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Retrospective Analysis of Nodal Spread Patterns According to Tumor Location in Pathological N2 Non-small Cell Lung Cancer

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Abstract
Background The purpose of the present study was to determine the nodal spread patterns of pN2 non-small cell lung cancer (NSCLC) according to tumor location, and to attempt to evaluate the possible indications of selective lymph node dissection (SLND).
Methods We retrospectively analyzed nodal spread patterns in 207 patients with NSCLC of less than 5 cm with N2 involvement.
Results The tumor location was right upper lobe (RUL) in 79, middle lobe in 12, right lower lobe (RLL) in 40, left upper division (LUD) in 41, lingular division in 11, and left lower lobe (LLL) in 24. Both RUL and LUD tumors showed a higher incidence of upper mediastinal (UM) involvement (96 and 100 %, respectively) and a lower incidence of subcarinal involvement (15 and 10 %, respectively) than lower lobe tumors (UM; RLL 60 %, LLL 42 %; subcarinal: RLL 60 %, LLL 46 %, respectively). Among the patients with 24 right UM-positive RLL and 10 left UM-positive LLL tumors, 2 showed negative hilar, subcarinal, and lower mediastinal involvement, and cT1, suggesting that UM dissection may be unnecessary in lower lobe tumors with no metastasis to hilar, subcarinal, and lower mediastinal nodes on frozen sections according to the preoperative T status. Among the patients with 12 subcarinal-positive RUL and 4 subcarinal-positive LUD tumors, one showed negative hilar or UM involvement, suggesting that subcarinal dissection may be unnecessary in RUL or LUD tumors with no metastasis to hilar and UM nodes on frozen sections.
Conclusions The present study appears to provide one of the supportive results regarding the treatment strategies for tumor location-specific SLND.

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Introduction

Lobectomy with systematic mediastinal lymph node dissection (LND) has been considered the standard of care for resectable non-small cell lung cancer (NSCLC). Lymph node dissection was first reported by Cahan in 1960 [1] and is known to enhance staging accuracy by increasing lymph node harvesting and improving the identification of occult N2 disease. In contrast, other investigators claim that LND can potentially increased postoperative morbidity or may require longer operative time [2–5]. Some randomized controlled trials addressing the survival benefit of LND and mediastinal lymph node sampling showed no difference in survival outcome between patients undergoing LND and those undergoing lymph node sampling [3, 6, 7]. Whether or not patient outcome is improved by LND remains controversial.

At present, early lung cancers are more frequently encountered because of the widespread use of high-resolution computed tomography (CT) in routine practice and cancer screening [8, 9]. Therefore, the extent of LND should be tailored to each patient. Selective lymph node dissection (SLND) based on the tumor location-specific lymphatic pathway should be undertaken especially for patients with no apparent lymph node metastasis or with impaired pulmonary function, or for elderly patients. In the present study, we retrospectively reviewed the prevalence of lymph node involvement in each mediastinal region in

patients with N2 NSCLC according to the location of the primary tumor, and we attempted to evaluate the possible indications for SLND.

Patients and methods

Patients

From January 1990 to December 2007, a total of 2,195 patients underwent radical surgical resection of at least a lobectomy and systematic LND for NSCLC at our hospital. Of these 2,195 patients, we retrospectively analyzed lymph node spread patterns and outcome in 207 patients with NSCLC of less than 5 cm with N2 involvement. We excluded patients who had received preoperative treatment, including chemotherapy or chemoradiotherapy, those who had undergone only biopsy and SLND, and those who had low-grade malignant tumors. We also excluded patients with tumors spreading across lobar fissures and invading multiple lobes.

Preoperative evaluation included physical examination, chest radiography, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging of the brain, bone scintigraphy, and blood examination. We determined that a large lymph node over 10 mm in the shortest axis was positive for metastasis on CT scans. Positron-emission tomography (PET) scan (recently integrated PET-CT scan) was not routinely used for staging resectable tumors during the study period. In recent years, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was sometimes performed for the patients having suspected multiple N2 lymph node metastases, but it was not routinely used. Similarly, mediastinoscopic biopsy was not routinely performed. Patients with N2 lymph node positively diagnosed by EBUS-TBNA or mediastinoscopic biopsy were excluded from the group of operative indication candidates.

The stage of disease was determined according to the 2009 7th Edition of the TNM Classification for Lung and Pleural Tumors [10]. The institutional review board of our institution approved the data collection and analyses and waived the need to obtain written informed consent from each patient.

Operation

During thoracotomy, lymph nodes in the ipsilateral thoracic cavity were completely resected. Systematic nodal dissection, including the superior to inferior mediastinum, was then performed after pulmonary resection. In cases of left thoracotomy, upper mediastinal dissection indicated aortic and tracheobronchial node dissection. If intraoperative findings showed that hilar or mediastinal lymph nodes were highly suspicious for metastatic disease, the resected lymph node specimens were immediately examined pathologically in frozen sections. Whether or not the presence or absence of lymph node metastasis was judged by intraoperative diagnosis, systematic LND was performed in the present study patients. Mediastinal metastases were considered to be skip metastases if any of the N2 nodes, but not the N1 nodes, were involved.

Mediastinal lymph node stations were grouped into the "zones" proposed by the International Association for the Study of Lung Cancer (IASLC) lung cancer staging project [11]. We also reviewed the correlation between nodal zone spread pattern and tumor location. We classified lymph node stations into the following six zones: the right upper (RU) and left upper (LU) zones, each including #2R, #3a, #3p, and #4R nodes; the subcarinal (SC) zone, including #7 nodes; the right lower (RL) and left lower (LL) zones, each including #8 and #9 nodes; and the aortic-pulmonary (AP) zone, including #5, and #6 nodes.

Statistical analysis

Overall survival time was measured from the date of surgery to the date of death from any cause or the date on which the patient was last known to be alive. Survival curves were plotted according to the Kaplan–Meier method and compared with the log-rank test. Two-category comparison was performed by the Pearson χ^2 test and Fisher's exact test for quantitative data. All tests were two-sided, and p values of <0.05 were considered to indicate statistically significant differences. We used StatView 5.0 (SAS Institute Inc., Cary, NC) for the statistical analysis.

Results

Patient characteristics are summarized in Table 1. Of the 207 patients with NSCLC of less than 5 cm with N2 involvement, 55 (27 %) had skip metastasis, and 97 (47 %) had both hilar and the remaining 55 patients had metastatic segmental lymph nodes or subsegmenta lymph nodes with mediastinal lymph nodes metastasis. In addition, 74 (36 %) were diagnosed with cN2 disease by the chest CT. Lymph node spread patterns according to primary tumor location are presented in Fig. 1. The most common site of involvement for tumors of the right upper lobe (RUL; $n = 79$) was the RU zone ($n = 76$; Fig. 1a). Right upper lobe tumors showed a significantly higher incidence of RU zone metastasis than right lower lobe (RLL) tumors (96 vs. 60 %, $p < 0.001$: Fig. 1a, b). In contrast, when RU zone metastasis was present, RLL tumors showed a significantly higher incidence of simultaneous metastasis to the SC or RL zone

Table 1 Patient characteristics ($n = 207$)

	n	(%)
Overall	207	(100)
Sex		
Male	134	(65)
Female	73	(35)
Histologic type		
Adenocarcinoma	149	(72)
Squamous cell carcinoma	41	(20)
Others	17	(8)
Tumor size (cm)		
2.0	38	(18)
2.1–3.0	55	(27)
3.1–5.0	114	(55)
p-T status		
pT1	47	(23)
pT2	129	(62)
pT3	18	(9)
pT4	13	(6)
Hilar lymph node metastasis		
Present	97	(47)
Absent	110	(53)
Skip metastasis		
Present	55	(27)
Absent	152	(73)
Tumor location		
Right upper lobe	79	(38)
Right middle lobe	12	(6)
Right lower lobe	40	(19)
Left upper division	41	(20)
Left lingular division	11	(5)
Left lower lobe	24	(12)
Procedure		
Pneumonectomy	15	(7)
Bilobectomy	19	(9)
Lobectomy	173	(84)

than RUL tumors (28 vs. 11 %, $p = 0.026$: Fig. 1a, b). The incidence of skip metastasis to only the RU zone was statistically lower among patients with RLL tumors than among those with RUL tumors (8 vs. 30 %, $p = 0.005$: Fig. 1a, b). Right upper lobe tumors showed a significantly lower incidence of SC zone metastasis than RLL tumors (15 vs. 60 %, $p < 0.001$: Fig. 1c, d). Most RUL tumors with SC zone metastasis showed simultaneous metastasis to the RU zone or hilar lymph nodes, and only one patient showed skip metastasis to the SC zone (Fig. 1c).

The most common site of involvement for tumors of the left upper division (LUD) ($n = 41$) was the AP or LU zone ($n = 41$; 100 %: Fig. 1e). Left upper division tumors showed a significantly higher incidence of AP or LU zone metastasis than left lower lobe (LLL) tumors (100 vs. 42 %, $p < 0.001$: Fig. 1e, g). In contrast, when AP or LU zone metastasis was present, LLL tumors showed a higher incidence of simultaneous metastasis to the SC or LL zone than LUD tumors, but the difference was not significant (29 vs. 12 %, $p = 0.089$: Fig. 1e, g). The incidence of skip metastasis to only the AP or LU zone was 45 % in left lingular division tumors, 20 % in LUD tumors, and 0 % in LLL tumors, but the difference was not significant (Fig. 1e–g). Left upper division tumors showed a significantly lower incidence of SC zone metastasis than LLL tumors (10 vs. 46 %, $p < 0.001$: Fig. 1h, j). All LUD tumors with SC zone metastasis showed simultaneous metastasis to the AP or LU zone, but no patient showed skip metastasis to the SC zone (Fig. 1h).

Patients were further categorized as those with tumors of the lower lobes ($n = 64$; 40 of right and 24 of left) and those with RUL or LUD tumors ($n = 120$; 79 of RUL and 41 of LUD). The prognosis of patients with lower lobe tumors and RUL or LUD tumors was analyzed. The 5-year overall survival (OS) rates of patients with tumors of the lower lobes with upper mediastinal metastasis ($n = 34$, 22 %) were poorer than, but not significantly different from, those of the patients without upper mediastinal metastasis ($n = 30$, 34 %) ($p = 0.371$; Fig. 2). The 5-year OS rates of patients with RUL or LUD tumors with SC zone metastasis ($n = 16$, 14 %) were poorer than, but not significantly different from, those of the patients without SC zone metastasis ($n = 104$, 40 %) ($p = 0.073$; Fig. 3).

The combined treatment strategies for tumor location-specific SLND in N2 NSCLC patients according to clinical T status are summarized in Table 2. Among 24 patients with upper mediastinal metastasis from RLL tumors, nine showed no evidence of hilar, SC zone, and lower mediastinal metastasis. Of these nine patients, only one had clinical T1. Similarly, among ten patients with upper mediastinal metastasis from LLL tumors, only one showed no evidence of hilar, SC zone, and lower mediastinal metastasis, and clinical T1 status. Upper mediastinal dissection may be unnecessary in lower lobe tumors with negative hilar, SC and lower mediastinal nodes on frozen sections if the preoperative T status is T1 (Table 3). In contrast, among 12 patients with SC zone metastasis from RUL tumors, one showed no evidence of hilar or RU zone metastasis, and that tumor was classified as clinical T2. Among four patients with SC zone metastasis from LUD tumors, none showed evidence of hilar, upper mediastinal metastasis. This finding supports the hypothesis that SC dissection may be unnecessary in RUL and LUD tumors with no metastasis to hilar and upper mediastinal nodes on frozen sections, regardless of the clinical T status. Figure 4 shows diagrams of the main pathways of lymphatic spread of tumors according to tumor location.

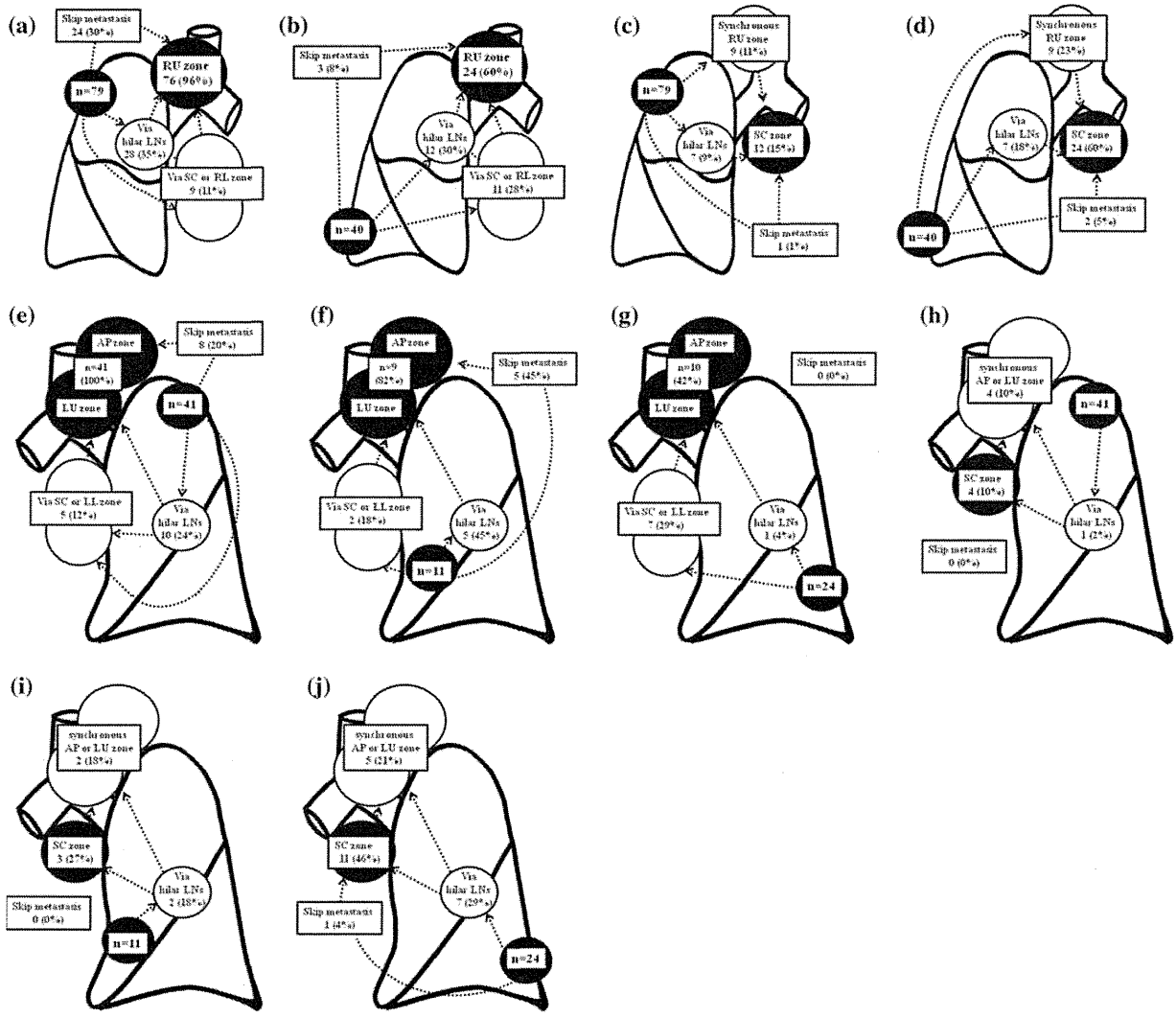

Fig. 1 Lymph node spread patterns according to the primary tumor location: **a** tumors of the right upper lobe (RUL) and right upper mediastinal metastasis. **b** Tumors of the right lower lobe (RLL) and right upper mediastinal metastasis. **c** Tumors of RUL and subcarinal metastasis. **d** Tumors of RLL and subcarinal metastasis. **e** Tumors of the left upper division (LUD) and left upper mediastinal metastasis. **f** Tumors of the left lingular division (LLD) and left upper mediastinal metastasis. **g** Tumors of the left lower lobe (LLL) and left upper mediastinal metastasis. **h** Tumors of LUD and subcarinal metastasis. **i** Tumors of LLD and subcarinal metastasis. **j** Tumors of LLL and subcarinal metastasis

Discussion

We set out to gain insight into the prevalence of lymph node metastasis in each mediastinal region in patients with pN2 NSCLC. The lymphatic pathways by which metastases from primary tumors in various segments and lobes spread toward the hilar and mediastinal lymph nodes have been investigated for over 50 years [12]. Studies of the patterns of location-specific lymphatic pathways of the lung have led to a better understanding of the importance of lymph node staging in the management of lung cancers. Although systematic LND consistently yields precise staging information, it may contradict the concept of the optimal extent of lymph node dissection based on the location of the tumor. Some authors have postulated that the dissection of lymph nodes without cancer cells causes higher morbidity and mortality because it extends the operative procedure [2, 6]. Moreover, the significance of LND regarding long-term outcome is still controversial. We therefore retrospectively reviewed the prevalence of mediastinal lymph node involvement in 207 patients with NSCLC of less than 5 cm with N2 involvement based on the location of the primary tumor, and we set out to determine the possible indications of location-specific SLND.

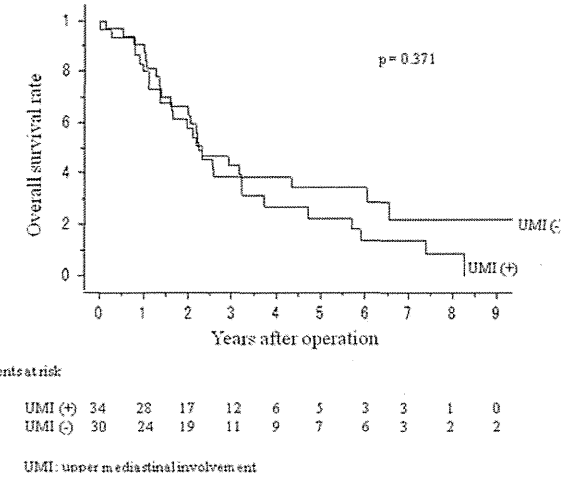

Fig. 2 Overall survival curves of lower lobe non-small cell lung cancer (NSCLC) pN2 patients, with or without upper mediastinal metastasis

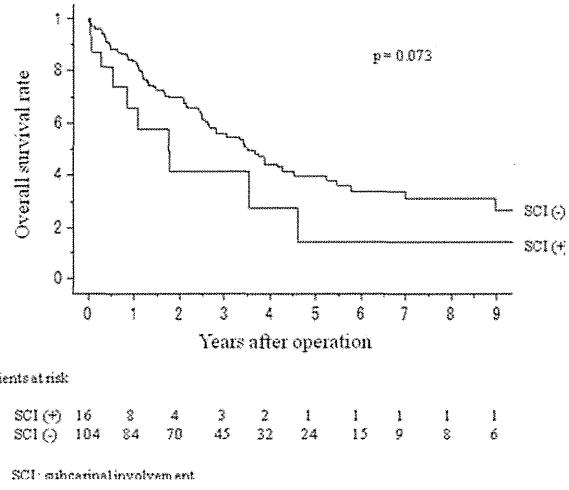

Fig. 3 Overall survival curves of right upper lobe or left upper division NSCLC pN2 patients, with or without subcarinal metastasis

Table 2 Strategy for tumor location-specific selective nodal dissection in N2 non-small cell lung cancer (NSCLC) patients: distribution of upper mediastinal involvement according to clinical T status

Tumor location					
	RUL *n* (%)	RLL	LUD	LLD	LLL
No. of patients with N2	79 (100)	40 (100)	41 (100)	11 (100)	24 (100)
No. of patients with UMI	76 (96)	24 (60)	41 (100)	9 (82)	10 (42)
Patients with UMI					
HI (–), SCI (–), LMI (–)	44 (56)	9 (23)	22 (54)	5 (45)	2 (8)
Clinical T1	14 (18)	1 (4)	5 (12)	2 (18)	1 (4)
Clinical T2–4	30 (38)	8 (21)	17 (41)	3 (27)	1 (4)

RUL right upper lobe, *RLL* right lower lobe, *LUD* left upper division, *LLD* left lingular division, *LLL* left lower lobe, *UMI* upper mediastinal involvement, *HI* hilar lymph node involvement, *SCI* subcarinal involvement, *LMI* lower mediastinal involvement

Table 3 Strategy for tumor location-specific selective nodal dissection in N2 NSCLC patients: distribution of subcarinal involvement according to clinical T status

Tumor location					
	RUL *n* (%)	RLL	LUD	LLD	LLL
No. of patients with N2	79 (100)	40 (100)	41 (100)	11 (100)	24 (100)
No. of patients with SCI	12 (15)	24 (60)	4 (10)	3 (27)	11 (46)
Patients with SCI					
HI (–), UMI (–)	1 (1)	3 (8)	0 (0)	0 (0)	3 (13)
Clinical T1	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Clinical T2–4	1 (1)	2 (5)	0 (0)	0 (0)	3 (13)

The IASLC staging project proposed the zone classification for future survival analyses [11]. Lee et al. [13] reported that grouping patients together according to zones provides accurate prognostic stratification for patients, and may resolve the ambiguity of the anatomical border, indicating applicability in the clinical setting. Therefore, we used the lymph node zone classification in this study.

Several retrospective studies have shown patterns of mediastinal lymph node metastases in relation to the location of the primary tumor [14–19]. Most of these studies have demonstrated that mediastinal lymph node metastases from RUL tumors occur predominantly in the RU area, but rarely in the SC area, whereas those from left upper lobe tumors occur most frequently in the AP or LU area, but those from tumors of the lower lobes rarely occur in the upper mediastinal area. In the present study, metastases to the SC zone from RUL or LUD tumors were significantly less frequent (15 and 12 %, respectively) than metastases to the SC zone from tumors of the lower lobes. The outcome of patients with RUL or LUD tumors with SC zone metastasis was poorer than, but not significantly different from, that of patients with RUL and LUD tumors without SC zone metastasis ($p = 0.073$). There was only 1 patient with only SC zone skip metastasis. Patients with upper lobe NSCLC involving SC nodes are reportedly rare [16, 18, 19], and they have poorer outcomes than those

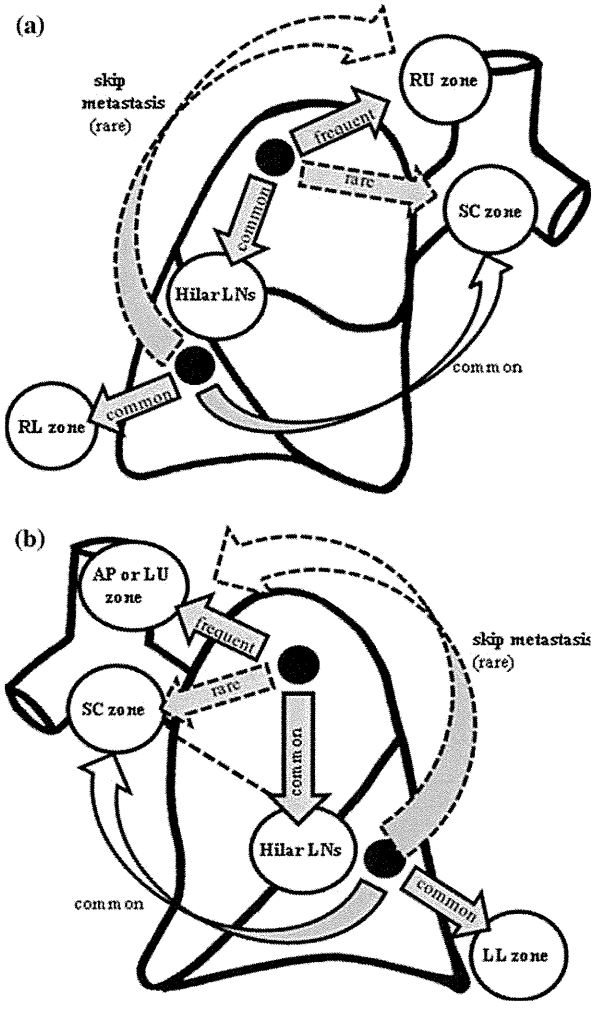

Fig. 4 Diagrams of the main pathways of lymphatic spread according to tumor location. **a** In right-side tumors, almost all RUL tumors metastasized to the RU zone directly or through the hilar lymph node. RUL tumors metastasized less frequently to the SC zone. *Right lower lobe* (RLL) tumors metastasized to various mediastinal lymph node zones, and skip metastasis to the RU zone was rare in RLL tumors. **b** In left-side tumors, all LUD tumors metastasized to the AP zone directly or through the hilar lymph node. *Upper lobe* tumors metastasized less frequently to the SC zone. *Left lower lobe* (LLL) tumors metastasized to various mediastinal lymph node zones, and skip metastasis to the AP zone was rare in LLL tumors

without SC node metastasis [19]. Based on these results, we also evaluated the possible indications of tumor location-specific SLND. Although we did not routinely perform frozen section diagnosis of sampled hilar lymph nodes, we conducted a frozen section examination intraoperatively if metastasis was suspected. There was only 1 patient with SC zone metastasis from RUL tumors who did not show any evidence of hilar and RU zone metastases, whereas no SC zone metastasis from any LUD tumors was observed when neither the hilar nor RU zone showed any evidence of metastasis. Resection of the SC zone in the case of RUL and LUD tumors may be unnecessary if neither upper mediastinal nor hilar lymph nodes show any evidence of metastasis on frozen sections, regardless of the clinical T status.

There were fewer patients with metastases to the upper mediastinal zone from tumors of the lower lobes than with metastases to the upper mediastinal zone from tumors of the upper lobes. The outcome of patients with tumors of the lower lobes with upper mediastinal metastasis was poorer than, but not significantly different from, that of patients with tumors of the lower lobes without upper mediastinal metastasis ($p = 0.371$). There was only one patient each with RU zone metastasis from a clinical T1 RLL tumor and AP zone metastasis from a clinical T1 LLL tumor, but neither showed any evidence of lymph node metastasis to the SC node, lower mediastinal zone, and hilum. Therefore resection of upper mediastinal zones in tumors of the lower lobes may be unnecessary even if the preoperative T status is T1, and if lymph node biopsies in the SC node, lower mediastinal zone, and hilum do not show any evidence of metastasis on frozen sections. However, former studies indicated that the superior and basal segment lung cancers in the lower lobe have different lymph node metastasis patterns [14]. Although there was no significant difference in the metastasis patterns of lower lobe tumors, this finding may be attributable to the small number of patients in the present study (data not shown). The strategy of lymph node dissection should be changed from extensive dissection to SLND, especially in early stage cancer or poor-risk patients, because SLND can reduce postoperative morbidity associated with such complications as bronchopleural fistula, chylothorax, or recurrent nerve palsy [2–5]. However, lung cancer can easily metastasize to the mediastinum, and therefore patient selection should be determined carefully. If patients are suspected of having advanced disease based on intraoperative findings, LND should be performed.

The present study has several limitations. It was a retrospective study, and possible bias may exist. First, we examined suspected hilar or mediastinal lymph nodes intraoperatively in frozen sections, but specific systemic sampling methodologies have been established and used in the past. Second, the number of patients in this study may be too small to draw any definitive conclusion. Third, current less-invasive staging modalities, including PET-CT or EBUS were infrequently used because of the inclusion of a large amount of data from old cases, collected at a time when these procedures were less well established. Thus we might have inadvertently performed some operations on undetected N3 disease.

In conclusion, we demonstrated the potential validity of refraining from resecting lymph nodes in the SC zone in

cases of RUL or LUD tumors, or those in the upper mediastinal zone in the case of tumors of the lower lobes. Considering the fact that NSCLC patients can benefit from SLND, a prospective study is essential to confirm the effect of tumor location-specific SLND on survival and optimal postoperative treatment.

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Prognostic factors and the significance of treatment after recurrence in completely resected stage I non-small cell lung cancer

Running head: Postrecurrence survival in stage I NSCLC

Category: Original article

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Disclosure of Potential Conflicts of Interest

All authors declare that they have no conflicts of interest associated with this study.

Abstract

Introduction: The objective of this study was to identify the clinicopathological factors influencing postrecurrence survival (PRS), and the effect of postrecurrence therapy (PRT) on patients with completely resected stage I non-small cell lung cancer (NSCLC).

Methods: We reviewed the data of 919 patients in whom complete resection of stage I NSCLC had been performed.

Results: Of the 919 patients, 170 had recurrent disease (18.5%). Initial PRT was performed in 118 (69.4%) patients (surgery 8, chemotherapy 79, radiotherapy 10, chemoradiotherapy 21). On multivariate analyses, PRT (HR0.542; 95%CI0.344-0.853; p=0.008), female gender (HR0.487; 95%CI0.297-0.801; p=0.005) and differentiation (HR1.810; 95%CI1.194-2.743; p=0.005) demonstrated a statistically significant association with favorable PRS. Bone metastasis (HR3.288; 95%CI1.783-6.062; p<0.001), liver metastasis (HR4.518; 95%CI1.793-11.379; p=0.001), chemotherapy (HR0.478; 95%CI0.236-0.975; p=0.040), epidermal growth factor receptor-tyrosine kinase inhibitors treatment (EGFR-TKIs; HR0.460; 95%CI0.245-0.862; p=0.015), and non-adenocarcinoma (HR2.136; 95%CI1.273-3.585; p=0.004) were independently and significantly associated with PRS in the 118 patients who underwent any PRT.

Subgroup analysis with a combination of these 5 PRS factors in the patients who underwent any PRT revealed median PRS times of 42.4 months for 20 patients lacking all 5 risk factors and 18.8 months for 98 patients with at least one of these risk factors, respectively (p=0.001).

Conclusion: PRT, gender and differentiation were independently associated with PRS. In the patients who underwent any PRT, PRS was related to EGFR-TKIs, chemotherapy, histology, and initial recurrence sites. One challenge for the future will be to create systematic treatment strategies for recurrent NSCLC according to the risk factor status of individual patients.

Introduction

Surgical resection with a curative intent is considered the standard of care for early stage non-small cell lung cancer (NSCLC), but more than 20% of patients had recurrence, even in pathological stage I cases.[1-6] Recurrence after complete resection for stages I-III of NSCLC ranges from 30% to 75%, and has been reported to depend on pathological staging and follow-up period.[1,6-8] The majority of recurrences occur within the first 2 years,[1,6] although there are several studies showing late recurrences 5 years or more after resection.[9-11] Long-term continuous follow-up is required to establish accurate recurrence rates and patterns.

Although several studies focusing on postrecurrence survival (PRS) of patients in stages I or stage I-III NSCLC have been reported,[2-4,8,12-14] no standard treatment strategy for recurrent disease based on prospective studies has been established. However, a standard treatment strategy is necessary because much longer follow-up periods and robust protocols are required to evaluate PRS objectively. It is difficult to generalize about multifactorial patient backgrounds, which depend on disease, treatment, and performance status (PS) at recurrence. The prognostic factors predicting PRS or the appropriate treatment are still controversial.

In recent years, encouraging new treatments (including epidermal growth factor

receptor-tyrosine kinase inhibitors [EGFR-TKIs], anaplastic lymphoma kinase inhibitors, pemetrexed, and bevacizumab) have afforded benefits to certain patients with advanced or recurrent NSCLC.[15-21] Advances in postrecurrence therapy (PRT) may provide improvement in overall survival (OS) among the patients who undergo surgery. The objective of the present study was to identify the clinicopathological factors influencing PRS, and their effect of PRT on stage I NSCLC.

Materials and Methods

From January 1990 through December 2007, 1214 patients underwent complete resection for pathological stage I NSCLC at our hospital. Complete resection was defined as demonstrating cancer-free surgical margins, both grossly and histologically. All patients underwent radical anatomical lobar resection and systematic mediastinal lymph node dissection. The following exclusion criteria were applied: preoperative chemotherapy, radiation therapy, or both (n = 38); low-grade malignant tumors, including carcinoids, mucoepidermoid carcinomas, or adenoid cystic carcinomas (n = 20); death within 30 days of operation (n = 9). Of the remaining 1147 patients, complete follow-up was available for 919 patients, who composed the subjects of this study.

Preoperative evaluation included physical examination, chest radiography, computed tomography (CT) of the chest and abdomen, bone scintigraphy, blood examination, and since the early 2000s, positron-emission tomography (PET) scan (recently integrated PET-CT scan). Histologic subtypes of lung cancer were determined according to the World Health Organization classification,[22] and disease stage was determined in accordance with the 7th Edition of the TNM Classification for Lung and Pleural Tumors.[23]

The follow-up schedule consisted of a clinic visit every 3 months in the first 1 year after resection, every 6 months from the 2nd to the 5th year, and annually thereafter, on an outpatient basis, and aimed at continuing follow-up for 10 years after resection. Follow-up procedures included physical examination, chest radiography, and blood examination (including serum tumor markers). CT of the chest and abdomen was performed every 6 months in the first 2 years, and annually from the 3rd to the 5th year. Whenever any symptoms or signs of recurrence were detected, magnetic resonance imaging (MRI) of the brain, and bone scintigraphy were performed.

Recurrences were diagnosed by physical examination and diagnostic imaging. Histological or cytological confirmation of the recurrence was made when clinically feasible. Local recurrence was defined as disease recurrence at the surgical margin,

ipsilateral hemithorax or mediastinum. Radiographic lymph node recurrence was defined as enlarged lymph nodes measuring > 1 cm on the short axis by CT and/or hypermetabolic lymph nodes on PET-CT scans. Pathological confirmation of recurrence was made by endobronchial ultrasound-guided transbronchial needle aspiration of enlarged lymph nodes during follow-up. Distant metastasis was defined as disease recurrence in the contralateral lung or outside the hemithorax and mediastinum. A second primary tumor was recorded when a patient presented with a new histological type, and with clinical features consistent with a new primary tumor. Data collected from our department database of patients, telephone interviews and correspondence from outside sources during the follow-up periods were included.

Clinical characteristics were retrieved from available clinical records. The following clinicopathological factors were assessed in the PRS analysis: age, gender, smoking status, T status (T1 vs. T2), tumor size (0-30 mm vs. > 30 mm), tumor differentiation (well/moderate vs. poor), pathological vascular invasion, pleural invasion, histology (adenocarcinoma vs. others), and extent of resection (single lobe lobectomy vs. more extensive resection, namely bilobectomy/pneumonectomy).

Length of the recurrence-free period was calculated in months from date of resection to date of initial recurrence or last follow-up showing no recurrence. To calculate the

recurrence-free proportion (RFP), patients who died without recognized recurrence or who were known to have no recurrence at the date of last contact were censored. Length of PRS was measured from date of initial recurrence to date of death from any cause or date on which the patient was last known to be alive. PRS and RFP curves were plotted using the Kaplan-Meier method, and differences in variables were determined using the log-rank test or the Breslow tests. Categorical comparison was performed using the χ^2 test for discrete data and Student's t-test for continuous data. Multivariate analyses were performed using the Cox proportional hazards regression model. A backward stepwise selection procedure was implemented. All tests were two-sided, and p-values of less than 0.05 were considered to indicate a statistically significant difference. Statview 5.0 software (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived, by the Institutional Review Board at Tokyo Medical University (No. 2133).

Results

Median follow-up time for survivors was 62.0 months (range: 1.4-247.6 months). The RFP was 82.2% at 5 years after operation. Of the 919 patients, 170

(18.5%) had recurrent disease, with a median age of 66 at the time of initial recurrence. Median PRS time for these patients was 17.6 months (range: 0.4-103.0 months). The 1- and 2-year PRS proportions were 73.5% and 51.4%, respectively (Figure 1).

Table 1 shows 5-year RFPs and univariate/multivariate analyses of recurrence according to clinicopathological characteristics of stage I NSCLC patients. Univariate analysis identified 5 significant risk factors: male gender, pathologically vascular invasion, pleural invasion, poorly-differentiated carcinoma, and non-adenocarcinoma. Multivariate analysis demonstrated that pathological vascular invasion (hazard ratio [HR] 2.306; 95% confidence interval [CI] 1.621-3.280; $p < 0.001$), pleural invasion (HR 1.489; 95% CI 1.048-2.115; $p = 0.026$), and poorly-differentiated carcinoma (HR 1.842; 95% CI 1.328-2.555; $p < 0.001$) were statistically significant predictors of recurrence.

Initial recurrence sites and PRT are shown in Table 2. Type of recurrence included only local in 43 patients (25.3%), distant in 113 (66.5%), and both in 14 (8.2%). Most commonly involved organs were the lung, the site of recurrence in 66 patients (ipsilateral 23, contralateral/bilateral 43), followed by regional lymph nodes in 37, brain in 30, bone in 21, and liver in 16. Initial PRT was performed in 118 (69.4%) patients, and included surgery for 8, chemotherapy for 79, radiotherapy for 10, and chemoradiotherapy for 21. Surgical resections in the 8 patients were in 3 with solitary

pulmonary metastasis, 3 with solitary brain metastasis, 1 with adrenal gland metastasis, and 1 with chest wall and axillary lymph node involvement. Forty-one (24.1%) patients had no treatment for recurrence. 118 patients who underwent any PRT, 66 (55.9%) underwent second-line or subsequent therapy, including chemotherapy for 58, and EGFR-TKIs for 27 (gefitinib 22, erlotinib 3, both 2). Among the latter 27 patients, EGFR mutations were detected in 12, 4 had wild-type *EGFR*.

Table 3 shows univariate/multivariate analyses of PRS. Univariate analysis identified 6 significant risk factors for PRS: male gender, smoker, poorly-differentiated carcinoma, non-adenocarcinoma, no PRT, and shorter recurrence-free interval ($\leq$ 24 months; median recurrence-free period was 24 months). Multivariate analysis demonstrated that PRT (HR 0.542; 95% CI 0.344-0.853; p = 0.008), female gender (HR 0.487; 95% CI 0.297-0.801; p = 0.005) and differentiation (HR 1.810; 95% CI 1.194-2.743; p = 0.005) had a statistically significant association with favorable PRS.

The results of multivariate analysis of PRS determined that PRT had strong impact on PRS. Therefore, we further examined PRS in the 118 patients who underwent any PRT (Table 4). Univariate analysis identified 9 significant risk factors for PRS: male gender, smoker, poorly-differentiated carcinoma, bone metastasis, liver metastasis, no chemotherapy or EGFR-TKI, no second-line therapy, and multiple organ metastases.

Multivariate analysis demonstrated that bone metastasis (HR 3.288; 95% CI 1.783-6.062; $p < 0.001$), liver metastasis (HR 4.518; 95% CI 1.793-11.379; $p = 0.001$), chemotherapy (HR 0.478; 95% CI 0.236-0.975; $p = 0.040$), EGFR-TKI therapy (HR 0.460; 95% CI 0.245-0.862; $p = 0.015$), and non-adenocarcinoma (HR 2.136; 95% CI 1.273-3.585; $p = 0.004$) had a statistically significant association with PRS.

Subgroup analysis with a combination of these 5 PRS factors (no EGFR-TKI and chemotherapy, presence of liver or bone metastasis, non-adenocarcinoma) in patients with recurrence who underwent any PRT revealed median PRS times of 42.4 months for 20 patients lacking all 5 unfavorable factors and 18.8 months for 98 patients with one of these risk factors, respectively (Figure 2). The difference in PRS was statistically significant between the two groups ($p = 0.001$).

Discussion

We set out to identify clinicopathological factors influencing PRS of stage I NSCLC patients. Although curative surgical resection is the most effective therapy for stage I NSCLC patients, a considerable number of patients will develop recurrence. In the current study, overall incidence of recurrence was 18.5%, and median PRS time was 17.6 months. Initial location of recurrence was at a distant site in 74.7%, and the