Received: 13 June 2022 | Accepted: 17 October 2022

DOI: 10.1111/1759-7714.14712

ORIGINAL ARTICLE

WILEY

Prognostic factors for survival in extensive-stage small cell lung cancer: An Italian real-world retrospective analysis of 244 patients treated over the last decade

Vito Longo | **Pamela Pizzutilo** | **Annamaria Catino** | **Michele Montrone** | **Francesco Pesola** | **Ilaria Marerch** | **Domenico Galetta**

Medical Thoracic Oncology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy

Correspondence
Vito Longo, Medical Thoracic Oncology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy.
Email: v.longo@oncologico.bari.it

Funding information
Ministero dell'Istruzione, dell'Università e della Ricerca; AstraZenecaOpen access funding provided by BIBLIOSAN.

Abstract

Background: Potential relationships with the prognosis of patients with extensive-stage non-small cell lung cancer (ES-SCLC) have been investigated without valid results.

Methods: A retrospective analysis of real-world data of consecutive patients with ES-SCLC admitted to our Medical Thoracic Oncology Unit was carried out from 2010 to 2020, focusing on identification of prognostic factors. Kaplan–Meier analysis was used to represent progression-free survival (PFS) and overall survival (OS). Univariable and multivariable Cox models were used to investigate prognostic factors.

Results: The analysis included 244 patients. The median OS was 8 months (95% confidence interval [CI]: 8–10) and the median PFS was 5 months (95% CI: 5–6). The univariable analysis showed that factors associated with shorter OS were older age ($p = 0.047$), TNM stage 4 versus 3 ($p < 0.001$), Eastern Cooperative Oncology Group (ECOG) performance status (PS) 1 and 2 versus 0 ($p < 0.001$), and >2 metastatic sites ($p = 0.004$). Mediastinal radiotherapy (RT) ($p < 0.001$), >1 irradiated site ($p = 0.026$), 3 and 4 chemotherapy (CT) lines versus 1 ($p = 0.044$ and 0.001, respectively), prophylactic cranial irradiation (PCI) ($p < 0.001$), and surgery ($p = 0.001$) correlated with longer OS. The multivariable analysis revealed statistically significant associations for TNM, ECOG PS 2 versus 0, number of CT lines, PCI, and surgery. A total of 23 patients (9.4%) survived ≥24 months, 39% of whom had received four CT lines and 48% had mediastinal RT.

Conclusions: Our data suggest that tumor burden, PS, and mediastinal RT strongly correlate with outcome. With the addition of immunotherapy to CT, the identification of new biomarkers as predictive factors is urgently required.

KEYWORDS
predictive factors, prognostic factors, small cell lung cancer

INTRODUCTION

Small cell lung cancer (SCLC) is an aggressive tumor of neuroendocrine origin, representing approximately 16% of all lung cancers, the leading cause of cancer deaths worldwide.[1] SCLC is characterized by rapid growth, early metastatic spread, and widespread dissemination. Patients are generally past or current heavy smokers and typically present with rapid onset of symptoms due to rapid local tumor growth. In 60%–65% of cases, metastatic disease is present at diagnosis and paraneoplastic syndromes also frequently occur.[2–4] Responsiveness of SCLC to initial therapy is generally high, but the disease may include extremely chemosensitive and chemoresistant clones, so that, despite the initial response, most patients eventually relapse.[4,5] SCLC is typically divided into two stages, limited and extensive, but in recent years there has been increased use of the tumor, node, and metastasis

(TNM) staging system for SCLC.[6–8] Extensive-stage (ES)-SCLC has a worse prognosis than limited-stage (LS) disease, and the therapeutic strategies are different. For patients with ES-SCLC, platinum-based chemotherapy (CT) has been the first-line standard of care for some time, generally combined with etoposide or irinotecan. Thoracic radiotherapy (RT) is used not only for LS-SCLC but also as consolidation radiotherapy for patients with ES-SCLC. On the other hand, the benefit of prophylactic cranial irradiation (PCI) for this group of patients remains uncertain.[4] Molecularly targeted therapy has not shown convincing clinical benefits.[5] The median overall survival (OS) of patients with ES-SCLC treated with standard frontline CT has been reported to be around 10 months.[9–11]

Although clinical progress in the treatment for SCLC has been slow,[3,5] the recent introduction of the immune checkpoint blocking strategy has provided new treatment opportunities, and immunotherapy (IT) has recently been approved as a first-line agent in metastatic SCLC in combination with CT. However, the benefits of adding IT are modest in SCLC, unlike in non-SCLC. In particular, only a small number of patients with SCLC benefit from immune checkpoint inhibitors (ICIs).[12–14] Survival of patients with ES-SCLC can differ dramatically, therefore various factors have been analyzed with the aim of exploring potential relationships with the prognosis of patients with ES-SCLC, but consensus has not been reached.[15,16]

Here, we present the demographic, laboratory, clinical, and therapeutic data of patients with ES-SCLC followed at our Medical Thoracic Oncology Unit in southern Italy from 2010 to 2020, focusing on identification of prognostic factors.

METHODS

Patient cohort

Consecutive patients with ES-SCLC presenting at the Medical Thoracic Oncology Unit of the Cancer Institute "Giovanni Paolo II" in Bari, Italy, from August 2010 to December 2020 were enrolled and followed up. Patients were included in the analysis if they had a pathological or cytological diagnosis of SCLC, confirmed staging of ES, and complete medical records as well as availability of pretreatment laboratory and radiological data.

Staging at diagnosis included a computed tomography scan of the chest and abdomen, a whole-body bone scan, and magnetic resonance imaging of the brain. Patient informed consent was not applicable due to the retrospective nature of the study. The study was approved by the Institutional Review Board.

Statistical analysis

Descriptive analyses were performed; qualitative variables are described by absolute and relative frequency, and quantitative variables by the mean, standard deviation, minimum and maximum.

Categorization in time was represented by dividing the patients into two groups according to the time of enrollment: from 2010 to 2015 (group A), and from 2015 to 2020 (group B). Log-rank (Mantel-Cox) nonparametric test was used to compare the survival distribution of the two groups and the characteristics of the two groups were compared using a t test for the continuous variables and chi-squared or Fisher's exact test for the categorical variables.

Kaplan–Meier curves were used to represent progression-free survival (PFS) and OS, and the results are reported as the median survival time with 95% confidence intervals (CIs). Univariable Cox proportional hazard models were used to investigate the prognostic factors for OS and PFS. Subsequently, two multivariable models were found including only the variables with a p-value <0.10 in the univariable analysis. All statistical analyses were performed with Stata, version 16.0 (Stata Corporation), and p-values <0.05 were considered statistically significant.

RESULTS

Patient characteristics

From August 2010 to December 2020, 244 patients with ES-SCLC treated in our unit fulfilled the inclusion criteria and were included in the analysis. Patients were mainly males (79%) and the mean age was 66 years (standard deviation, 10 years). Metastatic disease in liver ($n = 78$, 32%), bones ($n = 56$, 23%), brain ($n = 42$, 17%), or adrenal glands ($n = 37$, 15%) was reported in 145 patients. The demographic and main clinical features of the entire cohort and the two subgroups A and B are summarized in Table 1. Surgery was performed in 10 patients (4%), due to a misinterpretation of diagnostic biopsy. Thirty-nine percent of the patients underwent RT, 51 (21%) to the mediastinum as a consolidative treatment, 35 (14%) to brain metastases, 19 (8%) to bones, and 12 (5%) underwent PCI. Most patients ($n = 132$, 54%) underwent first-line CT with cisplatin-etoposide (CDDP/VP), and 98 (40%) were treated with carboplatin and etoposide (CBDCA/VP); in the remaining 12 patients (5%), first-line CT was combined with IT. Half of the patients received second-line CT ($n = 121$, 50%), 38 patients (16%) received third-line CT, and 14 (6%) received fourth-line CT.

There were statistically significant differences between group A ($n = 70$) and group B ($n = 174$) with regard to the percentage of patients with comorbidities (50% and 74% of patients, respectively; $p < 0.001$), bone metastases (11% and 28%, respectively; $p = 0.007$), and first-line CT (73% vs. 47% with CDDP/VP; $p < 0.001$).

Survival analysis

The median OS was 8 months (standard error [SE], 0.52; 95% CI: 8–10) in the overall population, 10 months (SE,

TABLE 1 Demographic and main clinical characteristics of the patients, overall and by treatment period

Patients characteristics	Overall ($N = 244$)	Group A ($n = 70$)	Group B ($n = 174$)	p-value
General characteristics				
Age (years), mean (SD) (min–max)	66 (10) (40–87)	65 (9) (43–82)	67 (10) (40–87)	0.099
Gender (male), *n* (%)	192 (79)	58 (83)	134 (77)	0.313
With comorbidities, *n* (%)	164 (67)	35 (50)	129 (74)	**<0.001**
Smoking status, *n* (%)				
Current or ex	231 (95)	65 (93)	166 (95)	0.716
Never	9 (4)	3 (4)	6 (3)	
Missing	4 (2)	2 (3)	2 (1)	
Disease characteristics				
ECOG PS, *n* (%)				
0	44 (18)	12 (17)	32 (18)	0.972
1	142 (58)	41 (59)	101 (58)	
2	58 (24)	17 (24)	41 (24)	
TNM, *n* (%)				
3	63 (26)	21 (30)	42 (24)	0.344
4	181 (74)	49 (70)	132 (76)	
Metastases, *n* (%)				
Liver	78 (32)	21 (30)	57 (33)	0.676
Bones	56 (23)	8 (11)	48 (28)	**0.007**
Brain	42 (17)	13 (19)	29 (17)	0.721
Adrenal glands	37 (15)	9 (13)	28 (16)	0.524
Metastatic sites, *n* (%)				
≤2	212 (87)	62 (89)	150 (86)	0.621
>2	32 (13)	8 (11)	24 (14)	
Treatments				
Mediastinal RT, *n* (%)	51 (21)	13 (19)	38 (22)	0.570
Irradiated sites, *n* (%)				
≤1	229 (94)	67 (96)	162 (93)	0.565
>1	15 (6)	3 (4)	12 (7)	
CT lines, *n* (%)				
1	242 (99)	69 (99)	173 (99)	0.492
2	121 (50)	37 (53)	84 (48)	0.517
3	38 (16)	15 (21)	23 (13)	0.110
4	14 (6)	6 (9)	8 (5)	0.227
First-line CT, *N* (%)				
CBDCA/VP	98 (40)	18 (26)	80 (46)	**<0.001**
CDDP/VP	132 (54)	51 (73)	81 (47)	
CT + IT	12 (5)	0 (0)	12 (7)	
PCI, *n* (%)				
Yes	12 (5)	4 (6)	8 (5)	0.747
No	232 (95)	66 (94)	166 (95)	

Note: p-values refer to the t test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. p-values in bold type are significant.
Abbreviations: CBDCA/VP, carboplatin and etoposide; CDDP/VP, cisplatin-etoposide; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IT, immunotherapy; PCI, prophylactic cranial irradiation; RT, radiotherapy; SD, standard deviation.

0.74; 95% CI: 8–12) in group A, and 8 months in group B (SE, 0.41; 95% CI: 7–9; log-rank test $p = 0.0958$) for equality of survivor functions between group A and group B. The median PFS was 5 months (SE, 0.24; 95% CI: 5–6) in the overall population, 6 months (SE, 0.28; 95% CI: 5–6) in group A, and 5 months (SE, 0.25; 95% CI: 4–5) in group B,

TABLE 2 Median overall survival and 95% confidence by general characteristics, disease characteristics, and treatments

		Univariable		Multivariable	
Patients characteristics	**Median OS (95% CI)**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
General characteristics					
Age					
<70 years	9 (8–11)	1.00	–	1.00	–
≥70 years	8 (6–9)	1.34 (1.00–1.78)	**0.047**	1.02 (0.73–1.44)	0.896
Gender					
Male	8 (8–10)	1.00	–	–	–
Female	7 (6–11)	1.09 (0.78–1.52)	0.613	–	–
Comorbidities					
No	11 (8–12)	1.00	–	–	–
Yes	8 (7–9)	1.26 (0.93–1.69)	0.131	–	–
Smoking status					
Never smoker	6 (2–31)	1.00	–	–	–
Current or previous smoker	8 (8–10)	0.95 (0.45–2.04)	0.903	–	–
Disease characteristics					
TNM					
3	16 (12–21)	1.00	–	1.00	–
4	7 (6–8)	3.56 (2.47–5.13)	**<0.001**	2.10 (1.36–3.25)	**0.001**
ECOG PS					
0	16 (12–31)	1.00	–	1.00	–
1	9 (8–10)	2.23 (1.49–3.35)	**<0.001**	1.23 (0.78–1.93)	0.369
2	5 (3–6)	6.09 (3.74–9.93)	**<0.001**	2.61 (1.50–4.53)	**0.001**
Metastatic sites					
≤2	9 (8–10)	1.00	–	1.00	–
>2	6 (5;8)	1.86 (1.22–2.84)	**0.004**	1.30 (0.83–2.04)	0.257
Treatments					
Mediastinal RT					
Yes	13 (9–19)	1.00	–	1.00	–
No	7 (6–8)	2.33 (1.62–3.35)	**<0.001**	1.40 (0.91–2.16)	0.128
Irradiated sites					
≤1	8 (7–9)	1.00 (reference)	–	1.00	–
>1	13 (8)	0.49 (0.26–0.92)	**0.026**	0.51 (0.25–1.03)	0.059
No. CT lines					
1	6 (5–7)	1.00 (reference)	–	1.00	–
2	9 (8–11)	0.79 (0.57–1.08)	0.135	0.72 (0.52–1.00)	**0.048**
3	12 (10–14)	0.62 (0.39–0.99)	**0.044**	0.48 (0.30–0.77)	**0.003**
4	30 (18–42)	0.37 (0.21–0.66)	**0.001**	0.25 (0.13–0.48)	**<0.001**
First-line CT					
CDDP/VP	9 (8–12)	1.00 (reference)	–	1.00	–
CBDCA/VP	8 (6–8)	1.34 (1.00–1.79)	0.051	1.05 (0.74–1.49)	0.800
CT + IT	7 (2–)	1.43 (0.58–3.55)	0.438	0.67 (0.26–1.68)	0.390
PCI					
Yes	30 (7–9)	1.00 (reference)	–	1.00	–
No	8 (7–9)	4.35 (1.92–9.86)	**<0.001**	3.39 (1.43–8.06)	**0.006**
Surgery					
Yes	– (7)	1.00	–	1.00	–
No	8 (7–9)	5.18 (1.91–14.06)	**0.001**	4.13 (1.39–12.28)	**0.011**

Note: Univariable Cox proportional hazards models and multivariable models including variables showing a *p*-value <0.10 in the univariable analysis. *p*-values in bold type are significant.

Abbreviations: CBDCA/VP, carboplatin and etoposide; CDDP/VP, cisplatin-etoposide; CI, confidence interval; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IT, immunotherapy; OS, overall survival; PCI, prophylactic cranial irradiation; RT, radiotherapy.

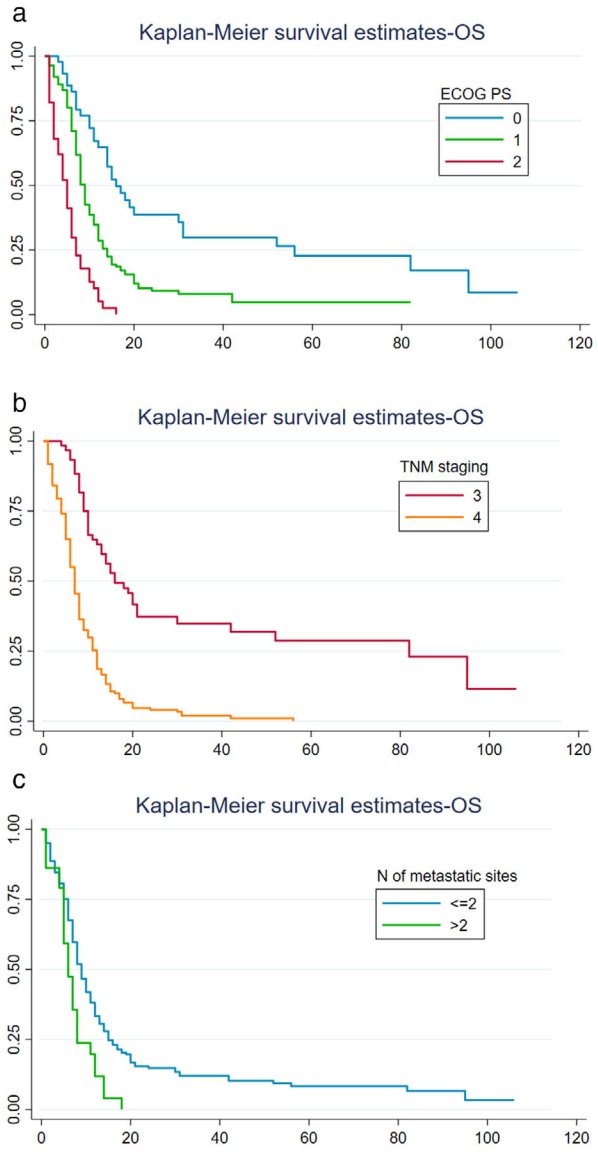

FIGURE 1 Disease factors associated with statistically significant differences in overall survival (Kaplan–Meier survival functions). (a) Eastern Cooperative Oncology Group performance status (ECOG PS); (b) TNM staging; (c) number of metastatic sites

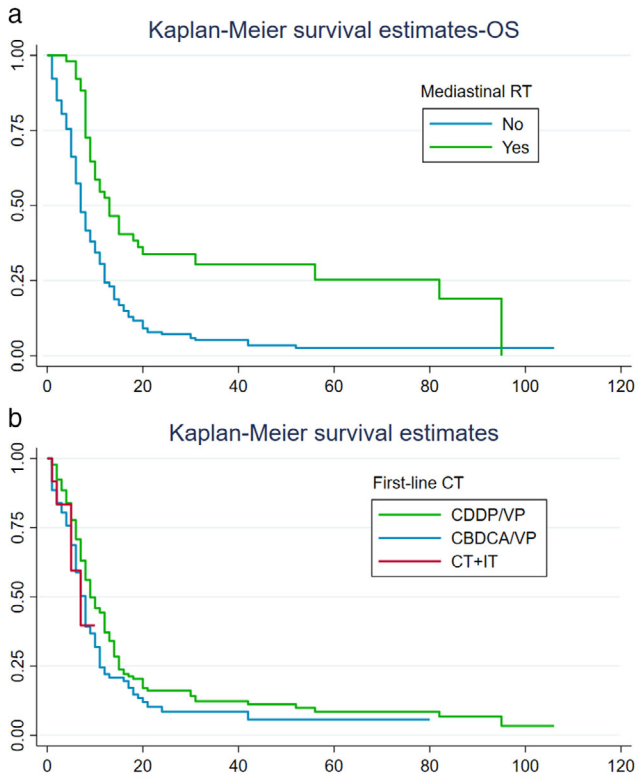

FIGURE 2 Kaplan–Meier curves for overall survival by treatments. (a) Mediastinal radiotherapy (RT) (yes/no); (b) type of chemotherapy (CT): Carboplatin and etoposide (CBDCA/VP) versus cisplatin-etoposide (CDDP/VP). IT, immunotherapy

with no significant difference between the groups ($p = 0.0720$).

Analysis of prognostic factors for overall survival

Patient and disease characteristics

The univariable analysis showed that older age was associated with shorter OS ($p = 0.047$) but this association was no longer significant in the multivariable analysis (Table 2). Regarding disease characteristics, in the univariable analysis, higher TNM ($p < 0.001$), Eastern Cooperative Oncology Group (ECOG) performance status (PS) ($p < 0.001$), and the number of metastatic sites ($p < 0.004$) were associated with shorter OS. The multivariate analysis showed that TNM 4 was associated with a shorter survival time versus TNM 3 ($p = 0.001$), as was ECOG PS 2 versus 0 ($p = 0.001$). Kaplan–Meier curves for OS by disease factors are shown in Figure 1.

Treatments

The univariable analysis showed that mediastinal RT ($p < 0.001$), PCI ($p < 0.001$), surgery ($p < 0.001$), and a higher number of irradiated sites (>1 irradiated site, $p = 0.026$) and CT lines (3 and 4 CT lines: $p = 0.044$ and $p = 0.001$, respectively). In the multivariable analysis, PCI, surgery, and a higher number of CT lines were significantly associated with longer OS. Kaplan–Meier curves for OS by treatment factors are reported in Figures 2–4.

Analysis of prognostic factors for progression-free survival

Median PFS values by disease characteristics and treatment are summarized in Table 3. The univariable analysis showed

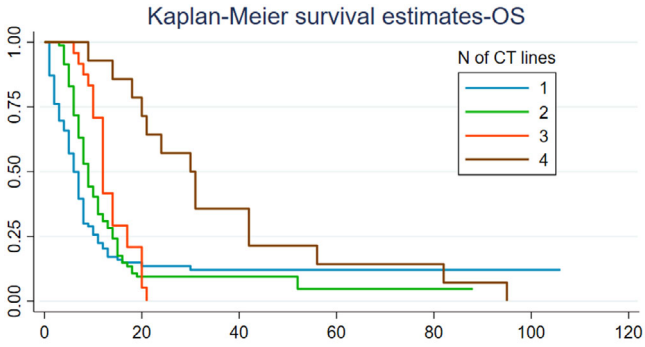

FIGURE 3 Kaplan–Meier curves for overall survival by chemotherapy (CT) lines

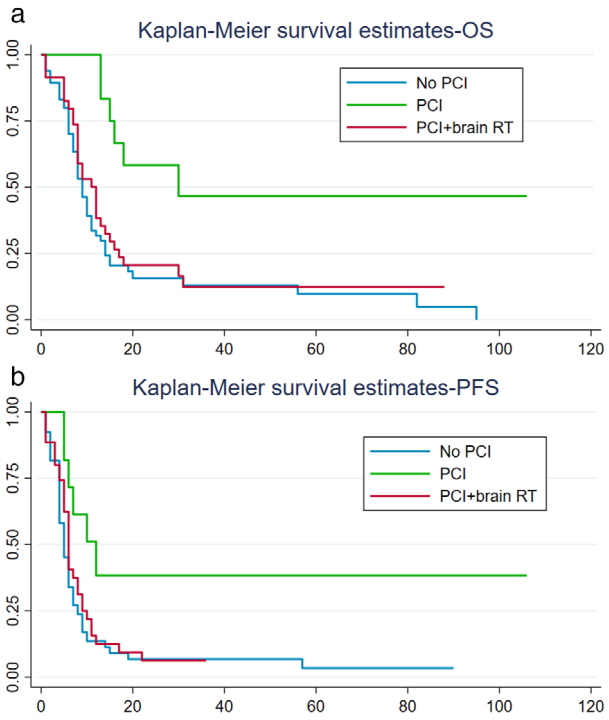

FIGURE 4 Kaplan–Meier survival curves by prophylactic cranial irradiation (PCI) (yes/no). (a) Overall survival (OS); (b) progression-free survival (PFS). RT, radiotherapy

that higher TNM (4 vs. 3: $p < 0.001$), ECOG PS (1 and 2 vs. 0: $p = 0.005$ and $p < 0.001$), and the number of metastatic sites (>2 metastatic sites: $p = 0.004$) were associated with shorter PFS. In the multivariable analysis, we found that TNM 4 versus 3 and ECOG 2 versus 0 were associated with shorter PFS ($p = 0.004$ and $p < 0.001$, respectively).

Treatments

In terms of treatments, the univariable analysis showed that mediastinal RT ($p < 0.001$), >1 irradiated site ($p < 0.034$), PCI ($p < 0.004$), and surgery ($p < 0.003$) were associated to longer PFS. However, these associations were no longer significant in the multivariable analysis.

Long-term survivors

A total of 23 patients (9.4%) survived ≥24 months, 12 in group A (17% of group A patients) and 11 in group B (6% of group B patients). The characteristics of these patients are shown in Table 4. Compared with the other patients, long-term survivors were younger ($p = 0.018$), had lower ECOG PS and stage ($p < 0.001$) and less frequent liver metastasis ($p = 0.002$). With regard to treatments, long-term survivors had received more mediastinal RT ($p = 0.001$), PCI ($p = 0.002$), surgery ($p = 0.001$), irradiation of >1 site ($p = 0.041$), and three or four CT lines.

DISCUSSION

This study analyzed a cohort of 244 consecutive patients with ES-SCLC diagnosed and managed at our Medical Oncology Unit from 2010 to 2020. Almost all patients were treated before immunotherapy was recommended in addition to CT as a first-line regimen for this type of cancer. Therefore, almost our entire population was treated medically with first-line CT alone, 55% with cisplatin/etoposide and 40% with carboplatin/etoposide; only 5% received combined CT + IT.

The median OS of the entire patient population was 8 months, which is lower than the OS of approximately 10 months recently reported in the literature.[9,10] We hypothesize that this may be due to the real-world, retrospective nature and the long duration of our observations; the above-mentioned literature data refer to randomized controlled trials. When splitting the cohort into the two 5-year periods, we found that the patients treated from 2010 to 2015 had a slightly longer median OS (10 months) compared with those treated from 2015 to 2020 (8 months) although this was not statistically significant. The difference might be due to an improvement in the management of hematological toxicity and in antiemetic therapies in recent years, which has led to active anticancer treatments for more frail patients who were once considered unfit for CT. Patients treated in the last 5 years had significantly worse PS, more comorbidities, and more liver metastases. They also received also less mediastinal RT, suggesting that they had more extensive metastatic disease.

There is increasing interest in identifying prognostic factors for survival in patients with ES-SCLC that could help improve future clinical decision making.[17–20] A recent study[16] analyzed detailed demographic, clinical and laboratory data of patients with ES-SCLC from 2011 to 2018, identifying age, bone multimetastases, tumor biomarkers (Cyfra 21.1, CA125), decreased serum sodium level, and a platelet-to-lymphocyte ratio <76 as independent prognostic factors for OS. Another even more recent and large real-world

TABLE 3 Median progression-free survival time and 95% confidence interval by general characteristics, disease characteristics, and treatments

		Univariable		Multivariable	
Patients characteristics	**Median PFS (95% CI)**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
General characteristics					
Age					
<70 years	5 (5–6)	1.00 (reference)	–	–	–
≥70 years	5 (4–6)	1.21 (0.91–1.60)	0.198	–	–
Gender					
Male	5 (5–6)	1.00 (reference)	–	–	–
Female	4 (4–6)	1.10 (0.79–1.51)	0.572	–	–
Comorbidities					
No	6 (4–6)	1.00 (reference)	–	–	–
Yes	5 (4–6)	1.21 (0.90–1.62)	0.210	–	–
Smoking status					
Never smoker	4 (1–9)	1.00 (reference)	–	–	–
Current or previous smoker	5 (5–6)	1.02 (0.48–2.18)	0.949	–	–
Disease characteristics					
TNM					
3	8 (6–10)	1.00 (reference)	–	1.00 (reference)	–
4	4 (4–5)	2.87 (2.02–4.07)	**<0.001**	1.79 (1.20–2.65)	**0.004**
ECOG PS					
0	8 (6–9)	1.00 (reference)	–	1.00 (reference)	–
1	5 (5–6)	1.72 (1.17–2.52)	**0.005**	1.35 (0.91–1.99)	0.138
2	4 (2–4)	3.71 (2.33–5.90)	**<0.001**	2.49 (1.54–4.01)	**<0.001**
Metastatic sites					
≤2	5 (5–6)	1.00 (reference)	–	1.00 (reference)	–
>2	4 (4–4)	1.85 (1.21–2.82)	**0.004**	1.28 (0.82–2.02)	0.277
Treatments					
Mediastinal RT					
Yes	7 (6–9)	1.00 (reference)	–	1.00 (reference)	–
No	5 (4–5)	1.96 (1.40–2.75)	**<0.001**	1.30 (0.88–1.93)	0.183
Irradiated sites					
≤1	5 (5–6)	1.00 (reference)	–	1.00 (reference)	–
>1	9 (5–12)	0.54 (0.31–0.96)	**0.034**	0.61 (0.33–1.14)	0.121
No. CT lines					
1	5 (4–6)	1.00 (reference)	–	–	–
2	5 (5–6)	1.12 (0.82–1.54)	0.459	–	–
3	6 (4–7)	1.05 (0.67–1.67)	0.824	–	–
4	8 (5–12)	0.75 (0.42–1.32)	0.312	–	–
First-line CT					
CDDP/VP	6 (5–6)	1.00 (reference)	–	–	–
CBDCA/VP	5 (4–6)	1.32 (0.99–1.77)	0.058	–	–
CT + IT	4 (2)	1.39 (0.68–2.86)	0.371	–	–
PCI					
Yes	12 (5)	1.00 (reference)	–	1.00 (reference)	–
No	5 (5–6)	3.28 (1.45–7.42)	**0.004**	2.16 (0.94–4.98)	0.071
Surgery					
Yes	11 (7)	1.00 (reference)	–	1.00 (reference)	–
No	5 (5–6)	3.90 (1.59–9.54)	**0.003**	2.51 (0.98–6.45)	0.056

Note: Univariable Cox proportional hazards models and multivariable models including variables showing a *p*-value <0.10 at the univariable analysis. *p*-values in bold type are significant.

Abbreviations: CBDCA/VP, carboplatin and etoposide; CDDP/VP, cisplatin-etoposide; CI, confidence interval; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IT, immunotherapy; PCI, prophylactic cranial irradiation; PFS, progression-free survival; RT, radiotherapy.

TABLE 4 Characteristics of the patients, overall and based on survival

Patients characteristics	Long-term survivors ($n = 23$)	Nonlong-term survivors ($n = 221$)	*p*-value
General characteristics			
Age (years), mean (SD) (min–max)	62 (11) (40–78)	67 (9) (43–87)	**0.018**
Gender (male), *n* (%)	17 (74)	172 (78)	0.669
With comorbidities, *n* (%)	12 (52)	152 (69)	0.106
Smoking status, *n* (%)			
Current or former	21 (91)	210 (95)	0.209
Never	2 (9)	7 (3)	
Disease characteristics			
ECOG PS, *n* (%)			
0	13 (57)	31 (14)	**<0.001**
1	10 (43)	132 (60)	
2	0 (0)	58 (26)	
TNM, *n* (%)			
3	16 (70)	47 (21)	**<0.001**
4	7 (30)	174 (79)	
Metastases, *n* (%)			
Liver	1 (4)	77 (35)	**0.002**
Bones	2 (9)	54 (24)	0.117
Brain	1 (4)	41 (19)	0.142
Adrenal glands	1 (4)	36 (16)	0.217
Metastatic sites, *n* (%)			
≤2	23(100)	189(86)	0.052
>2	0 (0)	32 (14)	
Treatments			
Mediastinal RT, *n* (%)	11 (48)	40 (18)	**0.001**
Irradiated sites, *n* (%)			
≤1	19 (83)	210 (95)	**0.041**
>1	4 (17)	11 (5)	
No. CT lines, *n* (%)			
1	23 (100)	219 (99)	1.000
2	14 (61)	107 (48)	0.256
3	9 (39)	29 (13)	**0.001**
4	9 (39)	5 (2)	**<0.001**
First-line CT, *n* (%)			
CBDCA/VP	6 (26)	92 (42)	0.151
CDDP/VP	17 (74)	115 (53)	
CT + IT	0 (0)	12 (5)	
PCI, *n* (%)			
Yes	5 (22)	7 (3)	**0.002**
No	18 (78)	214 (97)	
Surgery, *n* (%)	5 (22)	5 (2)	**0.001**

Note: *p*-values refer to the *t* test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. *p*-values in bold type are significant.

Abbreviations: CBDCA/VP, carboplatin and etoposide; CDDP/VP, cisplatin-etoposide; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IT, immunotherapy; PCI, prophylactic cranial irradiation; RT, radiotherapy.

study on both LS- and ES-SCLC found that ECOG PS 0–1, response to primary systemic treatment, aggressive RT, and three or more lines of CT were predictive of better OS in the whole group.[21] In the multivariable analysis, more advanced age was not an unfavorable prognostic factor. Even the presence of comorbidities did not have an impact on survival.

A TNM stage of 4 and an ECOG PS of 2 were negative prognostic factors for both PFS and OS. Patients with TNM 4 comprised 73% of the cohort, similarly distributed in the two subgroups of the study consistent with the study focus on ES-SCLC. Patients with ECOG PS 2 comprised 23% of the overall cohort and were significantly more represented in group B, supporting what we hypothesized about extension of CT to less fit patients in recent years. The analysis by Ma et al.[21] also concluded that stage is still one of the most important prognostic factors for survival and ECOG PS at diagnosis is also highly related to survival. Multimetastases represented a significant negative prognostic factor for both PFS and OS in our patients, in agreement with the data by Huang et al.[16]

In our study, we tried to focus on the impact of therapeutic strategies on survival. Few of our patients underwent surgery although they had ES disease; most were in group A, when surgery was still performed in a few cases of ES. That mediastinal RT was associated with longer OS is not surprising given that this therapeutic approach is typically intended for patients who responded to the first-line treatment.[22] RT on metastatic sites also had a positive impact on survival, in line with published data.[16,21] In particular, in our patients, RT was associated with prolonged survival when more than one disease site was irradiated compared with one single site. The positive prognostic impact of PCI was confirmed in our analysis, although in a limited number of patients, as reported in other studies.[16,23]

In agreement with the data in the literature, no difference was found between the two platinum-based CT regimens.[24,25] Receiving more than one CT line, be it two, three, or four, had a significantly favorable impact on OS, but not on disease progression. This may be related to the fact that patients receiving more than one CT line represent a selection of good CT responders with favorable biological features. In the study by Huang et al.[16] a highly significant difference was found for ≥4 CT lines compared with <4 for both OS and PFS. Our results also show the best OS curves for patients who received 4 CT lines.

Prognostic factors for PFS were broadly similar to those for OS, except for the number of CT lines. Although all statistically significant, the differences in PFS for some prognostic factors analyzed did not exceed 1 month. Undergoing mediastinal RT improved the median PFS by 3 months.

Approximately 10% of our population were long-term survivors, with a higher proportion in the oldest diagnosis and treatment group. This seems to suggest that the patient group treated in the first part of the last decade had more favorable baseline characteristics. Not surprisingly, most of the long-term survivors had received three or more CT lines and almost half of them had received mediastinal RT. Recently, the addition of ICI to CT has shown a slight increase in the rate of long-term survivors of 15%.[26]

Our study has some limitations. First, the population, referring to the past decade, includes only a small minority of patients treated with IT, as currently recommended. Second, its real-world retrospective design implied a heterogeneous population in terms of clinical history and therapeutic approach, and a certain inhomogeneity in the collected data. Furthermore, the number of patients in some comparison groups was small, thus impairing the reliability of the comparisons.

The data from our cohort of patients with ES-SCLC treated from 2010 to 2020 suggest that tumor burden, PS, and mediastinal RT strongly correlate with outcome. Nowadays, with the addition of IT to CT, the identification of new biomarkers as predictive factors is urgently required. Interestingly, our real-world data report that in recent years, there was a higher number of patients with low PS, comorbidities, and liver metastases compared with the past, suggesting an increased propensity to treat even frail patients.

AUTHOR CONTRIBUTIONS

Conceptualization: Vito Longo, Domenico Galetta and Pamela Pizzutilo. *Methodology*: Vito Longo, Domenico Galetta and Pamela Pizzutilo. *Investigation*: Pamela Pizzutilo and Vito Longo. *Formal Analysis*: Vito Longo and Pamela Pizzutilo. *Resources*: Domenico Galetta, Annamaria Catino, Michele Montrone, Pamela Pizzutilo, Vito Longo, Francesco Pesola, and Ilaria Marech. *Writing – Original Draft*: all authors. *Writing – Review & Editing*: all authors.

ACKNOWLEDGMENTS

Editorial and medical writing assistance was provided by Alessia Scotton (Editorial Project Manager, EDRA S.p.A, Milan, Italy) and Renata Perego, PhD, and supported by an unconditioned grant from AstraZeneca. Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Vito Longo https://orcid.org/0000-0001-7224-2111

REFERENCES

1. GLOBOCAN 2020. Lung. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf
2. Riihimäki M, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J, et al. Metastatic sites and survival in lung cancer. Lung Cancer. 2014;86:78–84.
3. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet. 2011;378:1741–55.
4. Bernhardt EB, Jalal SI. Small cell lung cancer. Cancer Treat Res. 2016;170:301–22.
5. Kalemkerian GP, Schneider BJ. Advances in small cell lung cancer. Hematol Oncol Clin North Am. 2017;31:143–56.
6. Vallières E, Shepherd FA, Crowley J, van Houtte P, Postmus PE, Carney D, et al. The IASLC lung cancer staging project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol. 2009;4:1049–59.
7. Eberhardt WE, Mitchell A, Crowley J, Kondo H, Kim YT, Turrisi A 3rd, et al. The IASLC lung cancer staging project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol. 2015;10:1515–22.

8. Feng SH, Yang ST. The new 8th TNM staging system of lung cancer and its potential imaging interpretation pitfalls and limitations with CT image demonstrations. Diagn Interv Radiol. 2019;25:270–9.
9. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379: 2220–9.
10. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394:1929–39.
11. Liu SV, Reck M, Mansfield AS, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). J Clin Oncol. 2021;39:619–30.
12. Yang S, Zhang Z, Wang Q. Emerging therapies for small cell lung cancer. J Hematol Oncol. 2019;12:47.
13. Calles A, Aguado G, Sandoval C, Álvarez R. The role of immunotherapy in small cell lung cancer. Clin Transl Oncol. 2019;21:961–76.
14. Konala VM, Madhira BR, Ashraf S, Graziano S. Use of immunotherapy in extensive-stage small cell lung cancer. Oncology. 2020;98: 749–54.
15. Alghamdi HI, Alshehri AF, Farhat GN. An overview of mortality & predictors of small-cell and non-small cell lung cancer among Saudi patients. J Epidemiol Glob Health. 2018;7(Suppl 1):S1–6.
16. Huang LL, Hu XS, Wang Y, Li JL, Wang HY, Liu P, et al. Survival and pretreatment prognostic factors for extensive-stage small cell lung cancer: a comprehensive analysis of 358 patients. Thorac Cancer. 2021;12:1943–51.
17. Shan Q, Li Z, Lin J, Wang Z, Wang H. A prognostic scoring model to determine which patients with metastatic extensive-stage small cell lung cancer could benefit from local radiotherapy: a large population-based study. Discov Med. 2019;27:255–65.
18. Shang X, Lin J, Li Z, Wang H. Radiotherapy may improve survival of ES-SCLC with distant metastasis only for patients with one metastatic site: a population-based study. Oncol Lett. 2020;19:139–46.
19. Gao H, Dang Y, Qi T, Huang S, Zhang X. Mining prognostic factors of extensive-stage small-cell lung cancer patients using nomogram model. Medicine (Baltimore). 2020;99:e21798.
20. Moser SS, Bar J, Kan I, Ofek K, Cohen R, Khandelwal N, et al. Real world analysis of small cell lung cancer patients: prognostic factors and treatment outcomes. Curr Oncol. 2021;28:317–31.
21. Ma X, Zhang Z, Chen X, Zhang J, Nie J, da L, et al. Prognostic factor analysis of patients with small cell lung cancer: real-world data from 988 patients. Thorac Cancer. 2021;12:1841–50.
22. Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, el Sharouni SY, Hatton M, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet. 2015;385:36–42.
23. Yu J, Ouyang W, Yang Y, Zhang X, Zhou Y, Zhang J, et al. Prophylactic cranial irradiation for extensive-stage small cell lung cancer: analysis based on active brain MRI surveillance. Clin Transl Radiat Oncol. 2020;25:16–21.
24. Kim E, Biswas T, Bakaki P, Dowlati A, Sharma N, Machtay M. Comparison of cisplatin/etoposide versus carboplatin/etoposide concurrent chemoradiation therapy for limited-stage small cell lung cancer (LS-SCLC) in the elderly population (age >65 years) using national SEER-Medicare data. Pract Radiat Oncol. 2016;6:e163–9.
25. Karam I, Jiang SY, Khaira M, Lee CW, Schellenberg D. Outcomes of small cell lung cancer patients treated with cisplatin-etoposide versus carboplatin-etoposide. Am J Clin Oncol. 2015;38:51–4.
26. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021;22:51–65.

How to cite this article: Longo V, Pizzutilo P, Catino A, Montrone M, Pesola F, Marerch I, et al. Prognostic factors for survival in extensive-stage small cell lung cancer: An Italian real-world retrospective analysis of 244 patients treated over the last decade. Thorac Cancer. 2022;13(24):3486–95. https://doi.org/10.1111/1759-7714.14712