Wedge resection before lobectomy for patients with T1N0M0 non-small cell lung cancer: a propensity score matching analysis

Yuan Zeng[1#], Ying Huang[1#], Junhui Fu[1,2#], Ke Xu[1], Wenhua Liang[1], Fei Cui[1], Zhexue Hao[1], Xukai Li[3], Tuo Xing[1], Jianxing He[1], Jun Liu[1]

[1]Department of Thoracic Surgery and Oncology, The First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, Guangzhou, China; [2]Department of Surgical Oncology, Shantou Central Hospital, Shantou, China; [3]Department of Thoracic Surgery, Guangdong Second Provincial General Hospital, Guangzhou, China

Contributions: (I) Conception and design: Y Zeng, Y Huang, J Fu, J He, J Liu; (II) Administrative support: W Liang, F Cui, J He, J Liu; (III) Provision of study materials or patients: Y Zeng, Y Huang, F Cui, Z Hao; (IV) Collection and assembly of data: Y Zeng, Y Huang, J Fu, K Xu, X Li, T Xing; (V) Data analysis and interpretation: Y Zeng, Y Huang, J Fu, J He, J Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Prof. Jun Liu and Prof. Jianxing He. Department of Thoracic Surgery and Oncology, The First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, Guangzhou, China. No. 151, Yanjiang Rd, Guangzhou 510120, China. Email: liujun9707@sina.com; drhe_jianxing@163.com.

Background: Whether wedge resection of a tumor before lobectomy (Wed + Lob) can improve the prognosis of non-small cell lung cancer (NSCLC) has yet to be determined comprehensively. This study aimed to compare the effects of Wed + Lob with those of direct lobectomy (Lob) on survival and tumor cell dissemination in patients with T1N0M0 NSCLC.

Methods: A cohort of 813 patients with T1N0M0 NSCLC who underwent lobectomy at a single center in China was investigated. After propensity score matching, the overall survival (OS) and disease-free survival (DFS) of patients were estimated using Kaplan-Meier plots. Associations between surgical strategies and patient survival were computed as hazard ratios and 95% confidence intervals using Cox proportional hazards regression models. Changes in folate receptor-positive circulating tumor cells (FR+ CTCs) after lobectomy were analyzed in another cohort from our hospital.

Results: A total of 401 Wed + Lob cases were matched with 255 Lob cases according to their propensity scores. Although no significant differences were found in OS, multivariate analysis showed that patients with T1N0M0 NSCLC in the Wed + Lob group had significantly improved DFS (HR =0.583; P=0.012) compared to those in the Lob group. After surgery, a decrease in FR+ CTCs was observed in 21 of 23 patients (91.3%) in the Wed + Lob group and in 16 of 23 patients (69.6%) in the Lob group [mean changes: 6.10 (±7.80) FU per 3 mL *vs.* 1.31 (±4.39) FU per 3 mL; P=0.014].

Conclusions: Wed + Lob may improve DFS and reduce tumor cell dissemination in patients with T1N0M0 NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); folate receptor-positive circulating tumor cell (FR+ CTC); lobectomy; wedge resection

Submitted Oct 01, 2021. Accepted for publication Jan 28, 2022.
doi: 10.21037/atm-21-5246
View this article at: https://dx.doi.org/10.21037/atm-21-5246

Introduction

According to recent epidemiological data, lung cancer ranks first among malignant tumors for incidence and mortality (1). About 85% of lung cancers are non-small cell lung cancer (NSCLC) (2). For patients with stages I, II, and a subset of stage III NSCLCs, surgery is the preferred treatment, with lobectomy advised as the standard surgical procedure for these patients (3,4). However, nearly 20% of patients experience distant metastases or local recurrence within 5 years after curative resection (5,6).

Recent advances in technical approaches have demonstrated that circulating tumor cells (CTCs) are important for the development of tumor metastasis and can serve as biomarkers for early detection, diagnosis, and prognosis in lung cancer (7,8). Recently, the probable value of CTCs as a liquid biopsy was established, and this detection method is necessary for tumors that are difficult to obtain by tissue biopsy, such as NSCLC (9,10). CTCs are introduced from the cancer into the blood and can spread to distant sites and develop into micrometastases (11,12). Studies illustrate that operative manipulation encourages the dissemination of tumor cells into the blood circulation. Theoretically, the risk of dissemination of cancer cells can be reduced if the tumor is resected before lobectomy (13-15). A recent study showed that wedge resection before lobectomy may be considered as a no-touch isolation technique for patients with NSCLC (16). Therefore, we hypothesized that performing Wed + Lob on patients with NSCLC may reduce the tumor burden, the tumor retention time during surgery, and the number of tumor cells entering the blood circulation during surgery, thus providing a survival benefit. However, because of a lack of sufficient research, the effects of Wed + Lob on the prognosis of patients with T1N0M0 NSCLC have yet to be comprehensively assessed. Therefore, in this study, we used a retrospective propensity score matching (PSM) analysis to explore the effects of Wed + Lob on CTCs and the prognosis of patients with T1N0M0 NSCLC undergoing lobectomy. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5246/rc).

Methods

Study population

The retrospective research was based on data gathered from the First Affiliated Hospital of Guangzhou Medical University. This study analyzed patients with NSCLC who underwent lobectomy between March 2014 to November 2017. Patients were included if they met the following criteria: (I) underwent standardized video-assisted thoracic surgery (VATS) lobectomy; (II) had pathologically confirmed NSCLC with stage T1N0M0, as determined by two experienced pathologists after surgery; (III) had a peripheral tumor suitable for wedge resection of the lung; and (IV) had a Karnofsky performance score ≥70. Patients who did not meet these inclusion criteria were excluded. Other exclusion criteria were as follows: (I) without systemic lymph node dissection during surgery; (II) patients with purely ground glass nodules; (III) patients with a pathological diagnosis of adenocarcinoma *in situ* or minimally invasive adenocarcinoma; and (IV) patients with missing information on extracted data. The eighth edition of the American Joint Committee on Cancer (AJCC) was used for TNM staging.

According to their operation records, the patients were grouped into the wedge resection of the tumor followed by lobectomy (Wed + Lob) group and the direct lobectomy (Lob) group. Data for the patients including patient demographics, preoperative investigations, and postoperative factors were gathered and examined. The patients were staged according to the eighth edition of the TNM classification for lung cancer (17). PSM was performed to balance selection bias between the two groups.

CTC study

An exploratory study was also conducted to investigate the levels of folate receptor-positive CTCs (FR+ CTCs) in patients with NSCLC who were treated at the First Affiliated Hospital of Guangzhou Medical University from September 15, 2018, to April 15, 2020. Patients with preoperative and postoperative FR+ CTC results were included. The inclusion and exclusion criteria used were the same as those above. Preoperative blood samples were harvested from patients on the second day of hospitalization. Postoperative blood samples were gathered instantly after chest closure. PSM was performed to balance selection bias between the Wed + Lob group and the Lob group.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College approved this study (approval No. 18-014/166; issued date 15/3/2018). Individual consent for this retrospective analysis was waived.

CTC analysis

CTC analysis was performed using the CytoploRare method (GenoSaber Biotech Co. Ltd, Shanghai, China) (9). Before and after surgery, blood samples (3 mL) from included patients were collected in a vacuum tube using EDTA for anticoagulation. All blood samples were stored in a refrigerator at 4 ℃ and analyzed within 24 hours.

Enrichment of CTCs was initially achieved by performing erythrocyte lysis followed by immunomagnetic depletion of leukocytes from the whole blood. FR+ CTCs in each sample were quantified using ligand-targeted polymerase chain reaction. A CTC unit [denoted functional unit (FU)] extracted from a standard curve was applied to show the abundance of FR+ CTCs in 3 mL of peripheral blood.

Statistical analysis

In the retrospective analysis, PSM was accomplished using a logistic regression model to balance the clinical baseline. The Wed + Lob group was treated in the same manner as the Lob group, and the factors were age, sex, tumor location, tumor size, and histology. The patients in Lob and Wed + Lob groups paired with the closest propensity score were matched 1 to 2 with a caliper width of 0.2 of the standard deviation. After PSM, differences in categorical clinical characteristics were tested for significance using chi-square tests. Differences in CTC units between the two groups were compared using unpaired T tests. Overall survival (OS) was measured as the time from the date of surgery to death or the last follow-up. Disease-free survival (DFS) was defined as the time from surgery to the date of tumor progression, death from cancer, or the last follow-up. OS and DFS were assessed using the Kaplan-Meier method, and the survival difference was compared by log-rank test. Results of univariable and multivariable analyses are shown as the hazard ratio (HR) and 95% confidence interval (CI). Statistical analyses were conducted in SPSS 22.0 (IMB-SPSS Inc., Armonk, NY, USA) and R version 3.5.3 (https://www.rproject.org/). P<0.05 was considered statistically significant.

Results

Clinical characteristics

A total of 813 patients with T1N0M0 NSCLC were included, of whom 282 (34.7%) underwent Lob and 531 (65.3%) underwent Wed + Lob (Figure S1). The median follow-up time of the study population was 38.1 months. *Table 1* lists the baseline characteristics of patients and tumors. Female patients had a higher rate of Wed + Lob than did male patients. No significant differences were observed in age or tumor localization between the two groups. The clinical decision (Lob or Wed + Lob) of the surgeon was informed by the pathological type and size of the tumor and the presence or absence of lymph node metastasis.

PSM produced 401 cases from the Wed + Lob group and 255 cases from the Lob group. After PSM, the matched cohort was well balanced in all groups, and the clinical baseline characteristics were comparable between the two groups (*Table 1*).

Survival analysis in the matched cohorts

Survival analysis with log-rank tests indicated no difference in OS between the two groups (HR =0.621; 95% CI: 0.315 to 1.225; P=0.170). However, DFS (HR =0.569; 95% CI: 0.377 to 0.857; P=0.007) was better in the Wed + Lob group than in the Lob group (*Figure 1*). The 1-, 3-, and 5-year OS rates and DFS rates are shown in *Table 2*. After adjustment for age, sex, primary site, histology, and tumor size (Table S1), Cox proportional-hazards regression showed that the Wed + Lob group had significantly improved DFS (HR =0.583; 95% CI: 0.382 to 0.889; P=0.012) compared to the Lob group; however, no significant differences were found in OS (HR =0.706; 95% CI: 0.347 to 1.435; P=0.336).

CTC levels in patients

After PSM, 46 participants who were diagnosed with T1N0M0 NSCLC and were planning to undergo thoracoscopic lobectomy were included. *Table 3* lists the clinical baseline characteristics of patients with stage I NSCLC. FR+ CTCs are presented as the mean ± square error. The levels of FR+ CTCs were compared before and after surgery. After surgery, a decrease in FR+ CTCs was observed in 21 of 23 patients (91.3%) in the Wed + Lob group and in 16 of 23 patients (69.6%) in the Lob group. In the Wed + Lob group, FR+ CTC levels were significantly higher before surgery than they were after surgery [16.6 (±9.4) FU per 3 mL *vs.* 10.5 (±5.7) FU per 3 mL; P=0.011; *Figure 2A*]. In the Lob group, no significant changes in FR+ CTCs were observed before and after surgery [14.0 (±5.9) FU per 3 mL *vs.* 12.7 (±5.4) FU per 3 mL; P=0.44; *Figure 2B*].

Table 1 Baseline characteristics of patients before and after propensity score matching

Characteristics	Before matching (n=813)			After matching (n=659)		
	Wed + Lob (n=531)	Lob (n=282)	P value	Wed + Lob (n=401)	Lob (n=255)	P value
Age (years), n (%)			0.386			0.525
<60	236 (44.4)	122 (43.3)		180 (44.9)	112 (43.9)	
60–70	192 (36.2)	114 (40.4)		147 (36.7)	103 (40.4)	
≥70	103 (19.4)	46 (16.3)		74 (18.5)	40 (15.7)	
Sex, n (%)			0.078			0.769
Male	263 (49.5)	158 (56.0)		206 (51.4)	134 (52.5)	
Female	268 (50.5)	124 (44.0)		195 (48.6)	121 (47.5)	
Primary site, n (%)			0.05			0.674
Upper	310 (58.4)	140 (49.6)		226 (56.1)	131 (51.4)	
Middle	34 (6.4)	30 (10.6)		34 (8.5)	26 (10.2)	
Lower	174 (32.8)	105 (37.2)		133 (32.9)	91 (35.7)	
Unknown	13 (2.4)	7 (2.5)		10 (2.5)	7 (2.7)	
Histological type, n (%)			<0.001			0.183
Squamous cell	33 (6.2)	46 (16.3)		31 (7.7)	25 (9.8)	
Adenocarcinoma	468 (88.1)	203 (72.0)		341 (85.0)	203 (79.6)	
Other	30 (5.6)	33 (11.7)		29 (7.2)	27 (10.6)	
Tumor size, n (%)			<0.001			0.608
≤1 cm	81 (15.3)	28 (9.9)		48 (12.0)	28 (11.0)	
>1–2 cm	252 (47.5)	99 (35.1)		163 (40.6)	96 (37.6)	
>2 cm	198 (37.3)	155 (55.0)		190 (47.4)	131 (51.4)	

Lob, direct lobectomy; Wed + Lob, wedge resection of the tumor before lobectomy.

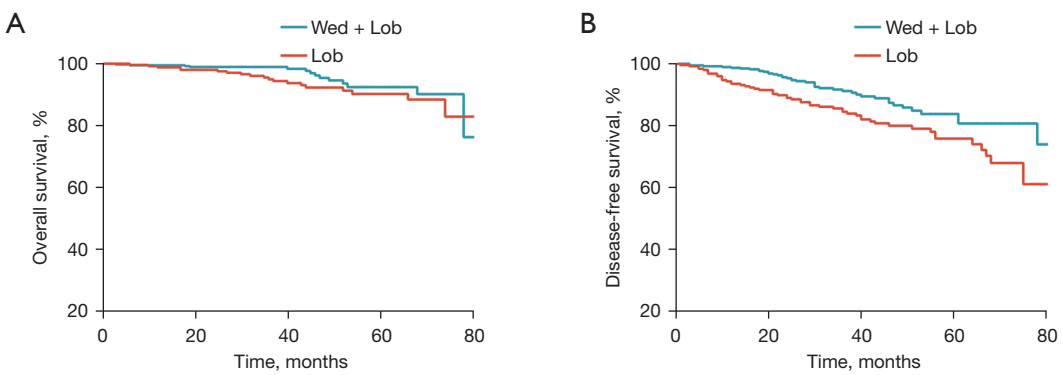

Figure 1 Kaplan-Meier estimates of overall survival and disease-free survival in the matched patients with T1N0M0 non-small cell lung cancer by surgical approach. HR, hazard ratio; Lob, direct lobectomy; Wed + Lob, wedge resection of the tumor before lobectomy.

Table 2 OS rate and DFS rate in the matched patients with T1N0M0 non-small cell lung cancer

Survival	Wed + Lob	Lob	P
OS rate (%)			0.17
1 year	99.2	98.8	
3 years	98.4	95.0	
5 years	89.9	88.4	
DFS rate (%)			0.006
1 year	98.7	94.0	
3 years	90.6	84.5	
5 years	82.2	74.0	

OS, overall survival; DFS, disease-free survival; Lob, direct lobectomy; Wed + Lob, wedge resection of the tumor before lobectomy.

Table 3 Baseline characteristics of patients in the CTC cohort before and after propensity score matching

Characteristics	Before matching (n=62)			After matching (n=46)		
	Wed + Lob (n=33)	Lob (n=29)	P value	Wed + Lob (n=23)	Lob (n=23)	P value
Age (years), n (%)			0.201			0.525
<60	15 (45.5)	17 (58.6)		11 (47.8)	12 (52.2)	
60–70	16 (48.5)	8 (27.6)		11 (47.8)	8 (34.8)	
≥70	2 (6.1)	4 (13.8)		1 (4.3)	3 (13.0)	
Sex, n (%)			0.961			0.767
Male	15 (45.5)	13 (44.8)		11 (47.8)	10 (43.5)	
Female	18 (54.5)	16 (55.2)		12 (52.2)	13 (56.5)	
Primary site, n (%)			0.498			0.76
Upper	21 (63.6)	16 (55.2)		15 (65.2)	14 (60.9)	
Lower	12 (36.4)	13 (44.8)		8 (34.8)	9 (39.1)	
Histological type, n (%)						
Squamous cell	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Adenocarcinoma	33 (100.0)	29 (100.0)		23 (100.0)	23 (100.0)	
Tumor size, n (%)			0.20			0.822
≤1 cm	3 (9.1)	2 (6.9)		2 (8.7)	1 (4.3)	
>1–2 cm	17 (51.5)	9 (31.0)		8 (34.8)	9 (39.1)	
>2 cm	13 (39.4)	18 (62.1)		13 (56.5)	13 (56.5)	

Lob, direct lobectomy; Wed + Lob, wedge resection of the tumor before lobectomy; CTC, circulating tumor cell.

The mean changes in FR+ CTC levels were 6.10 (±7.80) FU per 3 mL in the Wed + Lob group and 1.31 (±4.39) FU per 3 mL in the Lob group. A significant difference was observed in the change in FR+ CTC levels before and after surgery between the Wed + Lob group and the Lob group (P=0.014; *Figure 2C*).

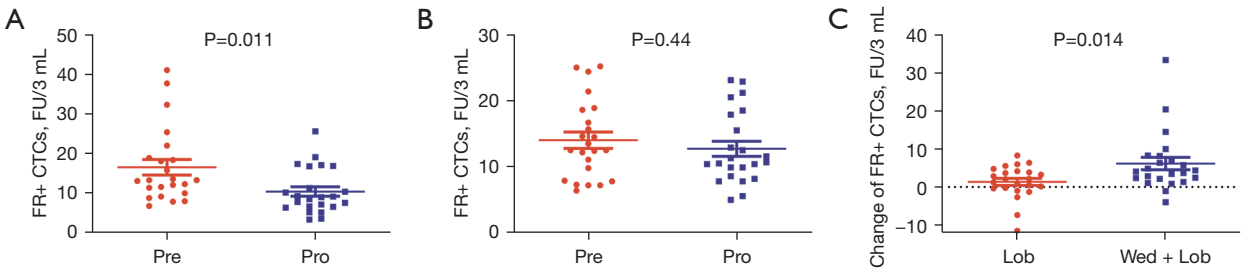

Figure 2 Folate receptor-positive circulating tumor cell (FR+ CTC) levels before and after surgery. The levels of FR+ CTCs before, during, and after surgery in the Wed + Lob group (A) and the Lob group (B). The changes in FR+ CTC levels before and after surgery in the two groups (C). FR+ CTC, folate receptor-positive circulating tumor cell; Lob, direct lobectomy; Wed + Lob, wedge resection of the tumor before lobectomy.

Discussion

At present, lobectomy is still the standard treatment for early-stage operable NSCLC (18,19). However, current research indicates that a certain percentage of patients with resected NSCLC experience recurrence *in situ* or distant metastases within 5 years (20,21). Patients with early-stage lung cancer are reported to have CTCs in their peripheral blood at the time of diagnosis (22-24), and studies have shown that operative manipulation can cause tumor cells to enter the peripheral blood circulation (13-15). This finding may be a reason that patients with early-stage lung cancer have recurrence and metastasis after curative resection. Therefore, in addition to early diagnosis and treatment, surgical plans also need to be further optimized to minimize the escape of tumor cells caused by surgery and improve the prognosis of patients with lung cancer.

Because pathological diagnosis before surgery is not possible for most lung tumors, many surgeons choose to first perform wedge resection. However, for a number of reasons, direct lobectomy might also be considered. Firstly, the imaging of lung tumors is based on an extremely high possibility of malignancy; therefore, direct lobectomy might shorten the operation time and reduce the cost. Secondly, some patients have preoperative pathology. Furthermore, for some patients, the lung tumor is located in a deep position and is large in size, which increases the difficulty of performing lung wedge resection. To our knowledge, our study is the first retrospective analysis to compare the effects of Wed + Lob and direct lobectomy on survival and circulating tumor cells in patients with T1N0M0 NSCLC. In the Wed + Lob group, due to selection bias, there was a higher proportion of women, more upper lobe tumors, more adenocarcinomas, and smaller tumor sizes than in the Lob group. Therefore, PSM analysis was performed to decrease the effects of selection bias. Also, we conducted an exploratory cohort study to analyze FR+ CTCs in the blood of patients with T1N0M0 NSCLC and compared the results with those of the retrospective analysis in patients with T1N0M0 NSCLC. Undergoing wedge resection of the tumor prior to lobectomy might have reduced the dissemination of tumor cells into the peripheral blood after lobectomy and thus may have potential DFS benefits for patients.

Wei *et al.* (25) used a similar method to illustrate that ligating effluent veins first during the operation might decrease tumor cell spread and increase survival outcomes in patients with NSCLC. Furthermore, in a recent study, Yasukawa *et al.* (16) indicated that wedge resection before lobectomy may be considered a no-touch isolation technique for patients with NSCLC because it was associated with better OS than direct lobectomy. Their study was primarily limited to significant differences in clinical characteristics between the two groups. In our study, multivariate analysis after PSM showed no significant differences in OS (HR =0.706; P=0.336) between the Wed + Lob and Lob groups of patients with peripheral T1N0N0 NSCLC. However, Wed + Lob resulted in better DFS (HR =0.583; P=0.012) than did Lob. This DFS benefit may be attributed to wedge resection of the tumor, which reduces both the patient's tumor burden and the number of tumor cells that enter the circulatory system during surgery. Performing wedge resection of the tumor before removing the lung lobes reduces repetitive surgical operations that squeeze and flip the tumor-bearing lobes during the procedure. Reducing the tumor load for a short time also reduces the number of tumor cells entering the bloodstream.

In our CTC study, no difference was found in age, sex, tumor location, tumor size, or histology. We found

that the levels of FR+ CTCs in the peripheral blood were significantly decreased after surgery in the Wed + Lob group but not in the Lob group. Furthermore, a notable difference was observed in the changes in FR+ CTC levels before and after surgery between patients who underwent Wed + Lob and those who underwent Lob. Several reasons may explain this decrease. Firstly, after wedge resection of the tumor, the tumor burden decreased immediately and the number of tumor cells in circulation reduced. Previous studies have reported a reduction in the number of CTCs in the peripheral blood after surgery, which is consistent with our findings (26-28). Secondly, surgical procedures, such as plunging pulmonary blood vessels and squeezing tumors, can cause CTCs to enter the bloodstream. For patients in the Lob group, the tumor stayed in the lung for a longer time than it did for patients in the Wed + Lob group, which may have led to more CTCs entering the bloodstream. Studies have reported that surgical manipulation can lead to tumor recurrence (13-15). This finding also supports the notion that surgery can facilitate the introduction of tumor cells into the blood (25,29). Therefore, undertaking wedge resection of the tumor first might aid in decreasing the number of tumor cells that are disseminated into the blood circulation in patients undergoing lobectomy. We therefore believe that wedge resection of the tumor followed by lobectomy should be given priority during radical resection of T1N0M0 NSCLC, which would help to standardize current surgical strategies.

Our study has some limitations. First, the retrospective nature of the data resulted in an unavoidable bias. For example, more patients with larger and deeper lung nodules underwent direct lobectomy. Therefore, our research topic was limited to T1N0M0 NSCLC, and PSM was performed to decrease the effects of selection bias. Second, the number of patients in this study was small. Only 659 patients were included after PSM and only 46 patients were covered in the studies of FR+ CTC levels. Moreover, although we determined DFS and OS in the PSM analysis, the survival results for the FR+ CTC study could not be obtained on account of an inadequate follow-up period. Therefore, further studies with larger sample sizes and prospective randomized clinical trials should be performed to evaluate the effects of Wed + Lob on the dissemination of tumor cells in patients with NSCLC.

Conclusions

Wed + Lob may result in decreased dissemination of tumor cells during surgery and improve DFS outcomes in patients with T1N0M0 NSCLC. Further prospective studies to determine the effects of Wed + Lob on these patients are warranted.

Acknowledgments

We thank International Science Editing for assistance with editing the manuscript.
Funding: This work was supported by the National Key R&D Program of China (Grant No. 2017YFC0907900/2017YFC0907903), Guangdong Provincial Basic and Applied Basic Research Fund of China (Grant No. 2020A1515110445), and The China State Key Laboratory of Respiratory Disease Independent Subject (Grant No. SKLRD-QN-201925).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-5246/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-21-5246/dss

Peer Review File: Available at https://atm.amegroups.com/article/view/10.21037/atm-21-5246/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5246/coif). JH serves as an Editor-in-Chief of *Annals of Translational Medicine* from June 2019 to May 2024. The other 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College approved this study (approval No. 18-014/166; issued date 15/3/2018). Individual consent for this retrospective analysis was waived.

Open Access Statement: This is an Open Access article

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
2. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2019;69:184-210.
3. Altorki NK, Wang X, Wigle D, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med 2018;6:915-24.
4. McDonald F, De Waele M, Hendriks LE, et al. Management of stage I and II nonsmall cell lung cancer. Eur Respir J 2017;49:1600764.
5. Demicheli R, Fornili M, Ambrogi F, et al. Recurrence dynamics for non-small-cell lung cancer: effect of surgery on the development of metastases. J Thorac Oncol 2012;7:723-30.
6. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res 2014;3:242-9.
7. Krebs MG, Sloane R, Priest L, et al. Evaluation and prognostic significance of circulating tumor cells in patients with non-small-cell lung cancer. J Clin Oncol 2011;29:1556-63.
8. Carter L, Rothwell DG, Mesquita B, et al. Molecular analysis of circulating tumor cells identifies distinct copy-number profiles in patients with chemosensitive and chemorefractory small-cell lung cancer. Nat Med 2017;23:114-9.
9. Chen X, Zhou F, Li X, et al. Folate Receptor-Positive Circulating Tumor Cell Detected by LT-PCR-Based Method as a Diagnostic Biomarker for Non-Small-Cell Lung Cancer. J Thorac Oncol 2015;10:1163-71.
10. Alix-Panabières C, Pantel K. Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy. Cancer Discov 2016;6:479-91.
11. Alix-Panabières C, Pantel K. Challenges in circulating tumour cell research. Nat Rev Cancer 2014;14:623-31.
12. Chemi F, Rothwell DG, McGranahan N, et al. Pulmonary venous circulating tumor cell dissemination before tumor resection and disease relapse. Nat Med 2019;25:1534-9.
13. Sawabata N, Okumura M, Utsumi T, et al. Circulating tumor cells in peripheral blood caused by surgical manipulation of non-small-cell lung cancer: pilot study using an immunocytology method. Gen Thorac Cardiovasc Surg 2007;55:189-92.
14. Yamaguchi K, Takagi Y, Aoki S, et al. Significant detection of circulating cancer cells in the blood by reverse transcriptase-polymerase chain reaction during colorectal cancer resection. Ann Surg 2000;232:58-65.
15. Hashimoto M, Tanaka F, Yoneda K, et al. Significant increase in circulating tumour cells in pulmonary venous blood during surgical manipulation in patients with primary lung cancer. Interact Cardiovasc Thorac Surg 2014;18:775-83.
16. Yasukawa M, Sawabata N, Kawaguchi T, et al. Wedge resection of the tumor Before Lobectomy for Lung Cancer Could Be a No-touch Isolation Technique. In Vivo 2020;34:779-85.
17. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
18. Deng HY, Zhou Q. Lobectomy should remain the first choice for treating early stage nonsmall cell lung cancer. Eur Respir J 2019;54:1900649.
19. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e278S-e313S.
20. Soneji S, Tanner NT, Silvestri GA, et al. Racial and Ethnic Disparities in Early-Stage Lung Cancer Survival. Chest 2017;152:587-97.
21. Cornwell LD, Echeverria AE, Samuelian J, et al. Video-assisted thoracoscopic lobectomy is associated with greater recurrence-free survival than stereotactic body radiotherapy for clinical stage I lung cancer. J Thorac Cardiovasc Surg 2018;155:395-402.
22. Crosbie PA, Shah R, Summers Y, et al. Prognostic and predictive biomarkers in early stage NSCLC: CTCs and serum/plasma markers. Transl Lung Cancer Res 2013;2:382-97.

23. Goodman CR, Seagle BL, Friedl T, et al. Association of Circulating Tumor Cell Status With Benefit of Radiotherapy and Survival in Early-Stage Breast Cancer. JAMA Oncol 2018;4:e180163.
24. Reddy RM, Murlidhar V, Zhao L, et al. Pulmonary venous blood sampling significantly increases the yield of circulating tumor cells in early-stage lung cancer. J Thorac Cardiovasc Surg 2016;151:852-8.
25. Wei S, Guo C, He J, et al. Effect of Vein-First vs Artery-First Surgical Technique on Circulating Tumor Cells and Survival in Patients With Non-Small Cell Lung Cancer: A Randomized Clinical Trial and Registry-Based Propensity Score Matching Analysis. JAMA Surg 2019;154:e190972.
26. Zhang Q, Shan F, Li Z, et al. A prospective study on the changes and clinical significance of pre-operative and post-operative circulating tumor cells in resectable gastric cancer. J Transl Med 2018;16:171.
27. Yu JJ, Xiao W, Dong SL, et al. Effect of surgical liver resection on circulating tumor cells in patients with hepatocellular carcinoma. BMC Cancer 2018;18:835.
28. Haga N, Onagi A, Koguchi T, et al. Perioperative Detection of Circulating Tumor Cells in Radical or Partial Nephrectomy for Renal Cell Carcinoma. Ann Surg Oncol 2020;27:1272-81.
29. Huang HB, Ge MJ. The Effects of Different Surgical Approaches on the Perioperative Level of Circulating Tumor Cells in Patients with Non-Small Cell Lung Cancer. Thorac Cardiovasc Surg 2016;64:515-9.

(English Language Editors: C. Mullens and J. Reynolds)

Cite this article as: Zeng Y, Huang Y, Fu J, Xu K, Liang W, Cui F, Hao Z, Li X, Xing T, He J, Liu J. Wedge resection before lobectomy for patients with T1N0M0 non-small cell lung cancer: a propensity score matching analysis. Ann Transl Med 2022;10(9):502. doi: 10.21037/atm-21-5246

Supplementary

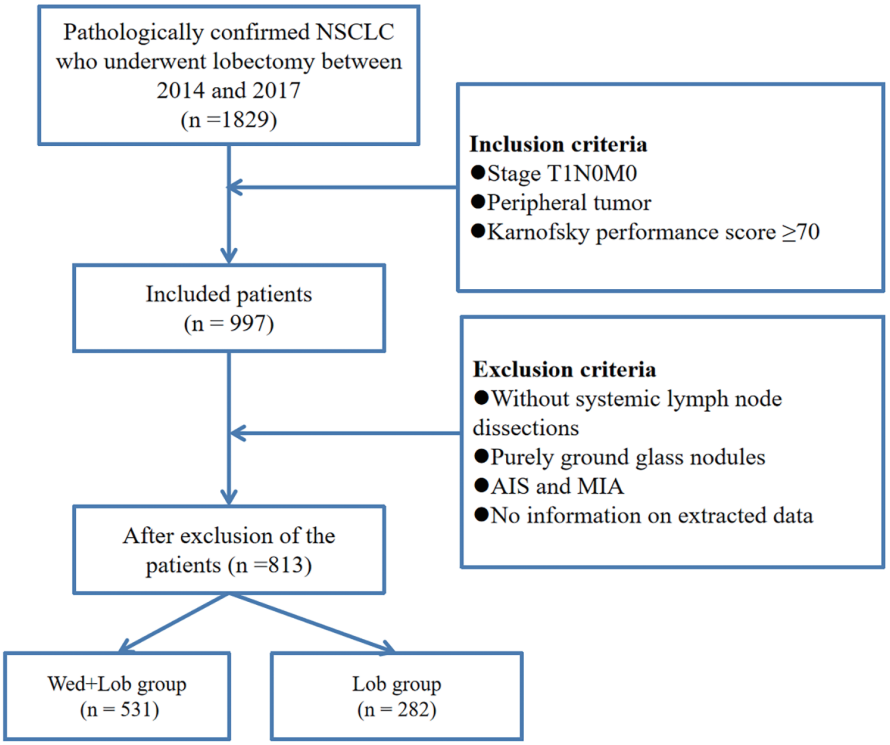

Figure S1 Flow chart of study development.

https://dx.doi.org/10.21037/atm-21-5246

Table S1 Multivariable analysis of OS and DFS in the matched patients with T1N0M0 non-small cell lung cancer

Characteristic	OS		DFS	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age (years)		0.133		0.038
<60	1 (reference)		1 (reference)	
60–70	2.123 (0.984 to 4.582)	0.055	1.814 (1.142 to 2.883)	0.012
≥70	1.179 (0.396 to 3.512)	0.768	1.259 (0.682 to 2.325)	0.462
Sex				
Male	1 (reference)		1 (reference)	
Female	1.179 (0.396 to 3.512)	0.183	0.829 (0.537 to 1.280)	0.397
Primary site		0.049		0.001
Upper	1 (reference)		1 (reference)	
Middle	0.495 (0.063 to 3.899)	0.504	0.886 (0.368 to 2.137)	0.788
Lower	1.997 (0.964 to 4.137)	0.063	1.439 (0.925 to 2.238)	0.107
Unknown	4.623 (1.220 to 17.529)	0.024	5.215 (2.224 to 12.231)	< 0.001
Histological type		0.572		0.052
Squamous cell	1 (reference)		1 (reference)	
Adenocarcinoma	1.789 (0.403 to 7.950)	0.445	0.494 (0.267 to 0.914)	0.025
Other	2.493 (0.452 to 13.749)	0.294	0.379 (0.149 to 0.965)	0.042
Tumor size		0.941		0.253
≤1 cm	1 (reference)		1 (reference)	
1.1–2 cm	1.020 (0.223 to 4.659)	0.98	2.330 (0.827 to 6.564)	0.11
>2 cm	1.153 (0.260 to 5.113)	0.851	2.361 (0.845 to 6.598)	0.965
Surgery type				
Lob	1 (reference)		1 (reference)	
Wed + Lob	0.706 (0.347 to 1.435)	0.851	0.583 (0.382 to 0.889)	0.012

OS: overall survival; DFS: disease-free survival; Lob: direct lobectomy; Wed + Lob: wedge resection of the tumor followed by lobectomy; CI: confidence intervals.

https://dx.doi.org/10.21037/atm-21-5246