Thoracic Radiotherapy for Extensive Stage Small-Cell Lung Cancer: A Meta-Analysis

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Abstract

This systematic review identified 2 randomized studies examining the role of thoracic radiotherapy (TRT) in patients receiving platinum-based chemotherapy for extensive stage small-cell lung cancer. Meta-analysis of these 2 trials of 604 patients indicates that TRT improves overall survival and progression-free survival, with a small incremental risk of esophageal toxicity and no increased risk of bronchopulmonary toxicity.

Background: Thoracic radiotherapy (TRT) has been evaluated as a means of improving overall survival and progression-free survival in patients with extensive stage small-cell lung cancer (ES-SCLC). **Methods:** A systematic review of Medline and Embase (inception to January 2015) was undertaken to identify studies of extensive stage SCLC patients receiving platinum-based chemotherapy and randomized to receive TRT versus no TRT. Studies were screened by title (n = 2343) and then abstract (n = 72), with subsequent full-text review (n = 16). Effect estimates (hazard ratios [HR] and confidence intervals) were abstracted, with a random-effects model created to estimate treatment effects. Cochrane's *Q* and I^2 statistics were used to assess study heterogeneity. **Results:** Two randomized studies were identified, including a total of 604 patients (302 TRT; 302 non-TRT). All patients received prophylactic cranial irradiation. The weighted median age was 62 years, and 56% were male. TRT was delivered as 30 Gy/10 fractions (n = 247) or 54 Gy twice daily/36 fractions (n = 55). Overall, the delivery of TRT was associated with improved overall survival (HR, 0.81; 95% confidence interval, 0.69-0.96; $P = .014$) and progression-free survival (HR, 0.74; 95% confidence interval, 0.64-0.87, $P < .001$). For both end points, the studies were not found to be heterogeneous ($P = .439$ and $P = .638$ respectively, $I^2 = 0$). Bronchopulmonary toxicity (grade 3 or higher) was similar in both groups ($\leq$ 2%). Esophageal toxicity (grade 3 or higher) was 6.6% in the TRT arm and 0% in the non-TRT arm ($P < .001$). **Conclusion:** This systematic review with meta-analysis of 2 randomized trials indicates that TRT improves overall survival and progression-free survival in patients with extensive stage SCLC, with a small incremental risk of esophageal toxicity.

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The majority of patients with small-cell lung cancer (SCLC) present with extensive stage (ES) disease, commonly defined as disease that cannot be safely encompassed within a radiotherapy treatment plan.[1] Although ES-SCLC is highly sensitive to chemotherapy and radiation, nearly all patients eventually experience relapse of disease, and 2-year overall survival (OS) is poor, at approximately 4% to 7%.[2] The standard treatment for ES-SCLC is platinum-based chemotherapy, which results in a median survival of approximately 8 to 10 months. More intensive chemotherapy strategies have not appreciably affected survival.[1,3,4]

Given the radiosensitive nature of SCLC, radiotherapy has been used in an attempt to improve OS, including radiotherapy directed at the brain, thorax, hemibody, or total body.[5-7] The role of prophylactic cranial irradiation (PCI) in limited stage SCLC was established in a 1999 meta-analysis of randomized trials involving 987 patients. The meta-analysis demonstrated improved OS in patients who experienced a complete response—often based on chest x-ray alone—after chemotherapy. In the PCI group, the relative risk of death was 0.85 (95% confidence interval [CI], 0.73-0.97; $P = .01$).[8] However, the analysis included 140 randomized

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patients (14%) with ES-SCLC. Although the meta-analysis was underpowered to assess the effect of PCI in ES-SCLC, it suggested benefit in that group: there was no interaction between stage and treatment effect on OS ($P = .62$), and the relative risk of death with PCI was 0.77 (95% CI, 0.54-1.11) in the ES-SCLC group. A subsequent large randomized trial of PCI in ES-SCLC patients who had any response to chemotherapy found a 14% absolute improvement survival at 1 year in patients receiving PCI (HR, 0.68; 95% CI, 0.52-0.88; $P = .003$) at the cost of a short-term impact on quality of life, particularly related to fatigue and alopecia.[9,10]

Thoracic tumor progression is a major cause of morbidity for patients with ES-SCLC. Even after chemotherapy, 75% to 90% of patients have residual intrathoracic disease, and approximately 90% develop intrathoracic progression in the first year.[9] The role of thoracic radiotherapy (TRT) has been examined in retrospective studies and in prospective randomized and nonrandomized trials.[7,11,12] Given the available evidence in this patient population, the goal of this study was to conduct a systematic review of the published literature to identify randomized trials evaluating the role of TRT in patients with ES-SCLC and to conduct a meta-analysis to estimate the effect of TRT on OS and progression-free survival (PFS).

Materials and Methods

Search Strategy

The systematic review aimed to identify randomized trials evaluating the role of TRT in patients with ES-SCLC receiving treatment with platinum-based chemotherapy. A literature search was performed in the Medline and Embase electronic databases from inception until January 1, 2015, in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,[13] incorporating 3 main concepts—small cell lung cancer, extensive stage, and thoracic radiotherapy—based on the following search strategy: ("small cell lung cancer" OR "SCLC") AND ("extensive" OR "ES-SCLC" OR "metastatic" OR "stage IV") AND ("thorax" OR "thoracic" OR "chest") AND ("radiation" OR "radiation therapy" OR "radiotherapy").

Only English-language articles were included. Studies were first screened by title and then by abstract (Figure 1). Sixteen full papers were selected for detailed review, which included a manual examination of their reference lists to ensure complete coverage of relevant publications. Randomized trials that included radiotherapy to additional sites beyond PCI and TRT (ie, abdominal radiation, half-body irradiation), non–platinum-based chemotherapy regimens, and/or intrathecal chemotherapy were excluded.

Data Abstraction and Statistical Analysis

Two randomized trials met the inclusion criteria (Table 1). Effect estimates (HRs) and CIs were abstracted from the published data, and where not provided, HRs and CIs were estimated from Kaplan-Meier curves using the stratified time-interval method independently by 2 investigators.[14] These were then evaluated with a sensitivity analysis by varying the estimate by 10%. A random-effects model was created to estimate the overall treatment effect. Heterogeneity was assessed by Cochran's Q statistic and I^2 statistics. Grade 3 to 5 radiotherapy toxicity was classified as bronchopulmonary (eg, dyspnea, cough) and esophageal (eg, esophagitis, dysphagia). Descriptive statistics were generated for available patient characteristics and compared between TRT and non-TRT groups by Fisher's exact test. Toxicity outcomes were compared by the Cochran-Mantel-Haenszel test stratified by trial. All analyses were performed by Comprehensive Meta-Analysis 3.3 (Biostat, Englewood, NJ) and SAS 9.4 (SAS Institute, Cary, NC) software, using 2-sided statistical testing at the .05 significance level.

Results

Study Population

Two studies met the inclusion criteria for this meta-analysis, including a total of 604 randomized patients (Table 1).[11,15] The TRT and non-TRT groups were well balanced across available baseline covariates (Table 2). The majority of patients were male (56%), with a weighted median age of 62 years in both groups. Good performance status was present in 90% of patients receiving TRT and 92% without TRT ($P = .469$), defined as Karnofsky performance status ≥ 70 or World Health Organization score 0 to 1. TRT was delivered either with 30 Gy/10 fractions for 247 patients or 54 Gy twice daily/36 fractions with low-dose daily etoposide–platinum in 55 patients.

Meta-Analysis

Results of the meta-analysis for OS are shown in Figure 2A. The use of TRT was associated with a significant improvement in OS (random-effects model HR, 0.81; 95% CI, 0.69-0.95; $P = .01$). Heterogeneity testing was negative ($Q = 0.598$, $df = 1$, $P = .439$, $I^2 = 0\%$), and the OS result remained significant in the sensitivity analysis.

PFS was evaluated as time until relapse/progression or death, whichever occurred first. The meta-analysis for the end point of PFS is shown in Figure 2B. The use of TRT was associated with a significant improvement in PFS (random-effects model HR, 0.74; 95% CI, 0.64-0.87; $P < .001$). There was no evidence of heterogeneity between studies ($Q = 0.222$, $df = 1$, $P = .638$, $I^2 = 0\%$), and the PFS result remained significant in the sensitivity analysis.

Radiotherapy Toxicity

Toxicity rates are shown in Table 3. There was no difference in rates of grade 3 or higher bronchopulmonary toxicity between the TRT and non-TRT groups (2.0% vs. 1.7%; $P = 1.00$). Rates of grade 3 or higher esophageal toxicity did differ by treatment arm, and were 6.6% (n = 20) in the TRT group and 0 in the non-TRT group ($P < .001$). Esophageal toxicity varied based on TRT prescription, with 27% grade 3 or higher toxicity in the trial delivering 54 Gy with low-dose etoposide–platinum versus 2% grade 3 or higher toxicity with 30 Gy TRT alone.

Discussion

This systematic review of the literature identified 2 randomized studies assessing the role of TRT in ES-SCLC in patients receiving etoposide–platinum chemotherapy. Meta-analysis of these 2 studies indicates that the use of TRT is associated with improvements in both OS and PFS. TRT appears to be well tolerated. Although esophageal toxicity was increased with the use of TRT, grade 3 or higher esophageal toxicity in the TRT arm remained uncommon (6.6%) and was infrequent in patients receiving a TRT dose of 30 Gy in 10 fractions (2%).