

Peer Review File

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Reviewer A

Comment 1. intro “(47.5 months Vs 27.1 months)[6].” With ref-6= N Engl J Med, 2018. 379(24): p. 2342-2350. >> suggest to update as “(47.5 months Vs 29.1 months)[6].” With ref-6=J Clin Oncol. 2022 Apr 20;40(12):1301-1311.

Reply: We have changed the reference to the more recent reference quoting the 47.5 Vs 29.1 months.

Comment 2. method “This approach would exclude patients that received consolidation or palliative RT” vs “encompass well schemas typically given for palliation” >> Please clarify whether patients treated with palliative RT were eligible or not.

Reply: Patients with palliative RT were eligible. We have included all patients that were treated with radiation in this study.

Comment 3. method “Between January 2007 to March 2017” >> Please clarify if Mar 2017 was the latest period for available data or was chosen for other considerations.

Reply: The latest period available in terms of data for this study was March 2017. The data included in this study span a 10-year period and provide a wealth of information on outcomes of patients with LA-NSCLC treated in Ontario in recent years. Having data available for the 2007 to 2017 period, we are able to provide 5-year survival outcomes for all eligible patients.

Comment 4. method “We grouped patients into three RT dose 1 categories of <40Gy, 40-55.9Gy and \geq 56Gy. With an a/b ratio of 10 for lung cancer, these categories include RT schemas with BED <50Gy, 50-65Gy and >65Gy and encompass well schemas typically given for palliation, short-term local control or definitive treatment, respectively” >> Please provide reference[s] for the chosen thresholds.

Reply: To date, studies mostly divided radiotherapy treatments into palliative vs curative, using doses of 40-45Gy as the cutoff point between the two intents. However, in clinical practice a number of dose/fractionation schemas are being used in patients that are not symptomatic but cannot received standard of care chemo-RT. Such patients are frequently treated with hypo-fractionation schemas given with the intention to provide local control. Therefore, we feel that separating patients into three RT treatment groups, as discussed, is more appropriate when one aims to dissect the association of RT dose with outcomes in the LA-NSCLC setting. Table s1 describes well frequently-used chest RT schemas and their BEDs and makes the case for the generation of the three RT groups.

Comment 5. conclusion: “managed with RT alone. In this understudied population, we find that higher chest RT dose and utilization of staging FDG-PET are associated with improved OS.” >> In the reviewer’s mind, it might be better to perform multivariate analyses [including RT dose and PET] for patients treated with RT alone.

Reply: We agree with the reviewer on this point. Indeed, we have provided the results of multi-variant analysis in Table 2.

Reviewer B

The whole manuscript is well written as a population based analysis. The demonstration of radiation dose and PET-CT utilization affecting survival is encouraging. Suggestions for amendments

Comment 1. Patient characteristics divided into the three groups - RT alone, cCRT, sCRT would be more informative.

Reply: We agree with the reviewer. However, the primary aim of this study was to help understand overall population outcomes for patients that received treatment with RT alone and those that receive standard of care concurrent-Chemo-RT (cCRT). Our study did not focus specifically on patients that received sequential chemo-RT but we have included the outcomes of such patients in our cohort. They are described in the manuscript and are illustrated in Tables s2 and s3. However, the timelines and treatment decision-making for patients receiving sequential chemo-RT (sCRT) are frequently complex and many times disease response to the first treatment determines the subsequent course of therapy in these patients. For that, our patient selection algorithm was designed to clearly separate such patients out from those receiving RT alone and those that received standard of care cCRT. Based on that, we feel that the outcomes obtained in this study may not represent well the average patient treated with sCRT. Therefore, we did not feel that it was appropriate to present these results in the main body of the manuscript.

Comment 2. Performance status and smoking status should be analysed in the multivariable analysis

Reply: Unfortunately, performance status (as this is assessed in the oncology setting) and smoking status data were not captured reliably in the databases used in this study and are not available for analysis. The Charlson Score (CCI) is captured in Ontario provincial databases. It did not appear to have prognostic value in multi-variable analysis (Table 2).

Comment 3. Age categories e.g. > 60 years vs < 60 yrs would provide a clearer picture for readers, though it is not statistically significant.

Reply: We agree, that analysis of data on the basis of patient age (>60 vs <60 years) may have been able to improve the analysis. However, as noted by the reviewer, in our cohort, age was not significantly associated with outcomes.

Comment 4. Radiation techniques e.g. IMRT/ Conformal RT, also your national acceptance of radiation dose for lung / heart that may affect your dose prescribed e.g. V20 < 35 % etc. or other factors that affect the prescription dose.

Reply: We agree with the reviewer that such data would be of value but this information was not captured reliably in the databases we used in this study and are not available for analysis.

Comment 5. Chemotherapy regimen used and number of cycles of chemotherapy given

Reply: Unfortunately, we do not feel that our databases contain reliable information of the chemotherapy regimens and number cycles used. The information is accurate for the timelines of chemotherapy treatments and it was used in the algorithm of patient selection.

Comment 6. Percentage of upstaged after using PET-CT

Reply: We agree, this type of information would have been very interesting. Unfortunately, we do not have access to that information.

Comment 7. Cancer specific survival may also be important for dose analysis (OS is biased by comorbidities etc).

Reply: While we completely agree with reviewer's point, cancer specific survival was not reliably captured in our data. Overall survival is the only survival outcome that is reliably captured in our databases and, clearly, this is more consistent with real world setting results.