Peer Review File
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Reviewer A

Comment 1: You may want to define what ACR and ARR in the abstract

Reply 1: We added the definition of out-of-field (distant) response rate (DRR) and distant disease control rate (DCR) to the abstract as suggested by the reviewer. "out-of-field (distant) response rate (DRR) and distant disease control rate (DCR) were defined in unirradiated lesions only." (line 45). Besides, in consideration of the fact that the present study cannot rigorously verify the abscopal effect, we have replaced "abscopal" with "distant" in the entire manuscript.

Comment 2: In the introduction you cite the PACIFIC trial but I would be careful here as the PACIFIC trial didn't answer whether radiation and immunotherapy can be delivered together and doesn't really follow along the point you are making.

Reply 2: PACIFIC trial demonstrate the long-term clinical benefit with durvalumab following CRT and further establish the PACIFIC regimen as the standard of care in this population for locally advanced non-metastatic.We have modified the point we were making, which was "The results of several clinical trials, including PACIFIC, have demonstrated that iRT has a promising impact on patients with specific types of cancer." (line 81)

Comment 3: The PEMBRO-RT trial did show a signal for PD-L1 negative patients leading to the current Alliance trial of PD-L1 negative NSCLC randomized to SOC systemic therapy with or without low-dose SBRT so I would mention that in your intro and discussion as it relates to your paper.

Reply 3: Thank you for your comment. We added the clinical study results on hypofractionated radiotherapy from the PEMBRO-RT trial as suggested by the reviewer. "The results of a randomized phase I/II trial investigating the treatment of lung and liver lesions in NSCLC patients have demonstrated that combining pembrolizumab with hypofractionated SBRT (50 Gy in 4 fractions) yields better out-of-field ORRs and longer median PFS times than combining pembrolizumab with traditional RT (45 Gy in 15 fractions). These findings suggest that hypofractionated radiotherapy may be more effective in coordinating the effects of immunotherapy (33051340)." (line 305)

Comment 4: What is the definition of efficacy evaluation which you mention in the methods? I would be more specific if this included imaging, such as a CT scan.

Reply 4: We added the the definition of efficacy evaluation as suggested by the reviewer. "Patients underwent imaging evaluations after completing radiotherapy but while still on immunotherapy. According to iRECIST (v. 1.1), MRI or CT scans of the brain, neck, chest, and abdomen for all patients were assessed by at least two associate chief physicians or higher-level

imaging specialists and one oncologist for a comprehensive evaluation of the patient's overall health status." (line 166)

Comment 5: Just to clarify, were EGFR and ALK mutated NSCLC excluded? Generally, these patients don't receive immunotherapy which is why I ask.

Reply 5: Patients EGFR and ALK mutated NSCLC were eligible to be included in this study if they met the inclusion criteria, and the patient number of different EGFR mutation states were listed in table 1.

Comment 6: Page 8, line 134. I would separate out the 101 (50%) into another sentence as it seems to be combined with the sentence discussing only those who received combination therapy.

Reply 6: We have separated out the 101 (50%) into another sentence according to the reviewer's suggestion. "Of the total patients, 155 were treated with anti-PD-(L)1 alone (ICI alone group) and 202 were treated with anti-PD-(L)1 in combination with radiotherapy (ICI+ radiotherapy group), 209 were treated with chemotherapy." (line 138)

Comment 7: Did any patients receive upfront radiation followed by immunotherapy? You don't mention any in the methods.

Reply 7: Yes, some patients received upfront radiation followed by immunotherapy, and it is already mentioned in line 139 "Of the 202 (56.6%) patients who received combination therapy, 160 (79.0%) were treated with radiotherapy prior to immunotherapy, 42 (20.8%) were treated concomitantly with radiotherapy and immunotherapy."

Comment 8: I am confused by what the definition of abscopal disease control rate is? How is this different than the ARR. Also how are you sure these are abscopal effects. Were the patients progressing in other sites prior to the radiation and then had a response? I would recommend being very clear on the definition of the abscopal effect because a patient for example who just starts on immunotherapy and gets radiation and on subsequent imaging has response in all sites would be unclear if abscopal or just a response to immunotherapy. You need to be clear that these patients defined as having an abscopal effect were progressing in other sites while on immunotherapy prior to radiation and then responded after the radiation to sites not treated by radiation.

Reply 8: The revision was made according to the comments. "Tumor control included complete response (CR) and Partial response (PR), both of which were classified as achieving ORR. Both Stable disease (SD) and Progressive disease (PD) were defined as no remission. We also used the Disease control rate including SD, PR, and CR. The rates of in-field objective response (ifORR) and in-field disease control (ifDCR) were defined in irradiated lesions only. In contrast, the rates of out-of-field objective response (distant response rate) and out-of-field disease control (disease control rate) were assessed in unirradiated lesions." (line 158)

Abscopal effect refers generally to distant effect related to the immune impact of radiotherapy,

and We cannot distinguish between abscopal effects and tumor regression caused by immunotherapy in a retrospective study. Consequently, we replace “abscopal” with “distant ” in the entire manuscript.

Comment 9: What was the radiation fractionation? Is this SBRT? I would elaborate on the various dose regimens and at least report the most common ones.

Reply 9: We’ve added various dose regimens in the method and listed them in table 2. “Patients received conventional fractionated radiotherapy or stereotactic radiotherapy. The single dose of conventional fractionated radiotherapy ranged from 1.23-4 Gy, and the number of fractions ranged from 10-38f. The single dose of stereotactic radiotherapy ranged from 5-8 Gy, and the number of fractions ranged from 3-10f. Treatment was given once daily, five times a week. The median biologically effective dose (BED) was 72 Gy, ranging from 12-175 Gy, with a total dose of 21-70 Gy. The duration of radiotherapy ranged from 5-49 days.” (line 144)

Reviewer B

The present study duplicates many other already published studies in this setting.
Authors however provide new data which is the comparison between irradiation before ICI versus irradiation during ICI.
They also report a cohort of 357 patients which is one of the largest cohort in this setting.
There are many parts to improve:
Comment 1: The « Abscopal » effect reported is inaccurate. Abscopal effect refers generally to distant effect related to the immune impact of radiotherapy. The present study cannot rigorously verify the abscopal effect since radiotherapy was not delivered at progression under ICI. The PFS advantage of the ICI+RT strategy suggest there was abscopal effect, but this is only a retrospective, non randomized study, so this is very speculative.
Consequently, please replace « Abscopal » with « distant » in the entire manuscript.

Reply 1: Thank you for your suggestion. We thus replaced “” abscopal” with “distant” in the entire manuscript.

Comment 2: Also, authors evaluated the « abscopal » effect in patients only treated with ICI, without radiotherapy, which is not possible; in this group authors can only evaluate the ORR : Figure 2B is then very confusing and authors shoudl clarify what they reported there.

Reply 2: We modified the caption of the figure legend in line 572. In the ICI group, only ORR was observed and not ARR, so here we compared the ACR in the radiation-immunotherapy

Comment 3: Authors did not detailed what type of anti-PD1 or anti-PDL1 was given: nivolumab? pembrolizumab ? durvalumab ? other ?They have to detail this.

Reply 3: We have added the types of ICIs to Table S1.

Comment 4: They also did not detail the radiotherapy regimen. They have to describe the median **number of fractions, dose per fraction, duration of radiotherapy and total dose** delivered.

Reply 4: We've added radiotherapy regimen in the method. And they were described in detail in Table 2. "The patients received conventional fractionated radiotherapy or stereotactic radiotherapy. The single dose of conventional fractionated radiotherapy ranged from 1.23-4 Gy, and the number of fractions ranged from 10-38f. The single dose of stereotactic radiotherapy ranged from 5-8 Gy, and the number of fractions ranged from 3-10f. Treatment was given once daily, five times a week. The median biologically effective dose (BED) was 72 Gy, ranging from 12-175 Gy, with a total dose of 21-70 Gy. The duration of radiotherapy ranged from 5-49 days." (line 144)

Comment 5: If different fraction among patients they should detail the median Biological Effective Dose and test the median BED rather than the 54 Gy cut-off.

Reply 5: The BED data was added to the newly added Table 2, and the details related to BED were added to the methods section. "The median biologically effective dose (BED) was 72 Gy, ranging from 12-175 Gy. The BED was calculated using the basic BED model in the literature, which takes into account the beam on time and the prescribed dose, and different alpha/beta ratio for different histological classes." (line 151)

Comment 6: Median PTV size is also needed since the volume of radiation could impact the lymphocyte blood count and ICI efficacy.
Median PTV should be tested as prognostic factor.

Reply 6: We have added Table 2 and updated the univariate and multivariate Cox regression data in Table 3. The median PTV size was 213.7ml, ranging from 9.9-2148ml. In multivariate analysis, we found that only PTV volume (≥213.7 ml vs <213.7 ml, HR: 1.97, 95% CI: 1.14-3.39, P=0.015) could serve as an prognostic factor. We supplemented relevant research on this part in line 342 of our discussion.

Comment 7: Typo, line 120: replace « age: » with « age; »

Reply 7: We have changed it accordingly.

Comment 8: Typo line 146: « Objective response rate (ORR) was defined 147 as the proportion of patients with CR or PR for at 12 weeks. » please rephrase.

Reply 8: We have rephrased the sentence as suggested by the reviewer. "Tumor control included complete response (CR) and Partial response (PR), both of which were classified as achieving ORR. We also used the Disease control rate included SD, PR, and CR." (line 158)

Comment 9: English has to be reviewed by an English native speaker.

Reply 9: The English text has been reviewed by a native English speaker.

Comment 10: Replace single site and multiples sites with « singe irradiated site » and « multiples irradiated site ».

Reply 10: We have made the changes as requested in Table 2,4, line 240.

Comment 11: Why p-value is missing in Table 1 for the comparison of « Line of ICI treatment » ?

Reply 11: We added it to Table 1"p=0.002"

Comment 12: Table 2:
the name of the first column is wrong: replace « Treatment-related Aes » with Variables

Reply 12: We have changed "Characteristic" to "Treatment-related Aes".

Comment 13: list the other factor tested for every variable: for example « Female Gender » below « Male Gender », « Concomitant radiotherapy » below « Combined with radiotherapy », etc …
Please do it also for other Tables.

Reply 13: We have listed the other factor for each variable tested in Tables 3, 4, and 6.

Comment 14: Generally, factors included in the multivariate analysis has not to be related. Authors should perform first a Spearmen Correlation to exclude factors that strongly correlated each other.
Please do it for all Tables.

Reply 14: A Spearmen Correlation was performed firstly, all the factors included in the multivariate analysis were not strongly correlated each other for all Tables （Line 179，Line 222，Line 244，Line 274）.

Comment 15: Also authors should detail the number of patients for each category (for example: number of male, number of female, etc…) which help to indicate the statistical powr of the analysis. For example, PD-L1 status was missing for most of patients (80-90%) and was included in the multivariate analysis in Table 2. This has considerably decreased the statistical power of the multivariate analysis.

Reply 15: We have detailed the number of patients in each category in a new Table 2.

Comment 16: Wild-type epidermal growth factor receptor (EGFR) was inclusion criteria (in Material and Methods chapter) and finally appear in Tables: what finally did authors? Did they include or exclude these patients?

Reply 16: Patients were eligible to be included in this study if they met the inclusion criteria, and the patient number of different EGFR mutation state were listed in table 1.