Short Commentary: The Role of Thoracic Radiotherapy in Extensive Stage Small Cell Lung Carcinoma – A Concise Review of the Latest Literature

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Extensive Stage Small Cell Lung Carcinoma (ES-SCLC) affects approximately 160,000 patients worldwide every year and their prognosis remains dismal [1,2]. Standard management for ES-SCLC focuses on the delivery of cytotoxic chemotherapy and traditionally, radiotherapy is reserved for palliation of symptoms [2]. For selected patients who are successfully down-staged to Limited Stage SCLC (LS-SCLC), thoracic radiotherapy (TRT) may be considered, if it is deemed safe and tolerable [2]. This management paradigm ignores the problem of intra-thoracic tumor control, wherein 75% of patients harbor persistent intra-thoracic disease after initial chemotherapy and about 90% manifest intra-thoracic disease progression at 1 year after completing initial chemotherapy [3]. However, new data is emerging from large database analyses and trials exploring the role of TRT in ES-SCLC, which suggest an expanded role of TRT in patients with ES-SCLC.

A Surveillance, Epidemiology, and End Results (SEER) database analysis of 10,150 ES-SCLC patients, classified and treated on the basis of the Veterans Administration Lung Study Group (VALSG) definition between 1988 to 1997, was recently reported by Mahmoud *et al*. [4]. In this analysis, patients with disease confined to thorax only, without distant metastases (T-ESCLC) had significantly better 2yr overall survival (OS) when TRT was delivered (13% vs 4.1%, $p < 0.001$). Even patients with distant metastases (M-SCLC) had significantly better 2yr OS when TRT was delivered (4.4% vs 2.8%, $p < 0.001$) and TRT improved the 2yr OS of the entire study cohort from 2.5% to 6% as well as median OS from 4 months to 7 months ($p < 0.001$). Similarly, Whole Brain Radiotherapy (WBRT) improved the 1-year OS from 16.5% to 22% and median OS from 5 to 6 months ($p < 0.001$). When TRT and WBRT were compared in competing risk models, TRT had a consistent impact on cause-specific survival (CSS) for both T-ESCLC & M-ESCLC, whereas WBRT improved CSS only for patients with T-ESCLC. Another finding from this analysis was that intra-thoracic ESCLC has an intermediate prognosis between LS-SCLC and metastatic ESCLC. The median OS of T-SCLC was 7 months compared to 5 months in M-ESCLC patients. However this analysis was limited by the absence of important details about systemic therapy and RT specifics such as total dose, fraction size, timing or intent of the treatment.

Two randomized controlled phase III trials, a randomized controlled phase II trial and a meta-analysis have been conducted so far which have explored the role of TRT in ES-SCLC, with conflicting results owing to differing patient selection criteria, therapeutic interventions and trial objectives. The first trial from Yugoslavia reported by Jeremic *et al.* in 1999, was a single institution, phase III trial which sought to determine the effect of an accelerated hyper-fractionated radiotherapy regimen with concurrent chemotherapy in patients with ES-SCLC who developed a complete response (at distant metastatic sites) to three cycles of induction chemotherapy (Figure **1A**) [5]. The authors reported a 52% complete response rate at DM sites and in these patients addition of TRT (with concurrent chemotherapy) resulted in an improved median OS(17m vs 11m, $p = 0.04$), 5 yr OS(9.1% vs 3.7%, $p = 0.04$), actual CR rate at end of treatment (96% vs 66%) and median duration of response (22m vs 16m, $p = 0.05$). Radiotherapy induced Grade 3 esophageal toxicity was higher in the experimental arm (27% vs 0%) however it did not result in significant treatment interruptions. Overall Grade 3 or

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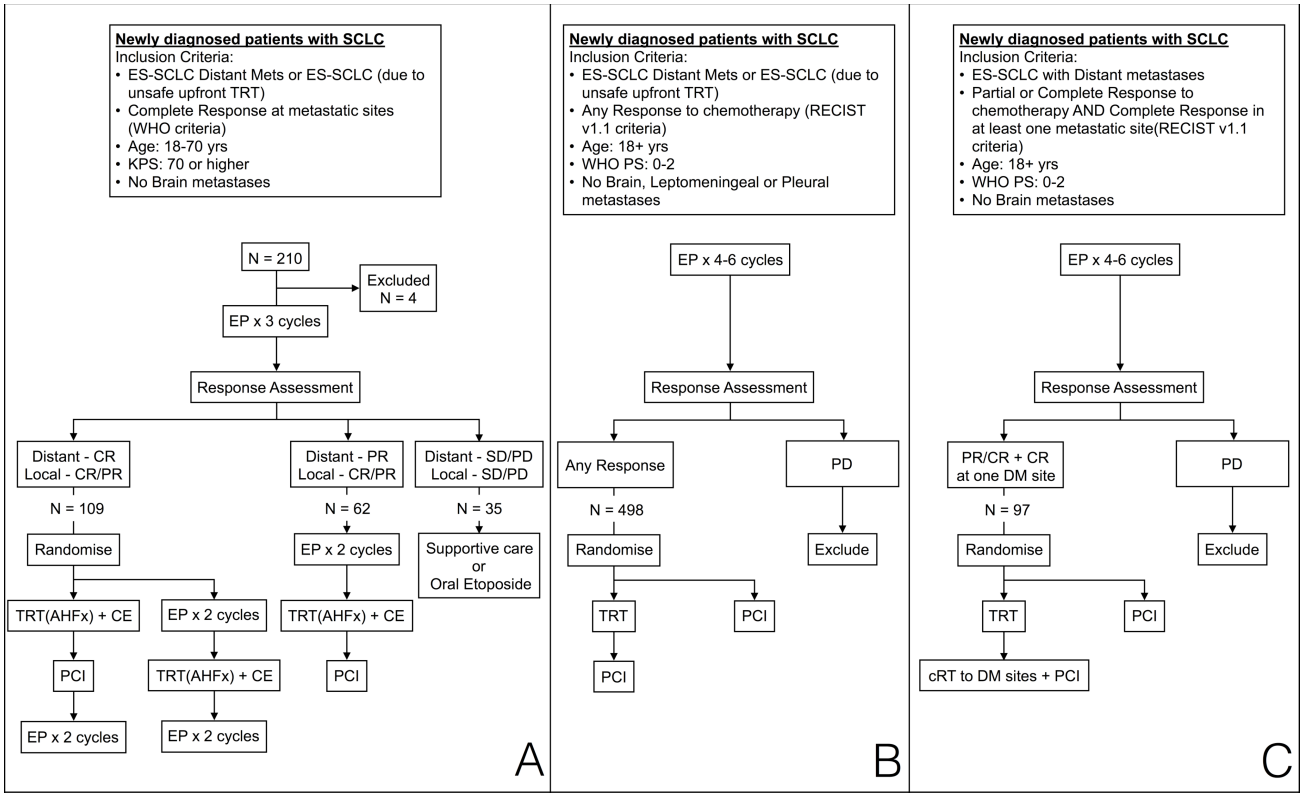

Figure 1: Study schema and inclusion criteria for trials evaluating the role of thoracic radiotherapy in ES-SCLC. (**A**) Yugoslavian Trial. (**B**) CREST. (**C**) RTOG 0937. *Abbreviations*: AHFx, Accelerated HyperFractionation; CE, Carboplatin-Etoposide; CR, Complete Response; cRT, consolidation RadioTherapy; DM, Distant Metastasis; EP, Etopiside-cisPlatin; KPS, Karnofsky Performance Score; PCI, Prophylactic Cranial Irradiation; PD, Progressive Disease; PR, Partial Response; PS, Performance Status; RECIST, Response Evaluation Criteria In Solid Tumours; SD, Stable Disease; TRT, Thoracic RadioTherapy; WHO, World Health Organization.

higher toxicity was lower in the experimental arm (88 events vs 145 events, p = 0.0000) and there was no difference in late toxicity.

Another phase III, multi-institutional European trial by Slotman *et al.* was reported in 2015 [6]. The Chest Radiotherapy in Extensive stage Small cell carcinoma Trial (CREST) was designed to investigate whether TRT could improve 1yr OS in patients with ES-SCLC, following any response to chemotherapy (Figure **1B**). The authors reported a 5% overall CR rate and addition of TRT resulted in a non-significant difference in 1yr OS, which was the primary endpoint. However, TRT improved 2yr OS (13% vs 4%, p = 0.04) and progression-free survival (PFS) at 6 months (24% vs 20%, p = 0.001). Patients receiving TRT also experienced reduced isolated intra-thoracic progression (19% vs 48%, p = 0.001) and intra-thoracic progression with progression elsewhere (43% vs 80%). Both arms experienced equivalent grade 3 or higher toxicities.

The data from these two trials highlight some obvious discrepancies. First, the difference in CR rates is striking; 52% CR at metastatic sites after three cycles of induction chemotherapy in the Yugoslavian trial versus 5% overall CR rate after 4-6 cycles of induction chemotherapy in the CREST trial. Second is the difference in 2yr OS; 20% for all patients in the Yugoslavian trial versus 13% in the intervention arm of the CREST trial. These discrepancies can potentially be explained by the imbalance in absolute number of metastatic sites included in both trials, exclusion of older patients in the Yugoslavian trial, higher Biologically Equivalent Dose (BED_{10}) of TRT in the Yugoslavian trial, higher potential cytotoxicity of concurrent chemo-radiotherapy regimen in the Yugoslavian trial or the inclusion of patients with stable disease in the CREST trial.

To resolve the discrepancies between these two trials, a meta-analysis of all randomized trials evaluating the role of TRT in patients with ES-SCLC receiving platinum-based chemotherapy was recently reported by Palma *et al*. [7]. They screened 2343 titles from an extensive search of MEDLINE and EMBASE databases, and finally selected the two afore-mentioned trials as the basis of their analysis. A total of

604 patients were included in this meta-analysis and results suggest a significant benefit of TRT on OS (HR, 0.81; 95% CI, 0.69-0.95; p = 0.01) and PFS (HR, 0.74; 95% CI, 0.64-0.87; p < 0.001) based on a random effects model. There was no difference in rates of grade 3 or higher broncho-pulmonary toxicity between the TRT and non-TRT groups (2.0% vs. 1.7%; P = 1.00). Rates of grade 3 or higher esophageal toxicity differed by treatment arm, and were 6.6% (n = 20) in the TRT group and 0 in the non-TRT group (P < .001). Esophageal toxicity varied based on TRT prescription, with 27% grade 3 or higher toxicity in the Yugoslavian trial versus 2% grade 3 or higher toxicity in the CREST trial. However, the results of this analysis are not without limitations, first and foremost, being limited to only two phase III RCTs and secondly, a disproportionately higher contribution of patients by the CREST trial, which represented 82% of the merged patient population.

An updated analysis of the CREST trial along with the results of the Yugoslavian trial also support the hypothesis that patient with ES-SCLC who harbor limited metastatic sites may be better candidates for TRT than those with widely metastatic disease [5,8]. In the Yugoslavian trial, 90% of patients who developed a CR to induction chemotherapy, had two or less DM sites [5]. Similarly, in the updated analysis of the CREST trial, patients with ES-SCLC who had two or less distant metastatic sites had a significantly better OS (HR, 1.43; 95% CI, 1.07-1.92; p = 0.02) and PFS (HR, 1.35; 95% CI, 1.02-1.78, p = 0.04). The authors also identified an adverse effect on OS in patients with liver or bone metastases [8].

Another intriguing question, which emerges from reviewing these data, is whether clinical outcomes can be improved further in ES-SCLC by targeting metastatic sites with RT after documented response to induction chemotherapy, which would lower the burden of disease and potentially result in delayed disease progression. The results of a recent phase II, multi-institutional RCT conducted by the Radiation Therapy Oncology Group (RTOG), was recently reported by Gore *et al*. [9]. RTOG 0937 was designed to detect a survival benefit in patients demonstrating a partial or complete response at the primary site and complete response in at least one DM site, who were then randomized to TRT+RT to DM site+PCI versus PCI alone (Figure **1C**). The trial was stopped early before reaching planned accrual due to interim futility analysis with no demonstrable difference in 1yr OS or median OS. Median PFS was longer in intervention arm (4.9 m vs 2.9 m, p = 0.01) and site of first failure was altered in intervention arm [61% failed at new sites (not present at diagnosis) vs 31% in control arm].

In the absence of endorsement of TRT in ES-SCLC by standard guidelines, it may be instructive to review a series of patterns-of-practice surveys conducted amongst North American radiation oncologists [10-12]. There was overwhelming support of the use of TRT in ES-SCLC amongst Canadian and American radiation oncologists, 88% and 96% respectively [10,11]. Another survey conducted amongst American radiation oncologists, specializing in thoracic oncology, reported universal support of TRT in the management of ES-SCLC based on the absence of poor prognostic factors [12]. The three most common factors cited as reasons for withholding TRT were poor performance status(ECOG-PS 3 or more, 91% of respondents), poor pulmonary function (requiring continuous oxygenation, 62% of respondents) and presence of extensive post-induction chemotherapy sites of extra-thoracic metastases (four or more sites, 58% of respondents) [12].

The literature cited in this article supports the following conclusions:

I. The continued use of the VALSG classification system ignores the existence of patient subgroups with different prognoses, leading to limited treatment options for these patients.

a. There exists a sub-category of patients who present with intra-thoracic ES-SCLC and have an intermediate prognosis between LS-SCLC and metastatic ES-SCLC. Approximately 17% of all ES-SCLC cases fall into this subcategory and the addition of TRT after induction chemotherapy improves OS in these patients [4].

b. Within the metastatic ES-SCLC group, a subgroup of patients with 2 or less DM sites (other than liver or bone) have a better prognosis than those with more widely disseminated disease or those with liver and/or bone metastases [5, 6, 8].

II. Thoracic RT is an important component in the management of ES-SCLC and should be considered as soon as the patient has been successfully down-staged with induction chemotherapy.

a. For patients with intra-thoracic ES-SCLC, TRT should be delivered as soon as the M1a

component [separate tumor nodule(s) in a contralateral lobe or malignant pleural/ pericardial effusion] of the disease resolves [4].

b. For patients with metastatic ES-SCLC (with two or less metastatic sites) who develop a CR at these sites after three cycles of induction chemotherapy, TRT with BED_{10} similar to the Yugoslavian protocol should be delivered [5].

c. For patients with metastatic ES-SCLC (with two or less metastatic sites) who develop at least a PR at these sites after three cycles of induction chemotherapy or those with metastatic ES-SCLC (with two or more metastatic sites) who develop at least a PR at these sites after full course of induction chemotherapy, TRT with BED_{10} similar to the CREST protocol should be delivered [5, 6, 8].

III. Since, the TRT regimen were different (with respect to fractionation, total dose and duration) in the Yugoslavian and CREST trials and a head-to-head comparison is not feasible in the foreseeable future, TRT dose should be delivered in accordance with BED_{10}.

IV. Besides palliation of symptoms, at present there appears to be no role for targeted RT to metastatic sites in the hope of improving outcomes in metastatic ES-SCLC [9].

In conclusion, the data cited in this article points to a survival advantage, in selected subgroups of patients with ES-SCLC. More trials are needed to further clarify the optimal TRT regimen and its applicability to these subgroups.

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