Author’s response to reviews

Title: Adjuvant chemotherapy versus chemoradiotherapy for small cell lung cancer with lymph node metastasis: a retrospective observational study with use of a national database in Japan

Authors:

Hirokazu Urushiyama (hirourushi@yahoo.co.jp)
Taisuke Jo (jo.taisuke2016@gmail.com)
Hideo Yasunaga (yasunagah-tky@umin.ac.jp)
Yasuhiro Yamauchi (yas-kkr@umin.ac.jp)
Hiroki Matsui (ptmatsui-tky@umin.ac.jp)
Wakae Hasegawa (wakaetnk0703@yahoo.co.jp)
Hideyuki Takeshima (Htakeshima-tky@umin.ac.jp)
Yoshihisa Hiraishi (blueeyesoul1980@gmail.com)
Akihisa Mitani (mitania-tky@umin.ac.jp)
Kiyohide Fushimi (kfushimi.hci@tmd.ac.jp)
Takahide Nagase (takahide-tky@umin.ac.jp)

Version: 1 Date: 22 Jul 2017

Author’s response to reviews:

July 22, 2017

Re: BCAN-D-16-02501

Response to the Reviewers’ comments

Dear Dr. Solera and Reviewers

Thank you for reviewing our manuscript “Adjuvant chemotherapy versus chemoradiotherapy for small cell lung cancer with lymph node metastasis: a retrospective observational study with use of a national database in Japan”, and for providing us with the opportunity to revise it.
We have addressed all the comments in the point-by-point responses below, and have revised the manuscript accordingly. The revised portions of the manuscript are highlighted in yellow.

We hope that we have addressed all of the reviewers’ comments satisfactorily and that the revised version of the manuscript will now be suitable for publication in BMC Cancer.

Sincerely yours,

Taisuke Jo, MD, PhD
Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: jo-taisuke@umin.ac.jp

RESPONSES TO REVIEWER 1 (Dr. Balazs Halmos)

We wish to thank the reviewer for their careful reading of our manuscript and for their insightful comments, which we believe have helped us to improve our paper.

Comment 1:

There are many obvious and less obvious biases introduced through such a non-randomized, retrospective effort. While the authors did their best to exclude major imbalances, still the data cannot be viewed as definitive.

Response 1:

We agree that this retrospective observational study in relatively rare cases of SCLC was unable to provide strong evidence comparable to a randomized controlled trial. However, the rarity of operable SCLC means that randomized controlled trials to compare postoperative adjuvant chemotherapy and chemoradiotherapy are difficult. We therefore believe that this study provides valuable information on the treatment of postoperative SCLC, despite the potential biases. We have added the following sentence to the Conclusions to highlight these limitations:

“However, this was a retrospective study in relatively rare SCLC cases, and the possibilities of selection bias and unmeasured confounders mean that the results are inconclusive.” (Page 9, lines 12-13)

Comment 2:
The database utilized covers 50% of inpatient data from Japan. It seems that most of the patients in Japan receiving chemotherapy and chemoradiation are inpatients but this should be made more clear as to what percentage of overall care delivery is in versus outpatient and could there be significant biases introduced as a result of for example adjuvant chemotherapy alone or vice versa patients receiving it more likely as an outpatient and simply missing key data from the database etc.. In other words, the authors should do a better job putting into perspective how representative the patients included in the database are of the overall Japanese SCLC population.

Response 2:

Both chemotherapy and chemoradiotherapy in SCLC are usually initiated during hospitalization in Japan, though no statistics are available. However, the public website of the National Cancer Center for Cancer Control and Information Services in Japan refers to the first course of chemotherapy usually being administered during hospitalization (http://ganjoho.jp/public/index.html). We therefore believe that most postoperative SCLC patients would have been included in our study. It is also logical to assume that most postoperative SCLC patients were followed up by a doctor at the same hospital where they underwent lung resection, and were admitted to the same hospital for examination and treatment for cancer relapses. However, as the reviewer notes, the absence of treatment data in the outpatient setting may have biased our results. We have therefore amended the Discussion as follows:

“The first course of chemotherapy or chemoradiotherapy for patients with SCLC is generally administered during hospitalization in Japan. Thus, most postoperative SCLC patients treated with adjuvant chemotherapy or chemoradiotherapy were likely to be included in our study. Patients may be followed up at the same hospital where they underwent lung resection, and may be admitted to the same hospital for examination and treatment of cancer relapse. This study may therefore have captured the initiation of chemotherapy or chemoradiotherapy and cancer relapse adequately, though lack of outpatient data may have biased the results.” (Page 8, lines 19-)

Comment 3:

In the end, more than 500 post-resection SCLC patients were identified in the database but only 75 of these patients received chemoradiation. The small number of patients in the latter group seems surprising and also might lead to false results due to small sample size. What explains the rare utilization of chemoradiation in Japan? Guidelines in general have advocated for the use of chemoradiation in node-positive patients.

Response 3:
We appreciate your comment. We think the main reason for the small number of patients in the adjuvant chemoradiotherapy group is because Japanese guidelines for SCLC, as well as European guidelines, recommend adjuvant chemotherapy for postoperative SCLC, regardless of the positivity of regional lymph nodes. We have amended the Background section accordingly:

“In the case of postoperative SCLC with regional lymph node metastasis, European Society for Medical Oncology guidelines [3] and Japanese consensus treatment guidelines recommend adjuvant chemotherapy, with adjuvant chemoradiotherapy as an alternative option, while National Comprehensive Cancer Network guidelines recommend adjuvant chemoradiotherapy, but also note the lack of any data to support this recommendation.” (Page 3, lines 8-10)

Comment 4:

About a third of the patients in the adjuvant chemotherapy group apparently never received etoposide or irinotecan. So what chemotherapy regimens did they receive in that case? Single agent platinum would seem odd and this suggests potentially missing data which could be of concern.

Response 4:

Thank you for pointing this out. We agree that adjuvant chemotherapy with a single platinum agent is an odd choice for postoperative SCLC. Most patients (69/75) treated with adjuvant chemoradiotherapy had received etoposide or irinotecan plus a platinum agent. However, we did not exclude patients who received neither etoposide nor irinotecan from the adjuvant chemotherapy group, because we were unable to distinguish between patients treated with platinum alone and those treated with platinum plus other agents, which were most likely not recommended in the guidelines for SCLC therapy. We have already referred to this potential bias in the Discussion on page 8, lines 1-4.

Comment 5:

The actual statistical analysis did not find a difference between the two groups so although there might be trends noted but these are not definitive and therefore the conclusion of the study seem stronger than what the data stands for and this should be modified accordingly.

Response 5:

Thank you for your advice. In accordance with the reviewer’s comment, we have amended the sentences in the Conclusions section of the Abstract as follows:
“There was no significant difference in recurrence-free survival between patients with SCLC and N1-2 lymph node metastasis treated with postoperative adjuvant chemotherapy and chemoradiotherapy.” (Page 2, lines 19-20)

Comment 6:
In the conclusion section there are statements that "our results suggest the dominance of surgery…"- unclear what results are being referred to and this section should be modified for accuracy.

Response 6:
Thank you for your suggestion. We have amended the Discussion section accordingly:

“Therefore, we were unable to demonstrate the treatment effect of additional radiotherapy in patients with SCLC who underwent lung resection followed by adjuvant chemotherapy.” (Page 7, lines 15-17)

Comment 7:
The conclusion section should do a better job enlisting the range of potential biases of this study.

Response 7:
We agree and have revised the Conclusions section accordingly, as indicated in the response to Comment 1 above.

Comment 8:
The lack of knowledge as to margin status and incomplete nodal evaluation is a concern as to the confidence in study results- it is quite likely that major imbalances might be present in these key factors between the two groups, were these data available.

Response 8:
Thank you for your comment. Unfortunately, the DPC database does not contain information on surgical margin status or the results of nodal evaluation. However, the Japanese Joint Committee for Lung Cancer Registration reported the T and N factors in all 11,663 patients in a retrospective observational study of patients who underwent surgery for lung cancer in 2004, with no unevaluable or missing statuses (1). Surgery for malignant lung cancer in Japan thus
takes account of the optimal surgical margins and appropriate lymph node dissections. We have already commented on the lack of data regarding surgical margin status and the results of nodal evaluation in the Discussion (Page 8, lines 5-).


Comment 9:

It is unclear whether table 3 includes only univariate or multivariate analyses. If multivariate analysis was not done, it should be explained why.

Response 9:

Thank you for pointing this out. Cox regressions are generally multivariable-adjusted analyses. We performed multivariable Cox regression analysis with adjustment for the following covariates: adjuvant therapies, N and T factors, age, sex, body mass index, Charlson comorbidity index, and Barthel index. In the revised manuscript, we have added the word “multivariable” to Table 3 and in the Abstract (page 1, line 12), Methods (page 5, line 6), and Results (page 6, line 11).

Comment 10:

There seem to be strong trends for better outcome in N2 patients with chemotherapy alone- it is this specific group where detail as to nodal involvement could be critical as to assessing the reliability of the data.

Response 10:

We appreciate your comments. The strong trends for better outcomes in N2 patients in the adjuvant chemotherapy group may have been due to the smaller number of patients with multiple N2 or bulky N2, compared with the chemoradiotherapy group. Unfortunately, we were unable to adjust accurately for N factors, because the DPC database did not contain the results of nodal evaluation. In accordance with this comment, we have added the following sentences to the Discussion:

“Furthermore, strong trends toward better outcomes in N2 patients in the adjuvant chemotherapy group may have been associated with the smaller number of patients with multiple N2, compared with the chemoradiotherapy group.” (Page 8, lines 12-14)
RESPONSES TO REVIEWER 2 (Dr. Grigorios Kotronoulas)

We wish to thank the reviewer for their careful reading of our manuscript and for their insightful comments, which we believe have helped us to improve our paper.

Comment 1:

The authors mention that "Our results suggest the dominance of surgery … in patients with limited-stage SCLC [9]." I am not sure (a) how the results of your study suggest the dominance of surgery and (b) how the Bonner et al. study on thoracic radiation twice daily v. once daily relate to your study. Please revise.

Response 1:

Thank you for your suggestion. In accordance with this comment, we have amended the Discussion section accordingly:

“Therefore, we were unable to demonstrate the treatment effect of additional radiotherapy in patients with SCLC who underwent lung resection followed by adjuvant chemotherapy.” (Page 7, lines 15-17)

Comment 2:

I wonder whether the authors could include a post-hoc power calculation to further support their findings.

Response 2:

Thank you for this suggestion. We conducted a post hoc power analysis using StatsToDo: Sample Size for Survival (Kaplan Meier Log Rank Test) (https://www.statstodo.com/SSizSurvival_Pgm.php). Alpha was set to 0.05 and the sample sizes and survival rates for chemotherapy alone and chemoradiotherapy were 489 and 75, and 0.61 and 0.48, respectively. The calculated power was 0.65. We further conducted a post hoc power analysis for the Cox proportional hazards model using Stata 14.0. Alpha was set to 0.05, and the sample size and hazard ratio were set to 564 and 1.29, respectively. The overall probability of an event was 0.41 and the estimated power was 0.49. However, the usefulness of post hoc power analysis in retrospective studies seems debatable, and we therefore prefer not to include these results in our manuscript.

Comment 3:
The chemoradiotherapy group comprised only 75 patients (compared with 489 patients in the chemotherapy group). Please discuss how this may represent a limitation for the study.

Response 3:

Japanese guidelines for SCLC recommend adjuvant chemotherapy for postoperative SCLC, regardless of the lymph node status, which may explain the relatively small number of patients who received adjuvant chemoradiotherapy. We have amended the Background as follows:

“In the case of postoperative SCLC with regional lymph node metastasis, European Society for Medical Oncology guidelines [3] and Japanese consensus treatment guidelines recommend adjuvant chemotherapy, with adjuvant chemoradiotherapy as an alternative option, while National Comprehensive Cancer Network guidelines recommend adjuvant chemoradiotherapy, but also note the lack of any data to support this recommendation.” (Page 3, lines 8-10)

Comment 4:

The authors have adjusted survival analyses for demographic and clinical characteristics. Postoperative symptom severity/distress at the beginning of adjuvant treatment could be another factor to affect outcomes. Could the authors discuss the potential implications.

Response 4:

Thank you for your valuable comment. Postoperative symptom severity/distress at the beginning of adjuvant treatment may have affected outcomes, but these parameters were unfortunately not available in the DPC database. Furthermore, we believe that activities of daily living (ADL) of the patients analyzed in this study had recovered at the time of chemotherapy or chemoradiotherapy, to the extent that they were able to receive these treatments. However, as pointed out by the reviewer, ADL after surgery or just before adjuvant therapy may have affected the choice of treatment. Nevertheless, the choice of treatment in patients with relatively poor ADL may have been biased towards chemotherapy alone, and would thus not help to explain the apparent ineffectiveness of chemoradiotherapy. In accordance with the reviewer’s comment, we have amended the Discussion as follows:

“There were several limitations of this study associated with a lack of information on the pathological status of the dissected lymph nodes, the intent and detailed method of radiotherapy, and the severity of postoperative symptoms. Furthermore, the selection bias in choosing patients for adjuvant chemotherapy or chemoradiotherapy was unknown and might have affected the outcomes.” (Page 8, lines 5-8)