Editorial

# Is chest radiation now a classical practice for extensive small cell lung cancer?

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**Abstract:** The recent phase III published by Slotman *et al*. addressed the question of additional chest radiation showing a benefit mainly in local control. A critical analysis of this trial point out all the limitations and in view of other studies, the real benefit of chest radiation for extensive small cell lung cancer (SCLC) remains unclear.

**Keywords:** Small cell lung cancer (SCLC); chest radiotherapy

Submitted Mar 20, 2015. Accepted for publication Mar 31, 2015.
doi: 10.3978/j.issn.2218-6751.2015.04.01
**View this article at:** http://dx.doi.org/10.3978/j.issn.2218-6751.2015.04.01

The paper by Slotman *et al*. is an interesting phase III trial testing the role of chest radiation for patients suffering from an extensive small cell carcinoma—small cell lung cancer (SCLC) presenting at least some response to chemotherapy (1). The interesting point is certainly the slight improvement seen in the 2-year survival rate but not at 1-year; so, the study failed with the initial endpoint of the statistical design. An interesting observation was the marked reduction in loco regional relapse: thoracic progression either alone or combined with other sites were seen in 108 patients in the radiotherapy group *vs*. 218 in the control arm.

Local progression after chemotherapy was already reported and observed in old series of the 1970s and the addition of chest radiotherapy to the chemotherapy was also addressed in small series (2). The Jeremic trial randomized chest radiotherapy (54 Gy in 38 fractions over 18 days with concurrent cisplatin and etoposide) to only additional cycles of chemotherapy (3). Patients had to have obtained a complete response at the metastatic sites and a complete or partial response at the level of the chest. There was a better survival in favor of the combined approach: median survival time was 17 *vs*. 11 months and 5-year survival rate 9.1% *vs*. 3.7%. A recent retrospective analysis of Toronto identified 19 patients out of 215 with extensive disease receiving chest radiotherapy with doses in excess of 30 Gy; most of them had metastatic disease in only one organ (4). The 2-year survival rate was 14% and the loco regional failure 39%.

The Slotman trial raised a lot of questions regarding patient selection, dose of radiotherapy, treatment at the time of disease progression and mainly a quality of life analysis. For the later, we should point out the good tolerance to the chest radiation with minimal reported toxicity: 1.6% of grade 3 esophagitis. The most common grade 3 or 4 toxicity in both groups was fatigue probably related to the disease or probably to the prophylactic cranial irradiation (PCI). Nevertheless, the dose used, 30 Gy in 10 fractions and 2 weeks, is rather a classical schedule used for palliation but not for cure (5). Indeed, one of the main goals to add radiation to the chest is to achieve a local control of the residual intrathoracic disease after chemotherapy. Today, there is a trend for more aggressive dose in treating patients with limited disease from the hyper fractionated schedule of 45 Gy in 3 weeks with 2 fractions a day to 70 Gy in 7 weeks. Those schedules are currently tested within phase III trials both in Europe and America. It seems clear that the dose used can be easily defended regarding the patient selection: all patients with some response to chemotherapy regardless of the number of metastases or sites involved. This is seen in the very low 2-year survival rate (13% *vs*. 3%) as well as the progression free survival but we may expect this kind of figures for this disease extent. Furthermore, they were unable to identify a group of patients with a greater benefit from the addition of chest radiotherapy: the type of response did not have a great impact but the number of patients presenting a complete response was quite low (25 patients) as well as how the extensive disease was defined, intrathoracic or distant metastases. It is clear that we need to identify those patients benefiting the most of this treatment,

both for the quality of life or progression free survival. Furthermore, the paper is certainly missing a quality of life study as for this group of patients besides survival data; this is certainly a main issue when using thoracic radiotherapy. An argument may be the better local control avoiding the symptoms due to a chest progression but in case of better survival should the figure remain the same. Clearly the key issue for those patients is to obtain a more efficient systemic treatment to control the metastatic disease.

An information missing is certainly the type of treatment at the time of progression: is the small survival benefit related only to the chest radiation or to the possibility that those patients at the time of disease progression were in a better shape and received more second line treatment. In the PCI trial, there was a major decrease in brain relapse (from 40% to 15%) after PCI translating in a survival benefit at 1-year (6). Nevertheless, the same criticism may be formulated as the patient in the PCI arm had at the time of disease progression more second line treatment: in case of extra cranial progression, 45% in the control arm received a second line chemotherapy in contrast to 68% for the PCI group and in presence of brain metastases, 35 patients out of 59 had a treatment in the no PCI arm.

Another weakness of the trial is the lack of a full reevaluation before randomization. So, we have no precise information on the real tumor extent, the number of sites involved or the number of metastases. In the International Association for the Study of Lung Cancer (IASLC) data base, patients with only a pleural effusion had a better survival than the classical stage IV disease (7). An evaluation of the tumor burden may be a good approach in the design of future trial for extensive SCLC. There is also the question of the place of positron emission tomography–computed tomography (PET/CT) for a better determination of intrathoracic disease extent before chest radiotherapy: would it be beneficial?

One very important question in extensive disease is the patient selection for a more aggressive treatment both to the primary site and the metastatic disease: this is the question raised by the concept of oligometastatic disease. A clear example is certainly the case of brain metastases as single site with some long term survivors. This question is now addressed by a randomized trial launched in the United States by the Radiation Therapy Oncology Group (RTOG).

In conclusion, the place of thoracic radiation for extensive SCLC remains unclear. Indeed, this phase III trial is interesting but it raises more questions than answers: patients selection, radiation dose are two questions even if the schedule used let to some clear better local control.

## Acknowledgements

None.

## Footnote

*Provenance:* This is a Guest Editorial commissioned by the Editorial Board Member Ying Liang [Department of Medical Oncology, Sun Yat-sen University Cancer Center (SYSUCC), Guangzhou, China].
*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Comment on:* Slotman BJ, van Tinteren H, Praag JO, *et al*. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015;385:36-42.

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**Cite this article as:** Van Houtte P, Moretti L, Roelandts M. Is chest radiation now a classical practice for extensive small cell lung cancer? Transl Lung Cancer Res 2015;4(3):209-210. doi: 10.3978/j.issn.2218-6751.2015.04.01