Radiotherapy in Small-Cell Lung Cancer

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Ganti and colleagues have provided a brief review on the diagnosis of small-cell lung cancer (SCLC) and the roles of chemotherapy and surgery in its management. Notably, in the past three decades, the most significant progress in the treatment of SCLC has mainly involved the use of radiotherapy. Thus, to complement their assessment, we will provide an overview of the role of radiation in the management of limited-stage and extensive-stage SCLC.

Radiotherapy in Limited-Stage SCLC

The standard of care in the management of limited-stage SCLC (LS-SCLC) includes multi-agent chemotherapy and thoracic radiotherapy (TRT). Two meta-analyses involving more than 2,000 patients investigated the benefit of TRT in LS-SCLC. The studies both demonstrated a 25% to 30% reduction in local failure and a 5% to 7% improvement in 2-year survival with the addition of TRT to standard chemotherapy.[1,2]

The optimal administration of radiotherapy depends on several factors, including timing (concurrent vs sequential, early vs late), dose, fractionation, and volume of radiotherapy.[3] Takada and colleagues investigated radiation timing by reporting on a randomization of 231 patients with LS-SCLC to TRT administered either sequentially or concurrently with chemotherapy. They reported longer survival with concurrent than with sequential radiation.[4] Turrisi and colleagues investigated radiation fractionation by randomly assigning 417 patients to receive either once-daily TRT (45 Gy in 5 weeks) or twice-daily TRT (45 Gy in 3 weeks). They reported a statistically significant difference in 5-year survival of 16% versus 26% favoring twice-daily radiotherapy ($P = .04$).[5] A caveat regarding the interpretation of these results is that once-daily radiation was not given at the maximum tolerated dose. Also, grade 3 esophagitis was significantly more frequent with twice-daily TRT, occurring in 27% of patients, compared with 11% of patients in the once-daily group ($P < .001$). Excellent performance status and pulmonary function is required to tolerate twice-daily radiotherapy, and these results may not be generalizable to patients with medical comorbidities. Further investigation is necessary to define the optimal dose of thoracic radiation in LS-SCLC (45 Gy bid vs 70 Gy qd vs 61.2 qd-bid), which is currently being evaluated in the clinical trial RTOG (Radiation Therapy Oncology Group) 0538. Although the volume of the radiation field has not been investigated in a prospective randomized study, emerging single-arm data suggest that involved-field radiation has a low rate of tumor failure (3%) in elective nodal areas, provided PET/CT data are used in treatment planning.[6]

Intracranial metastases occur in 50% of patients with SCLC.[3] The risk of brain metastasis can be reduced with prophylactic cranial irradiation (PCI), and category I evidence supports its use in selected patients with LS-SCLC. In a meta-analysis, Auperin and colleagues reported on seven trials that randomly assigned patients with a complete response to upfront therapy for LS-SCLC to receive PCI or no PCI. A 5.4% increase in the rate of survival at 3 years (20.7% in the treatment group versus 15.3% in the control group) was noted. PCI also increased the rate of disease-free survival (relative risk [RR], 0.75; 95% confidence interval [CI], 0.65-0.86; $P < .001$) and decreased the cumulative incidence of brain metastasis from 58.6% in the control group to 33.3% in the PCI-treated group (RR, 0.46; 95% CI, 0.38-0.57; $P < .001$). In subgroup analysis, larger doses of radiation (8 Gy, 24 to 25 Gy, 30 Gy, and 36 to 40 Gy) led to greater decreases in the risk of brain metastasis, but the effect on survival did not differ significantly according to dose. Furthermore, there was a trend noted ($P = .01$) toward a decrease in the risk of brain metastasis with earlier administration of cranial irradiation after the initiation of induction chemotherapy.[7] Further data from randomized trials support standard-dose PCI in LS-SCLC (25 Gy in 10 fractions) versus other fractionation schemes.[8]
Radiotherapy in Extensive-Stage SCLC
Extensive stage SCLC (ES-SCLC) is a systemic disease. Thus, radiotherapy has historically been reserved for the treatment for symptoms such as brain or bone metastasis or superior vena cava syndrome at diagnosis. Compelling data exploring the role of radiotherapy in ES-SCLC are emerging. In a single-institution study performed at the University Hospital in Kragujevac, Yugoslavia, Jeremic and colleagues designed a trial to identify a subset of ES-SCLC patients who might benefit from the addition of radiotherapy to chemotherapy. Patients were included in the study if they had a complete remission of their distant metastasis. The median survival time was 17 months in the patients who received TRT versus 11 months in those who received additional cycles of cisplatin and etoposide (P=.041). The 5-year survival rate was also improved with TRT (9.1% vs 3.7%). With regard to toxicity, the non-radiation group noted more nausea/vomiting, alopecia, and nephrotoxicity, whereas esophagitis was more common in the radiotherapy-treated group.[9] The value of consolidative radiotherapy in the chest for ES-SCLC is under investigation and the subject of a current multi-institutional RTOG trial (RTOG 0937).

In patients with ES-SCLC who have a partial response or complete response to upfront chemotherapy, category I data supports PCI in carefully selected patients. Slotman and colleagues randomly assigned patients with ES-SCLC who had a partial response or a complete response to either therapy with PCI or observation. They report an improvement in survival at 1 year in the PCI group compared with controls (27.1% vs 13.3%). While PCI is associated with a decrease in health-related quality of life because of fatigue and alopecia, there was no statistically significant difference seen between the study groups in cognitive functioning or emotional functioning.[10,11]

Summary
Radiotherapy is a critical component of multi-modality treatment of LS-SCLC and has an emerging role in ES-SCLC. Many of the recent advances in the management of SCLC have come by refining the role of radiotherapy in this disease. A significant amount of research is currently focused on the targeting of specific signaling cascades implicated in SCLC pathogenesis (eg Hedgehog, c-MET, insulin-like growth factor receptor 1 [IGFR-1R], mammalian target of rapamycin [mTOR], vascular endothelial growth factor [VEGF], and p53 and Bcl-2 pathways) and on other novel approaches to therapy including treatment with a novel oncolytic virus with tropism for neuroendocrine cells and CD56-targeted drug delivery. Clinical investigations of many of these therapies are ongoing, and the results may become available over the next several years.

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References:


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