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Outcomes and Prognostic Factors of Extensive Stage Small Cell Lung Cancer: A Retrospective Study

Veena PS[1] Sajeed A[1] Geethi MH[1] K. M. Jagathnath Krishna[2] Sivananadan CD[1] Arun Sankar S[1] Roshni S[1] Lijeesh AL[1]

[1] Department of Radiation Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India
[2] Department of Medical Biostatistics, Regional Cancer Centre. Thiruvananathapuram, Kerala, India

Address for correspondence Veena PS, MD Radiotherapy, Regional Cancer Centre, Thiruvananthapuram, Kerala 695011, India (e-mail: drveenaps@gmail.com).

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Abstract

Veena PS

Introduction Small cell lung cancer (SCLC) represents about 15% of all lung cancers. Extensive stage (ES) SCLC represents around 60% of diagnosed SCLC cancers. The median survival in untreated ES SCLC is 2 to 4 months and that of treated cases is 8 to 13 months.

Aim and Objectives This retrospective analysis aims to find out the clinical outcome of patients with ES SCLC and the prognostic factors affecting their survival.

Methods Details of patients registered in the department of radiation oncology from January 1, 2010 to September 30, 2019 were retrieved from the hospital records. This includes the demographic characteristics, treatment received, toxicity, and follow-up details.

Results Two-hundred eighty-three patients were included. Median age of presentation was 62 years. Around 97.5% of patients were men. Smokers constitute 94% of all cases. About 86.9% (246 patients) of cases were not alive at the end of the study period. The median estimated overall survival (OS) was 7 months $\pm$ 0.47 (95% confidence interval [CI]: 6.026–7.974) and progression-free survival (PFS) was 5 months $\pm$ 0.535 (95% CI: 3.952–6.048). Multivariate analysis showed that Eastern Cooperative Oncology Group performance status (ECOG PS), hyponatremia, number of chemotherapy cycles, consolidative radiotherapy (RT) and prophylactic cranial irradiation (PCI) were found to have prognostic effect on OS. Smoking, ECOG PS, number of chemotherapy cycles, consolidative RT, and PCI were found to have prognostic effects on PFS.

Conclusion There is a difference in OS and PFS patterns of ES SCLC patients among various Indian studies even though the available data is scarce. Our study shows that the OS and PFS of our study population are comparable to other South Indian studies available. PS, serum sodium level, number of chemotherapy cycles, consolidative RT, and PCI were found to be independent prognostic factors for survival of ES SCLC. The identification of these factors will help physicians to tailor treatment.

Keywords
- outcome
- PCI
- prognostic factors
- small cell lung cancer

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Introduction

As per Globocan data 2020, lung cancer accounts for 11.4% of all cancer incidence worldwide and 18% of all cancer-related deaths.[1] Small cell lung cancer (SCLC) represents about 15% of all lung cancers. As per the ICMR National Cancer Registry report 2020, SCLC accounts for 10% of all the lung cancer incidences in males and 6% among the female cases in India.[2]

SCLC is distinguished clinically from most types of non-small cell lung cancer (NSCLC) by its rapid doubling time, high growth fraction, and early development of metastases and very good sensitivity to chemotherapy and radiotherapy (RT). Patients with SCLC are typically divided into those with limited-stage (LS SCLC) and extensive-stage (ES SCLC) according to the Veterans Administration Lung Study Group (VALG) in 1957.[3] ES disease is one that extends beyond ipsilateral hemithorax, which includes distant metastases, malignant pericardial or pleural effusions, and those cancers that cannot be safely encompassed within a single radiation field. It has been found that around 60% of diagnosed SCLC cancers are of the ES.[4]

Combined modality treatment proved to be beneficial in the treatment of LS SCLC. The primary therapeutic modality is systemic chemotherapy in ES SCLC. The preferred combination of chemotherapy for is cisplatin-etoposide combination (EP).[5] Even though it responds well to chemotherapy, the majority of these patients progress and hence the survival is limited. Hence, for patients who respond well to initial systemic therapy, consolidative thoracic RT and prophylactic cranial irradiation (PCI) were found to provide additional benefits.[6–8]

The median survival in untreated ES SCLC is 2 to 4 months and it is 8 to 13 months in treated cases.[9] Less than 5% of those with ES-SCLC survive beyond 2 years.

Clinical parameters like age, sex, performance status (PS), smoking status; blood parameters like lactate dehydrogenase (LDH), sodium level; tumor related factors like initial tumor size, number and site of metastases are important prognostic factors in ES SCLC.[10,11]

This tertiary care center in South India registers around 1,000 lung cancers annually, of which around 10 to 15% is SCLC.[12] This retrospective analysis aims to find out the clinical outcome of patients with ES small cell carcinoma and the prognostic factors affecting their survival.

Materials and Methods

Study Population

Patients registered in a tertiary care center in South India from January 1, 2010 to September 30, 2019 with ES small cell carcinoma were identified from the hospital-based cancer registry. A total of 283 patients were included.

Data Collection

The demographic characteristics like age, gender, smoking status, Eastern Cooperative Oncology performance status (ECOG PS), and comorbid conditions were collected from the case files. Clinical parameters retrieved from the case files included the presenting symptoms and signs of SCLC, TNM stage at the time of diagnosis, site and size and the number of metastases. Biochemical characteristics like hemoglobin level, total count, baseline liver function test, renal function test and LDH, protein, and electrolyte values were retrieved from case files and in-hospital lab data. Treatment received, including the type of chemotherapy, number of cycles of chemotherapy, PCI and its dose, consolidative RT and its dose were collected from the case files and radiation treatment charts.

Follow-up details including the date of progression if available and date of last follow-up were retrieved from the hospital records. All the details were entered in a structured proforma. Data retrieved till January 1, 2021.

Endpoints and Statistical Analysis

Primary Objective

Overall survival (OS)

Secondary Objective

1) Progression-free survival (PFS)
2) To assess the clinicodemographic and hematological and biochemical factors affecting survival

OS was calculated from the date of histological diagnosis to the date of death or last follow-up. PFS was calculated from the date of histological diagnosis to the date of progression or death or last follow-up.

Continuous variables were expressed as mean and standard deviation and categorical variables as counts and percentage. OS and PFS were computed using the Kaplan–Meier method. The significant difference of various prognostic factors on OS and PFS was compared using a log-rank test. The risk of biochemical and prognostic factors was estimated using the Cox regression model. A p-value less than 0.05 was considered significant.

Results

Patient Characteristics

Data of 283 patients were available for retrospective analysis. Baseline characteristics are summarized in ►Table 1.

The majority of the cases were men (97.5%). The median age is 62 years. Smokers constitute 94% of all cases. ECOG PS was more than two in most cases (57.6%). About 50% of patients did not have any comorbidities at presentation.

The most common presenting symptom was cough (67%) and the most common presenting sign was pleural effusion (28.2%). Neurological impairment was present for 8% of cases and around 4.2% (12 patients) had paraneoplastic syndrome at the presentation. The most common paraneoplastic syndrome at presentation was hyponatremia associated with syndrome of inappropriate antidiuretic hormone (SIADH). One patient presented with paraneoplastic dermatitis.

About 92% had distant metastasis at presentation, of which 48.8% of cases had more than two sites of metastasis. The most common site of metastasis is the liver. About 73%

Table 1 Demographic features

Character	Number	Percentage
Mean age: 62 ± 8 years Range in years (40–84)		
Age < 65 years ≥65 years	170 113	60.1 39.9
Sex: Males Females	276 7	97.5 2.5
Smokers Nonsmokers Not available	266 12 5	94 4.2 1.7
Performance status: 0-1 ≥2	120 163	42.4 57.6
Comorbidity: Nil Present	142 118	50.2 41.7

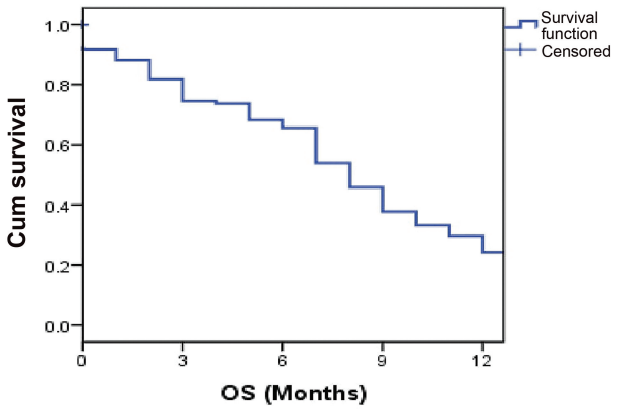

Fig. 1 Kaplan–Meier chart showing overall survival.

had a good baseline hemoglobin level of more than 12 gm/dL. LDH values were available only for 24% of patients. Among that, 23% had elevated LDH values. Abnormal sodium levels were seen in 42.4% of cases. For some patients, details of T stage and N stage were not available. Regarding the stage at presentation, about half of the cases are represented by composite stage IV B.

Treatment Characteristics

Around 75% of the total study population received some form of chemotherapy. Rest of the patients either received best supportive care or palliative RT due to poor general condition (GC) or defaulted treatment after workup. The majority of the patients received EP chemotherapy followed by Carboplatin- Etoposide combination and single agent Carboplatin. One person each (CAV) received cyclophosphamide, doxorubicin, and vincristine and single-agent etoposide. Around half of the population received more than four cycles of chemotherapy. Complete response after four cycles of chemotherapy was seen in 2.5% of the total study population (4.9% of those who completed more than 4 cycles of chemotherapy). Partial response was obtained for 33% of the study population (43% of those who received more than 4 cycles of chemotherapy). Data about the number of chemotherapy cycles was not available for one patient. Consolidative thoracic RT was received by 20.8% of cases and PCI by 24% of the total population. Among the patients who received more than four cycles of chemotherapy, consolidative RT was received by 39.4% and PCI by 49%. Most common dose used for consolidative RT was 30 Gy in 10 fractions and for PCI it was 25 Gy in 10 fractions. Consolidative thoracic RT and PCI were given concurrently for 8.8% of cases and for the rest of the patients, it was given sequentially.

Treatment-related complications were not available for most patients of the available data, leukopenia was the most common hematological toxicity found.

About 86.9% of cases were not alive at the end of the study period. Last follow-up details were not available for 31 patients. The median estimated OS was 7 months ± 0.47 (95% confidence interval [CI]: 6.026–7.974) and PFS was 5 months ± 0.535 (95% CI: 3.952–6.048) in our study. The 1-year survival probability is 19.5 ± 2.5% and 1 year PFS probability is 13.4 ± 2.1%. Two-year survival probability is 3.5 ± 1.5%. Two-year PFS probability is 2 ± 0.9% (►**Figs. 1** and **2**).

On univariate Cox regression analysis, we have found that PS, total white blood cell (WBC) count more than or equal to 10,000 cells /cm^3, serum glutamic oxaloacetic transaminase (SGOT) more than 45 units/L, hyponatremia, presence of paraneoplastic syndrome, chemotherapy received or not, number of chemotherapy cycles, consolidative RT, and PCI were the statistically significant prognostic factors for OS. Similarly, PS, smoking status, total WBC count more than or equal to 10,000 cells/cm^3, SGOT more than 45 units/L, hyponatremia, chemotherapy received or not and the number of chemotherapy cycles, and consolidative RT and PCI were the statistically significant prognostic factors for PFS

Multivariate analysis showed that ECOG PS, hyponatremia, number of chemotherapy cycles, and consolidative RT and PCI were the statistically significant prognostic factors for OS. Smoking, ECOG PS, number of chemotherapy cycles,

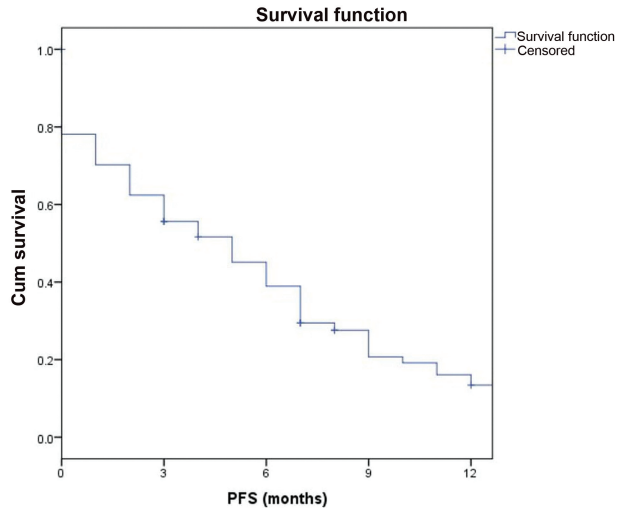

Fig. 2 Kaplan–Meier chart showing progression-free survival.

Table 2 Multivariate Cox regression for OS

Variables	*p*-Value	HR	95.0% CI for HR	
			Lower	Upper
PS (> 1 vs. 0 and1)	0.037	1.408	1.022	1.940
Na (<135 vs. 135–145)	0.012	1.544	1.102	2.164
Number of cycles (≥ 4 vs. < 4)	0.001	0.351	0.236	0.522
Consolidative RT (yes vs. no)	0.013	0.587	0.385	0.895
PCI (yes vs. no)	0.002	0.527	0.348	0.797

Abbreviations: CI, confidence interval; HR, hazard ratio; Na, serum sodium level; OS, overall survival; PCI, prophylactic cranial irradiation; PS, performance status; RT, radiotherapy.

and consolidative RT and PCI were the ones for PFS (►Tables 2 and 3).

ECOG PS less than or equal to 2 was associated with a median OS of 8 months ± 0.527 (95% CI: 7.006–8.994), whereas the ECOG PS of more than or equal to 2 was associated with a median OS of 5 months ± 0.811 (95% CI: 3.411–6.589). The median PFS in patients with ECOG PS less than or equal to 2 was 7 months ± 0.408 (95% CI: 6.200–7.800) and in those with more than or equal to 2 was 3 ± 0.552 (95% CI: 1.918–4.082) months.

Total chemotherapy cycles more than or equal to 4 were associated with a median OS of 10 months ± 0.531 (95% CI: 8.960–11.040) and if it was less than 4, the median OS was only 2 months ± 0.338 (95% CI: 1.337–2.663). The median PFS was 8 months ± 0.394(95% CI: 7.227–8.773) if the total number of chemotherapy cycles was more than 4 and it was only 1 month ± 0.378 (95% CI: 0.259–1.741) if it was only less than four cycles.

The median OS was 13 months ± 1.214 (95% CI: 10.620–15.380) if the patient received consolidative RT, whereas it was only 5 months ± 0.551 (95% CI: 3.921–6.079) without it. The median PFS was 11 months ± 1.225 (95% CI: 8.598–13.402) with consolidative RT and it was 3 months ± 0.362 (95% CI: 2.290–3.710) without consolidative RT.

The median OS was 11 months ± 0.929 (95% CI: 9.179–12.821) with PCI and 4 months ± 0.529 (95% CI: 2.963–5.037) without PCI. The median PFS was 9 months ± 0.745 (95% CI: 7.539–10.461) with PCI and 3 months ± 0.357 (95% CI: 2.300–3.700) without it.

The median OS was found to be 12 months ± 3.2 (95% CI: 5.571–18.429) in nonsmokers compared with 7 months ± 0.52 (5.981-8.019) in smokers. The median PFS in the case of normonatremia is 6 months ± 0.674 (95% CI: 4.680–7.320) and in the case of hyponatremia, it was 4 months ± 0.725 (95% CI: 2.579–5.421).

Discussion

SCLC is an aggressive neuroendocrine tumor. Even though it is highly sensitive to chemotherapy, it progresses rapidly after first-line chemotherapy and has a very poor outcome. In this retrospective study, we have analyzed the clinical outcome and prognostic factors affecting ES SCLC.

The median age was 62 ± 8 years in our study, which is like other published series.[13,14] Smoking is the most common etiology of lung cancer and the prevalence of smokers was 94% in our study population that is similar to available literature.[13,15] In our study, 97.5% were male patients.

In the study by Osterlind and Andersen, demographic factors like age, female sex, and good PS were found to be independent prognostic factors for survival.[16] In another study by De Almeida et al, PS and age less than 65 years were found to have prognostic significance in OS and PFS.[17–20] In our study, demographic features like PS and smoking were found to have a statistically significant relationship with PFS, whereas PS alone was a statistically significant prognostic factor for OS in both univariate and multivariate analysis. No statistically significant

Table 3 Multivariate Cox regression for PFS

Variables	*p*-Value	HR	95.0% CI for HR	
			Lower	Upper
Smoking (yes vs. no)	0.012	2.982	1.274	6.980
PS (> 1 vs. 0 & 1)	0.012	1.494	1.094	2.040
Number of cycles (≥ 4 vs. < 4)	0.001	0.410	0.278	0.605
Consolidative RT (yes vs. no)	0.011	0.608	0.413	0.894
PCI (yes vs. no)	0.006	0.557	0.368	0.844

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PCI, prophylactic cranial irradiation; PS, performance status; RT, radiotherapy.

prognostic benefit was found with other demographic features.

There is survival significance with the presenting symptom and sign as observed by Athey et al.[21] They have shown that patients who are presented with breathlessness, weight loss, chest pain, and systemic symptoms will be associated with less survival. But we could not demonstrate such a statistically significant benefit in our study. In the study by Shojaee et al, malignant pleural effusion is found to be a negative prognostic factor for survival.[22] But in our study, malignant pleural effusion was found to have a statistically significant negative prognostic effect for PFS in univariate analysis only.

Paraneoplastic syndrome at presentation was found to be associated with poor OS in univariate analysis in our study but did not get a similar result in multivariate analysis. It has got a borderline significance in PFS probability. This could be due to the very limited number of available data about paraneoplastic syndromes, for statistical analysis in our study. The most common paraneoplastic syndrome at presentation in our study was SIADH. The median OS and PFS of patients in the presence of paraneoplastic syndromes are about 2 months in our study. The study by Wang et al, which evaluated the role of SIADH and lung cancer, found that it is associated with poor OS and PFS.[23] The median PFS and OS in patients with SIADH were 6.7 months and 11.6 months in their study, which is much higher than our study group. This could be due to the presence of comorbid conditions and poor PS of our patient population.

The most common site of distant metastasis was the liver followed by bone and the brain in our patient population that is similar to available literature.[13,24] Patients with bone-only metastasis were found to have improved prognosis compared to liver and brain metastasis in some reports.[24,25] But no statistically significant prognostic benefit in survival or PFS was observed with the site of distant metastases or the number of metastases in our patient group similar to other reports available.[17,25]

Baseline blood parameters like normal WBC count, SGOT value, and normonatremia were found to have a statistically significant OS and PFS benefit in univariate Cox regression analysis in our study. The study by Mohan et al showed that laboratory parameters like hemoglobin more than 12.8 gm/dL and serum sodium level more than 138 mEq/dL were associated with a survival benefit.[26]

Hemoglobin level was not found to have any statistically significant survival benefit in our study population. The study by Kawahara et al showed that elevated LDH level is associated with poor survival in ES SCLC, but we did not get such a result in our study probably due to a very small number of patients whose baseline LDH values were available.[27]

No statistically significant association has been found with the tumor size or nodal stage or M stage or composite stage with the OS or PFS. Studies have shown that as the tumor size decreases, the survival will be better.[28]

Chemotherapy with EP regimen was the most common regimen used in our patient population. The number of chemotherapy cycles more than 4 has a statistically significant better OS and PFS benefit in multivariate Cox regression analysis compared to less than 4 cycles. The study by Hong et al suggested at least 6 cycles of initial chemotherapy is beneficial, whereas the one by Sallam et al suggested that there is no benefit of prolonging chemotherapy beyond 4 cycles.[20,29] Randomized controlled trial by Veslemes et al have shown that 6 cycles of chemotherapy have survival benefit only if patients do not have any completed response to 4 cycles.[30]

The addition of consolidative RT improved OS and PFS in this present study, similar to previous studies, but the magnitude of benefit is less, probably due to the poor PS of our study population.[31] Similarly, PCI also has shown survival and PFS benefit in multivariate Cox regression analysis as has been found with available literature.[7,32,33]

The median OS and PFS obtained in our study were 7 and 5 months, respectively. The retrospective analysis by Unalmis et al and Albain et al have shown a similar OS of 7 months in ES SCLC.[13,34] Many other studies have reported a higher median OS of more than or equal to 10 months, which we could not achieve, probably due to our patient population with poor PS and poor socioeconomic status, ignorance of clinical symptoms, delay in seeking and receiving treatment.[7,26,35]

CR in ES SCLC is around 15 to 20% in various studies.[17,36] It is less in our study population compared to other studies probably because only 50% of the total study population could complete more than 4 cycles of chemotherapy. There is paucity of data about ES SCLC in India. Very limited number of studies and data are available about ES SCLC. There is wide

Table 4 Survival of ES SCLC from various Indian retrospective studies

Study	Number of ES SCLC patients	Median OS in months	Median PFS in months
Mohan et al[26]	55	9.8	–
Puligundla et al[38]	103	7.2	5.6
Julka et al[39]	51	–	10.9
Murali et al[37]	36	5.3	4.9
Ganguly et al[40]	154	12.6	9.1
Our study	283	7	5

Abbreviations: ES, extensive stage; OS, overall survival; PFS, progression free survival; SCLC, small cell lung cancer.

difference between the OS and PFS among different Indian studies. The survival and PFS patterns of our study are comparable to similar South Indian study.[37,38] This could be due to the similar genetic profile, pattern of presentation, social reasons, and lack of access to treatment. The survival of ES SCLC from various retrospective studies from India is shown in ►Table 4.[26,37–40]

The limitation of this study is its retrospective nature, the nonavailability of data regarding the treatment-related toxicities, and follow-up details were not available to 11% of patients.

Conclusion

There is a difference in OS and PFS patterns of ES SCLC patients among various Indian studies, even though the available data is scarce. Our study shows that the OS and PFS of our study population are comparable to other South Indian studies available. PS, serum sodium level, number of chemotherapy cycles, and consolidative RT and PCI were found to be independent prognostic factors for survival of ES SCLC. The identification of these factors will help physicians to tailor treatment in future.

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Conflict of Interest
None declared.

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