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The Important Role of Radiation Therapy in the Treatment of Lung Cancer

New practice-changing study demonstrates survival benefit to consolidative thoracic radiotherapy in patients with extensive-stage small cell lung cancer

Randomized studies have shown a survival advantage to chest radiotherapy and prophylactic brain irradiation (PCI) in patients with limited stage (LS) small cell lung carcinoma (LS SCLC).(1,2,3,4) More recently, numerous trials are looking at the use of radiation in patients with extensive stage (ES) small cell lung carcinoma (ES SCLC) who show a response to chemotherapy. In 2007 a study randomized chemotherapy-responders to PCI vs no PCI in patients with extensive stage small cell lung cancer and found that adding PCI improved overall survival and reduced the incidence of brain metastasis—and is now considered standard of care.(5) In analyzing this trial, however, investigators noted intrathoracic progression of disease in 89% of patients. This observation led to the following study.

CREST trial Chest Radiotherapy Extensive Stage Trial—randomized 498 patients diagnosed with extensive stage small cell lung cancer. Patients were treated with 4-6 cycles of platinum based chemotherapy and were eligible for study if chemotherapy resulted in a response (complete, partial or “good”). Patients had to be free of brain, leptomeningeal and lung metastases. Trial participants were then randomized to receive PCI alone or both thoracic radiation and PCI. Thoracic radiation was 30GY delivered in 10 fractions. Patients who received thoracic radiation in extensive small –cell lung cancer improved their overall survival at 2 years, progression-free survival and intrathoracic control. Some of the pertinent numbers: thoracic progression occurred in 44% in patients treated with chest RT vs 80 % who did not ($p<0.0001$). 2-year overall survival was 13 percent in the chest radiotherapy and PCI arm vs 3% in the PCI only arm ($p=0.004$). Thoracic radiation was also well tolerated with only 4 of approximately 250 patients receiving thoracic radiation experiencing Grade 3 esophagitis.(6) This practice-changing study demonstrates an overall benefit to adding thoracic radiotherapy to PCI in patients with ES-SCLC who respond to initial chemotherapy.

Another group of investigators is looking at the utility of treating metastatic sites in addition to PCI in these patients-- In the RTOG 0937 study, ES-SCLC patients with up to three extrathoracic sites will be randomized to PCI only or PCI plus consolidative RT to the thorax and residual distant metastases to a total dose of 45 Gy in 15 fractions within 3 weeks.

Lastly, researchers at NRG Oncology (previously RTOG) have been developing and testing interventions to avoid memory toxicity from PCI using advanced radiotherapy techniques that minimize dose to the hippocampus (hippocampal avoidance), where memory-specific and highly radiosensitive neural stem cells are believed to reside. Based on highly promising memory-preservation results of hippocampal avoidance during whole-brain radiotherapy for patients with brain metastases, published recently in the *Journal of Clinical Oncology* (7), NRG Oncology is currently developing a phase IIR/III trial (NRG CC003) of PCI with or without hippocampal avoidance for ES- or LS-SCLC. This trial will be activated in early 2015.

Recommendations for treatment of small cell lung patients outside clinical trial (updated from (2))

Limited Stage:

Combination chemotherapy, generally consisting of cisplatin and etoposide, with concurrent thoracic RT. Thoracic RT should start early, preferably with first or second course of chemotherapy, to total dose of 45 Gy within 3 weeks if delivered twice daily or 50–60 Gy (possibly higher) within 5–6 weeks if delivered once daily.

Patients with response after chemoradiotherapy should receive PCI, which should be given to maximal dose of 25 Gy in 10 fractions (or equivalent).

Extensive Stage:

Combination chemotherapy (etoposide and cisplatin or carboplatin)

Patients showing any response should receive PCI, which should be given to maximal dose of 25 Gy in 10 fractions (or equivalent). These patients should also receive thoracic RT 30 Gy in 10 fractions (6).

Abbreviations: LS = limited stage; SCLC = small-cell lung cancer; RT = radiotherapy; PCI = prophylactic cranial irradiation; ES = extensive stage.

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6. Slotman B, Harm van Tinteren et al. **Use of thoracic radiotherapy for extensive stage small-cell lung cancer: A phase 3 randomised controlled trial.** *LANCET* 2014
7. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): A phase II multi-institutional trial. *J Clin Oncol* 2014. [Epub ahead of print].