Peer Review File

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Reviewer A

1.While this treatment approach of TRT with chemo+IO for pts with ES-SCLC is an important question, the current manuscript is lacking critical clinical data and information – and would benefit from a more narrow patient population to report on.

Reply 1: When we first conceived of this research, there were no relevant real-world studies on the use of TRT with chemo-immunotherapy for patients with ES-SCLC. When a new treatment mode is proposed, its safety is the first consideration. We wanted to use a large sample size to study the safety of this treatment, so we included as many patients as possible who were receiving this treatment. In terms of efficacy, our univariate and multivariate regression analyses showed that those who received consolidative TRT benefited more than those who received TRT as palliative or salvage treatment for superior vena cava syndrome or disease progression. In a future study, we plan to further explore the use of TRT with chemo-immunotherapy in a more narrowly defined patient population. Unfortunately, some clinical data and other information could not be traced in the study population of the present study. We provided the most complete clinical information available and modified the text accordingly.

2.Many confounding covariates analyzed, also how TRT was delivered quite heterogenous with respect to RT dose, timing, purpose. Authors should consider narrowing the patient population to be to report more interpretable conclusions, such as excluding the palliative and salvage RT pts and focusing on the consolidation TRT instead as an example.

Reply 2: Based on your comments, we re-conducted the univariate and multivariate regression analyses. The conclusion is that patients who received consolidative TRT benefited more than those who received TRT as palliative or salvage treatment for superior vena cava syndrome or disease progression. We did not exclude the patients who received palliative and salvage RT because it was important to have a large patient population for evaluation of safety. Importantly, this trial is still ongoing, and we will continue to follow these patients to record survival and determine whether more patients choose consolidation radiotherapy as a follow-up treatment.

Changes in the text: Table 3 and the area with grey highlights in Page 2, lines 46-49 and 52-55.

3.For a TRT paper, the actual TRT doses and fractionation used should be presented – see Table S2 comments. Also portions of Table S2 should probably be a Main Table.

Reply 3: We moved Table S2 to the main text and labeled it as Table 2.

Changes in the text: Table 2 and the area with grey highlights in Page 8, line 204.

4.All Tables (esp Tables 2, S3, S4)
Must label/include the reference value for these UVA and MVA analyses and hazard ratios for PFS.Age = younger or older, what was the cutpoint?Gender = is male is reference value? Or female? Purpose of TRT = which category is reference? Etc.

Reply 4： We labeled the reference values for the univariate and multivariate analyses and added the hazard ratios for PFS. We used the age of "65 years" as a cutoff, and "male" as the reference gender. We included "consolidative TRT" as a covariate in these analyses instead of "purpose of TRT". The reference values for other confounders were labeled in Tables 3, S2, and S3.
Changes in the text: Tables 3, S2, and S3.

Table 2
5.Immune maintenance therapy would be a confounder in this non-randomized study --- only pts who did not progress would then get maintenance. I caution against this as a covariate.
Reply 5: We carefully discussed your advice and checked the clinical data and text again. It is true that only patients who did not progress would receive immunotherapy as a maintenance treatment. We believe it is inappropriate to include "immune maintenance therapy" as a covariate in the univariate and multivariate analyses. We therefore excluded this and performed the analyses again.
Changes in the text: Table 3, S2 and S3.

6.Table 4 –add in more explicitly which is the "present study", re-label column #1
Reply 6: We made a clear statement regarding the "present study" and re-labeled column #1 accordingly.
Changes in the text: Area with gray highlights in Table 5 and Page 11, lines 290-293.

Table S2
7.Descriptions of "dose of thoracic RT" is in sufficient. What are the RT doses? And # of fractions for each of these categories?
Reply 7: Conventional radiotherapy is most commonly given as 1.8 to 2.2 Gy single fractions per day, 5 days per week for 3 to 9 weeks, with a maximum total dose between 60 and 90 Gy. Hyperfractionation refers to smaller doses of 0.5 to 1.8 Gy with multiple fractions per day for 2 to 4 weeks, and hypofractionation refers to single daily fractions of 3 to 20 Gy with a small number of fractions usually over one week.
Changes in the text: Area with gray highlights in Page 6, lines 138-144.

8.For the 32% who received concurrent TRT with systemic therapy – this is not the usual standard for ES-SCLC, why did these patients receive concurrent TRT? Can more detail be included? Where these lower bulk disease patients and more

'limited-stage' like?
Of note, in methods authors state ES-SCLC defined as disease beyond a single radiation port – then how were these pts eligible for concurrent TRT which is more of a LS-SCLC approach?
How were pts selected for concurrent vs sequential TRT?
Reply 8: We have reviewed the relevant literature and re-checked the clinical data and text regarding the included patients. The original text might have confused the definitions of concurrent and sequential TRT, leading to mistakes. We refined the detailed information of TRT according to the purpose of TRT (consolidative, palliative, or salvage treatment), and divided consolidative TRT into concurrent and sequential TRT. Thoracic radiation was given to 58 patients who responded to systemic treatment as consolidation therapy; TRT was given sequentially with chemo-immunotherapy in 45 patients and concurrently with chemo-immunotherapy in the other 13 patients. Eight of the patients who received TRT concurrently with chemo-immunotherapy had their immunotherapy halted during TRT. Most patients receiving TRT with concurrent chemo-immunotherapy were oligometastatic and had no local symptoms, and all of them had good ECOG performance status. Eleven of them had metastatic mediastinal lymph nodes.
In the Methods, we cited the definition of ES-SCLC from *Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology*. This considers ES-SCLC with a confirmed extensive stage due to distant metastasis or thoracic extensive disease beyond a single radiation port. All patients receiving TRT with concurrent chemo-immunotherapy definitely had distant metastases. The patients whose disease was beyond a single radiation port were treated with sequential TRT after shrinkage of the thoracic lesion.

The clinicians decided which patients received concurrent TRT or sequential TRT, and we could not identify the exact reasons by simple review of the medical records. However, we found that most of the patients receiving TRT with concurrent chemo-immunotherapy were oligometastatic, had no local symptoms, and had good ECOG performance status based on available clinical information.
Changes in the text: Area with gray highlights in Page 8, lines 202-206; Page 12, lines 321-325; Page 14, lines 371-382.

9.Was immunotherapy given concurrent with TRT? Or was it TRT alone then to immunotherapy maintenance?
Reply 9: TRT was given concurrently with chemo-immunotherapy in 13 patients, and 8 of these patients had the immunotherapy halted during TRT. Sequential TRT refers to TRT that was given alone between two cycles of chemo-immunotherapy (i.e., no overlap with any of the cycles of chemo-immunotherapy).
Changes in the text: Area with gray highlights in Page 14, lines 371-377.

10."Timing of TRT" is confounded by the "Purpose of TRT" if presented with SVCS I'm assuming TRT would have been 'early' – also conversely "salvage RT

after disease progression" would be 'late TRT'

Reply 10: TRT was given as consolidative, palliative, or salvage treatment, and consolidative TRT was divided into concurrent and sequential TRT. The TRT treatment was also stratified according to its timing: early-TRT or late-TRT. Early TRT means that TRT was administered within the first 3 cycles of systematic induction therapy, and late TRT means the TRT was administered after 3 cycles. In fact, patients receiving palliative TRT for SVCS were categorized as early TRT, and those who received salvage TRT for disease progression were categorized as late TRT which only occupied a small percentage.

Changes in the text: Area with gray highlights in Page 8, lines 209-211.

Table S1

11.Why for n=36 (46%) of pts did not receive immune maintenance therapy?

Reply 11: Among patients who did not receive immune maintenance treatment, some who underwent second-line therapy experienced disease progression during the first-line chemo-immunotherapy combined with radiotherapy, and some refused immune maintenance treatment due to poor health or financial constraints, and instead opted for regular follow-up or other maintenance therapies, such as etoposide capsules or anlotinib.

Changes in the text: Area with gray highlights in Page 8, lines 195-200.

Reviewer B

1.This is an interesting, well written manuscript that refers to the topic of major clinical and scientific interest. Its outcome is adequately described and discussed with reference to the most recently published studies. While this is a retrospective study the Authors well addressed most of its limitation.

The only (minor) issue that requires correction are Figures 1-2 that are difficult to read. Please use larger fonts in numerical and text description of the scales.

Reply 1: We modified Figures 1 and 2 according to your advice.

Changes in the text: Figures 1 and 2.

Reviewer C

In this study, the authors reported the safety and efficacy of thoracic RTx with chemo-immunotherapy in ES-SCLC patients. The role of thoracic radiation in ES-SCLC treatment remains controversial, but recently, several studies have reported the benefit of chemo-immunotherapy and radiation treatment for patients with ES-SCLC. I think it is a helpful, interesting dataset in clinical practice. However, there are certain points that the authors need to revise.

1.A precise definition of radiation therapy is needed

- CCRT as defined by the authors requires a description of the schedule.

- Sequential radiation means starting, after cytotoxic chemo+immunotherapy, or

while on maintenance immunotherapy?

Reply 1: We categorized TRT as consolidative, palliative, or salvage treatment according to the purpose, and divided consolidative TRT into concurrent and sequential TRT. Concurrent TRT means that the radiotherapy and chemo-immunotherapy overlapped in time. Sequential TRT means that the TRT was introduced alone between two cycles of chemo-immunotherapy without overlaps with any of the cycles of chemo-immunotherapy.

Changes in the text: Area with gray highlights in Page 8, lines 202-206 and Page 14, lines 371-377.

2.The authors reported that CCRT was the most effective radiation regimen, and later multivariate analysis showed that late radiation was a significant factor. Please explain this issue.

Reply 2: We have reviewed the relevant literature and re-checked the clinical data and text regarding the included patients. The original text may have led to confusion regarding the definitions of concurrent and sequential TRT. In the revised text, we defined TRT (according to its purpose) as consolidative, palliative, or salvage treatment, and then divided consolidative TRT into concurrent and sequential TRT. Univariate and multivariate analyses were performed using available clinical and demographic information. Patients who received consolidative TRT benefited more in terms of PFS than those who received palliative TRT for SVCS and tumor compression or salvage radiotherapy after intrathoracic disease progression. Our retrospective analysis found that early TRT (≤3 cycles of chemo-immunotherapy) provided no more benefit than late TRT (>3 cycles) in terms of control of distant metastases.

Changes in the text: Area with gray highlights in Page 9, lines 236-238 and 240-245.

3.I suggest more concise, understandable, and aggressive English proofreading is needed.

Reply 3: We worked with a professional medical writing service to improve language usage in the entire manuscript.

4.Please describe the number of participating cases for each center.

Reply 4: Thirty-six patients were from the General Hospital of Eastern Theater Command, and 42 patients were from Jiangsu Cancer Hospital, China.

Changes in the text: Area with gray highlights in Page 7, lines 174-176.

Reviewer D

1.In this work there is a high variability of radiotherapy treatments. Notably, many patients received radiotherapy during induction therapy. At the same time, many patients received palliative radiotherapy. The rate of consolidation radiotherapy which is the hot topic of the chemo-immunotherapy era is very low.

Reply 1: We reviewed the relevant literature and re-checked the clinical data and text regarding the included patients. Our original text may have led to confusion regarding

the definition of concurrent and sequential TRT. We defined TRT (according to the purpose) as consolidative, palliative, or salvage treatment, and then divided consolidative TRT into concurrent and sequential TRT. Thoracic radiation was given to 58 patients who had responses to systemic treatment as consolidation therapy; TRT was then given sequentially with chemo-immunotherapy in 45 patients and concurrently with chemo-immunotherapy in the other 13 patients. Eleven patients received palliative radiotherapy for SVCS and tumor compression, and 9 patients received TRT as salvage therapy for disease progression.