Original Article

Prognosis, Survival, and Clinicopathological Characteristics of Small Cell Lung Cancer with Pleural Fluid

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Abstract

Objective: While malignant pleural effusion (MPE) is generally observed in non-small cell lung cancer (SCLC) patients, its prevalence in SCLC has not been reported. **Methods:** Patients over 18 who were admitted to our hospital between January 2015 and December 2019 and diagnosed with SCLC histologically were retrospectively studied. Demographic data, tumor location, tumor stage, pleural fluid characteristics, radiological findings, and overall survival were recorded from hospital records. **Results:** Our study included 59 patients (48 [81.4%] men and 11 [18.6%] women), with a median age of 67. Forty-seven (79.7%) patients had a history of smoking. The patients had median tumor standardized uptake values (SUV) max levels of 11.9, a tumor diameter of 6 cm, and a follow-up period of 7 months. Protein levels in pleural fluid of the metastasizing group were significantly higher than in the nonmetastatic group ($P = 0.049$). In the univariate model, age, N stage, pleural fluid glucose, and pleural fluid protein levels were found significantly efficient in predicting disease-free survival ($P = 0.008$, $P = 0.001$, $P = 0.001$, and $P = 0.026$, respectively). In the multivariate reduced model, N stage, pleural fluid glucose, and pleural fluid protein levels were found independent predictive factors for disease-free survival ($P = 0.000$, $P = 0.000$, and $P = 0.009$, respectively). **Conclusions:** MPE is common at presentation (11%) in patients with SCLC and may be associated with reduced survival. Additional studies are needed to assess the treatment-adjusted survival rate in the MPE setting.

Keywords: Lung cancer, pleural fluid, pleural fluid protein, prognosis, small-cell lung cancer

Introduction

Lung cancer is the leading cause of cancer-related deaths in men and women worldwide, with an estimated 1.69 million deaths in 2015.[1] About 13% of patients with primary lung cancer are small cell lung cancer (SCLC).[2] SCLC tends to have high malignancy, rapid progression, and widespread metastasis. Survival rates of both localized and advanced SCLCs are quite low, despite advances in managing non-SCLC (NSCLC).[3] It is known little about the epidemiological or prognostic effects of pleural effusion (PE) in patients with SCLC.[4] Malignant PE (MPE) is defined by malignant cells in the pleural space, indicating M1a (or diffuse) disease. Therefore, determining the presence of pleural fluid and evaluating its characteristics are critically important for staging. In the case of MPE, TNM stage is classified as M1a and stage IV.[5] The study on the seventh edition of the TNM staging in 2007 found that SCLC patients' survival with MPE was between the limited and advanced stages of patients without PE.[6] Researchers have found that pleural fluid (PE) in lung cancer negatively affects the prognosis.[7-9]

In this study, we aimed to determine the incidence and prognostic value of MPE in patients with SCLC at admission.

Methods

Patients over 18 who were histologically diagnosed with SCLC between January 2015 and December 2019 at Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital were retrospectively studied. Age, gender,

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Table 1: Demographic, radiological, and pleural fluid characteristics

	Minimum-maximum	Median	Mean±SD/ *n* (%)
Age	37.0-87.0	67.0	65.2±8.9
Sex			
Female			11 (18.6)
Male			48 (81.4)
Smoking			
+			47 (79.7)
–			12 (20.3)
TM SUV maximum	3.8-33.1	11.9	13.5±5.5
Tumor diameter	2.0-14.0	6.0	6.8±2.4
Follow up time	1.0-36.0	7.0	8.9±7.9
N stage			
I			2 (3.4)
II			31 (52.5)
III			26 (44.1)
Pleural fluid			
PET uptake	1.5-16.9	3.4	4.2±2.7
Glycose	85.0-459.0	124.0	136.8±55.8
LDH	135.0-756.0	303.0	430.8±352.2
Protein	2.6-6.9	3.8	3.8±0.8
Hgb			
>12			37 (62.7)
<12			22 (37.3)
Albumin			
>3			6 (10.2)
<3			53 (89.8)
Pleural lesion			
+			8 (13.6)
–			51 (86.4)
Pleural thickening			
+			42 (71.2)
–			17 (28.8)
Pleural nodule			
+			13 (22.0)
–			46 (78.0)
Pleural nodule + thickening			
+			12 (20.3)
–			47 (79.7)
Fluid cytology			
+			27 (45.8)
–			32 (54.2)
Pleural biopsy			
+			11 (18.6)
–			48 (81.4)
Pleural fluid (cm)			
>1			40 (67.8)
<1			19 (32.2)
Metastasis site			
Cranial			11 (22.9)
Bone			32 (66.7)
Adrenaline			15 (31.3)
Liver			22 (45.8)
Opp. lung			3 (6.3)
Pancreas			4 (8.3)
Metastasis			
–			11 (18.6)
+			48 (81.4)

PET: Positron emission tomography, Hgb: Hemoglobin, TM: Tumor, SUV: Standardized uptake values, LDH: Lactate dehydrogenase, SD: Standart daviation

family history, tobacco consumption, tumor location, tumor stage, PE characteristics, radiological findings, and overall survival (OS) (OS was defined as the interval from diagnosis to death or last follow-up) were screened from the hospital records.

The informed consent form was waived off due to the retrospective nature of the study.

Database and patient selection

Patients admitted to our hospital between January 2015 and December 2019 who were pathologically diagnosed with small cell lung carcinoma and older than 18 were enrolled in the study. Demographic, clinicopathological, therapeutic, and prognostic data were analyzed systematically. Patients who did not meet all inclusion criteria were excluded from the study.

Ethical considerations

The Ethics Committee of the Health Sciences University Ankara Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital approved this study.

Statistical analysis

Mean, standard deviation, median, minimum and maximum values, frequency, and the ratio of the data were analyzed by descriptive statistics. The distribution of variables was searched with the Kolmogorov–Smirnov test. Unpaired *t*-test and Mann–Whitney *U*-test were used to analyze independent quantitative data. The Chi-square test was used to analyze independent qualitative data, and the Fisher test was used when the Chi-square test conditions were not met. Cox regression was used in the survival analysis. Statistical Package for the Social Sciences (SPSS) version 27.0 (SPSS, Chicago, IL, USA) program was used for the statistical analysis.

Results

The study population consisted of the following: 59 patients (48 men [81.4%] and 11 women [18.6%]); the median age is 67 years (age range, 37–87 years). Forty-seven patients (79.7%) had a smoking history.

All patients were classified according to the seventh edition of the TNM staging classification.[6] The patients had median tumor SUVmax levels of 11.9, a tumor diameter of 6 cm, and a follow-up period of 7 months.

Table 2: Comparison of data in the group with and without metastasis

	Metastasis (−)		Metastasis (+)		*P*
	Mean±SD/*n* (%)	Median	Mean±SD/*n* (%)	Median	
Age	62.5±10.2	62.0	65.9±8.5	67.0	0.102[m]
Sex					
Female	0		11 (22.9)		0.078χ^2
Male	11 (100.0)		37 (77.1)		
Smoking					
+	11 (100.0)		36 (75.0)		0.063χ^2
−	0		12 (25.0)		
TM SUV maximum	11.1±4.6	10.9	14.0±5.6	12.1	0.173[m]
Tumor diameter	6.0±2.2	6.0	7.0±2.4	6.0	0.254[m]
N stage					
I	2 (18.2)		0		0.364χ^2
II	6 (54.5)		25 (52.1)		
III	3 (27.3)		23 (47.9)		
Pleural fluid					
PET uptake	3.4±1.8	3.4	4.3±2.9	3.4	0.330[m]
Glycose	115.0±27.0	104.0	141.8±59.6	128.0	0.052[m]
LDH	404.6±262.6	294.0	436.9±371.8	312.0	0.892[m]
Protein	4.2±0.6	4.5	3.8±0.8	3.7	0.049[m]
Hgb					
>12	8 (72.7)		29 (60.4)		0.446χ^2
<12	3 (27.3)		19 (39.6)		
Albumin					
>3	0 (0.0)		6 (12.5)		0.582χ^2
<3	11 (100.0)		42 (87.5)		
Pleural lesion					
+	1 (9.1)		7 (14.6)		1.000χ^2
−	10 (90.9)		41 (85.4)		
Pleural thickening					
+	9 (81.8)		33 (68.8)		0.388χ^2
−	2 (18.2)		15 (31.3)		
Pleural nodule					
+	1 (9.1)		12 (25.0)		0.251χ^2
−	10 (90.9)		36 (75.0)		
Pleural nodule + thickening					
+	1 (9.1)		11 (22.9)		0.304χ^2
−	10 (90.9)		37 (77.1)		
Fluid cytology					
+	4 (36.4)		23 (47.9)		0.488χ^2
−	7 (63.6)		25 (52.1)		
Pleural biopsy					
+	3 (27.3)		8 (16.7)		0.415χ^2
−	8 (72.7)		40 (83.3)		
Pleural fluid (cm)					
>1	10 (90.9)		30 (62.5)		0.069χ^2
<1	1 (9.1)		18 (37.5)		

[m]Mann-Whitney *U* test/χ^2Chi-square test, Bold and italic indicate significant values: $P < 0.05$. PET: Positron emission tomography, Hgb: Hemoglobin TM: tumor, SUV: Standardized uptake values, LDH: Lactate dehydrogenase, SD: Standart daviation

The demographic, radiological, and PE characteristics for patients with small-cell lung cancer presenting with PE are summarized in Table 1.

The age and gender distribution of the patients did not show a significant difference in the metastasis and nonmetastasis groups ($P > 0.05$). The rate of smoking did not show a significant difference in the groups with and without metastasis ($P > 0.05$). There was no significant difference in tumor (TM) SUVmax levels and tumor diameter in the groups with and without metastasis ($P > 0.05$). N stage did not differ significantly in the groups with and without metastasis ($P > 0.05$). Positron

Table 3: Patient data in the univariate and multivariate model

	Univariate model			Multivariate model		
	HR	95% confidence	*P*	HR	95% confidence	*P*
Age	1.052	1.013-1.093	0.008			
Sex	0.829	0.419-1.640	0.590			
Smoking	0.693	0.358-1.343	0.277			
Tumor size	1.110	0.974-1.265	0.117			
N stage	2.552	1.450-4.494	0.001	3.088	1.673-5.697	***0.000***
TM SUV maximum	1.052	0.995-1.112	0.073			
Pleural fluid PET Uptake	1.040	0.947-1.142	0.408			
Pleural lesion	1.236	0.553-2.762	0.606			
Pleural thickening	1.123	0.602-2.096	0.715			
Pleural nodule	1.524	0.787-2.951	0.211			
Pleural nodule+thickening	1.373	0.696-2.709	0.361			
Fluid cytology	1.756	0.983-3.137	0.057			
Pleural biopsy	1.512	0.700-3.267	0.293			
Hgb	1.142	0.634-2.056	0.659			
Albumin	1.086	0.454-2.596	0.853			
Pleural fluid glycose	1.007	1.003-1.012	0.001	1.011	1.006-1.016	***0.000***
Pleural fluid LDH	1.000	0.999-1.001	0.861			
Pleural fluid protein	0.633	0.424-0.946	0.026	0.596	0.404-0.880	***0.009***
Pleural fluid <1 cm/>1 cm	0.839	0.465-1.516	0.562			

Cox regression (forward LR), Bold and italic indicate significant values: $P<0.05$. PET: Positron emission tomography, Hgb: Hemoglobin, TM: Tumor, SUV: Standardized uptake values, LDH: Lactate dehydrogenase, HR: hazard ratio, LR: Logistic regression

emission tomography (PET) uptake in PE, glucose, and lactate dehydrogenase (LDH) levels in the PE did not show a significant difference in the groups with and without metastasis ($P > 0.05$). The PE protein levels in the metastasized group were significantly higher than in the nonmetastasized group ($P = 0.049$). There was no significant difference in Hgb and albumin distribution in the groups with and without metastasis ($P > 0.05$). The group with and without metastasis, pleural lesion, pleural thickening, pleural nodule, pleural nodule + thickening, fluid cytology, pleural biopsy, pleural fluid ratio were did not show a significant difference ($P > 0.05$) [Table 2].

In the univariate model, age, N stage, PE glucose, and PE protein levels were found significantly efficient in predicting disease-free survival ($P = 0.008$, $P = 0.001$, $P = 0.001$, and $P = 0.026$, respectively). In the univariate model, no significant efficacy of gender, smoking, tumor diameter, TM SUVmax, PE PET involvement, pleural lesion, pleural thickening, pleural nodule, pleural nodule + thickening, fluid cytology, pleural biopsy, Hemoglobın (Hgb), albumin, PE ($P > 0.05$) of LDH, and PE diameter in predicting disease-free survival time was observed [Table 3].

In the multivariate reduced model, N stage, PE glucose, and PE protein levels were found independent predictive factors for disease-free survival ($P = 0.000$, $P = 0.000$, and $P = 0.009$, respectively) [Table 3].

Discussion

Although there is no epidemiological study, the estimated incidence of MPE is more than 150,000/year in the USA.[1] MPE is a common complication of various primary malignancies, but the most common cause is lung cancer (37.5%).[10,11] Although MPE is commonly seen in lung cancer, most studies evaluating the importance of MPE have a small sample size and concern primarily NSCLC. Morgensztern *et al*.[11] showed that the presence of MPE reduced the median OS from 5 months to 3 months in patients with stage M1b NSCLC in their study using the SEER database. The researchers also reported the MPE rate as 16% at the time of admission in their study, including 57,685 patients with NSCLC.[12] The prevalence of SCLC is 11.8% in 101 MPE patients.[13] They reported the incidence of PE in SCLC as 10%–20% in their review.[7] In their study on 360 patients, they reported 20.6% minimal PE and 23% MPE. They determined that the median survival showed a significant difference between patients with no PE, minimal PE, and no MPE (median survival: 11.2, 5.93, and 4.83 months, respectively). In addition, they reported that MPE had a significant prognostic effect in stage 1–3 patients (hazard ratio = 2.751), and this effect disappeared in stage four patients.[14] In addition, they evaluated the frequency of MPE in 68,443 SCLC patients and found an overall MPE rate of approximately 11% (7639 patients). In the same study, MPE was observed more frequently in N2 and N3 patients and patients with tumor size >3 cm.[15] They reported Eastern Cooperative Oncology Group performance score as the only independent predictive factor for survival in their study, in which the majority of patients were diagnosed with primary lung cancer, breast cancer, and lymphoma, and they did not detect any effect of age, gender, pleural cytology, pleural histology, and PE biochemical parameters.[16] In their

study, which included 591 patients with SCLC, Lim *et al*. have found that female gender was a prognostic factor for better survival in SCLC. On the contrary, gender did not significantly affect survival in our study.[17] On the other hand, Videtic *et al*. compared the groups of ex-smokers and active smokers who were diagnosed with SCLC and under treatment and found the OS rate was significantly lower in active smokers. We did not observe a significant independent effect of smoking status in our study.

Conclusions

The presence of MPE at admission is common in patients with SCLC and may be a poor prognostic indicator. There is limited evidence of the role and prognostic value of MPE in clinical practice when faced with SCLC patients. This study may provide additional support in decisions about treatment and palliation and help guide "patient-oncology team" decisions in care.

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Conflicts of interest

There are no conflicts of interest.

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