Final report of a prospective randomized study on thoracic radiotherapy target volume for limited-stage small cell lung cancer with radiation dosimetric analyses—reply

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Thank you for your interest in our study and we appreciate your constructive editorial comments on our recent publication: "Final report of a prospective randomized study on thoracic radiotherapy target volume for limited-stage small cell lung cancer with radiation dosimetric analyses" (1).

We agree with the editorial authors that in the domain of drug therapy for small cell lung cancer (SCLC), except for two recently published landmark studies using immunocheckpoint inhibitors (2,3), there has been little substantive progress in the past two decades.

However in the field of radiotherapy, some progresses have been made, such as the confirmation of the importance of thoracic radiotherapy (TRT) (4-6) and prophylactic cranial irradiation (7), these achievements changed the comprehensive treatment mode, and significantly improved the prognosis of patients with this stubborn disease.

On the basis of these masterpieces, the follow-up studies mainly focused on the optimization of TRT and radio-chemotherapy.

The study of the optimal target volume for TRT has been within this context. Of course, it is much easier to design the target volume for patients with simultaneous TRT and 1st cycle of chemotherapy. While the starting point of our study was for limited-stage SCLC patients who had received several cycles of induction chemotherapy. This is not uncommon in China, especially for patients with large tumor burden or with atelectasis or extensive mediastinal lymph node metastasis, induction chemotherapy can effectively reduce tumor volume thus facilitate the implementation of radiotherapy. As for the design of target volume in these patients, however, two main questions are prominent, namely, should we treat the pre-chemotherapy tumor volume or the post-chemotherapy residual tumor? Should we prophylactically treat the non-metastatic lymph node regions (elective nodal irradiation, ENI)?

Up till now, this is the only prospective randomized study on these issues. We used contemporary radiotherapy techniques, i.e., 3-dimentional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT). Eligible patients were randomized to receive TRT to the post-chemotherapy or pre-chemotherapy tumor volume, and involved-field radiotherapy (IFRT) was applied (no

ENI) for both arms. The results showed neither mediastinal lymph nodes nor primary tumor developed out-field recurrence. Moreover, treatment related toxicities were reduced in patients received radiotherapy to the post-chemotherapy tumor volume.

As TRT in our study was administered concurrently with cycle 3 chemotherapy, the editorial authors have raised the question of the timing of TRT. For our study was launched in 2002, when there was still controversy about the timing of radiotherapy. With the accumulation of evidences, we also advocate earlier initiation of TRT (with the 1st or 2nd cycle of chemotherapy), because that could improve prognosis (8-11), provided the patients could tolerate the potential treatment related toxicities. In CONVERT study (12), TRT was administered concurrently with cycle 1 chemotherapy, the authors reported 5-year survival rates of 34% and 31% respectively in patients who received twice daily and once daily radiotherapy, higher than that of our study. However, we have noticed that 15.7% (86/547) of patients in this study were in stage I-II. In contrast, 92.9% (287/309) of our patients were in stage III, and the proportion of patients with IIIB disease, in particular, was 63.4% (196/309). Consequently, the 5-year overall survival (OS) rate of about 25% in our study was still satisfactory. A South Korea phase III study (13) randomized 222 patients to receive TRT administered concurrently with cycle 1 (early TRT) or cycle 3 (late TRT) chemotherapy. The 5-year OS rates were not significantly different between the early or late TRT groups (24.3% *vs.* 24.0, P=0.69). While significantly more patients of the early TRT arm developed neutropenic fever than the late TRT arm (21.6% *vs.* 10.2%, P=0.02), which the investigators attributed to the larger radiotherapy volume in the early TRT arm. At present, it is acceptable to start TRT simultaneously with cycle 3 chemotherapy in the Chinese Society for Radiation Oncology guidelines for SCLC, but TRT should not be postponed any longer (to be published).

The editorial authors have addressed the important role of PET/CT in target volume definition. In two studies, PET/CT was applied in target volume definition for limited-stage SCLC (14,15). The results showed that only 1.7–3% of patients experienced isolated out-field nodal recurrences. The authors of the CONVERT study have also conducted a secondary analysis to investigate the role of PET/CT (16). Although there were no significant differences in terms of survival in patients staged with or without PET/CT, lower radiation doses to normal organs and lower incidence of late esophagitis was observed in the PET/CT arm. In our study, only 19.1% of (59/309) patients received PET/CT examination because it was not mandatory. Even though, the overall isolated out-field recurrence rate was low (3.3%, 10/300). One possible explanation is, by comparing lymph node size before and after chemotherapy, we could indirectly determine whether it was a metastatic lymph node or not so as to decide whether it should be included into target volume for irradiation. Moreover, after the interim analysis (17), all eligible patients received supraclavicular ultrasound examination and fine-needle aspiration was performed when any suspected lymphadenopathy was detected. Anyway, we agree with the editorial authors and PET/CT examination has already been listed as a routine item in our clinical studies and daily practice.

In their editorial, Jeremic *et al*. raised an open question of whether PET/CT metabolic imaging could be used for adaptive target delineation at some time during TRT to enable dose escalation. In a study of 42 patients with locally advanced non-small cell lung cancer, Kong *et al.* (18) adaptively escalated radiotherapy to the residual tumor, which was defined on mid-treatment PET/CT up to a total dose of 86 Gy in 30 fractions, and the risk of radiation induced lung toxicity was individualized to a fixed level. The 2-year rate of infield failure was 18%, with median OS time of 25 months and 5-year OS rate of 30%. Although the phase III prospective randomized CONVERT study showed that 66 Gy high-dose conventional fractionated radiotherapy was not superior to 45 Gy hyperfractionated radiotherapy in terms of both overall and progression-free survival, the PET/CT-adapted dose escalation have yet been investigated in SCLC patients.

As the editorial authors noted, lower rate of severe acute esophagitis in our study was reported compared with the recently published CONVERT study. One possible explanation is more patients in our study received IMRT (49.7% *vs.* 17.4% in CONVERT). Two retrospective studies have also indicated that compared with 3DCRT, IMRT was associated with a lower incidence of severe acute esophagitis (19,20). The mean esophagus dose and V5 through V40 of esophagus also predict acute esophagitis (20). Actually, our dosimetric study has shown that in patients who received IMRT, the incidental radiation doses delivered to mediastinal lymph node regions were significantly lower (in regions 1R, 9L, 9R, 10L, 10R) or tend to be lower (in regions 4L, 4R, 5, 6, 8) than that of the patients received 3DCRT. This also indirectly indicated that IMRT could reduce the dose to the tissues around the target volumes. Unfortunately, we did not conduct dosimetric study on

acute esophagitis.

We acknowledge that there are limitations in this study, as pointed out by the editorial authors. However, because patients with limited-stage SCLC who have received induction chemotherapy before TRT are ubiquitous in our clinical practice, this study provided a higher level of evidence for standardized and reasonable target design. In addition, the results of this study will also contribute to unify the definition of target volumes and improve the homogeneity when conducting multicenter clinical trials in this specific patient cohort in the future.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3841). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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