Original Article

Robotic and video-assisted lobectomy/segmentectomy for non-small cell lung cancer have similar perioperative outcomes: a systematic review and meta-analysis

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Background: At present, the clinical conclusion that robotic-assisted thoracic surgery (RATS) and video-assisted thoracic surgery (VATS), which is better for patients with non-small cell lung cancer (NSCLC) is not clear. Therefore, this meta-analysis aimed to compare the perioperative outcomes between RATS and VATS for NSCLC.

Methods: The Population, Interventions, Comparators, Outcomes, and Study design (PICOS) framework was employed to develop the search strategy, and the findings was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We searched EMbase, The Cochrane Library, PubMed, Web of Science, CNKI, and Wan Fang Data to collect clinical studies about RATS *vs.* VATS for patients with NSCLC from inception to October 2019. The following outcomes were measured: rate of conversion to thoracotomy, postoperative complications, postoperative hospital mortality, lymph node dissection, hospitalization time, operating time, and postoperative drainage days. Estimation of potential publication bias was conducted by Begg's test and Egger's test. The Standardized Mean Difference (SMD) and Odds Ratio (OR) with 95% confidence intervals (CI) were pooled using Stata 15.0 software.

Results: A total of 18 studies involving 60,349 patients were included. Among them, 8,726 cases were in the RATS group, and 51,623 were in the VATS group. The results of meta-analysis showed that the operation time of RATS group was longer than that of VATS group (SMD=0.532, 95% CI: 0.391–0.674, P=0.000). And the further meta-analysis suggested that the incidence of postoperative complications was lower in patients who underwent RATS after 2015 (OR=0.848, 95% CI: 0.748–0.962, P=0.010). Meanwhile, there was no significant difference between both groups in postoperative hospitalization time (SMD=0.003, 95% CI: −0.104–0.110, P=0.957). In addition, more lymph nodes were retrieved in RATS group than VATS (SMD=0.308, 95% CI: 0.131–0.486, P=0.001). However, the conversion rate, retrieved lymph node station, days to tube removal and in-hospital mortality rate have no significant differences between both groups.

Discussion: The current meta-analysis indicates that the perioperative outcomes of RATS and VATS for NSCLC are equivalence. Due to the limited quantity and quality of included studies, the above conclusions still need to be verified by more high-quality studies.

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Introduction

Lobectomy plus lymph node dissection is the standard method for radical treatment of early lung cancer (1). In recent years, due to the widespread use of low-dose computed tomography (CT), the number of early patients detected each year has greatly increased. These patients can be cured by lobectomy or segmentectomy. Since the 1990s, a variety of minimally invasive surgical methods have been used in the surgical treatment of lung cancer (2).

Kneuertz *et al.* reported that compared with traditional thoracotomy, video-assisted thoracoscopic surgery (VATS) can significantly reduce the incidence of postoperative pain, shorten hospitalization time and the duration of thoracic drainage (3). In addition, through faster recovery after surgery, it may contribute to the development of early adjuvant chemotherapy. Although VATS technology has been widely developed as a mature minimally invasive surgical technique, it still has some shortcomings, such as the lack of instrument flexibility, two-dimensional view interface, and loss of eye-hand-target axis, which make VATS lobectomy cumbersome. Therefore, thoracoscopic surgery can only be performed by senior deputy chief physicians and above.

In order to overcome these limitations, robotic-assisted technology came into being. In 2002, robotic-assisted thoracic surgery (RATS) was first applied to patients in the operating room (4). And compared with traditional thoracotomy, robotic-assisted technology has the characteristics of less postoperative pain, quick recovery and high survival rate in esophageal cancer (5).

Recently, many surgical centers have published clinical research articles on the application of robot-assisted technology in lung surgery. Many studies published in recent years have confirmed the feasibility and safety of RATS, which is of great significance for strengthening the status of RATS in the surgical treatment of non-small cell lung cancer (6). However, these studies are mostly single-center studies, with small sample sizes and different complications evaluation systems, making it difficult to obtain objective results. In clinical applications, the indications of RATS and VATS overlap each other, and the equivalence between robotic-assisted technology and video-assisted thoracoscopic technology and the advantages and disadvantages of both in tumor treatment are still inconclusive. Therefore, we conducted a meta-analysis to compare the perioperative safety and postoperative efficacy of the two in radical resection of lung cancer. We present the following article in accordance with the PRISMA Reporting Checklist (available at https://dx.doi.org/10.21037/tcr-21-646).

Methods

Search strategy

The study selection, data extraction, and reporting of results were all based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The established Population, Interventions, Comparators, Outcomes, and Study design (PICOS) framework was employed to develop an appropriate search strategy. All published studies on robot-assisted lobectomy or video-assisted lobectomy and video-assisted thoracoscopic lobectomy for NSCLC were searched in PubMed, Web of Science, China knowledge Network and Wan fang database. We further reviewed the reference lists of all of the included studies to identify the additional relevant literature. The following search terms were used: Leonardo Da Vinci surgical system, robot, robotic, video-assisted thoracic surgery, thoracoscope, minimally invasive therapy, and lung cancer. Previously published systematic reviews and meta-analyses were examined to determine that all relevant studies were included.

Inclusion and exclusion criteria

Inclusion criteria: (I) the study population were non-small cell lung cancer patients; (II) the intervention measures were Leonardo Da Vinci robot operation in RATS group and video-assisted thoracoscopic surgery in VATS group; (III) effective outcome information could be obtained from

the literature.

Exclusion criteria: (I) review articles, conference abstracts, case reports, editorials, expert opinions, comment and letters; (II) repeatedly published studies; (III) lack of data required for this study; (IV) research results other than Chinese and English.

Data extraction and quality evaluation

Data were extracted from the eligible studies and entered into a Microsoft Excel database. In order to compare the two surgical techniques, we collected the following information: (I) intraoperative variable: operation time, the rate of conversion to thoracotomy during operation, the number of lymph nodes were removed. (II) postoperative variable: postoperative hospital mortality, the incidence of postoperative complications, the length of hospital stays and the days of postoperative drainage. This process was independently completed by Mao Junjie (graduate student of the fourth Hospital of Hebei Medical University) and Tang Zilong (graduate student of the fourth Hospital of Hebei Medical University) in the form of double-blind. The differences were resolved through mutual discussion or with the cooperation of Wang Lei (chief physician of the fourth Hospital of Hebei Medical University). All included studies were assessed using the Newcastle-Ottawa Scale (NOS, for nonrandomized studies). The NOS analyzes three items: selection, comparability, and exposure, to evaluate study quality. The maximum possible score is 4 for selection, 2 for comparability, and 3 for exposure. A total score of 8 or 9 indicates high quality, and a score of 6 or 7 indicates medium quality.

Statistical analysis

The in-hospital mortality, the incidence of postoperative complications and the rate of conversion to thoracotomy in the robot-assisted group and video-assisted were calculated by odds ratio (OR) as a statistical index. The standardized mean difference (SMD) was used as the statistical index for the operation time, hospital stay, postoperative drainage days and the number of lymph node dissection in the two groups. We used Cochran Chi-square test and I^2 test to estimate the heterogeneity between the two groups. Statistical heterogeneity is defined in the study as the statistical value of the I^2 test is greater than 50% or P<0.05. If the test of heterogeneity was high (I^2>50% or P<0.05), a random-effect model was adopted. Otherwise, we used a fix effect model. Subgroup and sensitivity analyses were used to explore the potential sources of heterogeneity. If the study reported the median and range, then the average and standard deviation (SD) were calculated (7). In the inclusion study, only the data of median and maximum and minimum were mentioned, and then combined analysis was carried out after transformation according to the formula (7). The Begg's test and the Egger test were conducted to evaluate publication bias. After excluding the study with the lowest quality evaluation score, the sensitivity analysis was carried out. The statistical significance was bilateral (P<0.05). Stata 15.0 software was used for all statistical analyses.

Results

Literature screening process and results

A total of 458 related studies were obtained from the original search, and a total of 18 studies were included in the study (*Figure 1*). The literature screening process is shown in *Figure 1*. The basic characteristics and quality evaluation results of all included studies are recorded in detail (*Table 1*).

Results

Rate of conversion to thoracotomy during operation

A total of 9 studies were included (8-10,12-14,16,21,23). The results showed that the heterogeneity I^2 was 85.2% and the P=0.000, so the random effect model was used for Meta-analysis. The results showed that there was no significant difference in the rate of conversion to thoracotomy between RATS group and VATS group (OR=1.42, 95% CI: 0.70–2.88, P=0.336) (*Figure 2A*).

Postoperative complications

A total of 14 studies were included (8-14,16-18,20-22,24). The results showed that the moderate heterogeneity I^2=61.5% and P=0.001, so the random effect model was used for Meta-analysis. The results showed that there was no significant difference in the incidence of postoperative complications between RATS group and VATS group (OR=0.947, 95% CI: 0.79–1.14, P=0.564) (*Figure 2B*). However, according to the subgroup analysis according to the time of publication of the study, it was found that the literature published after 2015 showed that the incidence of postoperative complications in the RATS group was lower

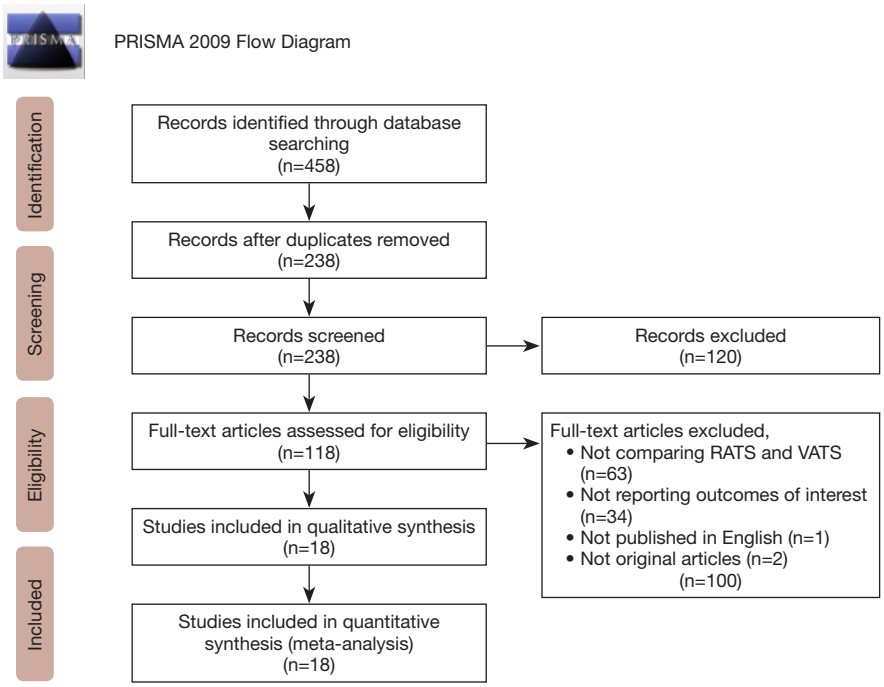
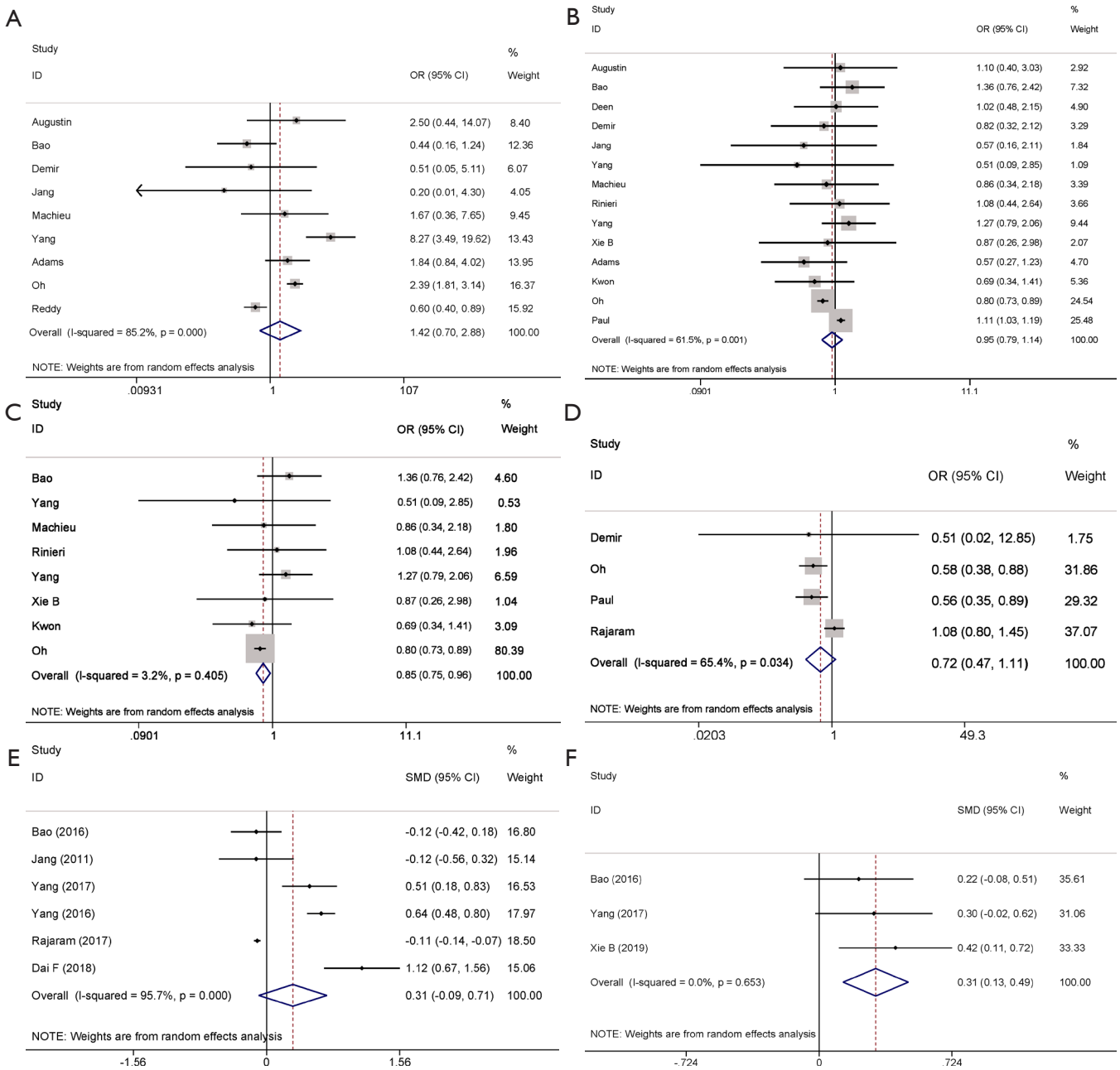


Figure 1 Flow chart showing literature search and study selection.

Table 1 Characteristics of the included studies in the meta-analysis

Inclusion study	Study type	Nation	RATS Group (M/F)	VATS Group (M/F)	Outcome indicators	NOS score
Adams, 2014, (8)	Retrospective	America	58/162	2,053/2,559	①②③⑤⑥⑦	8
Augustin, 2013, (9)	Retrospective	England	14/12	15/11	①②③⑤⑥⑦	7
Bao, 2016, (10)	Retrospective	China	26/45	49/64	①②③④⑤⑥⑦	8
Deen, 2014, (11)	Retrospective	Sweden	19/38	21/37	②⑤⑥	6
Demir, 2015, (12)	Retrospective	Turkey	26/13	39/21	①②③⑤⑥⑦	9
Jang, 2011, (13)	Retrospective	America	23/17	21/19	①②④⑤⑥⑦	8
Mahieu, 2016, (14)	Retrospective	France	19/9	22/6	①②③⑤⑥⑦	7
Mungo, 2016, (15)	Retrospective	America	40/40	40/40	①②⑤	9
Oh, 2017, (16)	Retrospective	America	1,397/1,597	4,218/5,142	①②③⑤⑥	8
Kwon, 2017, (17)	Retrospective	America	28/46	106/121	①⑤⑥⑦	8
Paul, 2014, (18)	Retrospective	America	1,207/1,290	16,219/21,348	②③⑤	6
Rajaram, 2017, (19)	Retrospective	America	1,662/2,027	5,771/7,219	③④⑤	7
Rinieri, 2016, (20)	Retrospective	France	12/5	17/17	①②⑤⑥	7
Yang, 2016, (21)	Retrospective	China	80/104	263/498	①②④	8
Yang, 2017, (22)	Retrospective	China	29/47	27/50	①②③④⑤⑥⑦	8
Reddy, 2018, (23)	Retrospective	America	567/640	1,054/1,287	⑤⑥	8
Xie, 2019, (24)	Retrospective	China	38/43	36/49	②④⑤⑥⑦	9
Dai, 2018, (25)	Retrospective	China	24/21	24/21	⑤⑥	8

①: intraoperative conversion to thoracotomy; ②: postoperative complication rate; ③: postoperative hospital mortality; ④: removal of lymph nodes; ⑤: hospitalization time; ⑥: operation time; ⑦: postoperative drainage days. RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracic surgery; NOS, Newcastle-Ottawa Scale.



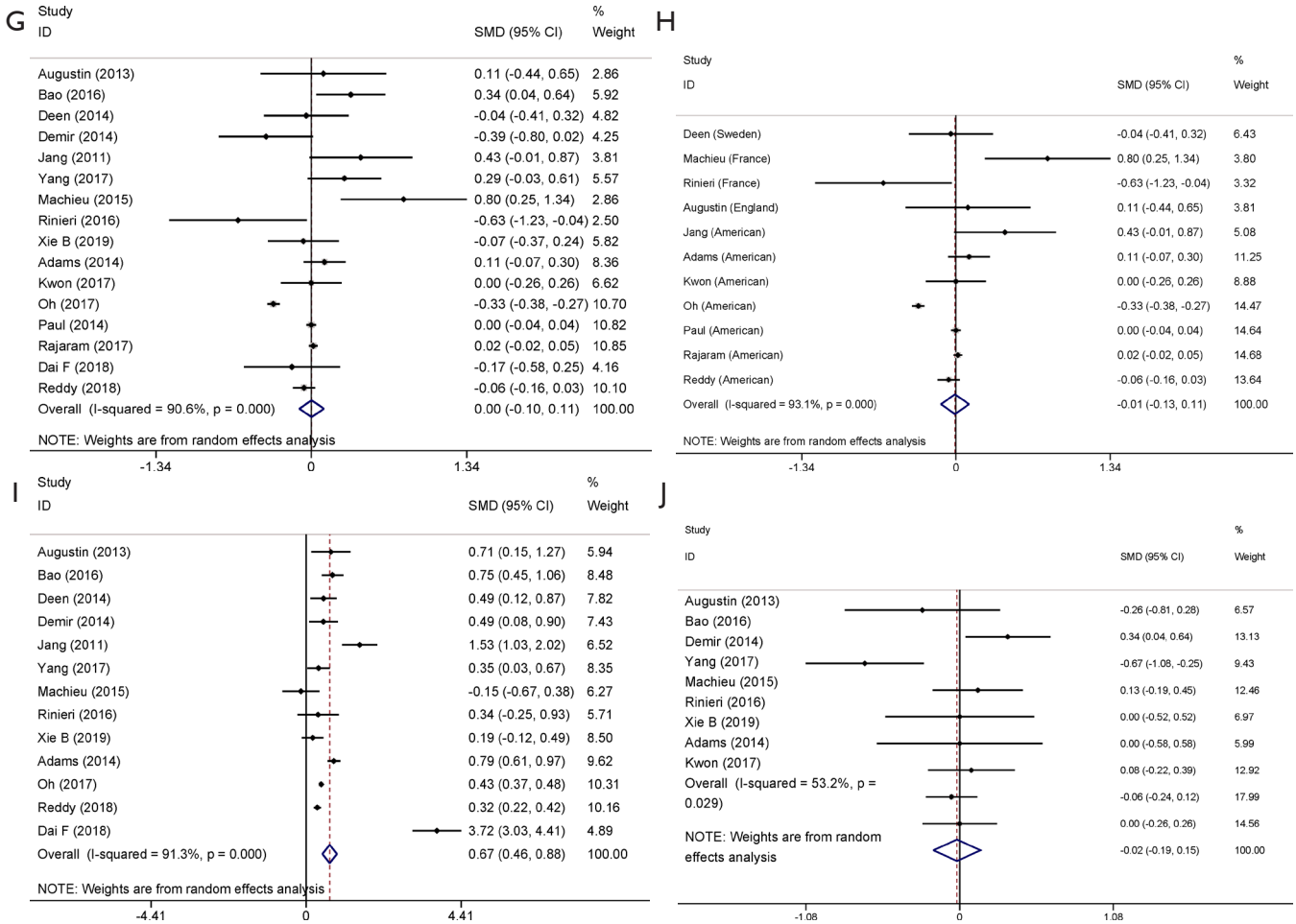


Figure 2 Comparison between the RATS group and the VATS group. (A) Conversion to thoracotomy during operation; (B) incidence of postoperative complications; (C) incidence of postoperative complications after 2015; (D) postoperative hospital mortality; (E) the number of lymph nodes groups dissection; (F) the number of lymph node dissection; (G) postoperative hospitalization time; (H) postoperative hospitalization time between developed and developing countries; (I) operation time; (J) postoperative drainage days. OR, odds ratio; SMD, standardized mean difference; CI, confidence interval.

than that in the VATS group (OR=0.85, 95% CI: 0.75–0.96, P=0.010) (*Figure 2C*).

Postoperative hospital mortality

A total of 8 studies were included (8,9,12,14,16,18,19,22). The postoperative hospital mortality in RATS group and VATS group in 4 studies was 0. The other four results showed that the moderate heterogeneity I^2=65.4% and the P=0.034, so the random effect model was used for Meta-analysis. The results showed that there was no significant difference in postoperative hospital mortality between RATS group and VATS group (OR=0.72, 95% CI: 0.47–1.11, P=0.139) (*Figure 2D*).

Lymph node dissection

Lymph node dissection includes the number of lymph node groups and the number of lymph nodes dissected. A total of 6 studies were included. Three of these studies evaluated the number of lymph nodes dissected (10,22,24), and 6 studies provided relevant data for evaluating the number of lymph node groups dissected (10,13,19,21,22,25). The results of random effect model Meta-analysis of the data related to the number of lymph nodes groups dissection showed that there was no significant difference between the two groups.

(SMD=0.31, 95% CI: −0.09–0.71, P=0.13) (*Figure 2E*). Meta-analysis of random effect model about the number of lymph node dissection showed that RATS was superior, (SMD=0.31,95% CI: 0.13–0.49, P=0.001) (*Figure 2F*).

Hospitalization time

A total of 16 studies were included (8-14,16-24). The results showed that the moderate heterogeneity I^2=90.6%, P=0.000, so the random effect model was used for Meta-analysis. The results showed that there was no significant difference in postoperative hospital stay between RATS group and VATS group (SMD=0.003, 95% CI: −0.10–0.11), P=0.957) (*Figure 2G*). Subgroup analysis was conducted according to the area of inclusion of patients, and it found that there was no significant difference between the RATS group and the VATS group in both developed and developing countries (SMD=−0.32, 95% CI: −0.37–−0.27, *P*=0.048) (*Figure 2H*).

Operation time

A total of 13 studies were included (8-14,16,20,22-25). The results showed that the moderate heterogeneity I^2=91.3%, P=0.109, so the random effect model was used for Meta-analysis. The results showed that the operation time of RATS group was longer than that of VATS group (SMD=0.671, 95% CI: 0.462–0.880, P=0.00) (*Figure 2I*). However, in the subgroup analysis according to the time of publication of the literature, it was found that there was no significant difference in the time of the two groups in the last 5 years.

Postoperative drainage days

A total of 9 studies were included (8-10,12,14,17,20,22,24). The results showed moderate heterogeneity, so the random effect model was used for Meta-analysis. The results showed that there was no significant difference in postoperative drainage days between RATS group and VATS group (SMD=−0.02, 95% CI: −0.19–0.15, P=0.817). After subgroup analysis, the results did not change (*Figure 2J*).

Publication bias and sensitivity analysis

The publication bias in this study was evaluated, the continuity variables were tested by Egger's test, and the binary variables were tested by Begg's test. The results showed that there was no publication bias. And the Begg's test indicated that the publication bias was not significant in the selected studies of operation time (P=0.23).

Sensitivity analysis showed that the analysis results did not affect the final results after the deletion of a single article.

Discussion

In recent years, due to the wide application of low-dose spiral CT in lung cancer screening, the detection of early lung cancer has become easier (26). Surgery is still the first choice for early lung cancer. As the gold standard surgical approach for early radical resection of lung cancer, VATS surgery has higher safety and effectiveness than traditional thoracotomy (27). Compared with thoracotomy, the hospitalization time of patients undergoing VATS surgery was significantly shorter, and the postoperative hospital mortality and the incidence of postoperative complications were also significantly lower. However, it also has some disadvantages: lack of three-dimensional vision, long learning curve, high rate of conversion to thoracotomy during operation and so on. RATS is a new method for resection of lung cancer, and Leonardo Da Vinci surgical support system (DVSS), is now increasingly used in lung surgery (28). In 2006, it was first reported that Leonardo Da Vinci robotic surgery system was introduced and successfully applied to cardiac surgery (29). In recent years, with the introduction of more and more Da Vinci robotic surgery systems, RATS technology has been widely used in the surgical treatment of lung cancer. Leonardo Da Vinci robotic surgery system has many advantages that video-assisted thoracoscopic surgery systems lack, and some studies have proved the safety and effectiveness of RATS technology in thymus surgery and esophageal cancer surgery (5,30).

This study systematically reviewed and compared the perioperative outcomes of RATS surgery and VATS surgery in the surgical treatment of lung cancer. As mentioned above, although the included studies are not randomized controlled trials, the included studies are of medium or high quality. We included a total of 18 studies involving 60,389 patients, reflecting the latest surgical results. In addition, we paid more attention to the perioperative and postoperative indicators of RATS and VATS surgery.

In this study, RATS surgery showed a better number of lymph node dissection than VATS surgery. Lymphadenectomy plays an important role in the surgical treatment of lung cancer. Good lymphadenectomy is very

important for accurate clinical staging of non-small cell lung cancer and guiding follow-up treatment (31). However, there was no significant difference in the number of lymph nodes groups removed between the two groups. Krantz and other research tables show that the prognosis was better for patients with more than 10 lymph nodes removed than for those with less than 10, when segmental resection was used to treat non-small cell lung cancer (32). W. L reported that more lymph node dissections have better long-term survival for resected non-small cell lung cancer patients (33). The results suggest that the total number of lymph node samples affects the overall survival rate and cancer-related survival rate, but this result is related to tumor stage. Therefore, the removal of more lymph nodes may have a positive impact on the prognosis. The advantages of Leonardo Da Vinci robotic surgery system mainly lie in the accurate positioning and magnification of the three-dimensional view of the operating area, precision multi-degree-of-freedom surgical instruments, computer-aided technology to reduce hand-related tremors, and so on. These advantages make it easier to remove lymph nodes close to the surface of the arteries and veins than in the past compared with VATS. At the same time, RATS minimizes the collateral damage to unrelated organs during operation, and reduces the damage to other organs caused by operation (14).

In the progressive analysis, it can be found that the time of RATS was longer than that of VATS. One is that the surgeon is unfamiliar with robotic surgery, and the other is that the process of robotic surgery is more complicated. But the results were highly heterogeneous. We believe that the reason for this is that, on the one hand, the number of cases selected between studies is different, and some of the studies are preliminary studies, which are easily affected by the learning curve. The study shows that robot-assisted Segmentectomy is safe and effective in the early learning process. After the initial 10 cases of surgery, the learning curve can go from the learning stage to the standard stage (34). On the other hand, because of the different surgical methods, we did not classify wedge resection, anatomical lobectomy and lobectomy.

In previous studies, RATS was considered that the incidence of postoperative complications was higher and the hospitalization time was longer than that of VATS (2,35). However, in recent years of research, compared with VATS, RATS showed some advantages in the incidence of postoperative complications. On the one hand, it is related to the mature operation skills of surgeons, and on the other hand, it may be due to the introduction of Leonardo da Vinci operation system is a large-scale surgery center. Large surgical centers have great advantages in postoperative nursing and preoperative evaluation.

In addition, we found that there were no statistical differences in the surgical drainage time of the patients, Hospitalization time and the rate of conversion to thoracotomy, but the heterogeneity was great, and the reasons for the heterogeneity may include the surgeon's intraoperative operation habits (such as the use of flushing fluid) and the experience of postoperative management. The patients come from China, Germany, Turkey, the United States, France and so on. The great differences in postoperative rehabilitation conditions and physical fitness of patients in different countries are also important reasons.

At present, most clinical studies on robotic surgery for non-small cell lung cancer only focus on short-term prognosis rather than long-term results. There is still a lack of long-term survival data comparing RATS surgery with VATS surgery. Therefore, we are unable to evaluate the long-term prognosis, such as recurrence rate, metastasis rate and overall survival rate. In a retrospective study of 945 patients with stage I lung cancer, there was no significant difference in the 2-year survival rate between RATS and VATS patients (21). In another retrospective study that reported 5-year survival data for patients with stage I lung cancer, there was no statistically significant difference in OS between the RATS group and the VATS group. However, there was a statistical difference in disease-free survival (DFS) (72.7% *vs.* 65.5%) between the two groups. In the following multivariate analysis, it was concluded that the mode of operation was not the cause of the difference (22). Therefore, they believe that the long-term survival rates of RATS surgery or VATS surgery in the treatment of stage I non-small cell lung cancer are similar. We need more studies to evaluate the long-term prognosis of patients with non-small cell lung cancer treated with two surgical procedures. At the same time, there was no significant difference in hospital mortality between the two groups, and the incidence of postoperative complications of RATS was even lower in recent 6 years. A randomized trial comparing video-assisted thoracoscopic surgery with robotic surgery for lung cancer (NCT02804893) is ongoing to evaluate adverse events (intraoperative and postoperative complications), operation time, number of lymph nodes removed, length of stay, pain, quality of life, immune response, and respiratory function. These findings will provide more evidence for the application of robotic surgery in the early stage of lung cancer.

However, this study still has several limitations, the most

important of which is its retrospective nature. Data included in the present meta-analysis were extrapolated from retrospective cohort studies, and bias might also exist due to the retrospective nature of the study. Second, although the hospitalization time and rate of conversion to thoracotomy were not significantly different, other outcomes were highly heterogeneous. Factors leading to high heterogeneity may include the level of experience of surgeons, the robot group with a shorter learning curve, and two groups with different baseline characteristics. Third, most of the included studies have a short follow-up period. As a result, we are unable to assess survival data, such as recurrence, metastasis and overall survival. Finally, we rely on published literature research data because we cannot obtain unpublished data.

The main technical defect of Leonardo Da Vinci robot is the lack of tactile feedback: the operator is unable to touch the texture, gap, vascular pulsation and so on. On the one hand, it affects the determination of the relationship between important organs; on the other hand, when dissociating tissue blood vessels and knotting, it is easy to cause cutting (36), resulting in massive bleeding. Secondly, the machine structure and technology of the system are extremely complex, so there is the possibility of failure, which may cause fatal damage. Because of the complex surgical techniques, the preparation before operation and the replacement of instruments during operation take a long time. High cost is another disadvantage of robotic surgery, which makes RATS surgery less competitive than VATS surgery. Deen reported that each RATS operation was on average US $3182 more expensive than VATS surgery (P<0.001) due to the cost of robotic-specific supplies and depreciation during pneumonectomy (11). RATS surgery must shorten the operation time, reduce the supply cost and overall cost, so as to be more economically competitive. In addition, the large-scale application of Leonardo Da Vinci robot is limited by its rare amount of equipment. From the point of view of patients, although they are still worried about the safety of robotic surgery, the development of technology is always accompanied by risks. Medical disputes about Leonardo Da Vinci robot infringement appeared in the 2005. At present, there are no relevant reports in China, and the consensus, guidelines and legal norms related to surgery need to be improved. The promotion of "surgical insurance" has also greatly reduced the occurrence of related medical disputes.

Conclusions

Meta-analysis of the existing data showed that there were no significant differences in the rate of conversion to thoracotomy, number of lymph nodes groups dissected, postoperative drainage days, hospitalization time and postoperative hospital mortality. It has some advantages in the number of lymph node dissection, and incidence of postoperative complications in the recent 6 years, but compared with VATS, RATS takes longer to operate. These findings support the application of RATS surgery in robotic surgery for early lung cancer. A large cohort study is needed to evaluate the safety and effectiveness of RATS and VATS operations.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/tcr-21-646

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-646). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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