Original Article

Therapeutic value of lymph node dissection for right middle lobe non-small-cell lung cancer

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Background: Superior mediastinal and #11i lymph node (LN) metastases are adverse prognostic factors in patients with middle lobe lung cancer. We aimed to clarify the benefit of thorough lymphadenectomy by LN station or zone in middle lobe non-small-cell lung cancer (NSCLC).

Methods: Among 295 patients who underwent pulmonary resection and thorough lymphadenectomy for primary right middle lobe (RML) NSCLC at two institutions, we enrolled 68 patients (33 men, 35 women) and retrospectively studied their data. We divided each N1 location (i.e., #10, #11s and #11i) into N1(–)N2(+) and N1(+)N2(+) and divided the #12m location into N1(+)N2(–), N1(–)N2(+) and N1(+)N2(+).

Results: Interlobar node involvement was rare in pN1 NSCLC when compared with that in other N1 nodes. Lymph node dissection (LND) was beneficial when the hilar zone (HZ)/interlobar zone (IZ) LNs were located at the intermediate point of the upper zones (UZs) and subcarinal zones (SCZs), with the therapeutic benefit at the SCZ being 2.8-fold higher than that at the UZ and 9.7-fold higher than that at the lower zone (LZ). Furthermore, LND evidently had greater therapeutic value for the SCZ than the UZ, which was compatible with skip N2 metastases.

Conclusions: For middle lobe NSCLC, mediastinal LND should be considered a priority in the SCZ than in the UZ. Moreover, the HZ/IZ is central to unfavourable prognoses in patients with pN2 middle lobe NSCLC.

Keywords: Lymph node dissection (LND); right middle lobe (RML); non-small-cell lung cancer (NSCLC); therapeutic index (TI); lung cancer

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Introduction

The standard treatment for non-small-cell lung cancer (NSCLC) involves lobectomy or pneumonectomy with radical lymphadenectomy (1). However, long-term outcomes following radical mediastinal lymph node dissection (LND) remain controversial, with two major randomized studies producing contradicting results (2,3). Mediastinal LND is essential for accurate staging and improved survival over sampling alone (2), but it does not improve survival in early-stage NSCLC (3). Meanwhile, other retrospective studies have published nodal spread patterns by tumour location (4,5), leading to modified and selective LND becoming increasingly prevalent. Concerns

that tumour location is not predictive of nodal metastasis have resulted in the argument that complete systemic mediastinal LND is the only acceptable intervention (6). The pattern of lymphatic drainage from right middle lobe (RML) NSCLCs extends to both superior and inferior mediastinal lymph nodes (LNs); in fact, a high incidence of metastases to these nodal zones has been reported (7,8). Superior mediastinal and #11i LN metastases have been reported to be significant adverse prognostic factors in patients with middle lobe cancer and are associated with each other (9). However, only a few articles have evaluated the therapeutic value of LND during surgical resection of RML NSCLCs. For gastric cancer, Sasako *et al.* evaluated the therapeutic effect of LND on the basis of incidence of metastasis and 5-year survival rates of those with nodal deposits at a particular station, irrespective of nodal metastasis to other LN stations including para-aortic nodes, to prevent selection bias (10). We therefore applied their methods to evaluate the therapeutic impact of LND on each nodal station or zone for advanced RML NSCLC.

Methods

Patients

We retrospectively studied patients with pN1–2 primary RML NSCLCs. All patients underwent middle lobe resection (at least lobectomy) with thorough mediastinal LND between January 1980 and December 2011. Participants were enrolled at the Aichi Cancer Center Hospital or the Cancer Institute Hospital, Japanese Foundation for Cancer Research. We excluded patients who had undergone pre-operative chemotherapy and radiotherapy and prior LN sampling.

Clinical staging data were obtained by chest and abdominal computed tomography, head magnetic resonance imaging, abdominal ultrasound, bone scintigraphy or positron emission tomography. Tumours were staged according to the TNM classification system (11). Pathological examination was based on the 2004 World Health Organization classification (12). LN location was based on the definitions of the Committee of the International Union against Cancer (13); [#, indicated LN number and (+) and (–) represented positive and negative status of the node, respectively.] The institutional review board of each hospital approved this study without the requirement to obtain patient consent because the identity of each individual patient was concealed.

Method for evaluating the therapeutic value of lymph node dissection (LND)

We used the method described by Sasako *et al.* to evaluate the therapeutic value of LND according to the index of the benefit for each station (10). The therapeutic index (TI) for every metastasis to a nodal station was calculated by multiplying its frequency by the 5-year survival rate.

Statistical analysis

All data were analysed using SPSS version 17.0 (SPSS Institute Inc., Chicago, Illinois, USA). Sensitivity and specificity were compared using standard formulas. Differences between two groups were calculated using the Mann-Whitney test. Analysis of survival rates was performed using the Kaplan-Meier method and survival rates between patient groups were compared by the log-rank test. A P value of <0.05 was considered to indicate statistical significance.

Results

Descriptive statistics and survival

There were a total of 295 patients with primary RML NSCLCs during the study period. We included the 68 (23.1%) eligible pN1–2 patients (33 men and 35 women) with LN metastases. The mean age of the patients was 68 years and they had confirmed adenocarcinoma (n=53), squamous cell carcinoma (n=11) and other carcinoma (n=4) (*Table 1*). The pathological nodal statuses were pN0, pN1 and pN2 in 227 (77.0%), 18 (6.1%) and 50 (16.9%) patients, respectively. The median follow-up duration was 1,016 days (range, 42–9,265 days), with the 5-year overall survival (OS) rate significantly higher for pN1 disease than for pN2 disease (58.3% *vs.* 28.6%; P=0.02).

Node metastasis and spread pattern

Table 2 summarizes the frequency of nodal involvement by station. Most were N1 nodes (#10–#14, 80.9%), and the numbers of superior (#2R–#4R, 48.5%) and inferior (#7–#9, 58.8%) mediastinal nodes were comparable. Skip node N2 (SN2) metastases were evident in 13 patients (26.0%), of whom 8 (61.5%) had visceral pleural invasion; the upper zone (UZ) and subcarinal zone (SCZ) were equally involved (P=0.69). For pN1 (n=18), the most frequent site for metastasis was #12m–#14 (15 cases, 83.3%), followed

Table 1 Baseline characteristics of patients with RML NSCLC

Variation	pN1–2 patients (n=68)
Age, mean [range]	68 [32–86]
Sex, male/female	33/35
Histology	
Adenocarcinoma	53
Squamous cell carcinoma	11
Others	4
cN status	
N0	40
N1	18
N2	10

RML, right middle lobe; NSCLC, non-small-cell lung cancer.

Table 2 Distribution of LN metastases in RML NSCLC

Nodes	Zone	Stations	n	Distribution (%)
SMNs	UZ	#2R–#4R	33	48.5
IMNs	—	#7–#9	40	58.8
	SCZ	#7	39	57.4
	LZ	#8–#9	4	5.8
N1Ns	—	#10–#12m	55	80.9
	H/IZ	#10–#11	33	48.5
	PZ	#12m	39	57.4
	—	#10	24	35.3
	—	#11s	10	14.7
	—	#11i	9	13.2
	—	#12m	36	52.9

#, indicates "lymph node number" as defined by the Committee of the International Union against Cancer (14). LN, lymph node; RML, right middle lobe; NSCLC, non-small-cell lung cancer; SMNs, superior mediastinal nodes; IMNs, inferior mediastinal nodes; N1Ns, N1 nodes; UZ, upper zone; SCZ, subcarinal zone; LZ, lower zone; H/IZ, hilar/interlobar zone; PZ, peripheral zone.

by #10 (2 cases, 11.1%) (P<0.01); the lobar nodes (#11s and #11i) were rarely involved (5.6% and 0%, respectively). For pN2 (n=50), the frequency of SCZ and UZ involvement was the same [39 (78.0%) patients *vs.* 33 (66.0%) patients; P=0.18]. Combined metastases to UZ and SCZ occurred in 23 patients (46.0%), whereas lower zone (LZ) metastases were noted in only 4 patients (8.0%). The results for the analysis of pN2 via #10 (n=24; P=0.34; *Figure 1A*), #11s (n=10; P=0.62; *Figure 1B*), #11i (n=9; P=1.00; *Figure 1C*) and #12m (n=36; P=0.35; *Figure 1D*) showed no significant difference between UZ and LZ among each N1 node category.

Predictive benefit of lymph node (LN) involvement in middle lobe non-small-cell lung cancer (NSCLC)

The 5-year OS rates of pN2 disease by LN zones were 10.5% (n=33) for UZ, 24.7% (n=39) for SCZ and 6.5% (n=23) for both UZ and SCZ. The 5-year OS rate was not significantly better for SN2 metastases compared with that for non-SN2 metastases (P=0.30). The 5-year OS rates were 38.9% for SN2 single-station (SS) metastases [N1(–) N2(+) (n=9)], 36.0% for non-SN2-SS metastases [N1(+) N2(+) (n=18)], 0.9% for non-SN2 multiple-station (MS) metastases [N1(+)N2(+) (n=19)] and 0% for SN2-MS metastases [N1(–)N2(+) (n=4)]. Comparison of most of these 5-year OS rates were not significant (P=0.06); however, a significant difference was noted between SS and MS 5-year OS rates (37.7% *vs.* 6.5%; P=0.01) (*Figure 2*).

Metastasis and 5-year survival rate

We explored the distribution of pN2 (n=50) and prognosis by N1 category. The #10, #11s, #11i and #12u populations accounted for 91.7%, 90.0%, 100% and 63.9%, respectively. Cases with pN2 metastases were divided according to N1 locations as N1(–)N2(+) and N1(+)N2(+). Cases with pN1–2 metastases were divided according to the #12m location as N1(+)N2(–), N1(–)N2(+) and N1(+)N2(+). The 5-year OS rates according to the divisions of pN2 and pN1–2 metastases are summarized in *Figure 3*.

Therapeutic value of lymph node dissection (LND) and associated clinicopathological features

SCZ (24.7%) and LZ (25.0%) nodal involvements had equivalent 5-year OS rates to hilar/interlobar zone (H/IZ) involvement (24.5%). The 5-year OS was best for the peripheral zone (PZ, 12m–#14) (36.3%), and worst for UZ (10.5%). Zone-specific prognostic tendency was identified by the distance of the primary tumour from the lymphatic location. The benefits of LND are summarized in *Figure 4*. The TI for SCZ (14.2) was superior to that for H/IZ (11.9), 2.8-fold higher than that for UZ and 9.7-fold higher than that for LZ. In pN2 NSCLC, the TI for the H/IZ positions #10, #11s and #11i fluctuated from 1.9 to 6.3 (*Figure 4*).

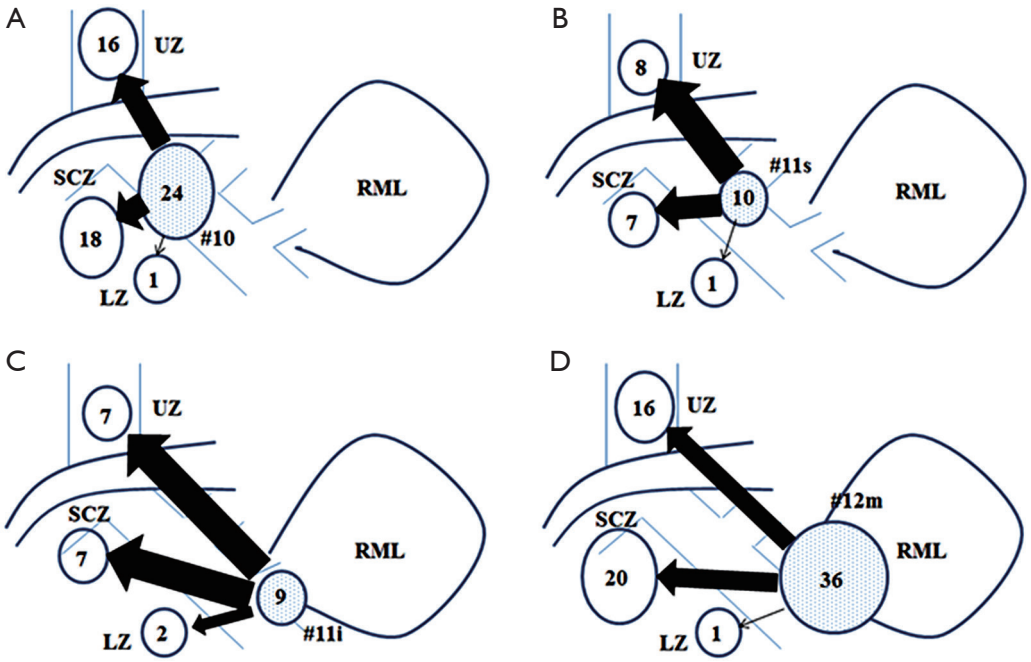

Figure 1 Distribution of metastatic nodes in pN2 NSCLC. (A) Hilar LN (#10); (B) interlobar LN, superior (#11s); (C) interlobar LN, inferior (#11i); and (D) lobar LN (#12m). #, lymph node number. LN, lymph node; NSCLC, non-small-cell lung cancer.

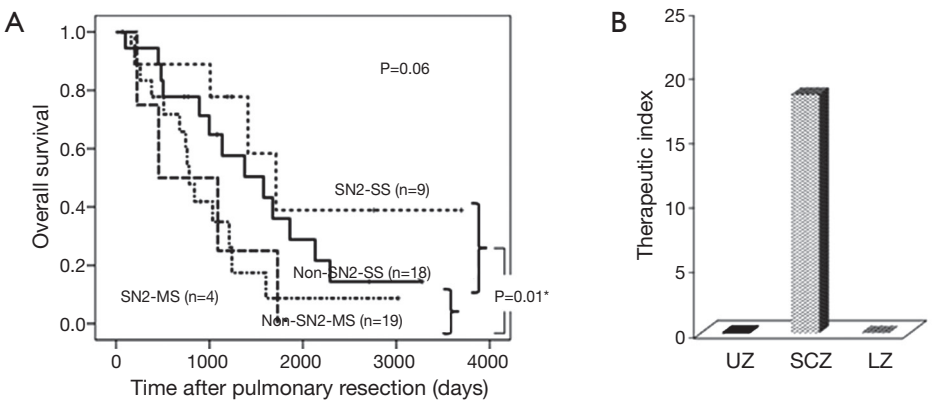

Figure 2 Kaplan-Meier plots of OS based of N2 LN metastases in NSCLC and the index of estimated benefit from LND in skip N2. (A) Black line, non-SN2-SS metastasis; dotted, SN2-SS metastasis; black and dotted, non-SN2-MS metastasis; short and long dotted, SN2-MS metastasis (P=0.06). Parentheses between SS and MS indicate P=0.01*; (B) graphs correspond to the TI at each zone. OS, overall survival; LN, lymph node; NSCLC, non-small-cell lung cancer; LND, lymph node dissection; SN2, skip node N2; SS, single station; MS, multiple stations; TI, therapeutic index.

Regional LNs defined as N2 status (SCZ, #7) by the American Joint Committee on Cancer classification system had a higher TI that than for those designated as N1 (H/IZ, #10, #11s, #11i). Furthermore, the TI for SCZ in patients with SN2 metastases was 1.3-fold higher than that in patients with pN2, but there was no expectation for UZ and LZ involvement (*Figures 2B*,*4*). The correlation between the clinicopathological features and TI for the pN2 zone [left UZ (LUZ) and SCZ] is shown in *Figure 5*. According to TI, LND for LUZ was not efficient for patients with clinical N1–2 (cN1–2) disease (*Figure 5A*); therefore, the patients were divided into two groups by tumour size. Although a

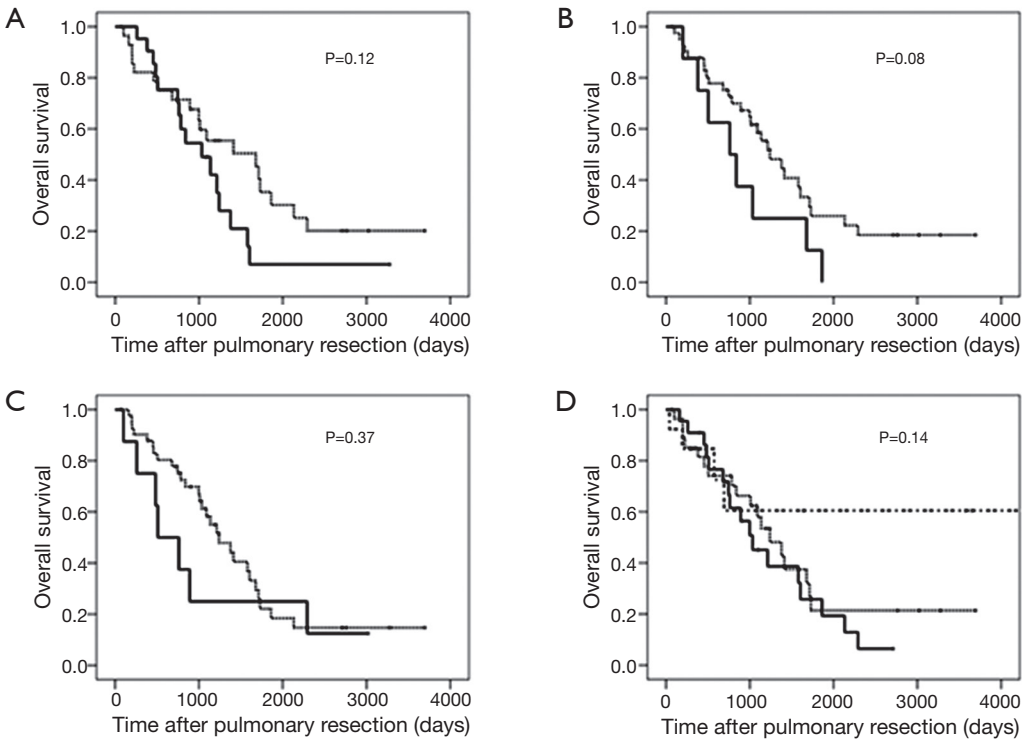

Figure 3 Kaplan-Meier graphs of OS in patients with RML NSCLC. (A) Black line, #10(+)N2(–); dotted, #10(–)N2(+), (P=0.12); black line, #11s(+)N2(–); dotted, #11s(–)N2(+), (P=0.08); black line, #11i(+)N2(–); dotted, #11i(–)N2(+), (P=0.37); black line, #12u(+)N2(–); dotted, #12u(–)N2(+); black and dotted, #N1(+), (P=0.14). #, lymph node number; (+) and (–), positive and negative status of the node, respectively. OS, overall survival; RML, right middle lobe; NSCLC, non-small-cell lung cancer.

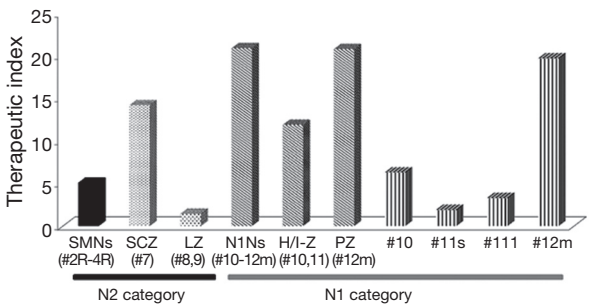

Figure 4 Index of estimated benefit from LND in middle lobe pN2 NSCLC. Graphs correspond to the TI at pN2 category (right, black) and pN1 category (left, grey). #, lymph node number. LND, lymph node dissection; NSCLC, non-small-cell lung cancer; TI, therapeutic index.

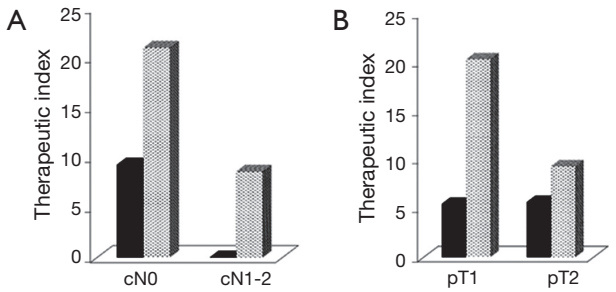

Figure 5 Index of estimated benefit from LND in middle lobe pN2 NSCLC with various issues. Graphs correspond to the TI in patients with cN1 or cN1–2 (A) and in those with pT1 or pT2 (B). Black chart, upper zone; dotted, subcarinal zone. LND, lymph node dissection; NSCLC, non-small-cell lung cancer; TI, therapeutic index.

difference in tumour size did not influence the TI for UZ, the TI for SCZ in patients with a pT1 tumour was 2.2-fold higher than that in patients with a pT2 tumour (*Figure 5B*).

Discussion

The reported frequency of metastasis for RML NSCLC is inconsistent. RML NSCLCs have been reported to be more likely to have N1 disease (33%) and pN2 disease (15%), with the latter result being consistent with ours (14). Furthermore, in the study by Riquet *et al.*, pN1 and pN2 disease occurred in 6.3% and 18.8% of lobotomized patients, respectively (7). However, our results support Yamanaka *et al.*, who reported frequencies of 4.5% (1/22) and 40.9% (9/22), respectively (15). However, it is important to note that most of these analyses have been confounded by limited data (7,14,15).

We have described three points about nodal metastases from middle lobe cancer. First, UZ and #11i metastases present significant adverse prognostic factors in patients with middle lobe lung cancer. Second, #11i metastases may result from mediastinal metastases (9). This is supported by our results that show rare involvement of the interlobar nodes of the middle lobe. Third, the prognostic impact must be different from that for other lobes (9). The findings of our study were consistent with those of other reports, with the prognosis being significantly worse for patients with mediastinal LN metastases than for those with N1 nodes only.

When examining whether the path of LN spread affected prognosis, no association existed for mediastinal LN metastases without H/IZ LN involvement, but a tendency did exist for #12. Although H/IZ and PZ belong to the same N1 group, the TI for the former was less. The effect of LND gradually weakened in N1 disease in the order #11i, #11s, #10 and #12m, with a three-fold difference between #10 and #12m.

In the development of an LN mapping system, early controversy centred on whether to classify tracheobronchial #10 nodes as N1 or N2 (16). LNs around the main bronchus have been designated as intermediate, with no distinction between N1 and N2 nodes (17). In this report, the TI for #10 was comparable to that for UZ, but was lower than that for SCZ. Moreover, the incidence of #11s metastases (5.6%) was similar to that reported in a previous study (9). We hypothesized that #11i metastases were retrograde because antegrade drainage to the superior mediastinum from mediastinal metastasis was disturbed. Although classified as pN1 nodes, H/IZ nodes may be handled by surgeons as pN2 disease.

Sasako *et al.* commented that their method attempted to determine the actual benefit of LND and that it circumvented the phenomenon of stage migration in gastric cancers (10). Although ipsilateral hilar and standard mediastinal LND is known to be the standard method of LND for RML NSCLCs, we intend to additionally quantify the role of extensive LND, specifically the priority LN stations or zones during middle lobe resection, using the TI described approximately 20 years ago. However, we considered that the TI was available to evaluate the classification and effectiveness of LND regardless of the number of LN metastases.

We have reported that UZ and SCZ nodes are major metastatic sites and that prognosis is comparable to that of multi-level N2 middle lobe cancer when superior mediastinal LNs is involved (9). Here we observed that the TI was higher for SCZ than for UZ or LZ, implying that precise pathological staging was probably more important than LND, perhaps because these generally need intensive treatment. Consistent with our previous report, patients with cN1–2 and pN2 middle lobe cancer gained little benefit from LND (18). Furthermore, the TIs among pN2 patients with pT1 and pT2 UZ disease were similar, suggesting that the pathological node status was more important than the tumour size as an adverse prognostic factor and that precise pathological staging was again more important than LND. We found no benefit from adjuvant chemotherapy. When planning LND for NSCLC, surgeons must know the expected benefit by nodal station or zone to ensure optimal LND and benefit from adjuvant chemotherapy. When considering which zone to prioritize, the frequencies were the same between UZ and SCZ; surgeons may prefer the latter, based on previous reports. SCZ nodes are more common in RML and lower lobe malignancies (19) and are generally grouped together (20). In addition, RML cancers metastasize to both UZ and SCZ with equivalent frequency (4,14,21). RML malignancies with LNs at the sump location can have metastatic involvement (16), with most LN drainage to the superior rather than the inferior LNs (22). Yamanaka have commented that the pattern of lymph drainage from the middle lobe to the interlobar LNs is similar to that in the basal segments of the lower lobe (15).

Next, we considered whether selective lymphadenectomy was possible. Good therapeutic effectiveness was obtained for SCZ and H/IZ, with benefit from UZ LND being approximately one-third of that from SCZ LND. Although

the numerical value was low for pre-operatively diagnosed cN1–2 or pT2 stage RML NSCLC, we considered it sufficient justification for LND. Pre-operative manipulation of patient selection to authentic pN0 by multi-detector row computed tomography (MDCT) was required for selective LND. We previously emphasized the correlation between LN metastases and mediastinal tumour size on MDCT despite evidence from retrospective studies and suggested the need for this manipulation (23). Therefore, our method of cN0 patient selection by MDCT was necessary for selective LND.

The #12u node dissection in RML lobectomy is technically more challenging and requires longer operative time, particularly when performed thoracoscopically. Considering that #12u is usually adjacent to #11s, *en-bloc* resection is often necessary while pulling the superior truncus artery and superior pulmonary vein. In Japan, the incidence of #12u involvement was 9.2% (14/152) in a study that recommended routine dissection in patients with carcinoma of RML, right lower lobe or left lower lobe (24). The TI of LND was calculated as 4.8 in that report, which was compatible with that for UZ and #11s nodes in our study. Although we found no reports regarding #12u metastases confined to the middle lobe, there is plausible evidence for #12u LND in this analysis. Further investigation is necessary to clarify the role of such dissection in RML NSCLCs.

Another important result was related to SN2 metastases in RML, which had equal incidences between UZ and SCZ involvement. The most favourable prognosis was for pN2 with SN2-SS metastases (38.9%), followed by non-SN2 metastases (23.0%). The 5-year OS rate of patients with SN2-MS metastases and involvement of both UZ and SCZ was 0% (n=4). Although no significant difference was found among the three groups, stratified prognosis was identified. The significance of SCZ dissection was higher for patients with SN2 metastases than for those with non-SN2 metastases. In addition, among patients with SN2 UZ involvement, six out of eight survived for less than 5 years post-operatively, whereas the remaining two survived for more than 3 years (mean, 1,216 days). This may be related to the fact that metastases to higher-position nodes are not searched during surgery, which is compatible with previous reports (10). Visceral pleural invasion was not applied to the correlation for middle lobe SN2 metastases because we included pN2 patients, not cIA NSCLC (25).

This study has some limitations, including its retrospective design, small sample size and inclusion of cases from the 1980s. To avoid institutional bias, this study was undertaken at two specialist centres in a cohort with different therapeutic strategies. Moreover, the study required lobectomy with thorough lymphadenectomy as the standard pulmonary resection, thereby precluding generalization. To provide valid prognostic data, a prospective study has been planned.

In conclusion, nodal H/IZ involvement in RML NSCLC had a tendency towards unfavourable prognosis. Interlobar node involvement was rare in comparison with hilar and lobar nodal metastases for middle lobe N1 NSCLC. The benefit from H/IZ dissection was intermediate to that from UZ and SCZ, whereas TI revealed greater effectiveness from SCZ over UZ dissection in pN2 middle lobe NSCLC, which was similar for SN2 metastases. H/IZ involvement, therefore, had a key role and mediastinal SCZ dissection should be prioritized over UZ dissection.

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None.

Footnote

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

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