Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-22-1649

Reviewer A

highlight box

COMMENT 1:

could be clearer in terms used.
line 35 'no synergy in toxicity between radiotherapy therapy'.
line 40 ' exposing patients to excess synergistic toxicity'.

REPLY 1:

We appreciate the reviewer's attention to our wording. Because we used the term synergy in parenthesis after "in other words" or "*i.e.*", we believe that these two explanations will communicate our paper's highlights with adequate clarity to a general audience.

CHANGES IN TEXT 1:

None

Abstract

COMMENT 2:

Sentence starting in line 51 could be clearer in intent.
missing a full stop on line 62.

REPLY 2:

We appreciate the reviewer's attention to our wording.

CHANGES IN TEXT 2:

On page 3: We have added additional text to line 52 (page 3) to clarify this sentence. We have added a full stop to line 62.

Discussion

COMMENT 3:

Again could be clearer in terms used.
line 221- a synergism in toxicity between RT and ICI.
line 223- The lack of synergisim in toxicity.
line 228- could use 'increased' instead of 'worse'.

REPLY 3:

We appreciate the reviewer's attention to our wording. While we agree with your comment about line 232 (228 in prior version) on page 6, and we made the associated change in the text, we prefer our wording for at lines 221 and 223. Our use of synergism is used intermittently and intentionally throughout the manuscript—synergism is a clinical/biological term and interaction is a statistical term – we wished to use these two terms throughout the manuscript to communicate that we tested for an interaction that communicates a meaningful synergy in causing pneumonitis.

CHANGES IN TEXT 3:

On page 6, We have made the requested changes to line 232 (worse → increased)

COMMENT 4:
For the patients who only received RT or ICI without use of the other modality in the following 3mths, is it possible these patients could have received the other modality of treatment in the second 3mths of the 6mths outcome assessment window? Was this data collected, could this affect the rates of pneumonitis in each cohort? Although the main outcome required is from treatment close together within 3mths, it may have confounded the RT or ICI alone outcome data for comparison.
REPLY 4:
We appreciate the reviewer's insightful comment. It is certainly true that patients could be treated outside of the "double exposure window". For this reason, we believe that our sensitivity analyses varying the allowable time between each treatment is critical to the relevance of our study. We found no differences in our results when varying this window.
CHANGES IN TEXT 4:
None

COMMENT 5:
It is clear the brain RT treatments have been removed from the data, but were all the other RT treatments to the thorax?
REPLY 5:
This is another insightful comment and a major limitation of studies of radiation in SEER-Medicare. This is also a subject of ongoing work by the investigators involved in this study. We conducted a sensitivity analysis requiring 5 fractions of SBRT and 15 fractions of conventional RT to qualify as thoracic RT. We have devoted a sentence to this important point on Page 5 line 142-143. We have also highlighted this limitation in our limitations section with additional text on Page 7 Lines 260-261.
CHANGES IN TEXT 5:
Page 7 Line 260-261: added reference to the unclear treatment site in SEER-Medicare data
Page 5 142-143: added "pneumonitis (including only measuring pneumonitis cases that resulted in steroid prescription"

Reviewer B

COMMENT 6:
Manuscript is well written and provides additional information on immunotherapy and RT treatment.
REPLY 6:
We appreciate the reviewer's comment about the clinical importance of our study.
CHANGES IN TEXT 6:
None

Reviewer C

COMMENT 7:
This is overall creative approach in assessing the potential synergistic risk of combining RT and ICI.
There are some minor concerns.
I advise the authors to use more plain languages. There are frequent uses of statistical terms which should be defined in easier language. I think the manuscript may be difficult for readers from non-English speaking countries.
REPLY 7:
We appreciate the reviewer's acknowledgement of our novel study design.
We agree with the outlined concerns below and that the language used may be unfamiliar to certain audiences.
We have attempted to make adjustments per comments 1-3 above.
CHANGES IN TEXT 7:
See comments 1-3.

COMMENT 8:
Furthermore, there are plethora information in the tables, figures and supplementary material, which were not described in the manuscript. You do not have to be redundant, but please be more descriptive about the key terms such as definition of pneumonitis, so readers would not lose the flow when the reading the manuscript.
REPLY 8:
This has been a challenging aspect of this investigation, and we appreciate the reviewer's attention to this detail. The primary analysis is described in detail in the results and discussion. While we did conduct a multitude of sensitivity analyses, we think that the details of those results should not be discussed in the main text. Those analyses were meant to be only supportive in nature, and when there were interesting trends/deviations we did discuss them (e.g., Page 7 line 239.).
CHANGES IN TEXT 8:
None

COMMENT 9:
Line 122-124
Please describe in details, how pneumonitis is defined. Add information about steroid use. Did all pneumonitis patients undergo minimum 7 days steroid use according to the algorithms?
REPLY 9:
We used a validated algorithm for assessing pneumonitis in claims databases. The details of these algorithms can be explored in the original validation study. Of note, our primary algorithm did not require steroid use, but we did conduct a sensitivity analysis using a more stringent definition and found no differences.
CHANGES IN TEXT 9:
Per another comment we made changes to Page 5 lines 142-143: adding details about the sensitivity analyses of pneumonitis definitions. We also clarified that our algorithm had high positive predictive value, further supporting our implementation, to page 4-5 lines 124-125.

COMMENT 10:
Line 184-186
Also, the RT and RT+ICI group had higher frequencies of patients with brain metastases at the time of lung cancer diagnosis (pI assume that the RT arm received the localized treatment to the brain metastatic lesions. The main limitation of this article is that only limited data on target of radiotherapy is shown. In stage IV NSCLC, curative RT to primary lung mass is not a consensus treatment yet.
REPLY 10:
We appreciate the reviewer's attention to this limitation. Please see reply to comment 5.
CHANGES IN TEXT 10:
See Comment 5

COMMENT 11:
Prior radiotherapy has been proven as a risk factor for ICI related pneumonitis in various studies, so if you present a rather contradictory conclusion, I recommend you to give some explanations about it.
REPLY 11:
Thank you for pointing out that our article does contradict the current dogma. We believe these surprising results merit discussion. We discussed how our findings contradict the PACIFIC trial and a recent FDA analysis, and we give explanation for why this might be.
CHANGES IN TEXT 11:
None

COMMENT 12:
In the Methods section, authors described briefly that radiotherapy for brain metastases were excluded, I recommend that you give some more explanations that only thoracic radiotherapy were included for analyses. In general, bone lesions are one of the most frequent sites of radiotherapy, were they excluded too?
REPLY 12:
This is an important comment that our group is currently investigating. It is important to remember that there is no clear indicator in claims databases for where patients have metastases and to which site they receive radiation. This is a major limitation that warrants future study. Please see reply to comment 5 and 10.
CHANGES IN TEXT:
See Comment 5

COMMENT 13:
Line 262-267
Despite your explanation about defining pneumonitis using ICD codes and validation efforts, I think more explanations should be provided to convince readers that this algorithm is a reliable one. Pneumonitis shows various clinical manifestations, and no CT findings are same. I am not sure if clinicians insert promised ICD diagnostic codes to show that the patients had immunotherapy related pneumonitis.
REPLY 13:

We appreciate the reviewer's comments about this issue. Studies of cancer treatment toxicity in claims databases are challenging, and we understand if some readers have skepticism about the validity of our inferences. In order to address this concern, we will add an additional sentence explaining the reasoning behind our comfort in applying this algorithm.

CHANGES IN TEXT 13:

We added a sentence to our methods section explaining why we believe our algorithm for identifying pneumonitis is valid (Page 4-5, lines 124-125).

COMMENT 14:

Please describe whether all patients underwent steroid treatment, which steroid regimens were the most frequently used, median day of steroid use, and all other relevant and available information about steroid use.

REPLY 14:

We appreciate the reviewer's interest in this nuance of our pneumonitis treatment. We believe addressing this concern would be beyond the scope of this study and impractical to include in this manuscript. That being said, this is an exciting line of inquiry, and our group would be excited to explore variations in prescribing in Medicare Part D.

CHANGES IN TEXT 14:

None

COMMENT 15:

What was the interval between steroid use initiation and date of the pneumonitis diagnostic codes insertion? Were they close enough to say that steroid was applied for immunotherapy related pneumonitis?

REPLY 15:

Thank you for this insightful comment. We encourage you to read our full validation study if you are interested in exploring these details (doi:10.1002/pds.5339). We believe addressing this comment would detract from our primary analysis, but we did make a change to our text per your specific comments below.

CHANGES IN TEXT 15:

None

COMMENT 16:

Were data on concurrent oxygen therapy available? Gr II pneumonitis can be defined as pneumonitis codes with steroid use only, and Gr III pneumonitis can be defined as pneumonitis codes, steroid use and additional oxygen supply.

REPLY 16:

This is a great point and worth exploring in another study. Our team is interested in exploring how pneumonitis can be better measured in claims databases. Our validation study for pneumonitis defined all grade pneumonitis which is what we implemented in this investigation. In our validation study, we show that the performance of our algorithm is superior when analyzing admissions to the hospital (presumably higher-grade pneumonitis). We also assessed steroid prescriptions in a subgroup analysis which had superior performance. While we did not look at oxygen, it is unclear how oxygen therapy would be included in claims databases.

CHANGES IN TEXT 16:

Per this reviewer's comment, we added some additional text to Page 5 line 142-143 to clarify how we defined pneumonitis in our sensitivity analyses.