Reviewer’s report

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

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Reviewer: Balazs Halmos

Reviewer's report:

The manuscript entitled "Adjuvant chemotherapy versus chemoradiation for small cell lung cancer with lymph node metastasis: a retrospective observational study with the use of a national database in Japan" addresses a clinically significant, although uncommon question regarding the need for the addition of adjuvant radiation to adjuvant chemotherapy in the setting of resected, node-positive small cell lung cancer. The study is a retrospective study utilizing a Japanese database spanning a period of 5 years between 2010-2015. With the use of database analyses with consideration of a number of clinical and pathological factors, the authors conclude that adjuvant chemotherapy might be preferred to adjuvant chemoradiation as recurrence-free survival appears to be longer (1146 vs 873 days) in the chemotherapy only group. This study is a valiant effort to address this elusive question where high level evidence is lacking and likely will not be available for a long time, possibly ever. Overall however, multiple shortcomings and biases make proper interpretation of the study difficult in its present state.

Major shortcomings are:

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.

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.

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

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.

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.

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.

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

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.

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

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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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