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# Correlation between tumor diameter, distant metastasis site, and survival in extensive stage small cell lung cancer

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## Abstract

**Background:** Small cell lung cancer (SCLC) is a malignant disease that spreads quickly. There is limited research on the relationship between tumor diameter and distant metastatic patterns in extensive stage small cell lung cancer (ES-SCLC). This study aimed to investigate the relationship between tumor diameter, distant metastasis site, and survival in extensive stage small cell lung cancer.

**Method:** Patients over the age of 18 who applied to Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital with the diagnosis of small cell lung cancer and distant organ metastasis between January 2015 and December 2019 were retrospectively analyzed.

**Results:** The study comprised a total of 178 patients, with 12 women (6.7%) and 166 men (93.3%) participating. The patient was followed for a period of 1 to 36 months, with a median value of 7 months. The univariate model showed that pancreatic metastasis, single metastasis, tumor diameter, and tumor N stage had a significant ( $p = 0.003$ ,  $p = 0.001$ ,  $p = 0.013$ ,  $p = 0.001$ , respectively) effect on survival. The N stage III group's expected life expectancy [6.8 months (5.8–7.7)] was considerably ( $p = 0.000$ ) lower than the N stage I–II groups [11.2 months (8.8–13.4)]. The predicted life expectancy for the group with pancreatic metastasis [4.1 months (2.6–5.5)] was significantly ( $p = 0.001$ ) shorter than that of the group without pancreatic metastasis [8.9 months (7.6–10.1)]. The predicted life expectancy for the group with tumor size  $> 7$  cm [6.7 months (5.4–8.0)] was significantly shorter than that of the group with tumor size of 0–3 cm [10.9 months (7.3–14.6)] ( $p = 0.019$ ) and 3–7 cm [9.2 months (7.5–11)] ( $p = 0.023$ ).

**Conclusion:** The authors of this study found that pancreatic metastasis, single metastasis, tumor diameter, and tumor N stage can be used as independent predictive factors for the survival of SCLC patients.

**Keywords:** Small cell lung cancer, Tumor size, Lymph node metastasis, Prognosis, Survival

## Introduction

Small cell lung cancer (SCLC) is a very aggressive cancer that affects about 31,000 people in the USA each year. It is responsible for 14% of all lung cancer diagnoses [1]. At the time of presentation, almost two-thirds of patients have distant metastases. Although practically any organ

can be affected, the bone, liver, and brain are the most common target areas in SCLC [2, 3].

Small cell lung cancer metastasis is influenced by a variety of parameters including tumor size, lymph node involvement, histological subtype, functional status, age, and gender [4, 5]. There are few researches addressing the association between tumor size and distant metastasis sites; therefore, our current understanding of the relationship between clinically relevant parameters and patterns of distant metastasis is limited [6–8].

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The capacity to forecast the probability of distant metastasis in SCLC using clinically important criteria has significant implications for the disease's therapy. The clinical stage is the most important prognostic factor for individuals with SCLC; patients with metastatic cancer have an average life of only 8–11 months.

“Limited” and “extensive” diseases are the two subtypes of SCLC. Tumors restricted to the hemithorax are classified as limited disease (LD), although local dissemination and ipsilateral supraclavicular nodes may be present if they are in the same radiation route as the original tumor. In the LD category, extrathoracic metastases are not permitted. All other patients are described as having an extensive disease (ED) [9].

This study intends to discover distinct metastatic patterns and survival rates in extensive stage SCLC patients based on tumor diameter.

## Methods

Advanced stage patients older than 18 years of age who applied to Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital between January 2015 and December 2019, were diagnosed with pathological small cell lung cancer, and presented with distant organ metastases were included in the study. Patients who did not meet all the inclusion criteria were excluded from the study. Patients were screened retrospectively using hospital data. Data on demographics, clinicopathology, therapeutics, and prognosis were all rigorously reviewed: age, gender, family history, smoking, pathological tumor type, tumor location, metastatic site, tumor stage, surgery, chemotherapy, radiation and targeted therapeutic procedures, and overall survival (OS). (OS was defined as the time from diagnosis to death or final follow-up [10]). It was aimed to determine the predictive factors for survival in SCLC patients with all collected and researched data. Tumor, node, and metastasis (TNM) classification was used to perform staging [11].

A total of 178 SCLC patients with histological confirmation between January 2015 and December 2019 were retrospectively analyzed. Our study is a single-center, observational, retrospective study to investigate the survival of SCLC patients. There is no need for an informed consent form as it is a retrospective record review. Health Sciences University Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee approved this study.

## Statistical analysis

The mean, standard deviation, median minimum, maximum, frequency, and ratio values were employed in the descriptive statistics of the data. The Kolmogorov-Smirnov test was used to determine the distribution of

variables. In the study of quantitative independent data, the Mann-Whitney *U* test was applied. For the study of qualitative independent data, the chi-square test was applied. For survival analysis, Cox regression (univariate-multivariate) and the Kaplan-Meier technique were used. The analysis was carried out using SPSS 27.0.

## Results

Our patients were on average 63 years old (36–85). The study comprised a total of 178 patients, with 12 women (6.7%) and 166 men (93.3%) participating. There were 18 (10.1%) patients with tumors measuring 0–3 cm, 90 (50.6%) patients with tumors measuring 3–7 cm, and 70 (39.3%) patients with tumors measuring more than 7 cm. There were 57 patients (32.0%) with metastasis in just one site, 73 patients (41.0%) with metastasis in two sites, and 46 patients (25.7%) with metastasis in three or more locations. Patients were followed for 1 to 36 months on average, with a median of 7 months. Table 1 summarizes the patient information.

There was no significant difference between the age and gender distribution of the patients in the living patient group and the deceased patient group ( $p > 0.05$ ).

**Table 1** Patients tumor characteristic

	Min-max	Median	Mean $\pm$ sd/n (%)
Age	36.0–85.0	63.0	62.5 $\pm$ 8.8
Sex			
Female			12 (6.7%)
Male			166 (93.3%)
Following time (months)	1.0–36.0	7.0	8.3 $\pm$ 7.3
<b>Metastasis</b>			
Brain			24 (13.5%)
Bone			133 (74.7%)
Liver			84 (47.2%)
Opp. lung			11 (6.2%)
Pleura			25 (14.0%)
Adrenal			52 (29.2%)
Pancreas			16 (9.0%)
Bone + brain			5 (2.8%)
Bone + liver			31 (17.4%)
Single metastasis			57 (32.0%)
Dual metastasis			73 (41.0%)
Three or more metastasis			46 (25.8%)
Tumor diameter (cm)			
0–3			18 (10.1%)
3–7			90 (50.6%)
> 7			70 (39.3%)
Tumor N stage			
I			6 (3.4%)
II			60 (33.7%)
III			112 (62.9%)
Living deceased			
Living			4 (2.2%)
Deceased			174 (97.8%)

Metastasis site distribution, tumor diameter, and tumor N stage did not differ significantly between the living group and the deceased group ( $p > 0.05$ ) (Table 2).

The univariate model demonstrated that age, gender, cranial, bone, liver, opposite lung, pleura, adrenal, bone + brain, bone + liver, dual metastasis, and 3 or more metastasis sites did not have a significant ( $p > 0.05$ ) effect on survival time. On the other hand, the univariate model showed that pancreatic metastasis, single metastasis, tumor diameter, and tumor N stage have a significant ( $p < 0.05$ ) effect on survival time (Table 3).

The N stage III group's expected life expectancy [6.8 months (5.8–7.7)] was considerably ( $p = 0.000$ ) lower than the N stage I–II groups [11.2 months (8.8–13.4)] (Fig. 1).

The group with pancreatic metastasis had a considerably ( $p = 0.001$ ) shorter life expectancy [4.1 months (2.6–5.5)] than the group without pancreatic metastasis [8.9 months (7.6–10.1)] (Fig. 2).

The predicted life expectancy for the group with multiple metastases accompanied by pancreatic metastases [7.0 months (5.9–8.1)] was significantly shorter than the group with multiple metastases without pancreatic metastases [11.5 months (9.0–14.2)], ( $p = 0.000$ ) (Fig. 3).

The estimated life expectancy for patients with tumors larger than 7 cm is 6.7 months (5.4–8.0). 10.9 months (7.3–14.6) was considerably shorter than that of the group with tumors measuring 0–3 cm ( $p = 0.019$ ), as well as 3–7 cm [9.2 months (7.5–11)] ( $p = 0.023$ ) (Fig. 4).

## Discussion

This study found that pancreatic metastasis, single metastasis, tumor diameter, and tumor N stage are independent predictive variables for survival in SCLC patients.

The group with tumors measuring  $> 7$  cm had a significantly reduced life expectancy than the groups with tumors measuring 0–3 cm and 3–7 cm. For several types of malignancies, including non-small cell lung cancer (non-SCLC), tumor size is a significant prognostic factor [12].

Larger tumors have been shown to have a bad prognosis in most cases. Zhang et al., leveraging the SEER data, developed an easy-to-use nomogram to estimate the relationship between tumor size and survival. In individuals with stage IV non-SCLC, there was statistical significance between tumor size and metastatic site. In the case of brain or lung metastases, it was discovered that a larger

**Table 2** Tumor characteristics in the group living and deceased patients

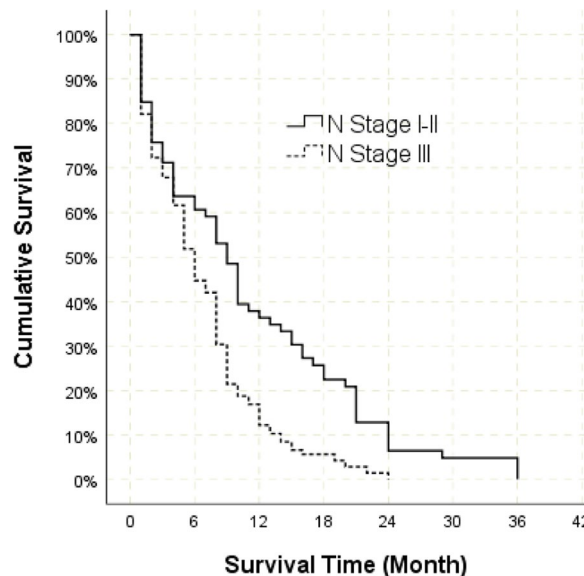
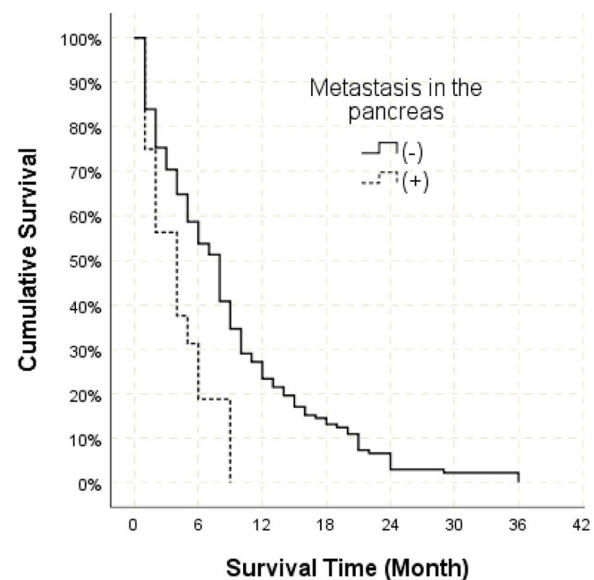
		Living		Deceased		<i>p</i>	
		Mean ± sd/ <i>n</i> (%)	Median	Mean ± sd/ <i>n</i> (%)	Median		
Age		70.3 ± 7.7	69.5	62.3 ± 8.7	63.0	0.087	m
Sex	Female	0 (0.0%)		12 (6.9%)		1.000	χ <sup>2</sup>
	Male	4 (100.0%)		162 (93.1%)			
<b>Metastasis</b>							
Brain		0 (0.0%)		24 (13.8%)		1.000	χ <sup>2</sup>
Bone		2 (50.0%)		131 (75.3%)		0.265	χ <sup>2</sup>
Liver		0 (0.0%)		84 (48.3%)		0.123	χ <sup>2</sup>
Opp. lung		0 (0.0%)		11 (6.3%)		1.000	χ <sup>2</sup>
Pleura		1 (25.0%)		24 (13.8%)		0.457	χ <sup>2</sup>
Adrenal		0 (0.0%)		52 (29.9%)		0.323	χ <sup>2</sup>
Pancreas		0 (0.0%)		16 (9.2%)		1.000	χ <sup>2</sup>
Brain + bone		0 (0.0%)		5 (2.9%)		1.000	χ <sup>2</sup>
Bone + liver		0 (0.0%)		31 (17.8%)		1.000	χ <sup>2</sup>
Single metastasis		4 (100.0%)		53 (30.5%)		0.010	χ <sup>2</sup>
Dual metastasis		0 (0.0%)		73 (42.0%)		0.145	χ <sup>2</sup>
Three or more met.		0 (0.0%)		46 (26.4%)		0.574	χ <sup>2</sup>
Tumor diameter (cm)	0–3	1 (25.0%)		17 (9.8%)		0.349	χ <sup>2</sup>
	3–7	2 (50.0%)		88 (50.6%)			
	> 7	1 (25.0%)		69 (39.7%)			
Tumor N stage	I	0 (0.0%)		6 (3.4%)		1.000	χ <sup>2</sup>
	II	1 (25.0%)		59 (33.9%)			
	III	3 (75.0%)		109 (62.6%)			

<sup>m</sup> Mann-Whitney U test/ $\chi^2$  chi-square test

**Table 3** Tumor characteristics in the univariate and multivariate models

	Univariate model			Multivariate model		
	HR	% 95 GA	<i>p</i>	HR	% 95 GA	<i>p</i>
Age	1.004	0.986–1.022	0.691			
Sex	1.569	0.869–2.834	0.135			
Brain	1.290	0.835–1.993	0.251			
Bone	1.107	0.784–1.563	0.565			
Liver	1.217	0.900–1.644	0.201			
Opp. lung	1.045	0.565–1.932	0.888			
Pleura	1.264	0.818–1.953	0.291			
Adrenal	1.127	0.813–1.563	0.473			
Pancreas	2.201	1.296–3.737	<b>0.003</b>	2.016	1.179–3.446	<b>0.010</b>
Bone + brain	1.324	0.541–3.237	0.539			
Bone + liver		0.756–1.659	0.572			
Single metastasis		0.407–0.797	<b>0.001</b>	0.643	0.457–0.906	<b>0.011</b>
Dual metastasis		0.951–1.766	0.100			
Three or more met		0.967–1.909	0.077			
Tumor diameter	1.357	1.065–1.729	<b>0.013</b>			
Tumor N stage	1.651	1.227–2.222	<b>0.001</b>	1.585	1.175–2.138	<b>0.003</b>

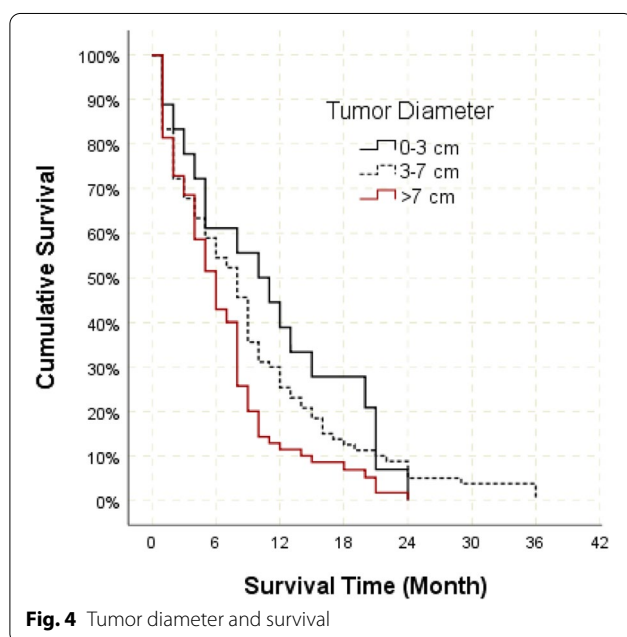
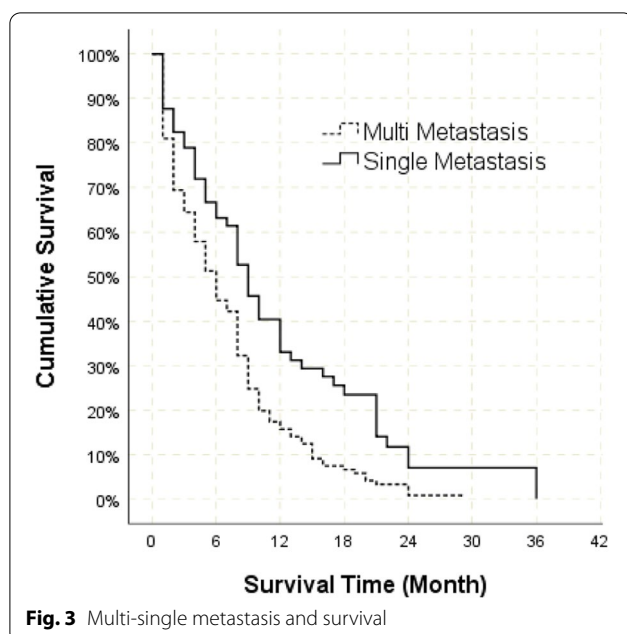
COX regression (forward LR)

Data in bold and italic indicate significant values:  $p < 0.05$ **Fig. 1** N stage and survival**Fig. 2** Pancreas metastasis and survival

tumor had an equivalent chance of developing metastasis [13].

Only a few studies have been done to estimate SCLC patients' survival depending on tumor size. Poor *performance status*, presence of disseminated disease, weight loss, and elevation of lactate dehydrogenase (LDH) are poor prognostic factors in SCLC [14].

According to Li et al., the model of distant metastasis of ES-SCLC is connected to tumor size, and tumor size is predictive of the metastatic site. Larger tumors are not linked to a higher risk of distant metastasis, but they are linked to the pattern of distant metastasis [15]. Vascular endothelial growth factor (VEGF) is a growth factor released by malignant tumors that promotes lymph node



(LN) metastasis by promoting lymphatic vessel expansion (lymphangiogenesis) in primary tumors and draining sentinel LNs. Lymphatic vessels have been shown in studies to not only act as passive routes for tumor propagation, but also to actively enhance tumor cell recruitment to LNs, cancer stem cell survival, and immune system function [16]. In a growing number of malignancies, there is persuasive evidence that tumor lymphangiogenesis and lymph node lymphangiogenesis are

valuable prognostic markers for future risk of metastasis and overall survival [17]. Masuda et al. looked at the relationship between lymphatic invasion and prognosis in non-small cell lung cancer (NSCLC) patients. The degree of lymphatic infiltration in lung squamous cell carcinoma (SqCC) and local tumor aggressiveness were investigated in this study. The authors came to the conclusion that lymphatic infiltration that was moderate or severe had a high malignant potential. In patients with lung SqCC, moderate or severe lymphatic invasion was found to be an independent indicator of poor outcome [18].

Increased carcinoembryonic antigen (CEA) levels were linked to a substantially higher rate of lymph node metastasis and a worse prognosis in small size NSCLC, according to Bao et al. [19]. Larger tumor size and many lymph node metastases were linked to poor survival in another study involving 78 individuals with stage IIIA SCLC [8].

In malignant tumors, the involvement of regional nodes is an adverse prognostic feature. The location determines the node (N) stage. According to our findings, increasing the node (N) stage is linked to a worse chance of survival. These results were in harmony with the previous studies (Jeong et al.) [20]. As is known, SCLC cause early and widespread metastasis due to their high cell proliferation feature. The extent of the disease is the most important prognostic factor. The high number of involved organs also negatively affects the prognosis. In untreated cases, the median survival time has been found to be 2–4 months [21].

In the natural course of SCLC, distant metastases are virtually invariably found. The distant metastasis rate is reported to be 40–60% at the time of the first diagnosis [2, 22]. Only 4% of patients who died of advanced disease had a disease that was restricted to the thorax, according to autopsies. According to Faruk Tas et al.'s research, patients with multiple organ metastases had a poorer overall survival rate than those with single site involvement. However, they found no correlation between the location of involvement and overall survival [4]. According to studies, the liver is the most common location of hematogenous metastasis in SCLC patients (61.9–64.5%) [22]. Cai et al. found that liver metastasis, alone or in combination with other organs, is a poor prognostic factor for SCLC patients with distant metastases, similar to prior findings [3]. In our study, metastases were most common in the bone, liver, and adrenal regions.

Our study determined liver metastasis at a rate of 47.2%. The most frequent metastasis site was bone with 74.7%. Our findings were comparable to those of Li et al [15].

Furthermore, our study detected pancreatic metastasis at a rate of 9.2%. Our results showed that the predicted life expectancy in the group with multiple



metastases was significantly shorter than that of the group without pancreatic metastases. Although autopsy series reported lung cancer pancreatic metastasis at rates of up to 40%, they are not observed at such a high rate at the clinic. The most prevalent histological type that metastasizes to the pancreas is small cell carcinoma, which has a poor prognosis. These results were consistent with the literature [23].

A few studies have shown that specific organ metastases at presentation have no effect on survival in SCLC patients [2]. However, many researchers have determined that specific organ metastases are one of the factors that cause poor prognosis, as in our study [24, 25]. The small sample size and single-center retrospective study was a limitation of this study.

## Conclusion

SCLC is a highly aggressive cancer that frequently has metastases when it is discovered. Tumor diameter has been linked to cancer survival and can be utilized as a prognostic indicator in a variety of malignancies. Furthermore, metastatic site, number of metastases, and tumor N stage are predictive factors for SCLC patients' survival.

In conclusion, pancreatic metastasis, solitary metastasis, tumor diameter, and tumor N stage can all be employed as prognostic indicators for SCLC patients' survival. The authors of this study found that pancreatic metastasis, single metastasis, tumor diameter, and tumor N stage can be used as independent predictive factors for the survival of SCLC patients.

## Abbreviations

SCLC: Small cell lung cancer; ES-SCLC: Extensive stage small cell lung cancer; OS: Overall survival; TNM: Tumor, node, and metastasis; LDH: Lactate dehydrogenase; LN: Lymph node; VEGF-C: Vascular endothelial growth factor; LNs: Sentinel lymph node; NSCLC: Non-small cell lung cancer; SqCC: Squamous cell carcinoma; CEA: Carcinoembryonic antigen.

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## Authors' contributions

FC, SD, MA, AS, and SA jointly conceived the study and contributed to the data acquisition. FC contributed to the analysis and interpretation of the data. All authors reviewed the manuscript prior to submission, and all accept the responsibility for the integrity of the research process and findings. All authors read and approved the final manuscript.

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## Availability of data and materials

The data sets generated and/or analyzed during the present study are not publicly available, but they are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

The Ethics Committee of the Health Sciences University Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital gave their approval to this investigation.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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