Peer review file

Article information: http://dx.doi.org/10.21037/jtd-20-1387

Reviewer A

Comment 1: This paper studied the treatment modality and trends in outcomes for a population-based cohort of stage I NSCLC patients. This article provided us real data of Ontario. However, new information in clinical practice for stage I NSCLC will be needed.
The proportion of surgery for the patients who were 70 and more years is remarkably low (20-30%). Why is the proportion low? If there is a suggestion, please describe this point.

Reply 1: We thank the reviewer for this comment. We agree that surgery for elderly patients is the best option when comorbidity permits. In this study as a population-based study a number of highly ill patients are included that may not typically be seen by many practitioners. This issue has already briefly been explained in the Discussion by including the following sentence "Elderly patients have typically had poor survival from lung cancer due to a lack of treatment. This is due to a combination of factors including comorbid illness, frailty, and a perceived lack of benefit with treatment (24)". In addition, we added the following statement in the Discussion:

Changes in the text (see Paragraph 3 under Discussion)**:** "Based on a systematic review of under-treatment in older patients, a vast range of factors were identified that may result in under-treatment (25). For instance, treatment options for older adults are highly affected by physician preferences (26,27), which results in the provision of less aggressive or less effective therapy in older patients (25). In addition to the suboptimal treatment options for the primary tumor, older patients also received differing treatments for the adverse effects of anticancer drugs, palliative care, pain management, and surgery (25)."

Comment 2: During the study period, the number of radiation therapy tended to increase in 80 years old patients. In 2015, a half of NSCLC patients underwent radiation therapy. Compared to other studies, the number is remarkably high. Okami et al. showed that the 5-year survival of patients ≧80 years with clinical stage I who underwent surgery was 55.7% (J Thorac Oncol 2009;4:1247-53). Patients ≧80 years could get a better survival by surgery. The reason why the high number of patients who received radiation therapy should be mentioned.

Reply 2: We agree that older patients are best treated by surgery where possible. We feel the observed changes relate to curative intent radiation being added to inoperable patients though there is a worry that patients operability is not being assessed by surgeons and multidisciplinary teams which is most appropriate. As we discussed in the Discussion section, the introduction of SBRT has substantially increased the proportion of radiation therapy. Also, as discussed in response to the previous comment, under-treatment seems to be an issue with elderly patients. Usually, patients who are perceived to be medically-fit undergo surgery, whereas those who are thought to be medically unfit receive radiation. In addition, the abovementioned study (J Thorac Oncol 2009;4:1247-53) only includes patients ≧80 years who underwent surgical resection and the results may not be quite comparable with our results which includes all patients (with or without surgery). However, as shown in Figure 2, the 5-year survival rate for elderly patients increased as the rate of radiation therapy increased, and the 5-year survival rate reached about 55% in 2015 for all elderly patients as a group which includes those who did and did not undergo

for surgical resection.

Comment 3: I could not catch what TNM classification was used. 7th or 8th edition? Additionally, there was no information about tumor size, i.e., T factor. Overall survival is different among T factors

Reply 3: Two editions of AJCC were used during the 9 years of study period (ref: Appendix 1.9 – CCO Staging Guidelines): AJCC TNM 6th edition for 2007-2009 and AJCC TNM 7th edition for 2010-2015. With regards to the comment regarding T-staging, this study included only patients with overall stage I NSCLC. The dataset, unfortunately, does not include all patient level data based on T factor.

Reviewer B

Thank you for giving me the opportunity to review this article "Change in treatment modality and trends in survival among stage I non-small cell lung cancer patients: A population-based study".

It is an interesting, well-written, retrospective study on a very large population; however, there are many arguments, which I believe, need to be addressed to improve the manuscript before to be accepted for publication. The following are part of the issues.

Comment 1: There is no information regarding the staging modality of the study population, total body TC, PET…

Reply 1: We thank the reviewer for this comment and agree that the method of staging is important. Generally, in Ontario patients undergo staging with CT and PET while MRI brain and invasive mediastinal staging reserved for those with a suspicion for mediastinal or distant metastases. However, the exact information regarding staging investigations is either not available or may be unreliable in large administrative databases. That said when the compliance with standards is evaluated Ontario performs very well relative to its international peers.
Comment 2: The study population includes two different types of population; pathologic and clinical TNM patients.

- How many R1 surgical resections?
- How many lymph nodes were removed?

Reply 2: While we agree with the reviewer that negative margins and R0 resections are extremely important prognostic factors, such detailed pathologic information is not available in large administrative datasets, and if available is often unreliable. When chart reviews are performed the R1/r2 is typically 1-2%.

Minor issues;
Introduction;
Comment 3: Lines 2/7 are unnecessary

Reply 3: We have deleted the most of this paragraph and combined it with the second paragraph.

Comment 4: Line 13/14; this sentence should be correct and reference number 7 should be updated.

Reply 4: Unfortunately, it is unclear what revision is being suggested. The sentence being referenced is "Lobectomy is the preferred operative approach, with preservation of pulmonary function and good oncologic outcomes." The reference has been updated.

Results
Comment 5: What is the definition of older group?

Reply 5: We changed one sentence in the Results section to make is clearer
Changes in the text (see Paragraph 2 under Results)**:** **"**The older the patients, the more likely they were to receive no treatment or radiation only**"**

Reviewer C

Comment 1: Please define NOS (not otherwise specified) in the paper.
Reply 1: We have modified our text as advised.

Comment 2: I am surprised by the number of pneumonectomies. Do you have any explanation?

Reply 2: The total number of pneumonectomies accounted for is less than 1% of all patients. As highlighted in the Discussion (paragraph 2), those patients undergoing pneumonectomy likely had central tumors. The proportion of patients undergoing pneumonectomy has decreased over time in Canada as techniques improved and staging practices are more robust.

Comment 3: Table 1 align each age group with their corresponding amounts.

Reply 3: We have modified the table to accommodate this suggestion. Also, instead of reporting the numbers for each year separately, we grouped years of diagnosis as 2007-2009, 2010- 2012, and 2013- 2015.

Reviewer D
This population-based study for stage I NSCLC by Akhtar-Danesh G includes several important messages according to the alteration of treatment strategy with its progression.

Comment 1: Author should discuss regarding the molecular target therapy with TKIs, which could definitively contribute to the improvement of survival outcome since 2007.

Reply 1: We appreciate the reviewer's comment and agree that advances in chemotherapy,

included targeted therapy with tyrosine kinase inhibitors, has contributed to the improvement in survival of lung cancer patients. However, the current study only captured patients with stage I disease, and these patients typically do not require chemotherapy. Nevertheless, the following statement has been added to the Discussion to address the reviewer's comments.

Changes in the text (see Page 12)**:** "Furthermore, advances in chemotherapy, including the introduction of targeted therapies such as epidermal growth factor receptor-tyrosine-kinase inhibitors (EGFR-TKIs), has been shown to have dramatically improved the survival of NSCLC patients, though within the context of this study only a small proportion of patients underwent chemotherapy, due to early stage disease."

Comment 2: The improvement of survival outcome overall could be caused by stage migration. Accurate staging using PET-CT or EBUS has been attempted recently. What do authors consider for this possibility?

Reply 2: We thank the reviewer for this comment and agree that improved staging techniques have also played an important role in the improved survival of lung cancer patients. The following statement has been added to the Discussion (paragraph 4) to reflect this comment:

Changes in the text (see Page 12)**:** "Finally, improvements in staging techniques including the increased uptake of PET/CT and endobronchial ultrasound (EBUS) have allowed for more accurate staging and a decrease in postoperative stage migration, subsequently improving stage-based survival."

Comment 3: IRB number should be included in text.

Reply 3: As suggested we have included the IRB number (2921) in the Ethical Statement under the Footnote.

Comment 4: Author should disclose the co-authors responsible to the results of statistical analyses in this study.

Reply 4: We included the following statement in the Autor Contributions: "(V) Statistical analysis: N Akhtar-Danesh".