Editorial

Consolidative radiation therapy for extensive-stage small cell lung cancer

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Abstract: Despite the use of systemic therapy and prophylactic cranial irradiation (PCI), outcomes for patients with extensive-stage small cell lung cancer (ES-SCLC) remain poor. Consolidative radiation therapy (RT) to the chest may improve outcomes by improving local control. In a recently completed multi-institutional phase III clinical trial, investigators randomized patients with ES-SCLC and response to chemotherapy to PCI with or without consolidative RT. Two-year overall survival (OS) and 6-month progression-free survival (PFS) were improved with the use of consolidative RT; however, the prognosis for ES-SCLC in the experimental arm was still poor and there was no statistically significantly difference in 1-year OS, the trial's primary endpoint. In this editorial, the results of this trial are discussed and the methods are compared to those used in other trials of consolidative RT in ES-SCLC. More research is needed to identify the optimal RT dose and fractionation and to clarify the role of consolidative RT in ES-SCLC.

Keywords: Small cell lung cancer (SCLC); extensive-stage (ES); radiation therapy (RT)

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Based on the meta-analyses by Pignon *et al.* (1) and Warde *et al.* (2), the role of thoracic radiotherapy in improving survival in limited-stage small cell lung cancer (SCLC) is well established; however, for extensive-stage small cell lung cancer (ES-SCLC), the ability of thoracic radiotherapy to improve survival is less clear. Recent results from the phase III randomized trial published in *The Lancet* by Slotman *et al.* (3) add evidence that consolidative radiation therapy (RT) to the chest may improve patient outcomes.

In this multi-institutional, phase III study, investigators randomized patients with ES-SCLC and any response to induction chemotherapy to prophylactic cranial irradiation (PCI) with or without consolidative RT to the chest. While there was no difference between groups in the primary endpoint of 1-year overall survival (OS), in a secondary analysis, there was a difference in 2-year OS (13% *vs.* 3%, with and without chest radiation, respectively, P=0.004). In addition, there was a difference in the secondary endpoint of 6-month progression-free survival (PFS) (24% *vs.* 7%, with and without chest radiation, respectively, P=0.001).

Through the use of consolidative RT to the chest, the investigators were able to impact OS and PFS in a disease associated with a poor prognosis. The thoracic RT regimen was not associated with a statistically significant increase in grade 3 toxicity, and 95% of patients were able to complete the regimen. A total of 498 patients were randomized with the intention to detect a difference in the primary outcome of 1-year OS.

A closer look at the design of the study may explain why it failed to meet its primary endpoint. While there was no difference in OS at 1-year, the study included patients with ES-SCLC based on determination of either distant spread or extensive intrathoracic disease. Patients with distant disease may not have seen a survival benefit from chest irradiation due to distant progression within the first year and this may help explain the similar 1-year but improved 2-year OS with chest irradiation. Although the study excluded patients with clinical evidence of brain, pleural,

or leptomeningeal involvement, only 13% of asymptomatic patients underwent brain imaging following completion of chemotherapy. It is therefore possible that patients with brain involvement were included in the randomization and this subgroup of patients would be expected to show a smaller survival benefit from chest irradiation.

The Lancet investigators reported that 40% of patients receiving thoracic RT progressed in the chest. The thoracic RT regimen used in this trial was 30 Gy in 10 fractions, a regimen with a lower biologically effective dose (BED) than that typically used in limited stage disease, and a lower dose than the 54 Gy in 35 fractions used in the randomized study by Jeremic *et al*. conducted in Yugoslavia between 1988-1993 (4). In this older study, the fractionation was accelerated so that 35 fractions were delivered in 18 days. In addition to gross tumor, the ipsilateral hilum and mediastinum, and often the bilateral supraclavicular region, were included in the radiation field, whereas in the recent *Lancet* study, only the post-chemotherapy tumor volume and pre-chemotherapy involved nodes were included. With the higher dose and larger treatment field, the study by Jeremic *et al*. reported a 65% 1-year OS rate, much higher than the 33% in Slotman *et al*. At the same time, the 1-year OS without RT was also much higher in Jeremic *et al*. compared to Slotman *et al*. (46% *vs*. 28%, respectively), and this may be attributed to the more stringent inclusion criteria in Jeremic *et al*., in which patients were required to achieve either a systemic complete response (CR) or a local partial response (PR) with CR at distant sites. Beginning in 1989 in the Jeremic *et al*.'s study, all patients were required to undergo CT imaging of the lung, brain, and abdomen; in contrast, in the study by Slotman *et al*., only a small percent of asymptomatic patients were staged with brain imaging.

Taken together with results from Jeremic *et al*., the recent phase III trial in *The Lancet* suggests that OS can be improved with the addition of chest irradiation. However, the optimal BED for chest irradiation in ES-SCLC is still unknown. Review of prior studies (4-8) in this patient population can provide insight for future trial design (*Table 1*), although the applicability of these trials is tempered by the variations in chemotherapy regimens and extent of the radiation fields. For example, a single arm trial published in 1995 incorporated hemibody RT and concurrent chemoradiation (5). More recently, a randomized phase II study in the United States, radiation therapy oncology group (RTOG) 0937 (9), randomized patients to PCI with or without consolidative RT to the chest and up to four metastatic sites. The study required post-chemotherapy imaging to establish the absence of brain metastases prior to enrollment. While the Slotman *et al*. study permitted multiple PCI regimens, the RTOG study mandated the use of 25 Gy in 10 fractions. The optimal dose and fractionation for PCI in ES-SCLC are not clear and in a prior randomized trial published by Slotman *et al*. (10), PCI using a variety of fractionation schemes improved OS in patients with ES-SCLC and response to chemotherapy. RTOG 0937 employed a higher BED regimen for the chest, 45 Gy in 15 fractions, but variations including the 30 Gy in 10 fractions used in Slotman *et al*. were permitted.

In light of the work by Jeremic *et al*., the higher BED employed in RTOG 0937 seemed promising; however, at planned interim analysis of the primary endpoint, the 1-year OS in the experimental arm of 0937 was not higher than that in the control arm, and the study was closed early due to futility (11). Based only on the results leading to premature closure of 0937, it is unknown what percent of patients in the experimental arm were treated to the chest with 45 Gy in 15 fractions *vs*. the alternative regimens of 30-40 Gy in 10 fractions and whether this might have affected thoracic disease control or OS. At interim analysis, the experimental arm was also associated with excessive grade 4 and 5 toxicities. Additional analysis will be needed to determine if the excess toxicity was due primarily to thoracic radiotherapy or the metastatic consolidative irradiation. The closure of 0937 raises questions regarding the optimal primary endpoint for trials in ES-SCLC. Indeed, the study by Slotman *et al*., also did not identify a difference in the primary endpoint of 1-year OS, but a meaningful increase in 2-year OS was identified.

Limiting the ability to define an optimal BED regimen for the chest is the fact that ES-SCLC carries a poor prognosis and radiotherapy regimens involving an increase in dose, number of fractions or number of radiated sites may be unfairly time consuming or excessively toxic for patients with a limited prognosis. More research is needed to determine the optimal field and dose and fractionation for chest RT, and to clarify the role, if any, of consolidative RT to asymptomatic metastatic sites, in ES-SCLC. It is possible that dose escalation and extended radiation fields may have a role in this poor-prognosis disease, but careful trial design and adequate safety monitoring will be needed to determine if any benefit outweighs toxicity to the patient.

Table 1 Comparison of RT regimens in ES-SCLC

Study	Study type	Lung RT dose [BED in Gy for α/β =10 for tumor]	PCI dose [BED in Gy for α/β =3 for normal tissue]	Concurrent chemotherapy	Survival time with lung radiation	Survival time without lung radiation
Bonner *et al*., 1995 (5)	Phase I/II non-randomized trial	20 Gy in 5 fractions [28]; hemibody RT also given	17 Gy in 5 fractions [36.3]	Yes	MST 11.5 months; 25% 2-year OS	NA
Jeremic *et al*., 1999 (4)	Prospective randomized trial	54 Gy in 35 fractions in 18 days [62.3]	25 Gy in 10 fractions [45.8]	Yes	MST 17 months; 38% 2-year OS	MST 11 months; 28% 2-year OS
Zhu *et al*., 2011 (6)	Retrospective study	Variable, 40-60 Gy at 1.8-2 Gy per fraction [47.2-72]	Not routine	Yes	MST 17 months; 35% 2-year OS	MST 9.3 months; 17% 2-year OS
Giuliani *et al*., 2011 (7)	Retrospective study	Variable; 40 Gy in 15 fractions in 16 of 19 patients [50.7]	8 of 19 patients, 25 in 10 fractions [45.8]	Variable	MST 14 months; 13% 2-year OS in patients presenting without brain metastases	
Yee *et al*., 2012 (8)	Prospective phase II non-randomized trial	40 Gy in 15 fractions [50.7]	25 Gy in 10 fractions [45.8]	No	MST 8.3 months; 0% 2-year OS	
Slotman *et al*., 2015 (3)	Phase III RCT	30 Gy in 10 fractions [39]	Multiple regimens [45.8-60]	No	MST 8 months; 13% 2-year survival	MST 8 months; 3% 2-year survival
RTOG 0937, unpublished (9)	Phase II RCT	45 Gy in 15 fractions, or 30-40 Gy in 10 fractions [39-58.5]	25 Gy in 10 fractions [45.8]	No	NA	NA

RT, radiation therapy; ES-SCLC, extensive-stage small cell lung cancer; BED, biologically effective dose; PCI, prophylactic cranial irradiation; MST, median survival time; OS, overall survival; NA, not applicable; RCT, randomized controlled trial; RTOG, radiation therapy oncology group.

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Footnote

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