Patient selection for thoracic radiotherapy in extensive-stage small-cell lung cancer

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Practice points

- Chemotherapy is the backbone of therapy for extensive-stage small-cell lung cancer.
- Consolidative chest radiotherapy has been evaluated in two randomized controlled trials, demonstrating improved intrathoracic disease control with a small survival benefit.
- Patient selection for consolidative chest radiotherapy is important due to the systemic nature of extensive-stage small-cell lung cancer. Subgroup analysis of the CREST study demonstrated the greatest benefit in those with residual intrathoracic disease after chemotherapy.

Treatment of extensive-stage small-cell lung cancer remains a challenge with poor local control and overall survival. Chemotherapy is the mainstay of treatment, consisting of a combination of a platinum agent plus etoposide. The role of consolidative chest radiotherapy in extensive-stage small-cell lung cancer remains controversial. Two randomized clinical trials have been published demonstrating improved intrathoracic disease control with a small survival benefit, though interpretation and application of these results to clinical practice has been debated. These two trials examined different radiotherapy techniques and doses, with a third trial treating consolidative chest and oligometastatic disease having closed prematurely due to an interim analysis demonstrating treatment futility plus increased toxicity. Patients with residual intrathoracic disease after chemotherapy appear to benefit the most from consolidative chest radiotherapy, offering a potential tool to help select appropriate patients.

First draft submitted: 2 March 2017; Accepted for publication: 4 July 2017; Published online: 17 November 2017

Keywords: consolidative radiotherapy • extensive-stage • patient selection • small-cell lung cancers

Small-cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers [1] with almost all cases related to cigarette smoking [2]. The clinical hallmarks of SCLC include rapid growth and a high propensity for metastatic spread, with only about a third of patients presenting with confined disease in the chest [3]. SCLC is generally very responsive to both radiotherapy and chemotherapy, but unfortunately, cancer recurrence is routine in the majority of patients [4]. Treatment of SCLC is usually conducted with combinations of chemotherapy, thoracic radiotherapy and prophylactic cranial irradiation (PCI); however, surgery can have a role in the management of surgically resectable early-stage disease [5]. The goals of treatment are highly dependent on multiple patient, tumor and treatment factors. The application and timing of thoracic radiotherapy can be highly dependent on cancer staging. This article aims to discuss the role of consolidative thoracic radiotherapy in extensive-stage SCLC (ES-SCLC). We will also provide the reader some additional information on the treatment of limited-stage SCLC and the use of PCI to provide background and context to the reader of this evolving clinical field.

Staging of SCLC

Although traditional TNM staging can be utilized for the reporting of clinical outcomes of SCLC, most clinicians (and clinical trial protocols) describe the staging of SCLC in terms of limited versus extensive-stage disease. The historical definition of limited-stage SCLC was in the context of known disease that can be safely encompassed in a radiotherapy field [6]. Given various advancements in pretreatment imaging and radiation planning, a more modern

definition relates to safe delivery of radiation treatment to a target volume in terms of various commonly accepted dose-volume parameters [3]. In terms of TNM staging, limited-stage SCLC should be stage I–III (nonmetastatic) that can be safely treated with radiotherapy, specifically excluding patients with large tumor volumes and/or multifocal disease that cannot be treated with a tolerable radiation plan [3,7]. ES-SCLC would consist of all stage IV patients and those stage I–III patients with large tumor volumes and/or multifocal disease that cannot be treated with a tolerable radiation plan [3,7].

The role of radiotherapy in SCLC

In limited-stage SCLC, two meta-analyses published in 1992 demonstrated the superiority of combining chemotherapy with radiotherapy over chemotherapy alone [8,9]. Contemporary chemotherapy regimens contain a platinum agent, cisplatin or carboplatin, combined with etoposide. This regimen allows for delivery of concurrent chemotherapy and radiotherapy treatments. Addition of radiotherapy early, less than 30 days after initiation of chemotherapy, results in a significant improvement in both local control and overall survival, an effect which is even more pronounced when radiotherapy is completed in less than 30 days [10–12].

The optimal dose of radiation in limited-stage SCLC is under investigation. Historically, SCLC is considered a radioresponsive tumor, and doses of 40–50 Gy given daily (q.d.) over 4–5 weeks were standard. Hyperfractionation per INT-0096 [13] (45 Gy given twice daily [b.i.d.] over 3 weeks vs 45 Gy given q.d. over 5 weeks) demonstrated improved overall survival, at the expense of increased esophageal toxicity. It is worth noting that while the doses in this trial are not biologically equivalent, 45 Gy given q.d. over 5 weeks was considered standard treatment at that time. If b.i.d. treatments are not feasible, dose escalation to 60–70 Gy has been recommended by several investigators [7,14]. Several dose escalation studies have demonstrated safety in limited-stage SCLC. CALGB 30610 [15] is a randomized clinical trial aiming to compare three dose levels in concurrent chemoradiation for limited-stage SCLC: 45 Gy given b.i.d. over 3 weeks; 61.2 Gy given in a q.d./b.i.d. stepwise fashion over 5 weeks, the maximal tolerated dose in RTOG 97–12 [16]; and 70 Gy given q.d. over 7 weeks, the maximal tolerated dose in CALGB 39808 [17].

Even with a good response to treatment, the risk of brain metastasis during the clinical course of SCLC is high. In historic retrospective cohorts, 50% of SCLC patients developed clinical brain metastases within 2 years, with an autopsy series demonstrating the actuarial risk to be potentially even higher at 80% at 2 years [18]. PCI was proposed to decrease this risk, with a meta-analysis in 1999, demonstrating both improved 3-year survival (21 vs 15%) and a decreased risk of brain metastasis at years (33 vs 58%) in limited-stage SCLC with complete response to chemotherapy [19].

Subsequently in EORTC 08993–22993, PCI in ES-SCLC also demonstrated improved survival (1-year survival, 27 vs 13%) and a decrease in symptomatic brain metastases (15 vs 40%) after any response to chemotherapy [20]. Sixty percent of patients were treated with 20 Gy in five fractions in this study. A recently published randomized III study of PCI in ES-SCLC has been performed by the Japan Clinical Oncology Group [21]. This study had more strict inclusion criteria and monitoring (including MRI of the brain at enrollment and routine follow-up). Futility was found at an interim analysis (median overall survival = 10.1 months with PCI vs 15.1 months without, $p = 0.09$, with a Bayesian predictive probability of superiority of 0.01%), despite a reduction of brain metastases from 58 to 32% ($p < 0.001$). Routine surveillance with MRI could be considered an acceptable alternative to PCI where feasible.

Other than PCI, radiotherapy for ES-SCLC has historically been reserved for symptomatic palliation, such as brain and bone metastases, with the backbone of treatment primarily consisting of chemotherapy.

Consolidative radiotherapy for ES-SCLC

Despite high initial response rates, the prognosis in ES-SCLC is uniformly poor, with a 2-year survival of 5% [22] and a median survival of 7–11 months. ES-SCLC is considered a systemic disease with treatment consisting of four to six cycles of a platinum agent, cisplatin or carboplatin, combined with etoposide. Attempts to use maintenance chemotherapy [23,24], new chemotherapeutic agents [25] or intensification of chemotherapy [26] ultimately have not resulted in improvement of overall survival, and may be associated with increased toxicity.

Controlling ES-SCLC within the chest remains a challenge, with 75% of patients having residual disease within the chest after chemotherapy, and 90% of patients progressing within the chest within 1 year [20]. The first randomized trial of consolidative chest radiotherapy in ES-SCLC was conducted by Jeremic *et al.* in Yugoslavia, published in 1999 [27]. After three cycles of cisplatin and etoposide, patients were restaged, and those with a complete response in distant disease, and either a complete or partial response in the chest were randomized to

either receive accelerated consolidative radiotherapy (54 Gy given b.i.d. over 18 days). Radiotherapy treatment planning was conducted using 2D imaging, with treatment volumes including the gross chest disease and ipsilateral hilum with a 2 cm margin, the entire mediastinum with a 1 cm margin and the bilateral supraclavicular fossae. 109 patients were randomized, with all receiving PCI (25 Gy in ten fractions). Both groups of patients received further chemotherapy during radiotherapy, followed by two further cycles of chemotherapy after radiotherapy.

Jeremic *et al.* demonstrated that consolidative chest radiotherapy resulted in improved overall survival ($p = 0.041$) with a median of survival of 17 months compared with 11 months in those who underwent chemotherapy alone. Both 3- and 5-year survivals were improved, with 22 and 9.1% of patients alive after consolidative radiotherapy, respectively, compared with 13 and 3.7% in chemotherapy alone. Local recurrence-free survival was improved in those receiving consolidative radiotherapy (median = 30 vs 22 months), though this was not statistically significant ($p = 0.062$). Increases in acute esophageal toxicity were seen, with 27% in the radiotherapy arm having grade 3 or 4 esophagitis. Bronchopulmonary toxicity was seen in 5% of patients undergoing radiotherapy.

Adoption of this treatment technique was not standard, and several further studies sought to evaluate the role of consolidative chest radiotherapy prior to publication of the next randomized controlled trial. A Canadian Phase II trial of 32 patients who received PCI and consolidative chest radiotherapy (Dose of 25 Gy in ten fractions for PCI, and 40 Gy in 15 fractions for chest radiotherapy [RT]) had tolerable side effects (18 patients with grade 2 esophagitis). Median survival was 8.3 months, with a median time to progression of 4.2 months, though no comparison group was available [28].

Several retrospective cohorts also described results of consolidative chest radiotherapy after publication of the Jeremic study. In a cohort of 119 patients, the addition of radiotherapy ($n = 60$) was found to increase survival to a median of 17 months, with 2- and 5-year survival rates of 35 and 7.1%, respectively, compared with chemotherapy alone ($n = 59$), which had a median survival of 9.3 months with 2- and 5-year survival rates being 17 and 5.1%, respectively ($p = 0.014$) [29]. An additional cohort of 215 patients with ES-SCLC were analyzed, which found that durable local control within the chest could be achieved with radiotherapy, with 74% of patients at 1 year, and 61% of patients at 2 years having stable chest disease, though this study is limited by the small number of patients who received radiotherapy ($n = 19$).

The CREST trial [30] is the largest randomized trial assessing the role of consolidative chest radiotherapy in ES-SCLC. Patients initially received four to six cycles of chemotherapy with a platinum agent plus etoposide, with those demonstrating any response to chemotherapy being randomized between consolidative radiotherapy (30 Gy in ten fractions) versus no radiotherapy. Treatment included residual gross disease with a 1.5 cm margin and prechemotherapy involved hilar and mediastinal lymph nodes, with no further details provided in the manuscript. 495 patients were included in analysis, and all underwent PCI (ranging from 20 Gy in five fractions to 30 Gy in 10–15 fractions).

The primary end point of the trial was 1-year survival, which was not significantly improved with consolidative chest radiotherapy (33 vs 28%; $p = 0.066$). Median survival was 8 months in both groups. Secondary analyses demonstrated improved 2-year overall survival (13 vs 3%; $p = 0.004$) and improved progression-free survival at 6 months (24 vs 7%; $p = 0.001$). Treatment was well tolerated, with no severe toxicity observed (grade 4 or greater) in the thoracic radiotherapy group, and grade 3 esophagitis observed in only 1.6% of patients. The conclusion of the authors was that thoracic radiotherapy should be considered for all patients with ES-SCLC who have responded to chemotherapy.

The aftermath of the CREST trial

In the accompanying commentary published with the CREST trial, interpretation was more cautious, believing only selected patients with response after chemotherapy should be considered [31]. Several letters to the editor discussed criticisms of the CREST trial [32–35]. These included: the negative primary end point of the trial, which was overall survival at 1 year; a short median follow-up of only 24 months, particularly given the importance placed on 2-year overall survival advantage; and the trial protocol not mentioning a planned secondary analysis of overall survival at 24 months. The conclusion of the CREST trial that chest radiotherapy should be routinely offered in ES-SCLC was challenged.

Several commentaries [36,37] further discussed challenges in interpreting the SCLC literature in general. It has been hypothesized that those undergoing consolidative chest radiotherapy may have had a better performance status at progression, allowing a greater likelihood of receiving second-line chemotherapy. A similar analogy for PCI has been hypothesized, with patients who received PCI being more likely to receive second-line chemotherapy,

Table 1. Summary of randomized studies of consolidative chest radiotherapy in extensive-stage small-cell lung cancer.

Study (year)	Population	Radiotherapy	Findings	Notes	Ref.
Jeremic <i>et al.</i> (1999)	109 patients, all received PCI (25 Gy in ten fractions)	54 Gy given b.i.d. over 18 days to gross chest disease, ipsilateral hilum, mediastinum, bilateral supraclavicular fosse	Improved median overall survival (17 vs 11 months). Increased esophageal toxicity	Radiotherapy using 2D technique, subsequent chemotherapy given after radiotherapy	[27]
CREST trial (2015)	495 patients, all received PCI (20 Gy in five fractions or 30 Gy in 10–15 fractions)	30 Gy in ten fractions to residual gross disease and prechemotherapy involved hilar and mediastinal lymph nodes	Improved 2-year overall survival (13 vs 3%, $p = 0.004$), no difference in 1-year overall survival or median survival	Negative trial as primary end point was 1-year overall survival	[30]
RTOG 0937 [abstract]	97 patients, all received PCI (25 Gy in ten fractions)	30–45 Gy in 10–15 fractions to residual disease within chest and 1–4 oligometastatic lesions	Terminated early due to toxicity in consolidative radiotherapy group, with no benefit to overall survival, improved time to any progression	Final publication pending	[44]

potentially providing an additional explanation for why there was a survival advantage [38]. The underutilization of the American Joint Committee on Cancer staging system for SCLC also remains a challenge, given the heterogeneous group of ES-SCLC when divided into the traditional limited versus extensive staging system. For example, in ES-SCLC, those with a pleural effusion do better than those with traditional-stage IV disease [39]. There remains the need to better identify those who would benefit from consolidative chest radiotherapy.

Supplementary data regarding patient selection in the CREST trial have been published [40,41]. As the presence of residual intrathoracic disease was a stratification variable at randomization, subgroup analyses demonstrated those with residual intrathoracic disease benefitted from consolidative radiotherapy in overall survival (hazard ratio [HR]: 0.81; 95% CI: 0.66–1.00; $p = 0.044$), progression-free survival (HR: 0.70; 95% CI: 0.57–0.85; $p = 0.0002$) and intrathoracic progression (43.7% in those who received thoracic radiation vs 81.3% in the control group; $p < 0.0001$) compared with those who received chemotherapy alone. No benefit for thoracic radiotherapy was seen in patients without residual intrathoracic disease after chemotherapy, suggesting the presence of residual intrathoracic disease is a factor that should be considered in patient selection [40]. Patterns of progression were different between the two groups, with thoracic progression occurring less frequently and later in the consolidative radiotherapy group than those who received PCI alone [41]. Ultimately, shared decision-making between clinicians and patients should be undertaken when discussing consolidative chest radiotherapy.

A systematic review and meta-analysis of consolidative thoracic radiotherapy in ES-SCLC was conducted, combining the Jeremic study with the CREST trial. No additional randomized studies were identified as of January 2015, and confirmed that thoracic radiotherapy results in improved overall survival (HR: 0.81; 95% CI: 0.69–0.96) and progression-free survival (HR: 0.74; 95% CI: 0.64–0.87) with manageable toxicity, primarily esophageal [42]. There was no significant heterogeneity between the two studies included.

It has been suggested that there may be a subset of patients who would benefit from a higher dose of consolidative radiotherapy, as seen in the Jeremic trial, considering 30 Gy in ten fractions is a palliative radiotherapy dose [43]. A third randomized Phase II study, RTOG 0937 [44], prematurely closed prior to target accrual due to an interim analysis demonstrating futility of consolidative RT, with higher than expected toxicity. The recently published abstract revealed that 97 patients were randomized between PCI and PCI plus consolidative radiation to the chest and oligometastatic sites, upto four extracranial sites. The preferred dose was 45 Gy in 15 fractions, with doses of 30–40 Gy in ten fractions also deemed acceptable [45]. While improved time to any progression was noted, no corresponding increase in 1-year overall survival was seen with the addition of radiotherapy (50.8% for PCI + RT vs 60.1% for PCI alone; $p = 0.21$). Publication of the entirety of the results with more mature data is pending, though dose escalation above 30 Gy in ten fractions should be approached with caution. A summary of randomized studies of consolidative chest radiotherapy can be found in Table 1.

Conclusion

The answer to the question whether all patients with ES-SCLC should undergo consolidative radiotherapy remains ‘It depends.’ Based on the Jeremic and CREST trials, there appears to be a small survival benefit in addition to better intrathoracic disease control with consolidative chest radiotherapy, with all patients receiving contemporary

chemotherapy and PCI. The presence of residual intrathoracic disease after chemotherapy appears to be an important stratification variable in the CREST study, and should be considered when discussing consolidative chest RT with patients. The toxicity of 30 Gy in ten fractions was observed to be minimal, and this favorable toxicity profile should be considered in shared decision-making. Both the Jeremic and CREST studies used different radiotherapy schemes and volumes, with the Jeremic study likely selecting a fitter patient population who underwent more aggressive treatment than would be presently considered to be standard. It is also worth noting a third Phase II study evaluating consolidative chest radiotherapy plus treatment of oligometastatic disease (RTOG 0937) appears not to have replicated these results, with excessive toxicity and treatment futility causing premature closure of the trial. Consolidative chest radiotherapy is a reasonable treatment option in ES-SCLC, though future studies should seek to evaluate patient populations who could be expected to benefit from this treatment.

Future Perspective

Future trials in this clinical space will need to focus on the optimization of systemic therapy to improve results for extensive stage small cell lung cancer. This would lead to a general improvement in survival for all patients but also may provide a renewed opportunity to assess oligometastatic consolidation in this patient population. New radiotherapy practices focused on reducing the treatment burden as well as better patient selection may still yet provide yet ungained benefits for oligometastatic patients with small cell lung cancer.

Acknowledgements

G Rodrigues would like to thank Tanya Berrang and David Palma for providing presentations on this topic as source materials for the writing of this management perspective manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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