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

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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. 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. 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. 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
Extensive-stage (ES)-SCLC

The median overall survival (OS) of patients with ES-SCLC is around 10 months. 

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,
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 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, \( n \) (%) |                          |                        |                         |              |
| \( \leq 2 \) | 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, \( n \) (%) |                          |                        |                         |              |
| \( \leq 1 \) | 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.
### Table 2: Median overall survival and 95% confidence by general characteristics, disease characteristics, and treatments

| Patients characteristics | Median OS (95% CI) | Univariable HR (95% CI) | p-value | Multivariable 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)        | 0.133   | 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                      | –       |
| CBPDA/VP                 | 8 (6–8)            | 1.34 (1.00–1.79)        | 0.051   | 1.05 (0.74–1.49)        | 0.800   |
| CT + IT                  | 7 (2–7)            | 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                      | 3 (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.
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...
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 multimeetases, 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
| Patients characteristics | Median PFS (95% CI) | Univariable | Multivariable |
|--------------------------|---------------------|-------------|---------------|
|                          | 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.
A 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. 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.

### 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 (%)                   |                               |                                  |         |
| Yes                              | 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.
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. 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.

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. RT on metastatic sites also had a positive impact on survival, in line with published data. 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.

In agreement with the data in the literature, no difference was found between the two platinum-based CT regimens. 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., 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%.

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.

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