Does an extended mediastinal lymphadenectomy improve outcome after R0 resection in lung cancer?

Nan Wu*, Shi Yan*, Chao Lv, Shaolei Li, Yuan Feng, Yuzhao Wang, Jia Wang, Qingfeng Zheng, Yue Yang

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Thoracic Surgery II, Peking University Cancer Hospital & Institute, Beijing 100142, China

*These authors contributed equally to this work.

Correspondence to: Yue Yang, MD. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Thoracic Surgery II, Peking University Cancer Hospital & Institute, Beijing 100142, China. Email: zlyangyue@bjmu.edu.cn.

Objective: This retrospective study was conducted to investigate the impact of more extended mediastinal lymphadenectomy on the outcome of lung cancer patients treated with R0 resection.

Methods: During the investigation period, 325 lung cancer cases were enlisted and 278 cases entered the analysis. The patients were divided into Control group (n=116) and Research group (n=162) according to the different extents of mediastinal lymph node clearance at different time periods. Three major parameters were retrospectively assessed to compare the quality of surgical care: extent of lymph node clearance, resection volume, and postoperative recovery process and common complications. Comparison of the outcome between two groups was carried out.

Results: Research group showed a significant quality improvement of lymphadenectomy, such as more mediastinal node stations investigated (more than 3 N2 stations investigated: Research group, 90.7% *vs.* Control group, 55.2%; P=0.001) and more nodes collection (total nodes 26.1±10.0 *vs.* 19.1±8.3, P=0.000; N2 nodes 15.5±7.2 *vs.* 9.8±5.6, P=0.000). However, overall survival (OS) and disease-free survival (DFS) were not significantly different either between two groups (5-year OS: Control group, 56.4±4.6% *vs.* Research group, 62.6±4.3%; P=0.271) or between subgroups from stage I to IIIa. TNM stage and histology were significant factors associated with OS and DFS in multivariate analysis; extent of mediastinal lymphadenectomy was not associated with OS or DFS.

Conclusions: More radical mediastinal lymphadenectomy may not lead to an improved oncological outcome for lung cancer treated with R0 resection.

Keywords: Lung cancer; lymphadenectomy; outcome; quality

Introduction

The 5-year survival rate for lung cancer has improved significantly from 12.3% in 1975-1977 to 16.9% in 2002-2008 (1). This progress may be attributed to the widespread application of multidisciplinary treatments for lung cancer. Meantime, surgery remains a key treatment in the medical interventions for lung cancer, especially for those with early stage disease. Surgical techniques have evolved rapidly in the past several decades. However, substantial differences are still observed in the quality evaluation standards for

lymphadenectomy defined by individual academic societies and research groups.

Successful lung cancer surgery requires complete resection, removal of an adequate anatomic volume of lung tissue and removal of the draining lymph nodes in the lung and mediastinum (2). Lymph node examination is directly linked with the quality of pathological staging. Sufficient tissue supplies will secure the accurate staging based on acceptable lymph node clearance procedures. But it still needs to investigate whether a more radical extent of lymph

node clearance could yield a better survival and meanwhile recovery process remained similar. Thus we designed this retrospective study to investigate the impact of quality improvement of lymphadenectomy on the outcome of lung cancer patients treated with R0 resection.

Patients and methods

Subjects

From September, 2003 to December, 2007, consecutive patients of stage I, stage II and resectable stage IIIa non-small cell lung cancer (NSCLC) were eligible in the study protocol. Patients diagnosed with pulmonary malignancies other than primary lung cancer were excluded from the study. Cases with N3 or bulky N2 disease (3) after induction chemotherapy were excluded.

All operations were performed by a single surgical group. Pulmonary function testing and cardiac evaluation were required as preoperative assessments. Brain magnetic resonance imaging (MRI) or computed tomography (CT), positron emission tomography/CT (PET/CT) scans, bone scintigraphy, and abdominal and supraclavicular ultrasound scanning were used to rule out potential metastatic lesions or N3 disease. Pulmonary resections, including wedge resection, lobectomy, bilobectomy, sleeve-lobectomy and pneumonectomy were selected on the basis of tumor location. Lymph-node stations were defined according to the International Association for the Study of Lung Cancer (IASLC) manual (4). The status of the residual tumor after surgical treatment was defined as three categories: R0 resection (no residual tumor present), R1 resection (microscopically residual tumor) and R2 resection (macroscopically residual tumor) (5).

With the gradual acceptance of systematic mediastinal lymph node dissection (SMLD) in our clinical practice, a transition of surgical techniques on mediastinal lymphadenectomy occurred during the period from December, 2005 to January, 2006. Therefore, the entire patient cohort was artificially divided into two subgroups, according to the extent of mediastinal lymphadenectomy. From September, 2003 to December, 2005, the surgeons resected the mediastinal lymph nodes based on palpation and inspection, which was defined as Control group. From January, 2006 to December, 2007, SMLD was performed using a standard procedure according to IASLC (4) and this group was defined as Research group.

Methods

Briefly for SMLD, all fatty tissue and lymphatic tissue

in the right upper mediastinum (No. 2 and No. 4 on the right) were removed en bloc from the superior vena cava anteriorly, to the trachea posteriorly, and from the takeoff of the right upper lobe inferiorly, to the caudal border of the innominate artery superiorly. The lymph nodes located between the trachea and the esophagus (No. 3P), and the lymph nodes anterior and medial to the superior vena cava at the insertion of the azygous vein (No. 3A) were also dissected. On the left side, dissection of No. 6 was carried out by the removal of all fat pads and lymph nodes anterior and lateral to the ascending aorta and the aortic arch. No. 5 was dissected by removal of the fatty-lymphatic tissues lateral to the ligamentum arteriosum and proximal to the first branch of the left pulmonary artery. No. 4 was dissected from the left side of the trachea medially to the ligamentum arteriosum laterally, and from the upper margin of the aortic arch to the takeoff of the left main bronchus inferiorly. For No. 7, surgeons ensured that the carina, and the left and the right main bronchi were exposed and free of fatty tissue after dissection. Lymph nodes adjacent to the inferior pulmonary ligament were also removed.

The tissues and lymph nodes were sent for paraffin embedding and routine pathologic analysis. The lymph nodes were bisected along their longitudinal axis and submitted for total microscopic evaluation. Small nodes (0.4 cm or less) were submitted without bisection. A single hematoxylin-eosin (H&E)-stained slide was produced from each block.

Statistical analysis

The Institutional Review Board of the Peking University Cancer Hospital approved this retrospective study. The requirement of patient consent was waived. Comparison of the outcome between Control group and Research group was analyzed using the log-rank test and Kaplan-Meier curves were generated for overall survival (OS) and disease-free survival (DFS). Multivariate Cox regression analyses were used to determine the factors significantly associated with survival. Values were expressed as the $\bar{x} \pm s$ (or median, ranges). The Student's t-test or Mann-Whitney U-test was used for the analysis of normally or non-normally distributed data, respectively. The Pearson's chi-square (χ^2) test was used to compare proportions (or the Fisher's exact test as required). $P < 0.05$ was considered statistically significant. SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA) was used for all analyses.

Table 1 General characteristics of two groups of lung cancer patients

Characteristics	Control group (n=116)	Research group (n=162)	P
Male/female	78/38	112/50	χ^2=0.112, P=0.738
Age (year)	59.7±9.8	59.6±10.0	t=0.068, P=0.946
Body Mass Index	23.8±3.4	24.3±3.2	t=−1.254, P=0.211
Tumor marker [median (range)]			
CEA	3.0 (0.2-629.8)	2.7 (0.2-184.5)	Z=−0.157, P=0.875
CYFAR21-1	2.8 (0.5-23.1)	2.6 (0.7-27.8)	Z=−1.541, P=0.123
SCC	0.5 (0-15.7)	0.4 (0-9.9)	Z=−0.487, P=0.626
Clinical stage [n (%)]			
I	78 (67.2)	105 (64.8)	χ^2=0.400, P=0.817
II	9 (7.8)	16 (9.9)	
IIIa	29 (25.0)	41 (25.3)	
Pathological stage [n (%)]*			
Ia/Ib	15 (12.9)/31 (26.7)	34 (21.0)/32 (19.8)	χ^2=5.104, P=0.277
IIa/IIb	17 (14.7)/11 (9.5)	27 (16.7)/10 (6.2)	
IIIa	40 (34.5)	57 (35.2)	
Histology [n (%)]			
Adenocarcinoma	68 (58.6)	90 (55.6)	χ^2=0.533, P=0.991
Squamous cell	37 (31.9)	57 (35.2)	
Large cell	2 (1.7)	2 (1.2)	
Small cell	5 (4.3)	7 (4.3)	
Other types	4 (3.5)	6 (3.7)	
Perioperative chemotherapy [n (%)]			
Neo-adjuvant	8 (6.9)	13 (8.0)	χ^2=0.123, P= 0.726
Adjuvant	59 (50.9)	64 (39.5)	χ^2=3.534, P=0.060
Tumor size (cm) [median (range)]	3 (1-15)	3 (0.5-10)	Z=−0.136, P=0.892

*, Postoperative staging. In Control group, 1 case of TxN0M0 and 1 case of T3NxM0 were not included, and in Research group, 1 case of T2NxM0 and 1 case of T1aNxM0 were not included (Tx, pCR after induction therapy; Nx, no lymphadenectomy due to calcified nodes fixed to the mediastinum); CEA, carcinoembryonic antigen; CYFER21-1, serum cytokeratin 19 fragment; SCC, squamous cell carcinoma antigen.

Results

Three hundred and twenty-five cases of primary lung cancer were treated during the period of investigation, comprising 290 cases of R0 resection, 10 cases of R1 resection and 25 cases of R2 resection. R1 or R2 resection was excluded from further analysis. In addition, five R0 cases were also excluded from the analysis, including three patients who died within 30 d of surgery, and two patients who died due to non-cancerous causes within the postoperative multi-modality treatment period (one sudden death due to bronchopleural fistula; one severe infection due to grade 4 leukocytopenia during adjuvant chemotherapy). Follow-up ended on June 30, 2011; seven cases were lost during the investigation period and thus excluded from the study (two in Control group and five in Research group). Ultimately, a total of 278 patients were analyzed for OS in this study and 242 cases were analyzed for DFS (36 cases were discarded from DFS analysis because their recurrence information was lost). After a median follow-up of 48.95 months (range, 3.7-92.3 months), 113 patients (40.65%) had died. The 5-year OS rates for the whole group, pathological stage I (n=112), stage II (n=65) and stage IIIa (n=97) were 58.9±3.2%, 74.2±4.7%, 64.8±6.1% and 38.8±5.3%, respectively.

The general characteristics of the patients in Control group and Research group are summarized in *Table 1*.

Table 2 Comparison of quality of lymphadenectomy in two groups of lung cancer patients

	Control group (n=116)	Research group (n=162)	P
Number of mediastinal lymph node stations investigated (n/%)			
0-2 stations	52/44.8	15/9.3	χ^2=47.751, P=0.001
≥3 stations	64/55.2	147/90.7	
Total number of mediastinal lymph nodes collected			
Left side	9.2±5.2	14.3±7.1	t=−4.228, P=0.001
Right side	10.3±5.9	16.2±7.3	t=−5.611, P=0.001
The whole group	9.8±5.6	15.5±7.2	t=−7.409, P=0.001
Total number of lymph nodes collected (N1+N2)			
Left side	19.8±8.7	24.8±9.6	t=−2.782, P=0.006
Right side	18.5±8.1	26.9±10.2	t=−5.643, P=0.001
The whole group	19.1±8.3	26.1±10.0	t=−6.219, P=0.001
% of positive nodes/total nodes			
Median (IQR)	0 (0-18.2)	0 (0-10.3)	Z=−0.604, P=0.546
Resection volume (n/%)			
Wedge resection	3/2.6	7/4.3	χ^2=3.587, P=0.310
Lobectomy (including bi-lobectomy)	92/79.3	125/77.2	
Sleeve lobectomy	13/11.2	25/15.4	
Pneumonectomy	8/6.9	5/3.1	
Postoperative total drainage (mL)			
Median (IQR)	1,620 (1,200-2,250)	1,705 (1,227.5-2,340.0)	Z=−0.829, P=0.407
Chest tube duration (d)			
Median (IQR)	8 [6-10]	8 [6-10]	Z=−0.415, P=0.678
Complications (n/%)			
Chylothorax	0/0	2/1.2	χ^2=2.194, P=0.139
Postoperative hemorrhage	0/0	1/0.6	χ^2=1.094, P=0.296
Cardiac arrhythmia	12/9.8	23/13.7	χ^2=0.989, P=0.320
Bronchopleural fistula	0/0	4/2.4	χ^2=4.408, P=0.036
Qualified lymphadenectomy			
By NCCN standard [n (%)]	50 (43.1)	128 (79.0)	χ^2=37.844, P=0.000
By IASLC standard [n (%)]	8 (7.0)	45 (27.8)	χ^2=19.102, P=0.000

IQR, inter-quartile range; NCCN, National Comprehensive Cancer Network; IASLC, Association for the Study of Lung Cancer.

One hundred and sixteen cases were enlisted in Control group and 162 cases in Research group. The two groups were equally matched in terms of gender, age, Body Mass Index (BMI), pathological staging, histology, and the ratio of perioperative chemotherapy. To compare the quality of lymphadenectomy and surgical care between the two groups, the following parameters were analyzed: the extent of lymph node clearance (number of mediastinal node stations and number of lymph nodes), the resection volume, and the postoperative recovery process and common complications (*Table 2*).

Significant differences were observed in the number of mediastinal lymph node stations investigated (more than 3 N2 stations investigated, 55.2% in Control group *vs.* 90.7% in Research group, P=0.001), the total number of lymph nodes harvested (19.1±8.3 in Control group *vs.* 26.1±10.0 in Research group, P=0.000), and the total number of N2 nodes collected (9.8±5.6 in Control group *vs.* 15.5±7.2 in Research group, P=0.000). There was no significant difference in other quality-related items, such
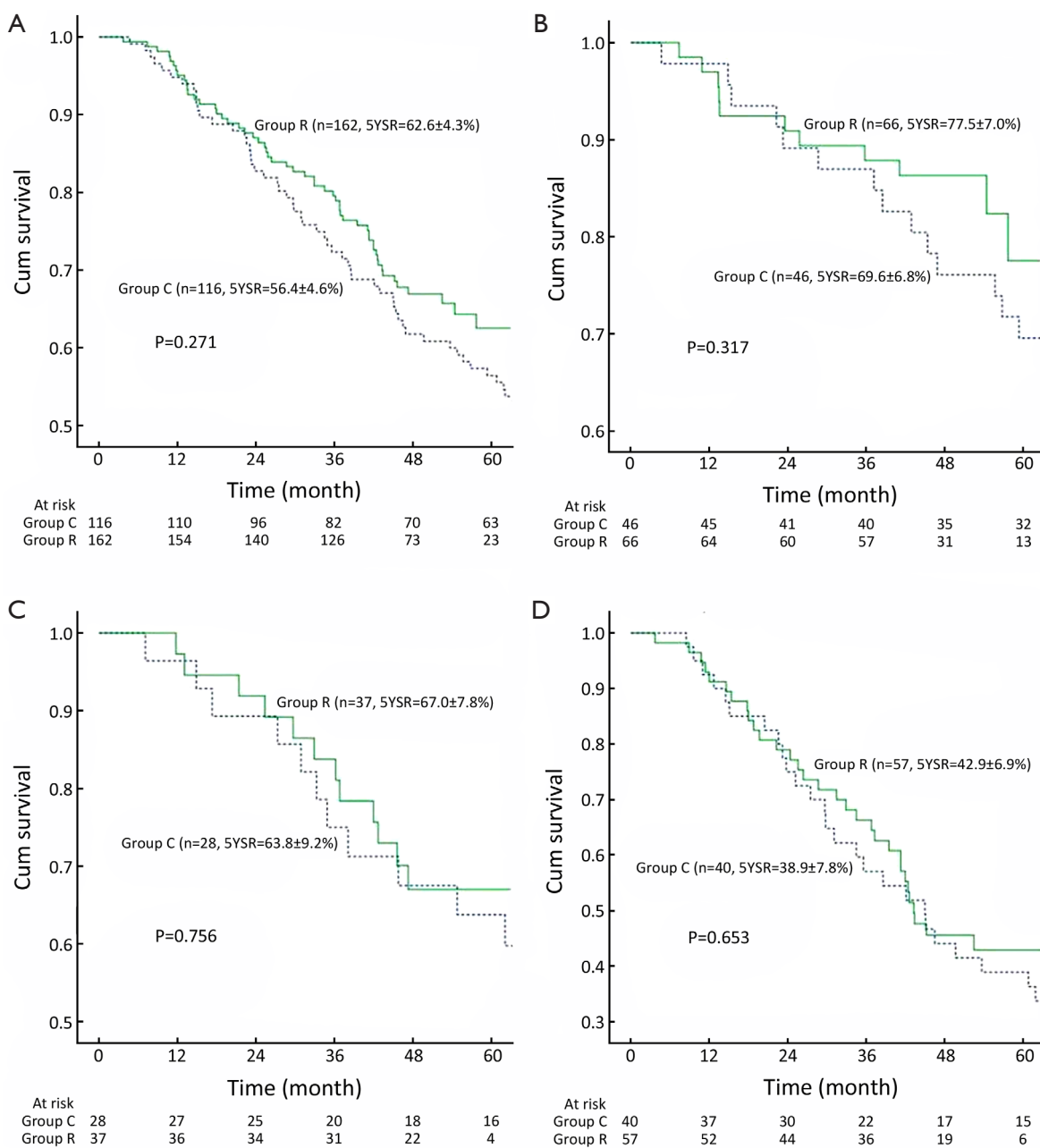
Figure 1 The overall survival (OS) for Control group (Group C) and Research group (Group R). The whole group (A) and the subgroups stratified by pathological stage: stage I (B), stage II (C) and stage IIIa (D). 5YSR, 5-year OS rate.

as the proportion of metastatic nodes, resection volume, or recovery and common complications (chylothorax, postoperative hemorrhage, and cardiac arrhythmia).

The Kaplan-Meier OS curves are depicted in *Figure 1*. Control group had a similar outcome compared with Research group. The 5-year OS rates were 56.4±4.6% in

Control group and 62.6±4.3% in Research group (P=0.271, *Figure 1A*). Significant differences in OS were not observed between Control group and Research group when the patients were stratified into stage I (*Figure 1B*), stage II (*Figure 1C*) and stage IIIa (*Figure 1D*). The difference in DFS between Control group and Research group was not
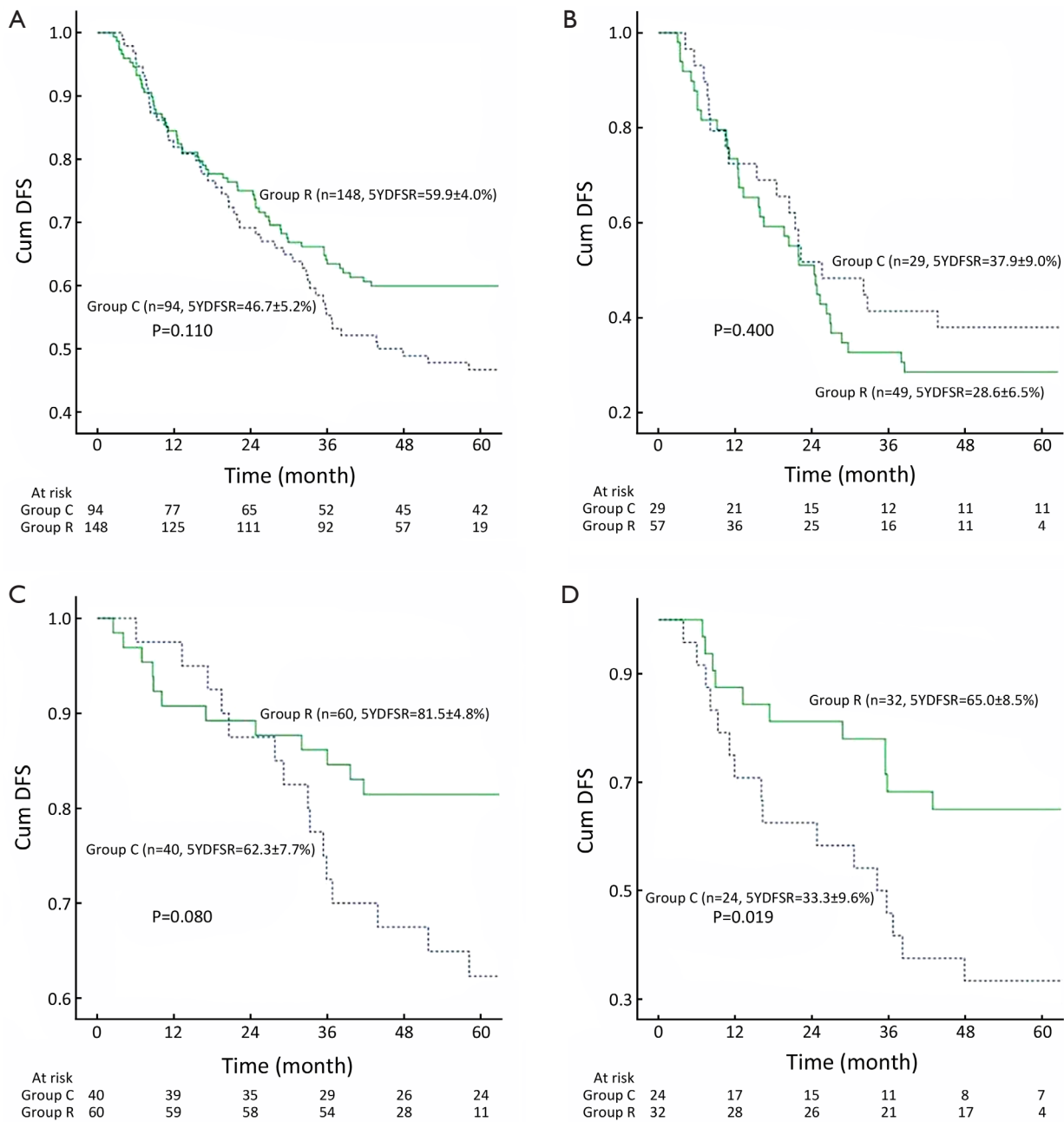
Figure 2 The disease-free survival (DFS) for Control group (Group C) and Research group (Group R). The whole group (A) and the subgroups stratified by pathological stage: (B). 5YDFSR, 5-year DFS rate, stage I (C), stage II (D) and stage IIIa.

significant in the whole group (*Figure 2A*) and in stage IIIa patients (*Figure 2B*). However, DFS in stage I (*Figure 2C*) and stage II (*Figure 2D*) patients tended to be longer in Research group.

In multivariate analysis, the significant factors associated with OS were TNM classification, gender, and histology, as shown in *Table 3*. Meanwhile, TNM classification and histology were significant factors associated with DFS. Quality-related factors, such as the extent of mediastinal lymph node clearance, the number of mediastinal node stations investigated and the resection volume were not significantly correlated with OS or DFS.

Table 3 Cox multivariate analysis of OS and DFS for entire group of lung cancer patients (n=278)

	OS		DFS	
	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)
TNM staging	0.001		0.001	
Stage I	Reference	1.000	Reference	1.000
Stage II	0.015	2.022 (1.143-3.577)	0.001	3.088 (1.742-5.476)
Stage IIIa	0.001	3.496 (2.157-5.666)	0.001	4.073 (2.515-6.598)
Gender				
Female	Reference	1.000	Reference	1.000
Male	0.065	1.522 (0.974-2.377)	0.231	1.329 (0.835-2.118)
Age				
≤60 years	Reference	1.000	Reference	1.000
>60 years	0.339	1.223 (0.810-1.847)	0.854	1.041 (0.679-1.595)
Surgical extent of mediastinal lymphadenectomy				
Control group	Reference	1.000	Reference	1.000
Research group	0.555	0.878 (0.569-1.354)	0.237	0.773 (0.504-1.185)
Resection volume				
Sub-lobectomy	Reference	1.000	Reference	1.000
Lobectomy & pneumonectomy	0.581	1.497 (0.358-6.261)	0.950	0.962 (0.292-3.172)
Lymphovascular invasion				
No	Reference	1.000	Reference	1.000
Yes	0.891	0.963 (0.561-1.653)	0.875	1.046 (0.601-1.820)
Grade				
G0/G1	Reference	1.000	Reference	1.000
G3/G4	0.052	1.527 (0.996-2.342)	0.294	1.270 (0.812-1.986)
Histology	0.020		0.000	
SCC	Reference	1.000	Reference	1.000
ADC	0.014	1.806 (1.125-2.899)	0.000	2.896 (1.736-4.833)
Other	0.017	2.166 (1.145-4.096)	0.017	2.814 (1.422-5.567)
Neo-adjuvant chemotherapy				
No	Reference	1.000	Reference	1.000
Yes	0.171	0.559 (0.243-1.286)	0.079	0.450 (0.185-1.097)
Adjuvant chemotherapy				
No	Reference	1.000	Reference	1.000
Yes	0.159	0.734 (0.478-1.129)	0.433	1.200 (0.761-1.892)
Number of mediastinal lymph node stations investigated				
0-2 stations	Reference	1.000	Reference	1.000
≥3 stations	0.623	0.881 (0.531-1.462)	0.629	1.147 (0.659-1.996)

OS, overall survival; DFS, disease-free survival; 95% CI, 95% confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma.

Discussion

The quality of lymphadenectomy is a comprehensive concept, in which the surgeons' understanding and practice form a solid foundation. High quality of lymph node investigation is supposed to lead to more accurate staging. In this retrospective study, 75.9% of the whole group received lymph node resection at more than three N2 stations; the median number of mediastinal lymph nodes and total lymph nodes collected was 13 and 22, respectively. Research group received a more radical extent of mediastinal lymphadenectomy compared with Control group, as indicated by investigation of a larger number of N2 stations and harvesting of more lymph nodes (N2 or total). More cases attaining National Comprehensive Cancer Network (NCCN) (6) or IASLC criteria for qualified lymphadenectomy occurred in the Research group. Although the Kaplan-Meier curves on OS and DFS both showed a tendency toward slightly improved outcome, they were not statistically different. These results suggest that extended mediastinal lymphadenectomy may not yield a potential therapeutic benefit.

Lymphadenectomy is considered to be a key component of surgical quality; however, several procedures are available, such as SMLD, systematic sampling (SS) and random sampling (7). In stage I NSCLC, lymphadenectomy was associated with increased OS and DFS, compared with that of patients who did not receive lymphadenectomy (8). Gajra *et al*. indicated that SMLD and SS could lead to the collection of a larger number of lymph nodes in stage I NSCLC, and these techniques were associated with improved survival (9). Thus, a certain extent of lymphadenectomy, such as SMLD or SS, seems to secure a survival benefit in early stage lung cancer. However, debate still exists regarding the optimal method for qualified mediastinal lymphadenectomy in lung cancer. Doddoli *et al*. suggested that, compared with sampling, SMLD improved survival in a retrospective study of stage I NSCLC (10). The largest randomized control trial (RCT) in this field, the Z0030 trial, demonstrated that SMLD did not improve survival over SS in patients with no mediastinal and hilar lymph node metastasis (11). Two other smaller trials also suggested that SMLD might not affect OS in lung cancer patients (12,13). Only one RCT trial has demonstrated a survival benefit for SMLD (over sampling) in a cohort of 532 cases; however, the sampling procedure, defined as the removal of suspected nodes larger than 1 cm or hard nodes, was more likely to be random sampling (14).

So far there are no prospective studies on how to perform qualified mediastinal lymphadenectomy for more advanced disease, especially at stage II or IIIa. In this study, more extended lymphadenectomy may not achieve an OS benefit in stage II, even though the PFS in Research group was better than that of Control group, which implies the role of multidisciplinary treatment in this group. The latest American College of Chest Physicians (ACCP) guideline also suggests every patient should have systematic mediastinal lymph node sampling and SMLD may be performed without increased morbidity in early stage lung cancer (15). Thus, both methods may be feasible in dealing with mediastinal lymphadenectomy for clinical early stages. However, for stage IIIa, it is still unknown that whether SMLD could be superior to SS. But at least, complete resection should be advised in single zone N2 node involvement or mediastinal downstage after induction therapy (16).

As SS yielded similar rates of survival and comorbidity compared with SMLD, this raises the question of whether SS represents the lowest, acceptable standard for curative resection in lung cancer. Unfortunately, the evidence is not yet strong enough to reach a conclusion, especially for stage II and stage IIIa patients. In a previous study, we reported that the negative predictive value of SS, in terms of mediastinal lymph node metastasis, was 86.8% for the right side and 95% for the left side. Additionally, the diagnosis after SS was pathologically understaged in 8.2% of cases, compared with staging after SMLD (17). Therefore, further investigation is needed to clarify the indication of SS, which may yield a similar outcome at certain stages for operable lung cancer.

Retrospective analysis and non-randomization are the major limitations of this study. However, to explore the quality improvement of lymphadenectomy, randomization design might put the Control group at risk of insufficient lymph node clearance. It is reasonable to perform the clinical trial in early stage disease. But retrospective analysis is suitable for more advanced disease. The Z0030 trial (14) has provided the strongest evidence to date to suggest that SMLD does not improve survival in patients with stage I lung cancer. However, more studies are needed to explore the effect of lymphadenectomy on the outcome for the advanced lung cancer patients. Sample size was another limitation of the study. A larger sample size study and multicenter participation might reduce the bias for this purpose.

In summary, more radical mediastinal lymphadenectomy

may not lead to an improved oncological outcome for lung cancer treated with R0 resection.

Acknowledgements

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