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Recent advances in surgical management of NSCLC

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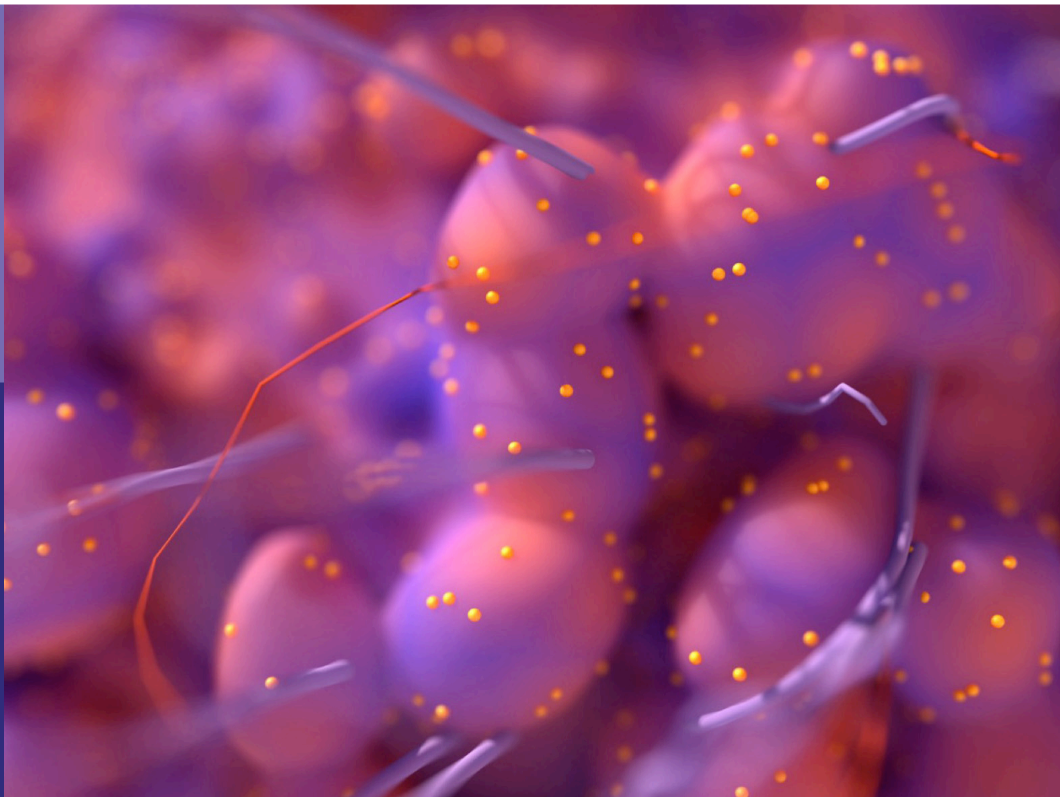

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Recent advances in surgical management of NSCLC

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Editorial: Recent advances in surgical management of NSCLC

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KEYWORDS

VATS, individualization, NSCLC, precision surgery, sublobar, artificial intelligence, AI

Editorial on the Research Topic
Recent advances in surgical management of NSCLC

Lung cancer remains a leading cause of cancer-related deaths worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. Despite advances in therapy, surgical resection remains the cornerstone of treatment for early-stage NSCLC.

Over the past few years, there have been significant advances in the surgical approach and operative techniques for the management of NSCLC. After decades where lobectomy was the most common operation performed for early NSCLC, more and more signals suggest that the approach for T1N0 NSCLC has shifted to segmentectomy or wedge resection (1–8).

This Research Topic collected 12 publications: four original research papers, one brief research report, three systematic reviews, two reviews, and two case reports. The Research Topic is a valuable resource and platform for thoracic surgeons and oncologists, with the aim of improving outcomes for lung cancer patients, and provides a comprehensive overview of recent advances in the surgical management of NSCLC.

Various aspects of NSCLC management, including surgical approaches (RATS, VATS multiportal or uniportal) and techniques, perioperative care, and outcomes are presented in the Research Topic.

Song et al. compared survival after lobectomy and wedge resection for stage IA second primary NSCLC (SP-NSCLC) patients with previous lung cancer-directed surgery using overall survival (OS) and lung cancer-specific mortality as outcomes. The authors showed a 5-year overall survival (OS) was 61.3% with wedge resection and 66.1% with lobectomy. They concluded that wedge resection is comparable to lobectomy in OS for stage IA SP-NSCLC patients with previous lung cancer-directed surgery. In short, this paper shows that wedge resection may be sufficient for stage IA SP-NSCLC.

Ding et al. showed that wedge resection plus adequate lymph nodes resection was comparable to lobectomy for small-sized non-small cell lung cancer. The authors identified patients diagnosed with node-negative NSCLC ≤2 cm who underwent wedge resection or lobectomy (2004-2015). Then patients were stratified by the procedure (wedge resection or lobectomy) and the size of NSCLC (≤1 cm, 1-2 cm). For lesions ≤1 cm and receiving lobectomy, lymph nodes resection had no impact on survival. Wedge resection and lobectomy were comparable when one or more nodes for lesions ≤1 cm and six or more nodes for lesions 1-2 cm were resected.

Lu et al. conducted a meta-analysis based on randomized controlled trials comparing lobectomy and sublobar resection for stage I non-small cell lung cancer. Their systematic analysis included five RCTs and 2222 patients. The authors showed no statistical difference in OS (HR=0.87, p=0.445) and DFS (HR=0.99, p=0.918) between patients who underwent lobectomy and sublobar resection during the total follow-up period. The strong findings led the authors to suggest that lobectomy is usually not a justified operation for stage I NSCLC.

Although retrospective, the articles of Song et al., Ding et al., and Lu et al. are significant because the results are similar to those of the prospective randomized trial performed by Altorki et al. (9, 10). A question arises. What could happen in the future on the basis of the results of their studies? Their results suggest that minimal lung resection, even a wedge, will be sufficient to guarantee long-term survival in early-stage NSCLC patients and therefore larger resection, such as segmentectomy or even lobectomy, will be performed less. It will take years to change practice worldwide, but it will certainly happen.

Pan et al. evaluated, through a propensity score-matched comparison, the results of robotic- and video-assisted thoracoscopic surgery and open lobectomy (OL) for non-small cell lung cancer patients aged 75 years or older. The authors reported that RATS possessed superiority in better perioperative outcomes over VATS and OL in very old NSCLC patients.

Huang et al. performed a systematic review and meta-analysis of prospective studies comparing robot-assisted thoracic surgery to video-assisted thoracic surgery. Of 614 patients, 299 patients were treated by RATS and 315 by VATS. In the RATS group, blood loss was lower (P = 0.009) and more nodes stations were dissected in RATS (P < 0.001). Nevertheless, no significant difference occurred between RATS and VATS in length of hospital stay, readmission, operative time, conversion, number of dissected lymph nodes, upstaging rate, time of chest tube drainage, or post-operative complications. The authors concluded that, except for the higher total cost, RATS has obvious advantages in lymphadenectomy and bleeding.

What is important after reading these two articles comparing RATS with VATS is that surgeons should not confound the approach with the operation. In fact, as expected, the different surgical approaches achieved comparable survival outcomes. This is due to the fact that, although different approaches have been used, the surgeon inside the chest performs an identical operation (lung resection and lymphadenectomy), and therefore survival is the same. This result confirms that the surgeon should use the approach that suits them best to enhance treatment of the patient (11).

Gallina et al. analyzed the predictive factors of unforeseen nodal metastases in resected clinical stage I NSCLC. With a total of 297 patients, the authors showed a significant correlation with the upstaging rate. This result was confirmed in the multivariate analysis with an OR= 2.545 (p=0.02) for the number of resected lymph nodes and an OR=2.717 (p=0.01) for the high-grade pattern of adenocarcinoma. The Italian group have shown that, in patients with clinical stage I NSCLC, the number of resected lymph nodes and the histological subtype of adenocarcinoma can be significantly associated with nodal metastasis. Certainly in the future, this result will encourage thoracic surgeons to perform a better and more extended lymphadenectomy.

Abbaker et al. wrote an interesting and comprehensive review of the current state of artificial intelligence (AI) applications in lung cancer management. In the preoperative phase, AI enhances diagnostics and predicts molecular biomarkers, especially in cases with limited biopsy materials. Intraoperatively, AI transforms surgery by providing real-time guidance and decision support. Postoperatively, AI aids in pathological assessment and predictive modeling for refined care. AI could certainly be of help when interpretability is difficult and different opinions arise between physicians and surgeons on how to conduct a treatment strategy. Although the role of 3D reconstruction in thoracic surgery and artificial intelligence is at its beginning, there are a lot of expectations for the future. We believe that there is a need for clearer indications because, at the moment, there are no well-defined guidelines and confusion exists.

Kamigaichi et al. discussed the indications of segmentectomy, especially for patients with radiologically pure-solid NSCLC. Although radiologically pure-solid NSCLC, lacking ground-glass opacity (GGO) components, could represent highly malignant neoplasm with poor prognoses compared to those containing GGO components, the subgroup analysis of the JCOG0802/WJOG4607L proved the efficacy of segmentectomy for pure-solid NSCLC. Recently, the JCOG1211 demonstrated the efficacy of segmentectomy even for NSCLC measuring up to 3 cm with GGO predominance and for some tumors measuring > 2–3 cm. The authors expect that segmentectomy may become an appropriate treatment modality for radiologically pure-solid NSCLC of 2–3 cm because of the survival benefits associated with the lung-sparing approach. However, the benefits of segmentectomy for patients with pure-solid NSCLC of 2-3 cm must be confirmed by future clinical trials.

Zhang et al. made an interesting review on the clinical application of three-dimensional (3D) technology in video-assisted thoracoscopic surgery sublobectomy and its future direction. It is evident that a more frequent use of 3D technologies in locating pulmonary nodules and identifying variations in target lung segmental vessels and bronchi play pivotal roles in VATS sublobectomy, especially in preoperative planning, intraoperative navigation, and doctor-patient communication.

Li et al. described the detailed classification of the interlobar artery and the artery crossing intersegmental planes in the right upper lobe, which is useful during segmentectomy. The authors demonstrated over 600 cases in which variation types of blood vessels in the right upper lobe were complex. This article could help thoracic surgeons understand anatomy variations, accurately locate lesions before surgery, and effectively plan surgeries.

Although the role of 3D reconstruction in thoracic surgery is well known, it also has the potential to help surgeons to know the anatomical variation of pulmonary vessels or bronchi preoperatively and to demonstrate intersegmental planes to perform precise operations such as segmentectomy; it is also useful for intraoperative navigation. In the future it will certainly be used more.

Finally, the Research Topic includes two very interesting case reports.

Tombelli et al. reported their experience with three successful left tracheal sleeve pneumonectomies and one neocarina reconstruction surgery for benign lesions without lung resections and without cardiovascular support such as cardiopulmonary bypass. These three case reports confirm the good long-term survival demonstrated in previous experiences on tracheal sleeve pneumonectomy after induction therapy (12, 13). Wu et al. reported uniportal video-assisted (3) thoracoscopic segmentectomy for a low-grade type fetal adenocarcinoma patient with poor pulmonary function.

In conclusion, while reading the papers presented in this Research Topic, a significant positive correlation between sublobar resection and long-term survival in NSCLC less than 2 cm was found. The results suggest that lobectomy will probably be less used in the upcoming years for initial-stage lung cancers. Although wedge resection seems appropriate for peripheral lung tumors, its significance for individualizing treatment is still a source of discussion. Artificial Intelligence and 3D technology will contribute to the modern revolution in the practice of thoracic surgery. Other areas of research which have not been discussed in depth in this Research Topic are immunotherapy (4), the treatment of ground-glass opacities (5, 6), and the treatment of locally advanced lung cancer (7). Furthermore, it appears evident that, in the future, individualization of surgery (8) for NSCLC would be the more appropriate approach to achieving long-term survival.

Author contributions

MM: Writing – review & editing, Writing – original draft. DG: Writing – review & editing. MC: Writing – review & editing.

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Survival after wedge resection versus lobectomy for stage IA second primary NSCLC with previous lung cancer-directed surgery

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Background: The surgical procedure for early-stage second primary non-small cell lung cancer (SP-NSCLC) remains controversial, especially for patients with previous lung cancer-directed surgery. This study aims to compare the survival after wedge resection and lobectomy for these patients.

Methods: Stage IA SP-NSCLC patients with clear clinical information were searched from the Surveillance, Epidemiology, and End Results (SEER) database. The Cox proportional hazard model, the competing risk model, and the Kaplan–Meier survival curve were used to describe the survival difference between wedge resection and lobectomy. A 1:1 propensity score matching (PSM) method was also performed to reduce the potential impact of confounding factors between the two groups.

Results: Of the 320 eligible stage IA SP-NSCLC patients included in this study, 238 (74.4%) patients underwent wedge resection and 82 (25.6%) patients received lobectomy. The 5-year overall survival (OS) was 61.3% with wedge resection and was 66.1% with lobectomy. Both before and after PSM, wedge resection showed similar OS and lung cancer-specific mortality as lobectomy in the entire cohort. Additionally, in all subgroup analyses, wedge resection demonstrated equivalent survival to lobectomy. However, in the female, sublobectomy for the first primary lung cancer, and interval ≤ 24 months subgroups, wedge resection displayed a higher lung cancer-specific mortality than lobectomy (fine-gray test, all $p < 0.05$).

Conclusion: Overall, wedge resection is comparable to lobectomy in OS for stage IA SP-NSCLC patients with previous lung cancer-directed surgery. Therefore, we believe that wedge resection may be sufficient for these patients, although, in some cases, wedge resection has a higher lung cancer-specific mortality rate than lobectomy.

KEYWORDS

second primary lung cancer, second primary NSCLC, lobectomy, wedge resection, SEER

Introduction

With the advancement in early detection technology of lung cancer and the close postoperative follow-up of lung cancer patients, the detection rate of second primary lung cancer (SPLC) has been growing. The efficacy and safety of surgical treatment for second primary non-small cell lung cancer (SP-NSCLC) patients have also been demonstrated in several studies (1–7). For the patients with resectable early-stage NSCLC, lobectomy remains the accepted standard surgical procedure (8). However, with the continuous improvement of medical technology and treatment concept, the treatment of lung cancer has become individualized and standardized. Two "maxima", namely, maximum removal of tumor and maximum preservation of normal lung tissue, have become the development direction of lung tumor surgery. For lung cancer patients with previous lung cancer-directed surgery, in addition to having less lung tissue, they would also have a higher risk of developing another new primary lung cancer than the general population (9). Clinically, it may be difficult to accurately identify the second tumor as primary, recurrent, or metastatic. Since 1975, when Martini and Melamed came up with the diagnostic criteria (10) for multiple primary lung cancer (MPLC), there have been more and more reports on MPLC. In the SEER database, there is also a dataset on multiple primary events. The relevant information can be available to us from this website (https://seer.cancer.gov/tools/mphrules/). As with the Martini–Melamed criteria (10), SEER also considers tumor histology, location, and time since initial diagnosis to determine multiple primary events. However, there are still no clear treatment guidelines and plans for MPLC. For patients with SPLC with previous lung cancer-directed surgery, especially for patients who are elderly, have severe cardiopulmonary diseases, or are unwilling to undergo surgery, the limited residual lung tissue makes them more cautious when they face the surgical removal of the second tumor lesion. Radiotherapy, especially stereotactic radiotherapy, may be a good option for such patients (11). Compared with surgical resection, stereotactic radiotherapy has the advantages of non-invasive treatment, the immediate recovery of activity after treatment, and the treatment of multiple lesions simultaneously. However, everything has two sides. Radiotherapy-related toxicities, such as bronchial stenosis, necrosis, and esophageal ulcers, have increased the concern (12). Surgery, to our knowledge, is still currently the only treatment offering potential cure and long-term survival in patients with SPLC. Despite significant breakthroughs in the diagnosis and treatment of lung cancer, it has not been determined whether lobectomy has a better survival advantage than wedge resection for patients with early-stage SP-NSCLC, especially those with a history of radical surgery for the first primary lung cancer (FPLC). A recent SEER-based study (13) has reported that SPLC demonstrated similar survival with lobectomy and wedge resection. However, the study did not delve into the differences in survival between the two procedures in various specific circumstances. Faced with the complexity of patients' clinical situation, further stratified analysis is still necessary. Thus, combining with a variety of methods, this study compared the survival after lobectomy and wedge resection using overall survival (OS) and lung cancer-specific mortality as outcomes.

Abbreviations: FPLC, first primary lung cancer; SPLC, second primary lung cancer; SP-NSCLC, second primary non-small cell lung cancer; MPLC, multiple primary lung cancer; OS, overall survival; SCLC, small cell lung cancer; AJCC, American Joint Committee on Cancer; ICD-O, International Classification of Diseases for Oncology; SEER, Surveillance, Epidemiology, and End Results.

Materials and methods

Data source and patient selection

Using SEER*Stat 8.3.5 software (http://seer.cancer.gov/seerstat/), we extracted data from the SEER database, which was open to the public for research purposes. A total of 320 patients with dual primary non-small cell lung cancers were extracted from the SEER database. Patients meeting the following criteria were included in this study: ① Year of diagnosis was between 2007 and 2015. ② Site and morphology. Site recoded ICD-O-3/WHO 2008: Lung and Bronchus. ③ Events (1 of 124 selected for display): lung and bronchus. Furthermore, cases with three or more primary lung cancers and whose first or second primary cancer was small cell lung cancer (SCLC) were excluded from this study. Cases without clear status, survival time, and American Joint Committee on Cancer (AJCC) stage were also removed. The specific inclusion and exclusion criteria, as well as the case screening process of this study, are detailed in Figure 1. The 8th edition of the TNM staging system was applied in the present study. The collected variables included age at diagnosis, sex, "race record", "primary site-labeled", laterality, "ICD-O-3 Hist/behav, malignant", tumor size, "months since index" (the time interval between two primary tumors), AJCC Stage, "COD to site recode", "Rx Sumn-Surg Prim Site (1998+)", "radiation record", and "chemotherapy record".

Description of surgery types and histological types

In this study, sublobectomy includes wedge resection (SEER surgery codes: 21) and segmental resection (SEER surgery codes:

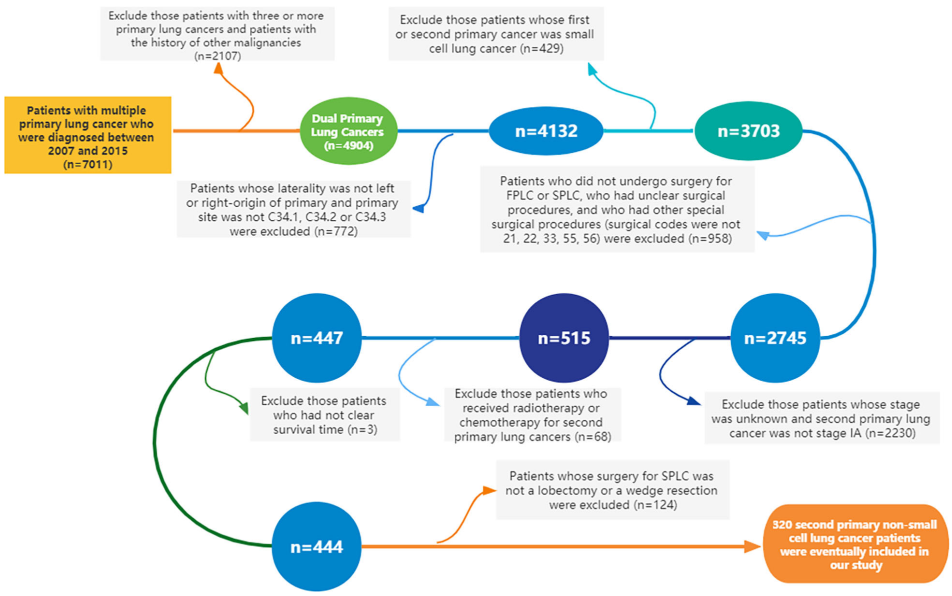

FIGURE 1
Flowchart of the inclusion and exclusion criteria for the cases in this study (FPLC, first primary lung cancer; SPLC, second primary lung cancer).

22). Lobectomy means lobectomy with mediastinal lymph node dissection (SEER surgery codes: 33) and pneumonectomy contains complete pneumonectomy, sleeve pneumonectomy, standard pneumonectomy, total pneumonectomy, and resection of whole lung (SEER surgery codes: 55) and with mediastinal lymph node dissection (radical pneumonectomy) (SEER surgery codes: 56). Other surgery codes were excluded in our study. The detailed SEER surgery codes can be viewed from the website (https://seer.cancer.gov/manuals/2018/AppendixC/Surgery_Codes_Lung_2018.pdf#search=surgery%20lung).

In addition, by the following International Classification of Diseases for Oncology histology codes, we categorized histology into three groups: ① adenocarcinoma (8140, 82508255, 8260, 8310, 8323, 8480–8481, 8550, and 8574); ② squamous cell carcinoma (8070–8074 and 8083); ③ other NSCLCs (8012–8013, 8020, 8022, 8033, 8046, 8230, and 8246). The present study did not include the histological type of SCLC (8041 and 8045), either FPLC or SPLC.

Statistical analysis

In this study, categorical variables were represented by number (percentage), and continuous variables were expressed as mean (standard deviation, SD). The Chi-square test or Fisher's exact test was used to compare differences in baseline characteristics, as appropriate. The Cox proportional hazard model, the competitive risk model, and the Kaplan–Meier survival curve were used to describe the survival difference between wedge resection and lobectomy. Statistical comparisons between survival curves were performed with the log-rank test. To reduce the influence of confounding factors, we performed propensity score matching (PSM) for some important clinical factors including age at the SPLC, sex, race, histology of SPLC, tumor distribution of two lesions, grade of SPLC, interval between two lesions, surgery types of FPLC, AJCC stage of FPLC, tumor size of SPLC, radiation for FPLC, and chemotherapy for FPLC. PSM was performed using the "nearest" method with a caliper of 0.05 to reduce the potential impact of confounding factors between the two groups. The "MatchIt" package in R was adopted to calculate propensity scores. In addition, subgroup analysis was also performed to better characterize the prognostic differences between the two operations (wedge resection and lobectomy). All analyses were performed in version 3.6.0 of R software. A p-value of less than 0.05 was accepted for statistical significance.

Results

Patient characteristics

Following the detailed screening procedures in Figure 1, 320 patients with stage IA SP-NSCLC diagnosed from 2007 to 2015 were eventually included in this study. Wedge resection (n = 238, 74.4%) was performed on significantly more patients than

TABLE 1 Characteristics of patients in the wedge resection group and the lobectomy group before PSM.

Characteristics	Subgroups	Lobectomy, *n* (%)	Wedge resection, *n* (%)	*p*-value
Total	—	82 (100%)	238 (100%)	
Age (years)	Continuous (mean, SD)	68.34 (8.48)	68.44 (9.05)	0.930
Sex	Female	59 (72.0)	131 (55.5)	0.011
	Male	23 (28.0)	107 (45.0)	
Race	White	72 (87.8)	201 (84.5)	0.724
	Black	6 (7.3)	20 (8.4)	
	Others	4 (4.9)	17 (7.1)	
Histology of SPLC	Adenocarcinoma	59 (72.0)	173 (72.7)	0.317
	Squamous CC	21 (25.6)	50 (21.0)	
	Other NSCLCs	2 (2.4)	15 (6.3)	
Tumor distribution	Same lobe	5 (6.1)	4 (1.7)	0.014
	Ipsilateral different lobes	7 (8.5)	45 (18.9)	
	Bilateral	70 (85.4)	189 (79.4)	
Grade of SPLC	I well	25 (30.5)	55 (23.1)	0.232
	II moderate	28 (34.1)	109 (45.8)	
	III/IV poor/undifferentiated	23 (28.0)	53 (22.3)	
	Unknown	6 (7.3)	21 (8.8)	
Interval (months)	Continuous (mean, SD)	36.15 (21.96)	32.86 (21.38)	0.234
Surgery types of FPLC	Sublobectomy	13 (15.9)	35 (14.7)	0.581
	Lobectomy	69 (84.1)	200 (84.0)	
	Pneumonectomy	0 (0.0)	3 (1.3)	
AJCC stage of FPLC	Stage I	68 (82.9)	173 (72.7)	0.274
	Stage II	6 (7.3)	23 (9.7)	
	Stage III	7 (8.5)	33 (13.9)	
	Stage IV	1 (1.2)	9 (3.8)	
Tumor size of SPLC	<10 mm	12 (14.6)	86 (36.1)	<0.001
	≥10 mm, <20 mm	50 (61.0)	126 (52.9)	
	≥20 mm, ≤30 mm	20 (24.4)	26 (10.9)	
Radiation for FPLC	Unknown/No	81 (98.8)	225 (94.5)	0.191
	Yes	1 (1.2)	13 (5.5)	
Chemotherapy for FPLC	Unknown/No	80 (97.6)	228 (95.8)	0.698
	Yes	2 (2.4)	10 (4.2)	

lobectomy (n = 82, 25.6%). The detailed clinicopathological features are shown in Table 1. Of the 320 patients included, 190 were female and 130 were male; 68.95% (131/190) of the female patients and 82.31% (107/130) of the male patients underwent wedge resection for the second NSCLC. The average age of patients with lobectomy and wedge resection was similar, 68.34 ± 8.48 and 68.44 ± 9.05 years, respectively. Adenocarcinoma was predominant in the lobectomy group and wedge resection group (72.0% and 72.7%, respectively). Wedge resection was performed in the overwhelming majority of patients (45/52) when the two lesions were located in the ipsilateral different lobes. There were 259 patients with two lesions in the bilateral, and only 27.03% (70/259) chose lobectomy for the second lesion. Additionally, it could also be observed that regardless of the surgical procedures (sublobectomy, lobectomy, or pneumonectomy) performed on the first lesion, wedge resection was performed on the second lesion significantly more than lobectomy. In the lobectomy group, patients with a tumor diameter of less than 10 mm were the least, accounting for 14.6%. In the wedge resection group, patients with a tumor diameter ranging from 20 to 30 mm were the least, accounting for 10.9%.

Survival after lobectomy versus wedge resection before and after PSM

To reduce the potential impact of differences in clinical features between the lobectomy group and the wedge resection group on outcomes, we performed PSM. After 1:1 matching, the differences in clinical variables between the two groups were significantly reduced, as shown in Table 2. To further compare survival after lobectomy and wedge resection, OS and lung cancer-specific mortality were used as the main prognostic indicators. We found that OS after wedge resection and lobectomy were comparable both before (log-rank test, p = 0.724; Figure 2A) and after (log-rank test, p = 0.308; Figure 2B) PSM. In the entire cohort (n = 320), the 5-year OS was 61.3% with wedge resection and was 66.1% with lobectomy. The two were also comparable in lung cancer-

TABLE 2 Characteristics of patients in the wedge resection group and the lobectomy group after PSM.

Characteristics	Subgroups	Lobectomy (No. , %)	Wedge resection (No. , %)	*p*-value
Total	—	70 (100%)	70 (100%)	
Age (years)	Continuous (mean, SD)	68.59 (8.18)	69.30 (9.01)	0.624
Sex	Female	49 (70.0)	52 (74.3)	0.706
	Male	21 (30.0)	18 (25.7)	
Race	White	60 (85.7)	61 (87.1)	0.771
	Black	6 (8.6)	4 (5.7)	
	Others	4 (5.7)	5 (7.1)	
Histology of SPLC	Adenocarcinoma	50 (71.4)	52 (74.3)	0.925
	Squamous CC	18 (25.7)	16 (22.9)	
	Other NSCLCs	2 (2.9)	2 (2.9)	
Tumor distribution	Same lobe	1 (1.4)	4 (5.7)	0.366
	Ipsilateral different lobes	6 (8.6)	7 (10.0)	
	Bilateral	63 (90.0)	59 (84.3)	
Grade of SPLC	I well	18 (25.7)	21 (30.0)	0.494
	II moderate	25 (35.7)	29 (41.4)	
	III/IV poor/undifferentiated	22 (31.4)	14 (20.0)	
	Unknown	5 (7.1)	6 (8.6)	
Interval (months)	Continuous (mean, SD)	35.10 (21.24)	36.67 (21.90)	0.667
Surgery types of FPLC	Sublobectomy	12 (15.7)	16 (22.9)	0.392
	Lobectomy	59 (84.3)	54 (77.1)	
	Pneumonectomy	0 (0.0)	0 (0.0)	
AJCC stage of FPLC	Stage I	57 (81.4)	57 (81.4)	0.847
	Stage II	6 (8.6)	4 (5.7)	
	Stage III	6 (8.6)	7 (10.0)	
	Stage IV	1 (1.4)	2 (2.9)	
Tumor size of SPLC	<10 mm	10 (14.3)	11 (15.7)	0.960
	≥10 mm, <20 mm	45 (64.3)	45 (64.3)	
	≥20 mm, ≤30 mm	15 (21.4)	14 (20.0)	
Radiation for FPLC	Unknown/No	69 (98.6)	70 (100.0)	1.000
	Yes	1 (1.4)	0 (0.0)	
Chemotherapy for FPLC	Unknown/No	68 (97.1)	70 (100.0)	0.476
	Yes	2 (2.9)	0 (0.0)	

FPLC, first primary lung cancer; SPLC, second primary lung cancer; Squamous CC, Squamous cell cancer; NSCLC, non-small cell lung cancer.

specific mortality (fine-gray test, all $p > 0.05$), as shown in Figure 3.

Survival comparison based on subgroup analysis

To further clarify the survival after lobectomy and wedge resection in different clinical subgroups, we conducted subgroup analysis based on age, sex, histology, grade, tumor size, tumor distribution, time interval between two primary cancers, and type of first operation. We found that in all clinical subgroups, wedge resection demonstrated equivalent OS to lobectomy (all $p > 0.05$; Figure 4). Similarly, wedge resection and lobectomy had similar lung cancer-specific mortality in most clinical subgroups (Figures 5, 6A). However, in the female, sublobectomy for FPLC, and interval ≤ 24 months subgroups, wedge resection had a higher lung cancer-specific mortality than lobectomy (fine-gray test, all $p < 0.05$; Figure 6B).

Discussion

At present, there is no uniform standard for the surgical method of MPLC. Some scholars (14–16) have reported that lobectomy should be the first choice for the second primary tumor, followed by segment or wedge resection. However, sublobectomy, including segmentectomy and wedge resection, has also been studied as the main surgical method (3, 17). At the cost of damaging more pulmonary functional reserve compared with segmentectomy or wedge resection, lobectomy can remove more intrapulmonary lymph nodes and significantly reduce the recurrence rate of tumor (8), which can undoubtedly affect the postoperative quality of life of patients, especially those with a history of lung cancer-directed surgery. For stage IA SP-NSCLC patients with previous lung cancer-directed surgery, to date, it has not been fully understood whether lobectomy is more conducive to survival than wedge resection. Although several retrospective studies (18–20) and a recent SEER-based study

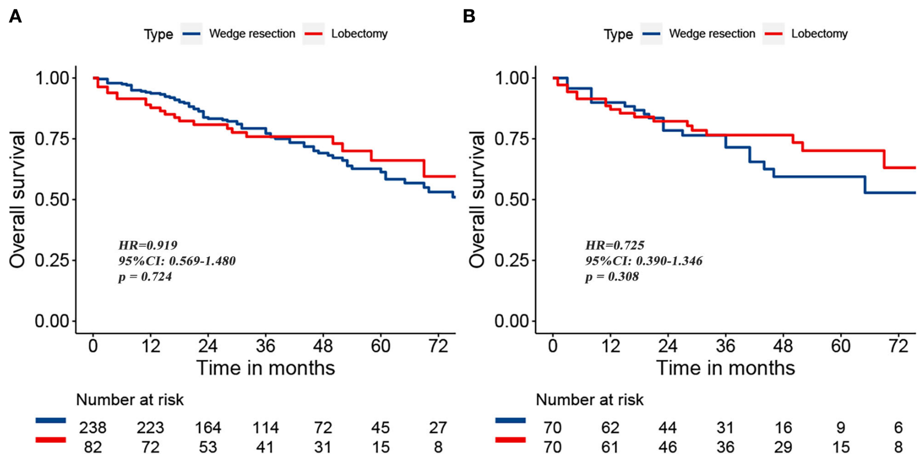

FIGURE 2
Overall survival after wedge resection versus lobectomy before **(A)** and after **(B)** PSM.

(13) have found that lobectomy did not show a significant survival advantage over sublobectomy for SPLC patients, these studies still lacked an in-depth study on SPLC patients who have undergone radical surgery for primary lung cancer. To better solve this problem and provide references for further clinical research and practice, we carried out this study.

In the present study, wedge resection demonstrated equivalent OS to lobectomy, both before and after PSM. Similar results were observed in all clinical subgroups. Unlike the previous studies (4, 16, 17, 21), participants in this study were patients with stage IA SP-NSCLC with previous lung cancer-directed surgery. Moreover, the sublobectomy mentioned in their studies included not only wedge resection,

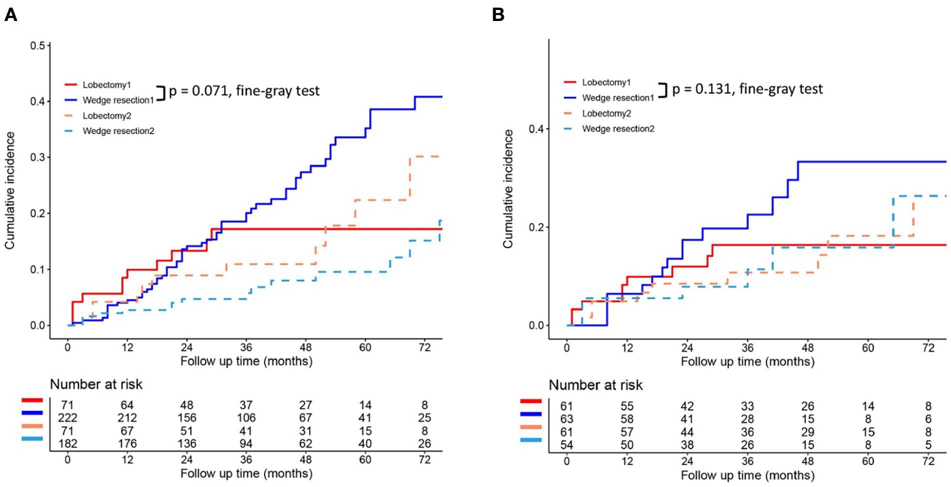

FIGURE 3
Lung cancer-specific mortality after wedge resection versus lobectomy before **(A)** and after **(B)** PSM. These figures show a comparison between the cumulative incidence of lung cancer death and that of other causes in the two surgical procedures (lobectomy and wedge resection). **Note:** "Lobectomy 1" refers to the cumulative incidence curve of such patients who underwent lobectomy and died of lung cancer. "Wedge resection 1" refers to the cumulative incidence curve of such patients who underwent wedge resection and died of lung cancer. "Lobectomy 2" refers to the cumulative incidence curve of such patients who underwent lobectomy and died from other causes. "Wedge resection 2" refers to the cumulative incidence curve of such patients who underwent wedge resection and died from other causes.

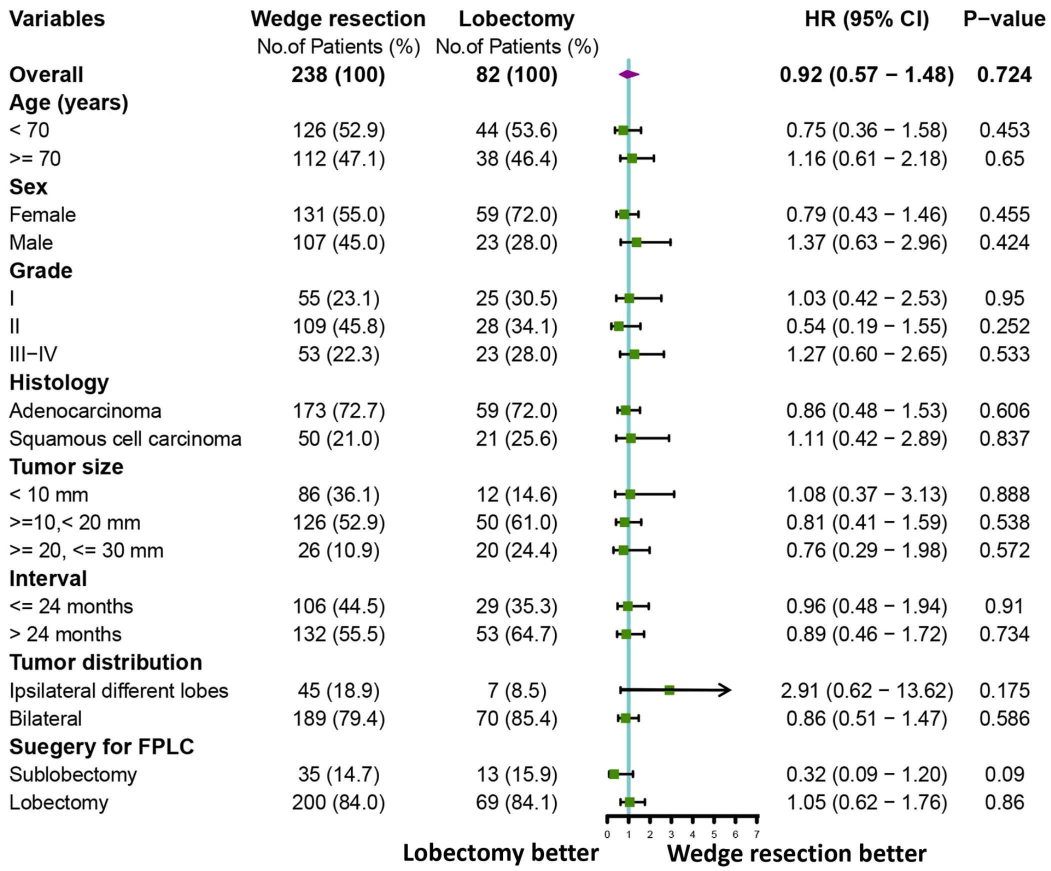

FIGURE 4
A forest plot showing the overall survival comparison between the two operations (lobectomy and wedge resection). Univariable Cox analysis and subgroup analysis were performed.

but also other surgical methods such as segmental resection. To our knowledge, although wedge resection and segmentectomy were classified as sublobectomy, there were significant differences between them. Wedge resection was defined as non-anatomical resection of the lung parenchyma, and was not necessary to determine the histological structure of bronchus and pulmonary vessels, while segmentectomy was the anatomical resection of the lung parenchyma, and required the disconnection of segmental bronchus, segmental vessels, and segmental parenchyma. In view of the different anatomical pathways of wedge resection and segmentectomy, it was necessary to discuss the two surgical methods separately. Therefore, this study emphasized the difference in survival between wedge resection (rather than segmentectomy and/or wedge resection) and lobectomy. This study further confirmed that stage IA SP-NSCLC patients with previous lung cancer-directed surgery demonstrated similar OS with lobectomy and wedge resection.

In clinical practice, the relative location of two primary tumors had an extremely important influence on the final selection of surgical procedure. Generally speaking, when two tumor lesions were in the ipsilateral different lobes, lobectomy for the second lesion tended to lead to pneumonectomy, which was a risk factor affecting the prognosis of patients (4, 16, 20). This study found that when the two lesions were in the ipsilateral different lobes, wedge resection demonstrated equivalent OS to lobectomy. Thus, we believe that in this case, lobectomy for the second lesion may not result in a greater survival benefit than wedge resection. In agreement with our research, Ishigaki and his colleagues (4) suggested that if FPLC and SPLC were on the same side of the lung and FPLC received lobectomy, sublobectomy should be a priority for the SPLC. Additionally, surgical choice regarding the optimal extent of resection for a second primary tumor on the contralateral side is also controversial. Yang et al. (18) reported that a limited resection (sublobectomy) for the contralateral second tumor did not have a negative effect on OS in these patients with stage I bilateral MPLC. This was also confirmed by the findings of this study. Similarly, other previous studies (1, 16, 19, 20) did not demonstrate a significant difference in prognosis

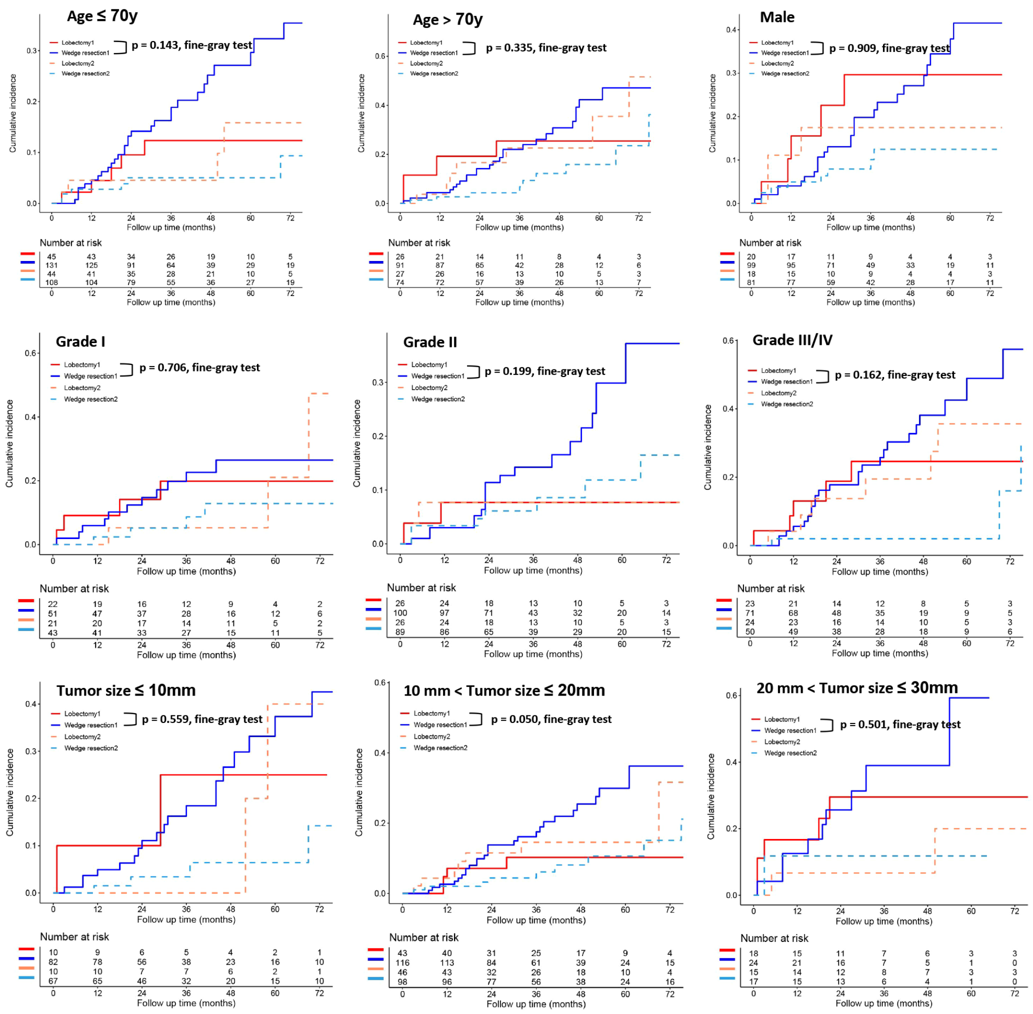

FIGURE 5
The differences in lung cancer-specific mortality between the two operations (lobectomy and wedge resection) based on subgroup analyses of factors with prognostic significance (such as age, sex, grade, and tumor size). These figures show a comparison between the cumulative incidence of lung cancer death and that of other causes in the two surgical procedures (lobectomy and wedge resection). **Note:** "Lobectomy 1" refers to the cumulative incidence curve of such patients who underwent lobectomy and died of lung cancer. "Wedge resection 1" refers to the cumulative incidence curve of such patients who underwent wedge resection and died of lung cancer. "Lobectomy 2" refers to the cumulative incidence curve of such patients who underwent lobectomy and died from other causes. "Wedge resection 2" refers to the cumulative incidence curve of such patients who underwent wedge resection and died from other causes.

with respect to lobectomy versus sublobectomy for the second tumor. The choice of surgery for the second primary tumor is challenging for thoracic surgeons, especially for patients with a history of lobectomy or pneumonectomy. In addition to the maximum preservation of pulmonary functional reserve, maximum tumor resection is also an oncological principle to be followed. An adequate margin (>2 cm or the tumor diameter) is a prerequisite for sublobectomy. In a number of studies (19, 22), sublobectomy has been proved to have similar therapeutic effect to lobectomy for patients with early single primary lung cancer. Therefore, we believe that under strict patient screening criteria, sublobectomy including wedge resection is worthy of choice for thoracic surgeons.

Overall, this study provided evidence that wedge resection produced similar survival rate to lobectomy in stage IA SP-NSCLC patients with previous lung cancer-directed surgery, and wedge resection and lobectomy had similar lung cancer-specific mortality in most cases. A correct understanding of the difference in OS and lung cancer-specific mortality between the two surgical approaches might help clinicians make more reasonable choices.

This study still has the following limitations. First, much of the detailed information (such as imaging findings, pulmonary

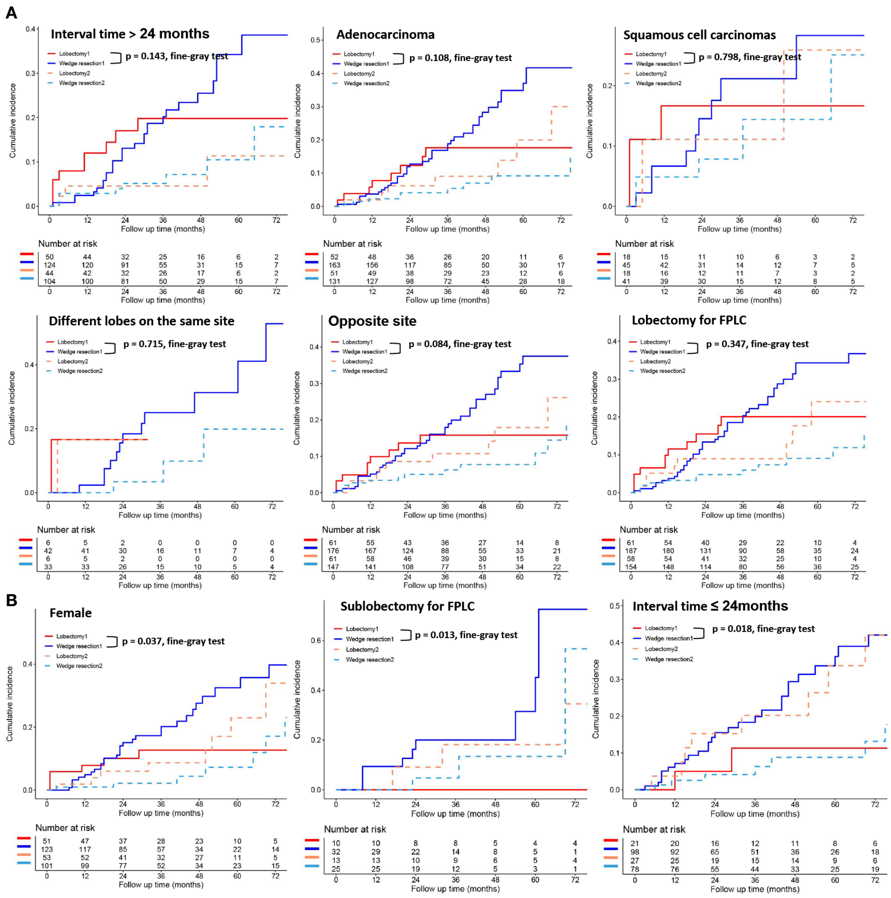

FIGURE 6
The differences in lung cancer-specific mortality between the two operations (lobectomy and wedge resection) based on subgroup analyses of factors with prognostic significance (such as interval time between the two primary lesions, histological types, location of the two primary lesions, the operation method for FPLC and sex). These figures show a comparison between the cumulative incidence of lung cancer death and that of other causes in the two surgical procedures (lobectomy and wedge resection). "Lobectomy 1" refers to the cumulative incidence curve of such patients who underwent lobectomy and died of lung cancer. "Wedge resection 1" refers to the cumulative incidence curve of such patients who underwent wedge resection and died of lung cancer. "Lobectomy 2" refers to the cumulative incidence curve of such patients who underwent lobectomy and died from other causes. "Wedge resection 2" refers to the cumulative incidence curve of such patients who underwent wedge resection and died from other causes.

function index, and related basic diseases), which may be an important reference for clinicians to make treatment decisions, is not available in the SEER database. Second, the number of patients with stage IA SP-NSCLC included in this study was still relatively small, and the postoperative follow-up time was also short. Third, the nature of a retrospective study and the strict screening criteria in this study inevitably resulted in selection bias. Considering the deficiency of retrospective analysis, further prospective analysis is recommended.

In conclusion, wedge resection demonstrated equivalent survival to lobectomy in Stage IA second primary NSCLC patients with lung cancer-directed surgery. Considering the limitations of the present study, relevant prospective studies are still necessary.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The SEER database is a public database with free access to data, so ethics committee approval is not required for this study. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CS designed the study and reviewed relevant literature and drafted the manuscript. CS, ZL, and DL conducted all statistical analyses. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Propensity score-matched comparison of robotic- and video-assisted thoracoscopic surgery, and open lobectomy for non-small cell lung cancer patients aged 75 years or older

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Introduction: Although robot-assisted thoracoscopic surgery (RATS) has been widely applied in treating non-small cell lung cancer (NSCLC), its advantages remain unclear for very old patients. The present study compared the perioperative outcomes and survival profiles among RATS, video-assisted thoracoscopic surgery (VATS), and open lobectomy (OL), aiming to access the superiority of RATS for NSCLC patients aged ≥75 years.

Methods: Pathological IA-IIIB NSCLC patients aged ≥75 years who underwent RATS, VATS, or OL between June 2015 and June 2021 in Shanghai Chest Hospital were included. Propensity score matching (PSM, 1:1:1 RATS versus VATS versus OL) was based on 10 key prognostic factors. The primary endpoints were perioperative outcomes, and the secondary endpoints were disease-free (DFS), overall (OS), and cancer-specific survival (CS).

Results: A total of 504 cases (126 RATS, 200 VATS, and 178 OL) were enrolled, and PSM led to 97 cases in each group. The results showed that RATS led to: 1) the best surgical-related outcomes including the shortest operation duration (p <0.001) and the least blood loss (p <0.001); 2) the fastest postoperative recoveries including the shortest ICU stay (p = 0.004), chest tube drainage duration (p <0.001), and postoperative stay (p <0.001), and the most overall costs (p <0.001); 3) the lowest incidence of postoperative complications (p = 0.002), especially pneumonia (p <0.001). There was no difference in the resection margins, reoperation rates, intraoperative blood transfusion, and volume of chest tube drainage among the three groups. Moreover, RATS assessed more N1 (p = 0.009) and total (p = 0.007) lymph nodes (LNs) than VATS, while the three surgical approaches dissected similar numbers of N1, N2, and total LN stations and led to a comparable incidence of postoperative nodal upstaging. Finally, the three groups possessed comparable DFS, OS, and CS rates. Further subgroup analysis found no difference in DFS or OS among the three groups, and multivariable analysis showed that the surgical approach was not independently correlated with survival profiles.

Conclusion: RATS possessed the superiority in achieving better perioperative outcomes over VATS and OL in very old NSCLC patients, though the three surgical approaches achieved comparable survival outcomes.

KEYWORDS

non-small cell lung cancer, robot-assisted thoracoscopic surgery, video-assisted thoracoscopic surgery, open lobectomy, elderly patients, propensity score-matched study

Introduction

Lung cancer is one of the most prevalent and deadly malignancies worldwide, and non-small cell lung cancer (NSCLC) occupies 80-85% of total lung cancer morbidities (1). Optimal surgical treatment is critical for patients with resectable NSCLC to achieve good long-term outcomes and is becoming increasingly important given the implementation of lung cancer screening approaches has contributed to the earlier diagnosis of the malignancy (2). However, with the average age at diagnosis of approximately 70 years, most NSCLC patients are elderly and are frequently associated with comorbidities and poor cardiopulmonary functions, which have created great challenges for surgical treatments (3). More importantly, NSCLC patients aged ≥75 years who represent up to 40% of total NSCLC cases are associated with less surgical frequencies, more preoperative comorbidities, increased postoperative complications, and worse long-term outcomes compared with those aged 65-74 years (4, 5). Therefore, great attention should be attached to identifying well-tolerated and oncological effective surgical approaches for these very old populations.

Although open lobectomy (OL) is still the standard surgical approach for resectable NSCLC, it is associated with considerable postoperative complications and even surgery-related mortalities, especially in elderly patients (6). Thus, minimally invasive surgeries (MISs) which could reduce postoperative complications and shorten postoperative hospital stay, such as video-assisted thoracoscopic surgery (VATS), have been widely adopted (7). Numerous studies have suggested that VATS achieved better perioperative outcomes and similar long-term survival compared to OL for older NSCLC patients (8–10). Nowadays, robotic-assisted thoracoscopic surgery (RATS), an innovative MIS with high-quality visualization and great maneuverability which allows surgeons to perform complex operations with great convenience and precision, has been increasingly applied in treating NSCLC (11). Currently, a few studies evaluated the safety and effectiveness of RATS in NSCLC patients aged 65 years or older, suggesting that RATS reduced postoperative complications and noncancer-specific mortalities than OL, and assessed increased lymph nodes (LNs) than VATS (3, 12, 13). However, merely a few patients aged ≥75 years were included in these studies, and the advantages of RATS specified for this important group of populations remain unknown.

The present study retrospectively investigated the perioperative outcomes and survival profiles of RATS, VATS, and OL in NSCLC patients aged ≥75 years, aiming to assess the superiority of RATS for very old NSCLC cases. Propensity score-matched (PSM) analysis was applied to mitigate the patient selection bias.

Methods

Study design

This study was a single-center retrospective cohort study focusing on NSCLC patients aged ≥75 years who underwent lobectomy at the Department of Thoracic Surgical Oncology, Shanghai Chest Hospital. The Institutional Review Board of Shanghai Lung Tumor Clinical Medical Center, Shanghai Chest Hospital, Shanghai Jiao Tong University approved this study (No. KS1735). All procedures conducted on human participants were following the Declaration of Helsinki (as revised in 2013).

Patient selection and data collection

We retrospectively identified NSCLC patients aged ≥75 years receiving lobectomy from June 2015 to June 2021. Preoperative exams including pulmonary function testing, electrocardiogram, and echocardiography were conducted to ensure the operation tolerance of patients. Distant metastasis was evaluated by using positron emission tomography/CT (PET/CT), bone scintigraphy, and cranial enhanced magnetic resonance imaging (MRI). Contrast-enhanced chest CT imaging was conventionally used to assess the mediastinal and pulmonary lymph nodal involvement, and PET-CT, endobronchial ultrasound trans-bronchial needle aspiration (EBUS-TBNA), and/or mediastinoscopy were further applied when CT scan indicated a short-axis >1 cm of lymph nodes for suitable patients. For a few patients who could not tolerate or rejected the invasive assessments, CT scan and/or PET-CT were applied for the preoperative lymph nodal evaluation. The inclusion criteria included: aged ≥75 years, underwent RATS, VATS, or OL combining with systemic LNs dissection, and pathologically diagnosed NSCLC. The exclusion criteria included: malignancy other than NSCLC, surgical methods other than lobectomy, neoadjuvant therapy, and preoperative distant metastasis. A total of 504 cases were finally included and divided into the RATS, VATS, and OL groups. Following data were recorded: clinicopathological characteristics including age, gender, smoking status, body mass index (BMI), preoperative comorbidities, pulmonary functions [% of predicted forced expiratory volume in 1 s (FEV1%) and % of predicted diffusing capacity for carbon monoxide (DLCO%)], anatomic location, tumor size, histological type, visceral pleural invasion, and pathological T (pT), N (pN), and TNM (pTNM) stage; perioperative outcomes including resection margins, operation duration, conversion rates, blood loss, intraoperative blood transfusion, ICU stay, duration and volume of chest tube drainage, length of postoperative stay, overall costs, and postoperative complications; LNs assessment including the number of total dissected lymph nodes (LNs) and LN stations, number of harvested N1 and N2 LNs and LN stations and postoperative nodal upstaging; survival profiles including 1-, 3-, and 5-year disease-free (DFS), overall (OS), and cancer-specific survival (CS). Among 504 NSCLC patients identified in our database, 418 cases were staged by the 8th edition of the tumor-node-metastasis (TNM) staging system of the International Association for the Study of Lung Cancer. However, the other 86 enrolled cases were staged according to the 7th TNM version in the database, and therefore these patients were all restaged by the 8th TNM version based on their postoperative paraffin pathology reports before the analyses and propensity score matching.

Surgical procedures

RATS, VATS, and OL were conducted according to the procedures described previously (6, 14, 15). Briefly, patients received general anesthesia with double-lumen tracheal intubation and contralateral single-lung ventilation and underwent radical pulmonary lobectomy combined with systemic pulmonary and mediastinal LNs dissection. RATS was performed using the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). For RATS and VATS, 4 incisions were created without rib-spreading. For OL, patients received a conventional rib-spreading thoracotomy through an incision of about 15 cm.

Postoperative management and follow-up

After surgery, patients were discharged from the hospital 1-2 days after removing drainage tubes unless there were comorbidities requiring intervention. Follow-up assessments included thoracic CT and brain MRI scans and were conducted every 3-6 months after the surgery during the first 2-year period and once a year afterward. For patients who did not come to the outpatient clinic regularly, telephone follow-up was performed every 1 year until death or June 2022. Patients lost to follow-up were evaluated based on the latest electronic medical records.

Statistical analysis

We performed the statistical analysis according to the methods published previously (6, 16–18). Variables were expressed using appropriate descriptive statistics, including frequencies and percentages for categorical variables, and mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Pearson's chi-square tests or Fisher's exact tests with Bonferroni *post-hoc* tests were applied to compare categorical variables. For continuous variables, the normality of distribution and homogeneity of variance was analyzed by Kolmogorov-Smirnov tests, and analysis of variance (ANOVA) was performed if a normal distribution and homogeneity of variance were assumed. If not, the Kruskal-Wallis rank sum tests were performed to compare the three groups, followed by Dunn's multiple comparisons tests to correct for multiple comparisons. Wilcoxon rank sum tests were applied to compare the conversion rates of RATS and VATS. Survival profiles were analyzed by Kaplan-Meier curves log-rank (Mantel-Cox) tests. Factors relevant to DFS and OS were further analyzed using multivariable Cox's regression model analysis. Statistical analysis was conducted using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA), and survival profiles were analyzed using GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA, USA). The p value of less than 0.05 was considered to be statistically significant.

To mitigate potential selection bias, propensity score matching (PSM) was applied to balance baseline confounding features of patients among the three groups using the nearest matching method with a 1:1:1 RATS versus VATS versus OL group ratio. Enrolled patients were matched by the following variables: age, gender, history of smoke, BMI, FEV1%, DLCO%, tumor size, anatomic location, histological type, pT, and pN stage. PSM was conducted using R version 4.1.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinicopathological characteristics of patients

The baseline clinicopathological characteristics of patients were expressed in Table 1. Among the three groups, the OL group had the highest proportion males (OL 64.05% vs RATS 53.97% vs VATS 51.50%, p = 0.039), the lowest FEV1% (OL 85.40 ± 16.52 vs RATS 90.23 ± 18.42 vs VATS 89.63 ± 15.94, p = 0.022) and DLCO% (OL 86.11 ± 19.98 vs RATS 89.14 ± 18.71 vs VATS 93.19 ± 18.70, p <0.001), and the largest tumor size (OL 4.05 ± 2.15 vs RATS 2.58 ± 1.16 vs VATS 2.67 ± 1.29 cm, p <0.001). The three groups also differed in the tumor location (p = 0.034), histology type (p <0.001), pT (p <0.001), pN (p = 0.009), and pTNM (p <0.001) stage. Therefore, PSM was used to balance the baseline characteristics of patients among the three groups. Finally, a total of 291 cases were included. As summarized in Table 2, three groups were well balanced with a similar distribution of all included characteristics following the application of PSM.

Perioperative outcomes

The perioperative outcomes of enrolled patients were shown in Table 3. Patients who underwent RATS were associated with the shortest operation duration (RATS 100.85 ± 29.06 vs VATS 113.75 ± 33.40 vs OL 112.76 ± 22.85 mins, p <0.001) and the least blood loss (p <0.001). RATS also led to the shortest ICU stay (RATS 0[0-1] vs VATS 1[0-1] vs OL 1[0-1] days, p = 0.004), chest tube drainage duration (RATS 4[3-6] vs VATS 5[4-6] vs OL 5[5-7] days, p <0.001) and postoperative stay (RATS 5[4-6] vs VATS 5[4-7] vs OL 6[5-8] days, p <0.001) among three surgical approaches, and had a similar conversion rate compared with VATS (p = 0.184). However, the overall cost in the RATS group was $14838.26 ± 2841.65, which was significantly higher than that in the VATS ($13190.51 ± 2120.18, p <0.001) and OL ($13429.58 ± 2582.36, p <0.001) group. There was no significant difference in terms of the resection margins (p = 0.608), reoperation rates (p = 0.543), intraoperative blood transfusion (p = 0.377), and volume of chest tube drainage (p = 0.061) among the three groups. Moreover, patients in the RATS group had the lowest incidence of postoperative complications (RATS 30.93% vs VATS 41.24% vs OL 55.67%, p = 0.002). More importantly, patients who received RATS were associated with a significantly lower incidence of pneumonia than those who received VATS (p <0.050) or OL (p <0.050). Finally, there was no in-hospital or 30-day mortality in all three groups.

LNs assessment

As expressed in Table 4, OL harvested the highest number of N1 (OL 5.79 ± 3.62 vs RATS 5.10 ± 2.40 vs VATS 4.18 ± 2.78, p <0.001), N2 (OL 7.74 ± 4.29 vs RATS 6.91 ± 4.50 vs VATS 5.63 ± 3.53, p <0.001), and total (OL 13.54 ± 6.05 vs RATS 12.01 ± 5.55 vs VATS 9.81 ± 4.55, p <0.001) LNs. Nevertheless, RATS dissected comparable N1 (p = 0.730), N2 (p = 0.289), and total (p = 0.075) LNs than OL. When comparing the two MISs, RATS assessed a higher number of N1 (p = 0.009) and total (p = 0.007) LNs than VATS, while having no superiority over VATS in assessing N2 LNs (p = 0.056). Finally, three surgical approaches dissected similar numbers of N1 (p = 0.415), N2 (p = 0.298), and total (p = 0.124) LN stations, and also led to a comparable incidence of postoperative nodal upstaging (p = 0.356).

Survival profiles

The median follow-up of the RATS, VATS, and OL groups was 43[7-80], 44[3-80], and 53[1-81] months, respectively. In the RATS group, 1-, 3-, and 5-year DFS rates were 96.78%, 80.00%, and 67.72%, respectively, and 1-, 3-, and 5-year OS rates were 95.81%, 87.19%, and 59.26%, respectively (Figure 1). Besides, patients receiving VATS had the 1-, 3- and 5-year DFS rates of 89.69%, 79.33%, and 61.85%, respectively, and possessed the 1-, 3- and 5-year OS rates of 94.85%, 80.90%, and 55.07%, respectively. Moreover, OL led to the 1-, 3- and 5-year DFS rates of 88.51%, 81.58% and 67.46% respectively, and 1-, 3- and 5- OS rates of 95.88%, 77.61% and 59.87%, respectively. The three groups possessed comparable DFS (p = 0.574) and OS (p = 0.704). Moreover, the three surgical approaches also achieved similar CS rates (p = 0.470, Supplementary Figure S1). Further subgroup analyses also suggested no survival profile difference among the three groups in terms of pTNM or pN stage (Supplementary Figure S2). Furthermore, we found that the surgical type was not independently correlated with DFS [hazard ratio = 1.190, p = 0.478; Table 5) or OS (hazard ratio = 1.162, p = 0.480) through multivariable Cox regression analysis. Nevertheless, the LNs metastasis was independently correlated with shortened DFS (HR = 3.785, p <0.001) and OS (HR = 1.857, p <0.001).

Discussion

The robot-assisted surgical system provides surgeons with wide visibilities through high-definition three-dimensional views, improved dexterity by wide-range motioned mechanical wrists, and better maneuverability by delicate instruments, allowing operators to perform complex operations with great convenience and precision (19, 20). Previous studies have shown that RATS led

TABLE 1 Baseline clinicopathological characteristics of unmatched populations.

Characteristic	RATS (N = 126)	VATS (N = 200)	OL (N = 178)	*p* Value
Age (y), mean ± SD	77.18 ± 2.42	76.93 ± 1.85	77.38 ± 2.31	0.216
Gender, n (%)				0.039
Male	68 (53.97%)	103 (51.50%)	114 (64.05%)	
Female	58 (46.03%)	97 (48.50%)	64 (35.95%)	
Smoking status, n (%)				0.274
Never	59 (46.83%)	92 (46.00%)	71 (39.89%)	
Former	21 (16.67%)	28 (14.00%)	21 (11.79%)	
Active	46 (36.51%)	80 (40.00%)	86 (48.32%)	
BMI (kg/m^2), mean ± SD	23.75 ± 2.95	23.83 ± 3.26	23.51 ± 2.96	0.596
DM, n (%)	19 (15.08%)	34 (17.00%)	26 (14.61%)	0.797
CAD, n (%)	15 (11.90%)	20 (10.00%)	19 (10.67%)	0.863
HP, n (%)	48 (38.10%)	81 (40.50%)	74 (41.57%)	0.828
COPD, n (%)	11 (8.73%)	19 (9.50%)	18 (10.11%)	0.921
FEV1 (% of predicted), mean ± SD	90.23 ± 18.42	89.63 ± 15.94	85.40 ± 16.52	0.022
DLCO (% of predicted), mean ± SD	89.14 ± 18.71	93.19 ± 18.70	86.11 ± 19.98	<0.001
History of malignancy, n (%)	5 (3.97%)	9 (4.50%)	8 (4.49%)	0.969
Tumor location, n (%)				0.034
Right upper lobe	50 (39.68%)	83 (41.50%)	61 (34.27%)	
Right middle lobe	20 (15.87%)	24 (12.00%)	26 (14.61%)	
Right lower lobe	23 (18.25%)	25 (12.50%)	18 (10.11%)	
Left upper lobe	11 (8.73%)	41 (20.50%)	42 (23.60%)	
Left lower lobe	22 (17.46%)	27 (13.50%)	31 (17.42%)	
Histology type, n (%)				<0.001
AIS/MIA	9 (7.14%)	10 (5.00%)	0 (0.00%)	
Adenocarcinoma	90 (71.43%)	147 (73.50%)	91 (51.13%)	
Squamous cell	16 (12.70%)	32 (16.00%)	69 (38.76%)	
Mixed/large cell/others	11 (8.73%)	11 (5.50%)	18 (10.11%)	
Tumor size (cm), mean ± SD	2.58 ± 1.16	2.67 ± 1.29	4.05 ± 2.15	<0.001
Visceral pleural invasion, n (%)	25 (19.84%)	36 (18.00%)	45 (25.28%)	0.207
Pathological T stage, n (%)				<0.001
pTis	3 (2.38%)	1 (0.50%)	0 (0.00%)	
pT1	71 (56.35%)	107 (53.50%)	53 (29.78%)	
pT2	45 (35.71%)	68 (34.00%)	84 (47.19%)	
pT3	6 (4.76%)	18 (9.00%)	25 (14.04%)	
pT4	1 (0.79%)	6 (3.00%)	16 (8.99%)	
Pathological N stage, n (%)				0.009
pN0	106 (84.13%)	160 (80.00%)	121 (67.98%)	
pN1	14 (11.11%)	23 (11.50%)	33 (18.54%)	
pN2	6 (4.76%)	17 (8.50%)	24 (13.48%)	
Pathological TNM stage, n (%)				<0.001
0	3 (2.38%)	1 (0.50%)	0 (0.00%)	
IA	67 (53.18%)	96 (43.00%)	40 (22.47%)	
IB	26 (20.63%)	36 (18.00%)	39 (21.91%)	
IIA	6 (4.76%)	12 (6.00%)	15 (8.43%)	
IIB	15 (11.90%)	29 (14.50%)	43 (24.16%)	
IIIA	9 (7.14%)	22 (11.00%)	34 (19.10%)	
IIIB	0 (0.00%)	4 (2.00%)	7 (3.93%)	

RATS, robotic-assisted thoracoscopic surgery; VATS, video-assisted thoracoscopic surgery; OL, open lobectomy; SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; CAD, coronary artery disease; HP, hypertension; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; DLCO, diffusing capacity for carbon monoxide; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.

to better perioperative outcomes than OL and harvested more lymph nodes than VATS, and was also associated with the best cost-effective among the three surgical approaches (3, 21–23). Nowadays, the continuing aged population and increased prevalence of NSCLC have contributed to the rapid growth in the number of older people diagnosed with NSCLC (24). Given the increased incidence of preoperative comorbidities and worsening cardiopulmonary functions when individuals grow older, very old patients more

TABLE 2 Baseline clinicopathological characteristics of matched populations.

	RATS (N = 97)	VATS (N = 97)	OL (N = 97)	*p* Value
Age (y), mean ± SD	77.39 ± 2.63	77.12 ± 1.96	77.58 ± 2.51	0.555
Gender, n (%)				0.423
Male	60 (61.86%)	61 (62.89%)	68 (70.10%)	
Female	37 (38.14%)	36 (37.11%)	29 (29.90%)	
Smoking status, n (%)				0.951
Never	42 (43.30%)	44 (45.36%)	39 (40.21%)	
Former	17 (17.53%)	16 (16.49%)	16 (16.49%)	
Active	38 (39.18%)	37 (38.14%)	42 (42.30%)	
BMI (kg/m^2), mean ± SD	23.92 ± 3.04	23.91 ± 3.36	23.66 ± 3.05	0.892
DM, n (%)	15 (15.46%)	13 (13.40%)	12 (12.37%)	0.816
CAD, n (%)	10 (10.31%)	12 (12.37%)	12 (12.37%)	0.875
HP, n (%)	38 (39.18%)	40 (41.23%)	37 (38.14%)	0.904
COPD, n (%)	8 (8.25%)	7 (7.22%)	7 (7.22%)	0.952
FEV1 (% of predicted), mean ± SD	88.85 ± 18.69	89.48 ± 14.77	88.17 ± 17.36	0.876
DLCO (% of predicted), mean ± SD	88.94 ± 18.32	89.81 ± 15.47	88.68 ± 17.28	0.803
History of malignancy, n (%)	2 (2.06%)	3 (3.09%)	3 (3.09%)	1.000
Tumor location, n (%)				0.959
Right upper lobe	36 (37.11%)	39 (40.21%)	37 (38.14%)	
Right middle lobe	16 (16.49%)	12 (12.37%)	14 (14.43%)	
Right lower lobe	15 (15.46%)	13 (13.40%)	12 (12.37%)	
Left upper lobe	10 (10.31%)	14 (14.43%)	16 (16.49%)	
Left lower lobe	20 (20.62%)	19 (19.59%)	18 (18.56%)	
Histology type, n (%)				0.840
TIS/MIA	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Adenocarcinoma	72 (74.23%)	71 (73.20%)	67 (69.07%)	
Squamous cell	16 (16.49%)	19 (19.59%)	19 (19.59%)	
Mixed/large cell/others	9 (9.28%)	7 (7.22%)	11 (11.34%)	
Tumor size (cm), mean ± SD	2.85 ± 1.15	2.75 ± 1.35	2.90 ± 1.26	0.693
Visceral pleural invasion, n (%)	21 (21.65%)	20 (20.62%)	26 (26.80%)	0.548
Pathological T stage, n (%)				0.981
pTis	0 (0.00%)	0 (0.00%)	0 (0.00%)	
pT1	49 (50.52%)	47 (48.45%)	47 (48.45%)	
pT2	41 (42.27%)	40 (41.24%)	40 (41.24%)	
pT3	6 (6.19%)	8 (8.25%)	9 (9.28%)	
pT4	1 (1.03%)	2 (2.06%)	1 (1.03%)	
Pathological N stage, n (%)				0.228
pN0	79 (81.44%)	76 (78.35%)	66 (68.04%)	
pN1	13 (13.40%)	13 (13.40%)	21 (21.65%)	
pN2	5 (5.15%)	8 (8.25%)	10 (10.31%)	
Pathological TNM stage, n (%)				0.707
0	0 (0.00%)	0 (0.00%)	0 (0.00%)	
IA	46 (47.42%)	41 (42.27%)	36 (37.11%)	
IB	22 (22.68%)	21 (21.65%)	19 (19.59%)	
IIA	6 (6.19%)	6 (6.19%)	4 (4.12%)	
IIB	14 (14.43%)	18 (18.56%)	26 (26.80%)	
IIIA	9 (9.28%)	10 (10.31%)	11 (11.34%)	
IIIB	0 (0.00%)	1 (1.03%)	1 (1.03%)	

RATS, robotic-assisted thoracoscopic surgery; VATS, video-assisted thoracoscopic surgery; OL, open lobectomy; SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; CAD, coronary artery disease; HP, hypertension; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; DLCO, diffusing capacity for carbon monoxide; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.

frequently experience postoperative complications, slow recoveries, and poor outcomes than younger individuals, which has promoted critical challenges to surgical resections (15, 25). Although the feasibility and oncological efficacy of RATS in younger NSCLC patients have been widely investigated and well established, the research on RATS for very old NSCLC patients is still limited. Our study compared the perioperative outcomes and survival profiles of RATS, VATS, and OL for NSCLC patients aged 75 years or older,

TABLE 3 Perioperative outcomes of matched populations.

Characteristic	RATS (N = 97)	VATS (N = 97)	OL (N = 97)	*p* Value	*RATS vs VATS*[b]	*RATS vs OL*[b]	*VATS vs OL*[b]
Resection margins[a], n (%)				0.608	>0.050	>0.050	>0.050
R0	89 (91.75%)	88 (90.72%)	84 (86.60%)				
R1	8 (8.25%)	9 (9.28%)	12 (12.37%)				
R2	0 (0.00%)	0 (0.00%)	1 (1.03%)				
Reoperation, n (%)	1 (1.03%)	3 (3.09%)	4 (4.12%)	0.543	>0.050	>0.050	>0.050
Operation duration (min), mean ± SD	100.85 ± 29.06	113.75 ± 33.40	112.76 ± 22.85	<0.001	0.009	<0.001	1.000
Blood loss (mL), n (%)				<0.001	<0.050	<0.050	<0.050
<100	72 (74.23%)	54 (55.67%)	35 (36.08%)				
≥100	25 (25.77%)	43 (44.33%)	62 (63.92%)				
Intraoperative blood transfusion, n (%)	0 (0.00%)	2 (2.06%)	3 (3.09%)	0.377	>0.050	>0.050	>0.050
Conversion to thoracotomy, n (%)	1 (1.03%)	4 (4.12%)	–	0.184	–	–	–
ICU stay (days), median [IQR]	0[0-1]	1[0-1]	1[0-1]	0.004	1.000	0.005	0.036
Chest tube drainage, median [IQR]							
Duration (days)	4[3-6]	5[4-6]	5[5-7]	<0.001	0.106	<0.001	0.095
Volume (mL)	800[580-1020]	820[650-1100]	800[650-1130]	0.061	0.464	0.052	0.459
Postoperative stay (days), median [IQR]	5[4-6]	5[4-7]	6[5-8]	<0.001	0.829	<0.001	0.002
Overall costs (USD$), mean ± SD	14838.26 ± 2841.65	13190.51 ± 2120.18	13429.58 ± 2582.36	<0.001	<0.001	<0.001	1.000
Postoperative complications, n (%)	30 (30.93%)	40 (41.24%)	54 (55.67%)	0.002	>0.050	<0.050	>0.050
Pneumonia requiring antibiotics	7 (7.22%)	21 (21.65%)	34 (35.05%)	<0.001	<0.050	<0.050	>0.050
Acute respiratory distress syndrome	2 (2.06%)	3 (3.09%)	2 (2.06%)	1.000	>0.050	>0.050	>0.050
Pulmonary embolism	0 (0.00%)	0 (0.00%)	2 (2.06%)	0.331	>0.050	>0.050	>0.050
Prolonged air leak >5 days	18 (18.56%)	17 (17.53%)	25 (25.77%)	0.302	>0.050	>0.050	>0.050
Subcutaneous emphysema	12 (12.37%)	10 (10.31%)	13 (13.40%)	0.797	>0.050	>0.050	>0.050
Bronchopleural fistula	0 (0.00%)	2 (2.06%)	2 (2.06%)	0.551	>0.050	>0.050	>0.050
Hemorrhage requiring intervention	0 (0.00%)	3 (3.09%)	3 (3.09%)	0.253	>0.050	>0.050	>0.050
Chylothorax	2 (2.06%)	2 (2.06%)	2 (2.06%)	1.000	>0.050	>0.050	>0.050
Pyothorax	0 (0.00%)	2 (2.06%)	3 (3.09%)	0.377	>0.050	>0.050	>0.050
Chest tube reinsertion	1 (1.03%)	3 (3.09%)	4 (4.12%)	0.543	>0.050	>0.050	>0.050
Atrial fibrillation	2 (2.06%)	2 (2.06%)	3 (3.09%)	1.000	>0.050	>0.050	>0.050
Recurrent laryngeal nerve injury	0 (0.00%)	1 (1.03%)	1 (1.03%)	1.000	>0.050	>0.050	>0.050
Wound infection	1 (1.03%)	2 (2.06%)	4 (4.12%)	0.512	>0.050	>0.050	>0.050
In-hospital mortality	0 (0.00%)	0 (0.00%)	0 (0.00%)	–	–	–	–
30 d mortality	0 (0.00%)	0 (0.00%)	0 (0.00%)	–	–	–	–
Readmission	1 (1.03%)	2 (2.06%)	4 (4.12%)	0.512	>0.050	>0.050	>0.050

[a]Resection margins: R0, no residual tumor; R1, residual microscopic tumor and/or positive upper paratracheal (#2) LN; R2, residual macroscopic tumor.
[b]adjusted p value of multiple comparisons between every two groups. RATS, robotic-assisted thoracoscopic surgery; VATS, video-assisted thoracoscopic surgery; OL, open lobectomy; SD, standard deviation; IQR, interquartile range.

suggesting that RATS led to the best surgical-related outcomes, the fastest postoperative recoveries, and the least postoperative complications, especially postoperative pneumonia, among the three surgical approaches, and also assessed more lymph nodes than VATS. Taken together, our results showed for the first time that RATS possesses the superiority in achieving better perioperative outcomes over VATS and OL in very old NSCLC patients.

The most interesting finding of our study was that RATS led to the lowest incidence of postoperative pneumonia, a prevalent postoperative complication that may be a marker of increased long-term mortality in NSCLC patients undergoing surgery, among the three surgical approaches in NSCLC patients aged ≥75 years (26). Such superiority might be partly attributed to the high-definition visualization and improved dexterity and maneuverability provided by the robotic-assisted surgical

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TABLE 4 LNs assessment of matched populations.

Characteristic	RATS (N = 97)	VATS (N = 97)	OL (N = 97)	*p* Value	*RATS vs VATS*[a]	*RATS vs OL*[a]	*VATS vs OL*[a]
Number of N1 LNs, mean ± SD	5.10 ± 2.40	4.18 ± 2.78	5.79 ± 3.62	<0.001	0.009	0.730	<0.001
Number of N1 LN stations, mean ± SD	2.38 ± 0.86	2.26 ± 0.82	2.40 ± 0.86	0.415	1.000	1.000	0.599
Number of N2 LNs, mean ± SD	6.91 ± 4.50	5.63 ± 3.53	7.74 ± 4.29	<0.001	0.056	0.289	<0.001
Number of N2 LN stations, mean ± SD	3.13 ± 1.34	3.14 ± 1.26	3.35 ± 1.24	0.298	1.000	0.427	0.718
Total number of LNs, mean ± SD	12.01 ± 5.55	9.81 ± 4.55	13.54 ± 6.05	<0.001	0.007	0.075	<0.001
Total number of LN stations, mean ± SD	5.52 ± 1.69	5.39 ± 1.57	5.72 ± 1.77	0.124	1.000	0.347	0.167
Nodal upstaging, n (%)	9 (9.28%)	10 (10.31%)	15 (15.46%)	0.356	>0.050	>0.050	>0.050
cN0-pN1	5 (5.15%)	6 (6.19%)	7 (7.22%)	0.837	>0.050	>0.050	>0.050
cN0-pN2	3 (3.09%)	3 (3.09%)	6 (6.19%)	0.609	>0.050	>0.050	>0.050
cN1-pN2	1 (1.03%)	1 (1.03%)	2 (2.06%)	1.000	>0.050	>0.050	>0.050

[a]Adjusted p value of multiple comparisons between every two groups. LNs, lymph nodes; RATS, robotic-assisted thoracoscopic surgery; VATS, video-assisted thoracoscopic surgery; OL, open lobectomy; SD, standard deviation.

system which allowed surgeons to perform surgeries more precisely to avoid causing unnecessary damage (19, 20). Besides, RATS also led to shorter surgical duration and fewer blood loss than VATS, which may mitigate the impact of mechanical ventilation and anesthesia and altered internal environments for patients. More importantly, to the best of our knowledge, it was the first time to find that RATS reduced postoperative pneumonia in old NSCLC patients compared with VATS, which might be attributed to the high incidence of this postoperative complication in the very old patients we enrolled which makes this superiority of RATS more apparent.

When considering surgical-related outcomes, RATS reduced intraoperative blood loss compared with VATS and OL. However, VATS had a similar conversion rate to thoracotomy compared with RATS, and all three groups achieved excellent bleeding control with low incidences of intraoperative blood transfusion. For these reasons, all three surgical approaches appear to be safe and effective with regard to bleeding control for elderly NSCLC patients. Moreover, according to previous studies reported by other surgical teams, the operative time is prevalently longer in robot-assisted surgery than that in VATS or OL due to the additional docking time and the impact of a learning curve (27–29). However, our study indicated that RATS was associated with shortened surgical duration than VATS and OL, which might be attributed to the well-organized surgical team and the experienced operators from a high-volume medical center.

The dissection of LNs is of key importance in the surgical resection of NSCLC. Similar to the results reported by previous studies that enrolled younger patients, the total number of LNs harvested by RATS was 12.01 ± 5.55 in our study, suggesting that LNs dissection using robot-assisted surgical systems may not be significantly affected by growth in ages (11, 15, 30, 31). Nowadays, numerous studies have compared RATS with VATS and/or OL in terms of LNs dissection, but have drawn conflicting conclusions. Jin *et al.* and Haruki *et al.* independently

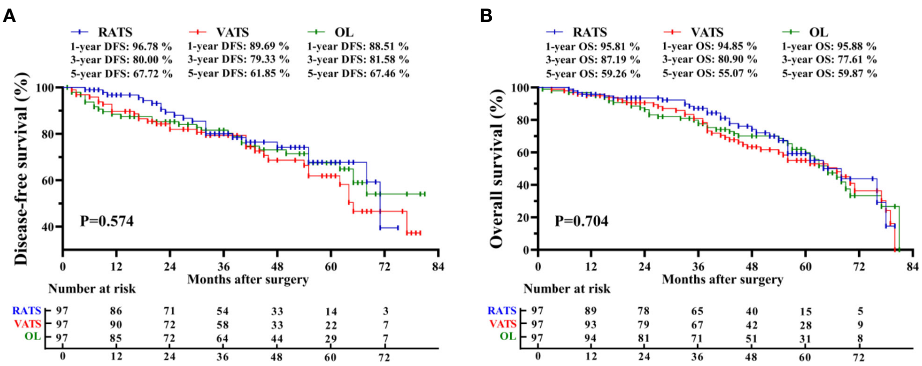

FIGURE 1
Kaplan-Meier survival curve of matched patients. Comparison of disease-free survival **(A)** and overall survival **(B)** among the RATS, VATS, and OL groups. *RATS, robotic-assisted thoracoscopic surgery; VATS, video-assisted thoracoscopic surgery; OL, open lobectomy.*

TABLE 5 Cox's proportional hazards regression model analysis for survival profiles of matched populations.

Predictors of survival	DFS			OS		
	p Value	HR	95% CI	*p* Value	HR	95% CI
Surgical type (RATS vs others)	0.478	1.190	0.736, 1.923	0.480	1.162	0.766, 1.764
Gender (male vs female)	0.462	0.836	0.518, 1.348	0.885	0.971	0.648, 1.453
Smoking history (yes vs no)	0.821	1.051	0.684, 1.613	0.631	1.093	0.759, 1.535
Histologic type (ADC vs SCC)	0.442	1.192	0.762, 1.864	0.675	1.086	0.738, 1.600
Tumor size (≤3 vs >3 cm)	0.888	0.995	0.928, 1.067	0.626	0.976	0.885, 1.077
LNs metastasis (yes vs no)	<0.001	3.785	2.727, 5.253	<0.001	1.857	1.348, 2.559

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; RATS, robotic-assisted thoracoscopic surgery; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

reported that RATS harvested more N1 and total LNs than VATS, while other studies indicated that RATS was comparable to VATS with regard to LNs dissection (11, 30). Moreover, by comparing RATS, VATS, and OL, Toker et al. found that RATS dissected more N1 and total LNs than VATS and OL (21). However, Kneuertz et al. reported that RATS, VATS, and OL dissected a similar number of LNs (32). Our study showed that LNs assessed by RATS were comparable to that dissected by OL and more than that harvested by VATS, suggesting that RATS was an effective surgical technic and even superior to VATS regarding LNs assessment in very old NSCLC patients. Although OL harvested the most LNs, the rate of nodal upstaging of the three groups was comparable. This might be explained by most of the enrolled cases had the early-stage disease without nodal involvement and three surgical approaches assessed a similar number of LN stations. The relevance between LNs assessment and long-term survival remains controversial. Dezube et al. and Hennon et al. independently reported that additional LNs dissection conferred no survival benefit for lobectomy, while other studies suggested that increased LNs assessment was associated with better long-term outcomes (33–36). In our study, increased LNs sampling was not correlated with prolonged DFS and OS in very old NSCLC patients undergoing lobectomy, and further follow-up is still necessary to confirm this result.

Although various kinds of preoperative LNs assessment approaches have been prompted, there is still a 3%-15% of rate occult N2 disease identified at the pathological stage (11, 32, 37–40). However, the occult N2 disease could lead to a poor prognosis and therefore influence the survival profiles in our study. In our hospital, mediastinal LNs were systemically assessed by using thoracic CT and PET-CT, and invasive approaches including EBUS-TBNA and mediastinoscopy were further applied when necessary to minimize the incidence of occult N2 disease. Moreover, in our study, the incidence of occult N2 disease in RATS, VATS, and OL groups was 4.12%, 4.12%, and 8.25%, respectively, which was consistent with many previous studies (11, 32, 37–40). Our results also showed that the three groups had comparable incidences of postoperative lymph nodal upstaging. Therefore, the occult N2 disease may not change our survival outcomes.

When considering the oncological effectiveness, our study showed that RATS achieved comparable DFS, OS, and CS as VATS and OL, and further subgroup analysis also indicated similar survival profiles in terms of pTNM and pN stages among three surgical approaches, suggesting that RATS might be an effective surgical method for both early- and advanced-stage resectable NSCLC patients aged ≥75 years. However, our recruitment ended in June 2021 and only a few patients had long-term follow-up data. In our hospital, RATS was performed for the first time in 2009 by our surgical team (which was also the first RAT in China mainland) and widely applied since 2015. The poor surgical tolerances and high surgical risks of very old NSCLC patients have created great challenges for our surgeons, requiring the operators to be experienced and highly skilled, therefore many enrolled patients underwent RATS in recent years. In order to avoid potential bias due to the surgical dates, we included patients who received RATS, VATS, or OL in a similar period. Consequently, long-term follow-up data were available for a few patients. Nevertheless, the median follow-up of the RATS, VATS, and OL groups was 43[7-80], 44[3-80], and 53[1-81] months, respectively, and follow-up of the particular patient was less than 1 year due to his/her death. Therefore, 3-year survival data were available for most patients, and our results suggested that the three groups possessed comparable 1- and 3-year DFS, OS, and CS. More importantly, the primary endpoints of our study were perioperative outcomes and the results showed that RATS possessed the superiority in achieving better perioperative outcomes over VATS and OL in very old NSCLC patients. The DFS, OS, and CS were the secondary endpoints and we are continuing the follow-up and also enrolling more eligible cases currently, aiming to further compare the long-term survival outcomes of RATS, VATS, and OL based on a larger cohort and the longer follow-up data, and the results will be reported afterward. We also noticed that for pathological I stage NSCLC, all three surgical approaches achieved lower 5-year OS than DFS. This was attributed to the fact that a high proportion of elderly patients with early-stage NSCLC died from non-tumor-specific factors, such as cardiovascular diseases, cerebrovascular accidents, and dysfunction of critical organs. Nevertheless, the relapse and metastasis of malignancy was still the major reason contributing to mortalities of II-III stage NSCLC patients in our cohorts.

There are still some limitations of this study. Despite PSM being used, enrolled patients were not randomized before the surgery and the retrospective nature of this study might lead to undiscovered selection bias. Thus, further randomized, controlled trials are necessary to validate the results of our study. Moreover, this study was performed in a single high-volume center, which largely limited the representativeness of participants, thus further multi-center researches are essential to confirm whether the present study could represent real-world practices. Finally, for patients with relapsed disease, the recurrence patterns (locally or distant) and the relevance to surgical approaches were not described, and further studies are needed.

Conclusion

In summary, we retrospectively compared the perioperative outcomes and survival profiles of RATS, VATS, and OL in treating NSCLC patients aged 75 years or older. The results suggested that RATS possessed the superiority in achieving better perioperative outcomes over VATS and OL in very old NSCLC patients, though the three surgical approaches achieved comparable survival outcomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Shanghai Chest Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JH and QL contributed to the study design. HP, ZG, and YT were responsible for interpreting the results. LJ, HZ, and JN contributed to the statistical analysis. JH and QL wrote the manuscript. All authors contributed to data collection and analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1009298/full#supplementary-material

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Wedge resection plus adequate lymph nodes resection is comparable to lobectomy for small-sized non-small cell lung cancer

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Objectives: The study investigated whether wedge resection plus adequate lymph nodes resection conferred comparable survival to lobectomy for node-negative non-small cell lung cancer (NSCLC) ≤2 cm.

Methods: The Surveillance, Epidemiology, and End Results database was used to identify patients diagnosed with node-negative NSCLC ≤2 cm and underwent wedge resection or lobectomy (2004-2015). Patients were stratified by the procedure (wedge resection, lobectomy) and the size of NSCLC (≤1 cm, 1-2 cm). We assessed survival between patients undergoing wedge resection and lobectomy. The optimal number of lymph nodes resected which made those two procedures comparable was explored by using Kaplan-Meier analysis and Cox regression analysis. Propensity score matching was performed to minimize the effect of confounding factors.

Results: 7893 patients with lobectomy and 2536 patients with wedge resection were identified. Wedge resection was associated with worse survival either in the ≤1 cm or 1-2 cm NSCLC before and after matching. For lesions 1-2 cm and receiving lobectomy, more lymph nodes resected conferred statistically significant increase on survival and six nodes were optimal. For lesions ≤1 cm and receiving lobectomy, lymph nodes resection had no impact on survival. Wedge resection and lobectomy were comparable when one or more nodes for lesions ≤1 cm and six or more nodes for lesions 1-2 cm were resected.

Conclusions: Wedge resection was inferior to lobectomy for NSCLC ≤1 cm and 1-2 cm. Wedge resection plus adequate lymph nodes resection was comparable to lobectomy.

KEYWORDS

lobectomy, wedge resection, non-small cell lung cancer, lymph nodes resection, overall surivival

Highlights:

1. Wedge resection was inferior to lobectomy for node-negative NSCLC ≤1 cm or 2 cm in the population.
2. Wedge resection plus one or more nodes resected for NSCLC ≤1 cm was comparable to lobectomy.
3. Wedge resection plus six or more nodes resected for NSCLC 1-2 cm was comparable to lobectomy.

Introduction

Accounting for more than 80% of lung cancer, non-small cell lung cancer (NSCLC) is becoming the most cancer-related deaths around the world (1). Owing to the spread of screening by computed tomography (CT), more and more small-sized NSCLCs are detected and diagnosed. For those early-staged lung cancer, surgery is the standard treatment of care and confers a favorable prognosis. Besides lobectomy, sublobar resection had been an important choice because of its minimal invasiveness and preservation of more lung function. Prior studies have compared the oncological outcomes of lobectomy and sublobar resection and exhibited contradictory results. For the population, sublobar resection seems to carry less survival benefit versus lobectomy (2, 3). However, when not selected as compromised procedure or for screen-detected lung cancer, sublobar resection is comparable to lobectomy (4).

Comprising approximately 80% of sublobar resection, wedge resection is more frequently performed compared to segmentectomy (5). Sampling lymph nodes in remaining pulmonary lobes is difficult and thus it is challenging to achieve complete lymph nodes resection for wedge resection. The necessity of lymph nodes resection and the exact number of examined nodes are questionable in consideration of its clinical benefit. Our previous study demonstrated that the number of resected lymph nodes during wedge resection significantly impact the overall survival among patients with node-negative NSCLC ≤2 cm (5). Herein, we compared the survival among patients with NSCLC ≤2 cm and receiving wedge resection or lobectomy after propensity score matching. Furthermore, we explored whether wedge resection plus adequate lymph node resection conferred comparable long-term outcomes to lobectomy in the population.

Abbreviations: CT, computed tomography; HR, hazard ratio; LOESS, locally estimated scatterplot smoothing; NSCLC, non-small cell lung cancer; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results.

Methods

Study population

The retrospective study was conducted by using the Surveillance, Epidemiology, and End Results (SEER) database. The characteristics of the SEER database have been well described (6, 7). Briefly, the SEER contains cases from more than 20 geographically different registries and covers approximately 48% of the population of the United States. We selected eligible patients by using the following inclusion criteria (1): pathologically confirmed NSCLC, (2) diagnosed between 2004 and 2015, (3) tumor size ≤2 cm (T1a or T1b), (4) lobectomy (code 30, 33) or wedge resection (code 21) performed, and (5) NSCLC as the only primary tumor until the end of follow-up period. We excluded patients with (1) unknown number of examined lymph nodes, (2) nodal disease, (3) distant metastasis (M1a or M1b), (4) follow-up time less than 2 months.

Data collection

Demographic variables (age, sex, race, and marital status), tumor characteristics (size, histologic type, site), and treatment information (surgical procedure and number of examined lymph nodes) were collected. Histologic types of NSCLC were categorized as adenocarcinoma (codes 8140, 8230, 8240, 8250, 251, 8252, 8253, 8254, 8255, 8260, 8310, 8333, 8470, 8480, 8481, 8490, 8550), squamous carcinoma (codes 8052, 8070, 8071, 8072, 8073, 8083, 8084) and other lung cancer (codes 8012, 8013, 8014, 8031, 8560, 8046). Survival time was retrieved from the SEER record. The database offered details on whether each patient survived or died due to lung cancer or other causes at the end of the last follow-up. Overall survival (OS) and cause-specific survival (CSS) were the primary end point for the study.

Statistical analysis

To minimize the effect of potential confounding factors, propensity score matching (method ="nearest", ratio=1:1) was performed for variables including sex, age, race, marital status, histologic type, and tumor site. To evaluate the effect of lymph node resection on survival in NSCLC undergoing lobectomy, we compared survival of cases with different number of resected lymph nodes with those without lymph nodes resection. The cutoff number of resected lymph nodes which conferred wedge resection non-inferior survival than lobectomy was determined as following: cases with more than a certain number of lymph nodes resected (starting from 0) were selected and after performing propensity score matching, survival was assessed between wedge resection group and lobectomy group until the difference did not reach statistical significance. The number of removed nodes was not included in the matching, as the previous study did (8).

Baseline characteristics were compared using independent sample *t* test for continuous variables and Pearson χ^2 test or Fisher's exact test for categorical variables. Cases were stratified by tumor size and generated two subgroups: 0-1 cm and 1-2 cm. Locally estimated scatterplot smoothing (LOESS) was performed to generate a smooth curve to describe the association between the number of resected lymph nodes and corresponding hazard ratio (HR). Kaplan-Meier method was used to estimate the association between the number of lymph nodes examined and survival by log-rank test. Cox proportional hazards modeling was performed to determine the potential effect of the number of lymph nodes examined on survival, with adjustment for sex, age, race, marital status, histologic type, and tumor site. All analyses were performed with R Statistical Software (version 4.1.1; Vienna, Austria). We considered two-sided p less than 0.05 as statistical significance. Cases were filtered and their corresponding information was obtained by using SEER*Stat version 8.3.9 software.

Results

Population characteristics

Totally, 10429 patients were extracted, including 7893 patients undergoing lobectomy and 2536 undergoing wedge resection (Table 1). The majority of patients were female (59.4%), >65 years old (61.1%), white race (85.2%), married (55.7%) and pathological confirmed adenocarcinoma (72.3%). There were differences in age, race, marital status, histologic type, grade and tumor site between lobectomy group and wedge resection group. Tumors undergoing wedge resection have smaller size and less lymph nodes resected. The proportional distributions of resected nodes in both groups are showed in Figure 1. Nearly 47.3% of tumors undergoing wedge resection had no nodes resected, while 3.5% of those undergoing lobectomy did. The ratio of cases with more than 10 nodes resected in wedge resection was much lower than that in lobectomy (6.1% *vs.* 29.6%).

Survival of lobectomy and wedge resection

Compared to wedge resection, the superiority of lobectomy for CSS and OS was determined in both tumors ≤1 cm and 1-2 cm in diameter (Supplemental Figure 1). After propensity score matching, clinicopathological features of both groups were well balanced (Supplemental Table 1). Multivariable Cox regression analysis revealed that wedge resection conferred worse OS than lobectomy regarding of the tumor size (0-1 cm: HR, 1.41, 95% CI: 1.18-1.68; 1-2 cm: HR, 1.72; 95% CI: 1.56-1.89). The results were similar when CSS were analyzed (Figure 2).

Survival and number of resected nodes in lobectomy

We compared OS in patients undergoing lobectomy with or without lymph nodes resection (Figure 3). For lesions ≤1 cm, patients derived no significant survival benefit from nodes resection (*log-rank* p=0.067). For lesions 1-2 cm, there was a remarkable increase of OS in patients with nodes resection (*log-rank* p<0.001). According to the number of resected nodes, we subclassified patients to four subgroups as our prior study did (5): 0 nodes, 1-3 nodes, 4-9 nodes and >9 nodes. On multivariable Cox regression analysis, a trend towards more favorable OS and CSS was observed in those who received more lymph nodes resected (Table 2 and Supplemental Table 2). When comparing the OS of cases with a specific number of nodes resected to those without any lymph nodes resected, the survival benefit elevated along with the increase of examined nodes number and peaked when 6 nodes resected as shown by the LOESS curve (Figure 3D and Supplemental Table 3). More than 6 nodes resected seemed not to generate additional survival benefit.

TABLE 1 Baseline characteristics of patients with NSCLC 2 cm or less undergoing wedge resection or lobectomy (n=10429).

Characteristic	Overall (n = 10429)	Lobectomy (n = 7893, %)	Wedge resection (n = 2536,%)	*p* value
Sex, female	6195 (59.4)	4705 (59.6)	1490 (58.8)	0.459
Age, >65 years	6375 (61.1)	4608 (58.4)	1767 (69.7)	<0.001
Race, nonwhite	1545 (14.8)	1212 (15.4)	333 (13.1)	0.007
Marriage				0.032
Married	5808 (55.7)	4452 (56.4)	1356 (53.5)	
Unmarried	4216 (40.4)	3143 (39.8)	1073 (42.3)	
Unknown	405 (3.9)	298 (3.8)	107 (4.2)	
Histologic type				<0.001
Adenocarcinoma	7541 (72.3)	5839 (74.0)	1702 (67.1)	
Squamous carcinoma	2178 (20.9)	1548 (19.6)	630 (24.8)	
Others	710 (6.8)	506 (6.4)	204 (8.1)	
Grade				<0.001
Well differentiated	2500 (24.0)	1870 (23.7)	630 (24.8)	
Moderately differentiated	4614 (44.2)	3590 (45.5)	1024 (40.4)	
Poorly differentiated	2460 (23.6)	1820 (23.1)	640 (25.2)	
Undifferentiated	109 (1.0)	75 (1.0)	34 (1.3)	
Unknown	746 (7.2)	538 (6.8)	208 (8.2)	
Site				0.001
Upper lobe	6573 (63.0)	4935 (62.5)	1638 (64.6)	
Middle lobe	599 (5.8)	494 (6.3)	105 (4.1)	
Lower lobe	3144 (30.1)	2380 (30.2)	764 (30.1)	
Others	113 (1.1)	84 (1.1)	29 (1.1)	
Tumor size, mean ± SD, cm	1.47 ± 0.39	1.51 ± 0.39	1.38 ± 0.42	<0.001
Lymph nodes examined, median (IQR)	6 (2-10)	7 (4-12)	1 (0-3)	<0.001
Follow-up time, median (range), months	65 (2-179)	69 (2-179)	57 (2-179)	<0.001

IQR, interquartile range; NSCLC, non-small cell lung cancer.

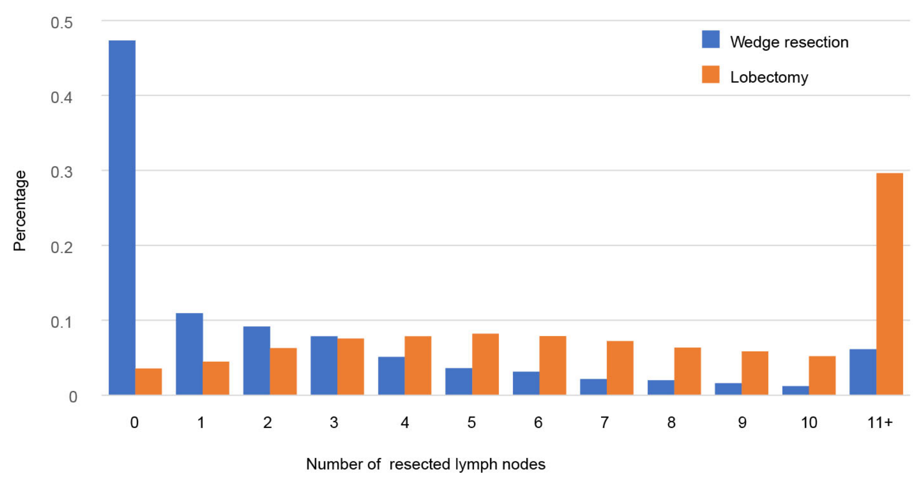

FIGURE 1
Distribution of the number of examined lymph nodes for wedge resection and lobectomy.

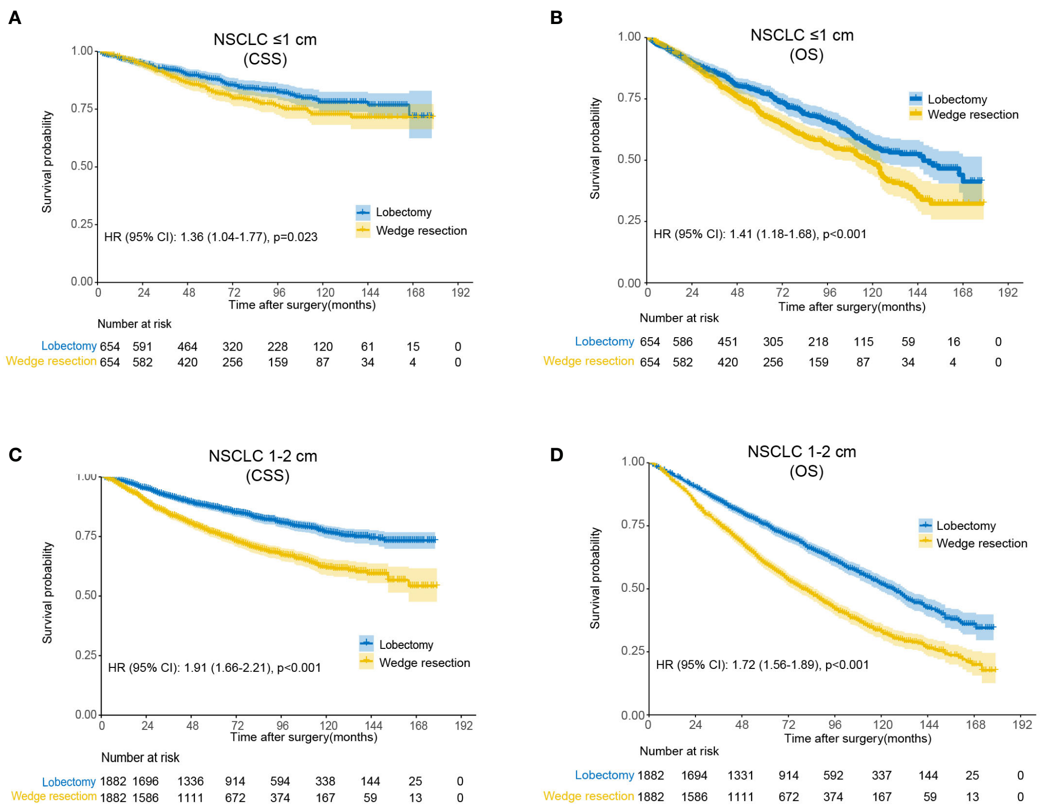

FIGURE 2
Kaplan-Meier analysis of survival between wedge resection and lobectomy after matching. **(A)** Cause-specific survival for non-small cell lung cancer (NSCLC) ≤1 cm; **(B)** overall survival for NSCLC ≤1 cm; **(C)** cause-specific survival for NSCLC 1-2 cm; **(D)** overall survival for NSCLC 1-2 cm.

Survival of wedge resection/lobectomy with adequate nodes resected

For NSCLC ≤1cm, patients derived similar CSS and OS under wedge resection or lobectomy with no less than 1 nodes resected (Figure 4 and Table 3). Notably, the lobectomy group have significantly more nodes resected over wedge resection group in the balanced population (median number, 7 versus 3, p<0.001). For NSCLC 1-2cm, wedge resection generated inferior CSS and OS versus lobectomy when less than 6 nodes were examined. In the subset including NSCLC with 6 or more nodes examined, the two procedures showed similar long-term outcomes (*log-rank* p=0.14). In the multivariable analysis, the increased risk of deaths in patients undergoing wedge resection descended gradually along with the increase of the number of resected lymph nodes (Table 3). Beyond 6 nodes, the difference on OS did not reach statistically significance (HR, 1.21, 95% CI: 0.93-1.59). The median number of resected lymph nodes between the two groups was similar as well (10 versus 9, p=0.544). Analysis on CSS draw similar conclusions as that on OS.

Discussion

Our study reveals that wedge resection led to worse OS than lobectomy for node-negative NSCLC ≤2 cm in the population. These two procedures were comparable when one or more nodes for lesions ≤1 cm and six or more nodes for lesions 1-2 cm were resected. For lesions 1-2 cm and receiving lobectomy, more nodes resected conferred statistically significant increase on OS, while for lesions ≤1 cm not.

The choice of surgical procedures for NSCLC ≤2 cm have gained remarkable attentions recently. The usage of high-solution CT scanning and the spread of lung cancer screening led to the high detection of those small pulmonary nodules. Suitable surgical treatment can effectively prevent the recurrence and achieve the goal of cure. Recently published results from JCOG0804 study suggested that the 5-year relapse-free survival of sublobar resection was 99.7% for ground-glass opacity (GGO) dominant peripheral lung cancer with maximum diameter less than 2 cm and consolidation/tumor ratio (CTR) ≤0.25 on the preoperative thin-section CT (9). For tumors ≤2 cm and CTR >0.5, JCOG0802

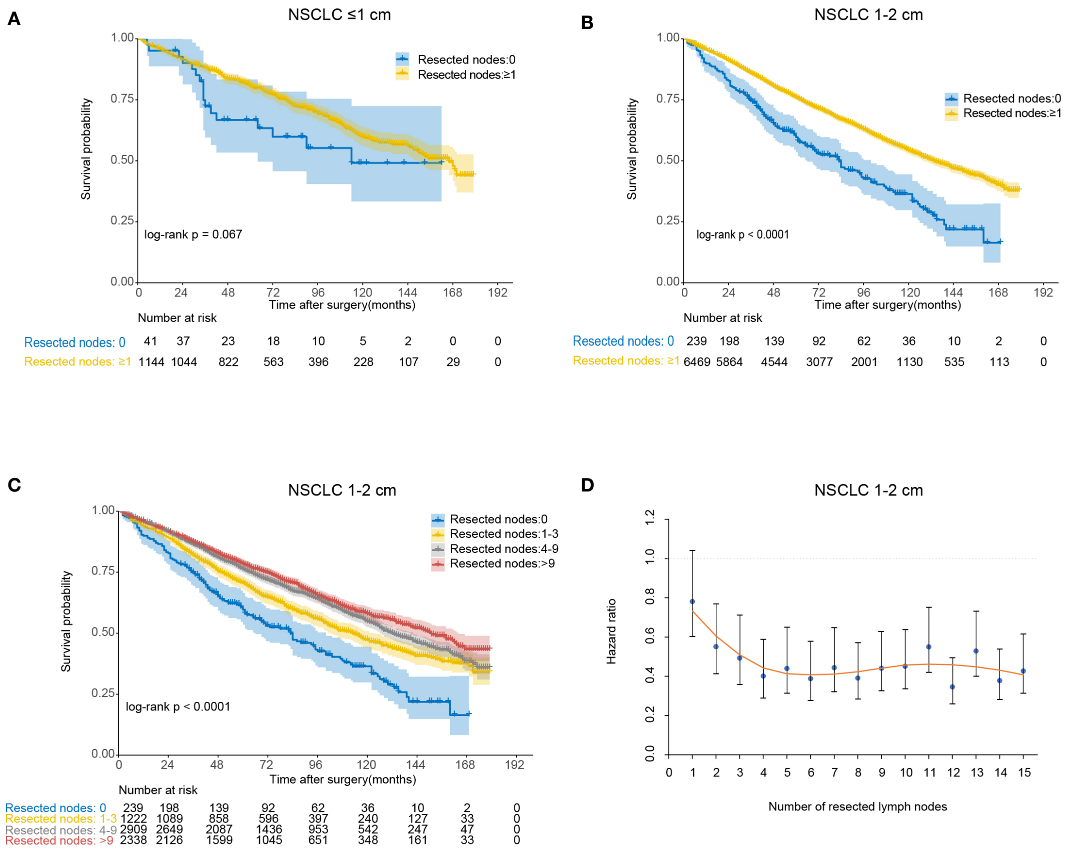

FIGURE 3
The association between the number of resected lymph nodes and overall survival for lobectomy. **(A)** Kaplan-Meier analysis of overall survival between no lymph nodes resected group and lymph nodes resected group for non-small cell lung cancer (NSCLC) ≤1 cm; **(B)** Kaplan-Meier analysis of overall survival between no lymph nodes resected group and lymph nodes resected group for NSCLC 1-2 cm; **(C)** Kaplan-Meier analysis of overall survival among different lymph nodes resected groups (0, 1-3, 4-9 and >9) for NSCLC 1-2 cm; **(D)** Locally estimated scatterplot smoothing (LOESS) curve describing the association between the specified number of resected lymph nodes and corresponding hazard ratio (HR) for NSCLC 1-2 cm.

TABLE 2 Univariable and multivariable analysis of overall survival among patients undergoing lobectomy with different number of lymph nodes resected (0 as reference).

Size		Univariable analysis		Multivariable analysis	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
0-1 cm					
	≥1 nodes	0.64 (0.39-1.04)	0.637	0.62 (0.37-1.01)	0.056
	1-3 nodes	0.71 (0.42-1.20)	0.205	0.67 (0.39-1.15)	0.144
	4-9 nodes	0.60 (0.36-0.99)	0.047	0.60 (0.36-1.00)	0.050
	≥10 nodes	0.64 (0.39-1.06)	0.086	0.60 (0.36-1.02)	0.057
1-2 cm					
	≥1 nodes	0.54 (0.46-0.64)	<0.001	0.60 (0.51-0.72)	<0.001
	1-3 nodes	0.66 (0.55-0.80)	<0.001	0.75 (0.62-0.91)	0.003
	4-9 nodes	0.53 (0.45-0.64)	<0.001	0.59 (0.50-0.71)	<0.001
	≥10 nodes	0.48 (0.40-0.57)	<0.001	0.53 (0.44-0.63)	<0.001

CI, confidence interval; HR, hazard ratio.

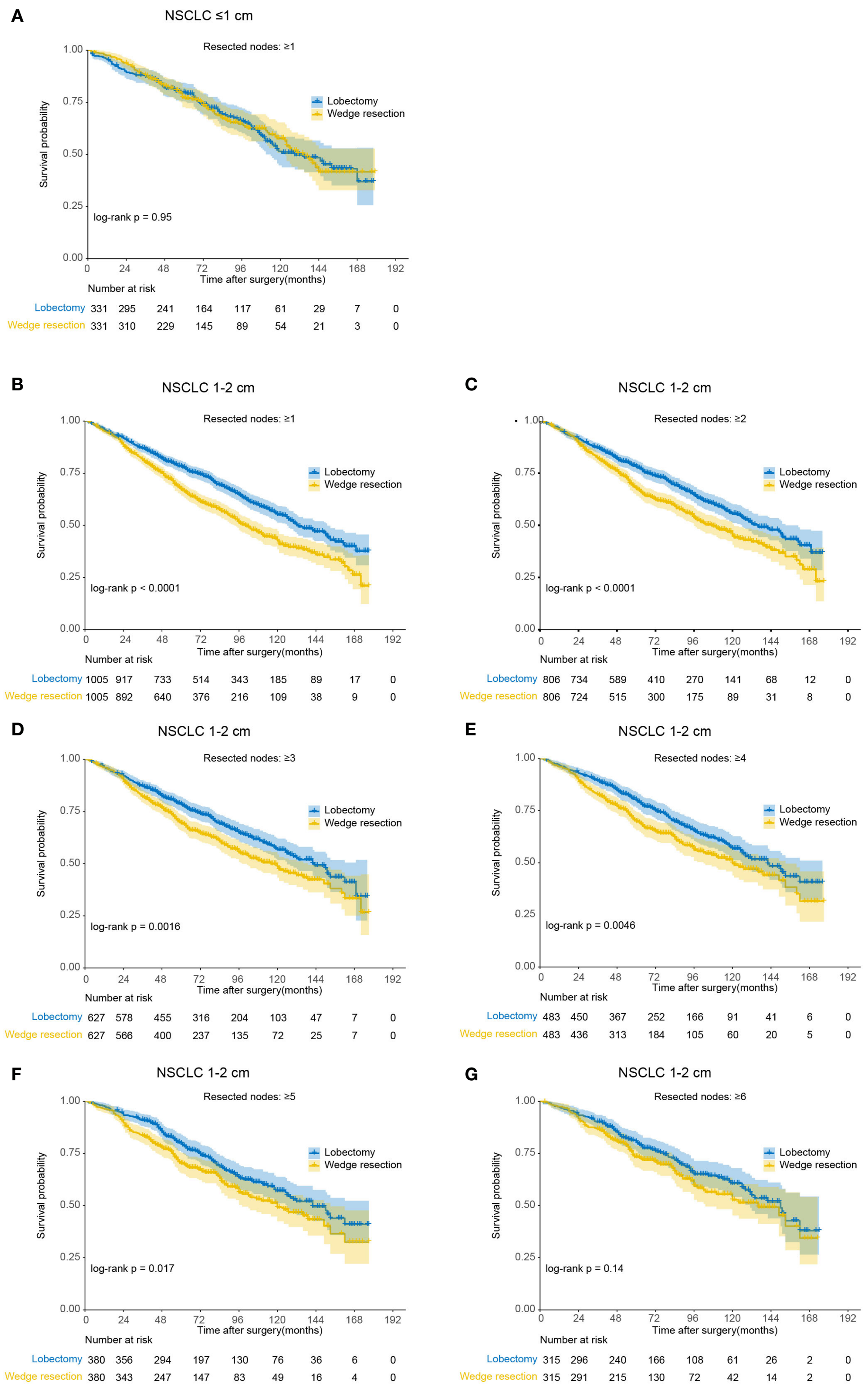

FIGURE 4

Kaplan-Meier analysis of overall survival between wedge resection and lobectomy for non-small cell lung cancer (NSCLC) with different number of nodes resected (after matching). **(A)** NSCLC ≤1 cm with ≥1 nodes resected; **(B)** NSCLC 1-2 cm with ≥1 nodes resected; **(C)** NSCLC 1-2 cm with ≥2 nodes resected; **(D)** NSCLC 1-2 cm with ≥3 nodes resected; **(E)** NSCLC 1-2 cm with ≥4 nodes resected; **(F)** NSCLC 1-2 cm with ≥5 nodes resected; **(G)** NSCLC 1-2 cm with ≥6 nodes resected.

TABLE 3 Univariable and multivariable analysis of cause-specific survival and overall survival among patients undergoing wedge resection or lobectomy with different number of lymph nodes resected (after matching).

Size	Cause-Specific Survival				Overall Survival				Number of lymph nodes examined, mean (median)		
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis				
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	Lobectomy	Wedge resection	*p* value
0-1 cm											
All	1.34 (1.03-1.74)	0.030	1.36 (1.04-1.77)	0.023	1.36 (1.14-1.63)	0.001	1.41 (1.18-1.68)	<0.001	8.9 (7)	2.4 (1)	<0.001
≥1 nodes	1.19 (0.82-1.74)	0.362	1.22 (0.84-1.78)	0.301	0.99 (0.77-1.28)	0.947	1.03 (0.80-1.34)	0.815	8.9 (7)	4.7 (3)	<0.001
1-2 cm											
All	1.88 (1.63-2.17)	<0.001	1.91 (1.66-2.21)	<0.001	1.69 (1.54-1.86)	<0.001	1.72 (1.56-1.89)	<0.001	8.7 (7)	2.8 (1)	<0.001
≥1 nodes	1.68 (1.36-2.07)	<0.001	1.67 (1.35-2.06)	<0.001	1.47 (1.28-1.69)	<0.001	1.45 (1.26-1.66)	<0.001	8.8 (7)	5.2 (3)	<0.001
≥2 nodes	1.50 (1.19-1.90)	0.001	1.51 (1.19-1.91)	<0.001	1.39 (1.19-1.63)	<0.001	1.37 (1.17-1.61)	<0.001	9.3 (8)	6.3 (4)	<0.001
≥3 nodes	1.40 (1.07-1.83)	0.014	1.41 (1.08-1.85)	0.012	1.34 (1.12-1.61)	0.002	1.34 (1.11-1.61)	0.002	9.8 (8)	7.5 (6)	<0.001
≥4 nodes	1.41 (1.04-1.93)	0.028	1.43 (1.05-1.95)	0.023	1.35 (1.10-1.67)	0.005	1.35 (1.10-1.67)	0.005	10.3 (9)	8.8 (7)	<0.001
≥5 nodes	1.45 (1.03-2.04)	0.035	1.45 (1.03-2.05)	0.036	1.33 (1.05-1.69)	0.017	1.32 (1.05-1.68)	0.020	10.9(9)	10.1 (8)	0.090
≥6 nodes	1.25 (0.85-1.84)	0.267	1.24 (0.84-1.82)	0.285	1.23 (0.94-1.61)	0.137	1.21 (0.93-1.59)	0.159	11.5 (10)	11.2 (9)	0.544

CI, confidence interval; HR, hazard ratio.

study showed that segmentectomy had improved OS over lobectomy, although segmentectomy had similar relapse-free survival and higher local relapse rate (10). The ongoing JCOG1211 study would explore the efficacy of segmentectomy for clinical lung cancer ≤2 cm with a CTR from 0.25 to 0.5 (11). Besides, National Comprehensive Cancer Network guidelines recommended sublobar resection for peripheral nodules ≤2 cm with adenocarcinoma *in situ* histology, or ≥50% ground-glass appearance on CT or a doubling time of ≥400 days (12). However, the JCOG trials had its limitations in clinical decision-making. Recommendations based on the combination of whole tumor size and CTR may be conflicting when considering the solid size (13).

Wedge resection was an essential choice of procedures when treating small-sized NSCLC. We found that wedge resection was performed for 22.9% patients with NSCLC less than 2 cm diagnosed between 2004 and 2015 in SEER database (lobectomy 71.4%, segmentectomy 5.7%). However, our study revealed that after propensity score matching, wedge resection resulted in 41% and 72% increase of death risk over lobectomy for lesions less than 1 cm and 1-2 cm, respectively. Therefore, it has clinical significance for wedge resection to achieve similar long-term outcomes compared with lobectomy. Considering the higher nonexamination rate of lymph node for wedge resection (47.3%) over lobectomy (3.5%), adequate lymph node resection can narrow the survival gap between those two procedures. As our prior study demonstrated, lymph node resection can improve long-term survival of wedge resection irrespective of the tumor size ≤1 cm or 1-2 cm (5). Increased number of lymph nodes resected were associated with more accurate pathological staging and better local control, which can guide the administration of adjuvant therapy and improve long-term survival after the curative intent operation (14). Wolf's study showed that sublobar resection (wedge resection, 130/154) with lymph nodes sampling had an similar OS and recurrence-free survival to that of lobectomy for NSCLC ≤2 cm (15). Ajmani's study showed that for cT1-2N0M0 NSCLC undergoing wedge resection, the rate of nodal upstaging rate increased from 4.4% for patients with 1-5 nodes harvested to 8.1% for patients with ≥10 nodes harvested (16). Unlike the results of our analysis, Stiles's study showed that the inferiority of sublobar resection over lobectomy disappeared when nine or more nodes resected (8). The study enrolled patients aged over 66 years and received wedge resection or segmentectomy between 2007 and 2012 from SEER-Medicare database. That may be the reason leading to the difference.

The study has several limitations. First, selecting bias existed due to the retrospective nature of the present study, although propensity score matching was performed to minimize that limitation. Second, several clinical factors such as pulmonary function, smoking history and main comorbidities can impact the choice of procedures and OS. However, those factors were not available in the SEER database. Third, besides the number of lymph nodes, the number of stations examined had prognostic effect during wedge resection. The prior study showed that compared to patients with only mediastinal lymph nodes (N2) or only one station of regional lymph nodes (N1) evaluated, those who had N1 stations or more than one N1 stations harvested achieved better OS and recurrence-free survival (17). Regrettably, SEER database does not record respective number of resected N1 or N2 nodes.

In conclusion, our study revealed the inferiority of wedge resection versus lobectomy for NSCLC ≤1 cm or 2 cm in the population. However, wedge resection plus adequate lymph node resection can generate equivalent clinical outcomes to lobectomy.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

Author contributions

Study concepts: HD, GJ, HW. Study design: HD, NS, HW. Data acquisition: HD, NS, PZ. Quality control of data and algorithms: NS, GJ, HW. Data analysis and interpretation: HD, NS. Statistical analysis: HD, NS. Manuscript preparation: HD. Manuscript editing: HD. Manuscript review: GJ, HW. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1022904/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Kaplan-Meier analysis of survival between wedge resection and lobectomy before matching. **(A)** Cause-specific survival for non-small cell lung cancer (NSCLC) ≤1 cm; **(B)** overall survival for NSCLC ≤1 cm; **(C)** cause-specific survival for NSCLC 1-2 cm; **(D)** overall survival for NSCLC 1-2 cm.

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The detailed classification of the interlobar artery and the artery crossing intersegmental planes in the right upper lobe

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Background: With the prevalence of three-dimensional computed tomography bronchography and angiography (3D-CTBA) and the development of anatomical segmentectomy, several studies have analyzed the branching patterns of peripheral segmental arteries in the right upper lobe (RUL). Nevertheless, the detailed classification of the branching patterns of the interlobar artery and the artery crossing intersegmental planes remains unknown. Thus, we conducted a retrospective study to analyze the variations of the interlobar artery and the artery crossing intersegmental planes in the RUL using 3D-CTBA.

Materials and methods: A total of 600 patients with ground-glass opacity (GGO) who had undergone 3D-CTBA preoperatively at Hebei General Hospital between September 2020 and September 2022 were used for the retrospective study. We reviewed the anatomical variations of the RUL arteries in these patients using 3D-CTBA images.

Results: The branching patterns of the RUL artery were classified into the following four categories: trunk superior (Tr. sup), Tr. sup + interlobar artery, Tr. sup + trunk inferior (Tr. inf), and Tr. sup + Tr. inf + interlobar artery. The branching patterns of the interlobar artery were subclassified into four subtypes: posterior ascending artery (A. pos), anterior ascending artery (A. ant), A. pos + A. ant, and ascending artery (A. asc). The artery crossing intersegmental planes contains two types: type A, anterior subsegmental artery crossing intersegmental planes (AX^1b); type B, recurrent artery crossing intersegmental planes (AX. rec).

Conclusion: The variation types of blood vessels in the RUL are complex. This study explored the detailed classification of the interlobar artery and the artery crossing intersegmental planes. It can help thoracic surgeons understand the anatomy variations, accurately locate lesions before surgery, and effectively plan surgeries.

KEYWORDS
right upper lobe (RUL), anatomy variations, pulmonary artery, anatomical segmentectomy, lobectomy, non-small cell lung carcinoma (NSCLC), video-assisted thoracoscopic surgery (VATS)

1 Introduction

Lung cancer (LC) is a common malignancy worldwide and is regarded as the leading cause of death (1). The high mortality of LC puts a tremendous strain on public health systems. In recent years, as high-resolution computed tomography (HRCT) is generally applied to health examinations, ground-glass opacity (GGO) is increasingly being confirmed. Surgery remains the best treatment option for early-stage LC. Studies showed that sublobar resection with adequate surgical margins is feasible and effective (2–6), particularly for lesions with a diameter of less than 2 cm and with a consolidation tumor ratio of less than 25%. The main forms of sublobar resection currently include wedge resection and anatomical segmentectomy. Additionally, anatomical segmentectomy preserves better lung function and minimizes lung volume loss. These benefits draw our attention to video-assisted thoracoscopic surgery (VATS) anatomical segmentectomy. However, the presence of anatomical variations may bring great difficulties and challenges to VATS anatomical segmentectomy.

The procedure of performing VATS anatomical segmentectomy is extremely risky with regard to the pulmonary artery as variable pulmonary artery branches are often encountered during dissociation. Without sufficient preoperative anatomy knowledge, it is difficult to accurately mutilate the artery of the target lung segment intraoperatively, which is likely to lead to the conversion of anatomical segmentectomy to lobectomy, which prolongs the surgical time and leads to loss of lung function. Therefore, a comprehensive understanding of the branching patterns of the peripheral segmental arteries is essential for the successful performance of segmentectomy and important to avoid intraoperative pulmonary vessel injury.

In the early days of lung segmental anatomy research, gross anatomical specimens were the primary source of information (7). In recent years, the technology of three-dimensional computed tomography bronchography and angiography (3D-CTBA) is developing rapidly, which extracts high-quality planar image data from computed tomography (CT) scans and creates three-dimensional (3D) virtual models of the lungs, including segments, subsegments, lesions, bronchi, and vessels. Several studies have analyzed the branching patterns of peripheral segmental arteries in the right upper lobe (RUL). However, there is no report showing the classification of the branching patterns of the interlobar artery and the artery crossing intersegmental planes. The aim of this study was to explore the branching patterns of the interlobar artery and the artery crossing intersegmental planes utilizing data from 3D-CTBA. To further advance our understanding of the branching patterns of the pulmonary artery in the RUL, we also compared the results of our study with a similar study that was previously conducted (8).

Abbreviations: LC, lung cancer; HRCT, high-resolution computed tomography; GGO, ground-glass opacity; VATS, video-assisted thoracoscopic surgery; 3D-CTBA, three-dimensional computed tomography bronchography and angiography; CT, computed tomography; 3D, three-dimensional; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; Tr. sup, trunk superior; Tr. inf, trunk inferior; A. pos, posterior ascending artery; A. rec, recurrent artery; A. ant, anterior ascending artery; A. asc, ascending artery; AX. rec, A. rec crossing intersegmental planes; AX^1b, A^1b crossing intersegmental planes; V. cent, central vein.

2 Materials and methods

2.1 Patient preparation

Between September 2020 and September 2022, 600 patients (336 female and 264 male) who underwent surgeries to treat lesions in the RUL at Hebei General Hospital were enrolled in this study. The mean age was 58 years. All procedures involving human participants in this study were in accordance with the Declaration of Helsinki (revised in 2013). This retrospective study was approved by the Research Ethics Committee at Hebei General Hospital (No. 2022119). The need for patient consent was waived because of the retrospective nature of the study (9).

Inclusion criteria:

1) GGO, with a diameter of less than 2 cm and with a consolidation tumor ratio of less than 25%, located in the RUL;
2) sublobar resection (segmentectomy or wedge resection) was performed; and
3) patients underwent routine chest-enhanced CT examinations preoperatively.

Exclusion criteria:

1) The images presented by enhanced CT lung examination were not clear, which affected the 3D reconstruction of the lung;
2) with a history of right lung surgery; and
3) with a history of pulmonary tuberculosis.

2.2 Reconstruction of 3D-CTBA

We performed preoperative chest-enhanced CT using Siemens 64-slice dual-source CT (Somatom Definition) with the contrast agent ioversol 350. A total of 70 ml of contrast medium (ioversol 350) was administered intravenously at a rate of 2–3 ml/s. Contrast-enhanced CT was performed using the fixed-time method. The arterial phase scans were taken 30 s after contrast injection, and the venous phase scans 90 s after contrast injection. The technical parameters used for the Siemens 64-slice dual-source CT were as follows: a collimator thickness of 0.6 mm, a reconstruction layer of 1.25 mm, and an interlayer space of 1 mm (9). By setting a scan start time, the CT values of the pulmonary veins and arteries revealed density variations in the images. The patients were required to hold their breath throughout the CT scan for appropriate bronchial inflation, and precautions were taken to avoid any potential side effects from the contrast agent following the scan. The volume data from both arterial and venous phases were imported into reconstruction software (Infer Operate Thorax Planning), which computed and processed the data before presenting them in 3D-CTBA images (9).

2.3 Definition of RUL artery branch

Six names of RUL artery branches were defined (Figures 1, 2): trunk superior (Tr. sup), trunk inferior (Tr. inf), posterior ascending artery (A. pos), recurrent artery (A. rec), anterior ascending artery (A. ant), and ascending artery (A. asc) (9).

2.3.1 Tr. sup

The Tr. sup is the first branch of the right main pulmonary artery and is often the chief source of the RUL artery (Figure 1). Originating from the mediastinal portion of the RUL artery, it lies below the azygos vein arch and flows into the RUL at the anterior side of the RUL bronchus (9).

2.3.2 Tr. inf

The Tr. inf (Figure 1), which also originates from the mediastinal portion of the RUL artery and passes anterior to B^3, has two definitions that depend on whether the Tr. sup is split into upper and lower parts (7–9). If it is, then the Tr. inf is the lower part; if not, it is the second branch of the right pulmonary artery, which arises between the distal region of the Tr. sup and proximal region of the first middle lobe of the pulmonary artery.

2.3.3 A. pos, A. ant, and A. asc

The artery branch originating from the interlobar portion of the right pulmonary artery is located at the posterior side of B^3 (Figure 1). The A. pos is named if it only supplies S^2, while the A. ant is named if it only supplies S^3, and the A. asc is named if it supplies both S^2 and S^3. Moreover, the A. ant usually arches over the central vein (V. cent) (7, 9).

2.3.4 A. rec

The A. rec is a branch of the Tr. sup and crosses behind B^1a to supply S^2 (Figure 1) (9).

2.3.5 AX^{1}b and AX. rec

According to Boyden's classification principle (7), the Tr. sup was divided into two types. The first type is the bifurcated Tr. sup (Figure 3), which is commonly separated into upper and lower segments. The lower segment is principally composed of A^3. The composition of the upper segment is variable, which is usually composed of either A^1 and the A. rec or only A^1. The second type is the trifurcated Tr. sup (Figure 3), which is divided into upper,

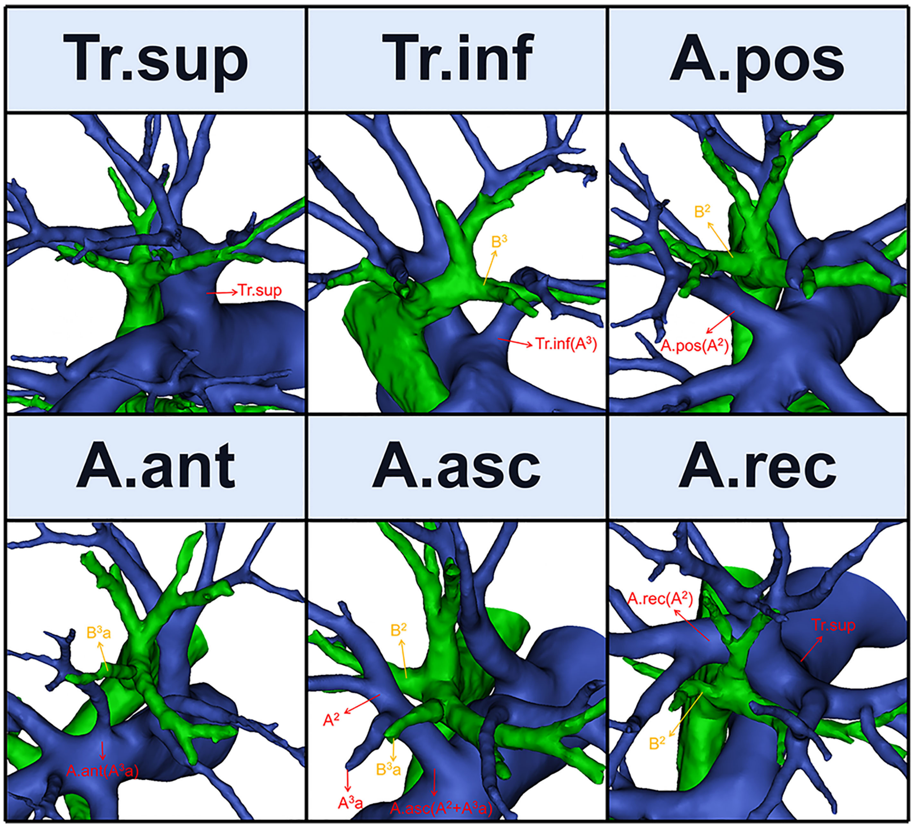

FIGURE 1
The 3D reconstruction model of Tr. sup, Tr. inf, A. pos, A. ant, A. asc, and A. rec.

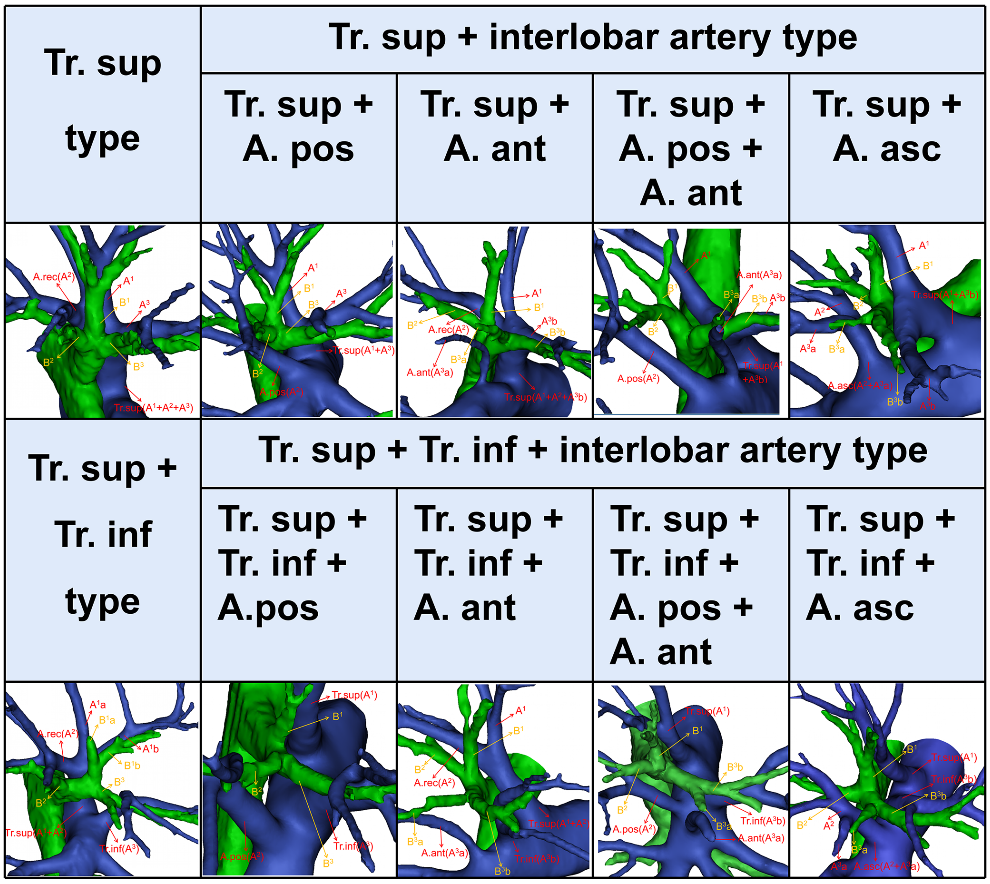

FIGURE 2
The 3D reconstruction model of the branching patterns of the RUL artery. RUL, right upper lobe.

middle, and lower segments. The composition of the upper and lower segments is similar to that of the bifurcated Tr. sup mentioned before. The middle segment is usually composed of the A. rec crossing intersegmental planes (AX. rec).

Thus, A^1b crossing intersegmental planes (AX^1b) is named when its origin descends to A^3 (Figure 3); AX. rec is named when it originates from the middle segment of the trifurcated Tr. sup or A^3 and crosses between B^1 and B^3 to supply the S^2 (Figure 3) (9).

2.4 Statistics

All statistical analyses were performed using SPSS 23.0 (SPSS, Chicago, IL, USA). Qualitative data were expressed as the number of cases (percentage). Pearson's chi-square test was used to evaluate the significance of dependencies between the groups. A p-value less than 0.05 was considered statistically significant.

3 Results

3.1 Branching patterns of RUL artery

The branching patterns of the RUL arteries were classified into four types (Table 1; Figure 2): type A, Tr. sup (25/600, 4.2%); type B, Tr. sup + interlobar artery (446/600, 74.3%); type C, Tr. sup + Tr. inf (15/600, 2.5%); type D, Tr. sup + Tr. inf + interlobar artery (114/600, 19.0%). According to the supplying range and the number of the interlobar artery branch, four types can be defined: A, A. pos; B, A. ant; C, A. pos + A. ant; D, A. asc. Thus, the "Tr. sup + interlobar artery type" and "Tr. sup + Tr. inf + interlobar artery type" were respectively subclassified into four subtypes (Table 1; Figure 2). In conclusion, the "Tr. sup + A. pos type" was evident in 272 cases (45.3%) and was the most common type. Moreover, there was no significant difference between the male group and the female group on the branching patterns of the RUL artery (Table 2).

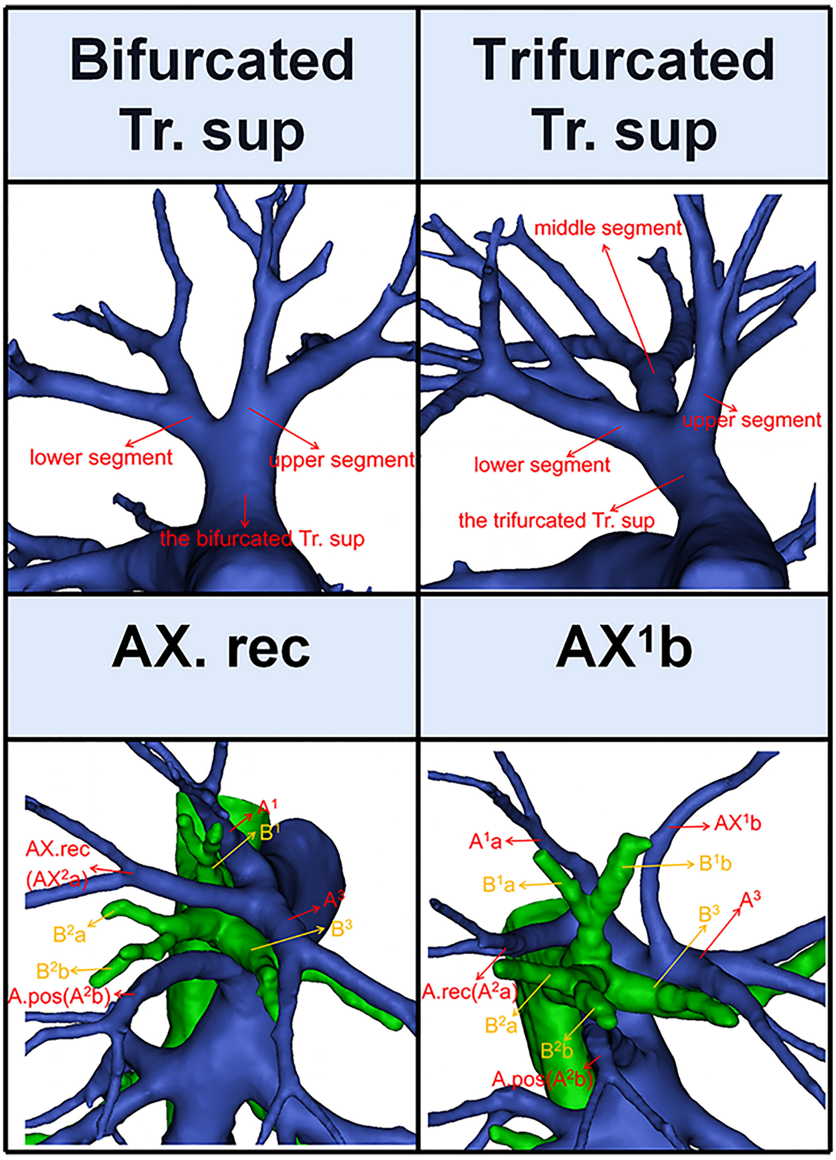

FIGURE 3
The 3D reconstruction model of the bifurcated Tr. sup, the trifurcated Tr. sup, AX. rec, and AX^1b.

3.2 The anatomical features of A. pos, A. ant, and A. asc

3.2.1 A. pos

In the following types, “Tr. sup + A. pos”, “Tr. sup + Tr. inf + A. pos”, “Tr. sup + A. pos + A. ant”, and “Tr. sup + Tr. inf + A. pos + A. ant”, the origin of the A. pos has two cases (Figure 4A, Table 3): A, the interlobar portion (374/410, 91.2%); B, A^6 (36/410, 8.8%). According to the supplying range of the A. pos, eight categories can be defined (Figure 4A, Table 3): A, A^2 (110/410, 26.8%); B, A^2a (9/410, 2.2%); C, A^2aii (11/410, 2.7%); D, A^2b (66/410, 16.1%); E, A^2bii (55/410, 13.4%); F, A^2aii + A^2b (89/410, 21.7%); G, A^2a + A^2bii (20/410, 4.9%); H, A^2aii + A^2bii (50/410, 12.2%).

3.2.2 A. ant

In the following types, “Tr. sup + A. ant”, “Tr. sup + Tr. inf + A. ant”, “Tr. sup + A. pos + A. ant”, and “Tr. sup + Tr. inf + A. pos + A. ant”, patients can be divided into one of the following two types based on the origins of the A. ant (Figure 4B, Table 4): A, interlobar portion (78/85, 91.8%); B, right middle lobe (RML) artery (7/85, 8.2%). Types can also be defined according to the supplying range of the A. ant (Figure 4B, Table 4): A, A^3a (16/85, 18.8%); B, A^3aii (69/85, 81.2%).

3.2.3 A. asc

In the following types, “Tr. sup + A. asc” and “Tr. sup + Tr. inf + A. asc”, the origin of the A. asc was split into two types (Figure 4B,

TABLE 1 Branching patterns of the right upper lobe artery.

	Our study (n = 600)		Nagashima (n = 263)	
	No.	%	No.	%
Tr. sup type	25	4.2	26	9.9
Tr. sup + interlobar artery type	446	74.3	189	71.9
Tr. sup + A. pos type	272	45.3	NR	–
Tr. sup + A. ant type	16	2.7	NR	–
Tr. sup + A. pos + A. ant type	53	8.8	NR	–
Tr. sup + A. asc type	105	17.5	NR	–
Tr. sup + Tr. inf type	15	2.5	9	3.4
Tr. sup + Tr. inf + interlobar artery type	114	19.0	36	13.7
Tr. sup + Tr. inf + A. pos type	75	12.5	NR	–
Tr. sup + Tr. inf + A. ant type	6	1.0	NR	–
Tr. sup + Tr. inf + A. pos + A. ant type	10	1.7	NR	–
Tr. sup + Tr. inf + A. asc type	23	3.8	NR	–
N/A	–	–	3	1.1

N/A, not available; NR, the type was not referred.

TABLE 2 Distribution of branching types of the right upper lobe artery between male and female patients.

	Male	Female	total	p-Value
Tr. sup type	11	14	25	$p > 0.05$
Tr. sup + interlobar artery type	202	244	446	
Tr. sup + Tr. inf type	7	8	15	
Tr. sup + Tr. inf + interlobar artery type	44	70	114	
Total	264	336	600	

Table 5): A, interlobar portion (121/128, 94.5%); B, A^6 (7/128, 5.5%). According to the shape of the A. asc branches, the A. asc can also be classified into two types (Figure 4B, Table 5): A, the bifurcation of the A. asc is V-shaped at the root (101/128, 78.9%); B, the bifurcation of the A. asc is V-shaped after a distance from the root (27/128, 21.1%).

3.3 Branching patterns of RUL segmental arteries

3.3.1 A^1

Compared to that of A^2 and A^3, the branching pattern of A^1 shows less diversity. There were two situations in which A^1 was supplied solely by the Tr. sup in 589 cases (98.2%) while jointly by the Tr. sup and Tr. inf in 11 cases (1.8%), depending on where the A^1 originated (Figure 5, Table 6). When A^1 was supplied solely by the Tr. sup, the branching patterns of A^1a and A^1b were divided into two subtypes. In 487 cases (82.7%), the A^1a and A^1b branched together directly from the upper segments of the bifurcated Tr. sup or the trifurcated Tr. sup (Figure 5). However, in 102 cases (17.3%), only A^1a branched directly from the upper segments of the bifurcated Tr. sup, and AX^1b branched from an A^3 that bifurcated from the Tr. sup (Figure 5).

3.3.2 A^2

The composition of A^2 is more complex (9). In this study, the compositions of A^2 were divided into the following three categories (Figure 6, Table 7). First, A^2 is only supplied by one branch of the artery: A. pos (110/600, 18.3%); A. rec (57/600, 9.5%); A. asc (24/600, 4.0%); Tr. inf (2/600, 0.3%). Second, A^2 is supplied by two branches of the artery: A. pos and A. rec (240/600, 40.0%); A. asc and A. rec (91/600, 15.2%); A. pos and AX. rec (37/600, 6.2%); A. asc and AX. rec (9/600, 1.5%); A. rec and AX. rec (3/600, 0.5%); A. pos and Tr. inf (5/600, 0.8%). Third, A^2 is supplied by three branches of the artery: A. pos, A. rec, and AX. rec (17/600, 2.8%); A. asc, A. rec, and AX. rec (4/600, 0.7%); A. pos, A. rec, and Tr. inf (1/600, 0.2%). To sum up, the most prevalent forms of A^2 composition are A. pos and A. rec.

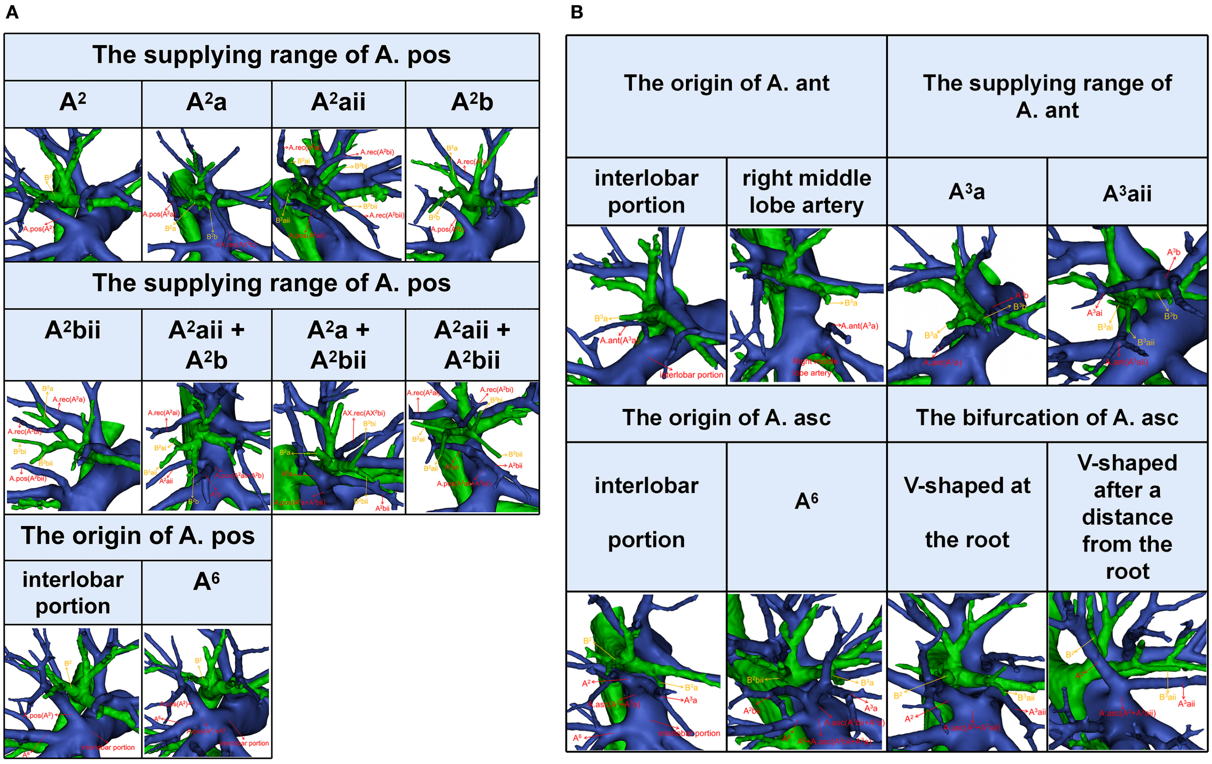

FIGURE 4
(A) The 3D reconstruction model of anatomical features of A. pos. **(B)** The 3D reconstruction model of anatomical features of A. ant and A. asc.

TABLE 3 The anatomical features of A. pos.

	Our study (n = 410)	
	No.	%
The origin of A. pos		
Interlobar portion	374	91.2
A^6	36	8.8
The supplying range of A. pos		
A^2	110	26.8
A^2a	9	2.2
A^2aii	11	2.7
A^2b	66	16.1
A^2bii	55	13.4
A^2aii + A^2b	89	21.7
A^2a + A^2bii	20	4.9
A^2aii + A^2bii	50	12.2

3.3.3 A^3

According to the compositions of A^3, three types can be defined (Figure 7, Table 8). First, A^3 is only supplied by one branch of the artery: Tr. sup (297/600, 49.5%) and Tr. inf (42/600, 7.0%). Second, A^3 is supplied by two branches of the artery: Tr. sup and A. ant (69/600, 11.5%); Tr. sup and A. asc (105/600, 17.5%); Tr. sup and Tr. inf (48/600, 8.0%); Tr. inf and A. ant (9/600, 1.5%); Tr. inf and A. asc (12/600, 2.0%). Third, A^3 is supplied by three branches of the artery:

TABLE 4 The anatomical features of A. ant.

	Our study (n = 85)	
	No.	%
The origin of A. ant		
Interlobar portion	78	91.8
Right middle lobe artery	7	8.2
The supplying range of A. ant		
A^3a	16	18.8
A^3aii	69	81.2

TABLE 5 The anatomical features of A. asc.

	Our study (n = 128)	
	No.	%
The origin of A. asc		
Interlobar portion	121	94.5
A^6	7	5.5
The bifurcation of A. asc		
V-shaped at the root	101	78.9
V-shaped after a distance from the root	27	21.1

Tr. sup, Tr. inf, and A. ant (7/600, 1.2%); Tr. sup, Tr. inf, and A. asc (11/600, 1.8%).

4 Discussion

With the widespread use of HRCT, increasing numbers of GGO are detected. Some previously published studies have indicated that the prognosis of segmentectomy is no worse than that of lobectomy in patients with early LC (2–6). The anatomical variations of the pulmonary artery make segmentectomy more difficult than lobectomy. Therefore, surgeons must have a comprehensive and accurate understanding of the anatomical characteristics of the branching pattern of the peripheral segmental arteries. Fortunately, advances in the volume-rendering reconstruction technique have enabled the reconstruction of 3D images. 3D-CTBA is a useful tool for thoracic surgeons to identify pulmonary anatomy. An accurate preoperative study can reduce the risk of unexpected bleeding to 2.6% and up to 0 when a printed 3D model is available (10, 11).

However, the branching patterns of the interlobar artery and the artery crossing intersegmental planes are rarely mentioned in previously published reports (7, 8, 12, 13). In the present study, we have comprehensively summarized and classified the branching patterns of the interlobar artery and the artery crossing intersegmental planes using 3D-CTBA.

In the present study (Table 1), the "Tr. sup type" was seen in 25 cases (4.2%), which was lower than that reported by Nagashima (9.9%). The rare anatomic variant of the RUL artery was "Tr. sup + Tr. inf type" (2.5%), which was similar to the findings of Nagashima (3.4%). According to the supplying range and the number of the interlobar artery branch, "Tr. sup + interlobar artery" and "Tr. sup + Tr. inf + interlobar artery" can be respectively divided into four subtypes, which have not been reported in previous literature (Figure 2, Table 1).

As shown in Figure 2 and Table 1, the branching patterns of the RUL artery in this study were somewhat different from those in previous reports (7, 8, 12, 13). The main reason is the specific classification of the interlobar artery as described above. Nagashima defined the interlobar artery as the A. asc. However, the interlobar artery can supply S^2, S^3, or S^2 and S^3. In this paper, the interlobar artery of the RUL was classified and summarized in detail by 3D-CTBA. The interlobar artery branch was defined as the A. pos when it only supplied S^2, while the interlobar artery was defined as the A. ant when it only supplied S^3. Similarly, the interlobar artery branch was nominated as the A. asc if it supplied both S^2 and S^3.

Moreover, the definitions of the Tr. inf were ambiguous in the previous studies, so these were redefined in this work. Boyden defined the Tr. inf as the inferior branch of the Tr. sup when it splits into two parts (7). Nagashima defined the Tr. inf as the second branch of the right main pulmonary artery, which arises from the mediastinal portion of the RUL artery between the distal region of the Tr. sup and the proximal region of the first middle lobe of the pulmonary artery (8). However, the two definitions of the Tr. inf are verified in clinical practice (Figures 1, 2). Furthermore, the boundary between the Tr. inf and interlobar artery branch is

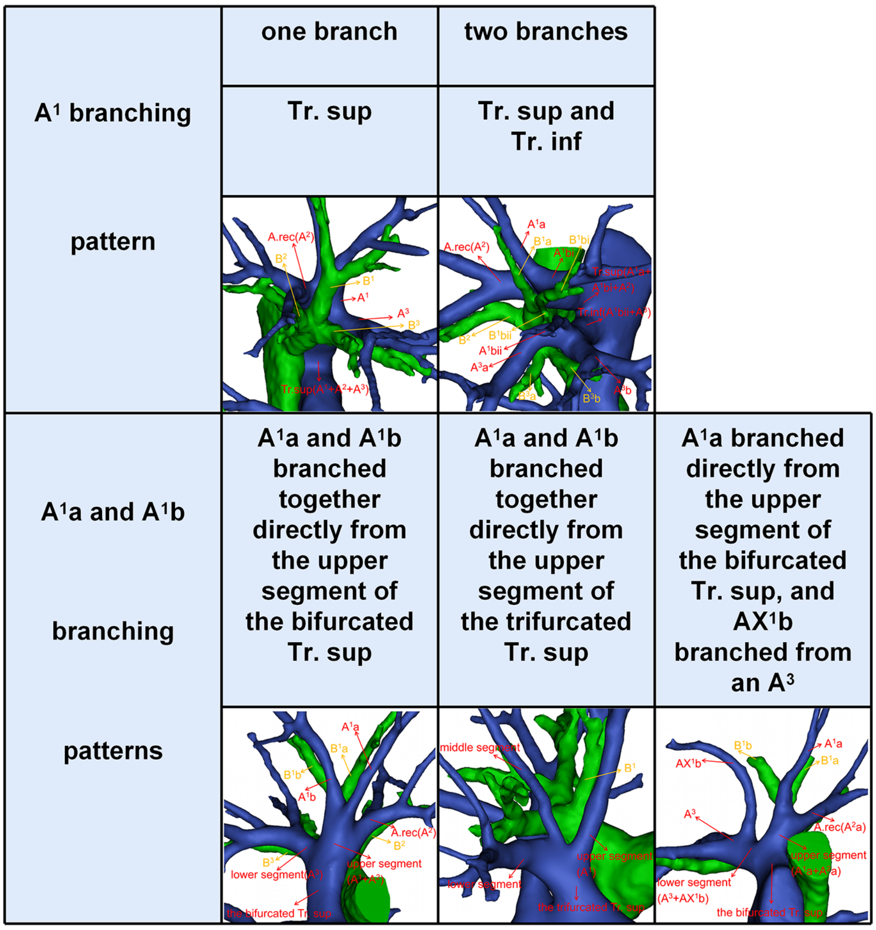

FIGURE 5
The 3D reconstruction model of the branching patterns of A^1.

controversial. Nagashima defined the boundary as the first middle lobe artery (8), while Boyden defined it as B^3 (7). Boyden indicated that the interlobar artery to the RUL occurs below the level of the highest middle lobe artery at 12% and at the level of 40% in the study of bronchovascular variations of the RML (14). Based on 3D-CTBA data from our study, we verified that the originating location of interlobar artery branches emerges at a higher position than the first middle lobe artery in 69.3% (388/560), below the level in 4.5% (25/560), at the level in 26.3% (147/560). We found that the Tr. inf is located at the anterior side of B^3 in 97.8% (126/129). Thus, it seems more appropriate to define the boundary as B^3.

An understanding of the origin of the interlobar artery branch is significant in clinical practice if a safe and accurate lobectomy is to be performed. The anatomical variation, whereby A^6 shared a common trunk with the A. pos, was found in 36 patients (Table 3). A^6 should be carefully separated from the A. pos before it is cut to avoid damaging A^6 in the RUL lobectomy (Figure 4A). Similarly, the A. pos should be carefully separated from A^6 before it

TABLE 6 Branching patterns of A^1.

	Our study (n = 600)		Nagashima (n = 263)	
	No.	%	No.	%
One branch (Tr. sup)	589	98.2	260	98.9
Two branches (Tr. sup and Tr. inf)	11	1.8	NR	–
N/A	–	–	3	1.1

N/A, not available; NR, the type was not referred.

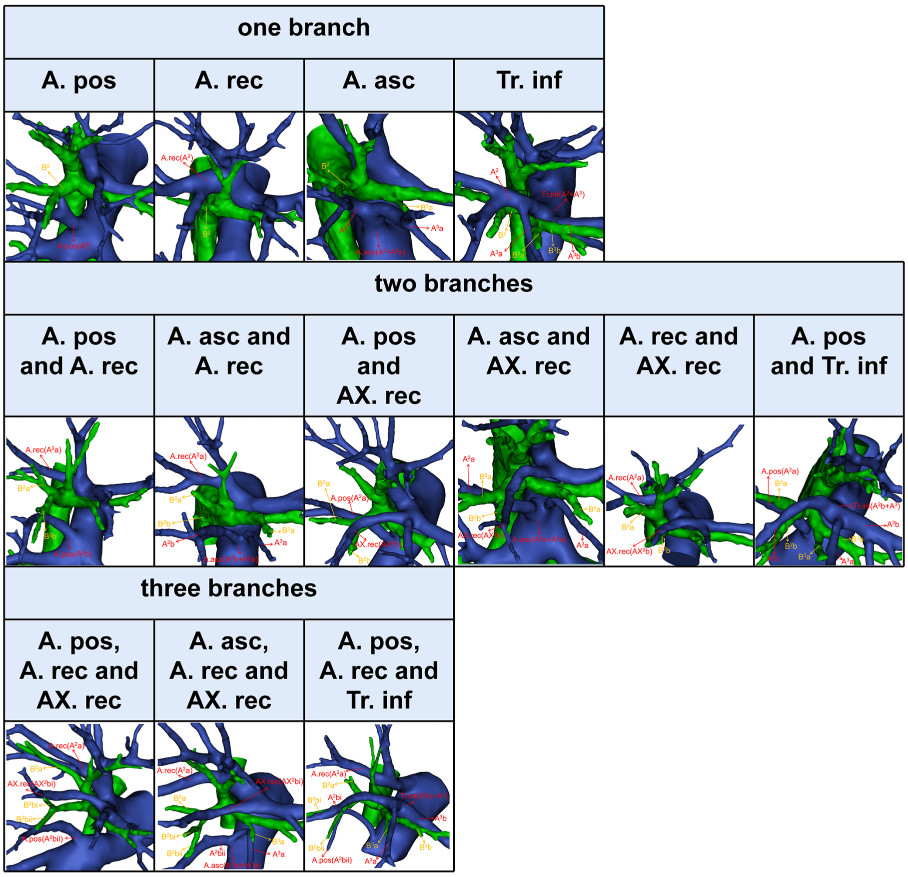

FIGURE 6
The 3D reconstruction model of the branching patterns of A^2.

is divided to avoid injuring the A. pos in the right lower lobe (RLL) lobectomy. Additionally, we also found that the A. asc shared a common trunk with A^6 in seven cases (Figure 4B, Table 5). This variation type is rare in clinical practice; however, if it occurs, it causes a great challenge in the performance of lobectomy. Furthermore, a common trunk for the A. ant and RML artery was observed in 8.2% of the cases (Figure 4B, Table 4). During the RML lobectomy, the A. ant must be protected because a pulmonary artery branch supplied the RUL obstruction that leads to surgical complications such as severe lung edema or extension of the planned lung resection.

The supplying range of the interlobar artery branch has its clinical significance for segmentectomy (Tables 3–5). For example, for an accurate S^2b segmentectomy, the intersegmental plane is easily altered without the knowledge of the supply range of the A. pos. If the A. pos supplies S^2a, a mistaken cut of it will result in an enlarged intersegmental plane (Figure 4A). Similarly, if the A. ant supplies S^3a, excess cutting of the A. ant will result in an enlarged intersegmental plane in S^3b segmentectomy (Figure 4B). If the A. asc supplies a part of S^3, we need to protect the artery branch supplying S^2 in the S^3 segmentectomy (Figure 4B). When the bifurcation of the A. asc is V-shaped after a distance from the root, it is necessary to dissect the A. asc in a center-to-periphery direction to identify the bifurcation in S^2 or S^3 segmentectomy (Figure 4B).

The branching patterns noted in the RUL segmental arteries differed greatly from those of previous reports (Tables 6–8) (7, 8, 12, 13). This can be explained by the specific classification of the interlobar artery and the artery crossing intersegmental planes. In anatomical segmentectomy, it is significant to understand the branching patterns of pulmonary segmental and subsegmental arteries.

For an accurate S^1 segmentectomy, it is significant to understand the branching patterns of A^1 pre-operatively. We found that the branching patterns of A^1 also had the following branching types: Tr. sup (98.2%), whose incidence is similar to that of Nagashima (98.9%); Tr. sup and Tr. inf (1.8%), which has not been reported in the literature (Table 6). When A^1 branched from the upper segments of the bifurcated Tr. sup or the trifurcated Tr. sup, the Tr. sup must be dissected in a center-to-periphery direction to identify A^1 (Figures 3, 5). When A^1bii branching from the Tr. inf runs deep within the lung parenchyma, A^1bii can be identified after resection of the B^1 (Figure 5). Additionally, we found that AX^1b bifurcated from A^3 in 102 cases (Figure 5). A mistaken cut at the

TABLE 7 Branching patterns of A^2.

	Our study (n = 600)		Nagashima (n = 263)	
	No.	%	No.	%
One branch	193	32.1	123	46.8
A. pos	110	18.3	NR	–
A. rec	57	9.5	39	14.8
A. asc	24	4.0	81	30.8
Tr. inf	2	0.3	1	0.4
AX. rec	NR	–	2	0.8
Two branches	385	64.2	137	52.1
A. pos and A. rec	240	40.0	NR	–
A. asc and A. rec	91	15.2	129	49.0
A. pos and AX. rec	37	6.2	NR	–
A. asc and AX. rec	9	1.5	7	2.7
A. rec and AX. rec	3	0.5	NR	–
A. pos and Tr. inf	5	0.8	NR	–
A. rec and Tr. inf	NR	–	1	0.4
Three branches	22	3.7	NR	–
A. pos, A. rec, and AX. rec	17	2.8	NR	–
A. asc, A. rec and AX. rec	4	0.7	NR	–
A. pos, A. rec, and Tr. inf	1	0.2	NR	–
N/A	–	–	3	1.1

upper segments of the bifurcated Tr. sup (A^1a) will result in a narrowed intersegmental plane. Thus, an understanding of the branches and direction of AX^1b before surgery allows the surgeon to carefully peel off this branch during the intraoperative anatomy, avoiding injury to A^3.

The branching patterns of A^2 have significant clinical significance for accurate S^2 segmentectomy (Table 7, Figure 6). A^2 can be composed of the following five components: A. pos, A. asc, A. rec, AX. rec, and Tr. inf (Figures 1, 3, 6) (9). Moreover, the AX. rec is also a new concept (9). Therefore, three basic approaches to identifying these branches were first reported in our previous paper (9). The A. pos and A. asc can be discriminated by dissecting interlobar fissures (interlobar approach). The Tr. sup can be dissected in a center-to-periphery direction to recognize the A. rec and AX. rec (center-to-periphery approach). The Tr. inf running deep within the lung parenchyma and supplying S^2 was distinguished after resection of B^2 (posterobronchial approach). If the A. pos supplies S^2 (Figure 6), the A. pos can be identified by adopting the interlobar approach. If the A. pos and AX. rec supply S^2, we need to use the interlobar approach and center-to-periphery approach to recognize the A. pos and AX. rec. If A^2 branched from the A. pos, A. rec, and Tr. inf, the interlobar approach, center-to-periphery approach, and posterobronchial approach should be respectively applied to identify the A. pos, A. rec, and Tr. inf.

Likewise, for an accurate S^3 segmentectomy, we need to comprehend that S^3 is supplied by how many arterial branches (Table 8, Figure 7). If the Tr. sup supplies S^3, the Tr. sup can be dissected in a center-to-periphery direction to distinguish A^3. Moreover, when the AX. rec or AX^1b share a common trunk with A^3 (Figure 3), it is necessary to fully dissociate along the Tr. sup intraoperatively to facilitate the disconnection of A^3 and the protection of AX. rec, or AX^1b. When the Tr. inf supplies S^3, the Tr. inf can be distinguished by dissecting the mediastinal portion of the right main pulmonary artery. If the A. ant supplies S^3a and the Tr. sup supplies A^3b (Figure 7), the A^3a can be identified by dissecting interlobar fissures, and the Tr. sup should be dissected in a center-to-periphery direction to identify A^3b. Therefore, it is significant to conduct a comprehensive and thoughtful investigation of anatomical variations preoperatively.

The incorrect vascular identification may lead to surgical complications in segmentectomy. Surgical procedure changes according to vascular variations, and therefore, accurate preoperative recognition of variations is a mainstay when planning RUL segmentectomy. Therefore, preoperative 3D-CTBA to understand the branching patterns of the segmental arteries in the RUL is necessary to perform an accurate segmentectomy and subsegmentectomy.

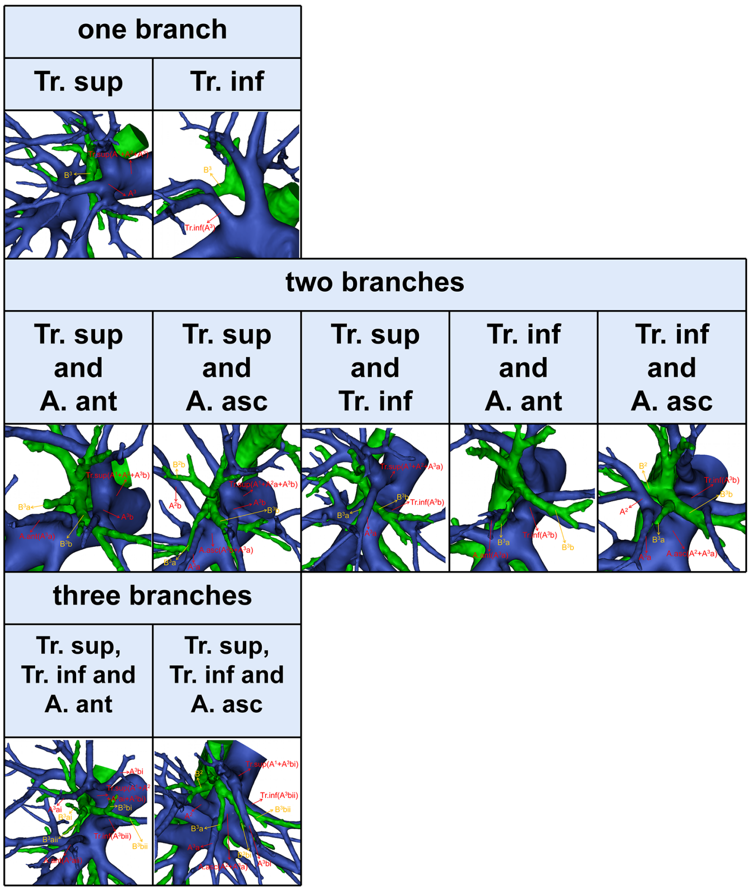

FIGURE 7
The 3D reconstruction model of the branching patterns of A^3.

TABLE 8 Branching patterns of A^3.

	Our study (n = 600)		Nagashima (n = 263)	
	No.	%	No.	%
One branch	339	56.5	200	76.1
Tr. sup	297	49.5	180	68.5
Tr. inf	42	7.0	20	7.6
Two branches	243	40.5	60	22.8
Tr. sup and A. ant	69	11.5	NR	–
Tr. sup and A. asc	105	17.5	35	13.3
Tr. sup and Tr. inf	48	8.0	20	7.6
Tr. inf and A. ant	9	1.5	NR	–
Tr. inf and A. asc	12	2.0	5	1.9
Three branches	18	3.0	NR	–
Tr. sup, Tr. inf and A. ant	7	1.2	NR	–
Tr. sup, Tr. inf and A. asc	11	1.8	NR	–
N/A	–	–	3	1.1

N/A, not available; NR, the type was not referred.

5 Conclusions

This is the first report to explore the detailed classification of the interlobar artery and the artery crossing intersegmental planes. We believe that our pulmonary artery data and our new nomenclature will facilitate preoperative simulation and intraoperative navigation when RUL segmentectomy is planned and performed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This retrospective study was approved by the Research Ethics Committee at Hebei General Hospital (No. 2022119). The need for patient consent was waived because of the retrospective nature of the study.

Author contributions

ZL: project design and initiation, data analysis, and manuscript writing. YK: project design and initiation, data analysis, and manuscript writing. BL: project design and initiation, data analysis, and manuscript writing. WL: data collection. XZ: supervisor. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comparison of lobectomy and sublobar resection for stage I non-small cell lung cancer: a meta-analysis based on randomized controlled trials

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Background: This meta-analysis aimed to compare the prognostic between lobectomy and sublobar resection in patients with stage I non-small cell lung cancer (NSCLC).

Methods: We conducted a detailed search in PubMed, Embase, Web of Science, and the Cochrane Library for randomized controlled trials (RCTs) comparing the prognosis of lobectomy and sublobar resection for stage I NSCLC, with the primary outcomes being overall survival (OS) and disease-free survival (DFS).

Results: A total of 2222 patients were included in the 5 RCTs. The results showed no statistical difference in OS (HR=0.87, p=0.445) and DFS (HR=0.99, p=0.918) between patients who underwent lobectomy and sublobar resection during the total follow-up period. In terms of dichotomous variables, there were no statistical differences in OS (relative ratio [RR]=1.05, p=0.848) and DFS (RR=1.21, p=0.075) between the two groups during the total follow-up period, as well as 5-year OS (RR=0.96, p=0.409) and 5-year DFS (RR=0.95, p=0.270). In addition, subgroup analysis showed a better prognosis for non-adenocarcinoma patients with sublobar resection than lobectomy (HR=0.53, p=0.037), but also an increased cause of cancer death (not limited to lung cancer) (RR=1.56, p=0.004).

Conclusion: Our results showed that for stage I NSCLC, lobectomy is usually not a justified operation.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023407301, identifier CRD42023407301.

KEYWORDS

stage I, non-small cell lung cancer, lobectomy, sublobar resection, meta-analysis, overall survival, disease-free survival

1 Introduction

As the second most widespread cancer and the leading cause of cancer deaths in the world, lung cancer has a cancer diagnosis rate of approximately 11.4% and a cancer mortality rate of 18.0% (1). Because of the advent of computed tomography (CT), more non-small cell lung cancers (NSCLC) are being diagnosed at an early stage (2). Lobectomy has long been the standard surgical treatment for stage I NSCLC (3), and patients who undergo lobectomy have an ideal overall survival (OS), with patients achieving a 5-year OS and 10-year OS of 77% and 70%, respectively, in one study (4). In theory, sublobar resection may offer anatomical and functional advantages over lobectomy because it preserves more lung tissue and improves the quality of patient survival, so there are proposals to reduce the extent of resection and preserve more lung function. However, another concern about sublobar resection is whether the prognosis of patients will be affected, and more studies are needed to compare the difference in prognosis between the two.

Liu et al. published a meta-analysis in 2014 comparing OS between lobectomy and sublobar resection in stage IA NSCLC, including 12 studies from 1993 to 2013 and found that OS was not as robust with sublobar resection as with lobectomy (5). In 2021, Lv et al. did another meta-analysis, including 12 studies from the establishment of the database to 2019. The analysis showed that patients with stage I NSCLC undergoing sublobar resection demonstrated poorer OS, while disease-free survival (DFS) was similar for both approaches (6), but neither article was based on randomized controlled trials (RCTs). Recently, the results of a new high-quality RCT study were published which showed similar prognostic outcomes for sublobar resection and lobectomy (7). Given the above situation, we believe that there is a compelling need to re-evaluate sublobar resection and lobectomy. Therefore, we performed a meta-analysis based on published RCTs to compare the differences between lobectomy and sublobar resection in prognosis in patients with NSCLC.

2 Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement: an updated guideline for reporting systematic reviews (8), registered in the “International Prospective Register of Systematic Reviews” (PROSPERO) in 2023 (CRD42023407301). The objective was to evaluate the prognosis of lobectomy and sublobar resection for stage I NSCLC by RCTs.

2.1 Literature search strategy

From the time of database establishment to March 2023, two researchers conducted a systematic and exhaustive screening of PubMed, Embase, Web of Science, and the Cochrane Library databases for articles on lobectomy and sublobar resection for NSCLC, using the following keywords:((lobectomy OR lobar resection) AND ((sublobar resection OR limited resection) OR (wedge AND segmentectomy)) AND ((lung cancer OR pulmonary cancer OR carcinoma of lung OR pulmonary carcinoma OR lung carcinoma OR lung neoplasms OR lung adenocarcinoma OR cancer of lung)). In particular, references to relevant literature were manually searched to avoid omitting any potentially relevant studies.

2.2 Inclusion and exclusion criteria

According to the PICOS principles, the criteria for inclusion in the studies were as follows: 1) patients were diagnosed with clinical stage I NSCLC (tumor size equal to or less than 3 cm, no regional lymph node metastasis), sublobar resection was extended to lobectomy if N1 disease is found during surgery; 2) intervention and control were sublobar resection and lobectomy; 3) outcomes of relevant included but were not limited to OS, DFS, recurrence rate, etc.; and 4) the included studies belong to the RCTs.

The exclusion criteria for this study were: 1) the full text of the study was not available; 2) the study data were not available, including the protocol; 3) when updating published articles for the same study cohort, studies that included the most recent or largest population were selected.

2.3 Data extraction

Data extraction was performed independently by 2 researchers according to a pre-designed form. For eligible studies, the following relevant information was extracted: 1) study characteristics: author, year of publication, country, sample size, and registration number; 2) participant characteristics: including tumor stage, histological typing, age, gender, follow-up time, etc.; and 3) survival outcomes applied for comparison.

2.4 Quality assessment

Two researchers used the Cochrane Collaboration’s tools to assess the quality of RCTs. Three indicators of “high risk”, “low risk”, and “unclear risk” were used to assess random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Two researchers, after discussion, will discuss and resolve differences in the evaluation, and bring in a third person when necessary.

2.5 Statistical analysis

This meta-analysis was performed using Review Manager, v.5.3, and Stata software, v.12.0. Hazard ratio (HR) and 95% confidence interval (CI) were used to evaluate continuous variables, and the

Abbreviations: NSCLC, non-small cell lung cancer; RCTs, randomized controlled trials; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; RR, relative ratio; CT, computed tomography; CI, confidence intervals; STAS, spreads through the air space.

relative risk (RR) and 95% CI were used to evaluate dichotomous information. Heterogeneity was calculated with the I^2 statistic; I^2>75% was considered severe heterogeneity, >50% and <75% high heterogeneity, >25% and <50% moderate heterogeneity, and <25% low heterogeneity. Due to the diversity of the population included in this study, a random-effects model was used uniformly to combine the results with the premise of improving the credibility of the results. A p-value <0.05 in a two-sided test is statistically significant (9). When more than ten studies were included, publication bias was investigated using Begg's test (10), and sensitivity analysis was conducted to evaluate the stability of the results.

3 Result

3.1 Description of the studies

6334 records were retrieved across the four databases using the set search strategy and no additional records were retrieved from other sources. After removing duplicates, 3064 records remained, and 2964 irrelevant articles were excluded by reviewing the titles and abstracts of the articles. After browsing the complete text, 95 articles were excluded, of which 88 were not RCTs, 5 due to duplication of data sources, 1 for being a research protocol, and 1 owing to unavailable data. In the finals, 5 RCTs (7, 11–14) were included in our meta-analysis. In Figure 1, the flowchart demonstrates the detailed process and the exclusion criteria.

Between 1995 and 2023, 5 RCTs compared survival outcomes of patients with stageINSCLC after lobectomy and sublobar resection. Of all patients, 1100 underwent sublobar resection, and the other 1122 underwent lobectomy. In three studies, sublobar resection included both segmental and wedge resection; the remainder included only segmental resection. In addition, all but one of the studies were for stage IA NSCLC with follow-up beyond 5 years and all provided OS and DFS. The characteristics of the studies included in this meta-analysis are outlined in Table 1 and Supplementary Table 1.

3.2 Risk of bias in the included studies

The quality assessment of the included studies is presented in Supplementary Figure 1 and Supplementary Figure 2. The quality of each RCT was evaluated using the Cochrane Collaboration's tool. All studies were assessed as low risk in terms of blindings of outcome assessment and incomplete outcome data. Most studies were assessed as low risk in three aspects: random sequence generation, allocation concealment, and selective reporting. A small number were considered an unclear risk. However, in terms of blinding of participants and personnel, three studies were of unclear risk, and the remaining two were of high risk, which was determined by the nature of the intervention. For other biases, the included studies were assessed as unclear risks.

3.3 Prognostic analysis

Three studies reported HR for OS in patients with stage I NSCLC who underwent sublobar resection versus lobectomy

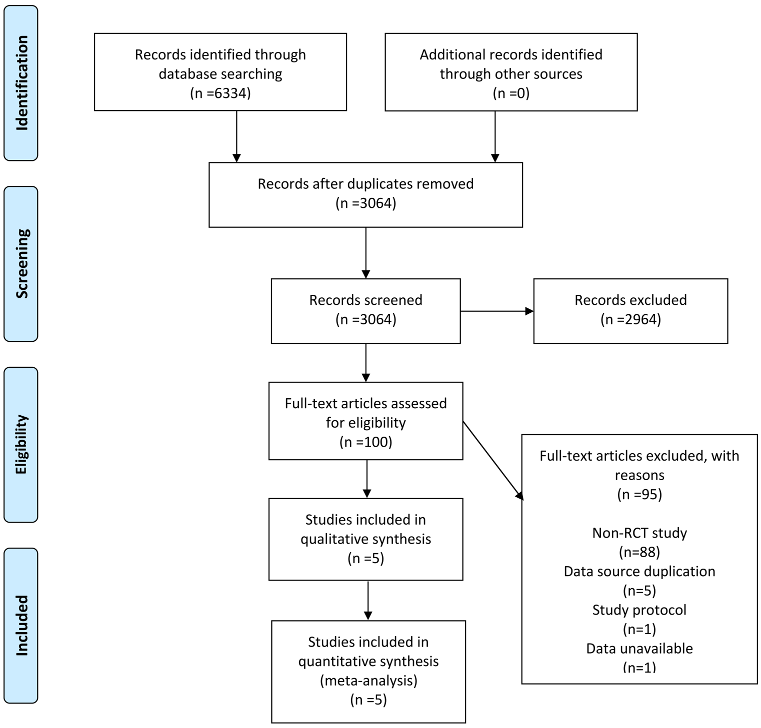

FIGURE 1
Flow diagram of selection.

TABLE 1 Characteristics of all the studies included in the meta-analysis.

Author	Year	Country	Treatment regimens		Number of patients		Neoplasm staging	Follow-up (years)	Outcomes
			Experiment	Control	Experiment	Control			
Robert J. Ginsberg	1995	America	Segmentectomy +wedge resection	Lobectomy	122	125	I	>4.5	DFS, OS
Terumoto Koike	2016	Japan	Segmentectomy +wedge resection	Lobectomy	33	32	IA	>5	DFS, OS
Nasser K Altorki	2022	Australia, Canada, America	Segmentectomy +wedge resection	Lobectomy	340	357	IA	>5	DFS, OS
Georgios Stamatis	2022	Germany, Switzerland, Austria	Segmentectomy	Lobectomy	53	54	IA	5	DFS, OS
Hisashi Saji	2022	Japan	Segmentectomy	Lobectomy	552	554	IA	>5	DFS, OS

I, tumor size equal or less than 3 cm; IA, tumor size smaller than 2 cm in longest dimension; DFS, Disease-free survival; OS, overall survival.

throughout the follow-up period, with pooled results indicating no difference in OS (HR=0.87, 95%CI=0.60-1.25, p=0.445) (Figure 2). In addition, from the perspective of dichotomous variables, the results showed no significant difference between the two groups in terms of OS during the follow-up period (RR=1.05, 95%CI=0.63-1.75, p=0.848) (Figure 3), but by a higher heterogeneity (I^2 = 75%, p=0.018). Five studies offered 5-year OS, and the results showed no difference in 5-year OS between the two groups (RR=0.96, 95% CI=0.89-1.05, p=0.409) (Supplementary Figure 3); the results were also highly heterogeneous (I^2 = 70%, p=0.010).

Three studies reported HR for DFS in patients with stage I NSCLC throughout the follow-up period, with pooled results showing no statistical difference in DFS between patients who underwent sublobar resection and those who underwent lobectomy (HR=0.99, 95%CI=0.84-1.17, p=0.918) (Figure 4). No heterogeneity was detected in the studies included (I^2 = 0).

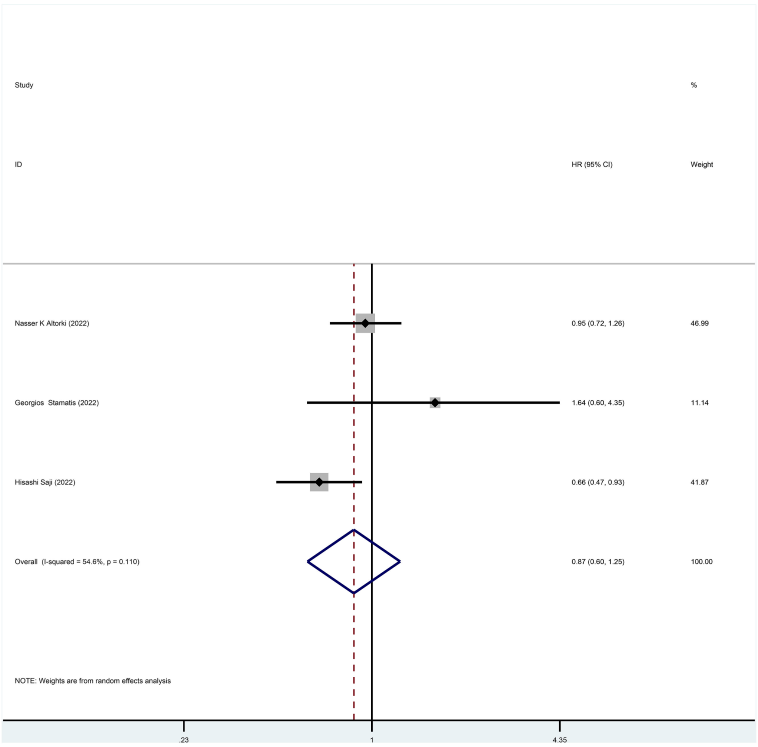

FIGURE 2
Forest plot of meta-analysis of the effects of sublobar resection and lobectomy on overall survival in stage I NSCLC (HR perspective, p=0.445).

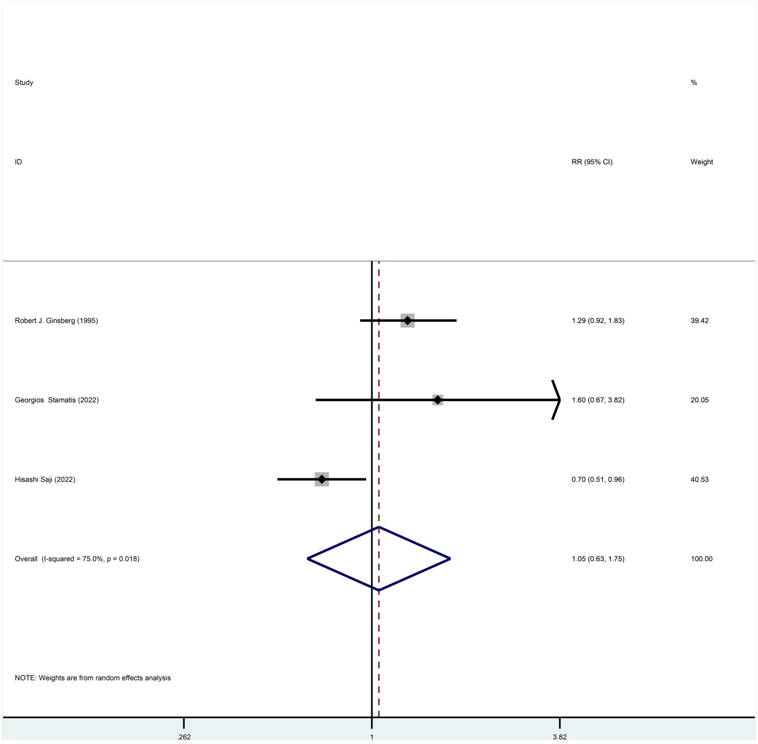

FIGURE 3
Forest plot of meta-analysis of the effects of sublobar resection and lobectomy on overall survival in stage I NSCLC (dichotomous variable perspective, p=0.848).

Moreover, from the perspective of dichotomous variables, there was also no difference in DFS among the two groups at the overall follow-up (RR=1.21, 95%CI=0.98-1.49, p=0.075) (Figure 5). Five studies delivered 5-year DFS and the statistical outcomes showed no significant differences in the 5-year DFS between the two groups (RR=0.95, 95%CI=0.86-1.04, p=0.270) (Supplementary Figure 4).

3.4 Subgroup analysis

Predefined subgroup analyses were performed, as detailed in Table 2. Subgroup analyses of OS considering gender, histological typing, and cause of death, were conducted. Subgroup analysis regarding gender showed no significant differences in OS between patients undergoing sublobar resection and lobectomy in the male (HR=0.99, p=0.981) or female groups (HR=1.45, p=0.534). For patients with adenocarcinoma, no difference was found in the OS after surgery between the two groups (HR=1.2, p=0.673). However, it is worth noting that for patients with non-adenocarcinoma, OS was statistically better for those who underwent sublobar resection than lobectomy (HR=0.53, p=0.037). When cancer cause of death (not limited to any cancer) was analyzed as the primary outcome, patients who underwent sublobar resection had a lower OS than those who underwent lobectomy (RR=1.56, p=0.004). For other causes of death (non-cancer), no difference in OS was observed between those who underwent sublobar resection and lobectomy (RR=1.13, p=0.552).

4 Discussion

Our results showed no difference in prognosis between patients with stage I NSCLC who underwent lobectomy and sublobar resection, using OS and DFS as the primary endpoints. Previously, the results of Nakamura et al. showed that the two surgical approaches were comparable in terms of OS (15), which is consistent with the results of the present study, whereas the results of Lv et al. showed comparable results between the two only in terms of DFS (6), while lobectomy was superior to sublobar resection in terms of OS, which is inconsistent with the findings of the present study. The present study is the first meta-analysis based on published RCTs and the results have a high level of confidence.

Since the publication of the results of the LSCG trial in 1995 (11), lobectomy has become the standard procedure for early-stage lung cancer. The extent of resection for early-stage NSCLC remains a controversial issue, but in all surgical resections, whether lobectomy or sublobar resection, the principles of oncologic treatment should be strictly adhered to, including radical resection of the tumor, reducing surgical risk and preserving the patient's organism as much as possible (16).

Our study showed no difference between the lobectomy and sublobar resection in OS and DFS over the total follow-up period in terms of the HR and the dichotomous variable perspective; 5-year OS and 5-year DFS were also comparable in terms of the dichotomous variable perspective. This may be due to the better

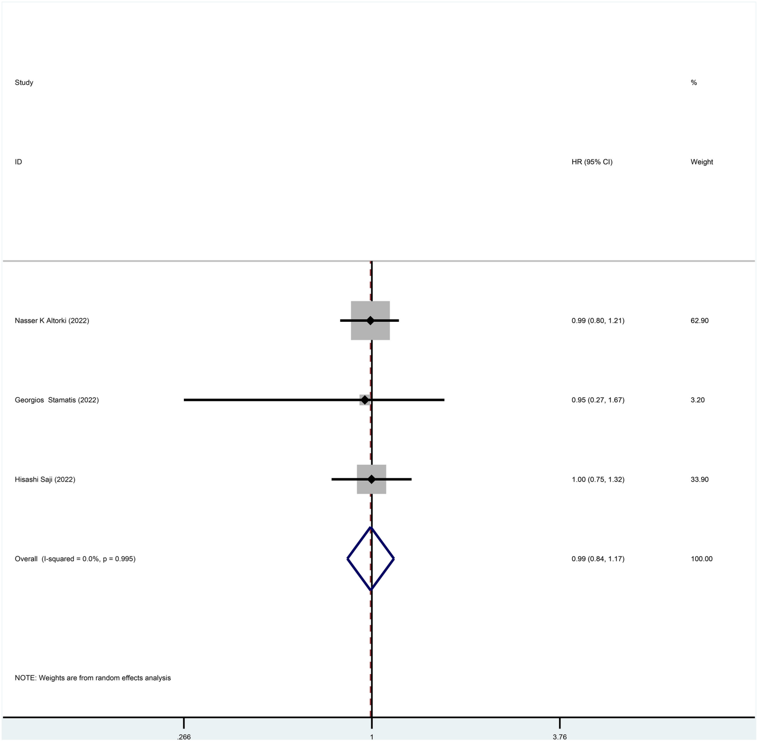

FIGURE 4
Forest plot of a meta-analysis of the effects of sublobar resection and lobectomy on disease-free survival in stage I NSCLC (HR perspective, p=0.918).

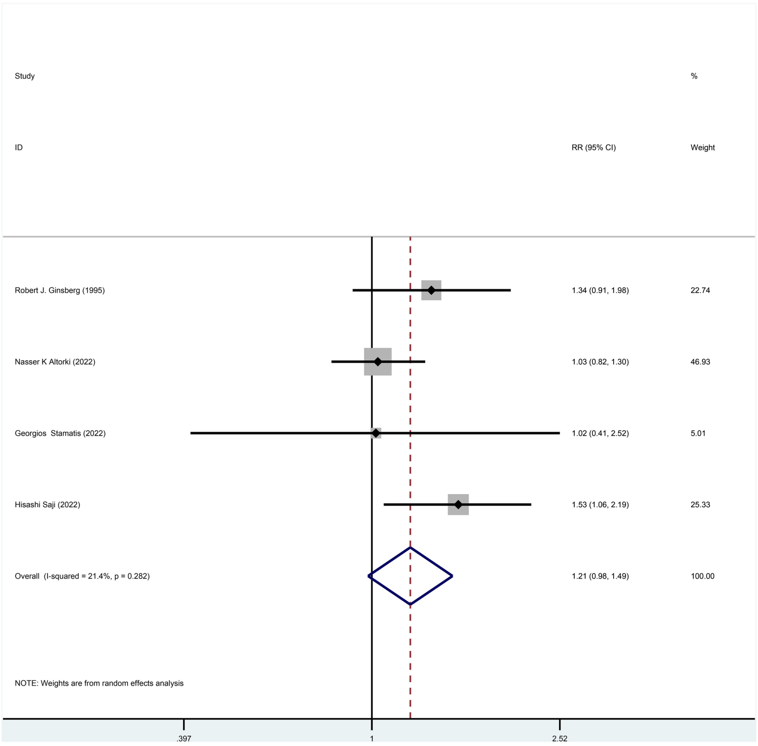

FIGURE 5
Forest plot of a meta-analysis of the effects of sublobar resection and lobectomy on disease-free survival in stage I NSCLC (dichotomous variable perspective, p=0.075).

TABLE 2 Subgroup analysis of overall survival.

	No. of studies	HR/RR	95%CI	P	Heterogeneity	
					I^2	P
Female	2	1.45	0.45, 4.61	0.534	82.8%	0.016
Male	2	0.99	0.37, 2.61	0.981	84.4%	0.011
Adenocarcinoma	2	1.26	0.43, 3.71	0.673	88.8%	0.003
Non-adenocarcinoma	2	0.53	0.30, 0.96	0.037	0	0.696
Death due to cancer	3	1.56*	1.15, 2.10	0.004	0	0.792
Death to other cause	3	1.13*	0.76, 1.69	0.552	0	0.959

HR, hazard ratio; RR, risk ratio; CI, confidence interval.
*The pooled effect size is RR.

prognosis of patients with stage I NSCLC, with data showing that the 5-year survival rate of patients with stageINSCLC in the United States was about 70% between 2001 and 2017 (17). Besides, a prospective trial of stage I NSCLC demonstrated a local regional recurrence rate of 2% and a 5-year survival rate of 91% in patients when the surgical margin distance was greater than the tumor size (18). Other studies have also demonstrated that the local recurrence rate after segmental resection for stage I NSCLC is in the range of 2%-8% (19–24). The key to sublobar resection is to ensure adequate margins, which are an important factor in local recurrence and prognosis. In the article by Georgios Stamatis et al., sublobar resection is an anatomical segmentectomy using a standardized protocol for anatomical segmentectomies. The segmentectomy by Hisashi Saji et al. includes one segmental resection and bi-segmental resection (including left tri-segmentectomy), excluding basal segmentectomy. The groups that performed sublobar resections in the remaining articles all performed segmental resections or wedge resections at the surgeon's discretion. All sublobar resection groups in the included studies had negative margins confirmed by margin lavage cytology or frozen section examination. So it is speculated that sublobar resection is sufficient for the complete resection of the tumor and surrounding subclinical lesions in stage I NSCLC.

In addition, the low rate of lymph node metastasis in stage I NSCLC may also be another factor, with the results of related studies showing that the rate of lymph node metastasis in stage I NSCLC ranges from 3.2% to 14.5% (25–27). An RCT comparing lymph node sampling and complete lymph node dissection in the mediastinum showed no difference in postoperative survival and recurrence rates between these two approaches (28), and other studies have also shown that lymph node dissection performed in early-stage lung cancer has no effect on patient survival (29–31), and given these results, it can be hypothesized that performing sublobar resection resulting in less lymph node dissection may not affect prognosis.

Regarding the effect of gender on OS after two surgical approaches, the results of Kim et al. showed that gender was not a factor affecting the survival rate of both surgical modalities (32) and a propensity-matching analysis study by Zhou et al. showed that in women, the lobectomy group was superior to the sublobar resection group, while in men, there was no difference between the two surgical approaches (33). However, there was no difference in OS between male and female patients with stage I NSCLC who underwent lobectomy or sublobar resection in the subgroup of this study. Presumably, as the sample size included in the analysis increases, gender is no longer a factor affecting OS.

Concerning histological staging, our meta-analysis showed that for non-adenocarcinoma in stage I NSCLC, OS was better and statistically significant for sublobar resection than with lobectomy. In contrast, for adenocarcinoma, there was no difference in OS between lobectomy and sublobar resection. This may be attributed to the fact that adenocarcinoma is more often seen in women, and most of its occurrence is not due to tobacco, but more likely to the increased inhalation of oil-based cooking fumes, household pollutants, and industrial dust (34), and one study suggests that increased frequency of cooking fume inhalation may be an important factor in lung cancer in non-smoking women (35). These patients are young, their lung function is better and, in theory, the more lung tissue preserved by sublobar resection, the less it will contribute to the improvement of lung function. While squamous carcinoma predominates in the non-adenocarcinoma population, the main bronchial squamous cell carcinoma is in turn associated with male smokers (34), such an incidence population is associated with older age, poor cardiopulmonary function and a higher risk of serious comorbidities, while sublobar resection preserves more lung substance, theoretically preserving more postoperative lung function and potentially reducing short- and long-term pulmonary complications, thus improving patient's OS.

Regarding the cause of death, the results of this study showed that the number of cancer deaths (not limited to lung cancer) was higher with sublobar resection than with lobectomy, with statistically significant results. Lung cancer probably accounts for the majority of the deaths. In addition to the possibility that cancer cells remaining at the surgical margin, it is also possible for lung cancer to spread through the air space (STAS). In 2015, the WHO defined "STAS" as the invasion of the airspace around the lung parenchyma by micropapillary, solid nests, or clusters of single cells beyond the tumor margin (18). Mino-Kenudson's study indicated that the frequency of STAS can range from 15% to 56% in different cohorts as well as in tumor stages (36). Some studies reported that STAS is an important independent factor for recurrence after sublobar resection in early NSCLC (37–40). The mechanism may be that STAS in the alveolar space beyond the surgical margins goes undetected, leading to increased mortality from lung cancer. In addition, sublobar resection preserves more lung tissue than lobectomy, increasing the probability of secondary lung cancer in patients. Among non-cancer causes of death, sublobar resection could theoretically reduce the incidence of postoperative complications and reduce non-cancer mortality because of the preservation of lung function. However, the combined results of the two groups did not differ, and sublobar resection did not reduce the risk of non-cancer causes of death relative to lobectomy. This may be because comprehensive postoperative treatment reduced the non-cancer mortality in the lobectomy group and does not exclude the fact that the study's included population had better lung function and that postoperative cardiopulmonary function was not severely affected even with lobectomy.

Besides, according to WHO statistics in 2019, cardiovascular disease has become the number one cause of death worldwide. Thus, considering competing mortality rates, survival rates for early-stage lung cancer are high, reaching 70% (17), while more patients die from heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, and other non-tumor factors, resulting in a smaller percentage of deaths from cancer, which may explain why there is no difference in OS between lobectomy and sublobar resection, while sublobar resection has a higher cause of cancer death than lobectomy, but the non-cancer cause of death rate is comparable between the two.

There are some limitations to this study. A total of 5 RCTs to date were included to compare the prognosis of lobectomy and sublobar resection. The small number of articles makes them more susceptible to chance. More detailed subgroup analyses, such as the effect of race, age, and thoracoscopic surgery on OS, or the differences between the different types of sublobar resection and their indications are difficult to perform because of the limited nature of the data. Large samples of RCTs and more detailed data are still needed for more detailed subgroup analyses of groups, specific staging, and histology for specific surgeries, leading to more specific conclusions. Due to differences in the populations included in the study, there was some heterogeneity in some of the results.

In conclusion, this meta-analysis showed that for stage I NSCLC, lobectomy is usually not a justified operation. Gender was not a factor affecting OS for lobectomy and sublobar resection in stage I NSCLC, and sublobar resection in non-adenocarcinoma patients had a better OS, but at the same time, sublobar resection might increase the risk of cancer death (not limited to lung cancer).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

GL: Writing – original draft, Conceptualization, Methodology. ZX: Writing – original draft, Methodology, Software. YZ: Data curation, Software, Writing – original draft. SD: Data curation, Methodology, Software, Writing – original draft. FT: Resources, Validation, Writing – original draft. RJ: Data curation, Methodology, Software, Writing – original draft. MD: Data curation, Validation, Writing – original draft. QZ: Resources, Validation, Writing – original draft. DZ: Conceptualization, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that this study received funding from Longyou County Guiding Science and Technology Project. The funder had the following involvement with the study: study design, analysis, interpretation of data, writing of this article, and the decision to submit it for publication.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1261263/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Risk of bias summary of the included RCTs.

SUPPLEMENTARY FIGURE 2
Risk of bias graph of the included RCTs.

SUPPLEMENTARY FIGURE 3
Forest plot of meta-analysis of the effects of sublobar resection and lobectomy on 5-year overall survival in stage I NSCLC (dichotomous variable perspective, p=0.409).

SUPPLEMENTARY FIGURE 4
Forest plot of a meta-analysis of the effects of sublobar resection and lobectomy on 5-year disease-free survival in stage I NSCLC (dichotomous variable perspective, p=0.270).

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Comparison of robot-assisted thoracic surgery versus video-assisted thoracic surgery in the treatment of lung cancer: a systematic review and meta-analysis of prospective studies

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Introduction: Previous studies have compared robot-assisted thoracic surgery (RATS) with video-assisted thoracic surgery (VATS) in the treatment of patients with lung cancer, but results were conflicting. The present meta-analysis aimed to compare the clinical outcomes of RATS with VATS in the treatment of patients with lung cancer.

Materials and methods: Web of Science, PubMed, Cochrane Library and Embase were comprehensively searched for randomized controlled trials or prospective cohort studies comparing the clinical outcomes of RATS and VATS from inception to 22 July 2023. The Cochrane Risk of Bias tool was used to assess risk of bias. Meta-analyses of length of hospital stay, postoperative duration of drainage, postoperative complications, operative time, conversion, estimated blood loss, the number of dissected lymph nodes and stations, 30-day readmission and 30-day mortality were performed.

Results: In total 5 studies were included in the meta-analysis. A total of 614 patients were included, of which 299 patients were treated by RATS and 315 patients treated by VATS. Blood loss was significantly less in RATS group than that in VATS (MD = –17.14, 95% CI –29.96 ~ –4.33, P = 0.009). More nodes stations were dissected in RATS group compared with VATS group(MD= 1.07, 95% CI 0.79 ~ 1.36, P < 0.001). No significant difference occurred between RATS and VATS in length of hospital stay(MD= –0.19, 95% CI –0.98~0.61), readmission(OR=0.74, 95% CI 0.36~1.51, P=0.41), operative time(MD=11.43 95% CI –8.41~31.26, P=0.26), conversion(OR=0.58, 95% CI 0.29~1.17, P=0.13), number of dissected lymph nodes(MD=0.98, 95% CI –0.02~1.97, P=0.05), upstaging rate(OR =0.67, 95% CI 0.38 ~ 1.18, P =0.16, $I^2 = 0\%$), time of chest tube drainage (MD= –0.34, 95%CI –0.84~0.15, P=0.17), post-operative complications(OR=0.76, 95% CI 0.52~ 1.11, P=0.16) and total cost(MD = 3103.48, 95% CI –575.78 ~ 6782.74, P=0.1, $I^2 = 99\%$).

Conclusion: RATS is a feasible and safe treatment that can achieve better surgical outcomes compared with VATS in terms of short-term outcomes. Except of higher total cost, RATS has obvious advantage in lymphadenectomy and control of intraoperative bleeding. However, large sample and long follow-up randomized clinical trials comparing RATS with VATS are still necessary to better demonstrate the advantages of RATS for lung cancer.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, Identifier CRD42023446653.

KEYWORDS

robot-assisted thoracic surgery[1], video-assisted thoracic surgery[2], lung cancer[3], non-small cell lung cancer[4], complication[5]

1 Introduction

Lung cancer is still the most common malignancy worldwide which seriously threaten human health and life, accounting for 11.4% of all cancer cases and 18% of all deaths due to cancer (1–3). Lung cancer has two subtypes: small cell lung cancer which account for 15% and non-small cell lung cancer (NSCLC) which account for 85% (4). The preferred treatment for NSCLC is surgical resection. Thought the traditional open surgery approach is effective, it has been shown to be associated with substantial postoperative complications and mortality (5). VATS has been widely used in thoracic surgery worldwide which could maintain similar long-term outcomes and obviously improve short-term outcomes compared with open thoracotomy (6, 7). However, VATS has several limitations, including of difficult hand-eye coordination, a long learning curve, lack of flexibility, and the disadvantage in terms of mediastinal lymphadenectomy, which may restrict its development (8–10). Since the first robot-assisted thoracic surgery(RATS) performed in 2003, RATS has developed quickly into a relatively new platform for surgical resection, which has been considered as an alternative to VATS (11). RATS seems to have some advantages over VATS, including of high definition three-dimensional optics, better ergonomics, shorter learning curve, small-wristed instrument motions, outstanding maneuverability of instruments and better tremor suppression, improving the perioperative outcomes (12–15).

Though previous systematic reviews and meta-analysis have sought to compare operative approaches for lung cancer, their conclusions were conflicting on whether or not it benefits to transitioning to RATS for surgeons who have mastered VATS (16–19). Due to the shortage of strict inclusion criteria, a large amount of low evidence level RATS studies such as retrospective studies, database studies, and even other metaanalysis was included in above studies, which led to duplication of studied patients and resulted in probably unreliable conclusions.

In the present study, strict inclusion criteria was performed and only randomized controlled trials or prospective cohort studies were included to compare outcomes of RATS versus VATS in the treatment of lung cancer. The primary objective of the review was to examine perioperative complications. Secondary outcomes included hospital stay, operation time, intraoperative bleeding, number of dissected lymph nodes stations, number of lymph nodes cleared during surgery, conversion rate during surgery, postoperative thoracic drainage time, postoperative hospital stay, incidence of early postoperative complications, 30-day mortality, 30-day readmission, total cost.

2 Materials and methods

2.1 Search strategy

Our study has been registered at PROSPERO under registration number CRD42023446653. The systemic review and meta-analysis was completed according to the Preferred Reporting Project for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. A systematic literature search for studies investigating RATS versus VATS for lung cancer was conducted in Medline (1946 to July 22, 2023), Embase (1974 to July 22, 2023), Web of Science (1966 to July 22, 2023), and CENTRAL(1995 to July 22, 2023) by two independent investigators, using the following searching terms: "Lung cancer" AND "Robotic" AND "Thoracoscopy" AND ("randomized controlled trial" OR "Prospective Studies"). The details of the searching record in four databases were shown in Supplement Tables 1–4. The bibliographies of the identified articles including of relevant reviews and meta-analyses were also manually checked to identify additional eligible studies. Besides, we also searched three clinical trial registries (ClinicalTrials.gov, Controlled-trials.com, Umin.ac.jp/ctr/index. The htm) for unpublished clinical studies.

2.2 Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) a randomized controlled trial or prospective cohort study comparing RATS with VATS for the treatment of lobectomy or segmentectomy in patients with lung cancer; (2)full-text articles reporting at least one of the following outcomes: perioperative complications, hospital stay, operation time, intraoperative bleeding, number of dissected lymph nodes stations, number of lymph nodes cleared during surgery, conversion rate during surgery, postoperative thoracic drainage time, postoperative hospital stay, incidence of early postoperative complications, 30-day mortality, 30-day readmission, total cost, upstaging rate; (3) if two or more researches included the same cohort, only the latest published one was included.

Literatures meeting the following criteria were excluded: (1) other types of articles, such an reviews, case reports, animal experimental studies, letters to the editor, conference abstracts, comments, database studies; (2) no lung cancer cases; (3)small sample size: less than 10 participants in RATS group; (4) retrospective studies.

2.3 Data extraction

Two independent investigators initially extracted relevant data of included studies, and a third reviewer checked it. The following data were extracted: publication year, country, first author, sample size (intervention arm and control arm), study design, surgical techniques, age, sex, site of tumor, TNM stage, the number of dissected lymph nodes, the number of dissected lymph stations, operative time, conversion, estimated blood loss, postoperative duration of drainage, length of hospital stay, postoperative complications, 30-day readmission, 30-day mortality, upstaging rate, total cost.

2.4 Risk of bias assessment

The risk of bias in the studies included was assessed by two independent reviewers using the Cochrane Risk of Bias tool, which includes seven domains: (1)random sequence generation; (2) allocation concealment; (3)blinding of participants and personnel; (4)blinding of outcome assessment; (5)incomplete outcome data; (6)selective reporting; (7)others bias. If there were discrepancies, the controversial results were resolved by group discussion.

2.5 Data analysis and statistical methods

The selection of studies and duplicate removal were conducted using EndNote (Version 20; Clarivate Analytics). All results of the studies were analyzed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Odds ratio (OR) with 95% confidence interval (CI) were used to compare binary variables. Continuous variables were compared using weighted mean difference (WMD) with a 95% CI. The medians and interquartile ranges of continuous data were converted to means and standard deviations. For all meta-analyses, the Cochrane Q p value and I^2 statistic were applied to check heterogeneity. Pooled data were analyzed using a fixed-effect model (FEM) if heterogeneity was low or moderate (I^2 <50%), or a random-effect model(REM) if heterogeneity was high (I^2 ≥50%). Statistical heterogeneity was assessed using a standard chi-square test and was considered significant at P<0.05. The potential publication bias was evaluated by visually inspecting the funnel plots.

3 Results

3.1 Literature search

The process of the studies selection and inclusion was shown in Figure 1. A total of 346 articles were retrieved from four databases, and 3 article was obtained by checking the bibliographies of the identified articles. Finally, a total of 5 prospective studies(20–24) were included in the final meta-analysis based on inclusion and exclusion criteria.

3.2 Characteristics of the included studies

In total, 5 studies consist of 614 patients were included in the meta-analysis, of which 299 patients were treated by RATS and 315 patients were treated by VATS. The five studies came from different countries (Korea, France, Brazilian, Italy, China) and were all prospective studies in recent 10 years. The detailed information and baseline characteristics of the included patients is presented in Table 1. Three of the studies were prospective randomized controlled trials, and another two were prospective non-randomized controlled studies with the choice between VATS and RATS depending on patient-preference or robot availability.

3.3 Risk of bias

The assessment of the risk of bias are summarized in Figure 2. Among the 5 studies, an adequate randomized sequence was reported in 3 studies, appropriate allocation concealment was generated in 3 studies, the blinding of participants was clear in 5 studies, the blinding of outcome assessors was generated in no studies, outcome data were complete in 5 studies, 5 studies had no selective reporting, and 4 studies had no other bias.

3.4 Clinical outcomes

Table 2 showed results of meta-analysis for all clinical outcomes. The operative time was reported in 5 literature, and no significant difference occurred between two groups(WMD =11.43, 95% CI −8.41 ~ 31.26, P =0.21, I^2 = 79%) (Figure 3A). Two studies reported the estimated blood loss. The estimated blood loss in RATS group was significantly lower than that in VATS group (WMD= −17.14, 95% CI −29.96 ~ −4.33, P=0.009, I^2 = 0%) (Figure 3B). Five studies reported the conversion cases, conversion rate was not statistically significant between two group (WMD=0.58, 95% CI 0.29 ~ 1.17, P =0.13, I^2 = 36%) (Figure 3C).

The number of dissected lymph nodes stations in RATS group was significantly more than that of VATS groups(WMD = 1.07, 95% CI 0.79 ~ 1.36, P < 0.001) (Figure 4A). Two studies reported

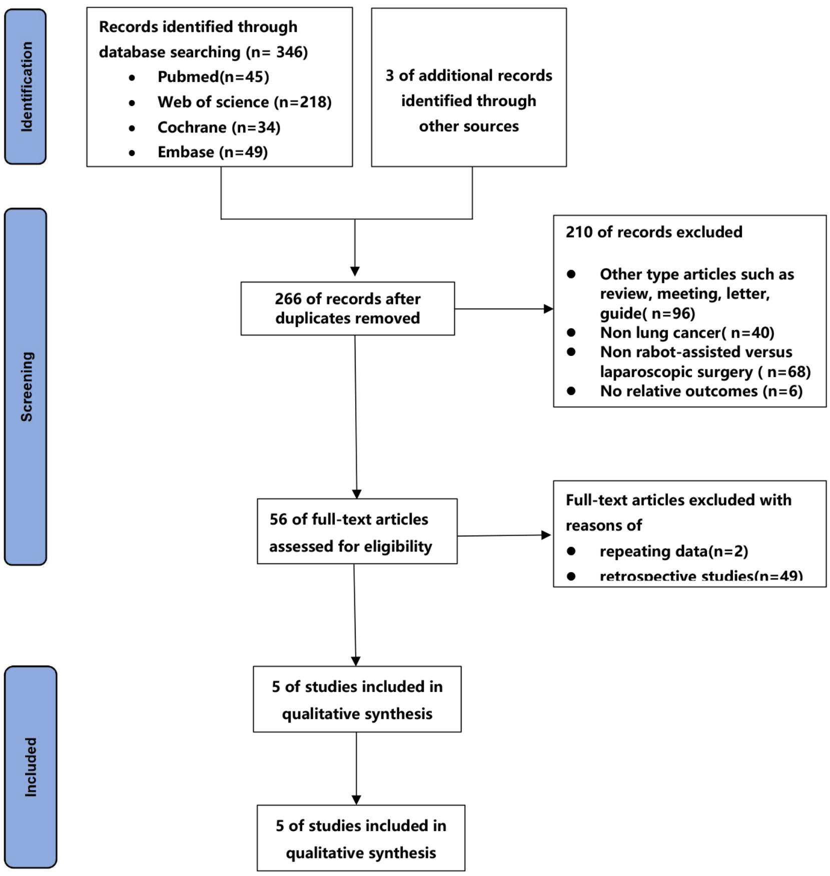

FIGURE 1
Flow chart of literature search strategies.

the number of dissected lymph nodes. Pooled analysis showed that the number of dissected lymph nodes had no significant difference between two groups(WMD = 0.98, 95% CI – 0.02 ~ 1.97, P = 0.05, I^2 = 0%) (Figure 4B).

The time of chest tube drainage had no significant difference between RATS group and VATS group(WMD = −0.34, 95% CI −0.84 ~ −0.15, P =0.17, I^2 = 50%) (Figure 5A). Pooled analysis showed that the length of hospital stay was not significant different between the RATS and VATS(WMD = −0.19, 95% CI −0.98 ~ 0.61, P =0.65, I^2 = 72%) (Figure 5B). Pooled analysis of 3 studies showed that no significant difference appeared in the 30-day mortality between RATS and VATS(WMD = 0.20, 95% CI 0.01 ~ 4.26, P =0.30) (Figure 5C). 30-day readmission was not significant different between RATS and VATS(OR = 0.74, 95% CI 0.36 ~1.51, P = 0.41,

TABLE 1 Characteristics of the included studies.

study	year	country	design	Study Period	group	cases	mean age	Sex (M/F)	Surgical techniques	Tumor Site (Right/Left)	TNM stage (0/I/II/III, IV)
Park	2017	Korea	P	2011-2013	RATS VATS	12 17	62.60 61.20	7/5 7/10	4 arms	6/6 13/4	0/29/0/0
Gonde	2017	France	P	2014-2015	RATS VATS	57 55	60.65 62.65	31/26 41/14	3 arms	NA	0/52/23/7/1
Terra	2019	Brazilian	P	2015-2017	RATS VATS	37 39	68.40 65.70	17/20 17/22	3 arms	25/12 21/18	NA
Veronesi	2021	Italy	P	2017-2018	RATS VATS	38 39	69.00 69.00	21/17 23/16	NA	24/14 23/16	0/67/5/0
Jin	2022	China	P	2017-2020	RATS VATS	157 163	60.30 60.95	81/76 76/87	3 arms	NA	3/265/25/27

P, Prospective Studies; RATS, robot-assisted thoracic surgery; VATS, video-assisted thoracic surgery; M, male; F, female; NA, not available.

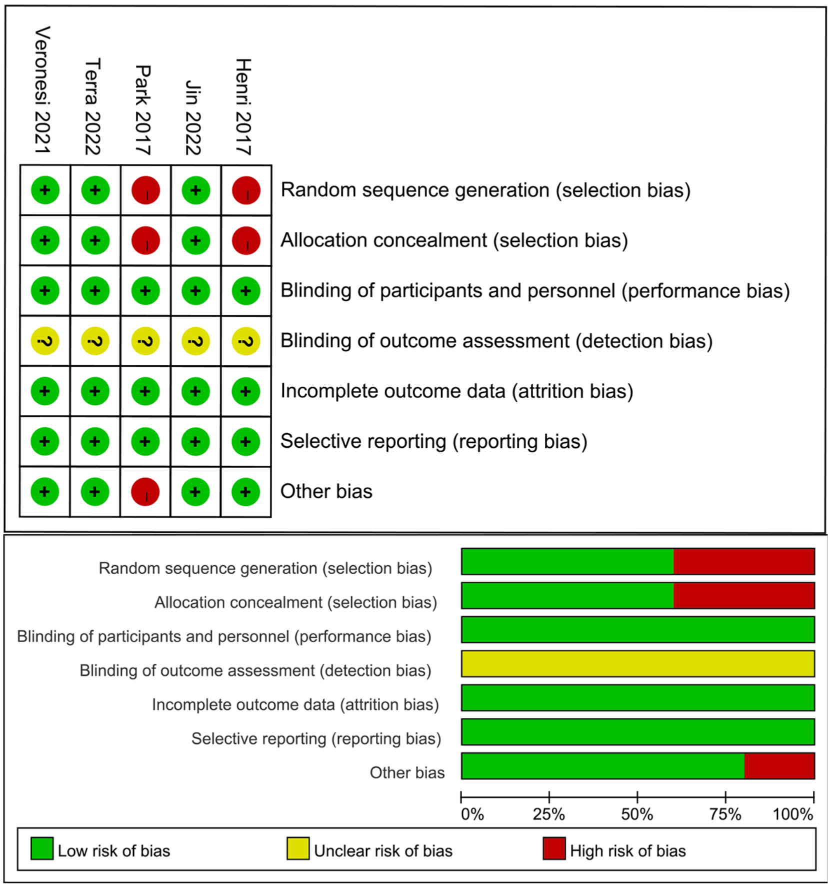

FIGURE 2
Risk of bias assessment for the included studies.

TABLE 2 Results of the meta-analysis.

Outcomes	No. of studies	Sample size	Heterogeneity		Overall effect size	95% CI of overall effect	P Value
		RATS VATS	I^2(%)	P Value			
Operation time (min)	5	299 315	79	<0.001	WMD=11.43	-8.41 ~31.26	0.26
Estimated blood loss (mL)	3	169 180	0	0.55	WMD=-17.14	-29.96~-4.33	0.009
Conversion	5	299 315	36	0.18	WMD=0.58	0.29~1.17	0.13
Dissected lymph node stations	2	195 202	0	0.38	WMD=1.07	0.79~1.36	<0.001
Dissected lymph nodes	2	169 180	0	0.65	WMD=0.98	-0.02~1.97	0.05
Time of chest tube drainage (days)	4	287 298	50	0.11	WMD=-0.34	-0.84~0.15	0.17
Length of hospital stay (days)	5	299 315	72	<0.001	WMD=-0.19	-0.98~0.61	0.65
30-day mortality	3	224 237	0	0	OR=0.20	0.01~4.26	0.30
30-day readmission	5	299 315	38	0.17	OR=0.74	0.36~1.51	0.41
Overall complications	5	299 315	14	0.32	WMD=0.76	0.52~1.11	0.16
Pneumonia	3	232 241	0	0.41	OR=1.65	0.43~6.43	0.47
Pleural effusion	3	232 241	0	1.00	OR=1.04	0.26~4.22	0.96
Atelectasis	2	75 78	19	0.27	OR=1.47	0.28~7.65	0.65
Arrhythmia	3	232 241	0	0.61	OR=1.26	0.37~4.28	0.71
Total cost	2	212 218	99	<0.001	WMD=3103.48	-575.78~6782.74	0.10

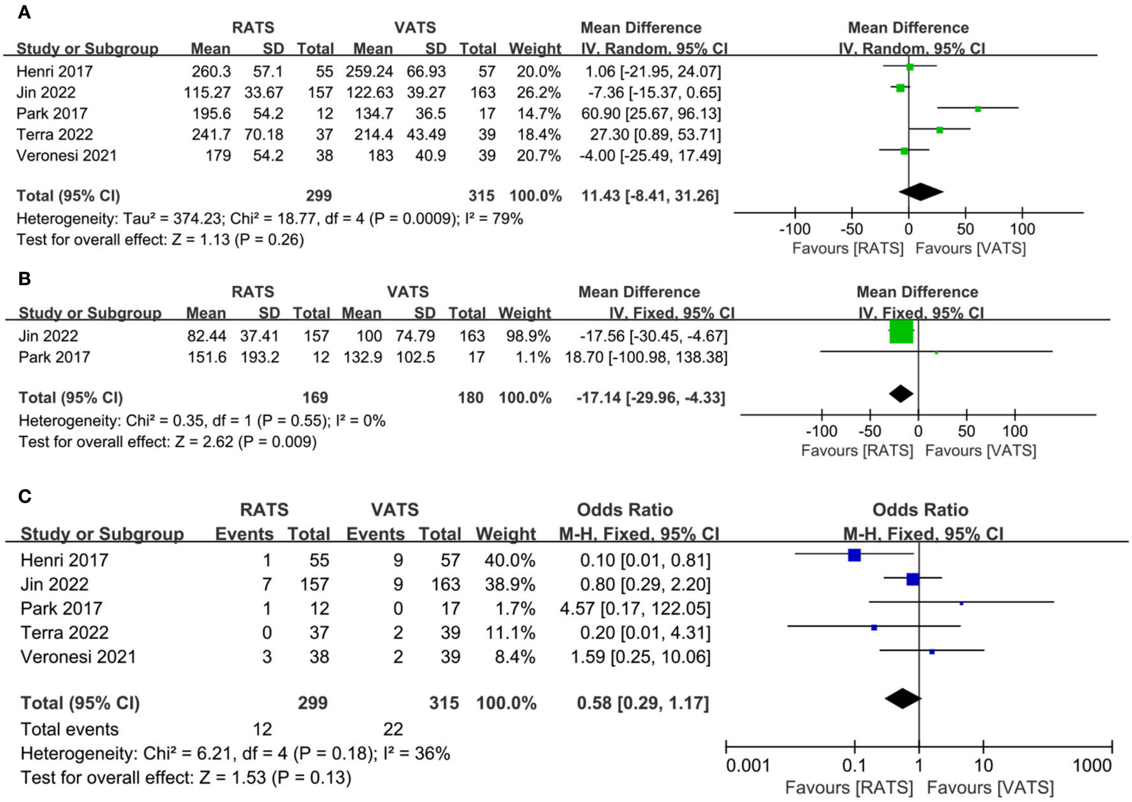

FIGURE 3
Forest plot of the meta-analysis for intraoperative parameters. **(A)** Operation time. **(B)** Estimated blood loss. **(C)** Conversion.

$I^2 = 38\%$) (Figure 5D). Five studies presented the overall postoperative complication. Pooled analysis showed that there was no significant difference in the rate of overall postoperative complication between the two groups(WMD = 0.76, 95% CI 0.52 ~ 1.11, P =0.16, $I^2 = 14\%$) (Figure 5E).

We also analyzed the common complications of RATS and VATS, including of prolonged air leak, pneumonia, pleural effusion, atelectasis, arrhythmia. The results of the analysis showed that RATS and VATS were not statistically significant in prolonged air leak(OR =0.93, 95% CI 0.43 ~2.05, P =0.87, $I^2 = 0\%$) (Figure 6A), pneumonia(OR =1.65, 95% CI 0.43 ~6.43, P =0.47, $I^2 = 0\%$) (Figure 6B), pleural effusion(OR =1.04, 95% CI 0.26 ~4.22, P =0.96, $I^2 = 0\%$) (Figure 6C), atelectasis(OR = 1.47, 95% CI 0.28 ~7.65, P = 0.65, $I^2 = 19\%$) (Figure 6D) and arrhythmia(OR = 1.26, 95% CI 0.37 ~4.28, P =0.71, $I^2 = 0\%$) (Figure 6E).

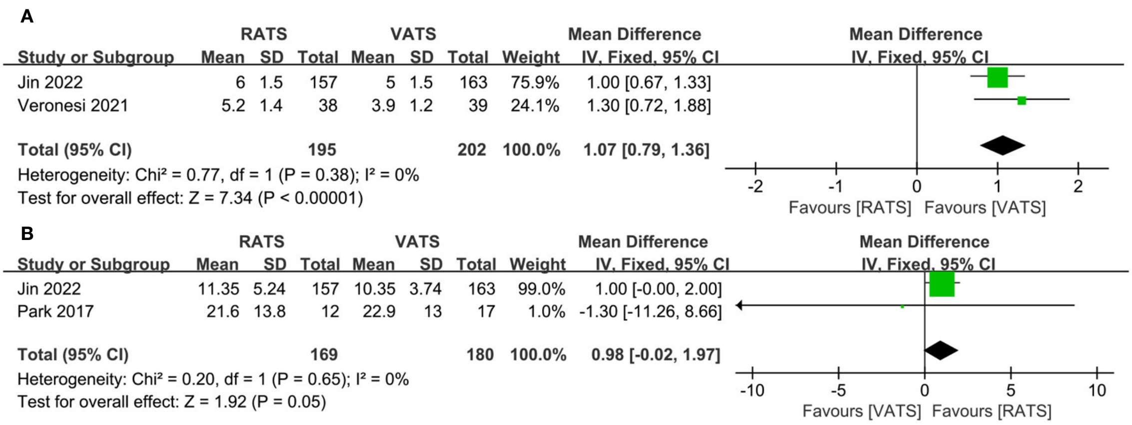

FIGURE 4
Forest plot of the meta-analysis for pathology details. **(A)** Number of dissected lymph node stations. **(B)** Number of dissected lymph nodes.

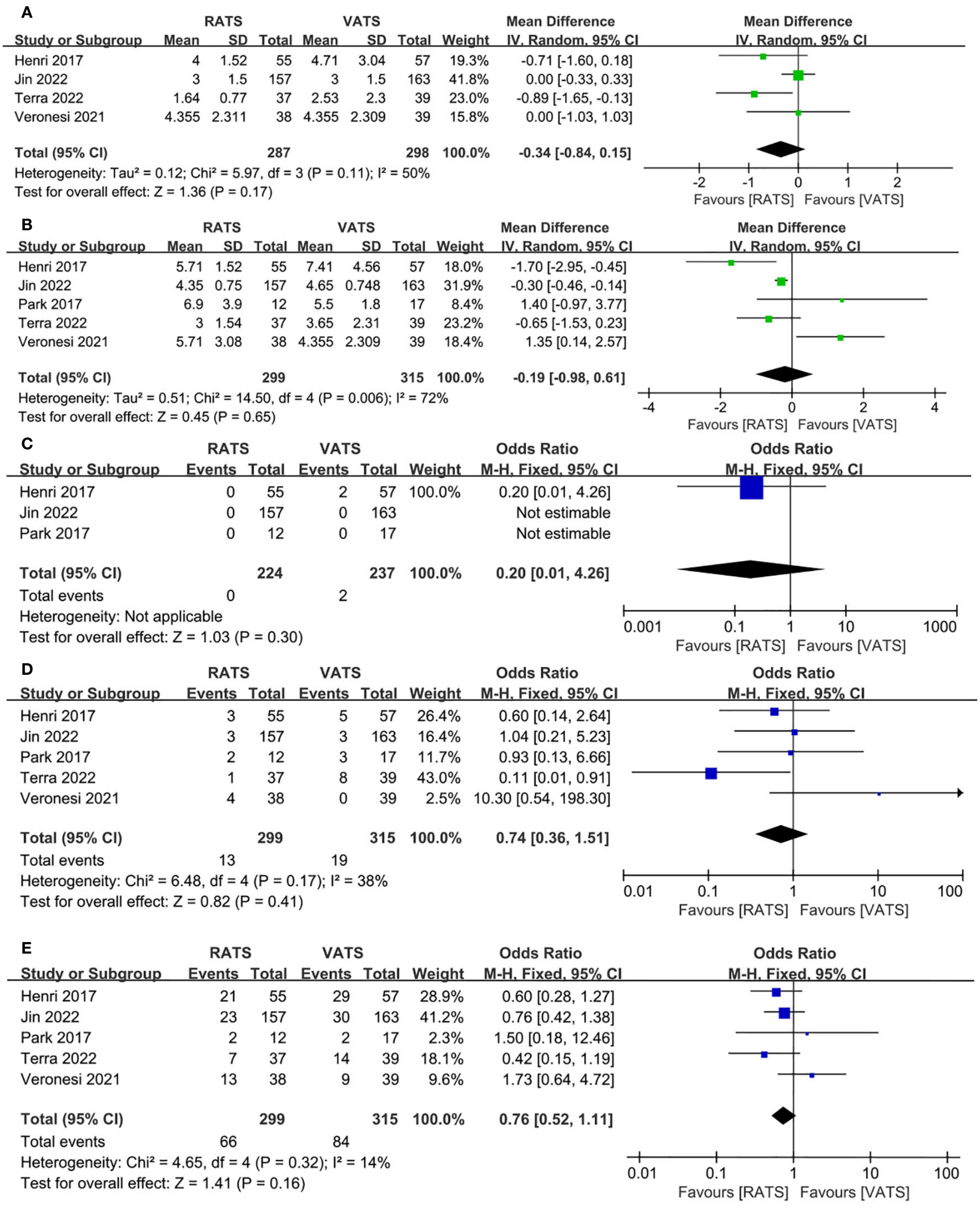

FIGURE 5
Forest plot of the meta-analysis for postoperative parameters. **(A)** Time of chest tube drainage. **(B)** Length of hospital stay. **(C)** 30-day mortality. **(D)** 30-day readmission. **(E)** Overall postoperative complication.

3.5 Total cost

Only two studies reported total cost for patients, and there was no significant difference between two group (WMD =3103.48, 95% CI −575.78 ~ 6782.74, P =0.1, I^2 = 99%) (Figure 7).

3.6 Upstaging rate

Four study reported upstaging rate, and there was no significant difference between two group (OR =0.67, 95% CI 0.38 ~ 1.18, P =0.16, I^2 = 0%) (Figure 8).

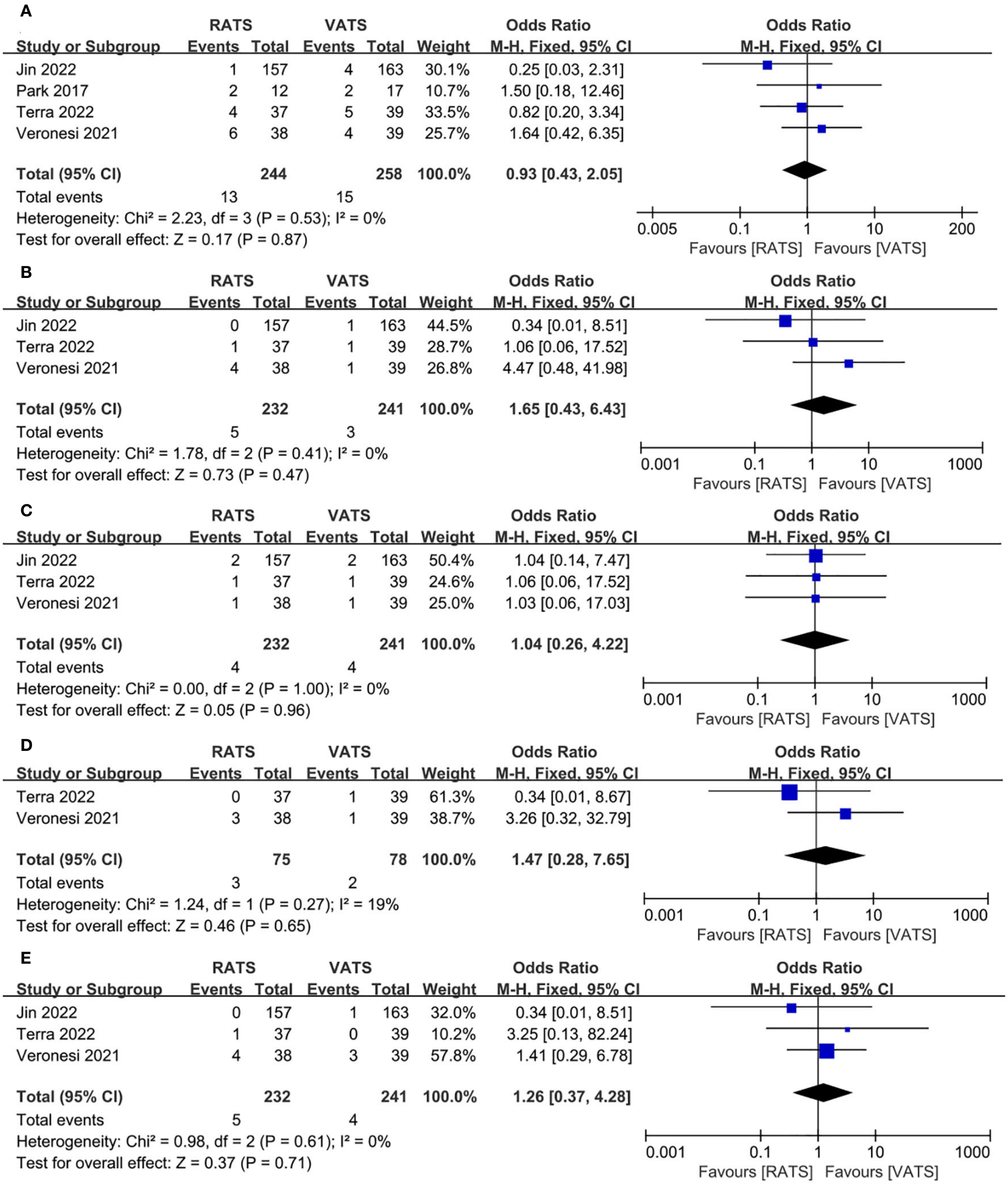

FIGURE 6
Forest plot of the meta-analysis for common postoperative complication. **(A)** Prolonged air leak. **(B)** Pneumonia. **(C)** Pleural effusion. **(D)** Atelectasis. **(E)** Arrhythmia.

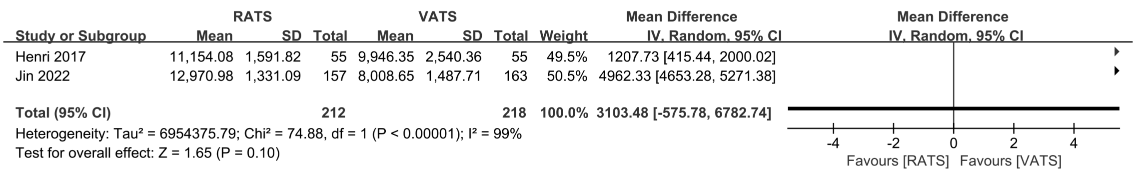

FIGURE 7
Forest plot of the meta-analysis for total cost.

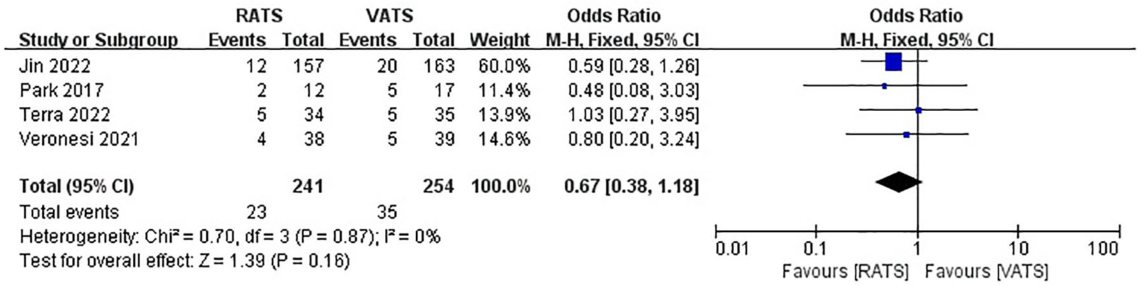

FIGURE 8
Forest plot of the meta-analysis for upstaging rate.

3.7 Publication of bias

Publication bias of the overall complication was assessed by a funnel plot. No obvious evidence of publication bias was observed in the bilaterally symmetrical funnel plot of overall complication (Figure 9).

4 Discussion

Radical resection with lymphadenectomy has become the gold standard surgery for NSCLC at an early stage (25, 26). There is an increased enthusiasm for minimally invasive approaches in the management of lung cancer during the past two decades (27). In recent year, as a relatively new platform for minimally invasive lung lobectomy, RATS has been proposed as an alternative to VATS (13). However, previous meta-analysis comparing the clinical outcomes of VATS with RATS has not been sufficient to prove the benefits of RATS (16–19). Due to shortage of high evidence level RATS studies such as randomized controlled trials, these meta-analysis might have a great risk of potential publication and selection bias, influencing the quality of meta-analysis. Therefore, we conducted a high quality meta-analysis including of only randomized controlled trials or prospective cohort studies to compare outcomes of RATS versus VATS in the treatment of lung cancer.

With respect to the operative time, our result showed that there was no statistical difference between RATS and VATS. Though some previous studies reported similar results to ours (18, 28), results of other studies was contrary to our results (6, 29, 30). At the beginning of the learning curve, due to the shortage of experience and knowledge of RATS surgeons who attempts to RATS for lung cancer might need more time to complete the operation. A previous study showed that there was a tendency of gradual shortening in operative time with the increased experience of RATS (31).

Our results showed that the intraoperative blood loss of RATS was less than that of VATS, which was similar to previous study (18). This is likely due to the advantages of more flexible equipment and a three-dimensional magnified vision,which help reveal the complex anatomy around the mediastinum and hilar accurately, resulting in precise manipulation and better control bleeding (17).

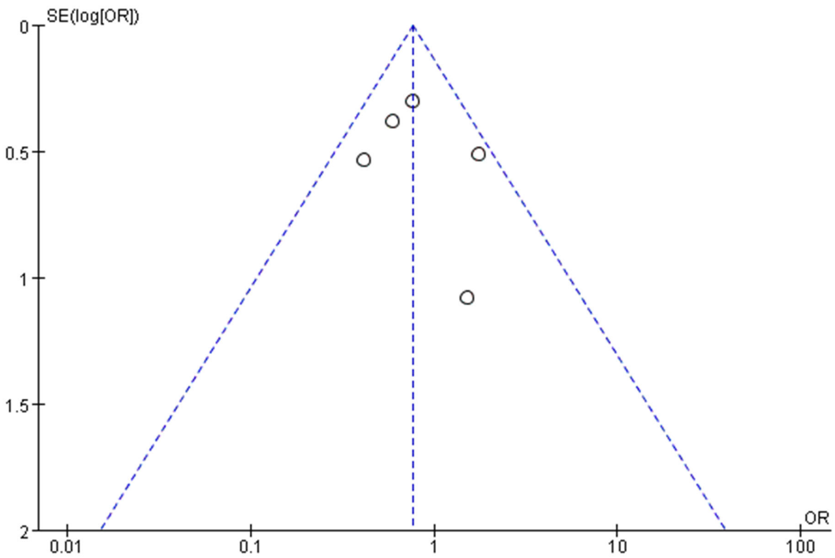

FIGURE 9
Funnel plot of the overall postoperative complications.

Regarding the conversion rate, the result in the present study revealed that the conversion rates were not significantly different between two groups.

In terms of lymphadenectomy, our results showed that the number of dissected lymph nodes stations was significantly more in RATS than that in VATS, but there was no significant difference in number of dissected lymph nodes and upstaging rate. Previous studies comparing lymphadenectomy have reported both equivalence (32) and favouring the robotic approach (18, 25, 33, 34). The superior vision and stability is one potential strength of RATS which allows surgeons to perform extensive lymphadenectomy.

Previous study reported shorter drainage and hospital stay of patients in the RATS group than in the RATS group (18), and explained that minimally invasive advantages of RATS contribute to more thorough hemostasis, more delicate operation, less irritation to surrounding tissues such as pleura, which results in less pleural effusion and shorter postoperative hospital stay. However, both time of chest tube drainage and length of hospital stay had no significant difference between two groups in the present study. The small sample size of the included patients may be the main reason.

Kent et al. reported a lower mortality with RATS relative to VATS (35). Liang et al (28) demonstrated the 30-day mortality was lower in RATS group. Another meta-analysis showed that RATS was associated with lower postoperative complication rate (18). The minimally invasive advantages of RATS contributes to less damage and fewer postoperative complications, resulting in lower mortality and readmission. However, regarding complications, 30-day mortality and 30-day readmission, there was no significant difference between two groups in our results. The possible reason is that the surgical outcomes might be affected by other factors, such as the surgeons experience, familiarity with the instrument, and compliance of assistant. Thus, the advantage of RATS need to be confirmed by more prospective randomized controlled studies.

Due to the cost to acquire robot, subsequent maintenance costs and the additional expense of disposable robotic instruments, the total cost of RATS is higher than that of VATS. The high current cost of robotic thoracic surgery may be a worrying limit for popularization and application of RATS. Our results demonstrated a higher total cost patients in RATS group, but this difference was not statistically significant. Since only two of studies included reported results about total cost, the sample size of the included patients was too small to reflect the difference between RATS group and VATS group.

To our knowledge, this is the first meta-analysis including of only randomized controlled trials or prospective cohort studies to compare outcomes of RATS versus VATS in the treatment of lung cancer, which could result in relatively robust conclusion. However, we acknowledge the possible limitations of our study. First of all, only five studies were included duo to our strict inclusion and criteria. The statistical results of partial clinical outcomes were difficult to reflect the difference between the two groups due to the small sample size. Second, we failed to analyse long-term outcomes such as 5-year overall survival because of the short follow-ups of the studies included. Besides, we failed to control confounding factors such as different inclusion criteria, differences on the population and the level of expertise of surgeons involved, which might result in heterogeneity of the studies and bias. Therefore, more clinical outcomes reported by prospective randomized controlled trials are necessary to further confirm the advantage of the RATS.

In conclusion, our study indicated that RATS is a feasible and safe technique that can achieve better surgical efficacy compared with VATS in terms of short-term outcomes. Except of higher total cost, RATS has obvious advantage in lymphadenectomy and control of hemorrhage. However, large sample and long follow-up randomized clinical trials comparing RATS with VATS are still necessary to better demonstrate the advantages of RATS for NSCLC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

WL: Funding acquisition, Project administration, Writing – review and editing. SH: Data curation, Writing – original draft. XH: Data curation, Writing – original draft. ZH: Formal Analysis, Conceptualization, Writing – original draft. RL: Visualization, Software, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1271709/full#supplementary-material

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Segmentectomy for patients with early-stage pure-solid non-small cell lung cancer

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For decades, lobectomy has been the recommended surgical procedure for non-small cell lung cancer (NSCLC), including for small-sized lesions. However, two recent pivotal clinical trials conducted by the Japanese Clinical Oncology Group/West Japan Oncology Group (JCOG0802/WJOG4607L) and the Cancer and Leukemia Group B (CALGB140503), which compared the survival outcomes between lobectomy and sublobar resection (the JCOG0802/WJOG4607L included only segmentectomy, not wedge resection), demonstrated the efficacy of sublobar resection in patients with early-stage peripheral lung cancer measuring ≤ 2 cm. The JCOG0802/WJOG4607L demonstrated the superiority of segmentectomy over lobectomy with respect to overall survival, implying the survival benefit conferred by preservation of the lung parenchyma. Subsequently, the JCOG1211 also demonstrated the efficacy of segmentectomy, even for NSCLC, measuring up to 3 cm with the predominant ground-glass opacity phenotype. Segmentectomy has become the standard of care for early-stage NSCLC and its indications are expected to be further expanded to include solid lung cancers > 2 cm. However, local control is still a major concern for segmentectomy for higher-grade malignant tumors. Thus, the indications of segmentectomy, especially for patients with radiologically pure-solid NSCLC, remain controversial due to the aggressive nature of the malignancy. In this study, we reviewed previous studies and discussed the efficacy of segmentectomy for patients with such tumors.

KEYWORDS
non-small cell lung cancer, segmentectomy, lobectomy, pure-solid, prognosis, recurrence

1 Introduction

In 1995, a randomized prospective trial conducted by the Lung Cancer Study Group (LCSG) reported that sublobar resection resulted in poorer survival rates with a higher recurrence rate compared to lobectomy in patients with early-stage non-small cell lung cancer (NSCLC) (1). Subsequently, lobectomy has been established as the standard surgical procedure for NSCLC, even for cases involving small-sized lesions. However, recent developments in clinical staging modalities, such as thin-section computed tomography

(CT) and 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography, have enhanced the detection of small-sized early-stage lung cancers and the diagnostic accuracy of clinical staging of NSCLC. Concurrently, some recent pivotal clinical trials conducted by the Japanese Clinical Oncology Group (JCOG), West Japan Oncology Group (WJOG), and the Cancer and Leukemia Group B (CALGB) have demonstrated the efficacy of sublobar resection compared to lobectomy in patients with early-stage small-sized NSCLC (2, 3). The JCOG0802/WJOG4607L trial demonstrated the superiority of segmentectomy over lobectomy in terms of overall survival (OS) and similar recurrence-free survival (RFS) in patients with radiologically solid-predominant peripheral small-sized NSCLC measuring ≤ 2 cm (2). Segmentectomy has garnered considerable attention due to its reduced toxicity and the improved survival benefits associated with lung parenchyma preservation.

Radiologically pure-solid NSCLC, lacking ground-glass opacity (GGO) components, represents a highly malignant neoplasm with worse prognoses compared to part-solid NSCLC containing GGO components (4–10). Consequently, concerns persist regarding certain disadvantages of segmentectomy, including the risk of postoperative recurrence. Therefore, the indication of segmentectomy, especially for patients with radiologically pure-solid NSCLC, remains controversial, necessitating further discussion on the appropriate treatment strategy for radiologically pure-solid tumors.

This study reflected on the evolving attitudes toward segmentectomy, reviewing previous studies, and evaluating the efficacy of segmentectomy for patients with early-stage radiologically pure-solid NSCLC. Moreover, we discussed the possibility of further expansion of the surgical indications of segmentectomy in the context of the new era of lung cancer surgery after the JCOG/WJOG and CALGB trials.

2 Transition in views on sublobar resection

Until the publication of the JCOG0802/WJOG4607L study, the only confirmatory phase III trial comparing lobectomy and sublobar resection was that conducted by the LCSG in North America (1). This trial enrolled 276 patients with stage IA NSCLC measuring ≤ 3 cm between February 1982 and November 1988. The results showed a 5-year survival rate of 63% in the lobectomy group versus 42% in the sublobar resection group (P = 0.088), indicating that sublobar resection is inferior to lobectomy. In addition, the rate of local recurrence was lower in the lobectomy group (6%) compared to the sublobar resection group (18%) (P = 0.008). Thus, based on the inferences from this trial, lobectomy served as a standard surgical procedure for patients with clinical stage IA NSCLC, and this practice has been followed until today.

However, the LCSG trial had some limitations. First, the accuracy of clinical staging was low due to the poor quality of imaging (posteroanterior and lateral chest radiography were mainly used). Second, clinical-stage IA NSCLC was considered to have a potential risk of unsuspected lymph node metastasis. Nevertheless, the sublobar resection arm included not only segmentectomy but also wedge resection without lymph node dissection. Third, non-peripheral tumors were also considered to be included; thus, sublobar resection for such tumors may not have ensured adequate surgical margins.

Because of these limitations, it was questionable whether lobectomy should continue to be the standard surgical procedure for early-stage NSCLC.

The JCOG0201 investigated the association between radiological findings and prognosis in patients with early-stage NSCLC to define radiologically non-invasive NSCLC (11). It defined radiologically non-invasive lung cancer as the presence of a maximum tumor diameter of 2 cm with a consolidation-to-tumor (C/T) ratio of ≤ 0.25, which was consequently changed to ≤ 0.5 due to its excellent prognosis (11). Based on the results of the JCOG0201 and specific features of sublobar resection, three confirmatory clinical trials investigating the efficacy of sublobar resection have been conducted in Japan: i.e., the JCOG0804/WJOG4507L (12), JCOG1211 (13), and JCOG0802/WJOG4607L (2) (Figure 1).

The JCOG0804/WJOG4507L was a single-arm confirmatory trial conducted to evaluate the efficacy and safety of sublobar resection for GGO-predominant peripheral NSCLC sized ≤ 2.0 cm with a C/T ratio ≤ 0.25 (12, 14). The JCOG1211 aimed to evaluate the efficacy and safety of segmentectomy for GGO-predominant NSCLC up to 3 cm in size (13). The JCOG0802/WJOG4607L was a randomized controlled non-inferiority trial comparing segmentectomy and lobectomy for radiologically solid predominant NSCLC sized ≤ 2 cm. In addition, the CALGB140503 was conducted in North America to compare lobectomy and sublobar resection, including segmentectomy and wedge resection, for NSCLC sized ≤ 2 cm, excluding pure ground-glass nodule (GGN) (Figure 1) (3).

In summary, all four trials demonstrated the efficacy of sublobar resection for small-sized NSCLC. Currently, preserving the lung parenchyma has become a global surgical trend for patients with early-stage NSCLC.

3 Tumor malignancy and prognosis of radiologically pure-solid and part-solid NSCLC

To date, thin-section CT is the optimal diagnostic modality for evaluating tumor malignancy and the invasiveness of early-stage NSCLC (11). The GGO component is a radiologically non-invasive area (11). Based on the presence of the GGO component on thin-slice CT, lung tumors are classified into radiologically pure-solid NSCLC without the GGO component, part-solid NSCLC with GGO, and pure GGN. Pure-solid NSCLC shows higher pathological invasiveness, including lymphatic invasion, vascular invasion, lymph node metastasis, spread through air spaces (STAS), and lymph node involvement compared to part-solid NSCLC with a GGO component (4–10). The supplementary analysis of JCOG0201 also showed worse OS in patients with radiologically pure-solid NSCLC compared to those with part-solid NSCLC (5). Thus, radiologically pure-solid NSCLC is oncologically highly invasive

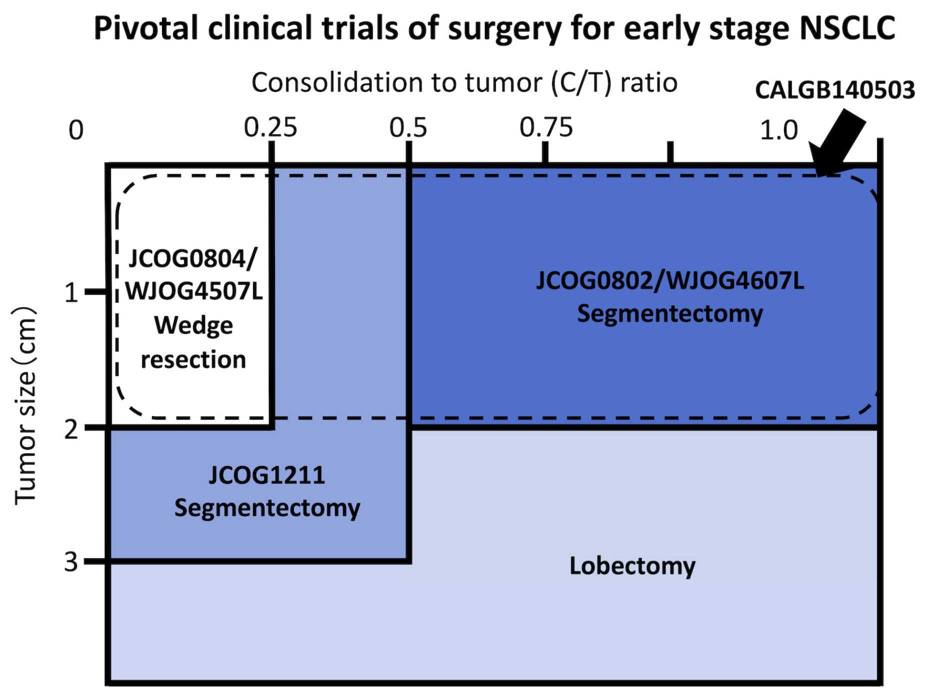

FIGURE 1
Schema of pivotal clinical trials conducted by the Japan Clinical Oncology Group (JCOG), West Japan Oncology Group (WJOG), and Cancer and Leukemia Group B (CALGB) Study.

and has a worse prognosis than part-solid NSCLC. Even the presence of a small GGO component is also reported to be associated with a favorable prognosis in patients with NSCLC measuring ≤ 2 cm (8, 9). Although the favorable impact of a small GGO component on malignant potential in NSCLC measuring > 2–3 cm is controversial, there is no doubt that radiologically pure-solid NSCLC has highly malignant characteristics (8, 9).

Furthermore, the validity of segmentectomy for patients with unsuspected lymph node metastasis is debatable (15, 16); however, unsuspected lymph node metastasis is a major concern since residual tumors could affect the outcome of sublobar resection. The frequency of unsuspected lymph node metastasis is reportedly 11.1–17.7% for clinical stage IA1-2 pure-solid NSCLC and 17.3–36.0% for clinical stage IA3 pure-solid NSCLC (8, 10, 17). On the other hand, the risk of lymph node metastasis reportedly depends on tumor location, i.e., central or peripheral, rather than the malignancy of the tumor itself (18, 19). The frequency of unsuspected lymph node metastasis was lower in peripherally located radiologically pure-solid NSCLC (≤ 2 cm: 7.8% and > 2–3 cm: 13.3%), which are generally candidates for sublobar resection, compared to their centrally located counterparts (≤ 2 cm: 29.8% and > 2–3 cm: 20.3%) (19). Regarding unsuspected hilar lymph node metastasis, the frequency in peripherally located tumors (≤ 2 cm: 6.7% and > 2–3 cm: 8.3%) was also lower than that in centrally located tumors (≤ 2 cm: 24.6% and > 2–3 cm: 17.4%) (19). Moreover, the frequency of hilar lymph node metastasis did not differ significantly between radiologically pure-solid NSCLC located in the peripheral lung fields measuring > 2–3 cm (8.3%) and those measuring ≤ 2 cm (6.7%) (19).

4 Prognostic impact of segmentectomy on patients with pure-solid NSCLC measuring ≤ 2 cm

4.1 Previous retrospective studies reporting the efficacy of segmentectomy for patients with pure-solid NSCLC measuring ≤ 2 cm

After the LCSG trial, several retrospective studies investigated the efficacy of segmentectomy for small-sized NSCLC ≤ 2 cm. Although there were concerns about the worsening of survival with the increase in local recurrence due to the highly malignant characteristics of radiologically pure-solid NSCLC, some of these retrospective studies reported the efficacy of segmentectomy for this type of NSCLC (Table 1) (20–24). Most studies indicated comparable survival outcomes, including OS and RFS, between segmentectomy and lobectomy for patients with radiologically pure-solid NSCLC sized ≤ 2 cm (20, 22–24), although one study reported worse locoregional recurrence-free survival in the segmentectomy arm (3-year rate, 82.2%) compared to the lobectomy arm (3-year rate, 90.6%, $P = 0.0488$) (21).

4.2 The efficacy of segmentectomy for patients with pure-solid NSCLC in the JCOG0802/WJOG4607L

The only confirmatory trial comparing segmentectomy to lobectomy in patients with small-sized NSCLC was the JCOG0802/WJOG4607L (2). This trial demonstrated not only the non-inferiority

TABLE 1 Summary of previous studies comparing segmentectomy and lobectomy for early-stage radiologically pure-solid NSCLC measuring ≤ 2 cm.

Author	Year	Study design	Seg (n)	Lob (n)	5-year OS (Seg vs. Lob)	5-year RFS (Seg vs. Lob)	Recurrence pattern
Koike et al. (20)	2016	Retrospective	87	87	84.0% vs. 85.0%, *P* = 0.767	77.0% vs. 80.0%, *P* = 0.635	Locoregional only: Seg: 6.9% Lob: 5.7% Distant only: Seg: 12.6% Lob: 13.8% Both: Seg: 3.4% Lob: 0%
Hattori et al. (21)	2017	Retrospective	29	183	3-year OS 93.1 vs 91.1%, *P* = 0.9491	3-year Locoregional RFS 82.2 vs 90.6%, *P* = 0.0488	N/A
Tsubokawa et al. (22)	2018	Retrospective	52	44	94.2% vs. 92.0% *P* = 0.723	84.1% vs. 82.2% *P* = 0.745 HR: 1.11 (0.40–3.06)	Locoregional only: Seg: 1.9% Lob: 9.1% Distant only: Seg: 5.8% Lob: 6.8% Both: Seg: 3.8% Lob: 0%
Soh et al. (23)	2022	Retrospective	346	1505	80.3% vs. 84.2% *P* = 0.080	74.0% vs. 75.0% *P* = 0.73	N/A
Zhihua et al. (24)	2023	Retrospective	98	246	97.8% vs. 90.0% *P* = 0.028 HR: 0.36 (0.08–1.59)	92.4% vs. 81.1% *P* = 0.011 HR: 0.72 (0.30–1.77)	Locoregional: Seg: 4.08% Lob: 2.85% Distant: Seg: 1.02% Lob: 10.57%
Saji et al. (2) Hattori et al. (25)	2022	RCT (Subgroup analysis)	279	274	92.4% vs. 86.1%, *P* = 0.0333 HR: 0.641 (0.424–0.969)	82.0% vs. 81.7% *P* = 0.9420 HR: 1.013 (0.723–1.417)	Locoregional only: Seg: 10.7% Lob: 4.4% Distant only: Seg: 1.8% Lob: 4.7% Both: Seg: 5.0% Lob: 3.3%

HR, hazard ratio; Lob, lobectomy; NSCLC, non-small cell lung cancer; N/A, not available; OS, overall survival; RCT, randomized controlled trial; RFS, recurrence-free survival; Seg, segmentectomy.

but also the superiority of segmentectomy over lobectomy with respect to OS in patients with peripherally located early-stage solid predominant NSCLC ≤ 2 cm. Although the rate of mortality due to primary disease was comparable between the segmentectomy and lobectomy groups, the rate of mortality due to other diseases, including second cancer, was lower in the segmentectomy group than in the lobectomy group. A greater proportion of patients in the segmentectomy group underwent curative surgery for a second primary cancer or postoperative local recurrence compared to that in the lobectomy group. These results imply that merely improving local control does not improve survival in patients with early-stage NSCLC, and preserving the lung parenchyma may have prolonged survival after lung surgery. In addition, in the JCOG0802/WJOG4607L, the finding of thin-section CT (solid/part solid) was set as a stratification factor, which formed the basis of the subgroup analysis. A greater survival benefit of segmentectomy was observed in the radiologically pure-solid NSCLC group compared to the part-solid NSCLC group [pure-solid group: hazard ratio (HR): 0.641 (95% confidence interval 0.424–0.969) and part-solid group: HR: 0.733 (95% confidence interval 0.413–1.301)] (2). A history of smoking was more frequent in patients with radiologically pure-solid NSCLC compared to those with part-solid NSCLC (10, 17, 26, 27). The proportion of patients with decreased lung function and those who developed a second disease, such as second primary cancer, was expected to be higher in patients with pure-solid NSCLC (28–30). Therefore, the survival benefit of preserving the lung parenchyma by segmentectomy was considered to manifest more in patients with radiologically pure-solid NSCLC. Furthermore, detailed data on the supplemental analysis of the JCOG0802/WJOG4607L, which investigated the survival of segmentectomy compared to lobectomy for radiologically pure-solid NSCLC, was presented at the 103rd Annual Meeting of the American Association for Thoracic Surgery (25). In the supplemental analysis, local recurrence occurred more frequently in the segmentectomy group (16.1%) than in the lobectomy group (7.7%). However, the RFS of segmentectomy was comparable to that of lobectomy [HR: 1.013 (95% confidence interval 0.723–1.417)]. In addition, the rate of mortality due to diseases other than primary lung cancer was higher in the lobectomy group (12.0%) than in the segmentectomy group (5.7%). Although this was a subgroup analysis, segmentectomy may provide survival benefits for patients with oncologically higher-grade tumors. Indeed, previous studies have demonstrated the efficacy of segmentectomy even for more aggressive hypermetabolic tumors or pathologically invasive cancers (31, 32).

The accuracy of lymph node dissection in sublobar resection is often debated, especially for lung cancers with a potentially high risk of unsuspected lymph node metastasis. In contrast, the JCOG0802/WJOG4607L trial found no difference in the frequency of nodal upstaging or hilar lymph node recurrence between the segmentectomy and lobectomy groups (2). This indicates that lymph node dissection could be performed adequately even with segmentectomy, although there are hilar lymph nodes that are difficult to dissect with segmentectomy. Furthermore, according to the JCOG0802/WJOG4607L, locoregional recurrence in the mediastinal lymph nodes was more frequent with segmentectomy compared to lobectomy (2). Even with segmentectomy, sufficient mediastinal lymph node dissection should be performed to avoid residual tumor cells and achieve accurate nodal staging (33). The results of the JCOG1413, which investigated the clinical efficacy of lobe-specific nodal dissection for clinical stage I–II NSCLC, may provide insights on the extent of mediastinal lymph node dissection (i.e., lobe-specific or systematic nodal dissection) (34).

4.3 The efficacy of sublobar resection for small-sized NSCLC reported in the CALGB140503

Furthermore, the CALGB140503 reported the non-inferiority of sublobar resection, including segmentectomy (40.9%) and wedge resection (59.1%), compared to lobectomy for patients with early-stage NSCLC measuring ≤ 2 cm with respect to disease-free survival (DFS) (3). Despite the lack of information on the CT findings (solid/part solid), the population of the CALGB140503 showed a worse prognosis (5-year DFS: 63.6% and 5-year OS: 80.3% in the sublobar resection group, 5-year DFS: 64.1% and 5-year OS: 78.9% in the lobectomy group) compared to that of the JCOG0802/WJOG4607L. In addition, an unplanned *post hoc* analysis, albeit statistically underpowered, showed that survival did not differ between segmentectomy and lobectomy (35).

Thus, we can infer that segmentectomy should be considered the standard procedure even for radiologically pure-solid lung cancer, although care must be taken to prevent local recurrence.

5 Expansion of the indications for segmentectomy to patients with radiologically pure-solid NSCLC > 2–3 cm

As mentioned above, segmentectomy has become a standard surgical procedure even for early-stage pure-solid NSCLC measuring ≤ 2 cm, and its indications are expected to be further expanded to include solid lung cancers measuring > 2 cm. However, radiologically pure-solid NSCLC measuring > 2–3 cm was not included in these trials. Thus, the only confirmatory trial that included patients with radiologically pure-solid NSCLC sized > 2–3 cm in the study population was the LCSG trial (1). Therefore, lobectomy remains the standard procedure for patients with these tumors.

Recently, the JCOG1211 demonstrated the efficacy of segmentectomy even for NSCLC measuring up to 3 cm with GGO predominance (13). This trial indicated that segmentectomy is technically feasible for tumors measuring > 2–3 cm. Thus, based on the aggregate technical feasibility and survival benefit of segmentectomy proven in the prospective trials, the need to clarify the oncological suitability of segmentectomy for radiologically pure-solid tumors sized > 2–3 cm has gained traction.

5.1 Retrospective studies reporting the efficacy of segmentectomy for patients with pure-solid NSCLC measuring > 2–3 cm

Table 2 shows the summary of previous studies comparing segmentectomy and lobectomy for patients with early-stage NSCLC measuring > 2–3 cm that were considered to include radiologically pure-solid tumors in the study population. The indications of segmentectomy include curative intent for patients who are fit to undergo lobectomy and passive intent for compromised patients who are unfit to undergo lobectomy. Basically, segmentectomy is performed with passive intent for patients with radiologically solid NSCLC measuring > 2–3 cm. Therefore, the survival results should be interpreted with caution due to the potential inconsistency of the patients' backgrounds. Nevertheless, some studies have reported the feasibility of segmentectomy for patients with such tumors (23, 36, 37, 39, 41, 42, 44).

Only two of these retrospective studies provided the results of the comparison of segmentectomy and lobectomy for radiologically pure-solid NSCLC (23, 44). A large-scale study using the Japanese Joint Committee of Lung Cancer Registry Database reported that segmentectomy tended to yield worse OS (P = 0.077) and DFS (P = 0.39) than lobectomy in patients with radiologically pure-solid clinical stage IA3 NSCLC, although the difference was not statistically significant (23). However, multivariable analysis adjusted for factors of patient background, such as performance status, comorbidities, and respiratory function, revealed that segmentectomy yielded survival outcomes (OS: HR, 1.177; 95% CI, 0.082–1.727; P = 0.405; DFS: HR, 1.055; 95% CI, 0.750–1.484; P = 0.758) comparable to those of other surgical procedures, including mainly lobectomy (lobectomy, 93.1%; wedge resection, 6.9%). Moreover, retrospective studies conducted by Kanagawa Cancer Center, Tokyo Medical University, and Hiroshima University found no significant difference in the recurrence risk and recurrence patterns between segmentectomy and lobectomy in patients with radiologically pure-solid NSCLC measuring > 2–3 cm (44). Although there is no information on the CT findings (solid/part solid), a single-center prospective study conducted at Kumamoto University, which included 31 patients with clinical T1cN0M0 NSCLC, reported the long-term prognosis after segmentectomy for clinical T1N0M0 NSCLC (45). The 10-year OS, recurrence-free probability, and local recurrence-free probability rates after segmentectomy in patients with clinical T1cN0M0 NSCLC were 75%, 69%, and 85%, respectively. Moreover, 3 of 31 patients (9.7%) with clinical T1cN0M0 NSCLC developed local recurrence (surgical margin recurrence in 2 patients and preserved lobe recurrence in 1 patient) after segmentectomy. However, these patients underwent additional treatment, such as lobectomy or radiation, for local recurrence. Consequently, no patient succumbed to primary NSCLC (45).

A study indicated that segmentectomy was inferior to lobectomy in patients with NSCLC measuring > 2–3 cm, but the prognosis of segmentectomy was comparable to lobectomy only in a subpopulation with a Charlson-Deyo Comorbidity Index score of 0 (43). On the other hand, only studies that did not adjust for patients' backgrounds suggested that segmentectomy was unsuitable for patients with NSCLC > 2–3 cm (38, 40). However, selection bias must be carefully considered while interpreting the results of these studies. Cao et al. attempted to minimize potential bias by employing propensity score-matched analysis, but it was insufficient to match the tumor and patient backgrounds between the lobectomy and segmentectomy groups (40).

TABLE 2 Summary of previous studies comparing segmentectomy and lobectomy for patients with early-stage NSCLC sized > 2–3 cm that were considered to include radiologically pure-solid NSCLC in the study population.

Authors	Year	Seg (n)	Lob (n)	C/T ratio	Survival (Seg vs. Lob)	Recurrence pattern
Okada et al. (36)[P]	2005	76	268	N/A	5-year CSS: 84.6% vs 87.4%	N/A
Carr et al. (37)[P]	2012	57	88	N/A	RFS: P = 0.423	Locoregional Seg: 5.3% Lob: 9.0% Distant Seg: 10.5% Lob: 20.5%
Deng et al. (38)[P]	2014	31	93	N/A	5-year OS: 55.8% vs. 77.6%, P = 0.05 5-year RFS: 54.1% vs. 74.7%, P = 0.05	N/A
Landreneau et al. (39)[c]	2014	N/A	N/A	N/A	TTR: P = 0.395	N/A
Cao et al. (40)[P]	2018	221 (PSM: 221)	5257 (PSM: 221)	N/A	Whole cohort OS: HR 1.698 (95% CI, 1.395–2.066), P < 0.001 PSM OS: HR 1.63 (95% CI, 1.210–2.197), P = 0.001	N/A
Kamigaichi et al. (41)[c]	2020	43 (PSM: 37)	154 (PSM: 37)	1 [IQR, 0.8–1.0]	Whole cohort 5-year OS: 90.6% vs. 80.0%, P = 0.42 5-year RFS: 82.7% vs. 73.4%, P = 0.30 PSM 5-year OS: 89.3% vs. 82.9% 5-year RFS: 80.1% vs. 79.5%	N/A
Chan et al. (42)[c]	2021	90 (PSM: 90)	276 (PSM: 90)	N/A	Whole cohort OS: HR 1.07 (95% CI, 0.74–1.52), P = 0.73 RFS: HR 1.19 (95% CI, 0.58–1.66), P = 0.32 TTR: HR 1.24 (95% CI, 0.78–1.97), P = 0.37 PSM OS: HR 1.23 (95% CI, 0.91–1.82), P = 0.17 RFS: HR 1.23 (95% CI, 0.82–1.85), P = 0.32 TTR: HR 0.95 (95% CI, 0.52–1.73), P = 0.87	N/A
Peng et al. (43)[P]	2022	945 (CDCI of 0 : 411)	18990 (CDCI of 0 : 9420)	N/A	Whole cohort 5-year OS 54.3% vs. 64.9%, P < 0.0001 CDCI of 0 5-year OS 64.3% vs. 69.6%, P = 0.133	N/A
Soh et al. (23)[c]	2022	102	1460	1	5-year OS: 70.0% vs. 79.2%, P = 0.077 5-year RFS: 63.1% vs. 67.1%, P = 0.39	N/A
Kamigaichi et al. (44)[c]	2023	44 (PSM: 41)	368 (PSM: 41)	1	CIR: HR 1.04 (95% CI, 0.48–2.30), P = 0.91 Whole cohort 5-year CIR: 21.9% vs. 20.8%, P = 0.88 PSM 5-year CIR: 20.6% vs. 22.8%, P = 0.55	Locoregional Seg: 6.8%, Lob: 9.0% Distant Seg: 11.4% Lob: 15.2%

*All studies were retrospective in design.
[c]The study population were defined by clinical staging.
[P]The study population were defined by pathological staging.
CDCI, Charlson-Deyo Comorbidity Index Score; CIR, cumulative incidence of recurrence; CSS, cancer-specific survival; C/T ratio, consolidation-to-tumor ratio; HR, hazard ratio; Lob, lobectomy; N/A, not available; NSCLC, non-small cell lung cancer; OS, overall survival; PSM, propensity-score matching; RCT, randomized control trial; RFS, recurrence-free survival; Seg, segmentectomy; TTR, time to recurrence.

5.2 Local control for patients with pure-solid NSCLC measuring > 2–3 cm

While segmentectomy may yield comparable survival to lobectomy even in patients with radiologically pure-solid NSCLC > 2–3 cm, local control is a major concern for larger and higher-grade tumors. Ensuring sufficient surgical margins and adequate lymph node dissection are crucial to preventing locoregional recurrence. The presence of STAS and a micropapillary component, which could be risk factors for margin recurrence after segmentectomy, should be considered (46). STAS was observed in 22% of patients with radiologically pure-solid NSCLC measuring > 2–3 cm (17). However, in previous studies, the prognosis was similar between segmentectomy and lobectomy for NSCLC with STAS if the surgical margin was adequate. According to these studies, a surgical margin ≥ 20 mm could prevent postoperative recurrence in the presence of STAS (47, 48). Furthermore, one study reported that 36% of lung adenocarcinomas > 2–3 cm included histopathologically micropapillary or solid subtypes (49). According to previous studies, surgical margins ≥ 10 mm could contribute to the decreased risk of local recurrence in lung adenocarcinomas, including these histological subtypes (50). By securing a sufficient surgical margin with appropriate lymph node dissection, segmentectomy may be suitable for larger, high-grade tumors, namely radiologically pure-solid NSCLC sized > 2–3 cm.

Sublobar resection includes not only segmentectomy but also wedge resection. Previous studies have indicated that cancer control was better in patients who underwent segmentectomy than those who underwent wedge resection for clinical stage IA NSCLC (51–53). Segmentectomy is an anatomic resection that can dissect the hilar lymph nodes, while wedge resection is a nonanatomic procedure that cannot dissect the hilar lymph nodes. Thus, lymph nodes are not as adequately evaluated by wedge resection as segmentectomy. Furthermore, although wedge resection was adopted for NSCLC sized ≤ 2 cm in the CALGB140503, it may be difficult to secure a sufficient surgical margin by wedge resection for tumors > 2 cm. Thus, wedge resection may be unsuitable for radiologically pure-solid NSCLC sized > 2–3 cm. A randomized phase III trial (JCOG1909) is currently underway to confirm the superiority of segmentectomy over wedge resection for patients with clinical Stage IA NSCLC with poor pulmonary reserve or other major comorbidities that are contraindications for lobectomy but can tolerate sublobar resection (high-risk operable) (54). The results of this trial will also provide insights into the difference in cancer control between segmentectomy and wedge resection for NSCLC measuring > 2–3 cm.

6 Discussion

As a result of the recent JCOG/WJOG and CALGB trials, the validity of sublobar resection became widely recognized, making sublobar resection for early-stage small-sized NSCLC a mainstream procedure worldwide. Although it was thought that segmentectomy may not be suitable for radiologically pure-solid NSCLC, several studies, such as the subgroup analysis of the JCOG0802/WJOG4607L, demonstrated the efficacy of segmentectomy even for radiologically pure-solid NSCLC (2, 20, 22–25). Based on these results, segmentectomy is expected to become the standard surgical procedure even for patients with radiologically pure-solid NSCLC sized ≤ 2 cm. As its less invasive nature, segmentectomy was reported to contribute to the preservation of postoperative respiratory function (2, 41, 55), nutritional status (56), and a reduction of the risk of postoperative complications compared to lobectomy (57). Above all, the fact that the frequency of other causes of death was lower in the segmentectomy group in the JCOG0802/WJOG4607L is a robust argument supporting the less invasive nature of segmentectomy (2). Clinicians should provide patients with lung surgeries that minimize invasion of the patient's physical function while achieving curative treatment of the cancer.

Despite the survival benefits associated with the preservation of the lung parenchyma, local control is a major concern in the expansion of the indications of segmentectomy for larger, high-grade tumors. Appropriate evaluation of sufficient surgical margins and lymph node status is crucial to preventing local recurrence after segmentectomy. If these objectives can be achieved, segmentectomy may become a suitable treatment modality for radiologically pure-solid NSCLC sized > 2–3 cm. However, future confirmatory clinical trials are warranted.

Author contributions

AK: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. AH: Conceptualization, Data curation, Investigation, Supervision, Writing – review & editing. YT: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Analysis of predictive factors of unforeseen nodal metastases in resected clinical stage I NSCLC

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Background: Despite notable advances made in preoperative staging, unexpected nodal metastases after surgery are still significantly detected. In this study we aim to analyze the upstaging rate in patients with clinical stage I NSCLC without evidence of nodal disease in the preoperative staging who underwent lobectomy and radical lymphadenectomy.

Methods: Patients who underwent lobectomy and systematic lymphadenectomy for clinical stage I NSCLC were evaluated. Exclusion criteria included the neoadjuvant treatment, incomplete resection and no adherence to preoperative guidelines.

Results: A total of 297 patients were included in the study. 159 patients were female, and the median age was 68 (61 - 73). The variables that showed a significant correlation with the upstaging rate at the univariate analysis were the number of resected lymph nodes and micropapillar/solid adenocar-cinoma subtype. This result was confirmed in the multivariate analysis with a OR= 2.545 (95%CI 1.136-5.701; p=0.02) for the number of resected lymph nodes and a OR=2.717 (95%CI 1.256-5.875; p=0.01) for the high-grade pattern of adenocarcinoma.

Conclusion: Our results showed that in a homogeneous cohort of patients with clinical stage I NSCLC, the number of resected lymph nodes and the histological subtype of adenocarcinoma can significantly be associated with nodal metastasis.

KEYWORDS

early stage NSCLC, upstaging, stage I, nodal disease, lymphadenectomy

1 Introduction

Non-Small Cell Lung Cancer (NSCLC) is the most frequent lung cancer subtype and represents the leading cause of cancer-related deaths in the world. Stage I NSCLC has an estimated 5-year overall survival rate of 90% after standard-of-care radical surgical resection. Metastatic spread to locoregional lymph nodes has a detrimental prognostic effect; standard-of-care (neo)adjuvant chemotherapy in node-positive NSCLC leads to improved disease-free survival and overall survival (1, 2). Thus, hilum-mediastinal staging for early detection of nodal metastases has a pivotal role in the multidisciplinary management of early-stage NSCLC. Preoperative clinical and invasive mediastinal staging hold the promise to accurately detect nodal metastases (3). Moreover, the survival benefit associated with lymphadenectomy has led to inconclusive results and questioned the degree to which hilar and mediastinal lymph nodes should be harvested (4). As a result, 42.4% of patients have no lymph nodes harvested at pulmonary resection for lung cancer and base their nodal staging solely on preoperative clinical or invasive staging (5). Despite the accuracy of preoperative staging procedures in detecting metastatic lymph nodes, a high rate of postoperative pathological upstaging is still detected (6). Indeed, recent reports have shown upstaging rates up to 25% in patients with early-stage NSCLC at surgery (7). Failure to identify these unexpected nodal metastases may lead to undertreatment. Furthermore, while neoadjuvant chemoimmunotherapy was recently shown to lead to clinically meaningful and statistically significant improvements in disease-free survival in stage I-III NSCLC over neoadjuvant chemotherapy, stage II-III tumors are likely to benefit most from this treatment option; baseline nodal staging is therefore critical to accurately advise multimodal treatment. By analyzing the surgical and histological features in a population of patients with clinical stage I NSCLC who underwent lobectomy and systematic lymphadenectomy, we aimed to identify the key factors contributing to upstaging in this particular cohort.

2 Materials and methods

The study was designed as a single-center, retrospective analysis of patients with clinical stage I NSCLC who underwent lobectomy and radical lymphadenectomy.

2.1 Inclusion criteria

- Patients with clinical stage I lung adenocarcinoma (LUAD).
- Complete preoperative staging in accordance with guidelines.
- Lobectomy and systematic hilum-mediastinal lymphadenectomy (in accordance with the IASLC definition of complete lymph node dissection of both N1 and N2 stations) with robotic surgery.

2.2 Exclusion criteria

- Patients with clinical stage II-III-IV.
- Sublobar resections and wedge resections.
- Incomplete lymphadenectomy.
- Patients who underwent preoperative chemotherapy or radiotherapy.

The aim of this study was to evaluate the association between surgical and histological variables with upstaging in patients with clinical stage I NSCLC who underwent radical surgical resection; all included patients received robotic surgery according to the preferences of the institution.

2.3 Preoperative staging

Prior to the surgical interventions, comprehensive preoperative investigations were conducted, including brain, thoracic, and upper abdominal computed tomography (CT) scans, as well as F18-fluorodeoxyglucose positron emission tomography (FDG-PET). These investigations were crucial to determine the absence of multiple pulmonary lesions and to rule out the presence of hepatic, adrenal, or brain metastases. Additionally, the status of hilar and mediastinal lymph nodes was assessed using these imaging modalities. In cases where indicated, a brain MRI was performed to ensure the exclusion of brain metastasis. To further evaluate the lymph node status, lymph nodes larger than 1 cm along the shortest axis or PET-CT avid nodes with standardized uptake value >1.5 underwent endoscopic or endobronchial ultrasonography fine-needle biopsy to exclude metastatic involvement. If clinically warranted, bone scintigraphy was also conducted. All patients provided informed consent for lobectomy before undergoing the surgical procedures.

2.4 Surgical technique

In all patients, a radical hilum mediastinal lymphadenectomy was performed following the guidelines. For tumors on the right side, systematic exploration of the paratracheal stations (2R and 4R), subcarinal station (7), paraoesophageal station (8), and inferior pulmonary ligament station (9) was carried out. For tumors on the left side, lymphadenectomy of the aorto-pulmonary window (5-6), subcarinal stations (7), para-oesophageal station (8), and inferior pulmonary ligament station (9) was usually performed. At the conclusion of the procedure, one chest tube was typically inserted using the camera port.

After surgery, all formalin-fixed paraffin-embedded (FFPE) tissue sections were reviewed by pathologists for histopathological confirmation and tumor content assessment. Predominant invasive LUAD histologic subtypes were classified as lepidic, acinar, papillary, micropapillary, or solid.

The primary endpoint was upstaging at surgical resection. Statistical analysis was performed by an experienced bio-statistician using SPSS 20 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). Descriptive statistics were calculated and expressed as median and interquartile ranges. Groups were compared using t-tests for continuous variables and chi-square for categorical data. A multivariable logistic regression model with stepwise regression was used (with forward selection, enter limit, and remove limit set at p = 0.10 and p = 0.15, respectively) to identify independent factors associated with the primary outcome measure. Cut-off for linear variables were calculated with ROC curve analysis.

3 Results

From January 2016 to September 2022, a total of 713 lobectomies and radical lymphadenectomies were performed for early stage NSCLC, of which 297 were clinical stage I. Of these, 159 patients were male. The clinical and pathological characteristics are reported in Table 1. The median age at diagnosis was 68 years (range: 61-73 years). A history of smoking was reported in 169 patients (56.9%). The median tumor diameter was 18 mm (range: 7-28 mm). A history of other cancers 5 years before the lung cancer diagnosis was reported in 15.8% of patients. All operations were carried out using robotic technology. Surgery was performed numerically more frequently on the right side (57.6%). According to the guidelines, all patients underwent the removal of at least 4 nodal stations. The median number of resected nodes was 12 (range: 8-16). The majority of patients presented a single metastatic nodal station, and the median number of metastatic lymph nodes after surgery was 2 (range: 1-4). After surgery, the majority of cases were adenocarcinoma, and one-third of patients showed a solid or micropapillary subtype (30.6%). In general, 36 (12.1%) patients reported upstaging, of whom 15 patients had mediastinal upstaging. As shown in Figure 1A, there was a significant but weak correlation between the number of resected and metastatic nodes in the adenocarcinoma group (p=0.022, ρ=0.13) upstaging was more frequent among micropapillary and solid adenocarcinoma subtypes ($\chi 2$ test, p= 0.04669, Figure 1B). Tumors with upstaging at surgical resection had a higher number of resected nodes (Wilcoxon p=0.016, Figure 1C).

We then proceeded with the univariable analysis with the following features: gender, age, smoking status, previous cancer, tumor location, tumor diameter, PET uptake, the number of resected lymph nodes, histology, and adenocarcinoma subtype. The variables that resulted statistically significant in terms of upstaging rate were the number of resected lymph nodes (OR=2.212, 95% CI 1.074-4.555; p=0.03) and the micropapillary/solid adenocarcinoma subtype (OR=2.039, 95% CI 0.979-4.246; p=0.04, Table 2).

The multivariable analysis, summarized in Table 3, confirmed the predictive value of the number of resected lymph nodes (OR=2.545, 95%CI 1.136-5.701; p=0.02) and the high grade pattern of adenocarcinoma (OR=2.717, 95%CI 1.256-5.875; p=0.01).

4 Discussion

Nodal upstaging in early-stage non-small cell lung cancer (NSCLC) can have a significant impact on disease management (8, 9). In this study, we aimed to analyze the clinical and histological features associated with nodal upstaging in a homogeneous cohort of patients with resected stage I NSCLC. We found that certain subtypes of adenocarcinoma, specifically the micropapillary and solid subtypes, were significantly associated with unforeseen nodal metastasis at the time of surgery. Additionally, the number of resected lymph nodes was found to be correlated with upstaging. These findings have important implications for treatment decisions and patient outcomes.

The aggressive patterns of adenocarcinoma represented by the micropapillary and solid subtypes, which were observed in at least 30% of the patients, were more likely to conceal unexpected nodal metastasis in early-stage clinical I NSCLC. These findings are consistent with previous studies that have demonstrated the prognostic role of adenocarcinoma subtypes in the early-stage setting (10). The association of specific subtypes with nodal metastasis could be relevant in guiding the decision for a more extensive resection or in assessing the need for adjuvant treatment (11). Furthermore, our analysis revealed that a higher number of resected lymph nodes was associated with upstaging. This underscores the importance of performing an adequate lymphadenectomy in improving the oncological outcomes of early-stage NSCLC patients (12). These findings align with other studies that have examined the number of harvested nodes at surgery and its association with survival (13). Patients who had a greater number of resected lymph nodes appeared to have better outcomes, and systematic lymphadenectomy with more than 10 harvested lymph nodes resulted in improved survival outcomes, particularly in a specific subgroup of patients with tumor diameter less than 20mm (14).

Despite a low rates of mediastinal N2 disease in early-stage NSCLC when following strict preoperative staging guidelines was found, the systematic mediastinal lymph node dissection for accurate staging and individualized treatment planning is of paramount importance. While imaging has improved, microscopic metastases can be missed, underscoring the need for lymphadenectomy. The inclusion of mediastinal lymph node dissection remains critical in achieving optimal outcomes for patients with early-stage NSCLC.

In our recent study concerning patients with stage I and II lung adenocarcinoma, who exhibit clinical node negativity, we have discovered intriguing connections between certain genomic features, such as ALK rearrangements, and the prediction of unexpected nodal metastasis. While these outcomes necessitate validation through a more extensive patient cohort, these revelations emphasize the significance of tumor biology (15). This importance extends beyond just medical treatment, as it

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TABLE 1 Surgical and histological characteristic of the total population and the upstaging and nonupstaging group.

	Total population (297)	Non upstaging (261)	Upstaging (36)	p- value
Age (median, IQR)	68 (61 – 73)	68 (60 – 73)	67 (61.75 – 73.25)	0.1
Sex (female), n (%)	138 (46.5)	125 (47.9)	13 (36.1)	0.4
Actual smokers, n (%)	169 (56.9)	146 (55,9)	23 (63.9)	0.3
Previous cancers, n (%)	47 (15.8)	42 (16.1)	5 (13.9)	0.3
Side (right), n (%)	171 (57.6)	165 (63.2)	15 (41,7)	0.1
Tumor diameter, (median, IQR)	18 (7-28)	17 (8-28)	18 (6-29)	0.7
Squamous histology, n (%)	31 (10.4)	26 (10)	5 (13.9)	0.2
Micropapillary or solid adc, n(%)	91 (30.6)	75 (28.7)	16 (44.4)	<0.05
Number of resected nodes (median, IQR)	12 (8–16)	12 (8–16)	16 (9.75–19.25)	<0.05
Number of harvested nodal station (median, IQR)	5 (4–6)	5 (4–5.5)	5 (4–6)	0.8

aids in patient stratification even prior to surgical interventions. In our present analysis, our focus was directed at clinical stage I NSCLC including the squamous histology. We meticulously examined both histological and clinical factors that are readily accessible within routine medical practice (16). However, looking ahead, it is imperative to delve further into this specific population. Utilizing a larger patient cohort, thorough investigation into genomic biomarkers as potential prognostic indicators and predictors of upstaging should be a priority for future research endeavors.

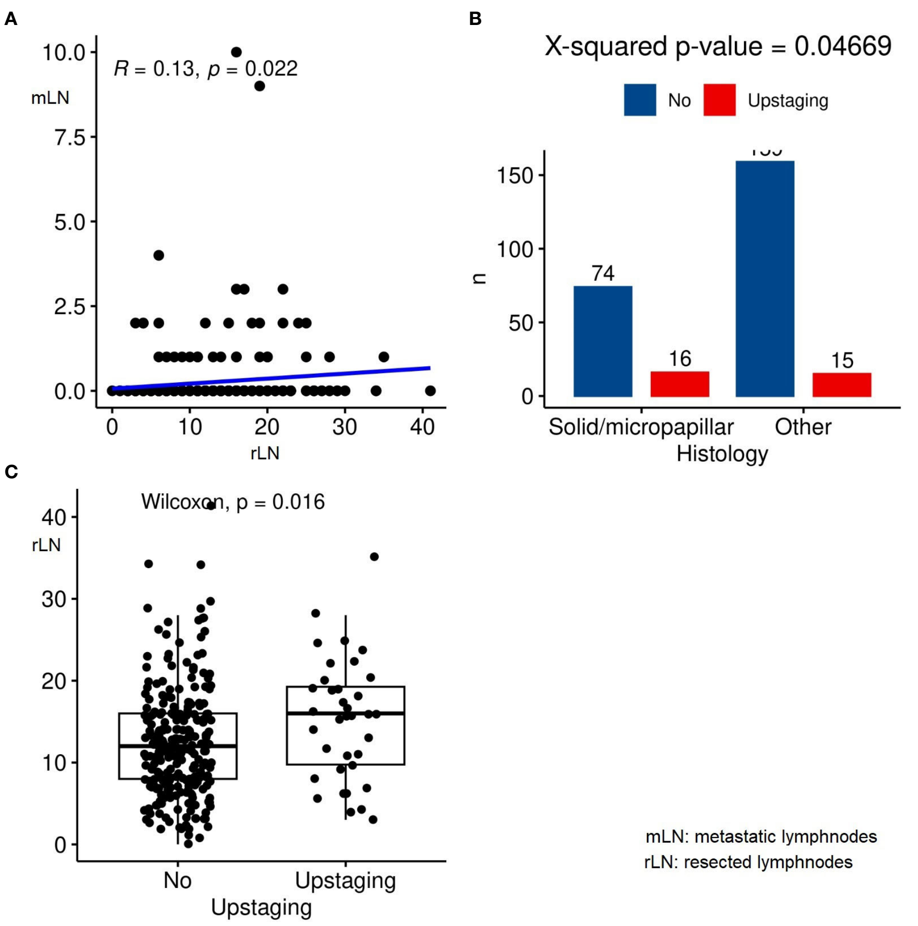

FIGURE 1
(A) Linear correlation between the resected lymph nodes and metastatic lymph nodes; **(B)** Correlation between adenocarcinoma subtypes and upstaging; **(C)** Correlation between resected lymph nodes and upstaging.

TABLE 2 Univariate analysis.

Variables	OR	p-value	95%CI
Age	1.128	0.249	0.857 – 1.341
Sex	0.975	0.187	0.625 – 1.266
Actual smokers	1.372	0.391	0.666 – 2.870
Previous cancers	1.125	0.231	0.875 – 1.178
Side	0.987	0.432	0.553 – 1.347
Tumor diameter	1.137	0.193	0.659 – 1.148
PET CT Uptake	1.012	0.102	0.898 – 1.101
Histology	1.098	0.103	0.876 – 1.231
ADC subtype	2.039	0.04	0.979 – 4.246
Number of resected nodes	2.212	0.03	1.074 – 4.555
Number of harvested nodal station	1.012	0.591	0.503 – 1.354

TABLE 3 Multivariate analysis.

Variables	OR	p-value	95% CI
Histological subtypes (micropapillary and solid adc vs others)	2.717	0.01	1.256 – 5.875
Number of resected nodes (cut-off: 13, ROC analysis)	2.545	0.02	1.136 – 5.701

Although our study provides valuable insights, it is essential to acknowledge its limitations. Firstly, the study design was retrospective, which inherently introduces certain limitations and potential biases. Additionally, the analysis was based on data from a single-center, which may limit the generalizability of the findings to other populations. Moreover, the sample size of the cohort was relatively small, which may limit the statistical power and precision of the results.

The study's exclusion of patients who did not undergo systemic lymph nodes dissection (LND) raises questions regarding the potential impact of this criterion on the results. By excluding individuals who did not meet this criterion, it becomes difficult to assess the role and effectiveness of systemic LND in revealing nodal upstaging. The study lacks the necessary comparison between patients who underwent LND and those who did not, making it challenging to determine the extent to which systemic LND contributed to the identification of unexpected nodal diseases. Furthermore, the absence of perioperative and follow-up data prevents us from understanding the risk-benefit profile of LND and its potential impact on patient survival.

The primary focus of the study was on patients who underwent robotic surgery for early-stage NSCLC at our institution. This specificity limits the generalizability of the findings to other surgical approaches such as video-assisted thoracic surgery (VATS) or open surgery. The outcomes and implications of different surgical techniques may vary due to variations in procedures, instrumentation, and surgeon expertise. Therefore, caution is warranted when applying the study's results to patients undergoing VATS or open surgery.

Lastly, given the retrospective nature of the study, another limitation of the study is that the determination of histological tumor types was frequently made post-surgery, rather than prior to the surgical procedure. This raises concerns about the practical implementation of the findings in guiding lymph node management during surgery. In order to guide lymph node dissection accurately and effectively during the operation, histological analysis of the tumor should ideally be performed before surgery. This would provide crucial information about the tumor characteristics, such as histological subtype or molecular markers, which could aid in determining the extent and approach of lymph node evaluation.

However, it is worth noting that despite these limitations, our findings align with those of previous studies that have examined early stages of NSCLC. Furthermore, efforts were made to minimize bias by including a homogeneous cohort of patients who underwent surgery according to the latest oncological guidelines.

In conclusion, our study demonstrates that the presence of the micropapillary and solid patterns of adenocarcinoma, as well as the number of resected lymph nodes, are statistically associated with the risk of unexpected nodal metastasis in a specific cohort of patients with clinical stage I NSCLC. If confirmed in larger cohorts, these findings could have implications in stratifying stage I NSCLC patients and guiding appropriate oncological treatment decisions. Moreover, the importance of performing an adequate lymphadenectomy cannot be understated, as it helps prevent inadequate staging, facilitates the appropriate administration of adjuvant treatment, and ensures optimal patient outcomes. These findings highlight the need for further research and validation in larger, multicenter studies to strengthen the evidence base and inform clinical practice in the management of early-stage NSCLC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee of the IRCCS Regina Elena National Cancer Institute; Approval Code: 1465/21 Approval Date: 23 February 2021. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization, FG, RT.; methodology, FG, EM, RT, IS; software, DF, RT, FLC; validation, FFu, FC, VA; formal analysis, FG, DM, DF, IS; investigation, FC, DM, PV; resources, FFa, EM,

GA, FLC; data curation, FG, RT, VA; writing—original draft preparation, FG, RT, EM, DF; writing—review and editing, EM, FFa, FC, DF; visualization, DM, FFu, PV; supervision, FFa, GA, EM; project administration, EM, FFa; funding acquisition, FFa; All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The future of artificial intelligence in thoracic surgery for non-small cell lung cancer treatment a narrative review

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Objectives: To present a comprehensive review of the current state of artificial intelligence (AI) applications in lung cancer management, spanning the preoperative, intraoperative, and postoperative phases.

Methods: A review of the literature was conducted using PubMed, EMBASE and Cochrane, including relevant studies between 2002 and 2023 to identify the latest research on artificial intelligence and lung cancer.

Conclusion: While AI holds promise in managing lung cancer, challenges exist. In the preoperative phase, AI can improve diagnostics and predict biomarkers, particularly in cases with limited biopsy materials. During surgery, AI provides real-time guidance. Postoperatively, AI assists in pathology assessment and predictive modeling. Challenges include interpretability issues, training limitations affecting model use and AI's ineffectiveness beyond classification. Overfitting and global generalization, along with high computational costs and ethical frameworks, pose hurdles. Addressing these challenges requires a careful approach, considering ethical, technical, and regulatory factors. Rigorous analysis, external validation, and a robust regulatory framework are crucial for responsible AI implementation in lung surgery, reflecting the evolving synergy between human expertise and technology.

KEYWORDS
NSCLC, artificial intelligence, thoracic surgery, deep learning - artificial intelligence, lung cancer

1 Background

The complexity of lung cancer, characterized by diverse histological subtypes, molecular variations, and intricate staging, necessitates a nuanced approach to diagnosis, treatment, and postoperative surveillance. Traditionally, these challenges have relied heavily on the expertise of pathologists, surgeons, and oncologists. However, the advent of AI has introduced a paradigm shift in how we comprehend, diagnose, and treat lung cancer.

Artificial intelligence (AI) has emerged as a transformative force in many industries (1–3). Mainly due to its spectrum of approaches that range from those striving to replicate human reasoning for effective problem-solving, to others that bypass human reasoning entirely and rely solely on extensive datasets to formulate a framework for addressing specific questions of interest (4, 5). AI technologies In thoracic surgery, primarily through machine learning (ML) techniques and natural language processing (NLP), have shown remarkable potential in enhancing the accuracy of diagnoses, the efficiency of treatments, and the effectiveness of postoperative care. ML algorithms are increasingly being utilized for detailed analysis of imaging data, aiding in the detection and classification of lung cancer, while NLP is transforming the way clinical data and patient histories are processed and interpreted (3). Thus, facilitating better clinical decision-making, minimizing medical errors, and elevating the overall quality and efficiency of patient care (2, 3).

However, the application of AI in thoracic surgery is not without its challenges. Issues such as data privacy, potential biases in AI algorithms, ethical concerns and the need for large, well-annotated datasets for training are significant concerns that need addressing. Moreover, there is a delicate balance between the benefits of AI-assisted decision-making and the preservation of the critical role of medical professionals in patient care (6). This narrative review explores the current state of AI integration in thoracic surgery for non-small cell lung cancer treatment. The subsequent sections provide a detailed examination of AI's role in preoperative planning, intraoperative guidance, and postoperative management, offering a comprehensive overview of its potential benefits and ongoing challenges.

2 Method

A review of the literature was conducted using PubMed, EMBASE and Cochrane to identify the latest research on artificial intelligence and lung cancer which is used to generate a narrative review.

3 Pre-operative planning

3.1 AI in diagnostics

Lung cancer, a leading cause of cancer-related mortality, necessitates precise histopathological diagnosis for effective therapeutic strategies. Molecular-targeted therapy and immunotherapy advancements have improved outcomes, but classifying subtypes, especially in poorly differentiated carcinomas, remains challenging.

To address these challenges, computational pathology, which involves the use of advanced technologies such as Whole Slide Images (WSI) and deep learning methods, has emerged as a promising avenue. One notable study by Kanavati et al. (7) focused on utilizing a convolutional neural network (CNN) and recurrent neural network (RNN) to predict subtypes of lung carcinoma, with a specific emphasis on transbronchial lung biopsies (TBLB). The deep learning model was meticulously trained on a substantial number of WSIs, prioritizing cases with poor differentiation. The study explored two distinct approaches for WSI diagnosis, both of which demonstrated exceptional accuracy in classifying adenocarcinoma (ADC), squamous cell carcinoma (SCC), and small cell lung carcinoma (SCLC) across diverse datasets.

In situations where diagnostic efficacy is hindered by sparse biopsy materials, AI becomes a pivotal tool, offering guidance to pathologists. Despite challenges posed by limited datasets in cytological slides, studies such as those conducted by Teramoto et al. (8) and Tsukamoto et al. (9), recognize the potential of deep convolutional neural networks (DCNNs) in the classification of these challenging microscopic images. These studies report promising accuracy rates in categorizing lung cancer cells, comparable to human cytotechnologists or pathologists.

Moreover, AI's significance becomes apparent in scenarios requiring special immunohistochemical staining for differential diagnosis. Studies by Baxi et al. (10) and Wang et al. (11) demonstrate how AI provides high-accuracy guidance from haematoxylin and eosin (H&E)-stained slides unaided by supplementary staining, reducing diagnostic subjectivity. A reduction is critical in the preoperative period, enhancing the reliability of diagnostic conclusions and, consequently, treatment decisions preoperatively.

Collectively, these advancements underscore the evolving landscape of AI applications in pathology, particularly in lung cancer diagnosis, and emphasize the potential for further research to refine classification methodologies and achieve comprehensive cell and array categorization.

3.2 Prediction of molecular biomarkers

With personalized cancer treatment, the integration of artificial intelligence (AI) with molecular biology presents a promising avenue, transcending conventional histopathology. This is exemplified in the challenges associated with distinguishing between adenocarcinoma (ADC) and squamous cell carcinoma (SCC) based on a single H&E slide obtained from a small biopsy or cytological material. To ensure precision in diagnosis, supplementary staining for immunohistochemical biomarkers such as TTF-1, CK5/6, CK7, pan keratin, p40, p63 and histochemical stains such as periodic acid-Schiff - PAS becomes essential. Numerous studies have tackled binary classification issues related to subtyping non-small cell lung cancer (NSCLC) from H&E slides, aiming for accurate and swift diagnoses. These studies predominantly feature ADC and SCC Whole Slide Images (WSIs), often sourced from The Cancer Genome Atlas dataset (12–15).

For example, Chen et al. (16) and Pao et al. (17) demonstrated the proficiency of DL in predicting ALK rearrangements and EGFR mutations, respectively, achieving commendable Area Under the Curve (AUC) values. These findings lay a foundation for personalized treatment strategies based on the molecular characteristics of the tumor. Moreover, Chen et al. (16) introduced WIFPS, a deep learning system capable of predicting lung cancer-related immunohistochemistry (IHC) phenotypes directly from H&E histopathologic slides. WIFPS exhibits high consistency with pathologists, offering potential assistance in accurate cancer subtyping, especially in scenarios where traditional methods are unavailable. While WIFPS shows promise in reducing the diagnostic ambiguity of cases labeled as "not otherwise specified" (NOS) and guiding targeted therapy, caution is exercised regarding the necessity for extensive validation studies and the translation of clinical benefits.

In the preoperative phase, the predictive capabilities of molecular biomarkers through AI offer valuable insights into the tumor's molecular landscape. This foresight enables the tailoring of treatment strategies based on the specific molecular characteristics of the tumor offering a personalized approach to optimizing therapeutic outcomes even in situations of biopsy scarcity. A factor that could lead in future to even less invasive approaches to cancer sampling. The adept handling of the intricacies of molecular data by AI adds a layer of sophistication to the preoperative decision-making process, which could ensure precision in aligning interventions with the unique molecular profile of the tumor.

3.3 Imaging and staging

In the preoperative evaluation of lung cancer, radiological imaging plays a pivotal role in further guiding clinical decisions related to staging and subsequent therapeutic pathways. AI applications in this are designed to enhance precision in tumor staging and prognostic assessments, integrating algorithms with established imaging modalities (18). This synergy, especially evident in CT image analysis, can result in a noticeable refinement of tumor staging methodologies (19).

The evaluation of AI-assisted CT diagnostic technology for classifying pulmonary nodules, as delineated by Huang et al. (20) study, showcases remarkable diagnostic performance with an exemplary Area Under the Curve (AUC) of 0.95, complemented by sensitivity, specificity, Positive Likelihood Ratio (PLR), and Negative Likelihood Ratio (NLR) values of 0.90, 0.89, 7.95, and 0.11, respectively. Such significant diagnostic prowess emphasizes the potential impact on lung cancer detection. From the physician's perspective, the study reported that their perception indicates widespread adoption in tertiary hospitals, citing reduced workload and enhanced efficiency. However, concerns about diagnostic accuracy, misdiagnosis risks, and patient privacy temper enthusiasm.

A broader systematic review of 14 studies by Amir et al. (19) reinforces the efficacy of AI-assisted diagnostic technology in the context of lung cancer. Employing observer-performance studies and Receiver Operating Characteristic (ROC) analyses, the review identified significant accuracy improvement in eight out of nine instances, affirming the beneficial impact of Computer-Aided Diagnosis (CADx) on lung cancer assessments. Despite variations in algorithm categories and a need for further data, the review supports the conclusion that CADx is poised for broader lung cancer screening and holds implications for advancing medical diagnostics across diverse organ systems, aligning with the evolving landscape of non-radiologic screening modalities. Limitations, including potential biases and a focus on Chinese public tertiary hospitals, warrant consideration in interpreting the generalizability of these findings.

In essence, AI's role in the preoperative period could be transformative for not only refining diagnostic accuracy in histopathology and predicting molecular biomarkers but also augmenting the precision of imaging-based staging, prognostic and screening assessments.

3.4 Surgical candidacy

In preoperative planning, surgical candidacy is usually a complex decision involving scientific, ethical, and legal aspects, especially in patients with pre-existing respiratory and cardiovascular conditions. Traditional risk indices, such as Goldman index for cardiac risk, and Torrington index for respiratory risk, while effective in classifying patients into risk groups, lack specificity and sensitivity for individualized operative risk assessment (21). The identification of lung nodules and their classification using AI has been shown to be superior to human identification in experimental studies. Esteva H, et al. (21)looked at comparing artificial Neural Networks (NN), which were designed to emulate the human neural system to estimate the postoperative prognosis comparatively to traditional risk indices following lung resection. NN was found to offer a more flexible and individualized approach with nearly 100% sensitivity and specificity for predicting patient outcomes. Similarly, Santos-Garcia G, et al. (22) found similar outcomes when using artificial NN, which offered high performance in predicting postoperative cardio-respiratory morbidity.

In lung cancer surgery, conventional methods, such as video-assisted thoracic surgery (VATS), have demonstrated benefits in terms of reduced trauma, faster recovery, and fewer complications. However, limitations exist, including blind spots in the operation and constraints on the flexibility of surgical instruments (23). AI promises to revolutionize surgical practices by providing real-time analysis of intraoperative progress, enhancing decision-making capabilities, and ultimately improving surgical outcomes.

The studies by Chang et al. (24) and Etienne et al. (25) both underscore the transformative role of artificial intelligence (AI) in reshaping medical practices, albeit in distinct domains. Chang et al. (24) delved into pre-anesthetic consultations, emphasizing the pervasive trend of comprehensive digitalization in recent medical practices. Their study illuminates the potential of AI to harness historical medical data for accurate predictions, avoiding invasive interventions. The presented AI-assisted prediction model not only facilitates integrated risk assessments but also addresses the challenges of dynamic data adjustments through manual input by clinicians, ensuring adaptability to diverse patient records.

In contrast, Etienne et al. (25) focused on thoracic surgery, particularly lobectomies and pneumonectomies for non-small cell lung cancer. Their exploration of AI as a decision-making aid in surgical risk assessment and prognosis aligns with Change et al.'s emphasis on individualized medicine. Both studies acknowledge the limitations of traditional risk indexes and highlight the precision and adaptability offered by AI in evaluating individual risk factors.

Etienne et al. (25) cite studies by Santos-Garcia et al. (22) and Esteva et al. (21), showcasing AI's successful application in predicting cardio-respiratory morbidity and post-operative prognosis for nonsmall cell lung cancer. This aligns with Chang et al. (24) proposition that AI, specifically the Naïve Bayes Classifier, is an optimal tool for predictive modeling. Furthermore, both studies stress the potential of AI collaborations among medical specialists, with applications ranging from distinguishing lung adenocarcinoma and squamous cell carcinoma to outperforming pulmonologists in interpreting pulmonary function tests.

Despite the promising outlook, both studies acknowledge challenges for broader AI acceptance. Chang et al. (24) discuss the drawbacks of traditional mathematical equation-based approaches, contrasting them with the adaptability and real-time capabilities of AI. Etienne et al. (25) specifically highlight the need for AI to address complex clinical questions, especially those involving patient comorbidities, to fully integrate into clinical practice.

In synthesis, these studies collectively show the potentially pivotal role of AI in reshaping medical decision-making, whether in pre-anaesthetic consultations or thoracic surgery. The emphasis on individualized, adaptive approaches and collaboration among medical specialists reflects a shared vision of AI as a transformative force in the future of medicine.

4 Intraoperative period

4.1 Surgical guidance and precision

The integration of artificial intelligence (AI) technologies is reshaping the intraoperative landscape of lung cancer management, notably in surgical precision and guidance. This is exemplified by Kanavati et al. (26) study which highlights the pivotal role of deep learning (DL) methodologies in real-time guidance. These DL algorithms, honed on extensive datasets, exhibit unparalleled precision in outlining tumor boundaries intraoperatively, surpassing human visual capabilities (26). This precision translates into tangible benefits during surgery, minimizing the risk of inadvertent tissue damage and optimizing tumor resection (27). The fusion of AI with intraoperative imaging modalities, showcased by Kanavati et al. (26) underscores the potential for informed decision-making, elevating the intraoperative environment's dynamic nature (26, 27).

Intraoperative imaging has evolved from X-rays to technologies like C-arm, intraoperative ultrasound (US), and intraoperative MRI. Molecular imaging, especially in radio-guided surgery, utilizes tracers like radioactive, fluorescent, magnetic, or hybrid options. Emerging technologies like multispectral optoacoustic tomography (MSOT), fiber-based microscopy, and Raman spectrometry contribute to these advancements.

The integration of AI with intraoperative imaging, exemplified by studies such as Kanavati et al. (21), is reshaping lung cancer surgery. DL methods, trained on extensive datasets, exhibit remarkable precision in real-time guidance, exceeding human capabilities. This convergence enhances surgical precision, minimizing the risk of unintended tissue damage, and optimizing tumor removal. Combining AI with intraoperative imaging not only aids decision-making but also injects dynamism into the surgical environment.

Navigation and visualization concepts for preoperative images seamlessly extend to intraoperative molecular images. Technologies like freehand SPECT, incorporating augmented reality (AR) and pointer navigation, exemplify this integration (28) The adaptability of intraoperative imaging to tissue changes, even post-lesion removal, and real-time feedback from methods like radio- or fluorescence guidance confirm successful lesion localization. This fusion of AI-guided precision and advanced intraoperative imaging transforms surgical practices and elevates the field's decision-making capabilities (28, 29).

4.2 Augmented reality and navigational assistance

The landscape of thoracic surgery could be undergoing a significant shift merging technology and precision. Li et al.'s (29) exploration dive into the long-standing use of thoracoscopic lobectomy for lung cancer, challenged by the rise in small tumor discoveries through improved CT imaging. This prompts the recommendation of wedge resection and segmentectomy for early non-small cell lung cancer, yet the complexity of segmentectomy planning, relying on 3D reconstructions with on-screen limitations, remains a hurdle.

To tackle these challenges, Li et al. propose a new approach, combining 3D printing and augmented reality (AR) technology. Creating 3D-printed lung models for pre-surgery planning gives surgeons a better view, addressing issues seen with traditional on-screen models. This innovation extends to the operating room, where tangible models, brought to life with AR, significantly improve surgeons' vision. The integration shows practical benefits, resulting in shorter surgery times, less blood loss, and shorter hospital stays.

The effectiveness of 3D printing and AR goes beyond surgery, aiding in the detailed task of identifying intersegmental planes during lung segmentectomy and reshaping surgical practices.

Beyond immediate applications, these technologies offer promise for medical education and surgical training, providing a hands-on learning experience for students dealing with the complexities of lung structures.

Moving to collaborative insights, Chiou et al.'s (30) AR system and Sedeghi et al. (31) PulmoVR tool, combined with Chen et al.'s (32) contributions, paint a vivid picture of cutting-edge advancements in future surgical operations. Chiou et al.'s (33) AR system shines for its intuitive spatial information and cost-effectiveness, particularly useful in resource-limited settings. Similarly, Moawad et al.'s (34) exploration of AI-enhanced AR overlays, offered real-time support for surgeons providing data and guidance. This integration of AI augments the surgeon's capabilities by offering intelligent support, such as identifying anatomical structures, providing diagnostic insights, or assisting in decision-making during surgery improving their precision and efficiency.

Addressing the complexities of pulmonary segmentectomies, the PulmoVR tool emerges as a potential player. This AI and VR-based planning tool navigates the challenges providing quick and comprehensive evaluations of patient-specific CT scans in immersive 3D. PulmoVR's strengths, efficiency, cost-effectiveness, and user-friendly immersive features—signal a new era of realistic in-depth perception (31). This amalgamation of studies shows a future of a dynamic intersection where AI, AR, and VR converge to enhance surgical practices.

4.3 Real-time decision support

The intersection of diagnoses and treatments in lung tumor management is a critical area explored by Liu et al. (35) The study emphasizes the challenges faced by specialists in managing slowly increasing lesions, highlighting the necessity for rapid on-site accurate diagnoses for effective surgical strategies in early-stage non-small-cell lung cancer. The integration of Optical Coherence Tomography (OCT) with Artificial Intelligence (AI) stands out as a promising solution to address the current time lag in obtaining post-surgery definite diagnoses. OCT's continuous slice images, particularly when integrated with AI (OCT-AI), demonstrate improved discrimination capabilities over traditional Frozen Sections (FS). Despite achieving an 80% accuracy rate, misclassifications are acknowledged, especially in scenarios with coexisting invasive and non-invasive features.

The study delves into the significance of tumor spread through air spaces (STAS) and OCT-AI's potential to suggest wide excision for small tumors with invasive adenocarcinoma (IA) features. Convolutional Neural Networks (CNNs) are justified for AI training, with a focus on image classification in lung cancer. The study employs t-distributed stochastic neighbor embedding (t-SNE) for model visualization and gradient class activation mapping (grad-CAM) for evaluating salient features. The development of an interactive human–machine interface (HMI) is highlighted, offering clinicians real-time information and additional probability data for decision-making, even in cases of misclassifications. The study concludes by recognizing the OCT-AI system's potential as an optional tool for rapid on-site diagnoses, with a commitment to continuous improvement and validation (35).

In parallel, Pao et al.'s (17) study illuminates the significant role of AI in enhancing intraoperative decision-making. DL algorithms are showcased for their ability to discern subtle pathological features intraoperatively, providing instantaneous insights into tissue histology. This real-time histopathological analysis facilitates dynamic adaptation of surgical approaches, ensuring thorough resection while minimizing unnecessary tissue excision. Thus, the integration of AI as a real-time decision support tool could enhance the intraoperative phase by combining surgeons' expertise with AI's analytical acumen, to bring about sophistication in lung cancer surgery.

The juxtaposition of these studies reveals a dichotomy between traditional surgical decision-making processes, influenced by factors like patient values, emotions, and decision complexity, as highlighted by Loftus et al. (6), and the potential advantages offered by AI-driven decision support systems. While the traditional model grapples with challenges and limitations, AI offers a transformative paradigm shift. Machine learning and deep learning present advantages in predicting medical outcomes, addressing the constraints of traditional approaches. Reinforcement learning further demonstrates AI's versatility in optimizing specific clinical decisions. The synthesis of these studies marks a promising future in advancing the sophistication and efficacy of intraoperative decision-making in lung cancer surgery.

5 Postoperative period

5.1 Pathological assessment and margin evaluation

In the aftermath of lung cancer surgery, the postoperative period unfolds as a critical phase where AI demonstrates its potential in pathological assessment. A multitude of studies, such as those by Sheikh (36) and DiPalma et al. (37), accentuate the role of DL methodologies in detailed histological subtyping. These studies looked into the complexities of a 5-class problem, addressing various histological patterns encompassing lepidic, acinar, papillary, micropapillary, and solid patterns. Sheikh et al. (36) explored the impact of multiple descriptors on a deep learning model's performance in the multi-class classification of WSIs. They found that augmenting inputs enhanced the discriminatory capabilities of the model. DiPalma et al. (37) introduced a Knowledge Distillation (KD) method, showcasing its superiority over baseline metrics in effectively classifying diseases such as celiac disease and lung adenocarcinoma. These studies highlight how AI not only aids in subtyping histology but also contributes to a more nuanced understanding of lung cancer, providing clinicians with a comprehensive diagnostic toolkit.

The emphasis on accurate subtyping is particularly pertinent in lung cancer, given its heterogeneity and the subsequent challenges it poses to precise pathological interpretation. However, a critical examination beckons: to what extent can AI truly replicate the expertise of pathologists in discerning these intricate patterns?

Moreover, the postoperative period demands a meticulous evaluation of surgical margins. The study by Kanavati et al. (7) delves into the prowess of DL algorithms in real-time surgical guidance, significantly impacting margin assessment. It raises an intriguing proposition — can AI serve as an adjunct, offering a second layer of scrutiny to ensure optimal margins? The challenge lies not only in the technical accuracy of AI but also in establishing a seamless integration with existing pathological workflows.

5.2 Prognostic insights and predictive modelling

The landscape of postoperative medical research unfolds with the synergy of artificial intelligence (AI) in treatment prediction. Dercle et al.'s (38) AI model represents a significant stride in predicting therapy responses, contributing to nuanced treatment decision-making. Simultaneously, concerns arise in ANN studies, notably regarding overfitting due to oversized networks, prompting reflections on reliability and validation. Ongoing efforts address these challenges, exemplified by a novel ANN tool tailored for small datasets and the underexplored potential of ensemble runs. The importance of refined variable selection comes to the forefront, with pruning emerging as a method to enhance input-to-output relationships in ANNs. Acknowledging the advantages of ANNs, such as learning without prior knowledge and suitability for clinical tasks, contrasts with persistent issues of overfitting. Within this context, the dynamic approach of ANNs in analyzing mortality risk, accommodating outliers and nonlinear interactions, underscores their potential amid challenges (39–43).

Shifting focus to lung cancer prognosis, AI plays a pivotal role in addressing multifaceted factors influencing outcomes, including age, tumor characteristics, and treatment modalities (44). Recognizing the limitations of single-test item prognostication, studies advocate for AI-integrated predictive models to enhance accuracy (44). Recent research illustrates the application of deep learning and imaging analyses, such as PET, effectively staging lung cancer (45). Notably, eXtreme Gradient Boosting (XGBoost), a deep learning library, contributes to constructing models by sorting feature importance based on decision tree models (46). Utilizing this approach, predictive models like the ITEN model offer personalized drug treatment recommendations, particularly for cases with bone metastasis, ultimately improving patient survival rates. The evolution of AI-driven models, incorporating neural networks in deep learning, signals a paradigm shift in treatment optimization. The ITEN model's consistency with published data reaffirms its reliability in predicting survival efficiency in non-small cell lung cancer patients (46). Integrating these advancements with ongoing efforts in AI-driven treatment predictions and evolving ANN methodologies enriches the landscape of medical research, providing a comprehensive approach to lung cancer prognosis and treatment optimization.

As the postoperative period sounds like a promising field for AI integration into routine clinical workflows, the concomitant challenges cannot be overlooked. The integration of digital pathology, as advocated by Pao et al. (17), necessitates a paradigm shift in infrastructure, storage, and data-sharing practices. The ethical dimension becomes pronounced, with concerns regarding patient data privacy and the development of regulatory frameworks surfacing prominently. Moreover, the dependence on extensive labeled datasets for training raises questions about the representativeness of these datasets and the potential biases embedded within them.

while AI promises to revolutionize the postoperative management of lung cancer, its implementation requires a judicious approach. The balance must be meticulously struck to ensure optimal outcomes in the postoperative care continuum (4).

6 Challenges and limitations

The integration of artificial intelligence (AI) into lung cancer management, as elucidated in the reviewed studies, brings forth a spectrum of challenges and limitations that merit careful consideration.

6.1 Lack of interpretability

A salient concern extracted from the systematic review is the conspicuous lack of interpretability and explanation within certain AI applications (47). While the proficiency of AI models in classification tasks is evident, the paucity of concerted efforts in addressing common sense reasoning, especially in deciphering the intricate physical characteristics of cells, poses a critical challenge (36). This interpretability gap, particularly pronounced in tasks requiring nuanced understanding, introduces a layer of complexity in the integration of AI insights into the clinical decision-making process. As clinicians often rely on interpretive skills honed through years of training, the opaque nature of AI outputs may impede the establishment of trust and hinder widespread adoption.

6.2 Training limitations with inadequate samples

The depth of learning algorithms, highlighted by multiple studies (8, 9, 36, 39, 41–43) necessitates substantial volumes of labeled data for effective performance. However, the pragmatic challenge arises when dealing with the sheer scale of annotations required, often dependent on the expertise of pathologists (37). This challenge is exacerbated in scenarios where specific histopathological subtypes or rare molecular profiles are encountered infrequently. The resultant scarcity of comprehensive datasets compromises the generalizability of AI models. Addressing this challenge demands collaborative initiatives for the meticulous curation of diverse datasets that mirror the true heterogeneity encountered in clinical practice.

6.3 Less power in problems beyond classification

While the prowess of AI, especially deep learning, in classification tasks is evident, the studies underscore its relatively diminished efficacy in addressing problems beyond classification (3). In the expansive landscape of lung cancer management, where intricate analyses involving regression, clustering, and multi-dimensional correlations are often required, the limitations of AI become apparent. Traditional machine learning techniques, capable of handling diverse problem sets, might outshine deep learning in these nuanced domains (48). This prompts a critical reflection on the strategic deployment of AI, emphasizing its alignment with the specific analytical demands of the clinical context.

6.4 Lack of global generalization

The pervasive challenge of the lack of global generalization in deep learning algorithms emerges consistently across studies (16, 26, 27, 49, 50). Overfitting tendencies, wherein models excel in performance on training data but falter when presented with new or unlabeled data, pose a substantial challenge. In the context of lung cancer diagnosis, characterized by variations in imaging techniques and equipment, achieving robust generalization becomes a formidable task (47). The demand for models that can seamlessly adapt to diverse clinical settings is not only an academic concern but a practical necessity for the broader implementation of AI in lung cancer care.

However, challenges to the widespread adoption of AI in healthcare are acknowledged, encompassing issues of data standardization, technology infrastructure, interpretability, safety, monitoring, and ethical considerations (19). The need for rigorous analysis, external validation, and mitigation of biases in training data is emphasized, particularly given the potential consequences of algorithmic errors (19). The ethical challenges surrounding biases in algorithm outputs and accountability underscore the necessity for a robust regulatory framework for AI in healthcare (19).

6.5 High memory and computational cost requirements

The ambition to deploy deep learning models in lung cancer diagnosis is tempered by the pragmatic constraints of high memory and computational costs, as underscored by (3, 51). The intricate nature of biopsy images, often high in resolution, demands sophisticated processing capabilities. This raises pertinent questions about the scalability and accessibility of such approaches in real-world healthcare settings. While advancements are underway to optimize computational efficiency, the inherent resource demands remain a critical consideration in the practical implementation of AI in routine clinical workflows.

In summary, the journey of AI in lung cancer management is not devoid of hurdles. A critical understanding of these challenges, fortified by insights from the review, becomes imperative for steering the trajectory of AI research and application toward meaningful and sustainable integration into lung cancer care.

6.6 Ethical dilemmas

The integration of Artificial Intelligence (AI) in thoracic surgery, especially in lung cancer treatment, brings to the forefront a spectrum of ethical considerations that are critical for maintaining patient welfare and integrity in medical practice. Central to this ethical framework is ensuring patient autonomy through informed consent, as AI's involvement in diagnostic and surgical decision-making introduces complexities requiring patient comprehension of AI's influence on treatment options and conscious choice-making (52). This aligns with the imperative need to safeguard patient data privacy and security, addressing the ethical challenges posed by AI's reliance on extensive health data for operation, thereby keeping patient trust and confidentiality (53). Equally crucial is addressing potential biases in AI, given its dependency on training data, to prevent the perpetuation of healthcare disparities, particularly in lung cancer treatment where demographic differences are significant (53, 54). Furthermore, the opacity of AI systems necessitates a robust approach to transparency and accountability, ensuring that AI supplements rather than supplants the expert clinical judgment of healthcare professionals (54, 55). The ethical integration of AI in thoracic surgery demands continuous monitoring and evaluation to assess its accuracy, effectiveness, safety, and overall impact on patient outcomes, ensuring that AI's deployment remains aligned with ethical standards and patient-centric values.

7 Conclusion

In conclusion, while the integration of artificial intelligence (AI) in lung cancer management shows promise across phases, it faces notable challenges. In the preoperative phase, AI enhances diagnostics and predicts molecular biomarkers, especially in cases with limited biopsy materials. Intraoperatively, AI transforms surgery by providing real-time guidance and decision support. Postoperatively, AI aids in pathological assessment and predictive modeling for refined care.

However, challenges include the lack of interpretability, training limitations affecting model generalizability, and AI's efficacy beyond classification. Global generalization, marked by overfitting, poses a challenge, along with high memory and computational costs and challenging ethical frameworks. Addressing these challenges requires a judicious approach, considering ethical, technical, and regulatory dimensions. Rigorous analysis, external validation, and a robust regulatory framework are crucial for responsible AI implementation in lung cancer care, emphasizing the evolving intersection of human expertise and technological advancement.

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Application of three-dimensional technology in video-assisted thoracoscopic surgery sublobectomy

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Background: Due to the widespread use of imaging techniques, the detection rate of early-stage lung cancer has increased. Video-assisted thoracoscopic surgery (VATS) sublobectomy has emerged as a prominent alternative to lobectomy, offering advantages like reduced resection range, better preservation of lung function, and enhanced postoperative quality of life. However, sublobectomy is more intricate than lobectomy, necessitating a higher level of surgical proficiency and anatomical understanding.

Methods: Three electronic databases were searched to capture relevant studies from January 2016 to March 2023, which related to the application of three-dimensional(3D) technology in VATS sublobectomy.

Results: Currently, clinical departments such as orthopedics, hepatobiliary surgery, and urology have started using 3D technology. This technology is expected to be widely used in thoracic surgery in future. Now 3D technology assists in preoperative planning, intraoperative navigation and doctor-patient communication.

Conclusion: 3D technologies, instrumental in locating pulmonary nodules and identifying variations in target lung segmental vessels and bronchi, play pivotal roles in VATS sublobectomy, especially in preoperative planning, intraoperative navigation, and doctor-patient communication. The limitations of 3D technology in clinical application are analyzed, and the future direction of existing 3D technology development is prospected.

KEYWORDS

3D reconstruction, 3D printing, sublobectomy, VATS, early lung cancer

Introduction

Low-dose spiral CT is widely utilized, leading to an increased detection of ground-glass nodules (GGNs) at an early stage. In the past, anatomical lung lobectomy with mediastinal lymph node dissection has been the most commonly used gold standard treatment for early-stage non-small-cell lung cancer (NSCLC). However, lung cancer predominantly affects the elderly, with the majority of cases occurring in individuals over 60 (1). These lung cancer patients generally have poor physical conditions. Although lobectomy removes the tumor, it also removes a large amount of healthy lung tissue, which greatly affects the patient's postoperative lung function and quality of life. Is there a more suitable and better surgical method to treat early NSCLC? Several scholars have undertaken comprehensive studies to address this question.

A series reports of the Japan Clinical Oncology Group (JCOG) 0802/0804/1211 and the latest multicenter non-inferiority verification study, such as CALGB140503 show that sublobectomy is safe and effective, which can preserve more lung function, improve the prognosis of patients with higher quality of life and longer survival time (2–5). While anatomical lobectomy remains the standard surgical procedure, sublobectomy is an optional approach for CT1N0M0 NSCLC patients who meet specific criteria (6). Although sublobectomy is a more suitable surgical option for some early lung cancer patients, it is more complex for doctors than lobectomy. It requires doctors to accurately locate tumors and identify lung segments, bronchi and pulmonary vessels that need to be removed during surgery. The requirements for doctors' mastery of anatomy, ability to read CT images, and surgical experience are stricter. Consequently, many surgeons explore auxiliary methods to simplify the demands of VATS sublobectomy.

Initially, 3D reconstruction technology was employed in fields such as orthopedics, oral surgery, and hepatobiliary surgery. Its applications in thoracic surgery have been steadily increasing. This technology assists sublobectomy by importing patient DICOM data, like CT angiography (CTA), into 3D reconstruction software. Taking the Mimics software (Materialise, Belgium) as an example (7), first generate the three-dimensional visualization (3DV) model of the main bronchus, then add the structure of small bronchi and segment tissues such as pulmonary vasculature and lymph nodes into different masks by setting appropriate thresholds. Unnecessary tissue masks are then removed, gaps filled, modifications made, and the model is smoothed out. It's then compared with original CT images to ensure accuracy. The final 3DV model, which includes bronchi, pulmonary vasculature, tumors, and lymph nodes, offers interactivity, allowing for enlargement, reduction, rotation, and translation. When a key observation structure needs to be highlighted, other surrounding tissues can be hidden to prevent the learner's vision from being disturbed by irrelevant structures. Through this technology with good interactivity, the patient's lung tumor and surrounding vessels can be more fully displayed on a two-dimensional screen before or during surgery to provide great help for the operation.

While 3D reconstruction technology offers numerous advantages, it lacks the tactile feedback and immersive experience provided by physical models. Hence, with the increasing precision demands of surgeries, 3D printing technology, capable of producing tangible models, has been introduced. In recent years, 3D printing has found extensive applications in the medical domain, especially in surgical simulation, preoperative planning, and the creation of surgical assistive tools (8). Clinical departments, including orthopedics, hepatobiliary surgery, and urology, have adopted 3D printing, and its potential applications in thoracic surgery are promising (Figure 1).

Materials and methods

We conducted a literature search on PubMed, Elsevier, and SpringerLink for publications from January 2016 to March 2023, focusing on the application of 3D technology in VATS sublobectomy. The search terms included: 3DV, 3D reconstruction, 3D printing, sublobectomy, lung nodule localization, lung nodule diagnosis, VATS, preoperative planning, intraoperative navigation, and doctor-patient communication. Exclusion criteria encompassed duplicate studies and those unrelated to 3D technology and VATS. The inclusion criteria targeted original articles pertinent to 3D technology and VATS. After screening titles for relevance and reviewing abstracts, studies that aligned with the research objectives and met the inclusion criteria were incorporated into our database.

Results

The keyword-driven database search and subsequent screening by inclusion criteria yielded an initial 244 relevant studies. Of these, 38 articles were ultimately selected for review (Figure 2). These studies indicated that 3D technology primarily finds application in

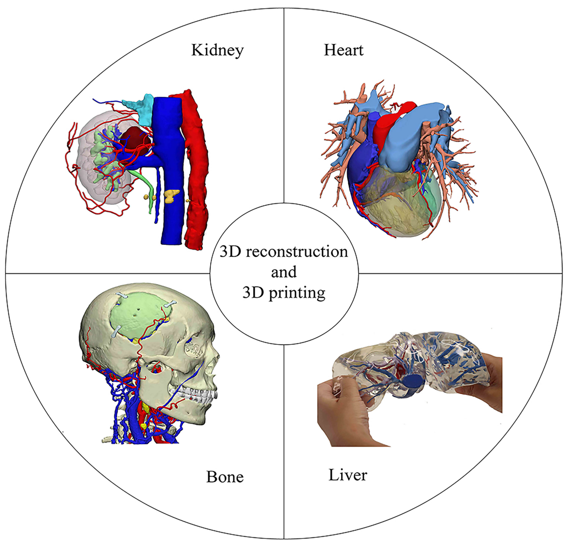

FIGURE 1
The application of 3D technology in our hospital.

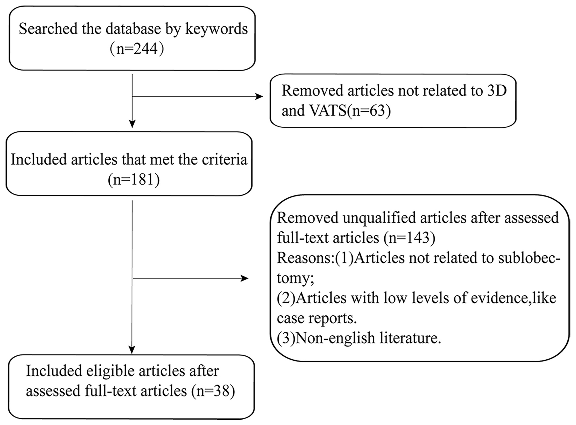

FIGURE 2
The flow diagram of articles identified and selected for inclusion in this review.

TABLE 1 Application of 3D technology in sublobectomy.

Documents	Keywords	Evaluation
2022, E H, et al. (9), 2017, Zhang L, et al. (10), 2020, Fu R, et al. (11), 2019, Zhang L, et al. (12)	navigational template; preoperative nodule localization	Feasible, safe, accurate, and fast
2019, Kitano K, et al. (13), 2018, Sato M, et al. (14).	VALMAP; preoperative nodule localization	For deep pulmonary nodules, it is a minimally invasive, safe, and reliable manner.
2022, Tang H, et al. (15)	navigation template; intraoperative nodule localization	feasible
2021, Fu R, et al. (16)	navigation template; intraoperative nodule localization; MR technology	For small and deep nodules, it is useful, accurate and safe.
2021, Zhao L, et al. (17)	dial positioning method; intraoperative nodule localization	This method is accurate, safe, fast, without radiation exposure
2019, Sun W, et al. (18)	navigation template; intraoperative nodule localization; multiple pulmonary nodules.	Applicable, safe, and uncomplex
2021, Ji Y, et al. (19), 2022, Li K, et al. (20).	3D solid model; multiple pulmonary nodules	Accurate, effective and feasible.
2021, Wu X, et al. (21), 2022, Lin KH, et al. (22), 2021, Wu YJ, et al. (23)	3DV models; preoperative planning; Intraoperative navigation	It is safe and accurate for lung nodules deep or adjacent lung segment borders.
2019, Wu WB, et al. (24)	combined sub-segmentectomy; 3D reconstruction	effective
2020, Chen Y, et al. (25)	VATS segmentectomy; 3D printing; 3D reconstruction.	3D printing technology is superior to 3D reconstruction technology.
2020, Qiu B, et al. (26)	APL; 3D reconstruction; 3D printing	3D printing models are more suitable for complex segmentectomy.

three facets of sublobectomy: the preoperative stage, the intraoperative stage, and doctor-patient communication (Table 1).

Application of 3D technology in the preoperative stage of sublobectomy

Prior to sublobectomy, accurate diagnosis of the target lung nodule is essential. Traditional clinical methods, such as fiberoptic bronchoscopy and lung puncture biopsy, are frequently employed to discern the benign or malignant nature of nodules. 3D reconstruction technology, a subset of 3D technology, facilitates the multi-angle, multi-directional 3D morphological reconstruction of lung nodules. Leveraging the 3D characteristics of nodules, along with related imaging metrics like nodule diameter, vascular bundle sign, and lobular sign, allows for a more precise assessment of nodule nature. This provides thoracic surgeons with enhanced diagnostic accuracy, aiding in the formulation of patient treatment plans (27). Moreover, 3D technology can notably enhance the success rate of preoperative lung nodule localization and planning. Lung nodules are categorized into solid and subsolid nodules. The latter is further classified into pure ground glass nodules (pGGNs) and mixed ground glass nodules (mGGNs) (28). pGGNs lack solid components and typically exhibit lower average CT values. In contrast, mGGNs comprise both solid and ground glass components, presenting with varied imaging manifestations and higher CT values. A study by Son et al., has found that increased density (75th percentile CT attenuation value on a histogram ≥-470 Hounsfield units), and entropy (a measure of heterogeneity by texture irregularity) predicted invasive adenocarcinoma (29). Therefore, we generally believe that the CT value of the solid component is higher than -470. The consolidation-to-tumor ratio (CTR) represents the ratio of the maximum consolidation size to the maximum tumor size (30). Numerous studies have affirmed the utility of CTR as a reference metric for distinguishing benign from malignant early-stage lung cancers (31). For example, JCOG 0201 has shown that the ground-glass opacity predominantly associated with excellent prognoses, and JCOG 0802 has defined radiologically non-invasive lung cancer as having a maximum tumor diameter of 2 cm with a consolidation-to-tumor ratio of 0.5 or less (2, 32). The IASLC Lung Cancer Staging Project also has found that there is a general correlation between solid patterns on CT scans and invasive patterns histologically (33). Meanwhile, according to a meta-analysis from 2023, its results suggested that higher CTR was associated with worse prognosis in NSCLC patients(the cut-off value was usually 0.5 or 0.75), and CTR can be used to predict the prognosis of NSCLC patients and guide the preoperative decision-making of patients with NSCLC (30, 34, 35). 3D measurements have identified a significant association between elevated CTR values and the invasiveness of lung adenocarcinoma (36). For T1N0M0 lung adenocarcinoma, a higher CTR value often suggests increased pathological invasiveness (37). 3D reconstruction technology not only visualizes lung nodules but also delineates their volume and CT values. The first step is to first create a tumor mask, and then remove the pulmonary arteriovenous mask so that only GGN components are left in the mask. Second, create a global mask with a threshold greater than -470.In the third step, the global mask greater than -470 is combined with the GGN mask after the removal of blood vessels to do the Boolean operation (intersection) to obtain the solid component mask. Then the GGN mask and the solid component mask are calculated as objects surrounded by triangular surfaces, and then the maximum diameter length of the GGN and the solid component is measured according to the definition calculated by CTR (Figure 3). This underscores the pivotal role of 3D reconstruction technology in the diagnostic differentiation of lung nodules (38).

While lung biopsy offers the highest diagnostic accuracy, it suffers from a notable limitation: a relatively high false-negative rate (39). Misdiagnoses can occur if the biopsy needle fails to intersect malignant tumor cells. 3D technology, leveraging its spatial positioning capabilities, can mitigate this limitation. Notable applications encompass 3D printing navigation template-guided lung puncture biopsy and 3D imaging-assisted bronchoscopy (9, 40), both of which demonstrate superior accuracy and safety compared to CT. Once the nature of the nodules is ascertained via biopsy, preoperative localization is typically undertaken for patients fitting surgical criteria. Currently, CT-guided Hookwire localization remains the predominant clinical method (41), but it poses risks of iatrogenic injuries and potential severe complications like pneumothorax, hemothorax, and air embolism (42). This method also demands significant technical expertise from the practitioner. Another prevalent approach is CT-guided percutaneous puncture injection using dyes. Indocyanine green, the most effective dye to date, boasts a high localization success rate and commendable safety. However, precise dosage control is crucial; excessive amounts can lead to fluorescence dispersion in the pleural cavity, while insufficient quantities might result in failed localization (43). Furthermore, these methods might not accurately pinpoint the lung segment housing the nodule or delineate the surgical safety margin for nodules.

In comparison to traditional CT-guided puncture localization, which has inherent limitations such as radiation exposure and accuracy influenced by nodule depth, 3D technology offers significant advantages in assisting lung nodule localization (44). A prevalent method involves reconstructing a digital pulmonary model, followed by designing and printing a 3D physical navigation template for preoperative localization (Figures 4A, C) (10). This navigation template typically aligns with anatomical markers, clearly indicating the direction, position, angle, and depth of the puncture point. Physicians can then perform punctures swiftly and simply along the designated tract (11). The success rate for template-guided puncture stands at 89%, markedly surpassing that of CT-guided puncture (6.3%). This method also considerably reduces positioning time and radiation exposure ($P < 0.001$) (12). Beyond the 3D navigation template, 3D technology offers a myriad of applications in aiding preoperative localization of pulmonary nodules. One notable technique is virtual-assisted lung mapping (VALMAP), rooted in 3D reconstruction technology, which proves invaluable for resecting multiple deep-seated pulmonary nodules. Preoperatively, a 3DV model of virtual bronchoscopy guides the procedure. Markings are made on the visceral pleura using dye injections under bronchoscopy, followed by 3D reconstruction to verify the accuracy of the marking range (13). However, mastering this method poses challenges, and potential severe complications like hypertension and hypoxemia can arise. Additionally, if the nodule's position is too deep, the likelihood of localization failure escalates (14). 3D technology also facilitates preoperative planning and simulation through virtual reality (VR) systems (45). Integrating conventional imaging modes with VR systems significantly enhances preoperative planning, bolstering the safety and precision of anatomical resection.

Research indicates that 3D technology equips physicians with a more comprehensive understanding of surgical intricacies preoperatively compared to conventional methods, simultaneously minimizing unnecessary preoperative trauma.

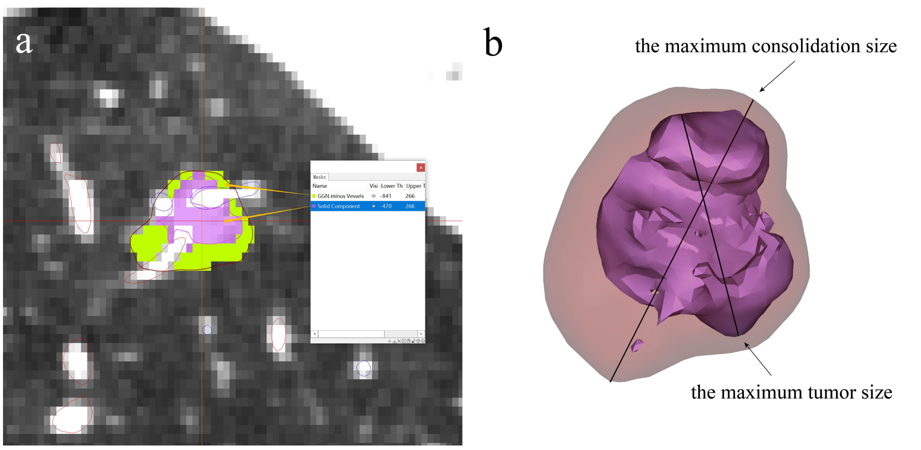

FIGURE 3
3D technology in lung nodule imaging diagnosis. **(A)** Nodule is divided into solid and ground glass component according to CT value, **(B)** CTR value can be obtained by calculating the maximum consolidation size to the maximum tumor size.

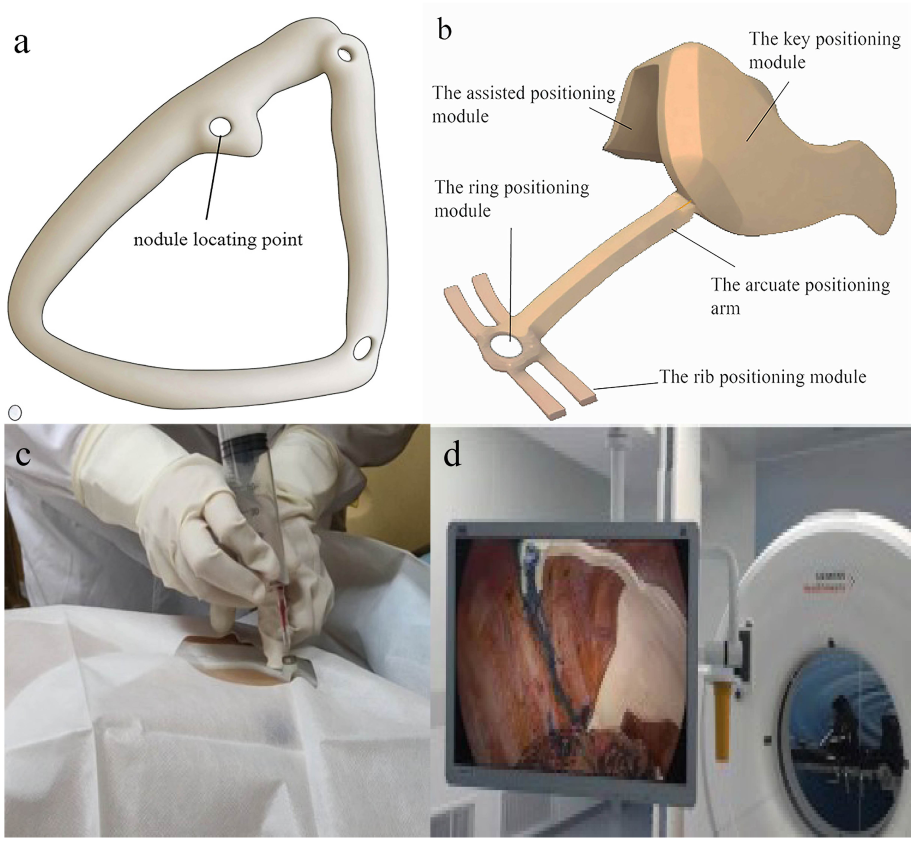

FIGURE 4
3D navigational template in preoperative and intraoperative lung nodule localization. **(A)** 3D preoperative navigational template. Surgeon puncture at the nodule locating point ; **(B)** 3D intraoperative navigational template. The key positioning module will be placed on the top of the pleural cavity and match with some anatomic landmark. according to the assisted positioning module and rib positioning module, the nodule will be located by the ring positioning module. Then doctor stain the corresponding location. **(C)** 3D preoperative navigational template in surgery. It is quoted from reference 22. **(D)** 3D intraoperative navigational template made by TPU in surgery. It is quoted from reference 37.

Application of 3D technology in the intraoperative stage of sublobectomy

While anatomical studies highlight the coexistence of bronchus and corresponding pulmonary artery, with the pulmonary vein traversing between segmental planes, variations in bronchus and pulmonary vessels are frequently observed across patients (46). Solely relying on standard pulmonary anatomy, without considering vascular variations evident in preoperative CT images, can lead to surgical complications such as erroneous ligation or intraoperative vascular injury. Moreover, certain nodules, due to their diminutive size, depth, and inaccessibility, pose challenges for intraoperative localization and resection (47). Traditional methods often fall short in addressing these challenges. In contrast to conventional 2D data sources like anatomical atlases and CT scans, 3D models vividly depict the lungs' three-dimensional internal and external structures, offering surgeons a more comprehensive, intuitive, and tangible grasp of the surgical region. To enhance nodule localization accuracy, delineate a safer resection boundary, mitigate the risk of inadvertent vascular injuries, and elevate surgical precision and safety, 3D technology has been integrated into the intraoperative navigation of VATS sublobectomy (48).

Certain nodules, due to their depth, present heightened risks associated with preoperative puncture. Additionally, some patients decline invasive preoperative examinations or localizations. Consequently, a significant number of nodules undergo resection without preoperative puncture. In VATS sublobectomy, the restricted access of the operation hole complicates direct nodule confirmation. To address this, 3D physical navigation templates crafted from thermoplastic polyurethanes (TPU) are employed. These templates can be introduced into the pleural cavity without preoperative puncture, facilitating intraoperative nodule localization and resection (15), thereby circumventing puncture-related complications and streamlining the localization process (Figures 4B, D). Intraoperative localization offers additional benefits: it eliminates the need to transfer patients from the radiology department to the operating room, conserves time, and spares patients from preoperative anxiety due to general anesthesia (11). 3D printed navigation templates can further integrate with mixed reality (MR) technology. Preoperatively, MR glasses allow surgeons to view a 3D-reconstructed virtual thoracic holographic projection. Using 3D printed navigation templates for tactile feedback, the puncture's point, angle, and depth can be ascertained in the operating room. This combined approach is viable even for impalpable lung nodules, eliminating patient transfers between CT and operating rooms (16).

Other innovative applications of 3D technology for intraoperative lung nodule localization have emerged. For instance, Zhao et al. introduced a dial positioning method (Figure 5) (17). This real-time intraoperative technique not only mitigates complications like hemothorax and pneumothorax but also operates independently of CT assistance, ensuring zero radiation exposure.

Current methods for localizing multiple lung nodules, such as employing markers like Hookwire for percutaneous puncture localization, necessitate multiple scans, proving to be intricate and time-intensive. Moreover, the recurrent insertion of localization devices can elevate the risk of pneumothorax, complicating the achievement of swift, safe, and effective localization. While electromagnetic navigation bronchoscopy (ENB) ensures a commendable success rate and safety for localization, it is predominantly utilized for solitary nodules and demands significant technical expertise from the operator (49). Conversely, 3D technology-assisted localization obviates the need for supplementary examination equipment and intricate operational procedures. After identifying the pulmonary vessels in the target region through preoperative 3D reconstruction and determining the pulmonary segment via the inflation-deflation method, surgeons can proceed directly to resection. 3D physical navigation templates can guide intraoperative localization of multiple lung nodules without relying on CT equipment (18). Additionally, direct reconstruction and 3D printing of physical models of multiple lung nodules can aid in preoperative planning and intraoperative navigation. The nodule positions depicted by the 3D printed model offer greater precision and clarity than pathological reports (19). Furthermore, 3D printed models can distinctly represent minor lesions that remain ambiguous in terms of benignity or malignancy, assisting physicians in assessing the surgical resection scope. Surgeons can opt to resect these minor nodules concurrently if they don't interfere with the primary surgical plan, potentially excising up to 12 nodules in one procedure (20) (Figure 6). If any of these nodules prove malignant, the patient can avoid a secondary surgery post-lung cancer recurrence, thereby preventing significant physical and economic repercussions.

Before undertaking a sublobectomy, it's imperative not only to pinpoint the location of lung nodules but also to comprehend the intricate anatomical structures of the neighboring sublobar units, encompassing arteries, veins, and bronchi (50). This knowledge facilitates the demarcation of sublobar unit boundaries, assessment of the spatial relationship between the nodule and the sublobar unit, and determination of the specific sublobar region for resection. Unlike 2D imaging modalities such as CT and MRI, 3D technology transforms these 2D images into comprehensive 3D representations of vascular and bronchial trees, effectively delineating vessel branching patterns and accentuating anatomical variations in both vessels and bronchi (51). Subsequent analysis of intersegmental veins within these sublobar anatomical units

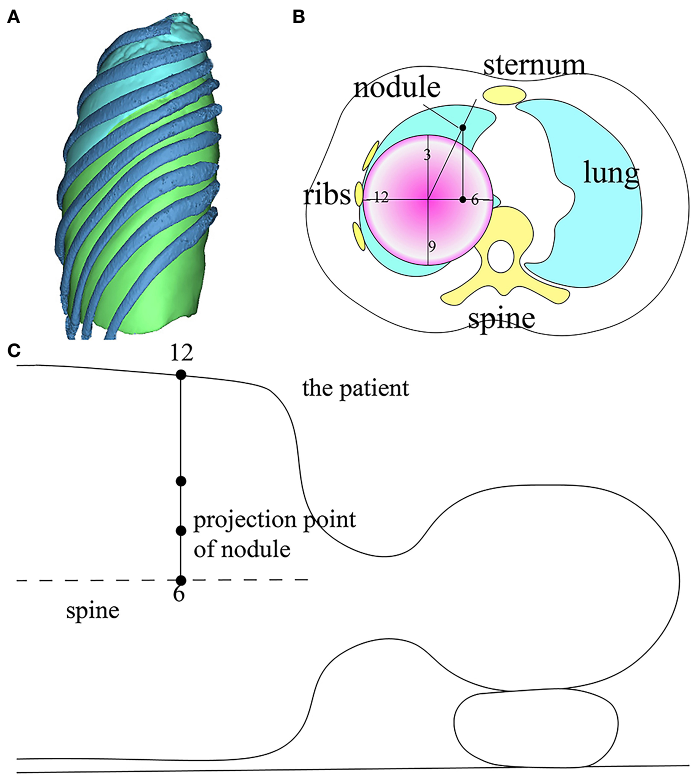

FIGURE 5
three-dimensional reconstruction combined with dial positioning in intraoperative lung nodule localization. **(A)** Reconstruct lung and ribs, and record the precise positional relationship between the nodule and the nearest rib; **(B)** Locate the plane of pulmonary nodule on horizontal CT, and draw a circular dial on the CT of affected lung. Record the orientation of the nodule. **(C)** Draw the horizontal lines of CT cross-resection and mark the projection point of nodule across the patient's body, then puncture and mark on the lung surface.

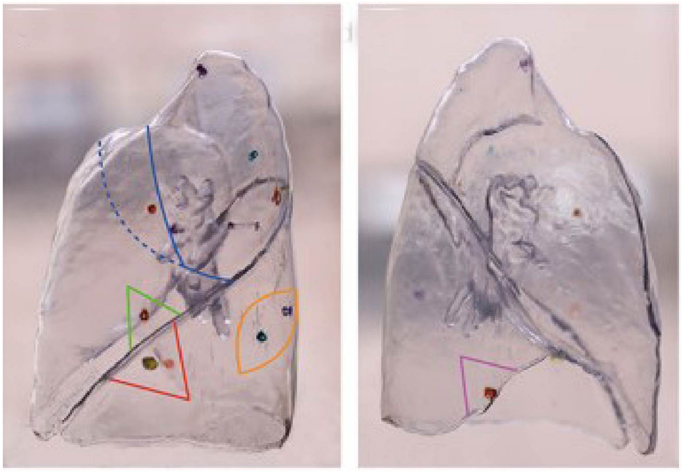

FIGURE 6
3D printing technology in locating lung nodules. It is quoted from reference 43.

allows for precise boundary identification. Moreover, this technology vividly illustrates the spatial relationship between the nodule and adjacent vessels, aiding in the accurate judgment and resection of target sublobar tissues while ensuring surgical margin safety.

For segmentectomy procedures, utilizing 3D reconstruction software, such as 3D Slicer and Mimics, for preoperative reconstruction and simulation offers advantages over traditional CT images. This method facilitates the creation of surgical plans and provides intraoperative navigation, proving especially beneficial for the precise excision of deep nodules or those situated along the borders of adjacent segments. Through the 3DV model, surgeons can ascertain the spatial relationship between nodules and segment borders, thereby determining the safe resection margin distance. This enhances surgical precision and safety, ensures adequate surgical margins (21), diminishes the recurrence rate of lung cancer (22), and preserves ample normal lung tissue. The 3DV model also provides a detailed visualization of the blood vessels and bronchi within the target lung segment, aiding surgeons in discerning the spatial relationship between the nodule, bronchus, and pulmonary vasculature. This clarity ensures accurate segment resection and minimizes the risk of intersegmental vein injury (23). Notably, for variant blood vessels and bronchi, surgical safety has seen marked improvement. Beyond static 3DV models, Tokuno J et al. introduced a semi-automatic simulation system for dynamic 3D images, capturing the intraoperative lung deformation (52).

In wedge resection, 3D reconstruction technology offers significant intraoperative assistance. Using the 3DV model, physicians can identify the clipping points based on the nodule's safe margins and adjacent blood vessels. Subsequently, the anticipated surgical incision line and resection plane for the wedge resection are delineated. The appropriate points are then marked on the lung using a marker pen, guiding the wedge resection (Figure 7) (53). This method streamlines preoperative planning, facilitates the estimation of lung tissue thickness for stapler use, and aids in selecting the appropriate stapler types or assessing the feasibility of a wedge resection (53).

Beyond segmentectomy and wedge resection, sublobectomy encompasses the more intricate combined sub-segmentectomy (51). This procedure is primarily tailored for lung nodules situated between lung segments. The surgical target area combines two adjacent lung subsegments with the nodule and neighboring intersegmental veins (54). As the surgical focus narrows from lung segments to subsegments, the procedure's complexity increases, necessitating meticulous preoperative planning. This ensures surgeons have a comprehensive understanding of the boundaries of the subsegments adjacent to the nodule and can determine the subsegments requiring resection. Compared to segmentectomy and wedge resection, the successful execution of combined sub-segmentectomy is more dependent on 3D technology for preoperative planning and intraoperative navigation (24).

Relative to 3DV models, 3D printed models excel in pinpointing nodules and delineating intricate vascular structures. These models not only enhance the success rate of nodule localization and resection but also surpass 3D reconstruction technology in terms of reducing surgical conversion rates (0% vs 10.5%), operation duration (2.07 ± 0.24h vs 2.55 ± 0.41h), and intraoperative blood loss (43.25 ± 13.63 mL vs 96.68 ± 32.82 mL) ($P<0.05$) (25). This superiority stems from the fact that 3D printed models offer surgeons a tangible 3D perspective during preoperative planning, facilitating the identification of nodules and the intricate network of blood vessels and bronchi, without the need for mental visualization. Qiu Bin et al. highlighted the pronounced benefits of both 3D reconstruction and 3D printed models in discerning vascular variations during anatomical partial-lobectomy (APL) (26). They further underscored the spatial and distance accuracy of 3D printed models, emphasizing their suitability for complex segmentectomy and the notable reduction in operation time compared to 3D reconstructed models.

Collectively, these studies underscore that 3D technologies, encompassing both 3D reconstruction and 3D printing, render

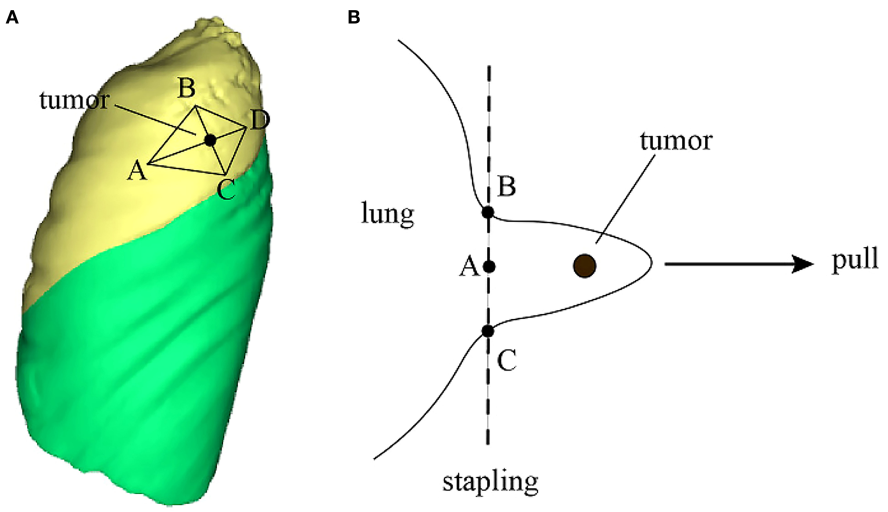

FIGURE 7
3D technology to improve surgical operation safety and quality. **(A)** Reconstruct the 3DV model and locate pulmonary nodule and draw a rhomboidal cut line and four marker points on the 3DV model; **(B)** According to the 3DV model, CT image and anatomical landmarks, mark correct points on the pleura, then resect the lung nodule along the cut line by a stapler.

VATS sublobotomy more rapid, safe, and efficient than conventional techniques, with 3D printing technology holding an edge over 3D reconstruction.

Application of 3D technology in doctor-patient communication

Lung cancer predominantly affects the elderly, a demographic often unfamiliar with medical intricacies. Given the specialized nature of medical professionals, a cognitive gap exists between doctors and patients, complicating effective communication. To secure informed consent for VATS sublobectomy, it's imperative that patients and their families grasp the tumor's location and size, the surgical approach, and potential postoperative complications. 3D technology, particularly 3D printing, can produce tangible models of a patient's lungs, offering a tangible medium for doctor-patient dialogue (55). The tangible nature of these models significantly enhances communication. For instance, a survey of early-stage lung cancer patients, where some were presented with 3D printed models during the informed consent process, indicated that these models enriched the patients' comprehension of their ailment (56). Another survey of surgeons utilizing 3D printed models as surgical aids revealed that 88% felt the models improved communication with patients and their families (26). This preference might stem from the tangible, stereoscopic nature of 3D printed models, which might resonate more with patients and their kin compared to 3DV models. Such studies suggest that 3D technology in doctor-patient communication can bridge the understanding gap, fostering a more collaborative doctor-patient dynamic. This approach might also mitigate potential doctor-patient conflicts and bolster the overall doctor-patient relationship. Based on our hospital's medical 3D printing center's experience, 3D printed models, when utilized in surgical planning, intraoperative navigation, and doctor-patient communication, yield superior results compared to 3D reconstructed digital models.

Conclusions

As advanced technology inevitably supersedes outdated methods, sublobectomy is poised to gain broader acceptance. Similarly, the closely related 3D technology will play an increasingly important role in thoracic surgery department.

Although 3D technology currently serves as an excellent auxiliary tool for VATS sublobectomy, it still has some limitations. First, the precision and comprehensiveness of models generated by 3D reconstruction hinge on the creator's expertise in interpreting CT images and their grasp of anatomy. Moreover, there is currently no structured training program specifically tailored for medical professionals in 3D technology. The thoracic surgery field urgently needs to establish quality control standards for 3D reconstruction and 3D printing and needs to stipulate to what level of refinement the reconstruction or printing can meet clinical application. According to the experience of the medical 3D printing center in our hospital, after reconstruction, the contours need to be verified through medical software certified by the medical software management department. If the reconstructed tissue is one level higher than the part involved in the surgery, the model is considered to meet the minimum requirements of the surgery. Second, the cost of 3D printing might be prohibitive for many patients. However, if one opts to 3D print only the physical navigation templates rather than the entire lung model, the cost is considerably reduced, averaging between $75-90 (9).The high cost of 3D printing technology impacts not just patients but also hospitals, encompassing expenses related to the purchase and maintenance of 3D printers, material costs for the models, and other factors that hinder its broad adoption. 3D reconstruction and printing are time-consuming processes; designing and printing a basic 3D physical navigation template can take between three to five hours (10). It takes longer to 3D print a complete model. When it comes to lung models, producing a qualified model can span 3-4 days.

In the realm of early lung cancer detection, 3D technology is anticipated to evolve towards cost and time efficiency. With ongoing advancements in 3D reconstruction and printing, challenges like high material costs and extended printing durations are expected to be addressed. Emerging artificial intelligence technologies are streamlining the adoption of 3D reconstruction techniques and enhancing the efficiency of 3DV model creation. This trend suggests a potential evolution in 3D technology towards greater intelligence and automation, which could significantly streamline the 3D reconstruction process and reduce manual input. According to the experience of our hospital, AI has better effects in the thoracic surgery field compared with other systems. This might be attributed to the inherent good contrast between pulmonary vascular tissue and the surrounding lung tissue. Thus, with the ongoing advancements in medical imaging technology and surgical techniques, we anticipate that 3D reconstruction and 3D printing-assisted VATS sublobectomy will have a promising future in the realm of early lung cancer treatment.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: http://pubmed.ncbi.nlm.nih.gov.

Author contributions

XZ: Writing – original draft. LL: Writing – review & editing. DY: Data curation, Writing – review & editing. ZH: Supervision, Writing – review & editing. XW: Supervision, Writing – review & editing. JW: Writing – review & editing. PL: Supervision, Writing – review & editing. SL: Writing – review & editing. KZ: Funding acquisition, Supervision, Writing – review & editing

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1280075/full#supplementary-material

SUPPLEMENTARY VIDEO 1

A presentation video of 3D reconstruction

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Case report: Complex left-carina resection: three-year single-center experience

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Carinal and tracheobronchial angle tumors have long been a contraindication for surgical removal; the technique of tracheal sleeve pneumonectomy makes it possible to approach this malignancy but still represents a surgical challenge. Left sleeve pneumonectomy is less common compared with right sleeve pneumonectomy and represents a minority component in the literature's case series due to the complexity of the anatomy. In addition, there is no standard for treatment strategy, and it must be assessed on a case-by-case basis. From 2020 to 2023, we performed three left tracheal sleeve pneumonectomies and one neocarina reconstruction surgery for benign lesions without lung resections. All cases were performed without cardiovascular support such as cardiopulmonary bypass and via median sternotomy. With a median length of stay of 21.5 days (between 14 days and 40 days), all patients were transferred to a physiotherapeutic rehabilitation facility for functional reactivation, where they received physiotherapeutic respiratory therapy given the slow functional recovery. The recorded 30-day mortality was 0. There is no standardized approach for left-sided sleeve pneumonectomy, and it is still a surgical challenge due to intraoperative and postoperative difficulties.

KEYWORDS

tracheal sleeve pneumonectomy, carina, carinal pneumonectomy, tracheobronchial angle, complex tracheobronchial resection

1 Introduction

For a long time, tumors arising less than 2 cm from the carina or with carinal invasion were considered inoperable and were treated with chemoradiotherapy (1), but, with the improvement of surgical techniques and advances in anesthesia, these malignant tumors can be resected by tracheal sleeve pneumonectomy (TSP). The first right pneumonectomy procedure with lateral resection of a tracheal wall was described by Abbott in 1950 (2); in 1959, Gibbon published the first TSP (3). It took until 1972 for Jensik to publish a consistent series of 17 patients who underwent this procedure, which was then updated in 1982 by the same authors in a series of 34 patients (4).

Over the years, several authors reported their personal experiences with encouraging long-term oncologic outcomes (5, 6). However, resection of tracheo-bronchial bifurcation (with or without pneumonectomy) is still considered a surgical challenge in terms of intraoperative and postoperative management, and there is no standardized approach.

2 Report

From 2020 to 2023, we performed three left tracheal sleeve pneumonectomies and one neocarina reconstruction surgery for benign lesions without lung resections (Table 1). All cases were performed without cardiovascular support such as cardiopulmonary bypass (CPB) and via median sternotomy.

The first case discussed is a 55-year-old male patient with a benign carinal tracheo-esophageal fistula. Because of the injury, the patient was fed via a jejunostomy and had an aspiration gastrostomy. The case was investigated with a CT of the chest and later with bronchoscopy to confirm the presence of a tracheoesophageal fistula. After discussion in the multidisciplinary meeting, the surgical indication was made, and, thus, the repair of the fistula with the creation of a neoacarina was indicated. In this case, the airway was approached through a median sternotomy with the intention of suturing the right main bronchus to the left in order to create the neocarina with the most anatomical reconstructions. The creation of the neobifurcation was performed as the anatomical conditions with the surrounding structures allowed; this represents a possible limitation to the possibility of performing this type of surgical reconstruction and, therefore, limits the number of cases. As taught by Grillo (7), a laryngeal release does not translate to relaxation at the carina. After the sternotomy, the pericardium was opened, and, then, a rigid retractor was placed between the superior vena cava and the aortic arch to allow visualization of the carina. The trachea was then mobilized in its distal part and the first 2 cm of the two main bronchi to preserve the greatest possible blood supply. The anterior esophageal wall was then repaired with a suture of the anterior muscular part after the anesthesiologist had placed a nasogastric tube. Once the airway was mobilized, a cold blade resection was performed at the level of the left and right main bronchus downstream of the lesion (this is not the case for a resection of a tumor lesion, and the margins were not explored intraoperatively) and at tracheal level upstream.

The neocarina was then packed by approximating the medial walls of the right and left main bronchi to each other to form a new carina with the trachea, as the mobility of the left main bronchus is restricted by its relations to the aortic arch. The two edges are then sutured together with a continuous polypropylene suture (Prolene, Ethicon, Sommerville, NJ). During this time, the lungs were alternately ventilated with apneic intermittent oxygenation. Suturing the two bronchi together tethers the newly created carina to the level of the lower edge of the aortic arch. Up to this level, the trachea was mobilized by pulling it downward to allow completion of the anastomosis, which was performed with continuous suturing using the same suture described above (Figure 1A). Once the anastomosis was completed, ventilation was restored via the extra-long monolumen orotracheal tube, and the suture leakage test was performed.

The other three cases were left tracheal sleeve pneumonectomies programmed for malignant lesions: two male patients and one female patient with a mean age of 61 years (range, 44–72). Two patients were active smokers at the time of surgery and two suffered from type 2 diabetes mellitus under oral antidiabetic therapy. All cases were discussed in a multidisciplinary team, and preoperative chest CT, PET-CT, and bronchoscopic examination were performed to identify airway wall involvement and determine the type of surgery. All patients underwent blood gas tests and respiratory function tests that were compatible with the planned surgery.

All three cases were operated on via a median sternotomy. The pericardium was then opened in a cranio-caudal L-shape, and, after opening the two pleural spaces, the left anonymous vein, the superior vena cava, and the ascending aorta were isolated (individually and then together with the right pulmonary boot). In the first case, we use a traditional retractor placed between the superior vena cava and aorta to expose the carina (Figure 1B). However, in addition to a spatial burden, this also posed an increased risk of injury to the vessel walls related to the rigidity of the instrument itself. It was then decided to use an octopus-type retractor that allows the vascular structures to be mobilized and thus expose the carina while causing less trauma to the walls of the great vessels (Figure 1C). This reduces the risk of damage to the vessels and creates a smaller space footprint being able to direct the body of the retractor where the surgeon wants it most.

We then isolate the two main bronchi and the trachea with a band. The lymphadenectomy of station 7 should be performed at this moment: dissection of the left vascular hilum, sequential isolation of the left upper vein and the main artery, and subsequent dissection with mechanical suturing. Once it is confirmed that resection and reconstruction are possible, we proceed with resection of the carina, cold blade section of the trachea and right main bronchus.

In the first case of TSP described, a monolumen tube was used for contralateral lung ventilation after airway resection, which was inserted from the surgical field directly into the right main bronchus and connected to the ventilator to continue ventilation. However, this technique requires the presence of the tube in the surgical field and thus limits the surgeon's view and available space. In our experience, we have, therefore, switched to the apneic oxygenation technique. After completion of the resection, hyperoxygenation is initiated by placing a small catheter (10F) across the surgical field into the contralateral main bronchus and connecting it to a sterile line that continuously delivers 10–15 l/min O_2 under minimal breathing pressure (0–1 mmH). This significantly reduces the size of the occupied surgical field. We continue with the end-to-end anastomosis between the trachea and the right main bronchus with a continuous polypropylene sutures (Prolene, Ethicon, Sommerville, NJ). Negative suture tightness test for air leakage is mandatory. After reconstruction, patients are ventilated with controlled pressure through the original tube (Supplementary Videos 1, 2).

TABLE 1 Patient's list.

	Gender	Age	Comorbidities	Intervention	Surgical access	Operative time (min)	Ventilation	ICU (h)	LOS (days)	Adverse event	Histology	Survival
Patient #1	Male	55	Carinal trachea-esophageal fistula, jejunostomy, and gastrostomy	Neocarina	Median sternotomy	210	Cross-field ventilation	48	14	None	Tracheo-esophageal fistula	Alive (3 years after surgery)
Patient #2	Male	44	Pulmonary mass, active smoker, and blood hypertension	Left TSP	Median sternotomy	210	Cross-field ventilation	72	22	None	NSCLC	Death 18 months after surgery (systemic recurrence)
Patient #3	Male	67	Pulmonary mass, active smoker, diabetes mellitus, previous acute myocardial infarction, and previous pancreatitis	Left TSP	Median sternotomy + posterolateral thoracotomy	360	Apneic oxygenation	72	15	None	Synovial Sarcoma	Death 18 months after surgery (systemic recurrence)
Patient #4	Female	72	Pulmonary mass, obesity, diabetes mellitus, and blood hypertension	Left TSP	Median sternotomy	180	Apneic oxygenation	960	40	Gastric paralysis and vocal cord mobility deficit (inhalation)	NSCLC	Alive (3 months from surgery)

In one case, it was recorded the presence of persistent adhesions between the left lower lobe, the site of the known tumor that completely occupies it, and the thoracic wall with doubtful infiltration of the VI coast. It was, therefore, not possible to free the posterior parenchyma, so it was decided to perform video-assisted thoracic surgery (VATS) in the right lateral decubitus shortly after closure of the sternotomy in a fashion standard; anterior thoracotomy according to the standard plan, from which the thoracoscope was inserted; partial dissection of the posterior adhesions, revealing infiltration of the wall requiring rib resection, for which a posterior thoracotomy with removal of the posterior arch of the sixth rib is performed under thoracoscopic view; and complete mobilization of the lung parenchyma and subsequent extraction en-bloc with the part of the resected coast. During the closure of the anterior surgical access, massive bleeding occurred, so it was necessary to pack the posterolateral thoracotomy, which was performed by connecting the two previous surgical accesses. It shows the origin of the haemorrhage from the suture of the superior lobar vein, which was repaired with continuous polypropylene sutures (Prolene, Ethicon, Sommerville, NJ).

All four patients described were transferred to the intensive care unit (ICU) monitoring after surgery. In the first three patients described, the average length of stay was 64 h (range, 48–72 h), during which they remained hemodynamically stable without pharmacological support. The female patient who underwent a left TSP was transferred to the ICU at the end of the operation for postoperative monitoring. Coronarography was performed 24 h after surgery due to an increase in myocardial troponins and suspected hypokinesia on control echocardiography: No coronary disease was found. Because of the progressive anemia, it was necessary to perform blood transfusions. Back on the ward, there was an episode of ab ingestis with loss of consciousness, so the patient was intubated with an orotracheal tube, sedated, and transferred back to the ICU for the necessary treatment.

Initially, the patient was mechanically ventilated via the orotracheal tube. On the fourth day after the operation, the patient was exubated and switched to high-flow oxygen therapy alternating with non-invasive ventilation cycles. In a septic state with respiratory failure, she was orotracheally intubated again 5 days after eustubation, and, 2 days later, a surgical tracheostomy was packed. Throughout the clinical course, she was frequently recruited and bronchoaspirated to detect secretions in the setting of ineffective cough and poor expectoration.

The course of all patients was characterized by a slow recovery of motor activity with gradual weaning from oxygen therapy until its complete removal. Fibrobronchoscopy tests were performed during hospitalization, which showed good suture tightness without air leakage and good tissue trophism.

With a median length of stay of 21.5 days (between 14 days and 40 days), all patients were transferred to a physiotherapeutic rehabilitation facility for functional reactivation, where they received physiotherapeutic respiratory therapy given the slow functional recovery.

The patient who was treated with a neocarina is still alive 3 years after surgery and has no comorbidities. Two patients died 17 months and 18 months after surgery with disease recurrence and systemic metastases.

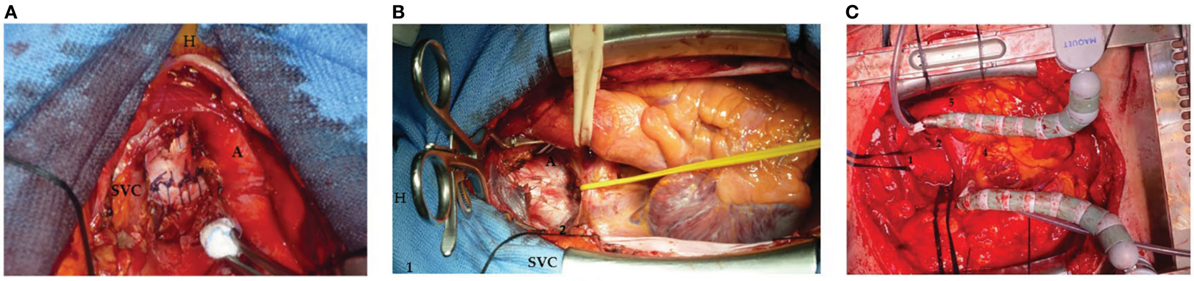

FIGURE 1
(A) Neocarina packed by approximating the medial walls of the right and left main bronchi to each other to form a new carina with the trachea with a continuous polypropylene suture (Prolene, Ethicon, Sommerville, NJ): superior vena cava (SVC), aorta (A), and patient's head (H). **(B)** A traditional retractor (1) placed between the superior vena cava (SVC) and aorta **(A)** to expose the carina (2) [patient's head (H)]. **(C)** The carina exposed trough a median sternotomy: 1, trachea; 2, left main bronchus; 3, right main bronchus; 4, heart; and 5, descendent aorta.

One patient, the most recent one, is still alive 3 months after surgery. At discharge to the rehabilitation and respiratory facility, which occurred 40 days after surgery, the patient shows a gradual and progressive recovery; apiretic, no antibiotic therapy; negative infection indices in blood tests; spontaneous breathing through tracheostomy; and good respiratory exchange on blood gas analysis.

3 Discussion

TSP is now the recommended treatment for non–small-cell lung cancer (NSCLC) invading the main bronchus, arising less than 2 cm distal to the carina (8) or involving the tracheobronchial angle with an extension of no more than three cartilage rings (9), and for other low-grade malignancies as well as benign disease involving the carina. However, due to the technical complexity, this procedure is only performed by a few highly qualified centers worldwide. Despite the high morbidity and mortality characteristic of this reconstructive technique of the tracheobronchial tree (from 11% to 53% and from 4% to 41%, respectively) (4, 6, 10, 11), recent series show good results (10–14) thanks to the improvement of the surgical technique and the intra- and post-operative management, making this surgery safe and acceptable in terms of long-term outcomes.

Among tracheal sleeve pneumonectomies, there is a notable difference between right and left pneumonectomy. The left is by far the rarest, as access to the carina trachea is restricted, leading to more technical difficulties with high postoperative complication and mortality rates (14), and, because left tumors are extending proximally, these are often already invading the subaortic space structures (15, 16).

The multidisciplinary assessment is fundamental in order to discuss the indications with the other specialists on a case-by-case basis. Pulmonary function tests, blood gas analysis, and cardiopulmonary exercise tests are mandatories for patient selection in order to exclude patients who could not tolerate a pneumonectomy. Ventilation/perfusion lung test could be performed to estimate the loss of lung function. Preoperative evaluation includes also a CT scan and PET-CT to assess the extent of the tumor above the tracheo-bronchial angle and the possible involvement of surrounding structures. If nodal involvement is suspected, then EndoBronchial Ultrasound (EBUS)/Endoscopic UltraSonography (EUS) or mediastinoscopy is mandatory: surgery is not indicated in two N2 nodal levels above 2R/L or N3 disease (17).

There are only a few clinical series in the literature that differ in the variety of surgical procedures. Intraoperative management is still controversial; the procedure can be performed in a single step or in two steps. The first approach includes left posterolateral thoracotomy, bilateral anterolateral thoracotomy, median sternotomy, clamshell (15, 17, 18), and, more recently, left VATS pneumonectomy followed by right thoracotomy (16). This technique, developed on the wave of an increasing diffusion of the minimally invasive techniques, however, has some disadvantages: it requires a position change, and there are also disadvantages relative to the ventilation during airway anastomosis, which is complicated and difficult to address in an emergency. Two-stage surgery includes a left proximal pneumonectomy, accepting a positive resection margin, followed by a carinal resection from the right side approximately 3 to 5 weeks later (19).

In our center, we have performed a median sternotomy in all cases to provide a good exposure to the carina, avoiding difficulties with the anastomosis behind the aortic arch. In one case, it was necessary to perform a left-sided VATS because of persistent adhesions between the left lower lobe and the thoracic wall with doubtful infiltration of the VI coast. This minimally invasive surgical approach may be useful in severe pleuro-parenchimal adhesions to achieve complete lymphadenectomy and complete hemostasis.

Dissection of the trachea must be limited to the anterior surface and the first 2 cm of the right bronchus, preserving the bronchial irroration as much as possible. The airways are divided and reconstructed in an end-to-end anastomosis before specimen removal (20).

After dissection of the airway, lung resection is performed; access to the hilium can be facilitated by a retractor. In the first two cases, we used a rigid retractor between the superior vena cava and the aortic arch before inserting an octopus-shaped retractor, which causes less trauma to the structures and, at the same time, leading to a less footprint of the surgical field.

Beyond the surgical challenge, we must consider the importance of adequate ventilation and oxygenation during anastomotic reconstruction. Various techniques for intraoperative airway management were presented, such as a single lumen endobronchial tube, cross-field ventilation, high-frequency jet ventilation (HFJV), intermittent apneic ventilation, and extracorporeal membrane oxygenation (21, 22).

A tight collaboration between surgeon and anesthesiologist is fundamental for an optimal airway management. For the first two cases, after the resection of the left lung, the contralateral lung was ventilated through a cross-field ventilation. This technique is associated with impediment in the operative field, a repetitive withdrawal of the endotracheal tube, which leads to a prolonged surgical time and to a risk of injury of the bronchus, as well as lung barotrauma (23). For the second two cases, we decided to change the ventilation mode to the apneic oxygenation technique: before performing the dissection, the patient is hyperventilated and hyperoxigenated with 100% (O_2) for 10 min in order to obtain an arterial PO_2 (partial pressure of oxygen) and pCO_2 (partial pressure of carbon dioxide) levels of 450 or greater and, respectively, 28 mmHg to 35 mmHg. The patient is than in complete apnea, and the airway is then resected. Hyperoxygenation is than obtained throw a small catheter (10F) across the surgical field, connected to a sterile line ensuring O_2 of 10 L/min to 15 L/min, constantly, associated to a minimal breathing pressure (0–1 mmHg), reducing the footprint of the operative field. Once the anastomosis is complete, the ventilation is assured by the original orotracheal tube (20). The use of a cardiovascular support, like the CPB, has not been used in our technique to minimize the blooding risk due to the circuit heparinization. The challenge in this kind of resections is to ensure both sufficient surgical exposure and adequate ventilation control. Cross-field ventilation with sterile tube can be replaced or partially combined with HFJV or high-flow oxygen insufflation via small-diameter catheters as described. The use of CPB in this type of surgery is considered more of a rescue tool in emergency situations due to the increased risk of bleeding (24). Extracorporeal membrane oxygenation may be indicated if the patient's condition does not allow safe single-lung ventilation. In this case, it can be effective and allow prolonged apnea avoiding prolonged cross-field ventilation (25).

4 Conclusion

Left sleeve pneumonectomy has no standardized approach and, with both intra- and postoperative difficulties, still represents a surgical challenge. With a careful selection of the patients through a collegial discussion and with cooperation between surgical and anesthesiological management, this technique represents a safe procedure with acceptable mortality and morbidity.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

This article does not contain any study with human participants or animals performed by any of the authors. Our institutional review board granted approval and waived the requirement for specific informed consent for this case report. Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

ST: Conceptualization, Data curation, Supervision, Writing – review & editing, Investigation. DV: Supervision, Writing – review & editing, Validation, Visualization. OS: Supervision, Writing – review & editing, Data curation, Investigation. MT: Data curation, Writing – original draft. LV: Supervision, Validation, Writing – review & editing. AG: Supervision, Validation, Writing – review & editing, Conceptualization, Data curation, Writing – original draft.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1367311/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Patient #3: Left tracheal sleeve pneumonectomy performed via median sternotomy.

SUPPLEMENTARY VIDEO 2
Pre-operative fibrobronchoscopy of Patient #4 reveals a lesion occupying the left main bronchus, completely blocking the left bronchial tree. Post-operative control was performed 30 days following a left tracheal sleeve lobectomy.

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Uniportal video-assisted thoracoscopic segmentectomy for fetal adenocarcinoma lung cancer with severe pulmonary emphysema: a case report

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Background: Fetal adenocarcinoma is a very rare subtype of lung adenocarcinoma. Its incidence ranges from 0.1 to 0.87% among all primary lung neoplasms. Low-grade types tend to appear in the younger generation, and the age ranges from 20 to 50 years with a mean age of around 35 years. Surgical resection is currently the best way to treat fetal adenocarcinoma lung cancer without distant metastasis.

Case report: This is a 56-year-old female who underwent low-dose computer tomography (LDCT) screening during the health examination. She used to be a heavy smoker for more than 30 years, and the CT images revealed severe bronchiectasis and emphysema. There is a solitary nodule with a diameter of 18.9 x 17.8mm in the central area of the left upper lobe. We decided to conduct left upper lobe S1~S3 segmentectomy under uniportal VATS. The surgery was successful, and the patient was discharged within one week and recovered well. The final diagnosis was fetal adenocarcinoma, low-grade (pT1cN0Mx, stage IA3).

Conclusion: The first case reported as fetal adenocarcinoma lung cancer who underwent uniportal video-assisted thoracoscopic segmentectomy. We believe it is a safe and feasible procedure for low-grade types fetal adenocarcinoma patient with poor pulmonary function.

KEYWORDS
fetal adenocarcinoma, lung adenocarcinoma, uniportal video-assisted thoracoscopic, pulmonary emphysema, case report

1 Introduction

Fetal adenocarcinoma is a very rare subtype of lung adenocarcinoma. Among all primary lung neoplasms, its incidence ranges from 0.1 (1) to 0.87% (2, 3). It is referred to as fetal adenocarcinoma because its tissue architecture and cell characteristics resemble fetal lung in 5–17 weeks of gestation (pseudoglandular stage). It was first considered the same disease as pulmonary blastoma (PB) in 1982 (4). However, since it lacks the mesenchymal components and has a completely different prognosis from PB, fetal adenocarcinoma was later on categorized as a variant of lung adenocarcinoma by the World Health Organization (5).

Microscopically, fetal adenocarcinoma consists of a complex glandular structure with glycogen-rich, non-ciliated cell linings. The cells have clear cytoplasm and characteristics of supranuclear or subnuclear vacuoles. Squamoid morules and fibroblastic stroma can be seen in the background (6). According to its histological patterns, it can be further divided into two groups: low-grade and high-grade types. Low-grade types show low nuclear atypia with frequent squamoid morules, which have pure patterns. In contrast, high-grade types exhibit prominent nuclear atypia, literally with few squamoid morules (3). Furthermore, other subtypes of lung adenocarcinoma usually present at the same time (7). Immunohistochemically, both low-grade and high-grade types show thyroid transcription factor 1 (TTF-1) positivity. On the other hand, beta-catenin is also related to fetal adenocarcinoma. In fact, studies demonstrated that morules and morule-like carcinomas in different organs were related to beta-catenin gene mutation (8). In low-grade types, tumor cells express abnormal nuclear and cytoplasmic staining of beta-catenin. As for high-grade types, these are not the cases. Another gene that can differentiate the two subtypes is *p53*, which is frequently mutated in high-grade types and usually absent in low-grade types (3).

Like other types of lung adenocarcinomas, fetal adenocarcinoma has those unspecific symptoms, such as cough, chest pain, pleural effusion, and so on. However, with the improvement of medical imaging tools, most cases are detected in the early stage and are diagnosed by histopathological findings. These clinical symptoms are, therefore, less important now; nevertheless, the clinical patterns of low-grade and high-grade types are different according to previous studies. Low-grade types tend to occur in young people aged 20–50 years, with a mean age of approximately 35 years (3, 9, 10). In contrast, high-grade types occur in older adult patients aged 50–75 years, with a mean age of approximately 65 years. Smoking history is highly related to high-grade type, with more than 90% of patients having smoking history (3, 7, 11–13). In low-grade types, lymphadenopathy, metastasis, and tumor recurrence are related to survival, but rarely occur. Surprisingly, tumor size is not related to prognosis. Moreover, the 5-year survival rate is >80% (17/21) (14). As for high-grade types, the prognoses are worse than the former because the disease usually presents symptoms in the later stage (3).

2 Case report

A 56-year-old woman was found to have bilateral lung nodules on low-dose computer tomography (CT) during a routine medical examination and was referred to our hospital. She denied any discomfort, such as cough, sputum, chest pain, or body weight loss. The patient has no underlying disease and has a family history of liver cancer (father). Most importantly, she used to be a heavy smoker for 30 years. On chest radiograph, an abnormal shadow was noticed in the left upper lobe. CT images revealed a solitary nodule with a diameter of 18.9 × 17.8 mm in the left upper lobe (Figure 1). Besides, severe bronchiectasis was found on CT as well. Therefore, she was admitted to National Taiwan University Cancer Center and underwent pulmonary function test and cardiac sonography. The results showed forced expiratory volume in the first second of 2.41 L, which is 115.2% as predicted, and good left ventricle contractility with left ventricle ejection fraction of 69.6%.

A left upper lobe S1-S3 segmentectomy and groups 5, 6, and 11 lymph node dissection were performed under uniportal video-assisted thoracoscopic (VATS) surgery. The intraoperative frozen biopsy showed adenocarcinoma with inflammatory cell-rich background. Grossly, the tumor was yellowish, well-defined, soft-to-elastic in texture tumor, and 21 × 15 × 14 mm in size (Figure 2). The pathological findings showed a complex glandular structure with frequent squamoid morules. The tumor cells have basally oriented nuclei and vacuolated cytoplasm. In addition, small foci of fibroblastic stroma are identified focally (Figure 3). Immunohistochemical stains showed TTF-1 positivity, CK (AE1/AE3) positivity, CDX-2 negativity, PAX8 negativity, and nuclear stain on beta-catenin. The low-grade fetal adenocarcinoma of lung origin was favored. Next-generation sequencing revealed no G719X and Exon 19 deletions, S768I, T790M, and Exon 20 insertions, and L858R and L861Q EGFR mutation.

No lymph node metastasis was detected. Moreover, both the postoperative follow-up of brain magnetic resonance imaging with/without contrast and whole-body fluorodeoxyglucose-positron

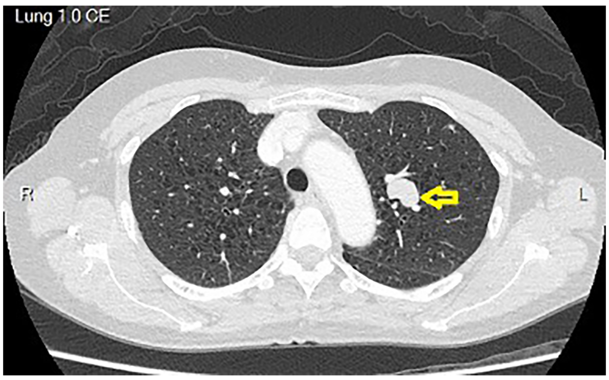

FIGURE 1
CT images revealed a solitary nodule with a diameter of 18.9 × 17.8 mm in the left upper lobe. The tumor is located in the hilum area. Besides, the CT images showed severe emphysematous change over bilateral lung parenchyma. CT, computed tomography.

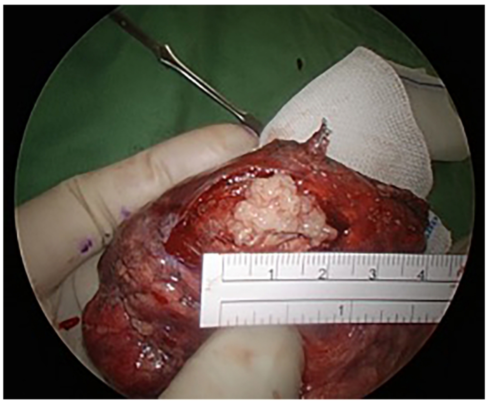

FIGURE 2
Grossly, the tumor was yellowish, well-defined, soft-to-elastic in texture tumor, and 21 × 15 × 14 mm in size.

emission tomography showed no distant metastasis. The final diagnosis was low-grade fetal adenocarcinoma (pT1cN0Mx, stage IA3).

3 Discussion

This is the first case of a patient with fetal adenocarcinoma lung cancer who underwent uniportal video-assisted thoracoscopic segmentectomy. In our hospital, we perform over 1500 lung tumor surgeries annually. Even with such a high volume, cases of fetal adenocarcinoma are still rare. In this case, the patient had no symptoms, and the lesion was found was found during routine imaging investigation.

According to studies, lobectomy remains the standard of care for tumors 2–3 cm in size (15, 16). However, because the tumor was closer to the upper tri-segment area of the lung, and it was harder it is to remove the tumor under wedge resection. Both characteristics of tumor size and location point to lobectomy. A tri-segment approach was adopted because patient could not afford lobectomy, because there is no evidence in the data provided of severe emphysema or other severe comorbidities that would prohibit major lung resection. According to Chan et al., the recurrence-free or overall survival at 5 years between segmentectomy and lobectomy for patients without nodal disease (AJCC 8th Edition Stage 1A NSCLC) showed no significant differences (17). Therefore, we decided to perform segmentectomy under uniportal VATS. Our surgical team believes uniport approach can provide enhanced outcomes (18). Some advantages meet our needs according to the patient status.

The prognosis of low-grade types is very good, especially those stage I cases, which can even be up to 90%. According to Sato et al., 22 cases were stage I disease among all resected 25 low-grade types cases. Among these stage I cases, three patients showed recurrence, and one died. However, all three patients with recurrence had tumor size >3 cm. As for tumors <3 cm, no recurrence or death was reported (1). Surgery is the standard treatment for low-grade type fetal adenocarcinoma. Some studies reported that chemotherapy did not result in long-term survival, but still prolonged survival (14). Another study demonstrated partial response of neoadjuvant

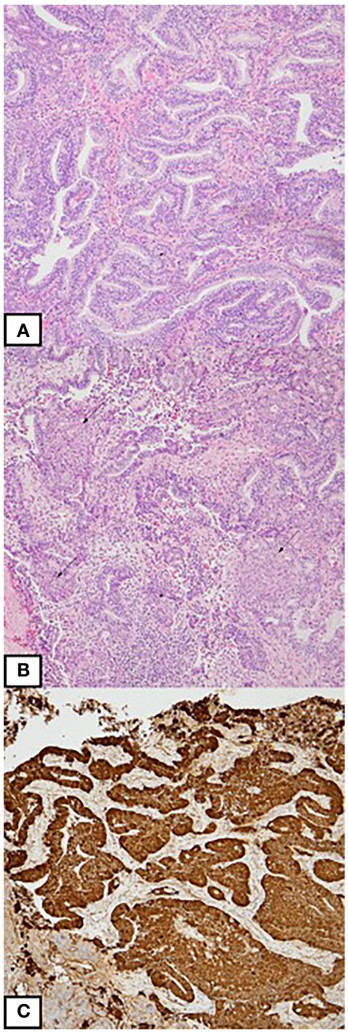

FIGURE 3
(A) An adenocarcinoma with complex glandular architecture. The tumor cells are columnar-shaped with vacuolated cytoplasm. **(B)** Morules formation is present (arrow). **(C)** Immunohistochemically, the tumor cells reveal aberrant nuclear expression of beta-catenin.

chemotherapy in low-grade type fetal adenocarcinoma. However, the effects of chemotherapy still need further evaluation. In summary, surgical treatment and regular follow-up are safe and feasible for such patients (pT1cN0Mx, stage IA3).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by National Taiwan University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

Y-SW: Data curation, Writing – original draft, Writing – review & editing. Y-TC: Data curation, Writing – review & editing. J-HC: Data curation, Writing – review & editing. H-CL: Conceptualization, Data curation, Formal analysis, Writing – review & editing.

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Conflict of interest

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