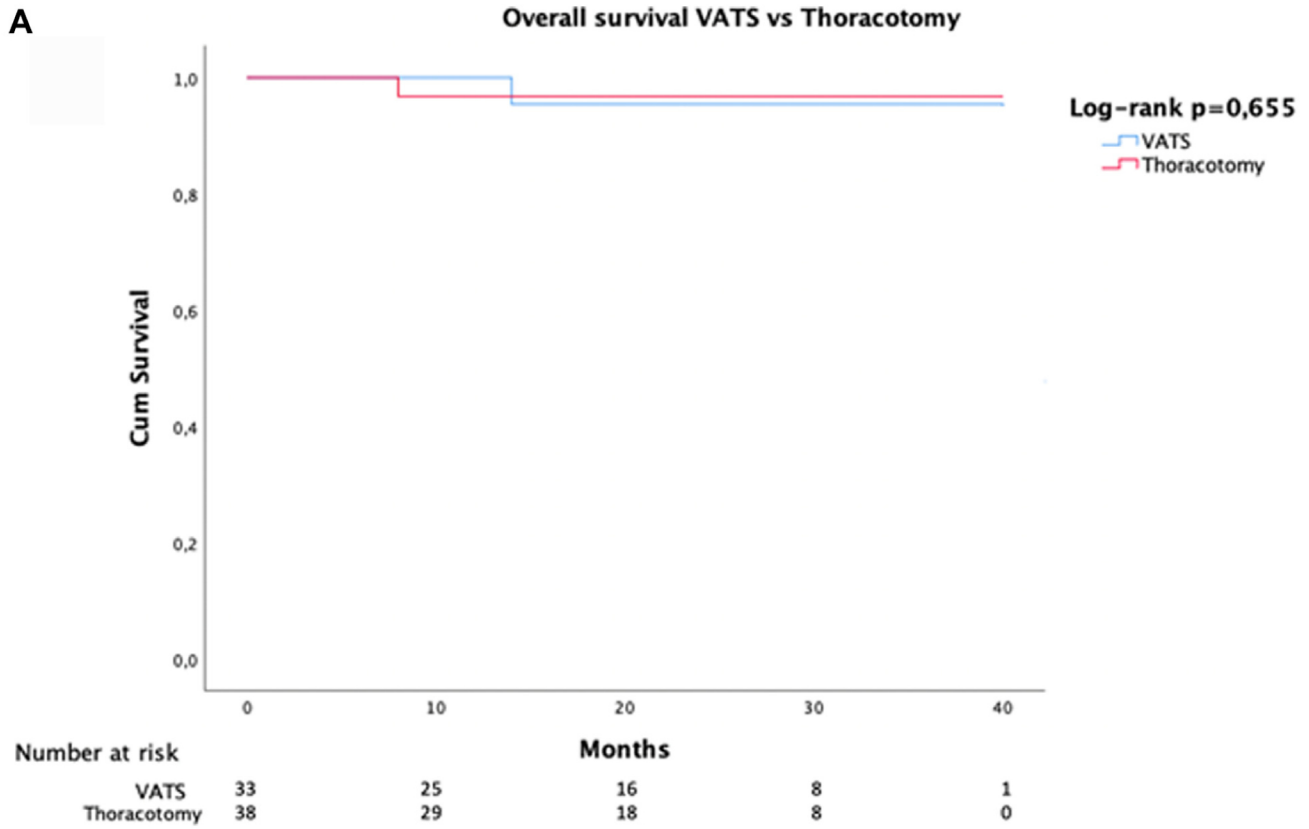


Fig. 2 – Three year–survival of ADV center study. (A) OS between VATS and thoracotomy groups. (B) DFS between VATS and thoracotomy groups.

**Table 3 – The descriptive characteristics of the nine studies comparing VATS versus open thoracotomy lobectomy after induction therapy.**

Author/ year	Country	Study design	NOS	Staging system	Median follow-up (months)	Surgical technique	Number of patients	Gender (M/F)	Mean age (years)	Clinical stage	
										IB n (%)	II n (%)
Petersen 2006	USA	Single RS	7	NA	14	VATS	12	6/6	56	2 (17)	1 (8)
						Thoracotomy	85	35/50	60	1 (1)	19 (22)
Kamel 2016	USA	Single PMS	9	AJCC 7th	75	VATS	40	29/11	68	NA	NA
						Thoracotomy	74	51/23	67	NA	NA
Yang 2016	USA	Single RS	8	NA	24	VATS	69	37/32	63.7	1 (1)	6 (9)
						Thoracotomy	203	84/119	58.3	3 (1)	14 (7)
Fang 2018	China	Single RS	7	AJCC 8th	15	VATS	14	3/11	61	0	0
						Thoracotomy	67	4/63	60	0	0
Jeon 2018	South Korea	Single RS	7	AJCC 7th	36.3	VATS	17	3/14	62	0	0
						Thoracotomy	18	1/17	60	0	0
Suh 2019	South Korea	Single RS	6	NA	12.6	VATS	26	8/18	64.3	NA	NA
						Thoracotomy	59	16/43	60.7	NA	NA
Thian 2019	China	Single PMS	7	AJCC 7th	NA	VATS	56	17/39	56.5	0	0
						Thoracotomy	71	6/65	58.7	0	0
Yang 2020	USA	Multi PMS	8	AJCC 7th	31.6	VATS	676	372/304	63	NA	NA
						Thoracotomy	2211	1077/ 1134	63	NA	NA
ADV center 2021	France	Single RS	7	AJCC 8th	33	VATS	33	10/23	60.5	0	0
						Thoracotomy	39	14/25	63,1	0	0

(continued)

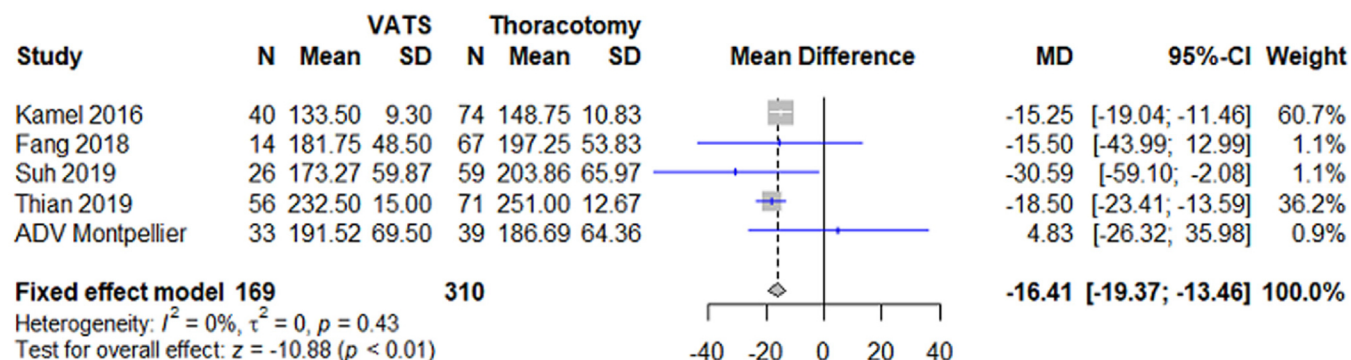


**Table 3 – (continued)**

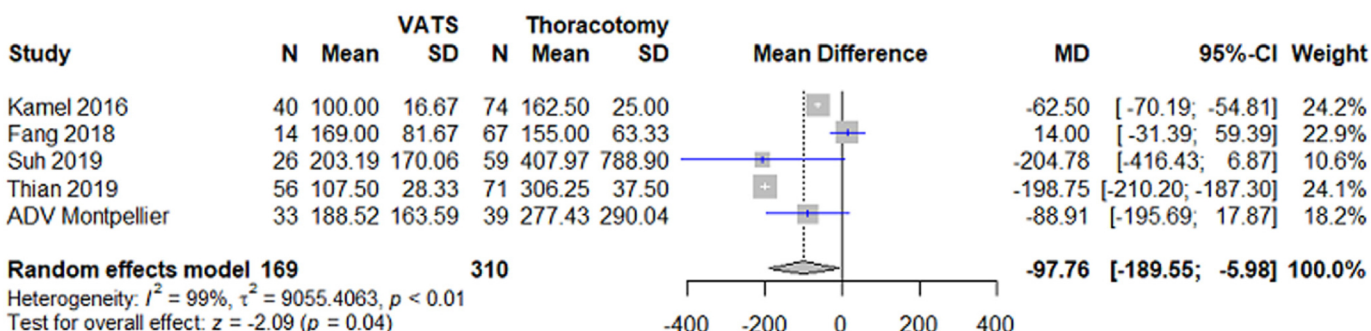
Clinical stage				Histology			Mediastinal assessment (%)	Induction therapy n (%)	Conversion rate (%)	R0 margin (%)
IIB n (%)	IIIA n (%)	IIIB n (%)	IV n (%)	ADC (n)	SC (n)	Other (n)				
0	4 (33)	3 (25)	2 (17)	6	4	2	M 12 (100)	PBDCT + RT = 8 (67) PBDCT = 4 (34)	8.3	12 (100)
0	49 (58)	8 (9.5)	8 (9.5)	31	23	31	M 85 (100)	PBDCT + RT = 66 (78) PBDCT = 19 (22)		85 (100)
NA	NA	NA	NA	31	6	3	NA	PBDCT	12.5	38 (95)
NA	NA	NA	NA	56	12	6	NA	CT + Cox2 inhibitor Others		71 (96)
3 (4)	44 (64)	3 (4)	5 (7)	35	24	10	M/PET/VATS	PBDCT = 57 (84) Others = 11 (16)	10.4	69 (100)
50 (25)	107 (53)	10 (5)	14 (7)	75	61	67	M/PET/VAT	PBDCT = 164 (81) Others = 39 (19)		203 (100)
1 (7.1)	7 (50)	6 (42.9)	0	0	14	0	NA	PBDCT = 14 (100)	0	13 (92.8)
13 (19.4)	32 (47.8)	22 (32.8)	0	0	67	0	NA	PBDCT = 67 (100)		59 (88)
0	17 (100)	0	0	12	5	0	M 5 (29) EBUS/PET 12 (70)	PBDCT + RT = 17 (100)	22.7	17 (100)
0	18 (100)	0	0	8	8	2	M 9 (50) EBUS/PET 9 (50)	PBDCT + RT = 18 (100)		18 (100)
NA	NA	NA	NA	15	10	1	NA	PBDCT + RT = 26 (100)	18 0.8	26 (100)
NA	NA	NA	NA	25	31	3	NA	PBDCT + RT = 59 (100)		58 (98)
4 (7.1)	49 (87.5)	3 (5.4)	0	31	24	1	NA	PBDCT + RT = 12 (21.4) PBDCT = 44 (78.6)	10.7	55 (98)
10 (14.1)	53 (74.7)	8 (11.3)	0	21	49	1	NA	PBDCT + RT = 19 (26.8) PBDCT = 52 (73.2)		61 (86)
NA	NA	NA	NA	381	214	81	NA	CT = 344 (50.9) CRT = 332 (49.1)	22.4	654 (96.7)
NA	NA	NA	NA	1110	835	266	NA	CT = 883 (39.9) CRT = 1328 (60.1)		2127 (96.2)
5 (15.2)	18 (54.5)	1 (3)	9 (27.3)	18	15	0	EBUS 16 (48.5) PET 17 (51.5)	PBDCT = 25 (75.7) PBDCT + RT = 8 (24.3)	9	32 (96.9)
3 (7.7)	21 (53.9)	4 (10.2)	11 (28.2)	25	13	1	EBUS 24 (61.6) PET 15 (38.4)	PBDCT 32 (82) PBDCT + RT 7 (18)		33 (84.6)

RS = retrospective study; PMS = propensity-matched study; ADC = adenocarcinoma; SC = squamous cell carcinoma; M = mediastinoscopy; PBDCT = platinum-based double chemotherapy; RT = radiotherapy; CT = chemotherapy; NA = not available.

## 1- Surgery duration



## 2- Intraoperative blood loss



## 3- Chest-tube drainage duration

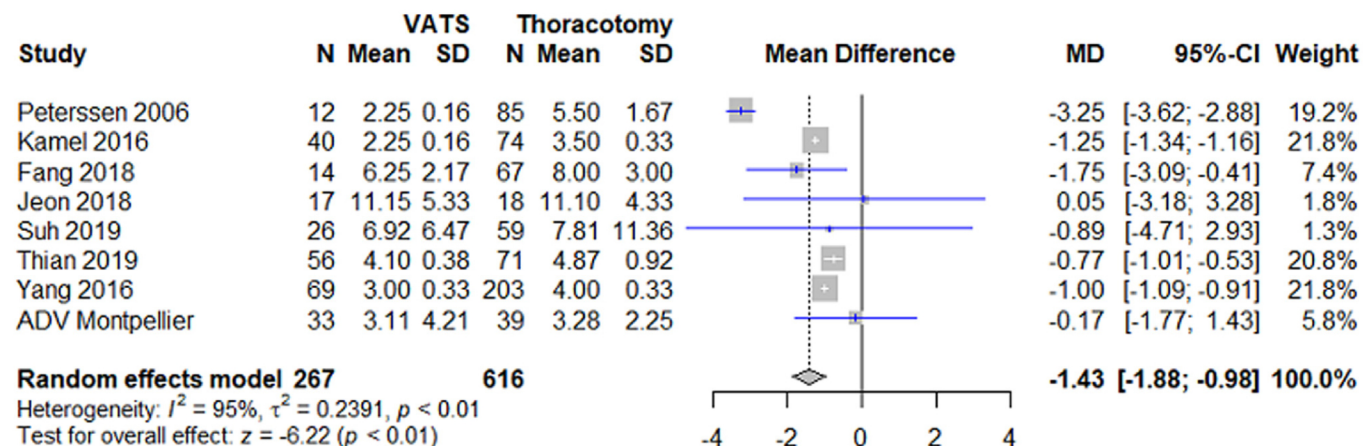
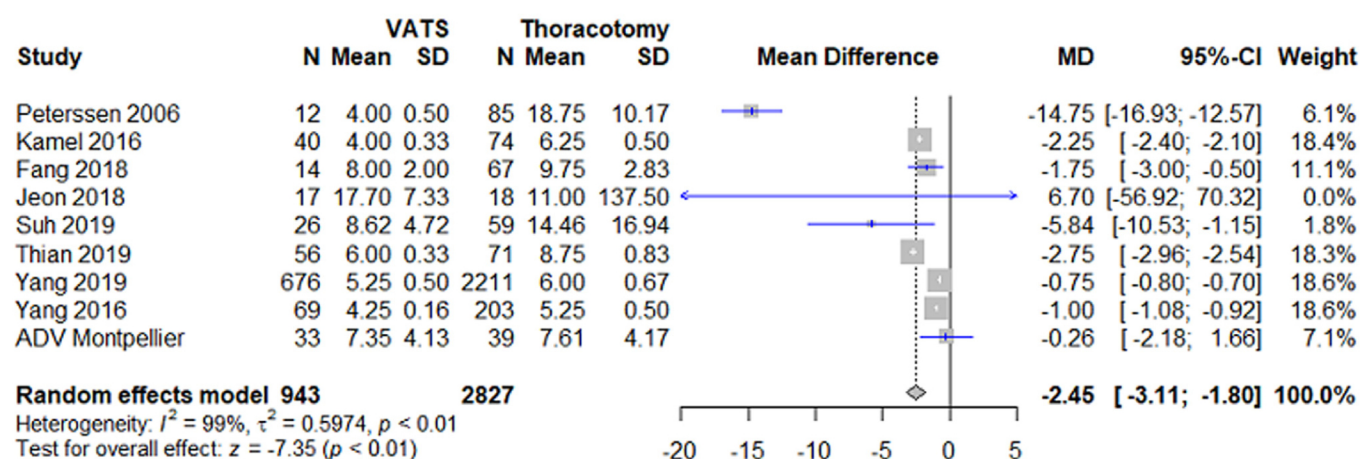
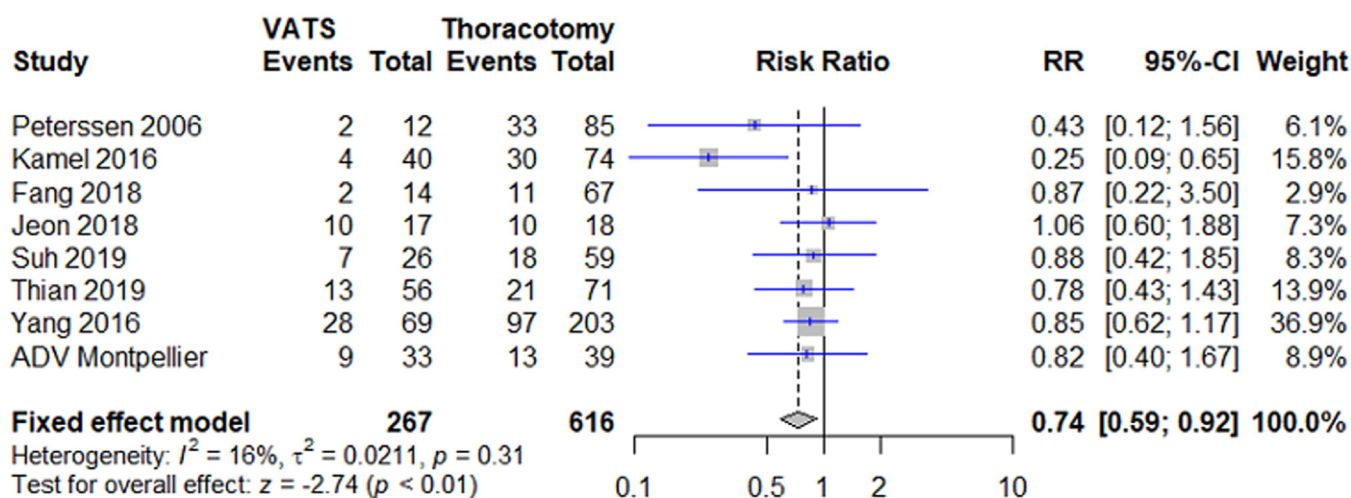


Fig. 3 – Forest plot of meta-analysis results for surgery duration, intraoperative blood loss, and chest-tube drainage duration.

#### 4- Length of hospital stay



#### 5- Perioperative complication rate



#### 6- 30-day mortality

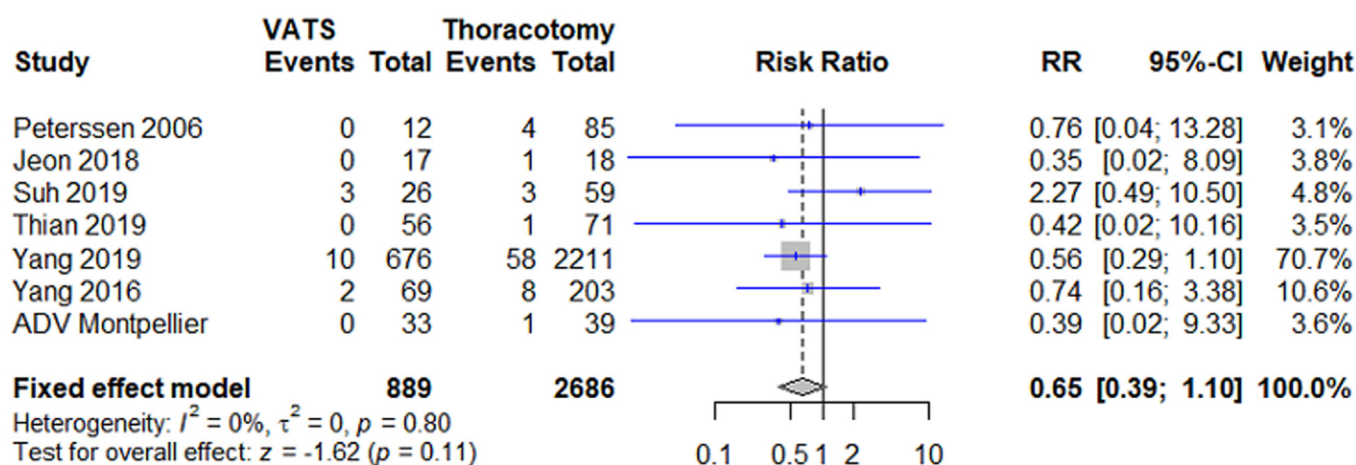
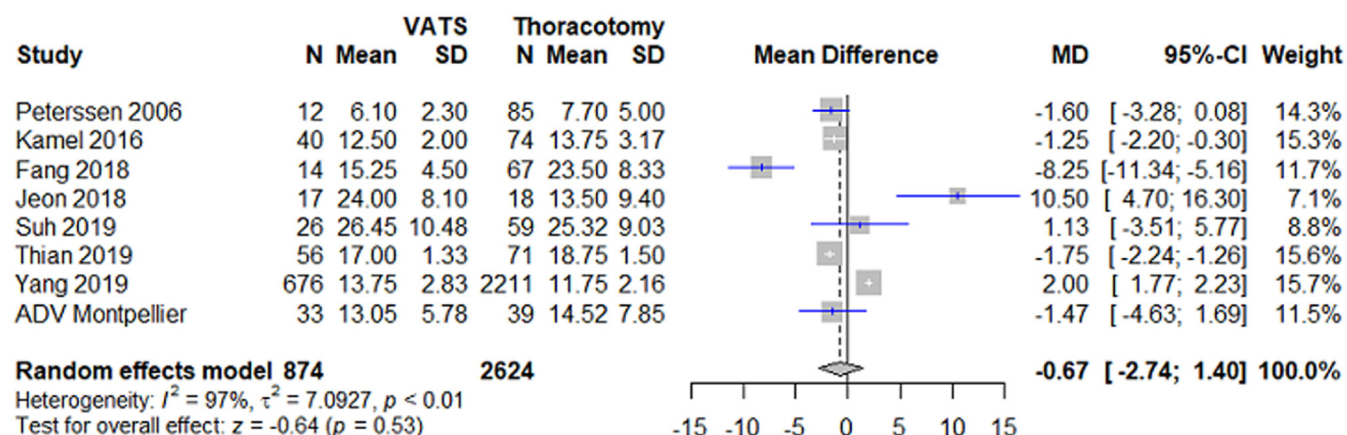


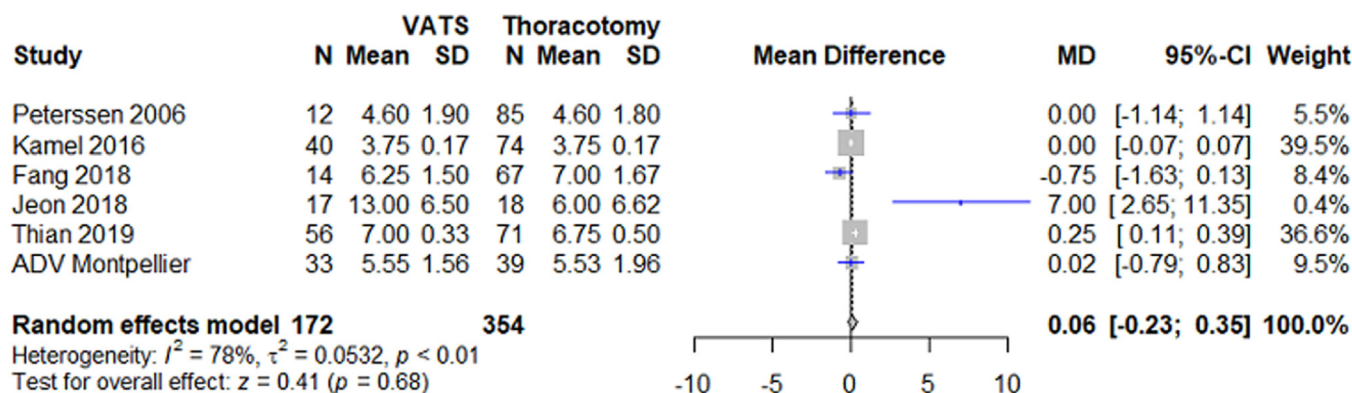
Fig. 4 – Forest plot of meta-analysis results for length of hospital stay, perioperative complication rate, and 30-d mortality.



## 7- Lymph node number ( LNN)



## 8- Lymph node station number (LNSN)



## 9- R0-resection margins

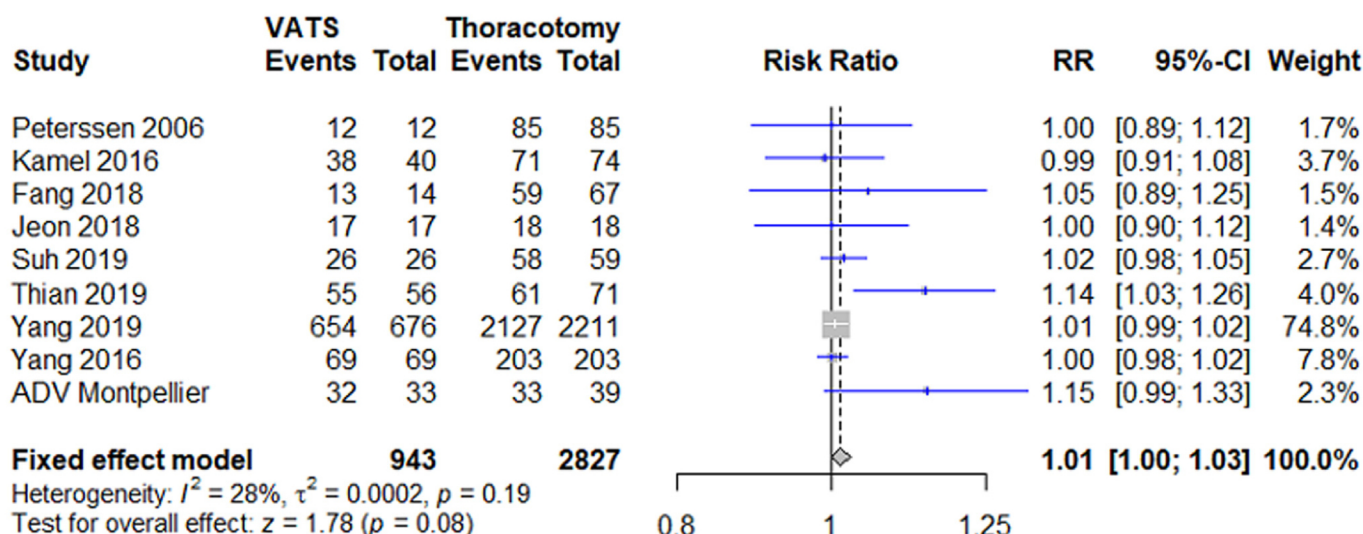
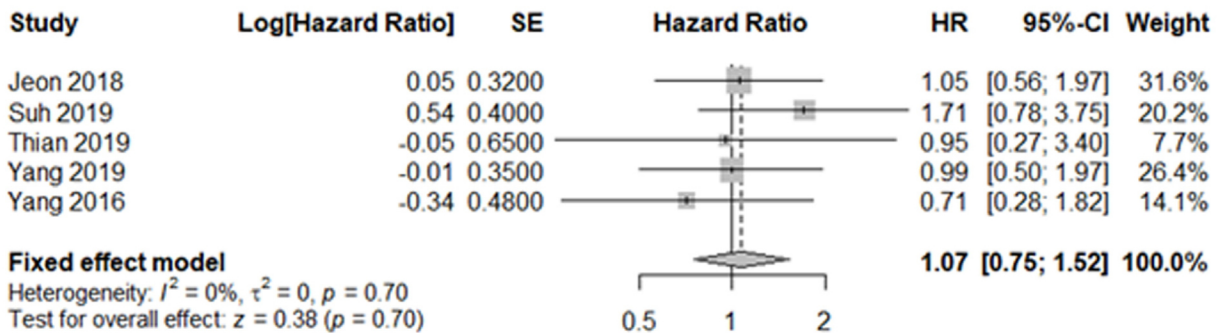


Fig. 5 – Forest plot of meta-analysis results for lymph node number dissected (LNN), lymph node station number dissected (LNSN), and R0-resection margins.

## 10- Three-year overall survival (OS)



## 11- Three-year disease-free survival (DFS)

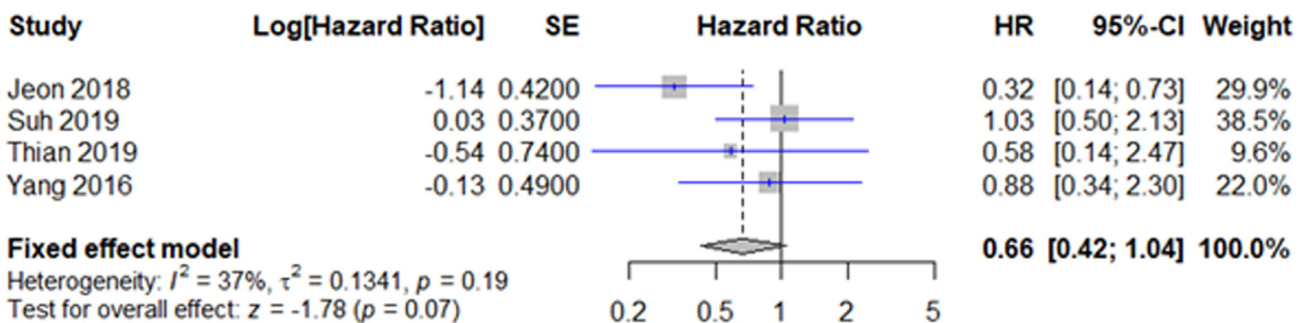


Fig. 6 – Forest plot of meta-analysis results for 3-y overall survival and 3-y disease-free survival.

group. Five studies were included in the analysis of OS, involving 844 patients in the VATS group and 2562 in the thoracotomy group. No heterogeneity was identified among the studies ( $I^2 = 0\%$ ,  $P = 0.70$ ). The three-year OS was comparable between both groups (combined HR = 1.07, 95% CI = [0.75; 1.52],  $P = 0.70$ ) (Fig. 6).

DFS was defined as the time period between surgery and recurrence or death. The three-year weighted mean DFS was 48.72% in the VATS group and 44.35% in the thoracotomy group. Four studies were included in this analysis, involving 168 patients in the VATS group and 351 patients in the thoracotomy group. There was no significant heterogeneity among the studies ( $I^2 = 37\%$ ,  $P = 0.19$ ). The combined HR for DFS was 0.66 (95% CI = [0.42; 1.04]) and DFS was not significantly different between both groups ( $P = 0.07$ ) (Fig. 6).

### Publication bias

No potential publication bias existed in the RRs for perioperative complication rates among included studies. The  $P$  value of the publication bias test (Egger's test) was not significant ( $P = 0.22$ ), meaning there is substantial Funnel plot symmetry.

Funnel plots for the other perioperative outcomes displayed no publication bias (Supplementary Figs. S2-S10).

## Discussion

In this study, we set out to compare outcomes of patients who underwent lobectomy by VATS or thoracotomy approach after induction therapy in our institution and then we performed a meta-analysis to assess whether VATS lobectomy achieves similar perioperative and oncologic outcomes compared to thoracotomy following induction therapy. Unlike other studies,<sup>12,13,23</sup> we could not find any significant difference in operative outcomes including surgery duration, chest-tube drainage duration, and length of hospital stay which can be explained by our drainage practices. We tend to remove the tube when it flows less than 400 mL daily leading to a longer length of stay. However, the VATS approach was associated with a trend toward less intraoperative blood loss and a greater R0-resection than thoracotomy, most likely related to the smaller tumor size in the VATS group. A VATS approach



was also associated with fewer perioperative complications when compared with thoracotomy. Comparable results have been reported by Kamel *et al.*<sup>12</sup> and Yang *et al.*<sup>13</sup> in a propensity score analysis. Regarding oncologic outcomes, VATS seems to achieve equivalent performance compared to thoracotomy in terms of lymph node dissection DFS and OS. These results are in line with all the included studies in the following meta-analysis.

The perioperative advantages of thoracoscopic lobectomy in patients with clinical stage-1 NSCLC are no longer a matter of discussion. Indeed, thoracoscopic lobectomy among these patients has shown reduced morbidity and a faster return to activities of daily living when compared to thoracotomy.<sup>7</sup> More importantly, VATS lobectomy has already shown at least similar, if not improved, OS and DFS compared with thoracotomy lobectomy.<sup>25</sup> As a result, VATS is currently recommended by the National Comprehensive Cancer Network (NCCN) guidelines, which advocate for the “strong consideration” of VATS lobectomy for resection of early-stage NSCLC.<sup>26</sup> Therefore, the purpose of applying a minimally-invasive approach to lung resection after neoadjuvant therapy would be to offer most patients improved perioperative outcomes without sacrificing oncologic efficacy. The toxic effects of neoadjuvant therapy may worsen the patient’s condition,<sup>27</sup> making these patients more suitable candidates for a less invasive treatment. However, induction treatment is associated with concerns regarding the propensity of increasing the difficulty of Hilar dissection and of effectively clearing positive lymph nodes.<sup>28</sup>

### Perioperative outcomes

Surgery duration, intraoperative blood loss, complication rates, and conversion rates are important indicators for assessing the technical issues and safety of VATS procedures. In this meta-analysis, surgery duration was significantly shorter for VATS by almost 16 min compared to thoracotomy. The volume of intraoperative blood loss was also significantly reduced by almost 100 mL. The pooled perioperative complications rate was 27.3% (range: 10%-58%) for the VATS group and 36.5% (range: 16%-55%) for the thoracotomy group, with a significant difference supporting superiority of the VATS approach. Given the implied operative challenges associated with induction therapy, one may question to what are these benefits attributed? It could be speculated that the surgeon’s technical expertise and the patient selection process, with the probability of larger and more central tumors selected in the thoracotomy group, could clearly influence the perioperative outcomes. Considering the evidence that induction therapy leads to a temporary decrease of approximately 20% in the diffusion capacity of the alveolar-capillary membrane,<sup>29</sup> another potential explanation for this lower complication rate could be better perioperative lung function preservation. This has been previously reported in studies investigating the potential benefits of VATS in patients with poor pulmonary reserve.<sup>30,31</sup>

The pooled conversion rate in this present study of 14% (range: 0%-22%) is relatively high compared with the rate of 6% reported by Cheng *et al.*<sup>32</sup> in a meta-analysis of 36 studies on VATS lobectomy for early-stage NSCLC. Nonetheless, none of

the patients who underwent conversion to thoracotomy died among the eight studies analyzed here. In these studies, the main reasons for conversion were anthracofibrotic nodes or dense adhesions around blood vessels especially after induction chemoradiotherapy. After radiation the Hilar and mediastinal structures become fibrotic and the planes between structures become indistinct,<sup>28</sup> making surgical dissection more challenging. In a large, multi-institutional, propensity-matched cohort study of 2887 patients, Yang *et al.*<sup>24</sup> evaluated the outcomes of patients who underwent VATS converted to open lobectomy. The authors found a higher conversion rate for the induction chemoradiation group compared to the induction chemotherapy group (25% versus 20%). However, there was no significant difference in terms of perioperative mortality between patients who underwent conversions and patients who underwent open lobectomy. These results may eliminate some apprehension about the safety of VATS after induction therapy.

Length of hospital stay and chest-tube drainage duration were also significantly lower for VATS. The mean chest-tube drainage duration was reduced by 1.42 d and length of hospital stay was reduced by 2.45 d. These results are generally in agreement with prior meta-analyses comparing VATS to thoracotomy lobectomy for early-stage NSCLC.<sup>32-34</sup>

### Oncologic outcomes

Lymph node evaluation, DFS, and most importantly OS, are key outcomes for evaluating oncologic effectiveness. Previous studies having compared the efficacy of lymph node dissection in VATS lobectomy in patients with stage-1 NSCLC demonstrated similar results to that of standard thoracotomy.<sup>35-37</sup> Concerns have been raised regarding the reliability and accuracy of the VATS procedure in achieving adequate lymph node dissection after induction therapy due to the necessity of tedious dissection through fibrotic planes and the risk of pleural dissemination after lymph node dissection, especially in patients with lymph node metastasis. Watanabe *et al.*<sup>38</sup> reported a similar rate of lymph node upstaging and 5-y recurrence-free survival between the VATS group and thoracotomy group for stage-1 NSCLC cN0-pN2, thus supporting the oncologic efficacy of VATS lymphadenectomy. Other authors state that the quality of the nodal evaluation is surgeon dependent<sup>39</sup> and may increase as the surgeon gains more VATS procedure experience.<sup>40</sup> Our analysis did not show a significant difference in LNN or LNSN between the VATS and thoracotomy approach. Furthermore, with a median of 15.8 lymph nodes and 6.8 lymph node stations dissected in the VATS group, the mediastinal lymph node assessment was in line with the current guidelines.<sup>41</sup>

The original results of each included study in the meta-analysis demonstrated that OS and DFS are comparable in VATS versus thoracotomy. Likewise, the meta-analysis did not show any differences in OS or DFS rates. These conclusions should however be interpreted with caution as the conduction of a robust meta-analysis on these outcomes was limited by the lack of available relevant data. Nevertheless, it is worth noting that VATS did not significantly differ in achieving negative margins and no interstudy heterogeneity was found upon the comparison of OS and DFS.

## Limitations

Several limitations of this study require highlighting. First, our institutional study was of retrospective nature with relatively small number of patients not allowing a propensity analysis. Hence, there was an obvious bias to the selection of the surgical approach that may have affected the outcomes. The meta-analyses whereas can be limited by the search strategy and publication bias. Indeed, we attempted to minimize these by performing searches across different databases using explicit selection criteria and meticulous data extraction. Second, all included studies were retrospective cohort studies with unavoidable selection and confounding bias, although most studies were deemed of good quality as per NOS criteria. Third, eight of the studies included for meta-analysis had small-sized cohorts<sup>12,13,19-23</sup> and the only large-scale multicenter study included<sup>24</sup> did not provide data on clinical tumor stage, type of chemotherapy received, surgery duration, blood loss, LNSN, postoperative complications, and DFS. This undoubtedly affected the results of our meta-analysis. Next, given that patient enrollment started in 1996,<sup>19</sup> there were differences between studies regarding the TNM staging system adopted, likely leading to an inaccurate evaluation owing to interstudy differences in clinical and pathological staging. Furthermore, there was a widespread variation in the indications for induction therapy, with stage III NSCLC accounting for more than half of them. The proportions of the different disease stages between the VATS and thoracotomy groups were not the same. In the absence of relevant data, we could not perform a subgroup analysis based on disease stage and the type of induction therapy. There were also no details regarding the central or peripheral tumoral location that may have affected the choice of the surgical approach. Following, some studies did not report the precise clinical stage and others did not explain the methods used for determining the disease stage. Invasive mediastinal staging was performed by mediastinoscopy for all patients in just one study.<sup>19</sup> In three other studies, patients were staged either by mediastinoscopy, EBUS, VATS, or even PET-CT<sup>13,21</sup> ADV center. The five remaining studies<sup>12,20,22-24</sup> did not provide specific information regarding the mediastinal assessment and only two studies provided data on postinduction therapy restaging<sup>19</sup> ADV center. The lack of uniformity in the methods, the uncertainty of the clinical stages, and the inconsistency of the criteria used for assessing the efficacy of neoadjuvant therapy could affect the reliability of our results.

This meta-analysis was also limited by an explicit bias regarding the selection of the surgical approach. Patient selection for VATS was based on the individual surgeon's judgment. In most studies, the criteria for selecting patients for VATS rather than open thoracotomy were not provided. Petersen *et al.*<sup>19</sup> applied the following inclusion criteria for VATS: tumors <6 cm and essentially without chest wall or central airway involvement and tumors without bulky N2 disease prior to induction therapy. Clearly, patient selection criteria must be more accurate to identify suitable patients for VATS from those who require thoracotomy.

Finally, our survival analysis had at least two limitations. First, the follow-up time period used for collection of survival data in all included studies was relatively short. Second, we extracted some three-year OS and DFS rates from Kaplan–Meier survival curves, thus increasing the potential for a measurement error. Such biases undermine the level of evidence for the oncologic efficiency of the VATS approach.

## Conclusion

Current evidence here suggests that compared to open thoracotomy and when applicable, the VATS approach could be associated with some perioperative benefits without jeopardizing oncologic outcomes in patients undergoing lobectomy for NSCLC after induction therapy. However, further investigations, ideally randomized trials, are required to identify the oncologic benefits of the VATS approach compared to thoracotomy.

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## Author Contributions

K.H. designed the study, contributed to data collection, interpretation, and manuscript writing. L.C. contributed to data collection, manuscript writing, and final revisions. Y.L., S.A., and N.M. performed statistical analysis and results interpretation. P.A. supervised the study, contributed to design, and final revisions. All authors read and approved the final manuscript.

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## Disclosure

None.

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