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Small-Cell Lung Cancer in a Cancer Center in Colombia

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Abstract

Objective: This study aimed to describe the principal clinical features, survival outcomes, and prognostic factors of patients with small cell lung cancer (SCLC) treated at the Instituto Nacional de Cancerologia (INC) between 2013 and 2018.

Methods: A retrospective analytical study was conducted.

Results: 35 patients with SCLC were included, with a median age of 61 years (IQR=54-71), 24 of which were men (68.6%); 23 patients (65.7%) were admitted with an ECOG score ≤2, and 5 (14.3%) had no smoking history. 26 patients (74.3%) had extended, and 9 (25.7%) had limited disease. Three patients (8.6%) underwent surgical management. Three patients with limited disease received definitive chemotherapy and radiotherapy. 23 (65.7%) patients received best supportive care and 6 (17.1%) patients with extended disease received palliative chemotherapy. The median survival of the entire cohort was 4.5 months (95% CI, 2.56-8.28). Overall survival (OS) at 1 and 3 years was 26.5% and 5.9%, respectively. The Kaplan-Meier curves showed that patients with an ECOG >2 ($p<0.0014$), smoking history ($p=0.0026$), and extended disease ($p=0.0035$) had a worse OS. The median survival of patients who received chemotherapy, palliative chemotherapy, and best supportive care was 29.0, 11.9, and 2.6 months, respectively. Multivariate analysis showed that the only independent variable for worse OS was ECOG >2 (HR: 2.59, 95% CI, 1.09-6.12, $p=0.031$).

Conclusions: SCLC has the worst prognosis among all types of lung cancer worldwide. In Colombia, the findings are no different, and additionally, survival was clearly affected in patients with ECOG>2, smoking history, and extended disease.

Keywords: Antineoplastic Agents; Cigarette Smoking; Chemoradiotherapy; Small Cell Lung Carcinoma

Introduction

The most common cause of death in cancer patients continues to be lung cancer, with approximately 350 deaths per day by 2022 in the United States, which is greater than the deaths caused daily by breast, prostate, and pancreatic cancer combined [1]. Small-cell lung cancer (SCLC) accounts for approximately 15% of lung cancer patients, and due to its increased incidence in women, the current male-to-female ratio is 1:1 [2,3]. In Colombia, lung cancer ranks sixth in frequency among malignancies reported annually and second in overall cancer mortality in both sexes, accounting for 11.8% of deaths [4]. In a case series that included 448 lung cancer patients managed

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at the Instituto Nacional de Cancerología (INC) in Bogotá, approximately 8% corresponded to SCLC [5]. Additionally, SCLC is a special type of lung cancer that is characterized by a favorable initial response to chemotherapy and short-term radiation therapy, but it also tends to have a high rate of aggressive proliferation and a high rate of metastasis [3]; 70% of patients with SCLC are diagnosed with extended disease [6]. In addition to this factor, others have been considered poor prognostic factors, such as smoking history and low socioeconomic status, while good prognostic factors consist of Asian ethnicity and female gender [7]. There is limited information in Colombia on the clinical characteristics and survival of patients with SCLC. Therefore, this study aimed to describe the principal clinical features, survival outcomes, and prognostic factors of patients with SCLC treated at the INC between 2013 and 2018.

Methods

A retrospective analytical study was conducted, including patients with a confirmed diagnosis of SCLC, treated at the INC between January 2013 and December 2018. The exclusion criteria were patients under 18 years of age, patients with incomplete follow-up at the INC that did not allow collecting the necessary information to fill in the capturing tool, or with other uncontrolled synchronous tumors. Medical records were reviewed, and a data capturing form was created on the RedCap 7.1.2 © platform to record the information. Demographic, clinical, and clinicopathological stage variables, as well as therapeutic strategies, were analyzed. Data analysis was performed in R v4.1.1. Central tendency and dispersion measures were used for continuous variables according to data normality, and frequencies and percentages to describe the categorical variables. The 1989 classification of SCLC by the International Association for the Study of Lung Cancer (IASLC) as an extended or limited disease was used. Overall survival (OS) was defined as the time elapsed between the pathology report's date confirming SCLC and the date of death or the last day of follow-up at the INC.

Survival analysis was performed using Kaplan-Meier curves and the log-rank test to assess differences between subgroups. Statistically significant associations were considered at $p<0.05$. A Cox regression for multivariate analysis was performed to identify factors related to survival. The project was approved by the Ethics and Research Committee of the INC (N° CEI-00554-19), and data were reviewed by the institutional monitoring group.

Results

Between 2013 and 2018, a total of 35 patients with SCLC were included, with a median age of 61 years [Interquartile range (IQR)=54-71], 24 of which were men (68.6%); 1 patient had a controlled second primary prostate cancer, 23 patients (65.7%) were admitted with an Eastern Cooperative Oncology Group (ECOG) score ≤2, and 5 (14.3%) had no smoking history. Of the patients included, 26 (74.3%) had extended, and 9 (25.7%) had limited disease (Table 1).

A total of 3 patients (8.6%) received initial extra-institutional surgical management. One of them had lobectomy with mediastinal nodal sampling; the surgery was R0, and the patient received cisplatin/etoposide and adjuvant radiotherapy, with a survival rate of 53.7 months. As for the other two patients, one underwent lobectomy, and the other had pulmonary wedge resection. Both had nodal sampling, but the surgeries had positive resection margins of lung parenchyma (R1). The median survival of these patients was 3 months. In addition, three patients in the limited disease group received definitive chemotherapy and radiotherapy; one of them also received prophylactic holocephalic radiotherapy. A total of 23 (65.7%) patients received best supportive care; of these patients, 47.8% had an ECOG = 3-4. Additionally, in the extended disease group, 6 (17.1%) remaining patients received palliative chemotherapy: 4 patients received cisplatin/etoposide, 1 patient carboplatin/etoposide, and another one received cyclophosphamide/doxorubicin/etoposide. The latter regimen was administered in another institution. One of these patients received topotecan as second-line treatment, 2 of them received palliative holocephalic radiotherapy, and 5 patients also required stent placement in the superior vena cava. The median survival of the entire cohort was 4.5

Table 1: Characteristics of patients included.

Characteristics n=35	n(%)
Median age: 61 (IQR: 54-71)	
Gender	
Female	11(31.4)
Male	24(68.6)
Oncological history	
Prostate	1(2.8)
No	34(97.2)
Smoking history	
Yes	30(85.7)
No	5(14.3)
ECOG	
0	1(2.8)
1	12(34.3)
2	10(28.6)
3	7(20)
4	5(14.3)
Disease	
Extended	26(74.3)
Limited	9(25.7)

Abbreviations: IQR- Interquartile range; ECOG- Eastern Cooperative Oncology Group

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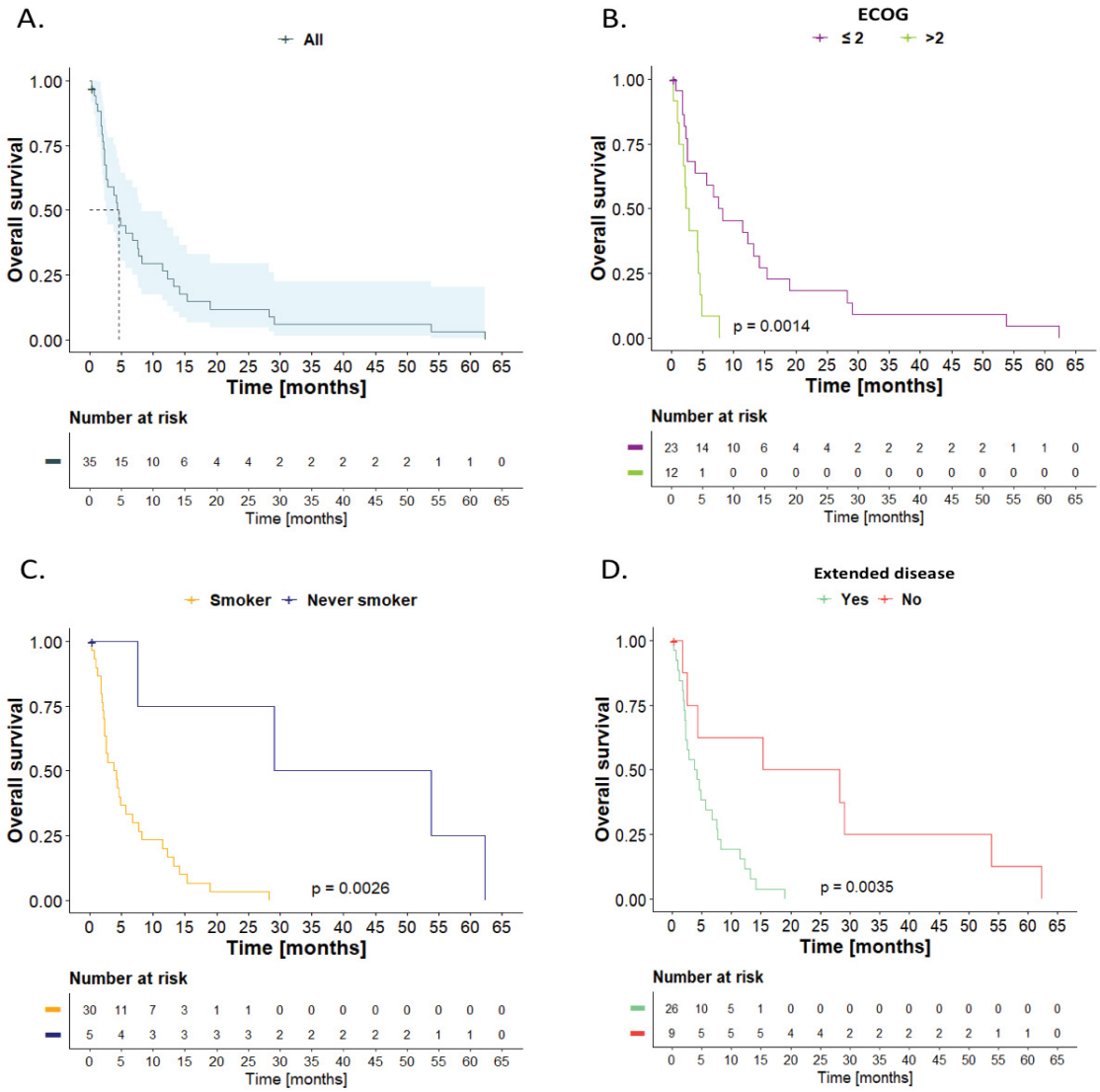

Figure 1: Overall survival, Kaplan-Meier curves: A) The entire cohort, stratified by: B) Eastern Cooperative Oncology Group (ECOG). C) Smoking history. D) Extended disease. Log-rank test comparison.

Table 2: Medians of overall survival and survival at 1 and 3 years.

Characteristics	Overall survival % [$_{95\%\ CI}$]			Median survival (months)
	12 months	36 months	p-value	
ECOG				
≤ 2	40.9 [24.8-67.6]	9.09 [2.43-34.1]	< 0.01	7.95
> 2	NE	NE		2.6
Smoking history				
Smoker	20.0 [9.78-40.9]	NE	< 0.01	4
Never smoker	75.0 [42.6-100]	50.0 [18.8-100]		41.4
Extended disease				
Yes	15.4 [6.25-37.9]	NE	< 0.01	4
No	62.5 [36.5-100]	25.0 [7.53-83.0]		21.8

Abbreviations: CI- Confidence Interval; NE- Not Estimable.

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months (95% CI, 2.56-8.28). Overall survival (OS) at 1 and 3 years was 26.5% and 5.9%, respectively (Figure 1A). The Kaplan-Meier curves showed that patients with an ECOG >2 (p<0.0014), smoking history (p=0.0026), and extended disease (p=0.0035) had a worse OS (Figure 1B-D). Table 2 summarizes median survival and 1- and 3-year survival rates according to ECOG, smoking history, and extended disease.

With respect to treatment, the median survival of patients who received chemotherapy, palliative chemotherapy, and best supportive care was 29.0, 11.9, and 2.6 months, respectively (Figure 2).

The Cox regression, including variables such as ECOG, smoking history, and extended disease, showed that the only independent variable for worse OS was ECOG >2 (HR: 2.59, 95% CI, 1.09-6.12, p=0.031) (Table 3).

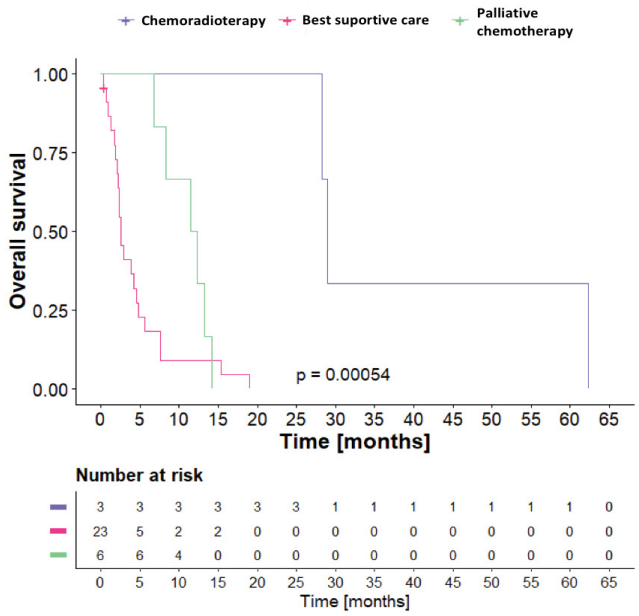

Figure 2: Overall survival according to treatment, Kaplan-Meier curves. Log-rank test comparison.

Discussion

This review evaluates the behavior of the classical variant of SCLC without including mixed-behavior tumors (non-small cell carcinomas with small cell components or large-cell tumors with neuroendocrine dedifferentiation). SCLC is the most aggressive form of lung cancer [8,9]; the reported 5-year OS is less than 10% [9], and not even screening programs with low-dose computed tomography have shown improvement in survival [10]. The OS of the entire study cohort at 1 and 3 years in our series was 26.5% and 5.9%, respectively, a finding that is consistent with the aggressive nature of this disease. Median survival intervals from the diagnosis of limited and extended diseases in multiple series are 15 to 20 months and 8 to 13 months, respectively. Approximately 20 to 40% of limited-stage patients and less than 5% of the extended-stage patients survive two years. These data do not include the possible impact of the introduction of first-line immunotherapy in extended disease on studies with atezolizumab or durvalumab [11-15]. This series represents a first approach to understanding the management of this pathology in Colombia and Latin America. The differences found regarding survival in our series are strongly related to the initial stage at the time of diagnosis of the patients, as well as to marked functional deterioration. Nevertheless, factors such as histopathological variants of the disease, considerations about tumor transcriptomics, opportunities for early access to treatment after diagnosis, and other barriers to accessing the health system were not analyzed. The SCLC classification that divides the disease into limited and extended was introduced in 1950 by the Veterans Administration Lung Study Group; later, in 1989, it was refined by the IASLC, and since 2007 this classification has been fully incorporated into the TNM system [8]. Despite this, in our series, we employed

Table 3: Cox proportional hazards model.

	Univariate		Multivariate	
Characteristics	HR [$_{95\% CI}$]	p-value	HR [$_{95\% CI}$]	p-value
ECOG				
≤ 2	Ref.	<0.01	Ref.	0.031
> 2	3.71 [1.57-8.74]		2.70 [1.15-6.35]	
Smoking history				
Smoker	12.6 [1.65-96.2]	0.015	7.35 [0.85-63.5]	0.07
Never smoker	Ref.		Ref.	
Extended disease				
Yes	4.73 [1.55-14.5]	<0.01	2.31 [0.73-7.25]	0.2
No	Ref.		Ref.	

Abbreviations: HR- Hazard Ratio; CI- Confidence Interval.

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the limited and extended disease classification because it was the most common in the clinical histories of the patients included. Arriola et al. [16] described that 70% of 26,221 patients with SCLC in the Surveillance, Epidemiology and End Results (SEER) database were diagnosed at stage IV; the median survival of these patients was 6 months (95% CI: 5.83-6.17), and 5-year survival was 1.6%. In our series, 74.3% of patients corresponded to extended disease, median survival was 4 months, 1-year survival was 15.4%, and 3-year survival was not estimable.

Due to the strong relationship between SCLC and smoking, it has been proposed that prevention of use or cessation of the habit may be the most effective strategy to reduce the impact of this disease on the general population [10]. However, assuring that this pathology only occurs in smoking patients is increasingly far from the reality since non-smoking patients with SCLC correspond to 2-3% in series from the United States and Spain [15,16] and 13-22% in series from Korea and China [17,18]. In our study, 14.3% of patients had no history of smoking. Additionally, these patients had a median OS of 41.4 months, clearly better than their smoking counterparts. These findings were similar to those described by Liu et al. [14], who reported that the median OS for patients with SCLC in non-smokers vs. smokers was 19.7 vs. 14.4 months (p=0.044), respectively; findings comparable to those reported by Torres-Duran et al. [12] in a series that included 32 patients with SCLC in never-smokers, where OS at 1 year was 34.4% and at 2 years, 21.9%. Varghese et al. [15] found that 17% of non-smoking patients with SCLC were patients who had a transformation to SCLC as a mechanism of resistance to the use of tyrosine kinase inhibitors (TKIs) in patients with mutated EGFR adenocarcinomas. In our series, none of the included patients presented this characteristic. The analysis of EGFR, ALK, and ROS-1 mutations in this population was not carried out; variables such as second-hand tobacco and radon exposure were also not analyzed. On the other hand, Belluomini et al. [20] described that special populations, such as elderly patients or patients with ECOG =2, have not been sufficiently studied in clinical trials to date. In our series, age was not associated with worse OS, but patients with ECOG>2 were, and although this association is expected, we consider that it is a factor that can contribute to decision-making in our daily clinical practice. Additionally, Arriola et al. [19], in the multivariate analysis of their SCLC series, found that women had a lower risk of death (HR=0.88, 95% CI: 0.86-0.90, p<0.0001) while patients ≥65 years were independently associated with lower OS (HR=1.43, 95% CI: 1.40-1.47, p<0.0001) [19]. These results were not found in our study, where 31.4% were women, and the median age was 61 years. In 2019, the National Comprehensive Cancer Network (NCCN) incorporated surgery as part of the multimodal treatment of SCLC, highlighting the role of surgery for early-stage disease [8]. According to the European Society for Medical Oncology (ESMO) guidelines, surgery should be considered a treatment option in patients with clinical stages I and II (cT1-2N0) and in those cases with mixed SCLC and non-small cell lung cancer (NSCLC) histology [9,21]. In our series, three patients with limited disease underwent surgical resection, but only one reached oncologic accuracy and completed multimodal management, obtaining a survival of 53.7 months. The median survival reported in the literature of surgically managed SCLC patients is approximately 20 months, and 5-year survival is between 11.1 and 52% [22]. Treatment with curative intent may be offered to patients with limited SCLC and consists of four cycles of platinum-based chemotherapy and concurrent radiation therapy, reporting median survival of approximately 27.2 months [23]. In our series, 8.6% of patients received definitive chemo-radiotherapy with curative intent, and the median survival was 29 months. On the other hand, the first line of treatment in metastatic SCLC is the combination of cisplatin or carboplatin and etoposide [23]. Patients who progress during treatment are known as platinum-resistant, those who progress within 90 days of treatment interruption are platinum-refractory, and those who progress after 90 days are known as platinum-sensitive [24]. In our series, patients who received palliative chemotherapy had a median survival of 11.9 months. It has recently been described that combining a PD-L1 inhibitor (durvalumab and atezolizumab) with etoposide-based chemotherapy may be an optimal first-line treatment option for patients with extended SCLC, improving OS [14,15]. Between 2013 and 2018, there were no data supporting the addition of these combinations to standard treatment, so none of the patients with SCLC managed at the INC had immunotherapy associated with their treatment. While the benefit of immunotherapy in extended disease appears to set a new direction in managing these patients, it is still unclear which subgroup may benefit the most in this regard. Gay et al. [25], using tumor expression and tumor transcriptomics data, have identified SCLC subtypes defined mainly by differential expression of transcription factors in three subtypes: ASCL1, NEUROD1, and POU2F3, or low expression of the three transcription factor signatures accompanied by an inflammatory genomic signature profile (SCLC-A, N, P, and I, respectively). They found that the SCLC-I profile receives the most benefit from adding immunotherapy to chemotherapy, while the other subtypes have distinct vulnerabilities, including poly (ADP-ribose) polymerase inhibitors, Aurora kinase inhibitors, or BCL-2 [25]. In our series, tumor transcriptome analysis was not performed; however, a better understanding of the biology of this type of tumor may help better select patients who may respond more efficiently to immunotherapy or other types of interventions. In our series, only one patient received prophylactic central nervous system radiotherapy, although the benefit of this intervention appears to be more consistent in limited-disease patients who have responded to or maintained

stable disease after treatment with systemic chemotherapies [26,27]. It is necessary to establish the behavior of the disease in the central nervous system and the impact of these interventions in terms of progression-free survival, OS, and neurocognitive impairment. The limitations of this study are related to the fact that it is retrospective, it was carried out in a single oncologic center with a small sample of patients, and there was difficulty in the complete collection of all clinical variables. Nevertheless, it is the first study in Colombia to describe the clinical characteristics and survival of patients with SCLC.

Conclusions

SCLC has the worst prognosis among all types of lung cancer worldwide. In Colombia, the findings are no different, and additionally, as found in this study, survival was clearly affected in patients with ECOG>2, smoking history, and extended disease. It leads us to think that it is essential to improve access routes for diagnosis and management in specialized oncology centers and to promote the prevention of tobacco use and smoking cessation in the country.

Conflicts of Interest

The authors declare no conflict of interest.

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