Original Article

Prognosis of pulmonary lymphangitic carcinomatosis in patients with non-small cell lung cancer

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Background: The eighth edition of the TNM classification for lung cancer does not provide a definite guideline for pulmonary lymphangitic carcinomatosis. The purpose of this retrospective case-control study is to evaluate the prognosis of pulmonary lymphangitic carcinomatosis in patients with non-small cell lung cancer compared with those with intrapulmonary metastases.

Methods: Non-small cell lung cancer (NSCLC) patients with pulmonary lymphangitic carcinomatosis detected on chest computed tomography scan during staging evaluation between 2000 and 2016 were included. The extent of pulmonary lymphangitic carcinomatosis was classified as being around the primary tumor (cLy1), at a distance from the tumor but confined to the same lobe (cLy2), in other ipsilateral lobes (cLy3), or affecting the contralateral lung (cLy4). Overall survival rates of the subjects were compared with those with intrapulmonary metastases.

Results: A total of 103 subjects with pulmonary lymphangitic carcinomatosis were analysed. The 5-year overall survival rates of the subjects with pulmonary lymphangitic carcinomatosis (n=103) and intrapulmonary metastases (n=111) were 33% and 21%, respectively. The 5-year overall survival rates of cLy1 (n=28), cLy2 (n=40), cLy3 (n=26) and cLy4 (n=9) were 54%, 35%, 12% and 11%, respectively. On multivariable analyses after adjusting for possible confounders, the subjects with cLy1 and cLy2 had better overall survival (adjusted hazard ratio for death, 0.34 and 0.49; 95% confidence interval, 0.24–0.73 and 0.30–0.80; P<0.001 and 0.004, respectively) and the subjects with cLy4 had worse overall survival (adjusted hazard ratio, 2.21; 95% confidence interval, 1.03–4.70; P=0.040) compared with those with intrapulmonary metastases.

Conclusions: The subjects with cLy1/2 had better overall survival than those with cLy3/4 or intrapulmonary metastases. cLy1/2 seems to be a T descriptor (T3/4) rather than an M1 descriptor.

Keywords: Non-small cell lung cancer (NSCLC); pulmonary lymphangitic carcinomatosis; overall survival

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide, accounting for 1.5–1.7 million deaths annually (1,2). Approximately 85–90% of lung cancer cases are of non-small cell lung cancer (NSCLC), and most patients with NSCLC present at advanced stages (1).

Pulmonary lymphangitic carcinomatosis (PLC) refers to the dissemination of malignant cells throughout the lymphatic system, associated with changes in the interstitium of lung (3). The pathology of PLC was first described in 1873 by Troisier as diffuse infiltrations of malignant cells into the lymphatics of both lungs (4,5). Representative radiological findings of PLC include thickening of the bronchovascular bundles, fissures, and the formation of interlobular septae and secondary pulmonary lobules (6-8). Radiological and pathological correlations were reported in the 1970s in a small number of cohorts evaluated via post-mortem histology (5,9).

PLC may be focal or diffuse (10,11), being either confined to one lobe or spread throughout both lungs. Given recent advances in high-resolution computer tomography (CT) (10,12), such distributions are being detected more often during lung cancer staging evaluation; therefore, the prevalence and prognosis of PLC must be addressed in lung cancer patients.

The extent of PLC could be of prognostic significance in lung cancer and it was listed as an optional descriptor (cLy) in the seventh edition of TNM classification of lung cancer (13,14). However, few cLy data are available in the International Association for the Study of Lung Cancer (IASLC) database, which includes predominantly surgically treated patients (15). Therefore, the eighth edition of the TNM classification for lung cancer does not address whether PLC is included in T, N or M descriptors (16). Although PLC was considered end stage disease in the past, there exist heterogeneous populations of patients with PLC. Therefore, in this study, we evaluated the prognosis of PLC detected on chest CT scan during staging evaluation in patients with NSCLC and investigated whether it should be included in T or M descriptors. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-677).

Methods

Study population and design

We conducted a retrospective case-cohort study of patients diagnosed with primary lung cancer between 2000 and 2016 at the Samsung Medical Center (a 1,979-bed referral hospital in Seoul, Republic of Korea). NSCLC patients with PLC (case) and intrapulmonary metastases (IM: control) detected on chest CT scan during staging evaluation were included in the study. Subjects with incomplete staging evaluation or distant metastasis (M1a/b/c) such as malignant pleural/pericardial effusions or extrathoracic metastases were excluded. There was a possibility that PLC confined to same lobe could be a T3 or T4 descriptor. Therefore, we also excluded the subject who had PLC confined to same lobe and other T4 disease since we would like to evaluate the prognostic implication of PLC confined to the same lobe as the T3 descriptor. One board-certified thoracic radiologist (HYL) and one board-certified pulmonologist (S-WU) reviewed chest CT scans from all extracted patients in consensus by using inclusion and exclusion criteria.

This study was approved by the Institutional Review Board of Samsung Medical Center, which waived the requirement for informed consent due to the retrospective nature of the study (IRB No. 2019-06-046). We only used de-identified data retrieved from electronic medical records. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Staging evaluation and data collection

Clinical characteristics, including age at diagnosis, sex, smoking status, and tumor histology were obtained from electronic medical records. Tumors were re-staged according to the eighth edition of the TNM classification (17). Patients' dates of death were collected from their medical records or the database of the national health insurance service.

Routine staging evaluation included chest CT scans, abdominal and pelvic CT scans, positron emission tomography (PET) or integrated PET/CT scans, bone scintigraphy, brain magnetic resonance imaging, and flexible bronchoscopy. Mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration of thoracic lymph node was performed according to our institutional protocol if needed during staging evaluation (18).

Definitions of PLC and IM

PLC was defined as uneven thickening of bronchovascular bundles, thickening of isolated interstitial lines, and presence of polygonal lines on chest CT scan (7). The location and extent of the PLC was classified as cLy1-

4 as below (13,14): (I) cLy1: lymphangitis confined to the area around the primary tumor; (II) cLy2: lymphangitis at a distance from the primary tumor but confined to the lobe of the primary tumor; (III) cLy3: lymphangitis in other ipsilateral lobes; (IV) cLy4: lymphangitis affecting the contralateral lung. Representative chest CT findings of patients exhibiting PLC are shown in Figure S1. IM was defined as the presence of peripheral, multiple round metastatic nodules of various sizes which were scattered throughout both lungs (19).

EGFR mutation and anaplastic lymphoma kinase (ALK) immunohistochemistry (IHC)

The details of evaluating EGFR mutation and ALK IHC are described in elsewhere (20). Briefly, after extracting genomic deoxyribonucleic acid (DNA) from formalin-fixed paraffin-embedded (FFPE) tissue, DNA sequencing for EGFR mutations in exons 18, 19, 20, and 21 was performed using real-time polymerase chain reaction and a peptide nucleic acid clamping EGFR Mutation Detection Kit (Panagene, Inc., Daejeon, Korea). ALK protein expression was evaluated by IHC (1:40, NCL-ALK, clone 5A4, Novocastra, Newcastle upon Tyne, UK) with FFPE tissue. Diffuse and strong cytoplasmic positivity of tumor cells was considered positive for ALK IHC. ALK IHC positivity was regarded as a surrogate marker for ALK gene rearrangement or amplification.

Statistical analyses

Data are presented as medians (interquartile ranges) or numbers (%). Categorical variables were compared using Pearson's χ^2 test and continuous variables were compared employing Kruskal-Wallis test. Overall survival (OS) was estimated using the Kaplan-Meier method and adjusted by Bonferroni method; the log-rank test was used to compare subjects with PLC and those with IM but no distant metastasis.

Univariate and multivariate Cox's proportional hazards regression analyses were performed to identify factors that significantly impacted on OS. Variables that were significant (P<0.05) in univariate analyses and those of known clinical importance were entered into multivariate analyses. The results are reported as unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

All tests were two-sided, and a P value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using R ver. 3.6.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

During the study period, 26,954 patients were diagnosed with primary lung cancer. In patients who had NSCLC (n=24,873), 5.5% (n=1,356) of patients had PLC in chest CT scan during staging evaluation. Subjects with malignant pleural/pericardial effusions or extrathoracic metastases (M1a/b/c) (n=945), those who had incomplete staging evaluation due to the absence of brain imaging and/or PET/CT scans (n=295) and who had concurrent T4 disease and PLC confined to the same lobe [n=13; size of primary lesion >7 cm (n=9), invasion of mediastinum (n=2) or trachea (n=2)] were excluded. Consequently, 103 subjects with PLC and 111 subjects with IM but no distant metastasis were finally included (*Figure 1*). PET or integrated PET/CT and brain MRI were performed on all subjects. Those with PLC were classified based on the location and extent of the lesion: cLy1 (n=28), cLy2 (n=40), cLy3 (n=26), and cLy4 (n=9).

Patient and tumor characteristics

When the 103 patients with PLC were compared to the 111 patients with IM (*Table 1*), the former were more likely to be ex- or current smokers (P=0.017). Regarding tumor histology and nodal stage, the proportion of squamous cell carcinoma was higher among those with PLC (P<0.001), and the proportion of cT2/T3 and cN2/N3 tended to be higher among those with PLC (P=0.034 and P=0.001, respectively). However, no significant differences were observed in terms of age, sex, and size of tumor (*Table 1*).

In subgroup analyses of patients with PLC, there was significant differences in size of tumor, T stage, nodal stage and treatment modality among the four groups (*Table 2*). However, there was no significant differences in age, sex, smoking status, and tumor histology (*Table 2*).

Regarding treatment, 97 (87%) patients received palliative chemotherapy and 14 (13%) patients had supportive care in patients with IM (*Table 1* and Table S1). In patients who had PLC, most common treatment modality was surgical resection (n=39, 38%) followed by palliative chemotherapy (n=37, 36%), supportive care (n=14, 14%) and concurrent chemoradiation (n=13, 13%) (*Table 1*). Cisplatin plus pemetrexed was the most common

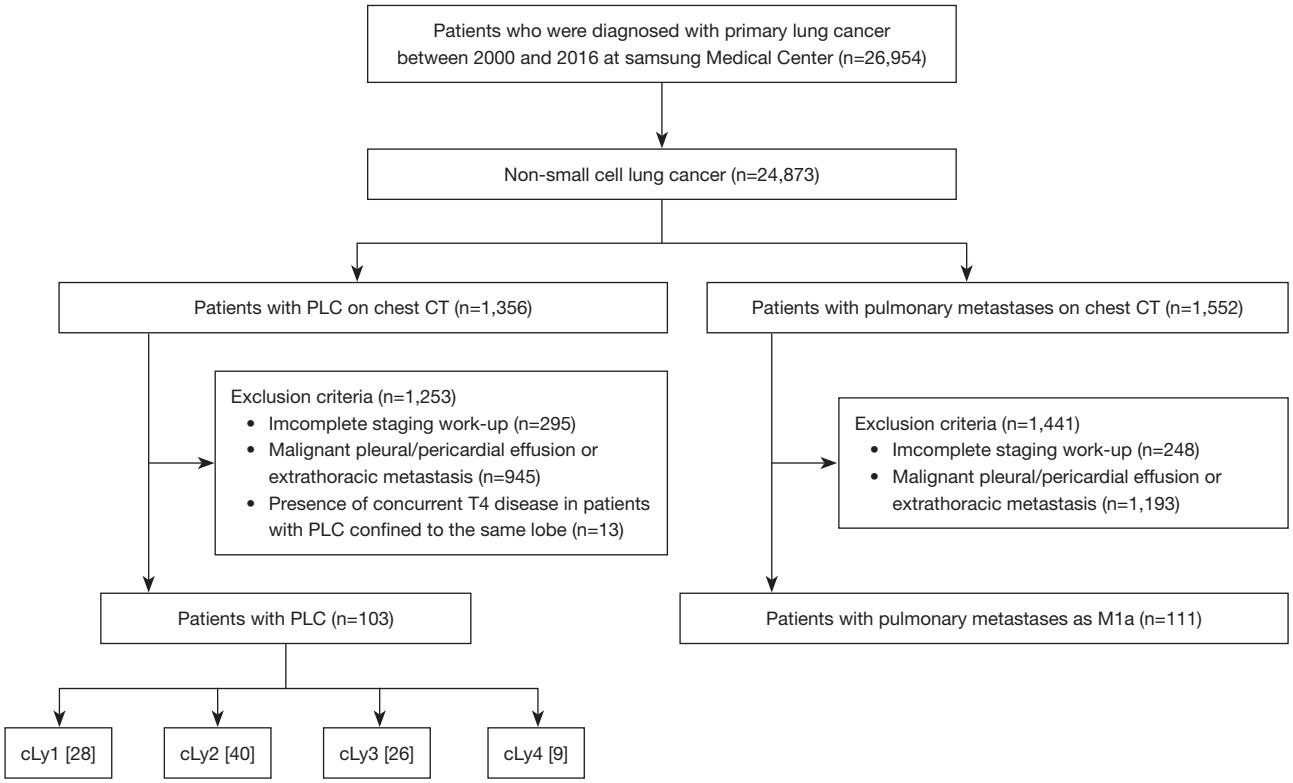


Figure 1 Flow chart of study subjects. PLC, pulmonary lymphangitic carcinomatosis; CT, computed tomography.

Table 1 Baseline characteristics of study subjects at the time of diagnosis by the patterns of tumor spread

Characteristic	PLC [n=103]	IM [n=111]	P value
Age, years	59 [47–69]	62 [54–69]	0.198
Sex, male	68 [66]	60 [54]	0.074
Smoking status			0.017
Never smoker	35 [34]	59 [53]	
Former smoker	37 [36]	26 [23]	
Current smoker	31 [30]	26 [23]	
Tumor histology			<0.001
Adenocarcinoma	68 [66]	78 [70]	
Squamous cell carcinoma	32 [31]	16 [14]	
Other NSCLC	3 [3]	17 [15]	
Size of primary lesion			0.068
≤3 cm	28 [27]	28 [25]	
>3 but ≤5 cm	48 [47]	42 [38]	
>5 but ≤7 cm	26 [25]	32 [29]	
>7 cm	1 [1]	9 [8]	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	PLC [n=103]	IM [n=111]	P value
ALK IHC			0.451
Positive [2+/3+]	5 [5/0]	4 [3/1]	
Negative	33 [32]	57 [51]	
Not available	65 [63]	50 [45]	
EGFR mutation			<0.001
Positive	12 [12]	37 [33]	
L858R	3 [3]	10 [9]	
Exon 19 deletion	7 [6]	20 [18]	
Exon 20 insertion	2 [2]	7 [6]	
Negative	30 [29]	33 [30]	
Not available	61 [59]	41 [37]	
T stage*			0.034
cT1	16 [16]	25 [23]	
cT2	44 [43]	34 [30]	
cT3	34 [33]	30 [27]	
cT4	9 [8]	22 [20]	
Nodal stage*			0.001
cN0	11 [11]	35 [32]	
cN1	7 [7]	7 [6]	
cN2	47 [46]	29 [26]	
cN3	38 [37]	40 [36]	
Treatment modality			<0.001
Palliative chemotherapy	37 [36]	97 [87]	
Concurrent chemoradiation therapy	13 [13]	0	
Surgical resection	39 [38]	0	
Supportive care only	14 [14]	14 [13]	
Deaths	69 [67]	86 [77]	0.086

Data are presented as medians [interquartile ranges] or n [%]. *, 8th edition of TNM classification for lung cancer. PLC, pulmonary lymphangitic carcinomatosis; IM, intrapulmonary metastases; NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; EGFR, epidermal growth factor receptor.

palliative chemotherapy regimen in both PLC (n=10) and IM (n=34) groups (Table S1). Six and twenty patients received the EGFR-tyrosine kinase inhibitor in PLC and IM groups, respectively (Table S1). The details of palliative chemotherapy regimens are summarized in Table S1. All patients (n=39) who underwent surgery were included in cLy1/2 group and there were lymphangitic invasions in all histopathologic specimens (*Table 2* and Table S2).

Follow-up and overall survival

In patients with PLC, 69 (67%) patients died during a

Table 2 Baseline characteristics of patients who had PLC by the extent of disease

Characteristic	cLy1 [n=28]	cLy2 [n=40]	cLy3 [n=26]	cLy4 [n=9]	P value
Age, years	62 [54–66]	60 [50–69]	62 [52–68]	56 [42–60]	0.527
Sex, male	18 [64]	25 [62]	19 [73]	6 [67]	0.841
Smoking status					0.822
Never smoker	10 [36]	13 [32]	7 [27]	5 [56]	
Former smoker	10 [36]	16 [40]	9 [35]	2 [22]	
Current smoker	8 [29]	11 [28]	10 [38]	2 [22]	
Tumor histology					0.422
Adenocarcinoma	17 [61]	25 [62]	18 [69]	8 [89]	
Squamous cell carcinoma	9 [32]	15 [38]	7 [27]	1 [11]	
Other NSCLC	2 [7]	0	1 [4]	0	
Size of primary lesion					0.011
≤3 cm	3 [11]	8 [20]	14 [54]	3 [33]	
>3 but ≤ 5 cm	15 [54]	22 [55]	8 [30]	3 [33]	
>5 but ≤ 7 cm	10 [36]	10 [25]	[12]	3 [33]	
>7 cm	0	0	1 [4]	0	
ALK IHC					0.105
Negative	13 [46]	13 [32]	5 [19]	2 [22]	
Positive	3 [11]	2 [5]	0	0	
Not available	12 [43]	25 [63]	21 [81]	7 [78]	
EGFR mutation					0.638
Negative	11 [39]	12 [30]	5 [19]	2 [22]	
Positive	4 [14]	5 [12]	2 [8]	1 [11]	
Not available	13 [47]	23 [58]	19 [73]	6 [67]	
T stage*					<0.001
cT1	3 [11]	3 [8]	9 [35]	1 [11]	
cT2	12 [43]	21 [52]	8 [31]	3 [33]	
cT3	13 [46]	16 [40]	2 [8]	3 [33]	
cT4	0	0	7 [27]	2 [23]	
Nodal stage*					0.010
cN0	2 [7]	7 [18]	2 [8]	0	
cN1	2 [7]	2 [5]	2 [8]	1 [11]	
cN2	20 [71]	17 [42]	9 [34]	1 [11]	
cN3	4 [14]	14 [35]	13 [50]	7 [78]	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	cLy1 [n=28]	cLy2 [n=40]	cLy3 [n=26]	cLy4 [n=9]	P value
Treatment modality					<0.001
Palliative chemotherapy	2 [7]	10 [25]	18 [69]	7 [78]	
Concurrent chemoradiation therapy	0	10 [25]	3 [12]	0	
Surgical resection	25 [89]	14 [35]	0	0	
Supportive care only	1 [4]	6 [15]	5 [19]	2 [22]	
Deaths	13 [46]	25 [62]	23 [88]	8 [89]	0.004

Data are presented as medians [interquartile ranges] or n [%]. *, 8th edition of TNM classification for lung cancer. PLC, pulmonary lymphangitic carcinomatosis; NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; EGFR, epidermal growth factor receptor.

median follow-up duration of 31 [12–60] months. Of patients with IM, 86 (77%) patients died during a median follow-up duration of 33 [25–43] months. The 5-year OS rate of patients with PLC was 33% (95% CI: 25–43%), statistically not different to that for patients with IM [21% (95% CI: 15–31%); P=0.118] (*Figure 2A*).

In subgroup analyses, the median follow-up duration of patients with cLy1, cLy2, cLy3, and cLy4 were 60 [24–60], 38 [13–60], 16 [10–34], and 12 [5–21] months, respectively. The 5-year OS rates of these patients were 54% (95% CI: 38–76%), 35% (95% CI: 23–54%), 12% (95% CI: 4–34%), and 11% (95% CI: 2–71%), respectively (*Figure 2B*).

Prognostic factors of mortality

In univariate analyses, old age, male gender, smoking status, histology (squamous cell carcinoma or other histology of NSCLC), a large size of primary lesion, T stage and the extent of PLC were significantly associated with mortality (*Table 3*). The subjects with cLy1 or cLy2 had better OS (unadjusted HR for death, 0.42 and 0.63; 95% CIs: 0.33–0.91 and 0.41–0.99; P=0.004 and 0.045, respectively) than patients with IM (*Table 3*).

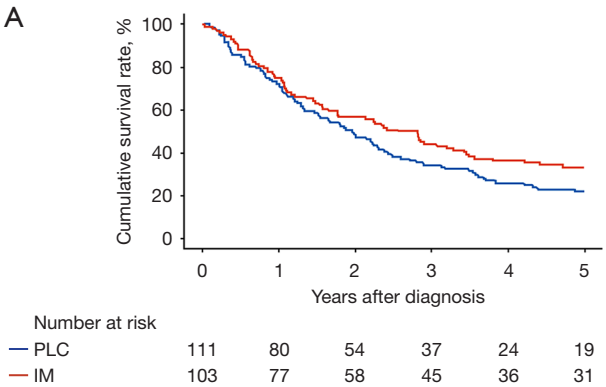
In multivariate analyses, patient-related (sex, age, and smoking history) and tumor-related (tumor histology, EGFR mutation status, T stage and nodal stage) factors were adjusted (*Table 4*). Patients with cLy1 had better OS (adjusted HRs for death, 0.35 and 0.34; 95% CIs: 0.19–0.63 and 0.18–0.62; P<0.001 and <0.001 in model 1 and 2, respectively). Patients with cLy2 also had better OS (adjusted HRs for death, 0.54 and 0.49; 95% CIs: 0.34–0.86 and 0.30–0.80; P=0.009 and 0.004 in model 1 and 2, respectively), but patients with cLy4 had worse OS (adjusted HRs for death, 2.36 and 2.21; 95% CIs: 1.12–4.99 and 1.03–4.70; P=0.023 and 0.040 in model 1 and 2, respectively) compared to those with IM.

Discussion

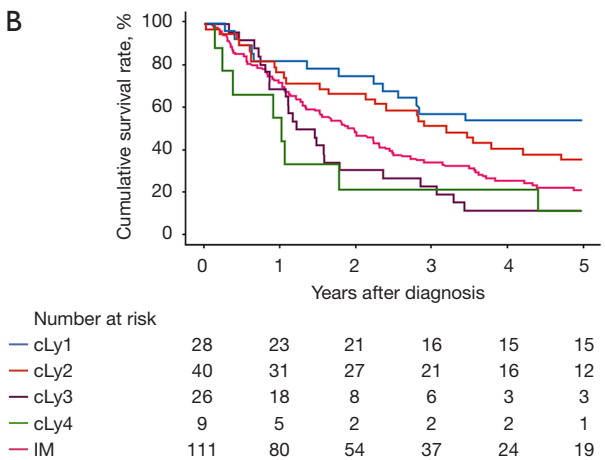
In this study, we investigated the prognostic implication of PLC detected during routine staging evaluation in patients with NSCLC. Subjects with cLy1 or cLy2 had better OS compared to those with IM (HR for death, 0.42 and 0.63, respectively). This effect persisted after adjusting for all potential confounders (adjusted HR for death, 0.34 and 0.49, respectively). However, subjects with cLy3 had similar OS compared to those with IM, and subjects with cLy4 had worse OS compared to those with IM after adjusting for all potential confounders (adjust HR for death, 2.21). To the best of our knowledge, this is the largest study to evaluate the prognostic significance of PLC detected on chest CT scan during staging evaluation in patients with NSCLC and the first study to confirm the prognostic difference according to the extent of PLC (cLy1-4).

PLC in lung cancer has been realized as a marker of disseminated disease with a poor response to chemotherapy (21,22). Although combination chemotherapy prolonged OS in a reported case with PLC confined to a different ipsilateral lobe (23), the prognosis is generally very poor (median survival 2–13 months) and has not improved much over time (24,25). These results suggested that the prognosis of PLC may vary by histology of the tumor and the definition of PLC. Therefore, research about prognostic factors for PLC is necessary.

In our study, 1,356 (5.5%) subjects had PLC during staging evaluation among 24,873 subjects with NSCLC; 103



	Median follow-up duration (IQR), months	5-year survival rate (95% CI), %
PLC	30.8 (11.9–60.0)	32.8 (24.8–43.2)
IM	23.6 (10.3–45.0)	21.3 (14.7–30.7)
P value	0.097	0.118



	Median follow-up duration (IQR), months	5-year survival rate (95% CI), %
cLy1	60.0 (24.1–60.0)	53.6 (37.9–75.6)
cLy2	38.4 (12.7–60.0)	35.2 (22.9–54.1)
cLy3	16.0 (10.2–34.2)	11.5 (3.98–33.5)
cLy4	12.4 (4.50–21.2)	11.1 (1.75–70.5)
IM	23.6 (10.3–45.0)	21.3 (14.7–30.7)
P value	0.003	0.002

Figure 2 Kaplan-Meier survival plots of study subjects. (A) Survival analysis of patients with PLC and those with IM. (B) Survival analysis of patients with PLC by the extent of disease (cLy1, cLy2, cLy3, and cLy4). PLC, pulmonary lymphangitic carcinomatosis; IM, intrapulmonary metastases; IQR, interquartile range; CI, confidence interval.

subjects were included in the final analyses after exclusion of subjects with incomplete staging evaluation, distant metastases, etc. However, the IASLC database identified only 69 (0.09%) subjects with lymphangitis among 77,156 subjects with NSCLC (15,17). This discrepancy in the prevalence of PLC may be attributable to differences in the study populations; 85% of all subjects in the IASLC database underwent surgery (17). Therefore, it is possible that the IASLC database underestimated the prevalence of PLC.

The strength of our study is that all included study subjects with PLC underwent complete staging evaluation including brain MRI and PET or integrated PET/CT. And we also excluded subjects who had M1 disease (malignant pleural/pericardial effusions or extrathoracic metastases) and in whom PLC was combined with another T4 disease. Thus, we focused on the prognostic implications of PLC isolated from any effects of distant metastases and T4 disease (in case of cLy1/2). A previous study that used the IASLC database found that the estimated 1-year survival for subjects with lymphangitis in ipsilateral different lobe (cLy3; 61%) was paradoxically higher than that of the subjects with lymphangitis confined to the primary lobe (cLy1/2; 41%) (15). We speculate that this contradictory result may be attributable to inclusion of lymphangitis subjects with distant metastases from the IASLC database.

One of our most notable findings was the difference in mortality according to the distribution of PLC; patients with cLy1/2 had a better prognosis. In previous IASLC staging cohort data, 5-year survival rates of cT2a, cT2b, cT3 and cT4 were 67%, 60%, 52% and 38%, respectively (26,27). Therefore, 5-year OS rates of 54% for cLy1 and 35% for cLy2 in this study are reminiscent of historical cT3 and

Table 3 Univariable Cox's regression analyses predicting mortality in all patients with PLC

Characteristic	HR [95% CI]	P value
Age, years	1.03 [1.01–1.04]	<0.001
Sex		<0.001
Male	Reference	
Female	0.54 [0.38–0.75]	
Smoking status		<0.001
Never	Reference	
Former smoker	1.60 [1.09–2.34]	0.016
Current smoker	2.42 [1.65–3.55]	<0.001
Tumor histology		0.003
Adenocarcinoma	Reference	
Squamous cell carcinoma	1.43 [0.98–2.09]	0.063
Other NSCLC	1.98 [1.20–3.28]	0.008
Size of primary lesion		0.014
≤3 cm	Reference	
>3 but ≤5 cm	1.31 [0.87–1.97]	0.189
>5 but ≤7 cm	1.32 [0.85–2.07]	0.217
>7 cm	3.95 [1.93–8.08]	<0.001
EGFR mutation		
Negative/not available	Reference	
Positive	0.79 [0.54–1.15]	0.223
T stage*		0.001
cT1	Reference	
cT2	1.27 [0.79–2.04]	0.316
cT3	1.41 [0.87–2.30]	0.164
cT4	2.68 [1.56–4.59]	<0.001
Nodal stage*		0.386
cN0	Reference	
cN1	1.03 [0.51–2.10]	0.925
cN2	0.98 [0.63–1.52]	0.931
cN3	1.22 [0.79–1.87]	0.367
PLC		0.024
IM	Reference	
cLy1	0.42 [0.24–0.76]	0.004
cLy2	0.63 [0.41–0.99]	0.045
cLy3	1.37 [0.86–2.18]	0.180
cLy4	1.63 [0.79–3.37]	0.185

*, 8th edition of TNM classification for lung cancer. HR, hazard ratio; CI, confidence interval; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; PLC, pulmonary lymphangitic carcinomatosis; IM, intrapulmonary metastases.

cT4, respectively. However, the 5-year OS rates of patients with cLy3 were 12%, which was not significantly different from that of patients with IM (21%; adjusted HR 1.19; 95% CI: 0.73–1.93; P=0.483), and the 5-year OS rates of patients with cLy4 were only 12%, which was significantly worse than that of patients with IM (21%; adjusted HR 2.21; 95% CI: 1.03–4.70; P=0.040). In this study, 25/28 (89%) of subjects with cLy1 and 14/40 (35%) of subjects with cLy2 underwent surgery (lobectomy or bilobectomy) and lymphatic invasion was confirmed in histopathologic examinations of all patients (Table S1). Among those patients who underwent surgery, 19 patients (49%, 14 for cLy1 and 5 for cLy2) are still alive with a median follow-up duration of 4.9 years (Table S1). Therefore, on the basis of our study, we recommend that the subjects with cLy1 and cLy2 should be considered surgical candidates unless distant or mediastinal nodal metastasis is detected during staging evaluation. However, the subjects with cLy3 and cLy4 seem to be candidates for palliative chemotherapy since they had the poor prognosis similar to or worse than those with IM (M1a) in this study.

The driver oncogenes such as EGFR mutation and ALK rearrangement could be associated with better OS in advanced stage NSCLC. Therefore, the status of driver oncogenes could be a potential confounder in this study. Although the proportion of EGFR mutation positivity was higher in IM group than in PLC group (33% *vs.* 12%, P<0.001), there was no significant difference in the proportion of EGFR mutation positivity among cLy1-4 groups in the subgroup analysis of patients with PLC. There was no significant difference in the proportion of ALK IHC positivity between PLC and IM groups. In the univariate analysis, EGFR mutation status was not associated with mortality (*Table 3*). In the multivariate analysis, the subjects with cLy1 or cLy2 had better OS and the subjects with cLy4 had worse OS compared to those with IM after adjusting for all potential confounders including EGFR mutation status. Therefore, the effect of the extent of PLC on OS does not seem to be related to EGFR mutation status.

There are several limitations in our study. First, this study was conducted in a single tertiary hospital, therefore our data should be interpreted conservatively. Further studies involving multiple centers are required to validate our results. Second, we only evaluated all-cause mortality, not cancer-specific mortality, due to a lack of detailed information in some patients who were transferred to other hospitals or were lost to follow-up.

In conclusions, subjects with cLy1/2 had better OS than

Table 4 Risk of death according to extent of disease in patients with PLC

Risk of death	IM [n=111]	cLy1 [n=28]	cLy2 [n=40]	cLy3 [n=26]	cLy4 [n=9]
No. of cases [%]	86 [78]	13 [46]	25 [64]	23 [89]	8 [89]
Unadjusted HR [95% CI: P value]	Reference	0.42 [0.24–0.76, 0.004]	0.63 [0.41–0.99, 0.045]	1.37 [0.86–2.18, 0.180]	1.63 [0.79–3.37, 0.185]
Model 1, adjusted HR [95% CI: P value]	Reference	0.35 [0.19–0.63, <0.001]	0.54 [0.34–0.86, 0.009]	1.17 [0.72–1.88, 0.519]	2.36 [1.12–4.99, 0.023]
Model 2, adjusted HR [95% CI: P value]	Reference	0.34 [0.18–0.62, <0.001]	0.49 [0.30–0.80, 0.004]	1.19 [0.73–1.93, 0.483]	2.21 [1.03–4.70, 0.040]

Model 1: adjusted for age, sex, and smoking history [never, former or current smoker]. Model 2: adjusted for age, sex, smoking history [never, former or current smoker], tumor histology [adenocarcinoma, squamous cell carcinoma or other NSCLC], EGFR mutation status [positive *vs.* negative/not available], T staging [T1, T2, T3 or T4] and nodal staging [N0, N1, N2 or N3]. HR, hazard ratio; CI, confidence interval; PLC, pulmonary lymphangitic carcinomatosis; IM, intrapulmonary metastases; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor.

those with cLy3/4 or IM. cLy1/2 seems to be a T descriptor rather than an M1 descriptor. Therefore, subjects with cLy1/2 without distant or mediastinal nodal metastases should be considered surgical candidates.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tlcr-21-677

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Samsung Medical Center, which waived the requirement for informed consent due to the retrospective nature of the study (IRB No. 2019-06-046). We only used de-identified data retrieved from electronic medical records.

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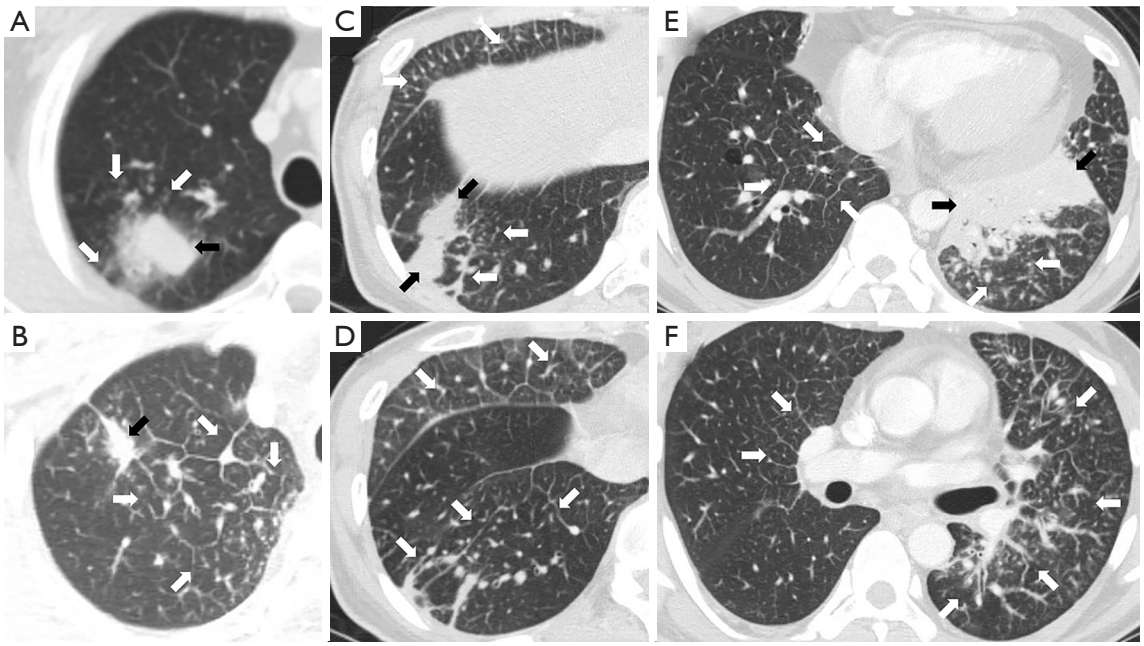

Figure S1 Representative radiologic findings of pulmonary lymphangitic carcinomatosis (PLC), classified as cLy1 (A), cLy2 (B), cLy3 (C,D), and cLy4 (E,F). (A) The primary tumor (black arrow) is in right upper lobe and PLC (white arrow) is confined to area around the primary tumor. (B) The primary tumor (black arrow) is in right upper lobe and PLC (white arrow) is at a distance from the primary tumor but confined to the same lobe. (C,D) The primary tumor (black arrow) is in right lower lobe, and PLC (white arrow) extends to the right middle lobe. (E,F) The primary tumor (black arrow) is in the left lower lobe, and PLC (white arrow) extends to the left upper, right lower, and right upper lobes.

Table S1 Summary of palliative chemotherapy which study subjects received

Characteristic	PLC (n=37)	IM (n=97)
Cytotoxic chemotherapy	31	75
Cisplatin + pemetrexed	10	34
Cisplatin + gemcitabine	9	20
Cisplatin + docetaxel	6	4
Cisplatin + paclitaxel	2	4
Carboplatin + gemcitabine	2	12
Carboplatin + paclitaxel	2	1
EGFR-TKI	6	20
Gefitinib	3	15
Erlotinib	2	4
Afatinib	1	1
ALK-TKI	0	2
Alectinib	0	2

Data are presented as number. PLC, pulmonary lymphangitic carcinomatosis; IM, intrapulmonary metastases; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitor.

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Table S2 Characteristics of patients with PLC who received surgical treatment

Characteristic	Patients (n=39)
Age, years	62 (55–66)
Sex, male	26 (67)
Smoking status	
Current smoker	14 (36)
Former smoker	15 (39)
Never	10 (26)
Neoadjuvant treatment	
No	5 (15)
Yes	28 (85)
Tumor histology	
Adenocarcinoma	25 (64)
Squamous cell carcinoma	13 (33)
Other NSCLC	1 (3)
Lymphatic invasion in surgical specimens	39 (100)
T stage*	
pT1	12 (31)
pT2	19 (49)
pT3	8 (20)
pT4	0
Nodal stage*	
pN0	10 (26)
pN1	6 (15)
pN2	22 (56)
pN3	1 (3)
Tumor location	
Right upper lobe	10 (26)
Right middle lobe	3 (8)
Right lower lobe	10 (26)
Left upper lobe	12 (30)
Left lower lobe	4 (10)
Extent of surgery	
Bilobectomy	3 (8)
Lobectomy	36 (92)
Adjuvant treatment	
Concurrent chemoradiation therapy	7 (18)
Chemotherapy	9 (23)
Radiotherapy	12 (31)
No adjuvant treatment	11 (28)
Prognosis	
No evidence of progression	13 (33)
Local relapse	12 (31)
Lung	7 (18)
Lymph node	5 (13)
Distant metastasis	14 (36)
Deaths	20 (51)

Data are presented as medians (interquartile ranges) or n (%). *, 8th edition of TNM classification for lung cancer. PLC, pulmonary lymphangitic carcinomatosis; IM, intrapulmonary metastases; NSCLC, non-small cell lung cancer.

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