Thoracic Radiotherapy Effect on the Outcome in Extensive Stage Small Cell Lung Cancer

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ABSTRACT

Objective: To evaluate the efficacy of thoracic radiotherapy to primary site in patients with extensive stage small cell lung cancer (SCLC) who had responded completely to systemic chemotherapy.

Study Design: Observational study.

Place and Duration of Study: Departments of Radiation and Medical Oncology, Baskent University and Dr. Ersin Arslan Research and Training Hospital in Turkey, between the years of 2011 and 2020.

Methodology: The study included 125 patients with extensive stage SCLC. Demographic data and outcomes of chemotherapy and radiotherapy were collected. The efficacy of thoracic radiotherapy to primary site was evaluated in patients who had responded completely to systemic chemotherapy, in terms of progression-free survival and overall survival (OS).

Results: The median follow-up time was 12 months and 98 (78.4%) patients died during follow-up. Seventy-three (58.4%) patients had complete response. Progression-free survival (PFS) for complete responder patients was 8 months, and OS for the whole group was found 13 months. Twenty (16%) patients received thoracic radiotherapy to primary site after complete response to platinum etoposide combination treatment. Patients receiving thoracic radiotherapy had better OS than those who did not (19 *versus* 12 months respectively and p=0.002). Patients receiving thoracic radiotherapy had better PFS than those who did not (11 *versus* 8 months, respectively, and p=0.01).

Conclusion: Thoracic radiotherapy to primary site may improve the survival outcomes in extensive stage SCLC patients who had complete response to initial systemic chemotherapy.

Key Words: *Small cell lung cancer, Thoracic radiotherapy, Complete response, Outcomes, Lung cancer.*

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INTRODUCTION

Small cell lung cancer (SCLC) is the most aggressive type of lung cancer.[1,2] SCLC typically presents at extensive stage (ES), and the treatment strategies have centred on systemic therapy with platinum-based chemotherap.[1,3,4] In ES-SCLC patients, immune checkpoint inhibitors (ICIs) have recently been shown to increase overall survival (OS).[5] It is shown that in patients who have responded to systemic treatments, PCI (prophylactic cranial irradiation) reduces the occurrence of brain metastases and provides a survival benefit.[6] Intrathoracic tumour progression occur approximately in 90% of ES-SCLC patients within the first year of treatment.[6]

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In literature, small retrospective studies have shown that thoracic radiotherapy improves survival in patients who has a response to initial systemic therapy.[7,8] Thoracic radiotherapy's importance and timing in these patients who had complete response is still inconclusive. As a result, it is not commonly used in oncology practice.

Despite the fact that chemotherapy and radiotherapy work well for SCLC, almost all patients relapse from disease, and 2-year OS is 4-7 percent.[1] The value of radiation methods used for consolidation therapy at an advanced stage disease has grown in importance.[3,4,9] The role of thoracic radiotherapy in patients with ES-SCLC is not well established. The aim of this study was to evaluate the efficacy of thoracic radiotherapy to the primary site in patients with ES-SCLC who had a complete response to chemotherapy.

METHODOLOGY

This was a hospital-based observational case-series conducted retrospectively between 2011 and 2020, at the Radiation Oncology and Medical Oncology Departments, Baskent University's and Dr. Ersin Arslan Research and Training Hospital's. One hundred and twenty-five patients participated in the study.

Extensive stage SCLC patients, who were treated with platinum-etoposide regimen, were included in the study, and limited-stage patients were excluded from the study. Demographic features and treatment modalities were recorded from patient electronic files. After platin-etoposide combination therapy, patients were separated into two groups: those who responded completely (group 1) (n: 73, 58.4%) and those who did not respond (group 2) (n: 52, 41.6%).

Patients who received thoracic radiotherapy to primary site following complete response systemic chemotherapy with different doses. Following the completion of chemotherapy, thoracic RT was planned using three-dimensional conformal radiotherapy and computed tomography-based simulation. The total dose of thoracic RT ranged from 30 Gy to 45 Gy at 1.8–3.0 Gy per fraction in 10-25 fractions. Fifty-eight (46.4%) patients received PCI. To encompass the entire brain planning target volume, the PCI dose-fractionation was 25 Gy/10 fractions, with right and left lateral fields parallel-opposed. Regardless of complete response status, the CTV (clinical target volume) was established as the hilar and mediastinal nodal stations that were considered involved prior to chemotherapy. The planning target volume was defined as the CTV plus a 5-8 mm margin to account for treatment set-up variability and target volume movement during the treatment.

All results for categorical values were presented as frequency and percentage, whereas, the mean and SD, median and IQR were used for continuous variables. To estimate survival curves, the Kaplan-Meier method was used. For estimation, the adjusted hazard ratio (HR) and 95% confidence intervals (95% CIs) were used. All statistical data were analysed using SPSS version 22.0, and a p-value of 0.05 was considered statistically significant.

RESULTS

The patients' median age was 61 (range 38-81) years. Out of 125 patients, and 112 (89.6%) were males and 13 (10.4%) were females. All of the patients (n:125) were in the advanced stage. Seventy-four patients (59.2%) had bone metastases, there were 21 (16.8%) cranial metastases and 45 (36%) liver metastases. The platinum etoposide combination regimen was administered to all patients and 118 of them (94.4%) were given cisplatin in addition. Seventy-three (58.4%) patients had complete response. Of these patients, 20 (16%) of them received thoracic radiotherapy to primary site after completion of systemic therapy and 58 (46.4%) patients received prophylactic cranial radiotherapy as shown in Table I.

The median duration of follow-up was 12 months, and 98 (78.4%) patients died during this time. PFS (Progression-Free survival) for complete responder patients was 8 months, OS for the entire group was found to be 13 months. Group 1 patients had recurrent disease in 66 (90.4%) cases and 41 (62.1%) of them recurred in less than 6 months. OS of group 1 patients', who had a complete response was statistically significantly higher than that of group 2 (nonresponders) (17 *versus* 10 months, p=0.001, Figure 1). Table I shows the patients' treatments and outcomes.

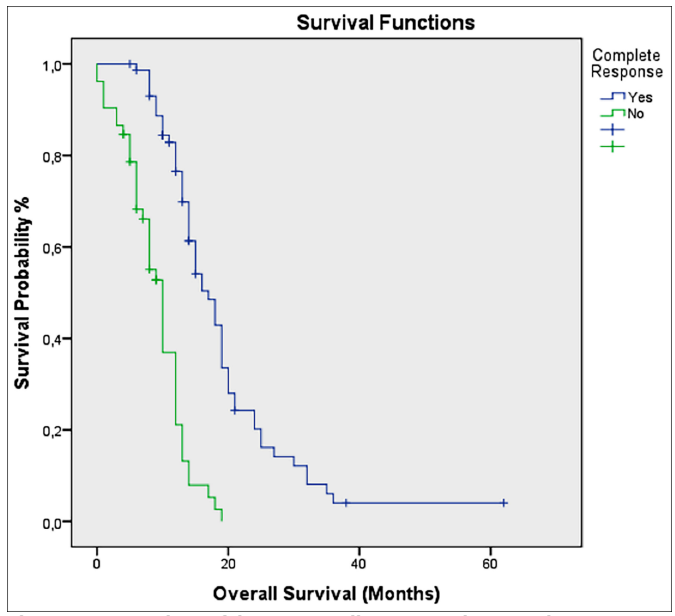

Figure 1: Comparison of the OS according to occuring complete response of chemotherapy.

Table I: Treatment and outcomes.

Characteristics	n (%)
Radiotherapy (RT)	
Thoracic RT	20 (16)
PCI	58 (46.4)
Chemotherapy Regimen	
Cisplatin-Etoposide	118 (94.4)
Carboplatin-Etoposide	7 (5.6)
Complete Response of 1st line	
Yes	73 (58.4)
No	52 (41.6)
Complete Response Time	
Interim Evaluation	20 (27.4)
End of Treatment	53 (72.6)
Disease Recurrence	
Yes	66 (90.4)
No	7 (9.6)
Disease Recurrence Time	
<6 Months	41 (62.1)
>6 Months	25 (37.9)
Final Status	
Died	98 (78.4)
Alive	27 (21.6)

Patients who received thoracic radiotherapy to the primary site after complete response had a better OS than those who did not (19 *versus* 12 months, p=0.002, Figure 2). Furthermore, patients who received thoracic radiotherapy to the primary site had a better PFS than those who did not (11 *versus* 8 months, respectively, and p=0.01, Figure 3). Patients who received prophylactic cranial radiotherapy outlived those who did not (17 *versus* 10 months, p=0.001). Patients with recurrent disease after 6 months had significantly better OS than patients with recurrent disease before 6 months (20 *versus* 14 months, respectively, and p=0.001). Patients with liver metastasis had a lower OS rate than other patients (10 *versus* 15 months, p=0.001). Table II depicts the relationship between treatment and clinical characteristics and survival parameters.

Table II: Relationship between treatment and clinical features with survival parameters.

Variables	Median OS		Median PFS	
	Months	p	Months	p
Thoracic RT		0.002[a]		0.01[a]
Yes	19		11	
No	12		8	
PCI		0.001[a]		0.35
Yes	17		8	
No	10		8	
Complete Response		0.001[a]		
Yes	17			
No	10			
Liver Metastasis		0.001[a]		0.44
Yes	10		8	
No	15		7	
Progression Time		0.001[a]		
<6 Months	14			
>6 Months	20			

OS: Overall Survival, PFS: Progression Free Survival, RT: Radiotherapy, PCI: Prophylactic cranium radiotherapy. [a]Statistically significant.

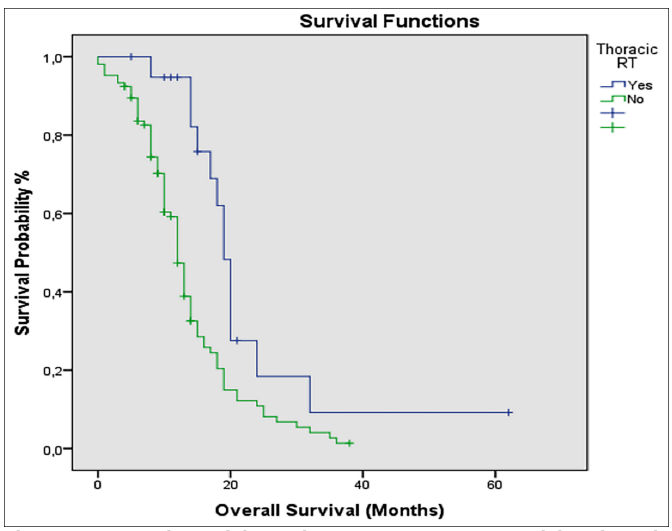

Figure 2: Comparison of the OS between two groups receiving thoracic radiotherapy and not receiving.

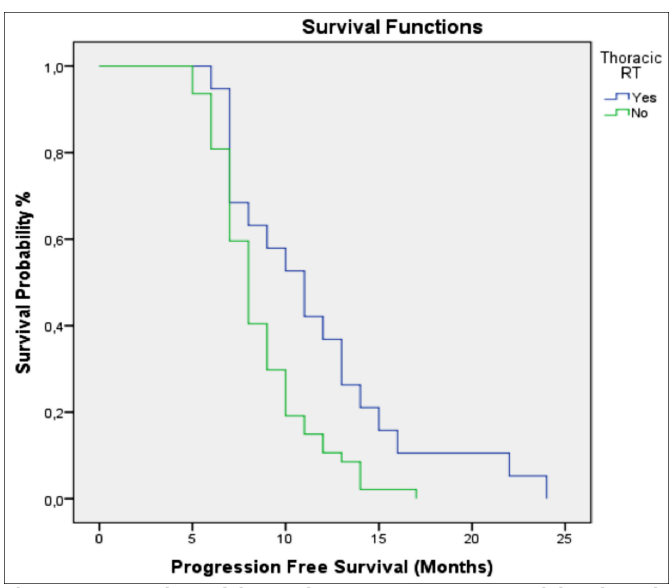

Figure 3: Comparison of the PFS between two groups receiving thoracic radiotherapy and not receiving.

DISCUSSION

SCLC is a highly aggressive malignant lung tumour, with two-thirds of patients presenting with advanced disease.[10,11] Chemotherapy alone, with or without PCI, has recently been the standard treatment for ES-SCLC.[6,12] Immunotherapy is increasingly being used as a part of the systemic treatment for ES-SCLC. In patients who have responded to chemotherapy, PCI reduces the prevalence of cranial metastases.[13] Several studies have looked into the role of thoracic radiotherapy and it is not included as a standard treatment strategy in patients with ES-SCLC. In literature, the studies are focused especially on the patients who have residual disease limited to chest after systemic therapy, thoracic radiation improves survival outcomes.[7,14] There is no research in the literature showing the impact of thoracic radiotherapy on long-term survival in the patients who have had a complete response to chemotherapy.

The CREST trial, a Dutch phase III study, in 2015, Slotman *et al*. investigated the effectiveness of thoracic radiotherapy (30 Gy in 10 fractions) in 498 ES-SCLC patients who responded to chemotherapy in some way. They showed that the patients receiving thoracic RT had a higher chance of survival (two-year OS rate 13 *versus* 3%), as well as a higher chance of PFS (24 *versus* 7 percent at six months).[7] However, the benefits of thoracic RT were limited to the patients with the postchemotherapy residual intrathoracic disease, rather than those who had a complete response.[15] In 206 ES-SCLC patients, Jeremic *et al*. demonstrated that, when compared to chemotherapy alone, thoracic RT significantly increased OS (median 17 *versus* 11 months, and 5 year survival rate 9 *versus* 4%, p=0.041) in a Yugoslavian trial.[16] Also in this study, radiotherapy was given to the patients with residual disease on thoracic region. Another study similar with these studies was published by Don Yee *et al.* showed that in a small patient group, post-chemotherapy (with responded patients), thoracic RT was associated with improved local control (n:33).[8] Despite of these non-randomised, small, inconclusive studies, the 2020 ASTRO Clinical Practice Guideline strongly recommend thoracic radiotherapy (dose of 3000 cGy in 10 fractions) for ES-SCLC patients who have a response to therapy and who has residual tumour in the thorax after completion of chemotherapy.[17,18]

In this study, 125 ES-SLLC patients were included, which was a higher number of patients than in previous thoracic radiotherapy studies. The median OS and PFS were found as 13-8 months, respectively. It was found that the patients who received thoracic radiotherapy following complete response systemic chemotherapy had better OS and PFS than those who did not. Furthermore, patients who received prophylactic cranial radiotherapy outlived those who did not. These findings suggest that thoracic RT may provide an additional survival benefit to these group patients who have complete response. There was no other study in the literature with more patients

examining the efficacy of thoracic radiotherapy in ES-SCLC patients than the present one. The study's limitations are that it was conducted at two centres with a limited number of patients using a retrospective design.

CONCLUSION

Thoracic radiotherapy may improve survival outcomes in patients with ES-SCLC, who have completely responded to systemic treatment.

ETHICAL APPROVAL:
The Health Sciences Ethics Committee approved this study of Baskent University, Faculty of Medicine, Adana, Turkey, with the decision dated 28/09/2021 and Document No. E-94603339-604.01.02-65575.

PATIENTS' CONSENT:
Written consents were obtained from all the participants.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
AKS, ATS: Conceived the study design, involved in data collection, performed the statistical analysis, interpreted data, and prepared the manuscript draft.
BAY: Conceived the study design and involved in data collection.
OO: Conceived the study design, involved in data collection, and supervised the study.
All the authors have critically reviewed the final version of the manuscript and approved it for publication.

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