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RESEARCH ARTICLE

Different approach to M descriptor for future staging of oligometastatic disease in SCLC: A cross-sectional survival analysis

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Abstract

Purpose This study aimed to investigate the impact of oligometastasis and the M descriptor on survival in small cell lung cancer (SCLC).

Methods This multicenter, retrospective study included patients with newly diagnosed extensive-stage SCLC(ES-SCLC) from 2010 to 2020. Subgroups: Group 1: single metastasis in a single organ, Group 2: 2–5 metastases in a single organ, Group 3: 6 or more metastases in a single organ, and Group 4: metastases in two or more organs. This classification was based on the 9th Staging-M descriptor. Three-year progression-free survival (PFS) and overall survival (OS) analyses were conducted.

Results The mean age of the 439 patients was 62 ± 10 years, and 89.5% of them were male. The mean PFS for Groups 1, 2, 3, 4 was 10.7 months (95% CI 8.9–12.5), 7.5 months (95% CI 5.6–9.4), 4.3 months (95% CI 2.9–5.7), and 5.4 months (95% CI 4.7–6.1), respectively. PFS in Group 2 was significantly higher. The mean OS for Groups 1, 2, 3, 4 was 13.3 months (95% CI 11.2–15.3), 9.5 months (95% CI 7.1–11.9), 7.1 months (95% CI 4.5–9.7), and 6.9 months (95% CI 6.0–7.9), respectively. OS in Group 1 was significantly higher. OS and PFS in the M1b group were significantly higher than in the M1c1 and M1c2 groups ($p < 0.05$) with no statistical difference between the M1c1 and M1c2 groups.

Conclusion There is no significant difference in survival between the M1c1 and M1c2 groups. In ES-SCLC, the number of metastases may be a more predictive factor for prognosis than the number of metastatic organs.

Keywords Small cell lung cancer · Oligometastasis · M descriptor · Metastasis · Survival · Prognosis

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Introduction

Despite all the recent advancements, lung cancer remains the leading cause of cancer-related deaths globally. About 15–17% of lung cancers are classified as small cell lung cancer (SCLC). This type of cancer is a highly aggressive neuroendocrine tumor that grows rapidly and spreads widely in the early stages [1]. As a result of its quick metastatic nature, around two-thirds of patients are diagnosed at extensive stages [2].

Historically, the Veterans Administration Lung Study Group (VALG) classification has been frequently used for staging lung cancer. Treatment plans are devised for both limited and extensive stages [3]. However, following the publication of the IASLC 8th edition staging system in 2017, the TNM classification (particularly T1-2 N0) has been recommended to identify operable patients, especially those in the limited stage [1].

SCLC initially responds rapidly to chemotherapy and is highly chemosensitive. While the combination of etoposide and carboplatin was the most widely accepted treatment, the addition of antiprogrammed death-ligand 1 (anti–PD-L1) in 1999 demonstrated superior survival benefits. Despite advancements in immunotherapy and targeted therapy for non-small cell lung cancer (NSCLC), similar improvements have not yet been realized in SCLC [4–6].

It has been shown that consolidative thoracic radiotherapy (TRT) after systemic treatment provides better local control and improved survival [7]. However, the critical question remains regarding the appropriate candidates for consolidative TRT.

Oligometastasis, first described by Hellman and Weichselbaum in 1995, hypothesizes that aggressive treatment of the primary lesion along with a small number of metastasis would lead to better survival outcomes [8].

The concepts of oligometastasis and multiple metastases remain subjects of ongoing debate. Definitions used for NSCLC, such as oligometastasis, are not yet routinely applied to SCLC. In the randomized controlled phase 2 study by Gomez et al. (2016), oligometastasis was defined as the presence of three or fewer metastases [9, 10]. In two different phase 2 studies conducted in 2019, oligometastasis was defined as having five or fewer metastases [11, 12]. All these studies demonstrated a progression-free survival advantage.

In the IASLC 9th staging system, the M descriptor was revised to reflect survival differences, defining two groups: single organ multiple metastases (M1c1) and multiple organ metastasis (M1c2) [13]. This revision was based on a database consisting of NSCLC patients.

Numerous studies have been published regarding treatment modalities for oligometastasis in NSCLC. Although approaches considering the concept of oligometastasis have curative intentions, these situations require clinicians to make decisions based on the number and location of metastasis.

There are limited studies on the concepts and treatment approaches of oligometastasis in SCLC. This study aims to compare the survival outcomes of oligometastasis versus multiple metastases in extensive stage SCLC (ES-SCLC) and to analyze survival in terms of the new M descriptor staging of SCLC (IASLC 9th edition).

Materials and methods

The study was conducted with a multicenter, retrospective, cross-sectional design. Ethical approval was obtained from the XXXXX Training and Research Hospital Local Ethics Committee (21.01.2021/710). The research was carried out under the auspices of the Turkish Respiratory Society Lung Cancer Study Group and involved five different tertiary training and research hospitals, all specializing in thoracic oncology. The data collection phase concluded in December 2023.

The study included patients newly diagnosed with extensive-stage SCLC between 2010 and 2020 who were older than 18 years of age, underwent positron emission tomography- computed tomography (PET-CT) or thorax-abdomen computed tomography, bone scintigraphy, and brain magnetic resonance imaging (MRI) at the time of diagnosis, whose complete data were accessible from the hospital database, and who were followed for three years, were included.

Patients with histological diagnoses other than SCLC and those with limited-stage disease were excluded from the study. Additionally, patients were excluded if data on their treatment regiments, imaging results, or survival times were unavailable. Furthermore, patients who were followed up and treated in different centers after being diagnosed at the study center were also excluded from the study.

The retrospective data were transferred to Microsoft Office Excel via the hospital information management systems. When mortality data could not be accessed through the system, attempts were made to obtain this information by contacting the patient or their relatives by phone. Demographic data, metastasis status and sites, and patient counts were recorded. Patients were divided into four groups based on the focus and number of metastases:

- **Group 1**: Single metastasis in a single organ.
- **Group 2**: 2–5 metastases in a single organ.
- **Group 3**: 6 or more metastases in a single organ.
- **Group 4**: Metastases in two or more organs.

Three-year progression-free survival (PFS) and overall survival (OS) analyses were conducted for patients across the metastasis groups. PFS was considered as time (months) from the first treatment until disease progression or death due to any cause. OS was considered as time (months) from the date of diagnosis of SCLC until the date of death from any cause or the last date of follow-up.

First-line treatments were classified into four categories: "chemotherapy (ChT), ChT + consolidative TRT) + prophylactic cranial irradiation (PCI), ChT + PCI, and supportive treatment." Three-year PFS and OS were analyzed separately for the single organ metastasis group (Groups 1, 2, 3) and the multiple organ metastasis group (Group 4).

According to the IASLC 9th staging system, groups 2 and 3 were classified as M1C1, and group 4 as M1C2 [13]. Group 1 was further divided into M1a and M1b based on the organ involved. Three-year PFS and OS analyses were performed between the M1a, M1b, M1c1, and M1c2 groups.

Statistical analysis

IBM SPSS Statistics for Windows, Version 26.0, was used for the statistical analysis. Initially, demographic data, sample numbers, and percentages were provided for the metastasis number groups. Normality analyses of the data were performed using the Shapiro–Wilk Test, histograms, and QQ-plots. Categorical data comparisons were conducted using Pearson Chi-Square tests, and these data were expressed as sample counts and percentages. Kaplan–Meier analysis was used for survival assessments, with the results expressed as expected mean and median survival times along with their 95% confidence intervals. The log-rank (Mantel-Cox) test was used to compare expected survival times between groups. A significance level of $p < 0.05$ was used for statistical tests. For pairwise subgroup analyses involving more than two groups with survival differences, the p-value was adjusted using Bonferroni correction.

Results

A total of 438 patients were included in the study, of whom 89.5% (n = 392) were male, with a mean age of 66 ± 10 years and 95.9% (n = 420) were mortal in three years. Among the patients, 87.0% (n = 381) underwent PET-CT and brain MRI scans, while 13% (n = 57) were scanned using thorax and abdominal CT, bone scintigraphy, and brain MRI. Metastasis was detected in a single organ in 42.7% (n = 187) of the patients, whereas 57.3% (n = 251) had metastases in multiple organs. Demographic data are presented in Table 1. There was a homogeneous distribution between metastasis classification groups in terms of gender and age (p = 537, p = 0.603; respectively). However, supportive treatment rates were higher in groups 3 and 4 ($p < 0.001$).

Table 1 Demographics, staging, metastasis, and treatment distribution

Variables	n	n %
Gender		
Male	392	89,5
Female	46	10,5
Age- Mean ± SD	66 ± 10	
Staging methods		
PET-CT + Brain CT/MRI	381	87,0
Thorax + Abdomen CT + Bone scintigraphy + Brain CT/MRI	57	13,0
First line treatment		
ChT	269	61,4
ChT + TRT + PCI	49	11,2
ChT + PCI	9	2,1
Supportive care	111	25,3
Metastasis -organ systems		
Single	187	42,7
Multiple	251	57,3
Metastasis classification groups		
Group 1	92	21,0
Group 2	52	11,9
Group 3	43	9,8
Group 4	251	57,3
M descriptor		
M1a	6	1,4
M1b	87	19,9
M1c1	94	21,5
M1c2	251	57,3
Chemotherapy regimens		
None	110	25,1
Etoposide + Cisplatin	224	51,1
Etoposide + Carboplatin	102	23,3
Irinotecan	2	0,5
Palliative radiotherapy		
None	236	53,9
Bone	118	26,9
Cranial	72	16,4
Thorax	2	0,5
Bone + cranial	10	2,3

SD Standard deviation, *CT* Computerized tomography, *PET-CT* Positron emission computerized tomography, *MRI* Magnetic resonance imaging, *ChT* Chemotherapy, *TRT* Thorax radiotherapy, *PCI* Prophylactic cranial irradiation

When individual organs were examined, metastases were found most frequently in the bone, brain, and liver in Groups 1 and 2; adrenal metastases were also present. In Groups 3 and 4, the most frequent metastatic sites were the bone and

liver (Table 2). The distribution between metastases classification groups is shown in Table 2.

First line treatments distribution according to metastasis groups are shown in Table 2. The curative treatment approach with ChT + TRT + PCI was applied in 21.4% of all groups with single organ metastases (Groups 1, 2, 3) and 3.6% in the group with multiple organ metastases (Group 4) (P < 0.001). The rates of those receiving ChT + TRT + PCI in Groups 1, 2, 3, and 4 were 27.2%, 19.2%, 11.6%, and 3.6%, respectively. Palliative RT was applied to a total of 202 patients. Palliative RT was given on bone, cranial metastasis and on thorax for vena cava syndrome. There was significant difference between these groups in terms of palliative RT treatment, the difference is originated from the difference in pairs of 1–3, 2–2, 3–4 (p > 0.001).

Patients within the single organ metastasis and multiple organ metastases groups were examined separately. The mean OS and PFS of the patients who received ChT, ChT + TRT + PCI, ChT + PCI, and supportive treatment approaches were presented in Table 3. PFS and OS were significantly higher in the CHT + RT + PCI arm in both the single organ metastasis group and the multiple organ metastasis group (p < 0.05; adjusted) (Fig. 1).

When comparing single and multiple metastases, the mean OS was found to be 10.8 months (95% CI 9.4–12.2) in the single organ metastasis group and 6.9 months (95% CI 6.0–7.8) in the multiple organ metastasis group (p < 0.001).

The mean OS and PFS among the four groups (Groups 1, 2, 3, 4) according to metastasis were shown in Table 3. The mean PFS was similar between patients with six or more metastases in a single organ and patients with metastases in two or more organs (4.3 vs. 5.4 months). The mean PFS was found to be statistically significantly different between Groups 1–3, 1–4, and 2–3 (p < 0.05, adjusted), but the differences were not significant between other pairs. PFS was significantly higher in Group 2 than in Group 3 (p < 0.05, adjusted) (Fig. 2). OS was similar in Groups 3 and 4. There were statistically significant differences between Groups 1 and 3 and Groups 1 and 4 (p < 0.05,

Table 2 Distribution of demographic features, metastasis localization, and treatment methods according to the metastasis classification

	Metastasis Classification Groups				
	Group 1	Group 2	Group 3	Group 4	p-value
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Gender					
Male	85 (92,4)	45 (86,5)	37 (86)	225 (89,6)	0.603*
Female	7 (7,6)	7 (13,5)	6 (14)	26 (10,4)	
Age- Mean ± SD	66 ± 10	64 ± 10	67 ± 10	67 ± 9	0.537**
Liver	13 (14,1)	6 (11,5)	6 (14)	–	< 0.001*
Bone	30 (32,6)	31 (59,6)	33 (76,7)	–	< 0.001*
Adrenal	11 (12)	2 (3,8)	0 (0)	–	< 0.001*
Brain	18 (19,6)	11 (21,2)	1 (2,3)	–	< 0.001*
Extrathoracic node	5 (5,4)	0 (0)	2 (4,7)	–	0.088***
Other	10 (10,9)	1 (1,9)	1 (2,3)	–	0.065***
Pleura	5 (5,4)	1 (1,9)	0 (0)	–	0.161***
First line treatment					
ChT	58 (63)	31 (59,6)	21 (48,8)	159 (63,3)	< 0.001*
ChT + TRT + PCI	25 (27,2)	10 (19,2)	5 (11,6)	9 (3,6)	
ChT + PCI	2 (2,2)	1 (1,9)	1 (2,3)	5 (2)	
Supportive care	7 (7,6)	10 (19,2)	16 (37,2)	78 (31,1)	
Palliative radiotherapy					
None	51 (55,4)	20 (38,5)	35 (81,4)	130 (51,8)	0.005***
Bone	28 (30,4)	21 (40,4)	7 (16,3)	62 (24,7)	
Cranial	13 (14,1)	10 (19,2)	1 (2,3)	48 (19,1)	
Thorax	0 (0)	0 (0)	0 (0)	2 (0,8)	
Bone + Cranial	0 (0)	1 (1,9)	0 (0)	9 (3,6)	

*Pearson Chi-squared test

**Kruskal Wallis test

***Analysis is not robust since there are not enough counts in the boxes for these variables

SD Standard deviation, *ChT* Chemotherapy, *TRT* Thorax radiotherapy, *PCI* Prophylactic cranial irradiation

Table 3 Estimated means and medians of survival

	Estimate mean (95% CI)	Estimate median (95% CI)	Log-rank (Mantel-Cox)
First line treatment			
Overall			
ChT	9 (8,2–9,7)	8 (7,3–8,7)	p < 0.001 The difference is originated from the differences between pairs 1–2, 1–4, 2–4, 3–4
ChT + TRT + PCI	21,7 (18,7–24,8)	20 (17,3–22,7)	
ChT + PCI	14,2 (8,7–19,7)	11 (9,5–12,5)	
Supportive care	1,6 (1,1–2)	1 (0,9–1,1)	
Overall	8,6 (7,8–9,4)	7 (6,2–7,8)	
PFS			
ChT	6,9 (6,4–7,5)	6 (5,5–6,5)	p < 0.001 The difference is originated from the differences between pairs 1–2, 1–4, 2–3, 2–4, 3–4
ChT + TRT + PCI	16,9 (14–19,8)	13 (8,7–17,3)	
ChT + PCI	9 (5,5–12,5)	8 (5,2–10,8)	
Supportive care	1,4 (1–1,7)	1 (0,9–1,1)	
Overall	6,7 (6,0–7,3)	5,0 (4,4–5,6)	
Single metastasis group- First line treatment			
Overall			
ChT	9,3 (8,1–10,6)	8 (6,9–9,1)	p < 0.001 The difference is originated from the differences between pairs 1–2, 1–4, 2–4, 3–4
ChT + TRT + PCI	21,9 (18,6–25,1)	20 (17,5–22,5)	
ChT + PCI	17,8 (7,3–28,2)	11 (7,1–14,9)	
Supportive care	1,7 (0,7–2,7)	1 (0,8–1,2)	
Overall	10,8 (9,4–12,2)	9 (7,7–10,3)	
PFS			
ChT	7,1 (6,3–8)	6 (5,2–6,8)	p < 0.001 The difference is originated from the differences between pairs 1–2, 1–4, 2–4, 3–4
ChT + TRT + PCI	17,3 (14,1–20,4)	16 (8,3–23,7)	
ChT + PCI	12,5 (6,1–18,9)	9 (1,2–16,8)	
Supportive care	1,2 (0,8–1,6)	1 (0,8–1,2)	
Overall	8,4 (7,2–9,5)	6 (5,1–6,9)	
Multiple metastases group- First line treatment			
Overall			
ChT	8,7 (7,7–9,7)	8 (7,2–8,8)	p < 0.001 The difference is originated from the differences between pairs 1–2, 1–4, 2–4, 3–4
ChT + TRT + PCI	21,2 (13,2–29,3)	14 (8,2–19,8)	
ChT + PCI	11,4 (7–15,8)	11 (4,6–17,4)	
Supportive care	1,5 (1–2)	1 (0,9–1,1)	
Overall	7 (6,1–7,9)	6 (4,5–7,5)	
PFS			
ChT	6,8 (6–7,5)	6 (5,4–6,6)	p < 0.001

Table 3 (continued)

	Estimate mean (95% CI)	Estimate median (95% CI)	Log-rank (Mantel-Cox)
			The difference is originated from the differences between pairs 1–2, 1–4, 2–4
ChT + TRT + PCI	15,3 (8–22,7)	11 (8,1–13,9)	
ChT + PCI	6,2 (4,6–7,8)	6 (3,9–8,1)	
Supportive care	1,5 (1–1,9)	1 (0,9–1,1)	
Overall	5,4 (4,7–6,1)	5 (4–6)	
Metastasis classification			
Overall			
Group 1	13,3 (11,3–15,4)	11 (9,1–12,9)	$p < 0.001$
			The difference is originated from the differences between pairs 1–3, 1–4
Group 2	9,5 (7,1–12)	7 (5,2–8,8)	
Group 3	7,1 (4,5–9,7)	4 (1,9–6,1)	
Group 4	7 (6,1–7,9)	6 (4,5–7,5)	
Overall	8,6 (7,8–9,4)	7 (6,2–7,8)	
PFS			
Group 1	10,7 (8,9–12,5)	9 (7,3–10,7)	$p < 0.001$
			The difference is originated from the differences between pairs 1–3, 1–4, 2–3
Group 2	7,5 (5,7–9,4)	6 (4,9–7,1)	
Group 3	4,4 (3–5,8)	3 (1,4–4,6)	
Group 4	5,4 (4,7–6,1)	5 (4–6)	
Overall	6,7 (6–7,3)	5 (4,4–5,6)	
M descriptor			
Overall			
M1a	6,8 (3,7–10)	6 (3,7–8,3)	$p < 0.001$
			The difference is originated from the differences between pairs 2–3, 2–4
M1b	13,7 (11,5–15,8)	12 (10,2–13,8)	
M1c1	8,5 (6,7–10,3)	6 (4,5–7,5)	
M1c2	7 (6,1–7,9)	6 (4,5–7,5)	
Overall	8,6 (7,8–9,4)	7 (6,2–7,8)	
PFS			
M1a	5,8 (3,4–8,3)	4 (2,4–5,6)	$p < 0.001$
			The difference is originated from the differences between pairs 2–3, 2–4
M1b	11 (9,1–12,8)	9 (7,2–10,8)	
M1c1	6,1 (4,9–7,4)	5 (4,1–5,9)	
M1c2	5,4 (4,7–6,1)	5 (4–6)	
Overall	6,7 (6–7,3)	5 (4,4–5,6)	

Estimation is limited to the largest survival time if it is censored

Bonferroni correction was applied in subgroup analyses

CI Confidence intervale, *PFS* Progression free survival, *ChT* Chemotherapy, *TRT* Thorax radiotherapy, *PCI* prophylactic cranial irradiation

adjusted). Although the mean OS in Group 2 was higher than in Groups 3 and 4, this difference was not statistically significant (Fig. 2).

Survival analyses were performed between groups according to the IASLC 9th staging system based on the M descriptor. The distribution of the four groups according to the M descriptor is presented in Table 1; it was found that all patients in the M1a group had pleural metastases.

Mean OS and PFS were shown in Table 3 in terms of M descriptor. While the mean OS in the M1b group was significantly higher than in the M1c1 and M1c2 groups ($p < 0.05$, adjusted). Although the OS in the M1c2 group

was low, there was no statistically significant difference between the M1c1 and M1c2 groups (Fig. 3). PFS was significantly higher in the M1b group than in the M1c1 and M1c2 groups ($p < 0.05$, adjusted). Although the PFS in the M1c2 group was low, there was no statistically significant difference in PFS between the M1c1 and M1c2 groups (Fig. 3). Age and gender distribution was homogeneous between M1c1 and M1c2 groups; However, it was observed

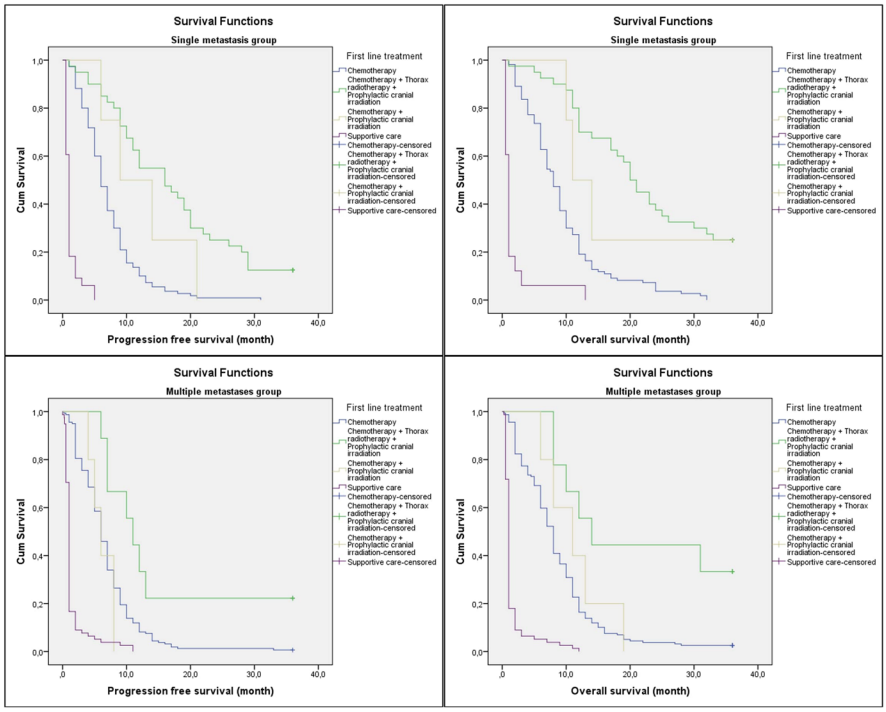


Fig. 1 Survival functions according to the first line treatment options

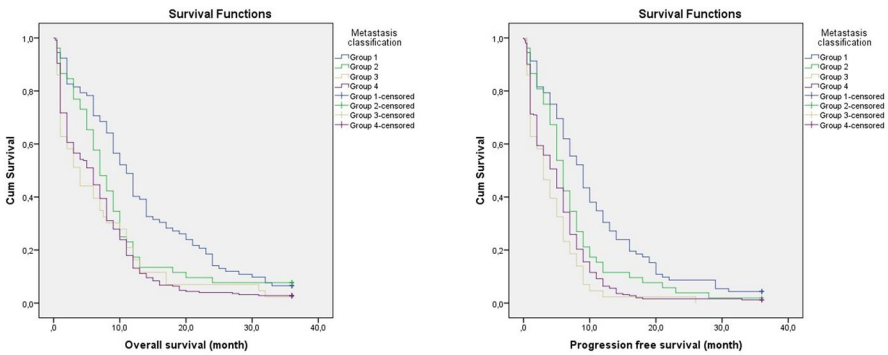


Fig. 2 Survival functions according to the metastasis classification

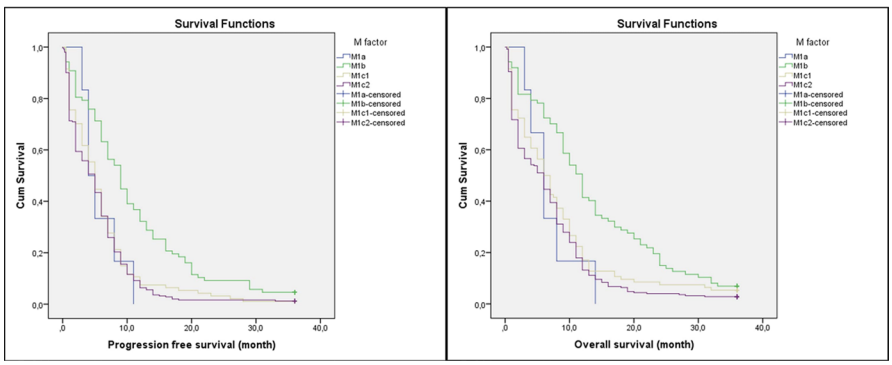


Fig. 3 Survival functions according to the M factor

that the ChT + TRT + PCI combination was applied more in the M1c1 group (16.0% vs 3.6%).

No sample size analysis was performed before the study, therefore with a two-tailed Type-1 error of 5% and a 3-year mortality rate of 96% obtained as a result of the study, the power of the study was determined to be over 95% in the post-hoc analysis.

Discussion

In our study, 3-year PFS and OS were found to be low, as expected in SCLC. When groups were evaluated based on the number and location of metastases, the mean OS was 10.8 months for those with single-organ metastases, whereas it was 6.9 months for those with multi-organ metastases.

Studies have shown that the timing of the diagnosis of oligometastasis impacts prognosis [14, 15]. The European Organization for Research and Treatment of Cancer (EORTC) defines synchronous metastasis as metastasis occurring within less than six months after diagnosis, and metasynchronous oligometastasis as occurring more than six months post-diagnosis [14]. In our study, we investigated the effect of synchronous oligometastasis, as patients were evaluated according to the metastatic foci detected during the initial scan at the time of diagnosis.

Mean PFS was found to be better in the group with fewer than six metastases in a single organ compared to those with six or more metastases in a single organ and those with metastases in two or more organs. We observed that OS gradually decreased from Group 1 to Group 4. Both PFS and OS were found to be similar in the groups with six or more metastases in a single organ and those with metastases in two or more organs. Accordingly, we should note that, in addition to the number of metastatic foci, having multiple metastatic foci in a single organ also indicates a poor prognosis.

The most common site of metastasis was found to be bone. In patients with fewer than six metastases, the frequent metastatic foci were bone, brain, and liver, respectively. In the group with six or more metastases, bone and liver were the most common foci. Previous studies have shown that the association between liver and bone metastasis is more common in ES-SCLC. It is thought that microvascular wall similarity plays a significant role in this regard [16, 17]. In the study by Megyesfalvi et al., the number of metastases was identified as an independent risk factor for poor OS, and OS was found to be lower in the presence of brain metastases, although no statistical difference was found [18].

When PFS and OS were evaluated according to treatment approaches, longer survival was observed in patients who received ChT + TRT + PCI treatment. It was observed that OS was better when TRT was added to the treatment in both the single organ and metastasis groups. Since ChT + PCI was administered to only five patients in the group with multiple organ metastases, it is not possible to draw definitive clinical and statistical conclusions. As the number of metastases increases, patient performance status may decline, and treatment tolerability may decrease due to the tumor burden. As the number of metastases increased, a higher rate of patients was followed up with only supportive care due to lower initial performance status, and this should be considered as a confounding factor for survival analysis.

Previous studies have also demonstrated improved survival with the addition of consolidative TRT in patients who respond to chemotherapy in the metastatic area in ES-SCLC [7, 19]. The European IASLC and the European Society for Radiotherapy and Oncology (ESTRO) recommend consolidative RT in patients who respond to initial systemic chemotherapy and have a low extrathoracic tumor burden. However, there is no consensus regarding the specific amount of extrathoracic tumor burden. Three different criteria have been considered: three metastases, absence of liver metastases, or a small number of asymptomatic metastases. It has been emphasized that there is limited data on this subject [20]. The NCCN guidelines do not mention oligometastasis for SCLC. However, the NCCN defines 3–5 metastases for NSCLC but does not specify the organs involved [21].

It was observed that curative treatment approaches were mostly applied to oligometastatic patients (those with fewer than six metastases in a single organ). The ChT + TRT + PCI combination was applied at a significantly lower rate in patients with six or more metastases in a single organ compared to those with fewer than six metastases (8.6% vs. 44.5%). This discrepancy may be related to clinicians trying to avoid treatment toxicity. Another possible reason is that the expected treatment response is not achieved after the initial treatment. It is known that as the response rate decreases, the rate of consolidative RT also decreases. Although there is no supporting data in our study, we believe that adding ablative treatment to the metastatic focus in addition to the curative treatment approach in oligometastatic diseases may have a positive effect on survival. Further studies are needed on this subject.

In the EORTC-LCG definition, oligometastasis is characterized by a total of five metastases in a maximum of three organs. However, this definition excludes serosal involvement such as the meninges, pericardium, pleura, and bone marrow. Intrathoracic lesion burden is considered an independent risk factor, but intrathoracic nodes are not counted as metastatic sites [22]. In contrast, Gomez et al. included intrathoracic nodes in the total number of metastases for NSCLC patients in their definition of oligometastasis. They counted a single site of disease regardless of the number of metastatic nodes involved [9]. Unfortunately, we cannot comment on serosal involvement and

oligometastasis due to the small number of patients with pleural involvement in our study.

There are very few studies in the literature on oligometastasis and prognosis in SCLC cases. In a study by Shirasawa et al., it was reported that the prognosis was better for oligometastatic patients with ES-SCLC, and that the disease generally progressed with local recurrence [23]. This allows for the easier application of local ablative treatments with less toxicity. In our study, it was observed that more curative treatment approaches were applied to patients with fewer than six metastases.

In the 9th staging study published by IASLC in January 2024, groups were generated based on the number of metastases (2–3, 4–5, 6–7, and 8 +), and it was observed that OS worsened as the number of metastases increased. According to the same database, the prognosis also deteriorated as the number of metastatic organs increased (1, 2, 3, and ≥ 4). The M1c group was divided using different cutoff values based on the number of metastatic organs, comparing pairs such as ≥ 2 vs. 1, ≥ 3 vs. 1–2, and ≥ 4 vs. 1–3. In all three comparisons, it was observed that the prognosis worsened as the number of metastatic organs increased, and each group had a worse prognosis compared to those with a single metastasis. The committee decided on seven extrathoracic metastases as the cutoff for oligometastasis but emphasized that the prognosis worsens with an increasing number of metastases in other groups. However, it was ultimately stated that the number of metastases is not an M identifier [13, 24].

Although there is no clear recommendation for oligometastasis with this staging system, it has been emphasized that it will serve as a guide to create a clearer database to define oligometastatic disease more precisely in the future [24]. The IASLC M descriptor evaluation was performed using the NSCLC patient database [13, 24]. IASLC staging is also recommended for SCLC [1]. However, there is a significant difference between the histological and clinical behaviors of these two types of cancer. In our study, no results were found to support the M descriptor as a determinant in the treatment decision in SCLC. The treatment approach may be more robust via the oligometastasis definition.

When our study population was evaluated based on the IASLC staging, Groups 2 and 3 were classified as M1c1, and Group 4 was classified as M1c2. Although the difference between these two groups was not found to be statistically significant, PFS and OS were lower in M1c2 group than the M1c1 group. This unexpected result may change with increasing the sample size; additionally, some comorbid diseases not included in the dataset may have also affected these results. Both OS and PFS were better in the M1b group than in the M1c1 and M1c2 groups. Considering that there were only six patients in the M1a group, it would not be correct to draw definitive conclusions about survival in this group.

Since SCLC is characterized by rapid progression, early metastasis, and a high spread rate, the similarity in survival rates between the M1c1 and M1c2 groups may be attributed to these aggressive disease characteristics. The Veteran classification is still frequently used, and treatment plans are often based on this classification [3].

The lack of difference between the M1c subgroups suggests that it may be more useful to emphasize oligometastasis using the Veteran classification when making treatment decisions for SCLC. According to our study, PFS and OS are better in patients with fewer than six metastases in a single organ. Therefore, it may be appropriate to use the term "fewer than six metastases" for the definition of oligometastasis.

Limitations

The retrospective design of this study should be considered a significant limitation. An important limitation is that the definition of oligometastasis was used based on the literature; a threshold value for the number of metastases was not analyzed. Due to the observational nature of the study, there was no standardization in treatment subgroups, as patients began treatment in different centers and years. The fact that the same radiological imaging method was not performed on all patients also disrupts standardization. The imaging method information on the date progression was detected is not available in the database.

Response rates after the first chemotherapy were not determined in the groups that did and did not receive consolidative radiotherapy. The lack of a definitive standardization between centers was a limitation since it is unclear whether thoracic radiotherapy was not administered due to an inadequate response to the initial systemic treatment or if it was solely the physician's decision. In future prospective studies, the indications for consolidative radiotherapy can be more clearly defined.

The absence of rate comorbid diseases in the data set stands out as other important confounders for survival analysis. Tobacco use, which is one of the main data for SCLC, could not be included in the analysis because the data were not reliable; this also excluded factors from the analysis, such as tobacco-related cardiovascular diseases.

Conclusion

In our study, OS and PFS were found to be lower in the group with six or more metastases in a single organ and in the group with metastases in at least two organs compared to the other groups. Based on the new classification, no statistical difference was detected between the M1c1 and M1c2

groups. In SCLC, the number of metastases may be a more predictive factor for prognosis than the number of metastatic organs. Further studies are needed to clarify the definition of oligometastasis.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(3):300–311. https://doi.org/10.1016/j.jtho.2015.10.008.
2. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primers. 2021;7(1):3. https://doi.org/10.1038/s41572-020-00235-0.
3. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: veterans administration lung study group versus international association for the study of lung cancer–what limits limited disease? Lung Cancer. 2002;37(3):271–6. https://doi.org/10.1016/s0169-5002(02)00072-7.
4. Ragavan M, Das M. Systemic therapy of extensive stage small cell lung cancer in the era of immunotherapy. Curr Treat Options Oncol. 2020;21(8):64. https://doi.org/10.1007/s11864-020-00762-8.
5. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–9. https://doi.org/10.1056/NEJMoa1809064.
6. Paz-Ares L, Dvorkin M, Chen Y, 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(10212):1929–39. https://doi.org/10.1016/S0140-6736(19)32222-6.
7. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial [published correction appears in Lancet. Lancet. 2015;385(9962):36–42. https://doi.org/10.1016/S0140-6736(14)61085-0.
8. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8–10. https://doi.org/10.1200/JCO.1995.13.1.8.
9. Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016;17(12):1672–82. https://doi.org/10.1016/S1470-2045(16)30532-0.
10. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy Vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, Phase II, Randomized Study. J Clin Oncol. 2019;37(18):1558–65. https://doi.org/10.1200/JCO.19.00201.
11. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a Phase 2 Randomized Clinical Trial. JAMA Oncol. 2018;4(1): e173501. https://doi.org/10.1001/jamaoncol.2017.3501.
12. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019;393(10185):2051–8. https://doi.org/10.1016/S0140-6736(18)32487-5.
13. Rami-Porta R, Nishimura KK, Giroux DJ, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groups in the Forthcoming (Ninth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2024;19(7):1007–27. https://doi.org/10.1016/j.jtho.2024.02.011.
14. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020;21(1):e18–28. https://doi.org/10.1016/S1470-2045(19)30718-1.
15. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [published correction appears in Ann Oncol. 2019;30(5):863–870. https://doi.org/10.1093/annonc/mdy474]. Ann Oncol. 2018;29(Suppl 4):iv192–iv237. https://doi.org/10.1093/annonc/mdy275.
16. Wang X, Wang Z, Pan J, et al. Patterns of extrathoracic metastases in different histological types of lung cancer. Front Oncol. 2020;10:715. https://doi.org/10.3389/fonc.2020.00715.
17. Cai H, Wang H, Li Z, Lin J, Yu J. The prognostic analysis of different metastatic patterns in extensive-stage small-cell lung cancer patients: a large population-based study. Future Oncol. 2018;14(14):1397–407. https://doi.org/10.2217/fon-2017-0706.
18. Megyesfalvi Z, Tallosy B, Pipek O, et al. The landscape of small cell lung cancer metastases: organ specificity and timing. Thorac Cancer. 2021;12(6):914–23. https://doi.org/10.1111/1759-7714.13854.
19. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. J Clin Oncol. 1999;17(7):2092–9. https://doi.org/10.1200/JCO.1999.17.7.2092.
20. Putora PM, Glatzer M, De Ruysscher D, et al. Consolidative thoracic radiotherapy in stage IV small cell lung cancer: Selection of patients amongst European IASLC and ESTRO experts [published correction appears in Radiother Oncol. 2019;141:332. https://doi.org/10.1016/j.radonc.2019.10.006]. Radiother Oncol. 2019;135:74–77. https://doi.org/10.1016/j.radonc.2019.02.010.
21. Riely GJ, Wood DE, Ettinger DS, et al. Non-small cell lung cancer, Version 4.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2024;22(4):249–74. https://doi.org/10.6004/jnccn.2204.0023.
22. Dingemans AC, Hendriks LEL, Berghmans T, et al. Definition of synchronous oligometastatic non-small cell lung cancer-a

consensus report. J Thorac Oncol. 2019;14(12):2109–19. https://doi.org/10.1016/j.jtho.2019.07.025.
23. Shirasawa M, Fukui T, Kusuhara S, et al. Prognostic differences between oligometastatic and polymetastatic extensive disease-small cell lung cancer. PLoS One. 2019;14(4): e0214599. https://doi.org/10.1371/journal.pone.0214599.
24. Fong KM, Rosenthal A, Giroux DJ, et al. The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: Proposals for the Revision of the M Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2024;19(5):786–802. https://doi.org/10.1016/j.jtho.2024.01.019

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