TRANSLATIONAL LUNG CANCER RESEARCH

Peer Review File

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Review Comments

Comment 1: Title is inconsistent with the work done by the authors. In fact, this is a prognostic factor study.

Reply 1: Thank you for your suggestion. We changed the title as advised (see Page 1, line 2-3 and Page 1, line 5.

Changes in the text:

(Page 1, line 2-3)

Prognostic factor in older patients with wild-type epidermal growth factor receptor advanced non-small cell lung cancer: a multicenter retrospective study

(Page 1, line 5)

Running title: Prognosis of elderly patients with EGFR-negative NSCLC

Comment 2: The conclusion should be specific to epidermal growth factor receptor mutation-negative advanced non-small cell lung cancer. The current conclusion is overstated.

Reply 2: Thank you for your suggestion. We modified the text as advised (see Page 4, line 67-69).

Changes in the text: Careful consideration should be given to the indications of chemotherapy for patients aged 81 years and above with wild-type epidermal growth factor receptor advanced non-small lung cancer.

Comment 3: Methods of abstract. A basic issue is no description of the age for inclusion of the study subjects.

Reply 3: Thank you for your suggestion. We modified our text as advised (see Page 3, line 50-53).

Changes in the text: This multicenter retrospective study was conducted at three Japanese institutions and involved patients aged 75 years and above with epidermal growth factor receptor mutation-negative advanced non-small cell lung cancer.

Comment 4: Median survival has a 22-week, over 5 months, difference. I think it is difficult to say no difference in the overall survival between the two groups. Please consider the statistical power of this analysis. The sample size is small.

Reply 4: Thank you for your suggestion. We agree with you. Indeed, there was no statistically significant difference in this study due to the small number of subjects, but Kaplan-Meier analysis showed a tendency for prolonged OS with chemotherapy. Individual diversity becomes more apparent in the elderly; hence, treatment policies should be carefully decided for patients aged 81 years and

above.

We modified and added our text as advised (see Page 3-4, line 59-61, Page 10-11, line 198-203, Page 13, line 255-261, and Page 17, line 327-332).

Changes in the text:

(Page 3-4, line 59-61)

In patients aged 81 years and above, the chemotherapy group tended to have longer survival than did the best supportive care group, but there was no statistically significant difference in the median overall survival between the two groups due to the very small number of subjects (n: 30 vs 12, median: 52 vs. 30 weeks, hazard ratio: 0.52, 95% confidence interval: 0.232-1.130, P = 0.088).

(Page 10-11, line 198-203)

Even in patients aged 81 years and above, the chemotherapy group tended to have longer OS than did the BSC group, but there was no significant difference in median OS between the two groups due to the very small number of subjects; n = 30 and 12, the median OS was 52 weeks and 30 weeks, respectively (hazard ratio: 0.52, 95% confidence interval: 0.232-1.13, P = 0.088; Figure 2C).

(Page 13, line 255-261)

In patients aged 81 years and above, the chemotherapy group tended to have longer OS than did the BSC group, but there was no significant difference in the median OS between the two groups due to the small number of subjects. As older people advance in age, their individual diversity and individual differences increase; hence, treatment policies should be carefully decided for those aged 81 years and above.

(Page 17, line 327-332)

Patients aged 81 years and above tended to have a longer OS in the chemotherapy group than in the BSC group, but the number of subjects was small, and the difference was not statistically significant. As older people advance in age, their individual diversity and individual differences increase; hence, treatment policies should be carefully decided for those aged 81 years and above.

Comment 5: The background talked a lot about lung cancer in older adults, but talked only a few about non-small cell lung cancer. Please provide more specific review on non-small cell lung cancer in older adults. More insights are also needed for the focus on subtype of epidermal growth factor receptor mutation-negative advanced. The objective of this study is prognostic factors, a review on prognostic factors of advanced non-small cell lung cancer in older adults is also necessary. I suggest the authors to re-write this part.

Reply 5: Thank you for your suggestion. We revised the background (Introduction) as follows (Page 5-6, line 75-102).

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Changes in the text: INTRODUCTION

In 2016, lung cancer was the leading cause of cancer-related mortality and the fifth leading cause of death due to any reason, with the World Health Organization (WHO) reporting 1.7 million deaths worldwide (1).

In an analysis in the USA, it was found that approximately half of all lung cancers are diagnosed in people aged >70 years, and approximately 15% are diagnosed in people aged >80 years (2) In contrast, in a study in Japan, over 40% of patients diagnosed with lung cancer were over 75 years old, and over 30% were >80 years old (3). The aged population shows significant heterogeneity; hence, advanced age should not hinder older adults from accessing the most appropriate treatment. Treatment of non-small cell lung cancer completely differs between epidermal growth factor receptor (EGFR)-positive and EGFR-negative cases.

The therapy for EGFR-positive advanced lung cancer in patients aged 75 years or older helps prolong overall survival (OS) similar to patients aged under 75 years (4).

In contrast, the 3rd generation chemotherapy is recommended for elderly patients with advanced lung cancer who are negative for EGFR or not indicated for other molecular targeted therapies (5,6).

However, some clinical trials restrict older patients with poor physical status from participation (2,7,8). Some clinical trials have shown an increase in the incidence of adverse events of standard treatment modalities in older patients (9,10). Due to the heterogeneity in the health background of elderly patients, treatment should be based on the level of fitness, frailty, or vulnerability.

Therefore, in this study, we aimed to identify predictive factors significantly correlating with the OS of older patients with wild-type EGFR advanced non-small cell lung cancer (NSCLC).

We present the following article/case in accordance with the STROBE reporting checklist.

Comment 6: In general, elderly patients are those aged 60 or 65 years. Please explain why focus on 75+ only?

Reply 6: Thank you for your suggestion. The definition of elderly people in Japan is 70 to 75 years old or older, and the 2010 edition of the Lung Cancer Practice Guidelines defined 70 years or older as elderly people. Besides, nearly half of lung cancer patients in Japan are 75 years old or older (*[1]), and in recent years, the second volume comparing third-generation cytotoxic anticancer drug monotherapy and platinum combination therapy included elderly people aged over 70 years old (*[2]). Most of the patients enrolled in both trials in the phase III trial were 75 years or older. The "Guidelines for Lung Cancer Treatment by EBM Method 2017" (Japan Lung Cancer Society, 2017) defines "75 years or older" as elderly with unresectable / metastatic recurrence non-small cell lung cancer. We

followed these guidelines to define elderly people.

*[1] Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan (Ministry of Health, Labour and Welfare, National Cancer Registry)

*[2] Abe T, et al. Randomized phase Ⅲ trial comparing weekly docetaxel plus cisplatin versus docetaxel monotherapy every 3 weeks in elderly patients with advanced non-small-cell lung cancer: the intergroup trial JCOG0803/WJOG4307L. J Clin Oncol 2015;33(6):575-81.

We added our text as advised (see Page 5, line 79-83).

Changes in the text: In an analysis in the USA, it was found that approximately half of all lung cancers are diagnosed in people aged >70 years, and approximately 15% are diagnosed in people aged >80 years (2). In contrast, in a study in Japan, about 50% of patients diagnosed with lung cancer were over 75 years old, and over 30% were >80 years old (3).

Comment 7: Methods. Please use separated paragraph to describe the data collection of outcomes and potential factor affecting prognosis, as well as the follow up procedures.

Reply 7: Thank you for your suggestion. We modified our text as advised (see Page 7, line 126-127).

Changes in the text: Pulmonologists were responsible for diagnosis and treatment selection as well as subsequent follow-ups.

Comment 8: Please consider to adjust for center effect, because this is a multi-center study.

Reply 8: Thank you for your suggestion. We modified our text as advised (see Page 16, line 311-314).

Changes in the text: Our study had several limitations. First, there was a potential bias related to the multicenter design; however, all the facilities are core hospitals with no difference. Second, our study involved a small number of subjects analyzed in a retrospective manner.

Comment 9: Physical conditions such as pain and DM also negatively influence the prognosis of patients, but the authors did not include these factors in their analysis.

Reply 9: Thank you for your suggestion. As a whole, there was no difference between the two groups (70% in BSC and 67% in the chemotherapy group) in stage 4, when it is considered that pain is conscious, so it is expected that the effect of metastasis/pain on PS was comparable.

The effects of other medical comorbidities that may affect OS (renal dysfunction, DM, etc.) were not included in the analysis and could affect the validity of our findings.

We modified our text as advised (see Page 16, line 315-318).

Changes in the text: Third, the effects of other medical comorbidities that may affect OS (renal dysfunction, diabetes mellitus, etc.) were not included in the analysis and could affect the validity of our findings.