Original Article

Comparison of lymph node dissection and lymph node sampling for non-small cell lung cancers by video-assisted thoracoscopic surgery

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Background: Video-assisted thoracoscopic surgery (VATS) has been increasingly used in the treatment of lung cancers. But it is still unclear whether mediastinal lymph node dissection (LND) under VATS is safe and feasible. The aim of this study is to figure out whether LND by VATS is safe and feasible.

Methods: Consecutive patients with primary resectable lung cancers referred for lobectomy and LND or sampling by VATS between January 2012 and December 2016 were retrospectively reviewed. Clinicopathological characteristics and perioperative results were collected for statistical analysis.

Results: Seven-hundred and seventy-three VATS lobectomy patients were included in this study, 494 received LND and 279 received lymph node sampling (LNS). There were more male patients, higher pathological T and N stage in the LND group than in the LNS group. Multivariate analysis suggested that clinical N stage higher than cN0 category and LND were independent risk factors for finding pN2 diseases in all lung cancers, while higher than cN0 category, solid or micropapillary component, and LND were independently related to finding pN2 stage in adenocarcinomas. Propensity-score matching rendered 279 pairs of patients with no significant difference in age, gender, co-morbidity, tumor location, or T stage. Although the LND group had longer operation time (128 *vs.* 114 minutes, P<0.001), higher amount of postoperative drainage (920 *vs.* 720 mL, P<0.001), longer postoperative hospital stay (6 *vs.* 4 days, P<0.001) than the LNS group, no difference was observed in overall morbidity or mortality between the two groups.

Conclusions: LND by VATS has acceptable perioperative results but can provide more accurate nodal staging compared with LNS. LND by VATS is safe, feasible, and should be recommended in patients with tumors in clinical N stages higher cN0 category or with more invasive histology.

Keywords: Lung cancer; surgery; lobectomy; video-assisted thoracoscopic surgery (VATS)

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Introduction

Lung cancer is the leading cause of cancer-related deaths and nearly 1.6 million deaths are expected worldwide annually (1). Lobectomy with lymph node sampling (LNS) or lymph node dissection (LND) is generally accepted as the standard procedure for medically operable patients with NSCLC. There have been increasing evidences showing that compared to open thoracotomy, lobectomy via video-assisted thoracoscopic surgery (VATS) is associated with less postoperative pain, shorter chest drain duration and hospital

stay (2,3). The long-term efficacy of lobectomy for clinical stage I lung cancer performed by VATS is not inferior to thoracotomy (4). It has now become recommended approach in clinical guidelines (5), accounting for more than 15% of lobectomies performed in the United States (6) to over 50% in large volume centers in China (7). However, one critical concern about minimally invasive lung cancer surgery is whether appropriate LND could be achieved by VATS (8,9). Although several randomized trials have compared the surgical and oncological outcomes between LNS and LND (10-14), most surgical approaches in those studies were open thoracotomy. It is still controversial whether LND by VATS is safe and feasible. We hereby performed a retrospective study to compare the efficacy of LND and LNS in VATS lobectomy patients with resectable NSCLC and their perioperative results using propensity-score matching.

Methods

Patients with primary lung cancers referred for lobectomy and LND or sampling by VATS at our unit between January 2012 and December 2016 were retrospectively selected from a prospectively maintained database. All patients were diagnosed with clinical stage I–IIIa diseases before operation. Preoperative workup included computed tomography (CT) of the chest, neck and abdominal ultrasonography for all the patients in this study. Patients with solid pulmonary nodule or mixed ground glass opacity (GGO) with more than 50% solid component also had magnetic resonance imaging (MRI) of brain and positron emission tomography (PET) scan. Fibrous bronchoscopy was not indicated in lesions located in the outer 1/3 of the pulmonary parenchyma. Mediastinoscopic biopsy or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was only performed for patients with suspected positive bulky mediastinal lymph nodes basing on PET scan. Histological confirmed N2 diseases before operation were excluded in this study. So the clinical N2 diseases were diagnosed only by image studies. All patients received lobectomy by VATS with tri-portal approach, with systemic LND or sampling, with patients receiving wedge resection, segmentectomy, bilobectomy and pneumonectomy excluded from the study. The extent and definition of LND and sampling was explained and performed according to the European Society of Thoracic Surgeons (ESTS) guideline (15). LND was indicated in patients with solid pulmonary nodule and mGGO with more than 50% solid component. A skeletonized LND removing all mediastinal lymph nodes together with surrounding fatty tissue was carried out according to the same standard in open surgery (13). Mediastinal LNS was reserved for patients with pure GGO or mixed GGO with less than 50% solid component or those considered of high surgical risks because of compromised cardiopulmonary functions. But hilar and intrapulmonary lymph nodes were all excised as the minimum requirement. All the procedures were performed by surgeons from a single team.

Comparisons between proportions were made by Pearson's χ^2 test or Fisher's exact test. Continuous variables were described as means and standard deviations or medians and range and Student *t*-test or Mann-Whitney test was used for comparison between two groups. Potential risk factors with a P value less than 0.1 were entered into multivariate analysis by logistic regression to identify independent risk factors for mediastinal lymph node metastasis. As the baseline characteristics in the two groups were not balanced, a propensity-score matched analysis was performed to compare perioperative results after LND or LNS. Patients were matched at a ratio of 1:1 with caliper distance limited to 20%. All statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). P values were 2-sided and those less than 0.05 were accepted as statistically significant.

Results

Among 773 VATS lobectomy patients included in this study, 494 (63.9%) patients received LND and 279 (36.1%) patients had LNS. Patient demographics and tumor characteristics are summarized in *Table S1*. There were more male patients, more lower lobe and higher pathological T/N stage tumors, more squamous histology but less adenocarcinomas in the LND group than in the LNS group. Rate of adenocarcinomas with micropapillary or solid predominant component was also significantly higher in the LND group than in the LNS group. There was no significant difference in age or co-morbidity between two groups.

Perioperative results are shown in *Table 1*. More lymph nodes and number of stations of nodes were harvested in the LND group than in the LNS group. After surgery, only one patient died of pulmonary embolism in the LND group. Comparing to the LNS group, patients in the LND group had significantly longer operation time, higher amount of postoperative drainage, longer postoperative hospital stay

Table 1 Perioperative results before propensity-score matching

Perioperative results	Patients with LND	Patients with LNS	P value
Case	494	279	
Operation time (min)	128 [42–304]	114 [33–272]	<0.001
Blood loss (mL)	100 [50–1,200]	100 [50–1,800]	0.068
Drainage (mL)	920 [30–10,852]	720 [12–5,020]	<0.001
LOS (day)	6 [3–72]	5 [2–29]	<0.001
Station of LN harvested	6.31±1.43	5.18±1.47	<0.001
Number of LN harvested	12.17±6.17	8.49±4.07	<0.001
Overall morbidity	51 (10.3%)	16 (5.7%)	0.029
Functional complications	40 (8.1%)	20 (7.2%)	0.643
Airleak	21 (4.3%)	8 (2.9%)	
Arrhythmia	15 (3.0%)	3 (1.1%)	
PE	3 (0.6%)	8 (2.9%)	
Delirium	1 (0.2%)	0 (0%)	
Stroke	0 (0%)	1 (0.4%)	
Technical complications	15 (3.0%)	0 (0%)	N/A
Chylothorax	7 (1.4%)	0 (0%)	
BPF	3 (0.6%)	0 (0%)	
RLNP	3 (0.6%)	0 (0%)	
Esophageal fistula	2 (0.4%)	0 (0%)	

LNS, lymph node sampling; LND, lymph node dissection; LOS, length of stay; BPF, bronchopleural fistula; PE, pulmonary embolism; RLNP, recurrent laryngeal nerve paralysis; LN, lymph node; N/A, not available.

and higher morbidity rate.

Propensity-score matching resulted in a final cohort of 558 patients (279 LND and 279 LNS) for further analysis of peri-operative results (*Table 2*). No statistics significance was observed in clinicopathological characteristics between the two groups except for the pN stage (*Table 3*). Number of lymph nodes harvested and number of stations of nodes dissected were still significantly higher in the LND group than in the LNS after matching. Patients in the LND group still had significantly longer operative time (but only 14 minutes), more postoperative drainage (200 mL), and longer postoperative hospital stay (1 day only) than patients in the LNS group. Statistical significance in post-operative morbidity was no longer observed between the two groups (8.6% after LND *vs.* 4.7% after LNS). However, technical complications such as bronchopleural fistula, esophageal fistula, chylothorax, and recurrent laryngeal nerve paralysis were seen only in the LND group.

Among all 773 patients enrolled in this study, 101 patients had pN2 lung cancers. Clinicopathological characteristics of patients with or without pN2 disease are shown in *Table 4*. Significantly more male, more left sided and higher clinical N stage tumors were observed in patients with pN2 disease. Multivariate analysis suggested that clinical N stages higher than cN0 category and LND were independent risk factors for detecting pN2 diseases in all lung cancers (*Table 5*).

Since most of the tumors in this series were adenocarcinomas, clinicopathological characteristics of 697 patients with lung adenocarcinoma were then studied separately. Significantly more male, more left sided and higher clinical N stage tumors, and more micropapillary or solid predominant or mucinous lesions were observed in pN2 lung adenocarcinomas (*Table S2*). Upon multivariate analysis, clinical N stages higher than cN0 category, solid or micropapillary component or mucinous adenocarcinoma or fetal adenocarcinoma, and LND were independently

Table 2 Perioperative results after propensity-score matching

Perioperative results	Patients with LND	Patients with LNS	P value
Case	279	279	
Operation time (min)	128 [42–304]	114 [33–272]	<0.001
Blood loss (mL)	100 [50–600]	100 [50–1,800]	0.160
Drainage (mL)	920 [30–10,852]	720 [12–5,020]	<0.001
LOS (day)	6 [3–72]	5 [2–29]	<0.001
Station of LN harvested	6.12±1.40	5.17±1.48	<0.001
Number of LN harvested	11.17±5.77	8.50±4.08	<0.001
Overall morbidity	24 (8.6%)	13 (4.7%)	0.061
Functional complications	17 (6.1%)	14 (5.0%)	0.579
Airleak	8 (2.9)	8 (2.9%)	
Arrhythmia	6 (2.2%)	3 (1.1%)	
PE	3 (1.1%)	2 (0.7%)	
Stroke	0 (0%)	1 (0.4%)	
Technical complications	9 (3.2%)	0 (0%)	N/A
BPF	3 (1.1%)	0 (0%)	
RLNP	3 (1.1%)	0 (0%)	
Chylothorax	2 (0.7%)	0 (0%)	
Esophageal fistula	1 (0.4%)	0 (0%)	

LNS, lymph node sampling; LND, lymph node dissection; LOS, length of stay; BPF, bronchopleural fistula; PE, pulmonary embolism; RLNP, recurrent laryngeal nerve paralysis; LN, lymph node; N/A, not available.

Table 3 Clinical and pathological characteristics of patients after propensity-score matching

Characteristics	Patients with LND	Patients with LNS	P value
Case	279	279	
Gender: male/female	109/270	107/172	0.862
Age	59.8±8.8	59.1±9.2	0.354
Co-morbidity	131 (47.0%)	143 (51.3)	0.310
HBP	63 (22.6%)	72 (25.8%)	0.374
DM	26 (9.3%)	33 (11.8%)	0.335
COPD	7 (2.5%)	6 (2.2%)	0.559
CHD	4 (1.4%)	2 (0.7%)	0.686
Arrhythmia	11 (3.9%)	12 (4.3%)	0.831
History of MT	7 (2.5%)	11 (3.9%)	0.338
Obesity	6 (2.2%)	8 (2.9%)	0.588
Smoke	7 (2.5%)	14 (5.0%)	0.119
Side: left/right	82/197	87/192	0.645
Lobe: upper/middle/lower	174/39/66	168/41/70	0.872
pT stage: T1(Tis)/T2/T3	214/57/8	216/58/5	0.701

HBP, high blood pressure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; MT, malignant tumor; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LNS, lymph node sampling; LND, lymph node dissection.

Table 4 Clinical and pathological characteristics of patients with pN2 lung cancers

Characteristics	Patients with N2	Patients without N2	P value
Case	101	672	
Gender: male/female	56/45	301/371	0.045
Age	61.3±9.4	59.2±9.4	0.064
Location			0.161
RUL	36 (11.8%)	270 (88.2%)	
RML	7 (7.9%)	82 (92.1%)	
RLL	16 (12.1%)	116 (87.9%)	
LUL	24 (18.3%)	107 (81.7%)	
LLL	18 (15.7%)	97 (84.3%)	
Side: left/right	42/59	204/468	0.026
Lobe: upper/middle (lower)	60/41	377/295	0.532
cTstage: cT1/cT2/cT3	57/43/1	482/179/11	0.004
cNstage: cN0/cN1/cN2	62/21/18	610/45/17	<0.001
Histology: ad/sq/other NSCLC	89/9/3	608/48/16	0.759
Lymph node: LND/LNS	82/19	412/260	<0.001

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; NSCLC, non-small cell lung cancer; LNS, lymph node sampling; LND, lymph node dissection.

Table 5 Multivariate analysis for risk of pN2 in lung cancer and lung adenocarcinoma

Variable	P value	OR	95% CI
NSCLC			
Gender	0.969	0.991	0.622–1.578
Age	0.349	1.012	0.987–1.038
Side	0.119	0.694	0.438–1.099
cTstage	0.299		
cT1 (Ref)			
cT2	0.796	1.069	0.746–1.767
cT3	0.140	0.195	0.022–1.710
cNstage	0.000		
cN0 (Ref)			
cN1	0.000	4.345	2.338–8.074
cN2	0.000	8.572	3.818–19.246
LNS/LND	0.001	2.472	1.423–4.295
Constant	0.000	0.033	
ad			
Gender	0.940	0.981	0.589–1.633
Age	0.529	1.009	0.982–1.037
Side	0.037	0.582	0.350–0.968
cTstage	0.731		
cT1 (Ref)			
cT2	0.938	0.978	0.563–1.699
cT3	0.429	0.361	0.029–4.501
cNstage	0.000		
cN0 (Ref)			
cN1	0.000	5.206	2.562–10.576
cN2	0.000	6.294	2.326–17.032
Histology	0.000		
Histology (Ref)			
Histology [1]	0.000	2.914	1.609–5.278
Histology [2]	0.000	5.598	2.977–10.526
LNS/LND	0.020	2.081	1.122–3.859
Constant	0.000	0.029	

NSCLC, non-small cell lung cancer; LNS, lymph node sampling; LND, lymph node dissection; ad, lung adenocarcinoma; Hisology (Ref), atypical adenomatous hyperplasia, adenocarcinoma *in situ*, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, acinar predominant adenocarcinoma without micropapillary component, papillary predominant adenocarcinoma without micropapillary component; Histology [1], adenocarcinoma with micropapillary component; Histology [2], solid predominant adenocarcinoma, invasive mucinous adenocarcinoma, fetal adenocarcinoma.

related to finding pN2 stage in adenocarcinomas (*Table 5*). However, due to the low rate of mucinous and fetal subtype in all adenocarcinomas, it is safe to only conclude solid or micropapillary component as an independent risk factor for detecting pN2 diseases in adenocarcinomas.

Discussion

In this study we carried out a propensity-score matched analysis to compare perioperative results between LND and LNS by VATS. Although LND was associated with statistically longer operation time, more postoperative drainage, and longer postoperative stay than LNS, the differences were of limited clinical significance. And difference in overall morbidity rates was only of borderline significance after LND and LNS. However, technical complications such as bronchopleural fistula, esophageal fistula, chylothorax, and recurrent laryngeal nerve paralysis were seen only in the LND group. On the other hand, multivariate analysis revealed higher clinical N stage category as an independent predictor for pN2 disease in all histologies, and micropapillary and solid predominant subtypes were found to be independent risk factors for pN2 involvement in lung adenocarcinomas. In both overall analysis or in adenocarcinomas specifically, LND turned out to be an independent risk factor for detecting pN2 nodal status.

One major concern for LND is whether it would increase surgical risks. It is still unclear whether LND by VATS is as safe as LNS. In the meantime, it is generally accepted that LND is indispensible for accurate pathologic staging. Previous study also proved mediastinal LND might have survival advantage when comparing with LNS in patients with resectable NSCLC (16). With minimally invasive surgery increasingly often used in management of lung cancers, concern has also been raised on whether similarly adequate nodal dissection could be accomplished under VATS as in open thoracotomy (17-19), making it necessary to evaluate the safety and efficacy of LND in VATS lobectomy.

In the current study, all patients received VATS lobectomy. And propensity-score matching was used in analysis of perioperative outcomes to reduce the potential influence of confounding biases to the greatest extent. Mean operation time was prolonged for merely 14 minutes, which was similar to the result of the ACOSOG Z0030 trial (10). Average postoperative drainage amount increased by only 200 mL in total, and hospital stay was prolonged for only 1 day after operation. These results suggest that LND under VATS has limited additional impact on the operative process or postoperative course, as compared with LNS only.

In our study only one patient died of pulmonary embolism after surgery, which was unrelated to extent of nodal dissection. Overall morbidity for LND and LNS was 10.3% and 5.7% in all patients, much lower than in the ACOSOG Z0030 trial (10). Several reasons may account for this result. First of all, only lobectomy cases were included in our study, while there were 42 pneumonectomies and 42 bilobectomies in the ACOSOG Z0030 trial. Second, surgical approach in our patients was solely by VATS, while 90% patients in the ACOSOG Z0030 trial received open thoracotomy. Lastly, the two studies were carried out in different time period. Continuing improvement in operative techniques and postoperative management might also have contributed to decreased morbidity.

Although no statistics significance was observed in overall morbidity between the two matched groups, certain technical complications such as bronchopleural fistula, esophageal fistula, chylothorax, and recurrent laryngeal nerve paralysis were noticed only in the LND group. Satoh proposed that decreased blood supply to the bronchial stump contributed to BPF (20). In this concern, ligation of bronchial artery during skeletonized LND in our patients might have affected the blood supply to the bronchus and increased the risk of BPF. Two patients developed small esophageal fistula after LND. Since there was no tumor invasion into the esophagus in these two cases, most probably this was caused by thermal injury from harmonic scalpel during LND in the subcarinal area. Incidence of chylothorax after LND was reported to be 2.1%-2.4%, with a higher incidence on the right side than on the left side (21,22). In our study, chylothorax happened in 1.4% cases and all of them were on the right side. It is likely due to damage of the lymphatic branches in the right upper mediastinum during dissection of 2R and 4R lymph nodes. Vocal cord paralysis was previously reported to be 3.7–31% in patients who underwent thoracic surgery, with a higher incidence on the left side (23-25). All cases of recurrent laryngeal nerve paralysis happened on the left side in our study. This is likely related to the location of the recurrent nerves as it is close by lymph node stations 4 and 5 on the left side but posterior to the vagus nerve on the right side where nodal dissection is mainly carried out anteriorly. These technical complications may be related to the skeletonized mediastinal dissection which has been our standard procedure. Care should be taken in the future

to avoid the surgical risks associated with these technical problems.

In our study in VATS lobectomy patients, significantly more number (12.2 *vs.* 8.5, P<0.001) and stations (6.3 *vs.* 5.2, P<0.001) of lymph nodes were resected in the LND group than in the LNS group. Upon multivariate risk analyses for pN2 disease, LND turned out to be an independent predictor both in all lung cancer histologies and in adenocarcinomas alone. The results indicated that systemic nodal dissection may help increase the accuracy of nodal staging in minimally invasive lung cancer surgery. Although only 4.5% patients were staged as cN2 before surgery in this study, 16.8% and 6.8% of them turned out to have N2 disease after LND and LNS (P<0.001). Our result was different from the ACOSOG Z0030 trial which showed merely 4% upstaging after LND (10). But in the ACOSOG Z0030 trial only patients with T1-2 tumors and non-hilar N1 were included, mediastinoscopy was used more often, and randomization was after negative mediastinal nodal sampling. The results are therefore not generalizable to patients staged radiographically or those with higher T stage tumors (10). It is interesting to notice that although clinical T staging was associated with higher rate of pN2 both in all lung cancers and in adenocarcinomas alone, it was not revealed as an independent risk factor for detecting pN2 disease in multivariate analyses. Previous study also showed the size of lesions was associated with risk of nodal involvement and it was the rate of lymph node metastasis that delineate the survival difference among different size categories in lung cancers (26). Preoperative N staging in our patients depended mostly on imaging studies, and PET scan or mediastinoscopy was not routinely used before operation, which explained for the high LND rate (63.9%) in this series (27). In addition to clinical N staging, LND was also an independent predictive factor for revealing pN2 disease. The findings of our study indicate that adequate LND should still be the surgical standard in radiographically staged patients and can be achieved by VATS as well as in open thoracotomy.

In the current series, no patient with AIS, MIA, or lepidic dominant adenocarcinomas were found to have pN2 disease, which was in accordance with the existing literatures (28-30). N2 involvement was found only in 6.6% and 10.5% of patients with papillary and acinar adenocarcinomas. But in micropapillary or solid dominant adenocarcinomas rate of mediastinal nodal metastasis was as high as 24.0% and 40.3%. Upon multivariate analysis in adenocarcinomas, histology subtypes was also revealed as an independent risk factor for N2 disease. Considering that patients with cN1 and cN2 tumors were associated with significantly increased risk of having pN2 metastasis than patients with cN0 tumors in both multivariate analysis, it seems that LNS may be acceptable for patients with cN0 tumors, and those with adenocarcinomas without micropapillary or solid component could be exempted from systemic LND and its associated surgical risks. But for patients with tumors in higher clinical N stage categories or more invasive histology, LND is still indispensible to ensure accurate tumor staging and completeness of resection.

There were certain limitations in this study, given its retrospective nature. Selection biases in treatment allocation were inevitable even though propensity-score matching was used. More patients with solid pulmonary nodule and mixed GGO with solid component more than 50% had LND than LNS, but this was less likely to be related to surgical morbidity. And upon multivariate analysis, LND was still found to be an independent predictive factor for detecting pN2 diseases. With minimally invasive approaches increasingly accepted in lung cancer surgery, a prospective study comparing LND and LNS under VATS would be helpful to further elucidate the safety and value of LND.

In conclusion, LND by VATS has acceptable perioperative results comparing with LNS. And systemic nodal dissection under VATS can help improve accuracy of staging by detecting more N2 disease as it does in open surgery. Although its long-term influence on patient survival still awaits further follow-up, LND should be an indispensable part of both minimally invasive and open surgery for NSCLC, especially those in higher clinical N categories and those with more invasive histologies. Since LND could be carried out in equal safety and efficacy under VATS as in open surgery, it should be taken as an integrated part of minimally invasive surgery for the treatment of resectable NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Institutional Review Board of the hospital (No. ks11318) and written

informed consent was obtained from all patients.

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Supplementary

Table S1 Clinical and pathological characteristics of patients before propensity-score matching

Characteristics	Patients with LND	Patients with LNS	P value
Case	494	279	
Gender: male/female	250/244	107/172	0.001
Age	60.0±9.5	59.1±9.2	0.199
Co-morbidity	246 (49.8%)	143 (51.3%)	0.932
HBP	126 (25.5%)	72 (25.8%)	
DM	49 (9.9%)	33 (11.8%)	
COPD	14 (2.8%)	6 (2.2%)	
CHD	7 (1.4%)	2 (0.7%)	
Arrhythmia	14 (2.8%)	12 (4.3%)	
History of MT	12 (2.4%)	11 (3.9%)	
Obesity	17 (3.4%)	8 (2.9%)	
Smoke	18 (3.6%)	14 (5.0%)	
Side: left/right	158/336	88/191	0.859
Lobe: upper/middle/lower	269/48/177	168/41/70	0.003
pT stage: T1(Tis)/T2/T3	267/199/28	216/58/5	<0.001
pN stage: N0/N1/N2	380/32/82	244/16/19	<0.001
Histology			0.007
ad	433 (87.7%)	264 (94.6%)	<0.001
AAH/AIS/MIA	28 (5.7%)	60 (21.5%)	
LPA	16 (3.2%)	29 (10.4%)	
APA	136 (27.5%)	74 (26.5%)	
PPA	107 (21.7%)	60 (21.5%)	
MA	82 (16.6%)	22 (7.9%)	
SPA	50 (10.1%)	12 (4.3%)	
IMA	12 (2.4%)	7 (2.5%)	
FA	2 (0.4%)	0 (0%)	
sq	46 (9.3%)	11 (3.9%)	
Other NSCLC	15 (3.0%)	4 (1.4%)	

HBP, high blood pressure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; MT, malignant tumor; LNS, lymph node sampling; LND, lymph node dissection; ad, adenocarcinoma; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant adenocarcinoma; APA, acinar predominant adenocarcinoma without micropapillary component; PPA, papillary predominant adenocarcinoma without micropapillary component; MA, adenocarcinoma with micropapillary component; SPA, solid predominant adenocarcinoma with or without micropapillary component; IMA, invasive mucinous adenocarcinoma; FA, fetal adenocarcinoma; sq, squamous cell carcinoma; other NSCLC, adenosquamous carcinoma, pleomorphic carcinoma, carcinoid, large cell carcinoma and lymphoepithelial carcinoma.

Table S2 Clinical and pathological characteristics of patients with pN2 lung adenocarcinoma

Characteristics	Patients with N2	Patients without N2	P value
Case	89	608	
Gender: male/female	46/43	242/366	0.033
Age	61.0±9.7	59.3±9.1	0.097
Location			0.100
RUL	33 (11.6%)	252 (88.4%)	
RML	5 (6.2%)	76 (93.8%)	
RLL	14 (12.1%)	102 (87.9%)	
LUL	21 (18.6%)	92 (81.4%)	
LLL	16 (15.7%)	86 (84.3%)	
Side: left/right	37/52	178/430	0.019
Lobe: upper/middle (lower)	54/35	344/264	0.466
cTstage: cT1/cT2/cT3	52/36/1	435/169/4	0.004
cNstage: cN0/cN1/cN2	55/20/14	552/39/17	<0.001
Histology			<0.001
AAH/AIS/MIA	0 (0%)	88 (100%)	
LPA	0 (0%)	45 (100%)	
APA	22 (10.5%)	188 (89.5%)	
PPA	13 (7.6%)	158 (92.4%)	
MPA	25 (24.0%)	79 (76.0%)	
SPA	25 (40.3%)	37 (59.7%)	
IMA	3 (15.8%)	16 (84.2%)	
FA	1 (50.0%)	1 (50.0%)	
Lymph node: LND/LNS	17/72	249/359	<0.001

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LNS, lymph node sampling; LND, lymph node dissection; ad, adenocarcinoma; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant adenocarcinoma; APA, acinar predominant adenocarcinoma without micropapillary component; PPA, papillary predominant adenocarcinoma without micropapillary component; MA, adenocarcinoma with micropapillary component; SPA, solid predominant adenocarcinoma; IMA, invasive mucinous adenocarcinoma; FA, fetal adenocarcinoma; LNS, lymph node sampling; LND, lymph node dissection.