Author’s response to reviews

Title: Management of patients with early stage lung cancer – why do some patients not receive treatment with curative intent?

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Reviewer comments:

Reviewer reports:
The authors present a study of 3331 cases of lung cancer, including 583 patients with early-stage disease, to identify factors associated with receipt of curative intent therapy. Importantly, the authors also aim to assess these factors within an indigenous population that has historically been under-served by the medical system, the Maori. Overall, approximately 70% of patients with stage I/II disease received curative-intent treatment, and the majority of those received surgery. Logistic regression indicated several factors associated with receipt of curative intent therapy, but did not detect differences in receipt of curative treatment or curative surgery between Maori and non-Maori patients. It think this is an important paper because it assess possible disparities in lung cancer treatment.

I have only a few minor suggestions:

- The paper would benefit from some suggestions on how to improve rates of access to curative-intent therapy, if possible.

Response: We have added some suggestions in the first paragraph in the discussion.

- The discussion sentence "Our study also shows that patients who identify as Māori are less likely to receive curative surgical resection of Stage I and II lung cancer than those who do not identify as Māori" is based on the unadjusted analysis. That should be noted in the sentence. Usually the findings from a multivariable analysis will supercede the findings from an unadjusted analysis, and this could suggest that the NZ system is ensuring equity of access to curative-intent treatments for all.

Response: We have added after this sentence “This finding was based on the unadjusted analysis, and the difference disappeared after adjustment for other factors. This could suggest that the New Zealand healthcare system is ensuring equity of access to curative surgical resection for all patients.”

- In Tables 3 and 4, the columns with the effect estimate (OR or HR) and 95% CIs should be to the left of the column with the p-values.

Response: We have done the required changes.
Ian Woolhouse (Reviewer 2):

The manuscript describes the treatment and outcome for patients with early stage lung cancer in New Zealand. In particular, the factors associated with the receipt of curative treatment. The manuscript is well written and appears to be based on sound statistical methods. The results serve as useful assurance for the local lung cancer service but do not add significantly to the literature on treatment and outcomes for lung cancer. Further comments are shown below:

The study is based on registry data but the sample size is relatively small at under 600 cases of stage I and II disease.

Registry data usually includes missing values. This is not described in the results. For example, were lung function test results available for all patients?

Response: All the missing values were recorded as unknown in Table 1. Sixty nine patients had no FEV1 results.

It is not clear from the methods if all of the analyses included multiple logistic regression to take into account the effect of cofounding variables. The results are difficult to interpret without this information.

Response: All the odds ratios and hazard ratios were adjusted. We have added “adjusted” in the table titles to make it clearer.

The finding that patients who are older with poor lung function and poor performance status are less likely to receive curative treatment is neither surprising or new. Of more interest is whether there was an opportunity to better optimise these patients to facilitate curative treatment and whether they were offered a second opinion or high risk surgery.

Response: With SABR being introduced in New Zealand, more patients who are not eligible or high risk for surgical resection were offered SABR as an alternative curative treatment. We do not have information on whether patients were offered a second opinion.

Comparing the outcome of surgery versus SABR is subject to selection bias and should be interpreted with extreme caution. This should explicitly stated in the manuscript.
Response: We have said in the sixth paragraph in the discussion: Patients with stage I and II NSCLC treated with SABR have comparable outcomes to those treated with surgery. This is despite the finding that those treated with curative intent with SABR tended to have additional risk factors including older age, higher ECOG status score, more comorbidities and more smokers. The numbers of patients treated with SABR is relatively small and further follow up of a greater number of patients is needed to confirm this finding but the initial results are very encouraging.

Joanna Broad (Reviewer 3):

Overall the manuscript reads well and I am confident will inform practice, both in terms of use of SABR and in management of Maori people with stage I or II lung cancer.

The main criticisms I have with the paper is firstly the classification of curative or palliative treatment. It is not currently clear to me how this occurred. The classification seems to have been made post-hoc, and based upon the treatment, although a reader may think it is based on intent. For at least some of the people involved the decision will have been made in the presence of information about survival, and I suggest cannot help but be influenced by that knowledge when classifying people.

Response: The recording of palliative treatment as opposed to curative intent in made at the MDM after a discussion about the likely benefits and harms of treatment. Many factors contribute to this decision such as stage of cancer, patients ECOG status, lung functions, technical difficulties of surgery, and patient’s wishes, but these categories have been applied before treatment and are not “post-hoc” categories.

Secondly, I do not see a Limitations paragraph in the Discussion that addresses this or other methodological concerns and would like to see one.

Response: We have added a strengths and limitations paragraph at the end of the discussion: One of the strengths of our study is that it was based on the comprehensive lung cancer register, with relatively complete data on patient demographics, tumour characteristics and treatment. The limitations of this study included the small number of patients and short follow-up time in some treatment group, e.g. SABR. Also as an observation study, this study is prone to selection bias.
More minor notes:

1. The abstract has several abbreviations that are not spelt out in full, and indeed that is the case in the manuscript too.

Response: We have added the explanation to the abbreviations.

2. Inclusion of basic information about follow-up would be helpful, such as mean or median length of follow-up, and how many deaths.

Response: We have added in the fourth paragraph “There were 217 death (37.3%) in this cohort with a median follow-up time of 27 months and a mean follow-up time 34 months.” The median follow-up time by treatment type can be observed from Figure 1 and Figure 2.

3. Use of a Cox model assumes the hazards are proportional, ie reasonably consistent throughout. Given the curved shape of the KM plots, did the authors consider alternative models, especially for Māori/nonMāori comparisons where the separation seems ot occur only after 18 months?

Response: We have thought about the competing risk methods but we do not have the cause of death data, and decided to use KM method and Cox model.

4. How variables were selected to be included in the models is unclear. Of note particularly is socio-economic status that is mentioned in the Discussion but it is not clear whether it was available for use.

Response: We do not have socio-economic status data. We know from other literature that Māori generally have lower socioeconomic status.

5. On p.7, line 57 European and Australian studies are mentioned - were the timeframes of those comparable? In particular, was SABR available for a similar proportion of the follow-up time, or might we have expected difference between them because of the usefulness of SABR?

Response: The studies referenced were from a time when SABR was not a factor in rate of surgical treatment. We have not gone into the likely influence of SABR on surgery/curative intervention rates. We believe it principally increases the proportion who can be offered curative intent, but does not affect the surgical rates.
6. On p.9, line 23 the word ‘cured’ is used. I'm wary of such a claim.

Response: We have quoted the term “cured”. We believe it is important message that a proportion of patients with early stage disease receiving treatment with curative intent can expect a cure without experiencing a recurrence of their cancer.

7. On p.11, Abbreviations SCLC is not included.

Response: the abbreviations of SCLC has been added.

8. It is not clear to me which people in the cohort were included in models, eg those with missing data for cell type, FEV1 or ECOG. Might the authors note this specifically, and suggest any changes to practice to ensure that this information is not missing going forward? How might the missingness impact on the models?

Response: All people were included in the models. Missing data for cell type, FEV1 and ECOG were coded as unknown as a separate group, so that we could have every patient in the model. 73% of patients had no missing data on cell type, FEV1 and ECOG, and we believe the results from the model are robust.

9. I note in Table 1 that the genders are not similarly distributes between Māori/ nonMāori. Do they suspect it reflects the high rate of smoking among Māori women? How might that influence the results? Was an interaction term tried?

Response: The percentage of women and men between Māori/ nonMāori were not substantially different (p-value=0.064). The p-value of the interaction term was 0.575 in the Cox model and therefore it was not included in the final results.

10. Including counts in each of the groups in the KM plot legends would be helpful.

Response: The counts (number of patients at risk by follow-up time) are already in the table under the figure.
11. Finally, although the Table 4 caption currently states the outcome of survival, it seems to be death. It is likely easier for a reader to interpret ORs and HRs that are in a similar direction, e.g., higher estimates are associated with either better, or worse, outcomes. Reversing the outcome variable in Table 4 would be straightforward and helpful, though not essential.

Response: We prefer to have the ORs and HRs in the current layouts.