

Robotic-assisted versus video-assisted lobectomy for resectable non-small-cell lung cancer: the RVlob randomized controlled trial



Zhenyi Niu,^{a,h} Yuqin Cao,^{a,h} Mingyuan Du,^{a,h} Sijing Sun,^a Yan Yan,^a Yuyan Zheng,^a Yichao Han,^a Xianfei Zhang,^a Zhengyuan Zhang,^b Ye Yuan,^c Jian Li,^d Yajie Zhang,^a Chengqiang Li,^a Dingpei Han,^a Hailei Du,^a Wei Guo,^a Kai Chen,^a Jie Xiang,^a Lianggang Zhu,^a Jiaming Che,^a Junbiao Hang,^a Jian Ren,^a Toni Lerut,^e Abbas E. Abbas,^f Jules Lin,^g Runsen Jin,^{a,**} and Hecheng Li^{a,*}



^aDepartment of Thoracic Surgery, Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, Shanghai, China

^bDepartment of Thoracic and Cardiovascular Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

^cDepartment of Thoracic Surgery, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

^dClinical Research Center, Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, Shanghai, China

^eDepartment of Thoracic Surgery, University Hospital Leuven, Leuven, Belgium

^fDepartment of Thoracic Surgery, Warren Alpert Medical School of Brown University, Providence, RI, United States

^gSection of Thoracic Surgery, University of Michigan Medical Center, Ann Arbor, MI, United States

Summary

Background The long-term survival and perioperative outcomes of robotic-assisted lobectomy (RAL) and video-assisted lobectomy (VAL) in resectable non-small-cell lung cancer (NSCLC) were found to be comparable in retrospective studies, but they have not been investigated in a randomized trial setting. We conducted the RVlob trial to investigate if RAL was non-inferior to VAL in patients with resectable NSCLC.

Methods In this single-center, open-label, and parallel-arm randomized controlled trial conducted in Ruijin Hospital (Shanghai, China) between May 2017 and May 2020, we randomly assigned patients with resectable NSCLC in a 1:1 ratio to receive either RAL or VAL. One of the primary endpoints was 3-year overall survival. Secondary endpoints included 3-year disease-free survival. The Kaplan–Meier approach was used to calculate overall survival and disease-free survival at 3 years. This study was registered with [ClinicalTrials.gov](https://clinicaltrials.gov), NCT03134534.

Findings A total of 320 patients were randomized to receive RAL (n = 157) or VAL (n = 163). The baseline characteristics of patients were well balanced between the two groups. After a median follow-up of 58.0 months, the 3-year overall survival was 94.6% (95% confidence interval [CI], 91.0–98.3) in the RAL group and 91.5% (95% CI, 87.2–96.0) in the VAL group (hazard ratio [HR] for death, 0.65; 95% CI, 0.33–1.28; P = 0.21); noninferiority of RAL was confirmed according to the predefined margin of –5% (absolute difference, 2.96%; a one-sided 90% CI, –1.39% to ∞; P = 0.0029 for noninferiority). The 3-year disease-free survival was 88.7% (95% CI, 83.6–94.1) in the RAL group and 85.4% (95% CI, 80.0–91.2) in the VAL group (HR for disease recurrence or death, 0.87; 95% CI, 0.50–1.52; P = 0.62).

Interpretation This study is the first randomized trial to show that RAL resulted in non-inferior overall survival compared with VAL in patients with resectable NSCLC. Based on our results, RAL is an equally oncologically effective treatment and can be considered as an alternative to VAL for resectable NSCLC.

Funding National Natural Science Foundation of China (82072557), National Key Research and Development Program of China (2021YFC2500900), Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant (20172005, the 2nd round of disbursement), program of Shanghai Academic Research Leader from Science and Technology Commission of Shanghai Municipality (20XD1402300), Novel Interdisciplinary Research Project from Shanghai Municipal Health Commission (2022JC023), and Interdisciplinary Program of Shanghai Jiao Tong University (YG2023ZD04).

*Corresponding author. Department of Thoracic Surgery, Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, 197 Ruijin Er Road, Shanghai 200025, China.

**Corresponding author. Department of Thoracic Surgery, Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, 197 Ruijin Er Road, Shanghai 200025, China.

E-mail addresses: lihecheng2000@hotmail.com (H. Li), nkvincent@163.com (R. Jin).

^hThese authors contributed equally as first authors.

eClinicalMedicine

2024;74: 102707

Published Online xxx
<https://doi.org/10.1016/j.eclinm.2024.102707>

Copyright © 2024 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Non-small-cell lung cancer; Overall survival; Robotic-assisted lobectomy; Video-assisted lobectomy; Randomized controlled trial

Research in context

Evidence before this study

We searched PubMed, Embase, Cochrane Library and Web of Science for relevant publications until December 31, 2023, using the search terms (“robotic-assisted” or “robotic” or “robot”) AND (“video-assisted” or “thoroscopic”) AND (“lobectomy” or “lobar resection”). The search was limited to clinical trials, with no language restrictions. Additionally, we searched for meeting abstracts of the American Society of Clinical Oncology, American Association for Thoracic Surgery, European Society of Medical Oncology, and World Conference on Lung Cancer. Identified published trials included five studies that compared robotic-assisted lobectomy (RAL) versus video-assisted lobectomy (VAL) in non-small-cell lung cancer (NSCLC) patients, which were the RVlob trial, RAVAL trial, BRAVO trial, ROMAN trial, and another trial conducted in Italy. These five studies compared the perioperative and patient-reported outcomes of NSCLC patients receiving RAL or VAL. However, there were no reports comparing overall survival in NSCLC patients receiving RAL and VAL.

Added value of this study

To our knowledge, RVlob is the first randomized trial to show that RAL resulted in non-inferior overall survival compared with VAL. Based on our results, RAL is an equally oncologically effective treatment and can be considered as an alternative to VAL in NSCLC patients.

Implications of all the available evidence

Our results combined with existing evidence support RAL as an equally effective treatment method for NSCLC as compared with VAL. The RAVAL trial, an international, multi-centered, blinded, randomized trial that compares RAL versus VAL, is still recruiting patients. One of the secondary objectives of this study is to compare the 5-year survival data between the two arms. This trial will provide useful information and could support our conclusions.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.¹ Approximately 85% of lung cancer is non-small-cell lung cancer (NSCLC).² For early-stage, resectable NSCLC, anatomical lobectomy and segmentectomy have been the standard mode of surgery since 1960.³ Currently, lobectomy is recommended to be done by minimally invasive techniques, which have been shown to be associated with fewer postoperative complications, shorter length of hospital stay, less surgical pain, and better quality of life compared with open surgery.^{4–6} The minimally invasive techniques for lobectomy consist of video-assisted lobectomy (VAL) and robotic-assisted lobectomy (RAL). With its 3-dimensional, high-definition view and small-tipped articulating instruments, the robotic-assisted surgery provides enhanced maneuverability and dexterity.⁷ Despite the gaining popularity of robotic-assisted surgery and numerous observational studies, its role and potential advantages in thoracic surgery have not been conclusively established.⁸

The RVlob trial is the first randomized controlled trial to compare the short-term outcomes and long-term survival between RAL and VAL for resectable NSCLC. In our previous report on the short-term outcomes of the RVlob trial, RAL (compared with VAL) was shown to have equivalent perioperative outcomes and a higher

lymph node (LN) yield compared with VAL.⁹ We also reported similar health-related quality of life (HRQoL) between the RAL and VAL groups.¹⁰ These findings are consistent with previous studies and meta-analyses showing comparable perioperative short-term outcomes and increased LN harvest by RAL.^{6,11–27}

Overall survival (OS) is considered to be the gold standard endpoint for evaluating lung cancer treatments in randomized trials.²⁸ Previous retrospective studies and meta-analyses showed that there were no statistically significant differences in terms of OS between RAL and VAL.^{6,16,19,20} However, evidence from prospective, randomized controlled trials has been lacking. Here, we report the long-term outcomes of RAL and VAL in the RVlob trial.

Methods

Ethics statement

The study protocol (see in [Supplemental Data](#)) was approved by the ethics committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (approval number, 2017-58). Written informed consent was obtained from all the patients prior to participation in the study. This trial was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Study design and participants

The RVlob trial was a single-center, open-label, parallel-arm, noninferiority, and randomized controlled trial comparing RAL with VAL for resectable NSCLC. The perioperative outcomes and health-related quality of life of this trial have been previously reported.^{9,10} Consolidated Standards of Reporting Trials (CONSORT) reporting guideline was followed. The trial was registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT03134534). Patients were included if they were aged 18–80 years; had pulmonary masses, nodules or partial solid ground-glass opacities (GGO) found in chest computed tomography examination which were deemed suitable for minimally invasive lobectomy; had adequate preoperative tests for surgery, such as routine blood examination, liver function, renal function, coagulation function, etc.; had an American Society of Anesthesiologists (ASA) score of I-III; could coordinate the treatment and research and signed the informed consent form. Patients were excluded if they had preoperative pathologically confirmed pulmonary tumors other than NSCLC, current or former comorbidity with other malignant tumors, or had received any treatment for NSCLC before surgery. There were also intraoperative exclusion criteria which were pathological diagnosis other than NSCLC on intraoperative frozen section examination, pleural dissemination detected during surgery, or intraoperative change of surgical plan. Intraoperative change of surgical plan is defined as inappropriateness for minimally invasive lobectomy based on intraoperative exploration, such as sub-lobar resection for a small lesion or extensive lung resection for a massive tumor. The detailed inclusion and exclusion criteria are noted in the trial protocol in [Supplemental Data](#).

Randomization and masking

Eligible patients were randomly assigned in a 1:1 ratio to the RAL group and VAL group. Simple randomization was conducted with a computer-generated random numbers table. A designated person in the study team, who did not take part in the screening of eligible patients, confirmed the assignments of the patients. Assignments were then sealed in opaque envelopes, which were opened by the surgeons when having preoperative discussion. The study was not blinded after randomization.

Interventions

RAL was performed using a da Vinci S/Si surgical robot (Intuitive Surgical, Inc, Santa Clara, CA) through five ports, while VAL was performed through a 4-cm incision in the fifth intercostal space (ICS) at the anterior axillary line. When necessary, an additional auxiliary port was placed in the sixth or eighth ICS at the mid-axillary line. All surgical instruments were inserted through the incision without spreading the ribs.⁹ The resection of lymph nodes in this study was performed en bloc. A minimum of three N2 stations were dissected

for all the patients. All surgeries were performed by the same surgical group headed by an experienced surgeon (Hecheng Li), who had an experience of more than 100 cases of both RAL and VAL before this study was started. The representative videos of RAL and VAL are available in [Supplemental Videos 1 and 2](#), respectively. For postoperative management, enhanced recovery after surgery was implemented in both groups, and rehabilitation therapists were involved.²⁹

The staging of the patients was in accordance with the 8th edition of the TNM classification for lung cancer.³⁰ Adjuvant therapy was recommended for patients with high-risk pathological stage IB and pathological stage IIA or higher stages.³¹ High-risk factors included poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, visceral pleural involvement. The choice of regimen and treatment duration was at the discretion of the treating oncologist.

Outcomes

One of the primary endpoints was 3-year OS. The 3-year OS was defined as the percentage of patients who were still alive 3 years after randomization. The secondary endpoints included 3-year disease-free survival (DFS), rate of R0 resection, duration of surgery, intraoperative blood loss, conversion rate, postoperative hospital stay, incidence of postoperative adverse events, and medical costs. Postoperative complications were evaluated using the Clavien-Dindo classification system.³²

A minimum follow-up of 36 months was required for each patient after surgery. Postoperative follow-up was conducted at 6-month intervals until patient death or the completion of the study. Measurement of tumor markers, chest X-ray, and chest computed tomography were performed at least every 6 months during the first 2 years and at least every 12 months thereafter.

Statistical analysis

Based on our previous clinical observations and published literature, we anticipated a 3-year OS of 81.5% for patients undergoing RAL. In comparison, the 3-year OS for patients in the conventional VAL group was estimated to be 74%.^{6,33} A sample size of 136 patients per group was determined to achieve 80% power with a –5% noninferiority margin and a two-sided significance level of 5%. For the other primary endpoint of LN dissection, 138 patients per group were required, assuming one additional LN dissected in the robot-assisted group with a standard deviation of 5^{12,19,23,34} and a noninferiority margin of –0.5, with a significance level and power set at the same values. To account for a potential 10% loss to follow-up, the final sample size was increased to 150 patients per group.

An intention-to-treat analysis was performed. For the dual primary outcomes, the Bonferroni-correction was used wherein the one-sided significance levels of 0.05 and 0.05 were allocated to the primary comparison of 3-

year OS and the extent of LN dissection, respectively. A one-sided 90% confidence interval (CI) of 3-year OS was calculated to decide the non-inferiority. All other analyses of DFS and secondary outcomes were performed using conventional 2-tailed tests with $\alpha = 0.05$ and with 2-sided 95% CIs. The categorical and continuous variables were compared using IBM SPSS Statistics (version 22). For categorical variables, we utilized Pearson Chi-squared test or Fisher exact test to compare the two groups. For 2×2 contingency tables, Pearson Chi-squared test is used when the minimum expected frequency is no less than 5 and the sample size is no less than 40. When the minimum expected frequency is less than 5 and no less than 1 and the sample size is no less than 40, the Pearson Chi-squared test with Yates' continuity correction was used. Fisher's exact test was used when the minimum expected frequency was less than 1 or the sample size was less than 40. For tables with larger dimensions than 2×2 , when more than 20% of cells have expected frequencies <5 or at least one cell has an expected frequency <1 , Fisher's exact test was used. Otherwise, Pearson Chi-squared test was used. The Kolmogorov–Smirnov test was used to test the normality of continuous variables. A *P*-value larger than 0.05 was considered as compliance to the normal distribution. For continuous variables that followed a normal distribution, they were presented as mean \pm standard deviation, and the Student's *t*-test was used for comparison. In cases of noncompliance with the normal distribution, continuous variables were presented as medians (interquartile range [IQR]) and compared using the Wilcoxon rank-sum test between the groups. The GraphPad Prism (version 8.0.0) was used to calculate the log-rank *P*-value and hazard ratio (HR). The R package of survminer (version 0.4.9) was used to draw the survival curves. The Kaplan–Meier approach was used to calculate OS and DFS at 1, 2, 3, 4, and 5 years through the R package of survival (version 3.4-0). Exploratory subgroup analyses were performed to assess the treatment effect according to patient characteristics. The R package of forestploter (version 1.1.1) was used to draw the forestplot of subgroup analysis.

Role of the funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. All authors had full access to the dataset. The corresponding authors had final responsibility for the decision to submit for publication.

Results

Patients

Between May 2017 and May 2020, 381 patients were evaluated, and 363 patients were enrolled for

randomization. Forty-three patients were further excluded before or during surgery due to withdrawal of consent (10/43, 23.3%), pathological results other than NSCLC on intraoperative frozen section (28/43, 65.1%), and intraoperative change in the surgical plan (5/43, 11.6%, mostly changed to segmentectomy). Ultimately, 320 patients were enrolled in this study and were randomly assigned to the RAL ($n = 157$) or VAL group ($n = 163$) (Fig. 1). Baseline characteristics have been previously published^{9,10} and were well balanced between the two groups (Table 1). Of the 320 enrolled patients, 157 (49.1%) patients were men, 188 (58.8%) patients were aged 60 years or older, 282 (88.1%) patients had adenocarcinoma, and 265 (82.8%) patients had pathological stage I disease (eighth TNM classification). There were three cases of sleeve lobectomies in the VAL group while no sleeve lobectomy was performed in the RAL group. Of the patients with available data, 16.7% (24/144) patients in the RAL group and 18.8% (29/154) patients in the VAL group received adjuvant therapy after surgery. The details of adjuvant therapy are described in Supplemental Table S1. At the data-cutoff date for the final analysis (August 27, 2023), 305 patients were available for analysis of OS while 296 patients were available for analysis of DFS (Fig. 1).

Overall survival

The median follow-up for OS was 61.0 months (range, 6–74) in the RAL group and 57.0 months (range, 1–74) in the VAL group. In the patients with available survival data, 33 deaths had occurred (13 in the RAL group and 20 in the VAL group). The causes of death among these patients are summarized in Table 2.

The 3-year OS was 94.6% (95% CI, 91.0%–98.3%) in the RAL group and 91.5% (95% CI, 87.2%–96.0%) in the VAL group (Fig. 2A). Noninferiority of RAL was confirmed according to the predefined margin of -5% (absolute difference, 2.96%; a one-sided 90% CI, -1.39% to ∞ ; $P = 0.0029$ for noninferiority), and the cumulative probability of death is shown in Supplemental Fig. S1. The HR for death was 0.65 (RAL versus VAL; 95% CI, 0.33–1.28; $P = 0.21$; Fig. 2A). The 5-year OS was 90.7% (95% CI, 86.0%–95.7%) in the RAL group and 86.3% (95% CI, 80.7%–92.3%) in the VAL group. The median OS was not reached in both groups. In the post hoc subgroup analysis, no significantly improved OS was observed in any subgroup (Supplemental Fig. S2). The OS for all patients and patients stratified by surgery type are summarized in Supplemental Table S2.

Disease-free survival

In the patients with active follow-up, 52 patients had recurrences (25 in the RAL group and 27 in the VAL group). Recurrence patterns and sites of the first recurrence are listed in Supplemental Table S3. The total recurrence pattern, including patients who had

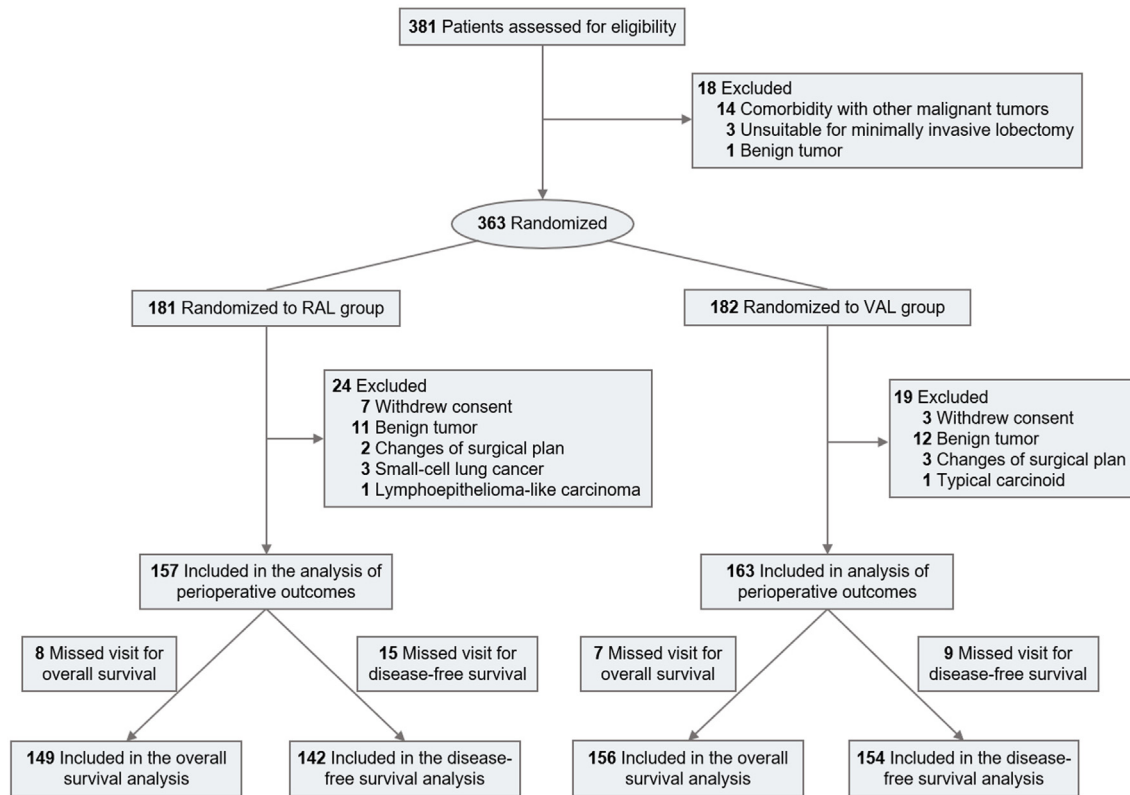


Fig. 1: Study enrollment and outcomes. RAL, robotic-assisted lobectomy; VAL, video-assisted lobectomy.

locoregional or distant recurrence alone plus those who had both, was similar in the RAL and VAL groups.

There was no significant difference in DFS between the two groups (HR for disease recurrence or death, 0.87; 95% CI, 0.50–1.52; $P = 0.62$; Fig. 2B). DFS at 3 years was 88.7% (95% CI, 83.6%–94.1%) in the RAL group and 85.4% (95% CI, 80.0%–91.2%) in the VAL group; at 5 years, the DFS rate was 83.7% (95% CI, 77.7%–90.3%) for RAL and 82.5% (95% CI, 76.6%–88.8%) for VAL (Fig. 2B). No significant differences of DFS were observed among subgroups in the post hoc analysis (Supplemental Fig. S3). The DFS for all patients and patients stratified by surgery types are summarized in Supplemental Table S4. The treatment after recurrence is described in Supplemental Table S5. Seven patients in the RAL group and 9 patients in the VAL group did not receive further treatment after recurrence.

Discussion

In the present study, we found RAL resulted in non-inferior OS and similar DFS at 3 years in patients with resectable NSCLC, as compared with VAL. This prospective, randomized controlled trial is, to the best of our knowledge, the first to report the long-term

outcomes in resectable NSCLC patients undergoing RAL and VAL.

Video-assisted thoracoscopic surgery (VATS) has been well established for the resection of NSCLC, owing to the improved early outcomes compared with thoracotomy, such as less postoperative pain, shorter length of hospital stay, better respiratory function preservation, and better quality of life.^{4–6} The robotic-assisted thoracoscopic surgery (RATS) technique is considered an evolution of the VATS approach for pulmonary resection. In addition to improved perioperative outcomes, both VATS and RATS have been shown to have similar long-term survival compared with thoracotomy.^{6,35,36} The current trial found that the 3-year OS in the RAL group (94.6%) was non-inferior to that in the VAL group (91.5%), using –5% as the noninferiority margin. There are potential advantages of robotic technology, such as the visualization, instrument articulation, and ergonomic benefits.³⁷ If the 3-year OS and perioperative outcomes of robotic-assisted lobectomy (RAL) were not inferior to those achieved by video-assisted lobectomy (VAL), we would consider RAL as an alternative to VAL for the treatment of resectable NSCLC. Therefore, we hypothesized non-inferiority of RAL compared with VAL in this study. With a long period of follow-up and comprehensive data analysis, the results of this study

Characteristic	RAL (n = 157)	VAL (n = 163)	P value
Sex, No. (%)			0.44
Male	81 (51.6)	76 (46.6)	
Female	76 (48.4)	87 (53.4)	
Age [year], median (IQR)	61 (54–66)	62 (53–68)	0.29
BMI [kg/m ²], median (IQR)	23.4 (21.7–25.6)	22.9 (21.4–24.4)	0.054
Smoking status, No. (%)			0.62
Smoker	110 (70.1)	110 (67.5)	
Never smoked	47 (29.9)	53 (32.5)	
Nodule type, No. (%)			0.34
Pure GGO	37 (23.6)	31 (19.0)	
Mixed GGO	46 (29.3)	42 (25.8)	
Solid	74 (47.1)	90 (55.2)	
cTNM staging, No. (%)			0.10
IA1	22 (14.0)	23 (14.1)	
IA2	75 (47.8)	58 (35.6)	
IA3	26 (16.6)	46 (28.2)	
IB	11 (7.0)	12 (7.4)	
IIA	1 (0.6)	5 (3.1)	
IIB	9 (5.7)	7 (4.3)	
IIIA	13 (8.3)	12 (7.4)	
pTNM staging, No. (%)			0.89
0	2 (1.3)	31 (0.6)	
IA1	40 (25.5)	39 (23.9)	
IA2	67 (42.7)	59 (36.2)	
IA3	15 (9.6)	20 (12.3)	
IB	12 (7.6)	13 (8.0)	
IIA	3 (1.9)	6 (3.7)	
IIB	7 (4.5)	9 (5.5)	
IIIA	10 (6.4)	14 (8.6)	
IIIB	1 (0.6)	2 (1.2)	
Histological type, No. (%)			0.36
Adenocarcinoma	141 (89.8)	141 (86.5)	
Non-adenocarcinoma	16 (10.2)	22 (13.5)	
Tumor location ^a , No. (%)			>0.99
Left lower lobe	21 (13.4)	22 (13.5)	
Left upper lobe	36 (22.9)	35 (21.5)	
Right lower lobe	21 (13.4)	22 (13.5)	
Right middle lobe	26 (16.6)	29 (17.8)	
Right upper lobe	53 (33.8)	57 (35.0)	
Operation time [min], median (IQR)	110 (95–140)	120 (97.5–150)	0.25
Blood loss [mL], median (IQR)	100 (50–100)	100 (50–150)	0.036
Conversion to thoracotomy, No. (%)	7 (4.5)	9 (5.5)	0.86
Postoperative hospital stay [d], median (IQR)	4 (4–5)	5 (4–5)	0.76
Postoperative complications, No. (%)	23 (14.6)	30 (18.4)	0.45
Clavien-Dindo I-II	18 (11.5)	24 (14.7)	0.49
Clavien-Dindo III-IV	5 (3.2)	6 (3.7)	>0.99

BMI, body mass index; GGO, ground-glass opacity; IQR, interquartile range. ^aTwo patients underwent bilobectomy in the video-assisted lobectomy group.

Table 1: Patient clinicopathological characteristics and perioperative outcomes.

will add to the evidence that RATS provided similar oncological efficacy as VATS.

This study reported an excellent survival rate in the RAL group of 94.6% and 90.7% at 3 years and 5 years,

	RAL (n = 149)	VAL (n = 156)
Total death	13	20
Lung cancer death	10	13
Other death	0	4
Respiratory disease	0	3
Accident	0	1
Unknown	3	3

Thirty-three patients died during follow-up period. RAL, robotic-assisted lobectomy; VAL, video-assisted lobectomy. ^aAt median follow-up of 58.0 months (range, 1–74).

Table 2: Summary of causes of death during follow-up.^a

respectively, compared to 91.5% and 86.3% in the VAL group (Supplemental Table S2). In all the enrolled patients with available survival data, the 3-year and 5-year survival were 93.0% and 88.5%. This compares favorably with ranges of previously reported 5-year OS for RAL (77%–80%)^{6,38,39} and for VAL (73.5%–74.9%).^{6,33,40} The relatively high rate of survival in this study may be attributed to following factors. First, nearly half nodules 48.8% (156/320) had the presence of a GGO component, which indicates better prognosis.⁴¹ Second, a high proportion of pathological stage I patients (82.8%, 265/320), smaller tumors (median, 1.5 cm), and fewer cases of LN involvement (11.9%, 38/320) may also contribute to the favorable outcomes in this study. Besides, the pathology of 88.1% (282/320) patients was adenocarcinoma. Squamous-cell carcinoma took up 9.4% (30/320). Large cell carcinoma, which is associated with a poorer prognosis, constituted only 0.9% (3/320) of the total cases. The OS was also higher than we expected when we calculated our sample size. The non-inferiority of RAL was confirmed according to our predefined margin, but the hazards of death in the RAL and VAL groups were not significantly different. It remains unknown whether this separation will become statistically significant with a longer period of follow-up.

The present study provides the long-term outcomes of patients receiving RAL or VAL in a randomized controlled trial. However, this study also has some limitations, which should be considered when interpreting these data. First, when we were calculating the sample size, the significance level was one-sided 5% while we claimed that it was a two-sided significance level of 5% in the study protocol. Moreover, we did not consider the multiplicity adjustment when calculating the sample size. Since this flaw was made in the protocol, this study is actually designed using a one-sided significance level of 10%. Second, this study was conducted at a high-volume clinical center. The single-center nature of this study makes it less persuasive than a multi-center clinical trial. Also, the results may not extend to surgeons with less intensive training. Currently, there are another two ongoing multi-centered, randomized controlled trials to compare RATS versus VATS (RAVAL trial,⁴²

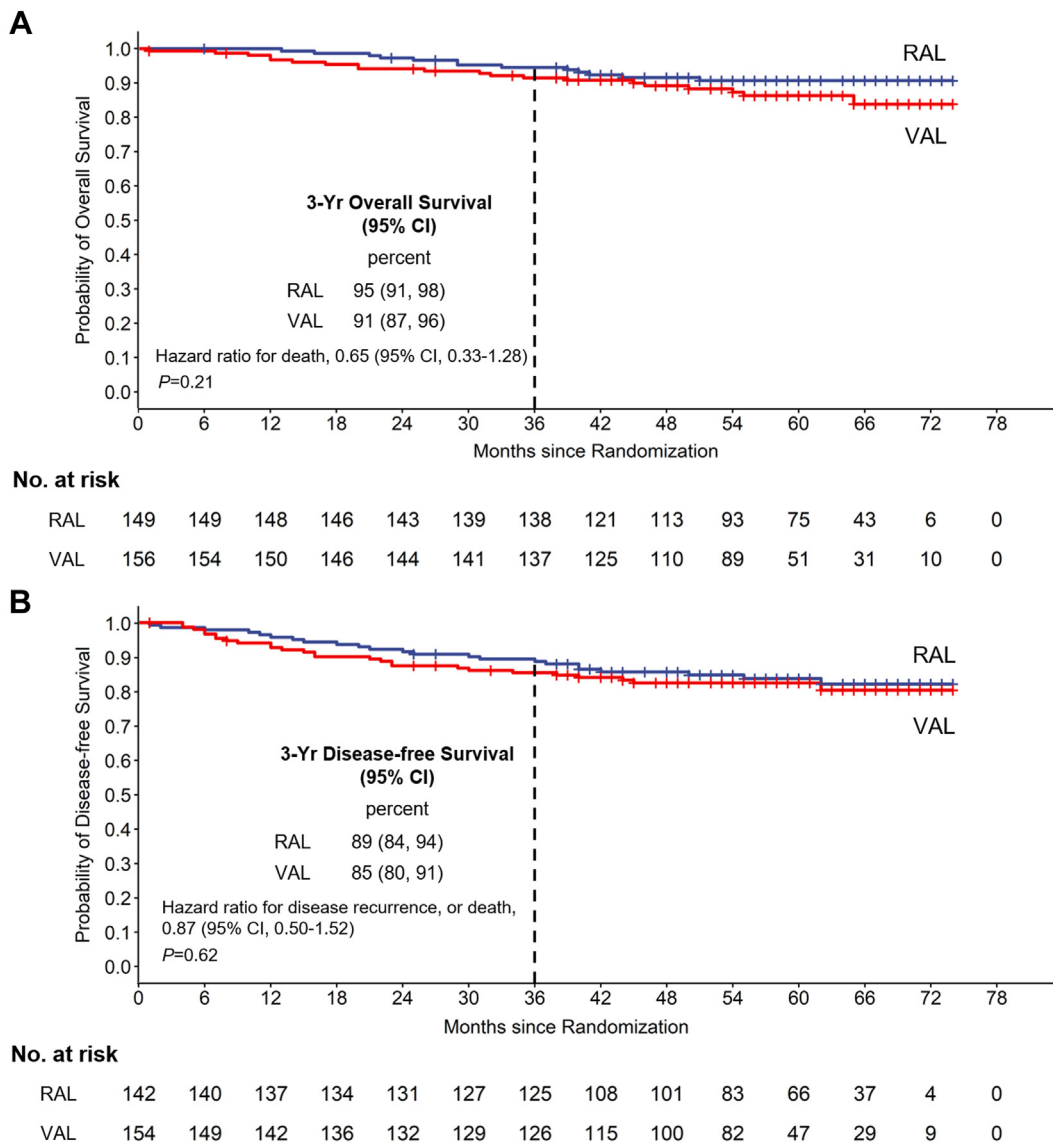


Fig. 2: Kaplan-Meier estimates of overall survival (A) and disease-free survival (B). HR, hazard ratio; RAL, robotic-assisted lobectomy; VAL, video-assisted lobectomy.

NCT02617186; RAVAR trial, ChiCTR2000034737), the results of which may provide further corroboration. Third, the patients enrolled in this study are mainly pathological stage I patients. The generalizability of these findings to patients with stage II or III NSCLC remains undefined. Fourth, there were more pathological stage II or III NSCLC patients in the VAL group than in the RAL group (21 in RAL group, 31 in VAL group). This may affect the comparison of OS between the two groups. Fifth, we excluded patients who received sublobar resections. As more early-staged NSCLC is being discovered, sublobar resections are getting more popular. The role of RATS sublobar resections is still undefined.

In conclusion, we report the long-term outcomes of the RVlob randomized controlled trial comparing RAL and VAL in the treatment of resectable NSCLC. Among patients with resectable NSCLC, RAL resulted in non-inferior OS at 3 years compared with VAL. Based on our results, RAL is an equally oncologically effective treatment and can be considered as an alternative to VAL.

Contributors

All authors confirm that they had full access to all the data in the study. Zhenyi Niu, Yuqin Cao, Mingyuan Du, Siying Sun, Yan Yan, Yuyan Zheng, Yichao Han, Xianfei Zhang, Zhengyuan Zhang, Runsen Jin and Hecheng Li verified the data. Zhenyi Niu, Yuqin Cao, Mingyuan Du,

Runsen Jin and Hecheng Li had final responsibility for the decision to submit for publication. Details of authors contributions are listed as follows.

Zhenyi Niu: Data curation, Formal analysis, Software, Methodology, Writing—original draft, Visualization.

Yuqin Cao: Conceptualization, Methodology, Software, Formal analysis, Writing—original draft, Visualization.

Mingyuan Du: Data curation, Software, Investigation, Data curation, Writing—original draft.

Siying Sun: Methodology, Software, Formal analysis, Writing—review & editing.

Yan Yan: Methodology, Software, Formal analysis, Writing—review & editing.

Yuyan Zheng: Conceptualization, Data curation, Writing—review & editing.

Yichao Han: Data curation, Writing—review & editing.

Xianfei Zhang: Data curation, Writing—review & editing.

Zhengyuan Zhang: Data curation, Writing—review & editing.

Ye Yuan: Conceptualization, Data curation, Writing—review & editing.

Jian Li: Conceptualization, Software, Formal analysis, Writing—review & editing.

Yajie Zhang: Conceptualization, Data curation, Writing—review & editing.

Chengqiang Li: Data curation, Writing—review & editing.

Dingpei Han: Conceptualization, Data curation, Writing—review & editing.

Hailei Du: Data curation, Investigation, Writing—review & editing.

Wei Guo: Data curation, Investigation, Writing—review & editing.

Kai Chen: Data curation, Investigation, Writing—review & editing.

Jie Xiang: Data curation, Investigation, Writing—review & editing.

Lianggang Zhu: Data curation, Investigation, Writing—review & editing.

Jiaming Che: Data curation, Investigation, Writing—review & editing.

Junbiao Hang: Data curation, Investigation, Writing—review & editing.

Jian Ren: Data curation, Investigation, Writing—review & editing.

Toni Lerut: Data Curation, Writing—review & editing, Supervision.

Abbas E. Abbas: Data Curation, Writing—review & editing, Supervision.

Jules Lin: Data Curation, Writing—review & editing, Supervision.

Runsen Jin: Conceptualization, Resources, Data Curation, Writing—review & editing, Supervision.

Hecheng Li: Conceptualization, Resources, Writing—review & editing, Supervision, Project administration, Funding acquisition.

Data sharing statement

Individual data will be made available following publication by reasonable request to the corresponding author. The study protocol is available in the [Supplemental Data](#).

Declaration of interests

All authors have no conflicts of interest to declare.

Acknowledgements

We thank the patients, their families, the investigators, and the teams who participated in this trial; and Yunpeng Zhu (Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, Shanghai, China) for writing assistance with an earlier version of the manuscript.

This study was supported by National Natural Science Foundation of China (82072557), National Key Research and Development Program of China (2021YFC2500900), Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant (20172005, the 2nd round of disbursement), program of Shanghai Academic Research Leader from Science and Technology Commission of Shanghai Municipality (20XD1402300), Novel Interdisciplinary Research Project from Shanghai Municipal Health Commission (2022JC023), and Interdisciplinary Program of Shanghai Jiao Tong University (YG2023ZD04).

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2024.102707>.

References

- Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249.
- Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature*. 2018;553:446–454.
- Cahan WG. Radical lobectomy. *J Thorac Cardiovasc Surg*. 1960;39:555–572.
- Situ D, Long H, Tan Q, et al. P2.05-018 video-assisted thoracoscopic surgery vs thoracotomy for early-stage non-small cell lung cancer: short-term outcomes of a randomized trial. *J Thorac Oncol*. 2017;12:S2410.
- Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. *Lancet Oncol*. 2016;17:836–844.
- Yang HX, Woo KM, Sima CS, et al. Long-term survival based on the surgical approach to lobectomy for clinical stage I nonsmall cell lung cancer: comparison of robotic, video-assisted thoracic surgery, and thoracotomy lobectomy. *Ann Surg*. 2017;265:431–437.
- Abbas AE. Surgical management of lung cancer: history, evolution, and modern advances. *Curr Oncol Rep*. 2018;20:98.
- Mahieu J, Rinieri P, Bubenheim M, et al. Robot-assisted thoracoscopic surgery versus video-assisted thoracoscopic surgery for lung lobectomy: can a robotic approach improve short-term outcomes and operative safety? *Thorac Cardiovasc Surg*. 2016;64:354–362.
- Jin R, Zheng Y, Yuan Y, et al. Robotic-assisted versus video-assisted thoracoscopic lobectomy: short-term results of a randomized clinical trial (RVlob trial). *Ann Surg*. 2022;275:295–302.
- Jin R, Zhang Z, Zheng Y, et al. Health-related quality of life following robotic-assisted or video-assisted lobectomy in patients with non-small cell lung cancer: results from the RVlob randomized clinical trial. *Chest*. 2023;163:1576–1588.
- Li C, Hu Y, Huang J, et al. Comparison of robotic-assisted lobectomy with video-assisted thoracic surgery for stage IIB-IIIa non-small cell lung cancer. *Transl Lung Cancer Res*. 2019;8:820–828.
- Nelson DB, Mehran RJ, Mitchell KG, et al. Robotic-assisted lobectomy for non-small cell lung cancer: a comprehensive institutional experience. *Ann Thorac Surg*. 2019;108:370–376.
- Li JT, Liu PY, Huang J, et al. Perioperative outcomes of radical lobectomies using robotic-assisted thoracoscopic technique vs video-assisted thoracoscopic technique: retrospective study of 1,075 consecutive p-stage I non-small cell lung cancer cases. *J Thorac Dis*. 2019;11:882–891.
- Casiraghi M, Galetta D, Borri A, et al. Ten years' experience in robotic-assisted thoracic surgery for early stage lung cancer. *Thorac Cardiovasc Surg*. 2019;67:564–572.
- Kneuert PJ, Cheufou DH, D'Souza DM, et al. Propensity-score adjusted comparison of pathologic nodal upstaging by robotic, video-assisted thoracoscopic, and open lobectomy for non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2019;158:1457–1466.e1452.
- Zhang J, Feng Q, Huang Y, Ouyang L, Luo F. Updated evaluation of robotic- and video-assisted thoracoscopic lobectomy or segmentectomy for lung cancer: a systematic review and meta-analysis. *Front Oncol*. 2022;12:853530.
- O'Sullivan KE, Kreaden US, Hebert AE, Eaton D, Redmond KC. A systematic review and meta-analysis of robotic versus open and video-assisted thoracoscopic surgery approaches for lobectomy. *Interact Cardiovasc Thorac Surg*. 2019;28:526–534.
- Guo F, Ma D, Li S. Compare the prognosis of Da Vinci robot-assisted thoracic surgery (RATS) with video-assisted thoracic surgery (VATS) for non-small cell lung cancer: a Meta-analysis. *Medicine*. 2019;98:e17089.
- Kneuert PJ, D'Souza DM, Richardson M, Abdel-Rasoul M, Mofatt-Bruce SD, Merritt RE. Long-term oncologic outcomes after robotic lobectomy for early-stage non-small-cell lung cancer versus video-assisted thoracoscopic and open thoracotomy approach. *Clin Lung Cancer*. 2020;21:214–224.e212.
- Shagabayeva L, Fu B, Panda N, et al. Open, video- and robot-assisted thoracoscopic lobectomy for stage II-IIIa non-small cell lung cancer. *Ann Thorac Surg*. 2023;115:184–190.

- 21 Miyajima M, Maki R, Arai W, et al. Robot-assisted vs. video-assisted thoracoscopic surgery in lung cancer. *J Thorac Dis.* 2022;14:1890–1899.
- 22 Zhang Y, Chen C, Hu J, et al. Early outcomes of robotic versus thoracoscopic segmentectomy for early-stage lung cancer: a multi-institutional propensity score-matched analysis. *J Thorac Cardiovasc Surg.* 2020;160:1363–1372.
- 23 Yang S, Guo W, Chen X, Wu H, Li H. Early outcomes of robotic versus uniportal video-assisted thoracic surgery for lung cancer: a propensity score-matched study. *Eur J Cardio Thorac Surg.* 2018;53:348–352.
- 24 Veronesi G, Abbas AE, Muriana P, et al. Perioperative outcome of robotic approach versus manual videothoracoscopic major resection in patients affected by early lung cancer: results of a randomized multicentric study (ROMAN study). *Front Oncol.* 2021;11:726408.
- 25 Terra RM, Araujo P, Lauricella LL, Campos JRM, Trindade JRM, Pêgo-Fernandes PM. A Brazilian randomized study: robotic-Assisted vs. Video-assisted lung lobectomy Outcomes (BRAVO trial). *J Bras Pneumol.* 2022;48:e20210464.
- 26 Patel YS, Baste JM, Shargall Y, et al. Robotic lobectomy is cost-effective and provides comparable health utility scores to video-assisted lobectomy: early results of the RAVAL trial. *Ann Surg.* 2023;278:841–849.
- 27 Catelli C, Corzani R, Zanfrini E, et al. Robotic-Assisted (RATS) versus Video-Assisted (VATS) lobectomy: a monocentric prospective randomized trial. *Eur J Surg Oncol.* 2023;49:107256.
- 28 Mauguen A, Pignon JP, Burdett S, et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. *Lancet Oncol.* 2013;14:619–626.
- 29 Zhang X, Jin R, Zheng Y, et al. Interactions between the enhanced recovery after surgery pathway and risk factors for lung infections after pulmonary malignancy operation. *Transl Lung Cancer Res.* 2020;9:1831–1842.
- 30 Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2016;11:39–51.
- 31 National comprehensive cancer work clinical Practice guidelines in Oncology (NCCN guidelines) for non-small cell lung cancer Version.5 2017. <https://www.nccn.org/home>; 2017.
- 32 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240:205–213.
- 33 Cao C, Zhu ZH, Yan TD, et al. Video-assisted thoracic surgery versus open thoracotomy for non-small-cell lung cancer: a propensity score analysis based on a multi-institutional registry. *Eur J Cardio Thorac Surg.* 2013;44:849–854.
- 34 Velez-Cubian FO, Rodriguez KL, Thau MR, et al. Efficacy of lymph node dissection during robotic-assisted lobectomy for non-small cell lung cancer: retrospective review of 159 consecutive cases. *J Thorac Dis.* 2016;8:2454–2463.
- 35 Situ D, Long H, Tan Q, et al. OA13.02 video-assisted thoracoscopic surgery vs. Thoracotomy for non-small cell lung cancer: survival outcome of a randomized trial. *J Thorac Oncol.* 2019;14:S240.
- 36 Tang A, Raja S, Bribriescio AC, et al. Robotic approach offers similar nodal upstaging to open lobectomy for clinical stage I non-small cell lung cancer. *Ann Thorac Surg.* 2020;110:424–433.
- 37 Catanzarite T, Tan-Kim J, Whitcomb EL, Menefee S. Ergonomics in surgery: a review. *Female Pelvic Med Reconstr Surg.* 2018;24:1–12.
- 38 Park BJ, Melfi F, Mussi A, et al. Robotic lobectomy for non-small cell lung cancer (NSCLC): long-term oncologic results. *J Thorac Cardiovasc Surg.* 2012;143:383–389.
- 39 Cerfolio RJ, Ghanim AF, Dylewski M, Veronesi G, Spaggiari L, Park BJ. The long-term survival of robotic lobectomy for non-small cell lung cancer: a multi-institutional study. *J Thorac Cardiovasc Surg.* 2018;155:778–786.
- 40 Lee PC, Nasar A, Port JL, et al. Long-term survival after lobectomy for non-small cell lung cancer by video-assisted thoracic surgery versus thoracotomy. *Ann Thorac Surg.* 2013;96:951–960. discussion 960-951.
- 41 Hattori A, Suzuki K, Takamochi K, et al. Prognostic impact of a ground-glass opacity component in clinical stage IA non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2021;161:1469–1480.
- 42 Patel YS, Hanna WC, Fahim C, et al. RAVAL trial: protocol of an international, multi-centered, blinded, randomized controlled trial comparing robotic-assisted versus video-assisted lobectomy for early-stage lung cancer. *PLoS One.* 2022;17:e0261767.