Radiotherapy tumor volume for limited-stage small cell lung cancer: less is more

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For the last 30 years, radiation therapy (RT) has been part of the standard treatment for limited-stage small cell lung cancer (LS-SCLC or stage I-III according to the TNM classification) (1,2). With advances in radiation techniques, questions were raised about the optimal RT treatment volumes, in addition to questions relating to the fractionation and timing of RT with chemotherapy (3,4). Historically, treatment volumes included all gross disease present at the time of initial diagnosis (pre-chemotherapy volume), as well as inclusion of adjacent uninvolved nodal regions (elective node irradiation: ENI). The available literature on volume reduction strategies is much more limited in SCLC compared to non-small cell lung cancer (NSCLC) but several reports (5,6), including two randomized trials, assessed RT target volumes in LS-SCLC (7-9).

The first question on RT target volume in LS-SCLC is related to the need to include ENI. In a phase II study including the pre-chemotherapy primary tumour and nodal volumes defined on CT scan (no ENI), De Ruyscher et al. reported an isolated nodal failure in 3/27 (crude rate of 11%) patients. All nodal failures were in the ipsilateral supraclavicular region (10). The same team subsequently published another prospective phase II study, this time the pre-chemotherapy primary tumour and nodal volumes (no ENI) was defined on 18FDG positron-emission tomography/computed tomography (PET-CT). They reported only two isolated lymph node recurrences out of the 60 patients (crude rate of 3%) studied. The authors concluded that RT limited to the involved lymph nodes is a safe treatment, provided that a PET/CT scan is used for target volume definition (11). A further retrospective study using the same strategy reported only one nodal failure among 60 (crude rate of 2%) LS-SCLC (12).

The second question on RT target volume in LS-SCLC is related to the need to include the pre or the post chemotherapy volume. In a retrospective study, no difference in outcomes was observed in LS-SCLC patients treated with thoracic RT fields that included the pre-chemotherapy or the post-chemotherapy primary tumour volumes (ENI in all patients) (13). Two randomized trials compared post-chemotherapy versus pre-chemotherapy volumes. The Southwest Oncology Group (SWOG) study, performed in the 1980s, included 198 LS-SCLC patients with stable disease or partial response after induction chemotherapy. They were randomized to receive RT either to the pre-chemotherapy or post-chemotherapy tumour volume. ENI was used in all patients. Baseline assessments
were performed with chest x-ray, bone scan, bone marrow aspiration/biopsy, and a CT scan of the abdomen. Induction chemotherapy consisted of MV-VAC (vincristine, methotrexate, VP-16, doxorubicin, and cyclophosphamide for 6 weeks). Treatment planning and response assessment were performed with chest X-rays (two dimensional RT, 2D-RT). After 2D-RT, patients received post-RT chemotherapy (VP-16 and cyclophosphamide for four cycles), and then reinduction chemotherapy (MV-VAC with dose reduction). Survival and pattern of failures were not different between both arms. An increase in severe toxicity (myelosuppression) was however reported for patients receiving RT larger pre-chemotherapy volumes.

The study of Hu et al. is the second randomized study in LS-CLC comparing irradiation to the pre-chemotherapy (control arm) and the post-chemotherapy (experimental arm) tumor volume after 2 cycles of induction chemotherapy. ENI was omitted in all patients. An interim analysis was published in 2012 (n=86) (8) and the final results were reported in 2019 (n=309) (9). Due to slow accrual (recruitment 2002-17), the study was prematurely closed. The initial target population was 504 patients and 309 were actually randomised. Some (n=9) patients were included in the intent-to-treat analysis of overall survival (OS) only. Baseline assessment included brain CT or MRI, body CT and bone scintigraphy. PET/CT was not mandatory and was performed in 19% of patients. After an interim analysis, some patients received supraclavicular fine-needle aspiration to confirm any suspected lymphadenopathy but results not reported. Chemotherapy consisted of standard etoposide and cisplatin for 4 to 6 cycles (mean 4.3±1.0). In this study conformal 3D thoracic RT was administered concurrently with the third cycle and consisted of 1.5 Gy twice a day in 30 fractions over a 3-week period to a total dose of 45 Gy, which is the international standard. However, evidence from clinical trials supports that thoracic RT should preferentially be initiated early (e.g., with the first or second cycle of chemotherapy) as it improves patients’ outcomes (4,14). Nonetheless in some situations it may be advantageous to obtain tumour shrinkage in order to reduce the risk of chemo-radiotherapy toxicity. In such cases starting RT with cycle 3 of chemotherapy may provide comparable results to starting with cycle 1 or 2, although the data are more limited (15,16). Almost half of participants (n=149/300; 49.7%) received thoracic intensity-modulated RT (IMRT). The use of 4DCT for RT planning and cone beam CT for treatment verification was not reported. Patients who achieved complete response of tumour after the completion of chemoradiotherapy were offered prophylactic cranial irradiation (n=195/300; 65%). Clinical target volumes (CTVs) included the pre- or post-chemotherapy primary tumour volume (control and experimental arm respectively) with a margin of 0.8 cm and the pre-chemotherapy nodal volume. The planning target volumes (PTVs) included the CTVs with a margin of 1.0–1.5 cm. The principal objective of this trial was 3-year local/regional progression-free probability non-inferiority of the experimental arm (post-chemotherapy primary tumour volume) compared with the control arm (pre-chemotherapy primary tumour volume).

Local/regional failure (P=0.77) was observed among 32 patients (34.2%) in the study arm and 46 (31.1%) in the control arm (median follow-up of 19.6 months, range, 0.7–165.0 months). Among these, isolated out-field lymph node failure developed in 4/152 (crude rate of 2.6%) in the post-chemotherapy experimental arm and 6/148 patients (crude rate of 4.1%) in the control arm, with 7 failures located in the supraclavicular regions and 3 located in contralateral hila. No out-field recurrence in the mediastinal lymph nodes was observed. There was no significant difference in 3-year local/regional progression-free and OS rates (65.5% and 58.2% and in the control and experimental arms respectively; P=0.44), and the absolute difference was −7.3% (95% CI, −18.2%, 3.7%). However as pointed out by the authors, the study was underpowered. Furthermore, the lower bound of the 95% confidence interval did exceed the lower bound of −10%, which was the defined study non-inferiority margin. It is therefore possible that the experimental arm could be inferior to the control arm. Rates of acute grade 3 esophagitis (P=0.01) and late grade 2-3 pulmonary fibrosis (P=0.01) were higher in the control arm than in the experimental arm. The authors should be commended for a very thorough dosimetric analysis showed that IMRT delivered more incidental doses to the non-involved lymph node region than with 3D-RT. It is possible that this incidental dose could play a role in eliminating the microscopically invaded lymphadenopathy (9).

The study by Hu et al. is the only randomized study to date that has compared irradiation of the pre-chemotherapy and post chemotherapy primary tumour volume after induction chemotherapy, with omission of ENI. This study confirms findings from other studies that have examined the concept of involved field RT. Isolated out-field lymph node failure rates (crude rate of 2.6%) was comparable to those described in studies including PET/CT for target definition (11,12). The randomized CONVERT study
comparing twice-daily to once-daily radiotherapy in LS-SCLC reported good outcome in patients treated without ENI (survival at 5 years 34% and 31% respectively) (3). Approximately half of the patients were staged with PET/CT. The risk of locoregional relapse was 14% for stage I and II and 17% for stage III SCLC (17). A pattern of relapse analysis based on the CONVERT data is under way. Finally, a recent study in the NSCLC setting has also confirmed that omission of ENI should be considered standard of care (18).

This study also included recent imaging and modern RT techniques (3D or IMRT). However, data on IMRT is limited in the SCLC setting. A retrospective study found comparable outcomes but fewer percutaneous feeding tube insertions (5% vs. 17%) in SCLC patients receiving IMRT (n=104) as compared to those receiving 3D-RT (n=119) (19). The study by Hu et al. reported lower rates of severe oesophageal toxicity compared to the recently published CONVERT study (10.7% vs. 19.4% in CONVERT). This is possibly explained by a larger proportion of patients treated with IMRT (50% in Hu vs. 17.4% in CONVERT) delivery (3).

In conclusion, in the LS-SCLC setting, treatment volumes should include the post-chemotherapy primary tumour volume and nodal regions involved at the time of initial diagnosis, omitting ENI (20). PET/CT is mandatory for RT planning. Pathologically confirmed lymph nodes on endoscopic ultrasound with or without fine needle aspiration techniques/mediastinoscopy, if available, should also be performed. Smaller fields lead to reduced toxicity from combined modality therapy without jeopardizing local control rates (7,11,21,22).

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Footnote

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