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Reviewer A

Given the fact that pulmonary lymphangitic carcinomatosis rarely occurs, and there are currently no effective strategies to treat PLC, this is a timely and important article on the prognosis of PLC in non-small cell lung cancer. The authors focus on comparing the prognosis of PLC and intrapulmonary metastases in patients diagnosed in Seoul, Republic of Korea.

While the study reported a higher overall survival rate of patients with PLC compared to those with IM, key subgroups such as cLy3 had similar OS to IM, and cLy4 had worse OS to IM. These findings are extremely useful in identifying patient-specific prognosis, as well as risk stratification and treatment options.

The manuscript is written clearly. The population size of patients with PLC is impressive and the data are valid. The report provides new information and is medically relevant. The conclusions are consistent with the evidence and arguments presented. However, I have two comments.

Comment 1(C1). In the abstract authors should not use any abbreviations or acronyms.

Response 1(R1). Thank you for your careful review and insightful comments. We agree with the reviewer's comments and have revised the abstract session by deleting all abbreviations or acronyms.

C2. Could you add information on what chemotherapy drugs patients received?

R2. Thank you for your comments. During the study period, a total of 134 patients received palliative chemotherapy (37 patients with pulmonary lymphangitic carcinomatosis and 97 patients with intrapulmonary metastases) and 13 patients with pulmonary lymphangitic carcinomatosis received concurrent chemoradiation therapy using weekly platinum + paclitaxel. For palliative chemotherapy, combination chemotherapy regimens using a platinum compound (cisplatin or carboplatin) plus a second active cytotoxic agent (pemetrexed, gemcitabine, docetaxel, or paclitaxel) were selected according to physician's preference, typically for four to six cycles. The patients, who had sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement, received EGFR tyrosine kinase inhibitors (gefitinib, erlotinib or afatinib), or ALK tyrosine kinase inhibitor (alectinib), respectively. We have added a new Table S1 summarizing the details of palliative

chemotherapy regimens as follows;

New Table S1. Summary of palliative chemotherapy which study subjects received

	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.

Abbreviations: PLC, pulmonary lymphangitic carcinomatosis; IM, intrapulmonary metastases; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitor.

Changes in the text: We have also revised the Result section to add the information about the palliative chemotherapy and concurrent chemoradiation as follows (Page 11, lines 209-218);

Before: “Regarding treatment, 97 (87%) patients received palliative chemotherapy and 14 (13%) patients had supportive care in patients with IM (*Table 1*). 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*). 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 S1).”

After: “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, the 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 using weekly platinum plus paclitaxel

(n=13, 13%) (*Table 1*). Cisplatin plus pemetrexed was the most common 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*)."

Reviewer B

The authors report the single-center observational study that evaluate the prognostic value of pulmonary lymphangitic carcinomatosis (PLC) in patients with non-small-cell lung cancer. In the study, they report that the patients with PLC within the same lobe as the primary tumor had better overall survival than those with intrapulmonary metastasis or more extended PLC.
The manuscript is well written and compliant to the reporting guideline (STROBE). Study theme is novel and interesting. Study design and statistical approach are appropriate. However, I have a major concern about an important potential confounder.

We thank the reviewer for these important comments on our work. Regarding to your concerns, we revised our manuscript based on your comments and suggestions.

Comment 1. The mutations of driver oncogenes such as EGFR, ALK, ROS1, and BRAF are strongly associated with better prognosis. Patients with these mutations often have PLC, however, targeted treatments for these gene mutations can achive relatively good prognosis. Thus, the mutaion status of driver oncogenes may be a potential confounder. Nevertheless, the authors don't describe this significant matter even as limitations of this study. To accept the revised manuscript, I recommend an additional data collection on driver oncogenes.

Response 1. Thank you for your careful review and insightful comments.

R1a) As the Reviewer B recommended, we have included the information about driver oncogenes such as EGFR mutation and ALK immunohistochemistry (IHC) in the revised manuscript. However, the data about ROS1 rearrangement and BRAF mutation was not available in our cohort. The proportion of EGFR mutation positivity was higher in patients with intrapulmonary metastases (IM) than in those with pulmonary lymphangitic carcinomatosis (PLC) (33% vs 12%, P<0.001). However, there was no significant difference in the proportion of ALK IHC between PLC and IM groups. We have added the status of EGFR mutation and ALK IHC in the revised Table 1 as follows;

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

	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)

Data are presented as n (%).
Abbreviations: ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; EGFR, epidermal growth factor receptor.

R1b) In subgroup analyses of patients with PLC, there was no significant differences in the proportion of ALK IHC and EGFR mutation positivity among cLy1-4 groups. We have added this information in the revised Table 2 as follows;

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

	cLy1 (n=28)	cLy2 (n=40)	cLy3 (n=26)	cLy4 (n=9)	P-value
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)	

Data are presented as n (%).

R1c) We have also performed univariate Cox's regression analysis using the status of EGFR mutation, the presence of EGFR mutation was not associated with mortality. We have also added this information in the revised Table 3 as follows;

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

	HR (95% CI)	P-value
EGFR mutation		
Negative/Not available	*Reference*	
Positive	0.79 (0.54–1.15)	0.223

R1d) We have reanalyzed multivariate Cox's regression including the status of EGFR mutation with patient-related (sex, age, and smoking history) and tumor-related (tumor histology, T stage, nodal stage) factors (revised model 2), the result of multivariate analysis grossly unchanged compared with the previous model 2 as shown in the

revised Table 4.

Revised 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)
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)
Revised 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 2: adjusted for age, sex, smoking history (never, former or current smoker), tumor histology (adenocarcinoma, squamous cell carcinoma or other NSCLC), T staging (T1, T2, T3 or T4) and nodal staging (N0, N1, N2 or N3).

Revised 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).

Changes in the text: We have modified the Results section (Page 12, Line 241-243) as follows;
Before: "In multivariate analyses, patient-related (sex, age, and smoking history) and tumor-related (tumor histology, T stage and nodal stage) factors were adjusted (*Table 4*)."
After: "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*)."

R1e) We have added the paragraph describing the methods for EGFR mutation and ALK immunohistochemistry analyses in the Methods section (Page 9, Line 152-163) as follows;

"EGFR mutation and ALK immunohistochemistry
The details of evaluating epidermal growth factor (EGFR) mutation and anaplastic lymphoma kinase (ALK) immunohistochemistry (IHC) are described in elsewhere (1). 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.**"**

References:

1. Choi Y, Kim KH, Jeong BH, Lee KJ, Kim H, Kwon OJ, Kim J, Choi YL, Lee HY, Um SW. Clinicoradiopathological features and prognosis according to genomic alterations in patients with resected lung adenocarcinoma. J Thorac Dis. 2020 Oct;12(10):5357-5368.

R1f) Finally, we have added the paragraph describing the issue of driver oncogene in the Discussion section as follows (Page 15, Line 303-314);

"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."