Journal of Cancer Research and Clinical Oncology (2023) 149:7275–7283
https://doi.org/10.1007/s00432-023-04686-2

RESEARCH

# Low diffusion capacity predicts poor prognosis in extensive stage small cell lung cancer: a single-center analysis of 10 years

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Received: 10 January 2023 / Accepted: 5 March 2023 / Published online: 13 March 2023


## Abstract

**Background** Poor pulmonary function and chronic obstructive pulmonary disease (COPD) are associated with poorer overall survival (OS) in non-small-cell lung cancer (NSCLC) patients. Few studies have investigated the association between pulmonary function and OS in small-cell lung cancer (SCLC) patients. We compared the clinical characteristics of extensive disease SCLC (ED-SCLC) with or without moderately impaired diffusion capacity for carbon monoxide (DLco) and investigated the factors associated with survival in ED-SCLC patients.

**Methods** This retrospective single-center study was performed between January 2011 and December 2020. Of the 307 SCLC patients who received cancer therapy during the study, 142 with ED-SCLC were analyzed. The patients were divided into DLco < 60% group and DLco ≥ 60% groups. OS and predictors of poor OS were analyzed.

**Results** The median OS of the 142 ED-SCLC patients was 9.3 months and the median age was 68 years. In total, 129 (90.8%) patients had a history of smoking, and 60 (42.3%) had COPD. Thirty-five (24.6%) patients were assigned to the DLco < 60% group. Multivariate analysis revealed that DLco < 60% (odds ratio [OR], 1.609; 95% confidence interval [CI], 1.062–2.437; P = 0.025), number of metastases (OR, 1.488; 95% CI, 1.262–1.756; P < 0.001), and < 4 cycles of first-line chemotherapy (OR, 3.793; 95% CI, 2.530–5.686; P < 0.001) were associated with poor OS. Forty (28.2%) patients received < 4 cycles of first-line chemotherapy; the most common reason for this was death (n = 22, 55%) from grade 4 febrile neutropenia (n = 15), infection (n = 5), or massive hemoptysis (n = 2). The DLco < 60% group had a shorter median OS than the DLco ≥ 60% group (10.6 ± 0.8 vs. 4.9 ± 0.9 months, P = 0.003).

**Conclusions** In this study, approximately one quarter of the ED-SCLC patients had DLco < 60%. Low DLco (but not forced expiratory volume in 1 s or forced vital capacity), a large number of metastases, and < 4 cycles of first-line chemotherapy were independent risk factors for poor survival outcomes in patients with ED-SCLC.

**Keywords** Diffusion capacity (DLco) · Prognosis · Small-cell lung cancer (SCLC)

## Introduction

Lung cancer is the leading cause of cancer deaths worldwide; there were an estimated 1.8 million deaths in 2020 (Jeon et al. 2015). Small-cell lung cancer (SCLC) is a smoking-related disease. SCLC represents approximately 15% of all lung cancers and is characterized by a rapid doubling time and early development of widespread metastases (Rudin et al. 2021). The overall mortality rate of SCLC has decreased in high-income countries as a result of a declining incidence of smoking (Rudin et al. 2021; Howlader et al. 2020). However, due to limited improvements in the treatment of SCLC, cancer-specific survival has remained low over the past two decades; the 2-year survival is 10% among men and 15% among women in the USA (Howlader

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et al. 2020; Paesmans et al. 2000). Extensive disease SCLC (ED-SCLC) comprises about two-thirds of SCLC cases and most patients die within 1 year despite initial chemotherapy response rates > 60% (Rudin et al. 2021).

Poor prognostic factors for survival of SCLC include older age, male sex, poor performance status, extensive disease, weight loss, and elevated lactate dehydrogenase (LDH) activity (Paesmans et al. 2000; Hong et al. 2010; Ma et al. 2021; Liu et al. 2015; Ganti et al. 2021; Albain et al. 1990). Younger age, good performance status, normal LDH activity, normal creatinine level, and a single metastatic site are favorable prognostic factors in patients with ED-SCLC (Ganti et al. 2021; Albain et al. 1990; Foster et al. 2009).

Preoperative spirometry predicts postoperative morbidity and mortality, and the diffusion capacity for carbon monoxide (DLco) is associated with long-term survival in non-small-cell lung cancer (NSCLC) patients (Ferguson et al. 2012; Brunelli et al. 2013). An association between pulmonary function and overall survival (OS) of SCLC patients has been reported (Videtic et al. 2004; Kang et al. 2018). According to Videtic et al. (Videtic et al. 2004), DLco < 60% is associated with toxicity-related treatment interruptions and decreased survival in limited-disease SCLC. Kang et al. (2018) reported that forced expiratory volume in 1 s ($FEV_1$) < 80% was an independent prognostic factor in patients with ED-SCLC. However, no study has analyzed the association between DLco and survival in ED-SCLC patients. Thus, we compared the clinical characteristics of ED-SCLC patients with and without an impaired DLco and investigated the factors associated with survival.

## Methods

### Study design and subjects

This retrospective observational study was performed between January 2011 and December 2020 at Yeungnam University Hospital, which is a 930-bed, university-affiliated tertiary referral hospital in Daegu, South Korea. Of the 307 SCLC patients who received cancer therapy during the study, 142 with ED-SCLC were analyzed. All patients with pathologically confirmed ED-SCLC and no history of treatment were included. Patients who lacked pulmonary function test (PFT) data and were untreated were excluded.

### Diagnostic procedure and pulmonary function testing

The staging procedure included routine laboratory tests, chest radiography, chest computed tomography (CT), a whole-body bone scan, 18F-fluorodeoxyglucose positron emission tomography-CT, and brain magnetic resonance imaging (MRI).

The PFTs were performed at the time of the lung cancer diagnosis following the 2005 American Thoracic Society and European Respiratory Society criteria (Miller et al. 2005; MacIntyre et al. 2005). Forced vital capacity (FVC) and $FEV_1$ were determined from a flow-volume curve drawn using a spirometer. The largest value from a minimum of three maneuvers was recorded (Miller et al. 2005). DLco was measured by single-breath diffusing capacity maneuvers during at least two valid tests (MacIntyre et al. 2005). PFT values are reported as percent predicted. Normal values of FVC, $FEV_1$ and DLco were calculated using the method described by Choi et al. (2005) and the European Community for Steel and Coal (Quanjer 1983).

### Data collection

We extracted the following data from the medical records: age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, PFT results, underlying diseases, metastatic sites, diagnosis to treatment interval, history of chemotherapy, first-line chemotherapy regimen, number of cycles, treatment response, survival status, and the date of death or last follow-up visit. Underlying comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, and hypertension were also investigated. The response to chemotherapy was evaluated by a CT scan (and brain MRI if a brain metastasis was present) after every two cycles, following the Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1 criteria (Eisenhauer et al. 2009).

### Statistical analyses

Patients were divided into DLco < 60% and DLco ≥ 60% groups. OS and predictors of a poor OS were analyzed. OS was defined as the time between the pathological diagnosis and date of death or last follow-up visit.

Student's *t*-test and the Mann–Whitney *U* test were used to compare continuous variables. Pearson's chi-square test was used to compare categorical variables and the results are expressed as frequencies (percentages). Univariate and multivariate analyses, the latter of which included factors with a P-value < 0.1 in univariate analysis, and Cox proportional hazards regression analyses were performed to identify prognostic factors for OS. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated for predictors that were significant in the multivariate analysis. Survival probability was calculated using Kaplan–Meier analyses and compared using the log-rank test. A two-sided P-value < 0.05 was considered significant for all tests. All

statistical procedures were performed with SPSS software (version 24.0; IBM Corp., Armonk, NY, USA).

### Ethics statement

This study was conducted following the tenets of the Declaration of Helsinki, and the protocol was reviewed and approved by the Institutional Review Board of Yeungnam University Hospital (YUH IRB 2022–08–016). The requirement for informed consent was waived because of the retrospective study design.

## Results

### Clinical characteristics

The baseline characteristics of the 142 ED-SCLC patients are presented in Table 1. The median age was 68 years (range: 50–85 years) and the majority were men (88.0%). The median BMI was 22.8 kg/m$^2$ and 111 patients (78.2%) had an ECOG PS of 0–1. In total, 129 (90.8%) patients had a history of smoking, and 60 (42.3%) had COPD. Fourteen (9.9%) patients had no metastases, and most patients (90.1%) had at least one metastatic organ. The most common metastatic organ was bone, followed by the pleura, liver, brain, and adrenal glands. The mean period from diagnosis to treatment was 11 days (range: 0–91 days). Most patients received the platinum-based doublet as first-line chemotherapy (93.7%) and the most common regimen was etoposide plus cisplatin (EP) (77.5%), followed by etoposide plus carboplatin (EC) (14.1%) and irinotecan plus cisplatin (IP) (2.1%). The median number of cycles of first-line chemotherapy was 5 (range: 1–13). The overall response and disease control rates for first-line chemotherapy were 27.4% and 87.3%, respectively.

Among the patients, 35 (24.6%) were in the DLco < 60% group (median, 52%; range: 33–59%) (Table 1). The DLco < 60% group had a lower FVC (82% vs. 66%, P < 0.001), lower $FEV_1$ (78% vs. 73%, P < 0.001), and underwent fewer first-line chemotherapy cycles (5 vs. 4, P = 0.005) than the DLco ≥ 60% group. The proportion of patients who received < 4 cycles of first-line chemotherapy was significantly higher in the in the DLco < 60% than ≥ 60% group (48.6% vs. 21.9%, P = 0.002). The number of metastatic organs tended to be higher in the DLco < 60% group (P = 0.050).

### Prognostic factors associated with overall survival

The median OS of the 142 ED-SCLC patients was 9.3 months. The OS rates estimated by the Kaplan–Meier method were 28.8%, 4.9%, and 0.7% at 12.5, 25, and 50 months, respectively (Fig. 1A). The median OS rates did not differ by FVC (≥ 60% vs. < 60% group) or $FEV_1$ (≥ 60% vs. < 60% group) (9.5 vs. 4.2 months, P = 0.511; and 9.9 vs. 6.9 months, P = 0.561, respectively) (Fig. 1B and C). However, the DLco < 60% group had a shorter median OS than the DLco ≥ 60% group (10.6 ± 0.8 vs. 4.9 ± 0.9 months, P = 0.003) (Fig. 1D).

Univariate analysis showed that DLco < 60% (OR, 1.809; 95% CI, 1.218–2.687, P = 0.003), the number of metastatic organs (OR, 1.453; 95% CI, 1.232–1.714, P < 0.001), liver metastasis (OR, 2.049; 95% CI, 1.416–2.966, P < 0.001), bone metastasis (OR, 1.841; 95% CI, 1.290–2.626, P = 0.001), first-line chemotherapy EP regimen (OR, 0.646; 95% CI, 0.414–1.008, P = 0.054) and < 4 cycles of first-line chemotherapy (OR, 3.805; 95% CI, 2.587–5.597, P < 0.001) were poor prognostic factors for OS (Table 2).

The multivariate analysis revealed that DLco < 60% (OR, 1.609; 95% CI, 1.062–2.437; P = 0.025), more metastatic sites (OR, 1.488; 95% CI, 1.262–1.756; P < 0.001), and < 4 cycles of first-line chemotherapy (OR, 3.793; 95% CI, 2.530–5.686; P < 0.001) were associated with a worse OS (Table 2). The Kaplan–Meier curves indicated that more metastatic organs was associated with a poor prognosis; as the number of metastatic organs increased, the survival rate decreased (no metastasis vs. four metastatic organs: median OS, 14.0 vs. 5.7 months, P < 0.001) (Fig. 2A). The < 4 cycles of chemotherapy group had a shorter median OS than the chemotherapy ≥ 4 cycles group (11.4 vs. 3.0 months, P < 0.001) (Fig. 2B).

### Reasons for incomplete first-line chemotherapy

In total, 40 of 142 (28.2%) patients received < 4 cycles of first-line chemotherapy; the most common reason for this was death (n = 22/40, 55%) from grade 4 febrile neutropenia (n = 15), infection (n = 5), or massive hemoptysis (n = 2) (Table 3). Other reasons for not completing first-line chemotherapy were a decrease in ECOG PS (n = 8), disease progression (n = 5), and adverse events during chemotherapy (n = 5) such as neutropenia and hepatitis.

## Discussion

In this study, we identified several clinical factors associated with the prognosis of ED-SCLC, including low DLco, large number of metastatic organs, and < 4 cycles of first-line chemotherapy. Our analysis showed that a lower DLco was an independent predictor of survival in patients with ED-SCLC. However, neither $FEV_1$ nor FVC was associated with a poor prognosis of ED-SCLC. To our knowledge, this is the first study to identify a relationship between DLco and the prognosis of ED-SCLC.

**Table 1** Baseline characteristics of the ED-SCLC patients

| Variables | Total (n = 142) | DLco ≥ 60% group (n = 107) | DLco < 60% group (n = 35) | P value |
|---|---|---|---|---|
| Age, years | 68 (50–85) | 68 (50–85) | 70 (52–85) | 0.120 |
| Male | 125 (88.0) | 94 (87.9) | 31 (88.6) | 1.000 |
| BMI ($kg/m^2$) | 22.8 (17.2–31.1) | 22.8 (17.2–31.1) | 22.9 (17.4–28.4) | 0.504 |
| ECOG PS | | | | 0.390 |
| 0 | 37 (26.1) | 25 (23.4) | 12 (34.3) | |
| 1 | 74 (52.1) | 58 (54.2) | 16 (45.7) | |
| 2 | 28 (19.7) | 22 (20.6) | 6 (17.1) | |
| 3 | 3 (2.1) | 2 (1.9) | 1 (2.9) | |
| Smoking | | | | 0.304 |
| Never smoker | 13 (9.2) | 11 (10.3) | 2 (5.7) | |
| Ex-smoker | 53 (37.3) | 41 (38.3) | 12 (34.3) | |
| Current smoker | 76 (53.5) | 55 (51.4) | 21 (60.0) | |
| Pulmonary function test | | | | |
| Percent predicted FVC | 78 (45–130) | 82 (45–130) | 66 (46–109) | < 0.001 |
| Percent predicted $FEV_1$ | 75 (44–150) | 78 (44–150) | 73 (60–144) | < 0.001 |
| Percent predicted DLco | 67 (33–144) | 73 (60–144) | 52 (33–59) | < 0.001 |
| Comorbidities | | | | |
| COPD | 60 (42.3) | 47 (43.9) | 13 (37.1) | 0.481 |
| DM | 38 (26.8) | 30 (28.0) | 8 (22.9) | 0.548 |
| HTN | 69 (48.6) | 53 (49.5) | 16 (45.7) | 0.695 |
| Number of metastatic organs | | | | |
| 0 | 14 (9.9) | 11 (10.3) | 3 (8.6) | 0.050 |
| 1 | 56 (39.4) | 46 (43.0) | 10 (28.6) | |
| 2 | 35 (24.6) | 28 (26.2) | 7 (20.0) | |
| 3 | 24 (16.9) | 13 (12.1) | 11 (31.4) | |
| 4 | 13 (9.2) | 9 (8.4) | 4 (11.4) | |
| Metastatic organs | | | | |
| Liver | 48 (33.8) | 33 (30.8) | 15 (42.9) | 0.192 |
| Brain | 34 (23.9) | 27 (25.2) | 7 (20.0) | 0.529 |
| Adrenal gland | 23 (16.2) | 16 (15.0) | 7 (20.0) | 0.482 |
| Bone | 75 (52.8) | 53 (49.5) | 22 (62.9) | 0.170 |
| Pleura | 50 (35.2) | 35 (32.7) | 15 (42.9) | 0.275 |
| Diagnosis to treatment interval, days | 11 (0–91) | 11 (0–91) | 10 (1–83) | 0.785 |
| First-line chemotherapy regimen | | | | 0.448 |
| EP | 110 (77.5) | 81 (75.7) | 29 (82.9) | |
| EC | 20 (14.1) | 17 (15.9) | 3 (8.6) | |
| IP | 3 (2.1) | 1 (0.9) | 2 (5.7) | |
| Others | 9 (6.3) | 8 (7.4) | 1 (2.9) | |
| First-line chemotherapy cycles | 5 (1–13) | 5 (1–13) | 4 (1–9) | 0.005 |
| < 4 cycles of first-line chemotherapy | 40 (28.2) | 23 (21.9) | 17 (48.6) | 0.002 |
| Response to first-line chemotherapy | | | | 0.084 |
| CR | 8 (5.6) | 3 (2.8) | 5 (14.3) | |
| PR | 31 (21.8) | 25 (23.4) | 6 (17.1) | |
| SD | 85 (59.9) | 67 (62.6) | 18 (51.4) | |
| PD | 5 (3.5) | 3 (2.8) | 2 (5.7) | |
| Not evaluable | 13 (9.2) | 9 (8.4) | 4 (11.4) | |

Data are presented as median (range) or number (%)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CR, complete response; DLco, diffusion capacity for carbon monoxide; DM, diabetes mellitus; EC, etoposide + carboplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; ED-SCLC, extensive disease small-cell lung cancer; EP, etoposide + cisplatin; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; HTN, hypertension; IP, irinotecan + cisplatin; PD, progressive disease; PR, partial response; SD, stable disease

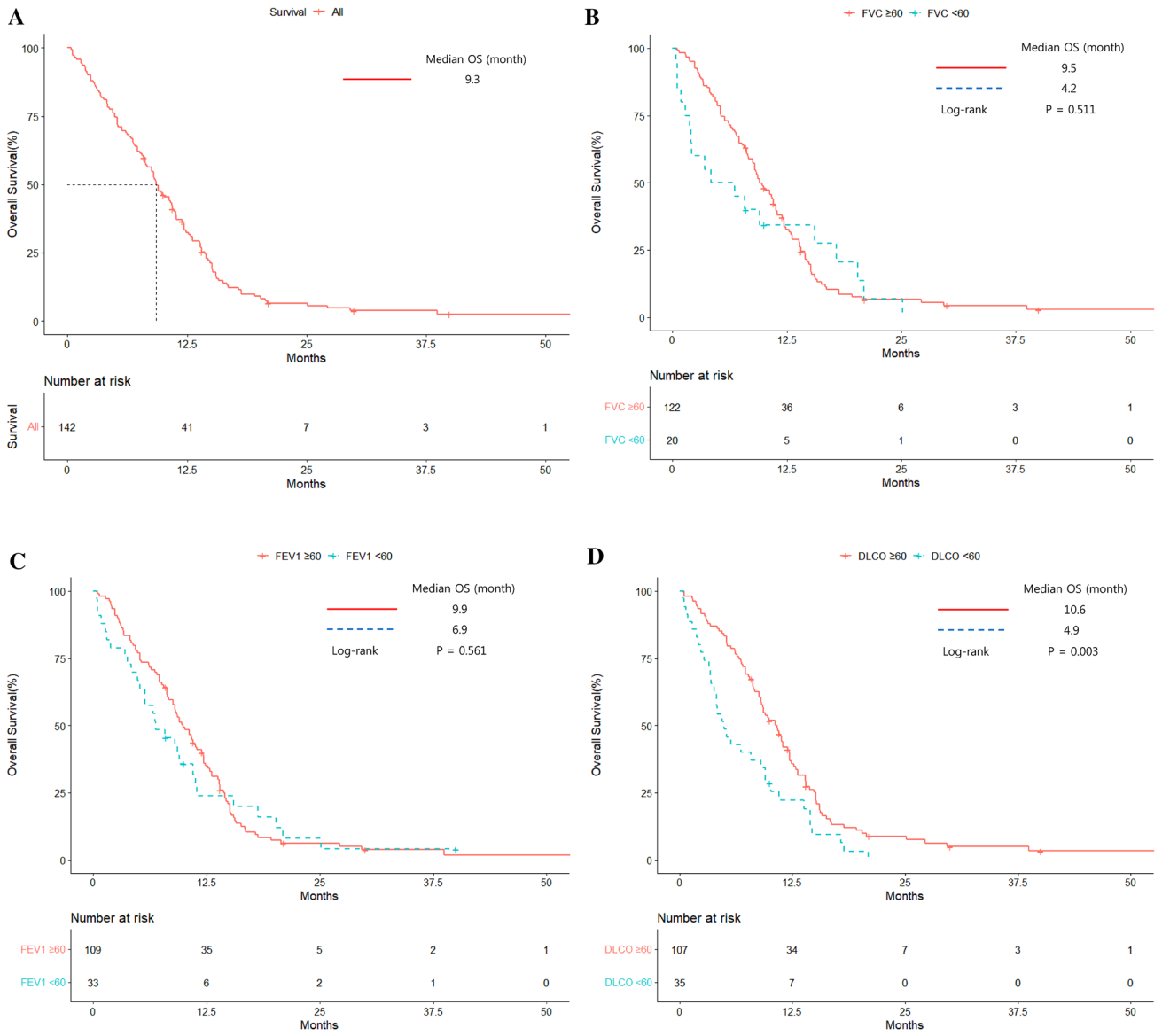


**Fig. 1** Kaplan–Meier overall survival curves. **A** Overall survival of all patients. **B** Overall survival according to forced vital capacity. **C** Overall survival according to forced expiratory volume in 1 s. **D** Overall survival according to diffusion capacity for carbon monoxide

DLco is a measure of gas transfer that reflects the complex interactions that occur at the alveolar-capillary interface. A low DLco is associated with destruction of the airspace secondary to emphysema and a lower pulmonary vascular volume (Balasubramanian et al. 2019). DLco provided insight into functional limitations in patients with COPD and lung cancer (Videtic et al. 2004; Balasubramanian et al. 2019; de-Torres et al. 2021). A low DLco is associated with reduced exercise performance, severe exacerbations, and all-cause mortality in patients with COPD (Balasubramanian et al. 2019; de-Torres et al. 2021).

DLco reflects the functional status of lung cancer patients and is a general indicator of patient performance (Ferguson et al. 1988, 2012; Brunelli et al. 2013; Videtic et al. 2004). A low preoperative DLco is a predictor of postoperative cardiopulmonary complications, mortality, and poor long-term survival in surgical patients, including those with a normal $FEV_1$ (Ferguson et al. 1988, 2012; Brunelli et al. 2013). According to Videtic et al. (2004), a low DLco is a marker of treatment tolerance and poor OS in patients with limited-disease SCLC. However, Lee et al. (2019) reported that a low DLco was not associated with poor survival in patients with ED-SCLC. In our study, the DLco < 60% group underwent fewer first-line chemotherapy cycles compared with the DLco ≥ 60% group (5 vs. 4, P = 0.005). The proportion of patients who received < 4 cycles of first-line chemotherapy

**Table 2** Cox regression analyses of overall survival in patients with ED-SCLC

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P-value | OR | 95% CI | P-value |
| Male | 1.543 | 0.905–2.631 | 0.111 | | | |
| Aged ≥ 65 years | 1.136 | 0.793–1.629 | 0.487 | | | |
| BMI | 1.104 | 0.957–1.073 | 0.643 | | | |
| ECOG PS ≥ 2 | 1.118 | 0.744–1.679 | 0.592 | | | |
| Current or ex-smoker | 1.447 | 0.785–2.665 | 0.236 | | | |
| Pulmonary function test | | | | | | |
| FVC < 60% | 1.183 | 0.714–1.958 | 0.514 | | | |
| $FEV_1$ < 60% | 1.130 | 0.745–1.714 | 0.564 | | | |
| DLco < 60% | 1.809 | 1.218–2.687 | 0.003 | 1.609 | 1.062–2.437 | 0.025 |
| Comorbidities | | | | | | |
| COPD | 1.024 | 0.721–1.457 | 0.893 | | | |
| DM | 1.307 | 0.894–1.913 | 0.167 | | | |
| HTN | 1.174 | 0.830–1.660 | 0.366 | | | |
| Number of metastatic organs | 1.453 | 1.232–1.714 | < 0.001 | 1.488 | 1.262–1.756 | < 0.001 |
| Liver metastasis | 2.049 | 1.416–2.966 | < 0.001 | | | |
| Brain metastasis | 1.271 | 0.855–1.889 | 0.236 | | | |
| Adrenal metastasis | 1.502 | 0.945–2.388 | 0.085 | | | |
| Bone metastasis | 1.841 | 1.290–2.626 | 0.001 | | | |
| Pleural metastasis | 1.018 | 0.705–1.472 | 0.923 | | | |
| Diagnosis to treatment interval, days | 1.004 | 0.990–1.018 | 0.617 | | | |
| First-line chemotherapy EP regimen | 0.646 | 0.414–1.008 | 0.054 | | | |
| First-line chemotherapy cycles < 4 | 3.805 | 2.587–5.597 | < 0.001 | 3.793 | 2.530–5.686 | < 0.001 |

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DLco, diffusion capacity for carbon monoxide; DM, diabetes mellitus; ECOG PS, Eastern Cooperative Oncology Group performance status; ED-SCLC, extensive disease small cell lung cancer; EP, etoposide + cisplatin; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; HTN, hypertension; OR, odds ratio

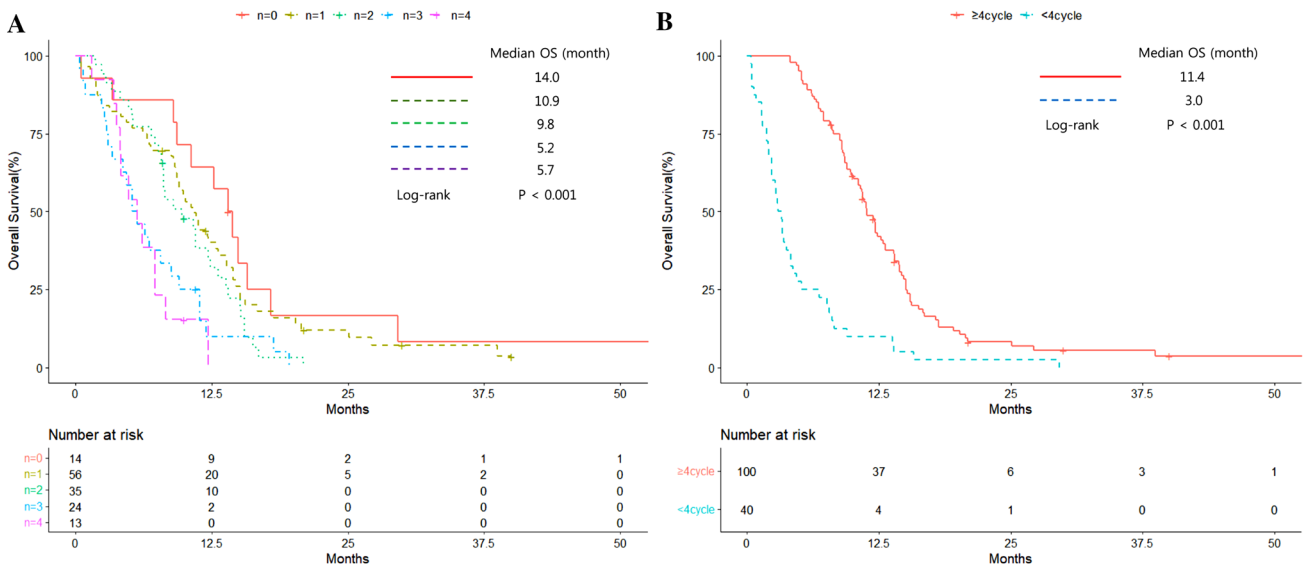


**Fig. 2** Kaplan–Meier overall survival curves according to **A** the number of metastatic organs and **B** number of first-line chemotherapy cycles. **A** Overall survival according to the number of metastatic organs. **B** Overall survival according to the number of first-line chemotherapy cycles

**Table 3** Reasons for < 4 cycles of first-line chemotherapy

| Cause | Total (n = 40) |
|---|---|
| Death | 22 (55) |
| Febrile neutropenia, grade 4 | 15 (37.5) |
| Infection | 5 (12.5) |
| Massive hemoptysis | 2 (5) |
| Decreased ECOG PS | 8 (20) |
| Progressive disease | 5 (12.5) |
| Adverse event of chemotherapy | 5 (12.5) |
| Neutropenia | 3 (7.5) |
| Hepatitis | 2 (5) |

Data are presented as numbers (%)

ECOG PS, Eastern Cooperative Oncology Group performance status

was significantly higher in the DLco < 60% than ≥ 60% group (48.6% vs. 21.9%, P = 0.002). The low DLco may have affected the treatment tolerance of ED-SCLC patients, and the relatively few chemotherapy cycles may have affected their survival.

Lee et al. (2021) analyzed the Korean Health Insurance Review and Assessment Service database and reported that COPD increases the risk of death 1.17-fold in ED-SCLC patients. Another study noted that $FEV_1$ < 80% was associated with shorter survival in patients with ED-SCLC (Kang et al. 2018). However, COPD and airflow limitation were not associated with survival in our study.

The number of metastatic sites at baseline is the most important prognostic predictor for OS in patients with ED-SCLC (Albain et al. 1990; Foster et al. 2009), and patients who have ≥ 2 metastatic sites have a significantly worse OS (Foster et al. 2009). Hong et al. (2010) confirmed that the disease extent, including liver metastasis, is a poor prognostic factor for SCLC. In an analysis of real-world data from 988 SCLC patients, Ma et al. (2021) showed that ED-SCLC without liver, bone, or subcutaneous metastases has favorable clinical outcomes. Our study confirmed that a high disease burden, i.e., more metastatic organs, was an independent risk factor for short OS in patients with ED-SCLC.

The standard treatment for ED-SCLC over the past two decades has been 4–6 cycles of a platinum-based etoposide regimen (Ganti et al. 2021). Liu et al. (2015) reported that ≥ 4 chemotherapy cycles (OR, 0.486; 95% CI, 0.301–0.786, P = 0.003) was a favorable prognostic factor for OS in SCLC patients. Other studies also reported that < 4 cycles of first-line chemotherapy predicted a shorter survival time in patients with ED-SCLC (Lee et al. 2019; Kim et al. 2022). However, some SCLC patients cannot undergo four cycles of full-dose chemotherapy because of old age or poor performance status (Kim et al. 2022). Kim et al. (2022) reported that first-line EP dose-reduced chemotherapy offered no significant survival disadvantage over full-dose chemotherapy in elderly ED-SCLC patients if they received a minimum of four cycles (median OS, 10.9 vs. 9.4 months, P = 0.817). Thus, a minimum of four cycles of dose-reduced chemotherapy should be considered in patients with SCLC who cannot tolerate full-dose chemotherapy.

First-line chemotherapy EP showed a trend toward good OS in the univariate analysis of our study, but was not associated with good OS in the multivariate analysis. In East Asian studies, IP as first-line chemotherapy improved survival compared with EP (Noda and Saijo 2002), but no significant difference was reported in western populations (Lara et al. 2009). According to a Korean nationwide cohort study (Lee et al. 2021), patients who receive IP have better survival outcomes than those who receive etoposide-based platinum therapy. In our study, no significant prognostic differences were detected between chemotherapy drug regimens.

The overall response rate to first-line chemotherapy in our study (27.4%) was lower than previous studies (Hong et al. 2010; Ma et al. 2021). Although the RECIST ver. 1.1 represents an evolution of these radiographic criteria, it relies on human measurement (Villaruz and Socinski 2013). The median OS (9.3 months), and disease control rate to first-line chemotherapy (87.3%) in our study were similar or superior compared to previous studies (Hong et al. 2010; Ma et al. 2021). Therefore, the difference in overall response rate is seen as a problem simply due to the difference in measurement between researchers.

This study had several limitations. First, it was a retrospective, observational single-center study with a small number of patients, although 10 years of medical records were available. However, considering the low prevalence of SCLC, it is not a number to be underestimated. Second, we did not evaluate potential confounding factors, such as hemoglobin, emphysema, destructive tuberculosis changes, pneumoconiosis, and pulmonary fibrosis. Given the high prevalence and morbidity of tuberculosis in Korea, the impact of these factors on DLco may be considerable. Finally, the prognosis of patients treated with immune checkpoint inhibitors was not analyzed. Adding an immune checkpoint inhibitor to platinum-based doublet therapy is the new standard of care for first-line treatment of ED-SCLC (Ganti et al. 2021). In South Korea, atezolizumab combined with EC therapy has only been available since August 1, 2020, so the effect of immunotherapy could not be assessed. Nonetheless, to our knowledge, this is the first study showing that a low DLco is associated with a poor prognosis in patients with ED-SCLC. Further prospective cohort studies are needed to verify whether DLco is a poor prognostic factor in SCLC patients.

## Conclusions

In this study, approximately one quarter of ED-SCLC patients had DLco < 60%. Lower DLco (but not $FEV_1$ or FVC), a large number of metastases, and < 4 cycles of first-line chemotherapy were independent risk factors for poor survival outcomes in ED-SCLC patients. Strategies to ensure completion of ≥ 4 cycles of first-line chemotherapy are needed to improve OS in patients with ED-SCLC.

**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JSK, EJK, JGJ, KSH and JHA. The first draft of the manuscript was written by JSK, EJK, KSH, JHA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Funding** This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Science & ICT (grant number NRF-2021R1C1C1009508).

**Data availability** The data set supporting the conclusions of this article is available from the corresponding author upon reasonable request.

## Declarations

**Conflicts of interests** The authors declare no conflicts of interest.

**Ethics approval and consent to participate** This study followed the tenets of the Declaration of Helsinki, and the protocol was reviewed and approved by the Institutional Review Board of Yeungnam University Hospital (YUH IRB 2022–08–016). The requirement for informed consent was waived because of the retrospective study design.

**Consent for publication** Not applicable.



## References

Albain KS, Crowley JJ, LeBlanc M, Livingston RB (1990) Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. J Clin Oncol 8:1563–1574

Balasubramanian A, MacIntyre NR, Henderson RJ, Jensen RL, Kinney G, Stringer WW et al (2019) Diffusing capacity of carbon monoxide in assessment of COPD. Chest 156:1111–1119

Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ (2013) Physiologic evaluation of the patient with lung cancer being considered for resectional surgery diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 143:E166–E190

Choi JK, Paek D, Lee JO (2005) Normal predictive values of spirometry in Korean population. Tuberc Respir Dis. 58:230–242

de-Torres JP, Oonnell DE, Marin JM, Cabrera C, Casanova C, Marin M et al (2021) Clinical and prognostic impact of low diffusing capacity for carbon monoxide values in patients with global initiative for obstructive lung disease I COPD. Chest 160:872–878

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247

Ferguson MK, Little L, Rizzo L, Popovich KJ, Glonek GF, Leff A et al (1988) Diffusing capacity predicts morbidity and mortality after pulmonary resection. J Thorac Cardiovasc Surg 96:894–900

Ferguson MK, Dignam JJ, Siddique J, Vigneswaran WT, Celauro AD (2012) Diffusing capacity predicts long-term survival after lung resection for cancer. Eur J Cardiothorac Surg 41:e81–e86

Foster NR, Mandrekar SJ, Schild SE, Nelson GD, Rowland KM, Deming RL et al (2009) Prognostic factors differ by tumor stage for small cell lung cancer a pooled analysis of North Central cancer treatment group trials. Cancer 115:2721–2731

Ganti AKP, Loo BW, Bassetti M, Blakely C, Chiang A, Damico TA et al (2021) Small cell lung cancer, Version 2.2022. J Natl Comprehens Cancer Netw. 19:1441–1464

Hong S, Cho BC, Choi HJ, Jung M, Lee SH, Park KS et al (2010) prognostic factors in small cell lung cancer: a new prognostic index in Korean patients. Oncology 79:293–300

Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA et al (2020) The effect of advances in lung-cancer treatment on population mortality. N Engl J Med 383:640–649

Jeon DS, Kim HC, Kim SH, Kim TJ, Kim HK, Moon MH et al (2022) Five-year overall survival and prognostic factors in patients with lung cancer: results from the Korean Association of Lung Cancer Registry (KALC-R) 2015. Cancer Res Treat 55:103–111

Kang HS, Shin AY, Yeo CD, Kim JS, Kim YH, Kim JW et al (2018) A lower level of forced expiratory volume in one second predicts the poor prognosis of small cell lung cancer. J Thorac Dis 10:2179–2185

Kim H, Choi E, Heo MH, Kim JY, Park KU (2022) Dose modification of etoposide plus platinum in elderly patients with extensive-disease small-cell lung cancer. Oncology 100:313–319

Lara PN, Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE et al (2009) Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 27:2530–2535

Lee SY, Choi YJ, Seo JH, Lee SY, Kim JS, Kang EJ (2019) Pulmonary function is implicated in the prognosis of metastatic non-small cell lung cancer but not in extended disease small cell lung cancer. J Thorac Dis 11:4562–4572

Lee JS, Kim S, Sung SY, Kim YH, Lee HW, Hong JH et al (2021) Treatment outcomes of 9,994 patients with extensive-disease small-cell lung cancer from a retrospective nationwide population-based cohort in the Korean HIRA database. Front Oncol 2021:11

Liu SJ, Guo HB, Kong L, Li HH, Zhang Y, Zhu H et al (2015) The prognostic factors in the elderly patients with small cell lung cancer: a retrospective analysis from a single cancer institute. Int J Clin Exp Pathol 8:11033–11041

Ma XJ, Zhang ZR, Chen XL, Zhang J, Nie J, Da L et al (2021) Prognostic factor analysis of patients with small cell lung cancer: real-world data from 988 patients. Thoracic Cancer 12:1841–1850

MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CPM, Brusasco V et al (2005) Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26:720–735

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A et al (2005) Standardisation of spirometry. Eur Respir J 26:319–338

Noda K, Saijo N (2002) Irinotecan in small-cell lung cancer—reply. N Engl J Med 346:1414–1415

Paesmans M, Sculier JP, Lecomte J, Thiriaux J, Libert P, Sergysels B et al (2000) Prognostic factors for patients with small cell lung carcinoma—analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. Cancer 89:523–533

Quanjer PH (1983) Standardized lung function testing. Report working party. Bull Eur Physiopathol Respir 19(5):1–95

Rudin CM, Brambilla E, Faivre-Finn C, Sage J (2021) Small-cell lung cancer. Nature Rev Dis Primers. 2021:7

Videtic GMM, Stitt LW, Ash RB, Truong PT, Dar AR, Yu EW et al (2004) Impaired diffusion capacity predicts for decreased treatment tolerance and survival in limited stage small cell lung cancer patients treated with concurrent chemoradiation. Lung Cancer 43:159–166

Villaruz LC, Socinski MA (2013) The clinical viewpoint: definitions, limitations of RECIST, practical considerations of measurement. Clin Cancer Res 19:2629–2636