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Reviewer A

In this manuscript, authors evaluated the impact of extranodal extension (ENE) in patients with pN1 NSCLC. I partly understand the authors conclusions though it is hard to imagine the actual status of hilar nodes. I think varieties of patterns exist in the nodal status, ENE limited to neighboring fat tissue, that with invasion to pulmonary artery, bronchus and another lobe. I suggest that authors explain the detail nodal status of ENE included in this study cohort to help readers understand.

Major Points
Comment 1: I propose the authors present the detail of ENE status and surgical procedure. Presentations of representative CT image and/or microscopic images are helpful.

Reply 1: Thank you for your suggestion. Extranodal Extension(ENE) started gaining attention 40 years ago regarding cervical node meta.(1) Since then, there have been studies on ENE in various carcinomas, but most studies only considered the presence or absence of ENE, similar to this study. However, since the extent of ENE can be linked to a proportionally poor prognosis, several grading methods have been proposed. (1-4) Thus, we definitely agree with you that it would have been more meaningful if the ENE had been analyzed in more detail. Unfortunately, however, when referring to the pathology reports of the patients who participated in this study, detailed information on ENE status could not be obtained, and only the presence or absence of ENE could be obtained. Therefore, we have added the points you raised in the limitation section as follows:

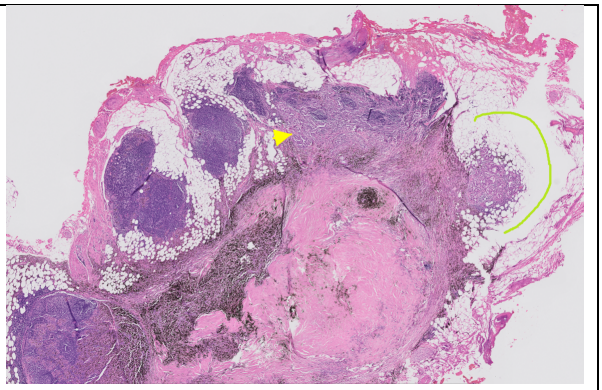
Regarding the surgical procedure, we describe the lymph node dissection method in more detail about this topic. Lung resection was performed first before mediastinal lymph node dissection. Then, lung specimens were removed, although it slightly differed with each of the six surgeons who participated in the study. Instead of lobe-specific lymph node dissection or mediastinal node sampling according to the location or character of the main mass, most patients underwent mediastinal node dissection, including up to 2R on the right side. In left surgery, some patients underwent routine dissection of up to 4L after general anesthesia through video-assisted mediastinoscopic lymphadenectomy (VAMLA). The average number of harvested lymph nodes was about 30 (Table 1). As many nodes as possible were removed, including surrounding fat tissue, and careful dissection was performed to avoid breaking the nodes.

Regarding the correlation between radiologic and pathologic findings of ENE, meta-analysis

results in the field of oropharynx reported sensitivity of 66–95% and specificity of 50–96% based on CT-scan modality for radiologic ENE and pathologic ENE.(5) Such a wide range of results seems to be because the sensitivity and specificity of radiologic ENE are related to the pathologic grade of ENE and timing and method of taking image modality.(2,3,5)

Radiologic ENE diagnosis is defined as the presence of non-specific nodal margins and irregular capsular contrast enhancement and/or infiltration into blood vessels, muscles, or surrounding fat.(6) However, as seen in our patient's preoperative CT image, even when the radiologic finding was expected to be negative, the pathologic finding was diagnosed as positive in ENE. This is thought to be due to the relatively low sensitivity of radiologic ENE.(2) Therefore, additional research on the radiologic diagnosis of ENE in patients with NSCLC is needed.

Changes in the text (Page 11, line 14-19): Fourth, although the detailed status of ENE could affect prognosis, only the presence or absence of ENE was used as prognostic factor. (18,19) It is because when referring to the pathology reports of the patients who participated in this study, detailed information on ENE status could not be obtained. However, there are still only a few studies on which methods of describing the extent of ENE are most appropriate for NSCLC. (12,20) Therefore, follow-up studies are needed regarding the detailed status of ENE.



LN#5 -> ENE (+)

References

1. Bhattacharya P, Mukherjee R. Lymph node extracapsular extension as a marker of aggressive phenotype: Classification, prognosis and associated molecular biomarkers. Eur J Surg Oncol 2021;47:721-31.
2. Almulla A, Noel CW, Lu L, et al. Radiologic-Pathologic Correlation of Extranodal Extension in Patients With Squamous Cell Carcinoma of the Oral Cavity: Implications for Future Editions of the TNM Classification. Int J Radiat Oncol Biol Phys

2018;102:698-708.
3. Shaw RJ, Lowe D, Woolgar JA, et al. Extracapsular spread in oral squamous cell carcinoma. Head Neck 2010;32:714-22.
4. Luchini C, Veronese N, Nottegar A, et al. Extranodal extension of nodal metastases is a poor prognostic moderator in non-small cell lung cancer: a meta-analysis. Virchows Arch 2018;472:939-47.
5. Mermod M, Tolstonog G, Simon C, et al. Extracapsular spread in head and neck squamous cell carcinoma: A systematic review and meta-analysis. Oral Oncol 2016;62:60-71.
6. King AD, Tse GM, Yuen EH, et al. Comparison of CT and MR imaging for the detection of extranodal neoplastic spread in metastatic neck nodes. Eur J Radiol 2004;52:264-70.

Comment 2: To further understanding of study population, the numbers of cases with invasion to PA, bronchus and neighboring lobe should be provided. And those of combined resection and plastic procedure may be also helpful.

Reply 2: Thank you for your meaningful comments. The detailed analysis of the study population of this study is summarized as follows. Based on the exclusion criteria, patients who received neoadjuvant therapy were excluded, and the number of advanced cases that you mentioned was relatively small. The classification criteria were based on resection status and ENE presence (Table 1).

	Pure R0	R0-ENE	R1/R2
Combined resection			
Aorta	2		
Chest wall	6	1	4
Diaphragm	2		
LA	1	1	
Pericardium	5	1	1
SVC			2
PA Angioplasty	10	9	2
Pleurectomy	5		
Bronchoplasty	2	2	1
Total Case	33	14	10
Total Patients	29	12	9

Comment 3: In line 10-11, page6, the authors described about adjuvant RT. The NCCC guideline the authors referred in the manuscript do not recommend RT in patients with R0 resection. The authors should describe the respective indications of adjuvant chemotherapy, RT and CRT in patients with R0 resection. Explanations of those in R0-ENE are also preferred.

Reply 3: The NCCN guideline recommends adjuvant CTx as category 1 for pN1 patients with stage IIB and R0 resection. In the case of stage IIIA with R0 resection, chemotherapy (category 1) or sequential chemotherapy are recommended, and RT are considered. In our institution,

adjuvant Tx. is determined according to the following protocol. [7]

1) For patients who need additional treatment, adjuvant modality is discussed through multidisciplinary treatment.

2) Considering the patient's performance status, expected treatment compliance, and patient's consent, the oncologist or radiologist decides whether to perform additional treatment.

As you pointed out, among the patients who underwent RT with R0 resection, the reason for implementing RTx is shown in the table below.

Pure R0 (N=117)
● Cancer invasion to peribronchial tissue: 80 ● Clinical trial related to lymphovascular invasion: 19 ● Cancer extension to adjacent organ: 9 ● Unknown: 8 ● Large node(22mm) : 1

R0-ENE(N=32)
● Cancer invasion to peribronchial tissue: 22 ● Clinical trial related to lymphovascular invasion: 4 ● Cancer extension to adjacent organ: 3 ● Unknown : 3

The most common reason for RTx in both Pure R0 and R0-ENE groups was that the bronchial resection margin was clear, but peribronchial tissue invasion was microscopically suspected. 68.4% (80/117) in the PureR0 group and 68.8% (22/32) in the R0-ENE group, respectively.

As mentioned above, the patient group that did not receive additional treatment even after becoming R1/R2 were those unable to continue treatment due to poor performance, patient disagreement, and side effects during medications.

Reference

7. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. J Natl Compr Canc Netw 2021;19:254-66.

Comment 4: I believe that survival differences between patients with R1 resection and those with R2 resection were widely accepted although both of them were evaluated as those with incomplete resection altogether in the present study. The author should provide respective number of R1 and R2 cases. And analyses of R0-ENE comparing with not only Pure-R0 but R1 are recommended.

Reply 4: Thank you for your insightful comments. The demographics of the R1 and R2 groups were added as a supplementary table. There were no significant differences in demographics between both groups. Of the 87 patients in the R1/R2 group, 80 were in R1, and 7 were in R2 (Supplementary Table 1).
Overall survival (OS) and recurrence-free survival (RFS) of the R0-ENE and R1 groups were compared (Supplementary Figure 4). No statistically significant differences were observed between the two groups [OS (P=0.85) RFS(P=0.22)], which might be due to small number of patients.

Changes in the text: Added Supplementary Table 1 and Supplementary Figure 4

Comment 5: In the figure 3, authors described the difference of RFS between Pure-R0 and R0-ENE was significant. Does this result, P=0.06, meet the statistical definition in this study? Please explain the interpretation of the result.

Reply 5: Thank you for the valuable comments that can improve the quality of this paper. Since the description used in the manuscript can cause confusion, as you pointed out, the description has been changed as follows. The RFS according to the presence or absence of ENE in the patient group that did not receive adjuvant CTx was statistically 0.06. It did not reach the 0.05 standard set in the paper but was marginally significant. When compared with RFS according to ENE of the group that received adjuvant CTx (Fig 3-B), there was a clear difference in tendency between the two groups.

Changes in the text (Page 9, line 13-15): Meanwhile, among patients without adjuvant CTx, the presence of ENE was significantly associated with poor OS (P=0.004) (Fig 3C), and the RFS had a marginally significant difference (P=0.06) (Fig 3D).

Comment 6: In line 9, page 11, the authors described about potential selection bias as a study limitation. What does this refer to. I hope the authors provide specific points of selection.

Reply 6: Thank you for your comments. As mentioned in the reference cited below, since it is a single-center study, we tried to describe the following limitations. [8]

1) Limited external validity: Research results from a single institution may not be generalizable to a larger population. The meaning of the results may vary when protocols of other institutions are used as the base.

2) Implausible effect size: Since a larger patient population is needed to enable statistical significance, this was another limitation of the single center study.

As you pointed out, we agree that the expression “selection bias” was inappropriate, so we edited it as follows.

Changes in the text (page 11, line 10-11): This study is a retrospective study conducted in a single institution. Therefore, external validation through multi-center and large sample-size studies is needed in the future.

Minor Points

Comment 1: In the methods section of abstract, the authors addressed to reviewed R0 resection cases, meanwhile they classified patients including R1/2 in the next sentence. The authors should the descriptions consistent.

Reply 1: Thank you for pointing this out and helping us to clarify our text. There was also an ambiguous expression in the Methods section (Patients subsection) in the main text, which we edited.

Changes in the text (page 3, line 5-6): From 2004 to 2018, we retrospectively analyzed the data of 862 patients with pN1 NSCLC who underwent lobectomy and more (lobectomy, bilobectomy, pneumonectomy, sleeve lobectomy).

Changes in the text (page 5, lines 20–21): We retrospectively reviewed the data of patients with pN1 NSCLC who underwent lung surgery at Asan Medical Center, Seoul, South Korea, between January 2004 and December 2018.

Comment 2: In Figure 1 and Figure 3, Pure-ENE were presented as variables. Were they correct? or mistakes of Pure-R0?

Reply 2: We have edited it per your suggestion. Thank you for your comments.

Change in the text (Figure 1 and Figure 3): Pure-ENE => Pure-R0

Reviewer B

This paper shows that among NSCLC patients with pN1 who underwent complete resection, those with extranodal extension (ENE) have more distant metastases than those without. On the other hand, it is interesting to note that postoperative adjuvant therapy eliminates the significant difference in prognosis between the two groups. The authors are correct that adjuvant therapy should be more strongly recommended for patients with ENE.
There are some following questions.

Comment 1: What is the “Pure ENE” listed in Figures, if you mean “Pure R0”, please correct.

Reply 1: Thank you for pointing this out. We have edited it per your suggestion.

Change in the text (Figure 1 and Figure 3): Pure-ENE => Pure-R0

Comment 2: The 5-year RFS for Pure ENE (=Pure R0) is listed as 53.0% in the text, whereas in Figure 1B it is described as 65.4%, which is different. Please correct.

Reply 2: There was an error in inputting a value while working on the figure. We have corrected it to 53.0% for pure R0 and 44.4% for the R0-ENE group, as stated in the main text. Thank you very much for pointing out this important error.

Change in the text (Figure 1B): pure R0 53.0%, R0-ENE 44.4%

Comment 3: Please show the HR and P-values for "Subdivided node status" and "Extranodal extension" for cases not treated with adjuvant therapy in Table 3.

Reply 3: As a result of multivariable Cox analysis on OS in patients who did not receive adjuvant therapy (Table 3), HR was 1.99 (1.25–3.16; P=0.004) in the pN1b group compared to pN1a. Regarding extranodal extension, HR was 1.58 (1.06–2.36; P=0.03) in the group with extranodal extension compared to the group without extranodal extension, which was significant and shown in the table.

Comment 4: Even though "DLCO" is not listed in Table 3, the abbreviation is spelled out.

Reply 4: Thank you for pointing out the unnecessary insertion. We deleted it.

Change in the text (Table 3): Deleted the DLCO abbreviation

Change in the text (Table 1): we replaced 66.22% with 66.2%
Change in the text (Supplementary Figure 3): Pure-ENE => Pure-R0