ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220325

What is the effect of tumor diameter, lymph node metastases, and SUVmax value on prognosis in limited-stage small cell lung cancer?

Filiz Çimen[1*], Melike Aloglu[1], Sevim Düzgün[1], Ayşegül Şentürk[1], Şükran Atikcan[1], Özlem Özmen[2]

SUMMARY

OBJECTIVE: This study was designed to investigate the link between survival and prognostic factors such as tumor size, lymph node metastasis, and metabolic activity detected on positron emission tomography/computed tomography in patients with limited-stage small cell lung carcinoma.

METHODS: Patients who were admitted to our hospital with pathological diagnosis of limited-stage small cell lung cancer between January 2015 and December 2019 and were older than 18 years were retrospectively screened.

RESULTS: A total of 77 patients, including 10 females and 67 males, were included in the study. While there were 39 patients over 60 years of age, 38 patients were under 60.

The ratios of male patients, N stage, multiple lymph nodes, distant metastasis, brain metastasis, and prophylactic cranial irradiation in the deceased patients' group were significantly (p=0.008, p=0.000, p=0.000, p=0.000, p=0.013, p=0.000, respectively) higher than those in the living patients' group. In the univariate model, we observed that gender, smoking, T stage, N stage, multiple lymph nodes, distant metastasis, brain metastasis, liver metastasis, sequential chemotherapy, sequential radiotherapy, concurrent chemoradiotherapy, and prophylactic cranial irradiation had significant effect (p=0.049, p=0.021, p=0.022, p=0.000, p=0.000, p=0.000 p=0.003, p=0.037, p=0.029, p=0.049, p=0.000, respectively) on survival time. In the multivariate model, smoking, N stage, liver metastasis, and prophylactic cranial irradiation demonstrated significant independent effect (p=0.010, p=0.003, p=0.004, p=0.000, respectively) on survival time.

CONCLUSION: Our findings provide useful information for better patient management, especially in terms of negative factors on the continuation of survival during and after the treatment of limited-stage small cell lung carcinoma patients.

KEYWORDS: Lung cancer. Small cell lung cancer. Lymph node metastases. PET-CT. Prognosis.

INTRODUCTION

Accounting for approximately 15% of lung cancers, small cell lung cancer (SCLC) is a high-grade neuroendocrine tumor characterized by rapid growth and early metastatic spread[1]. While SCLC incidence has decreased recently, SCLC patients have a poor prognosis and a 5-year survival rate is only about 6%[2].

The majority (around 70%) of SCLC patients are diagnosed with extensive-stage small cell lung cancer (ES-SCLC). Only 30% of SCLC patients are diagnosed with limited-stage small cell lung cancer (LS-SCLC); however, their prognosis does still not look optimistic with a median survival time of 15–20 months[3]. As per the conventional VALG staging, LS-SCLC is a disease that is restricted to one hemithorax and can be safely encompassed within a single radiation portal[4].

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is a valuable imaging method employed in staging SCLC[5]. PET can detect additional areas of disease that could not be detected by conventional computed tomography (CT). Furthermore, PET may be useful in predicting prognosis. Many studies confirmed the prognostic significance of metabolic parameters measured by FDG-PET in SCLC[6-8]. These parameters reflect the maximum standardized uptake value (SUV_{max}), disease activity, and tumor burden.

Recently, more studies have been conducted to investigate the prognosis-related risk factors to improve survival of SCLC patients. A variety of clinical factors, such as the patient's age, gender, performance status, and clinical stage, may affect the prognosis of SCLC patients[9]. Tumor size and lymph node (LN) metastasis were found to be a prognostic

[1]Ankara University, Faculty of Health Sciences, Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital, Chest Disease Department – Ankara, Turkish.

[2]Ankara University, Faculty of Health Sciences, Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital, Nuclear Medicine Department – Ankara, Turkish.

*Corresponding author: fhcimen@yahoo.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on April 01, 2022. Accepted on June 17, 2022.

factor of cancer in NSCLC[10,11]. These findings thus suggested that tumor size and LN metastasis may also be prognostic factors of SCLC.

The standard treatment recommended for LS-SCLC in the current NCCN guidelines is concurrent chemoradiotherapy (CRT)[12]; prophylactic cranial irradiation (PCI) is planned for LS-SCLC patients who respond well to induction therapy. While the effectiveness of first-line therapy is as high as 80%, recurrence is observed within 6 months of completion of initial therapy in most patients[13].

There are not comprehensive studies as to which PET parameters demonstrate better prognostic performance in LS-SCLC. We, therefore, aimed to examine prognostic roles of SUV_{max} parameters. This study is designed to investigate the link between survival and prognostic factors such as tumor size, LN metastasis, and metabolic activity detected on PET-CT in patients with LS-SCLC.

METHODS

We retrospectively screened patients who were admitted to Health Sciences University Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital with pathological diagnosis of LS-SCLC between January 2015 and December 2019 and were older than 18 years. Demographic characteristics, LN metastasis, tumor size, and metabolic activity uptake in PET, in addition to clinicopathological, therapeutic, and prognostic data, were systematically extracted from medical records and analyzed.

In this cohort, 77 LS-SCLC cases were identified. Clinical stage of the disease was determined by results obtained from CT, PET scans, and magnetic resonance imaging. PCI was also evaluated.

Since it is a retrospective record review, Informed Consent Form is not needed and there are no costs to the budget.

Statistical analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum–maximum, frequency, and ratio values were used. The Kolmogorov-Smirnov test was used to measure the distribution of variables. The Mann-Whitney U-test was used to analyze the quantitative independent data, while the chi-square test was used to analyze the qualitative independent data, and Fisher's exact test was employed when the chi-square test conditions were not met. Cox regression (univariate-multivariate) and the Kaplan-Meier method were used for survival analysis. SPSS version 27.0 program was used in the analyses.

RESULTS

A total of 77 patients, including 10 females and 67 males, were included in the study. While there were 39 patients over 60 years of age, 38 patients were under 60. Patients' data are summarized in Table 1.

Age, smoking rate, diagnosis method, tumor localization distribution, T stage distribution, mass diameter, local recurrence rate, and PET SUV_{max} value did not differ significantly ($p>0.05$) between the groups of the deceased and living patients. The ratio of male patients in the deceased patients' group was significantly ($p=0.008$) higher than in the living patients' group. The ratio of N stage in the deceased patients' group was significantly ($p=0.000$) higher than in the living patients' group. The ratio of multiple LNs in the deceased patients' group was significantly ($p=0.000$) higher than in the living patients' group (Table 2).

The ratios of distant metastasis in the deceased patients' group were significantly ($p=0.000$) higher than in the living patients' group. The rate of brain metastases with distant metastases in the deceased patient group was found to be significantly higher ($p=0.013$) compared to the living patients' group.

The ratios of bone, liver, adrenal, and contralateral lung metastases in the deceased and living patients' groups did not show significant difference ($p>0.05$) (Table 2).

The ratios of chemotherapy, radiotherapy (RT), and concurrent CRT in the deceased and living patients' groups did not show significant difference ($p>0.05$). The ratio of PCI in the deceased patients' group was significantly ($p=0.000$) higher than in the living patients' group (Table 2).

Key features and univariate analysis

In the univariate model, age, diagnostic method, localization, mass diameter, local recurrence, bone metastasis, adrenal metastasis, contralateral lung metastasis, PET SUV_{max}, and sequential RT were not observed to have a significant ($p>0.05$) effect on survival time. In the univariate model, we observed that gender, smoking, T stage, N stage, multiple LNs, distant metastasis, brain metastasis, liver metastasis, chemotherapy, RT, concurrent CRT, and PCI had significant effect ($p=0.049$, $p=0.021$, $p=0.022$, $p=0.000$, $p=0.000$, $p=0.000$, $p=0.003$, $p=0.037$, $p=0.029$, $p=0.0049$, $p=0.000$, respectively) on survival time (Table 3).

Multivariate analysis

In the multivariate model, smoking, N stage, liver metastasis, and PCI demonstrated significant independent effect ($p=0.010$, $p=0.003$, $p=0.004$, $p=0.000$, respectively) on survival time (Table 3).

Table 1. Patients' data.

		Min–Max	Median	Mean ± SD/n (%)
Age	≤60			38 ± 49.4
	>60			39 ± 50.6
Sex	Female			10 ± 13.0
	Male			67 ± 87.0
Smoking	No			17 ± 22.1
	Yes			60 ± 77.9
Diagnostic method	FOB			46 ± 59.7
	FNA			14 ± 18.2
	Mediastinoscopy			4 ± 5.2
	EBUS			13 ± 16.9
Localization	Right up			14 ± 18.2
	Right mid.			23 ± 29.9
	Right b.			4 ± 5.2
	Left up			33 ± 42.9
	Left b.			2 ± 2.6
T stage	I			18 ± 23.4
	II			49 ± 63.6
	III			10 ± 13.0
N stage	I			31 ± 40.3
	II			46 ± 59.7
Lymph node	Single			31 ± 40.3
	Multiple			46 ± 59.7
Tumor diameter		1 – 7	5	4.5 ± 1.5
Tumor diameter (cm)	≤4			32 ± 41.6
	>4			45 ± 58.4
Local recurrence	(–)			56 ± 72.7
	(+)			21 ± 27.3
Distance metastasis	No			41 ± 53.2
	Yes			36 ± 46.8
Brain				15 ± 19.5
Bone				12 ± 15.6
Liver				8 ± 10.4
Adrenal				3 ± 3.9
Contr. lung				4 ± 5.2
Chemotherapy	No			38 ± 49.4
	Yes			39 ± 50.6
Radiotherapy	No			45 ± 58.4
	Yes			32 ± 41.6
Concurrent CRT	No			40 ± 51.9
	Yes			37 ± 48.1
PCI	No			14 ± 18.2
	Yes			63 ± 81.8
Mortality	No			32 ± 41.6
	Yes			45 ± 58.4
Following time (month)		5 – 72	29	31.3 ± 16.3

FOB: Fiber optic bronchoscopy; FNA: Fine-Needle Aspiration; EBUS: Endobronchial ultrasound; T stage: Tumour stage; N stage: Node stage; Contr. Lung: Contralateral lung; CRT: Chemoradiotherapy; PCI: Prophylactic cranial irradiation.

Table 2. Comparison of living and deceased patients' data.

		Living		Deceased		p	
		Mean ± sd/n (%)	Median	Mean ± sd/n (%)	Median		
Age	≤60	16 ± 50.0		22 ± 48.9		0.923	X^2
	>60	16 ± 50.0		23 ± 51.1			
Sex	Female	8 ± 25.0		2 ± 4.4		0.008	X^2
	Male	24 ± 75.0		43 ± 95.6			
Smoking	No	11 ± 34.4		6 ± 13.3		0.028	X^2
	Yes	21 ± 65.6		39 ± 86.7			
Diagnostic method	FOB	19 ± 59.4		27 ± 60.0		0.856	X^2
	FNA	7 ± 21.9		7 ± 15.6		0.682	X^2
	Med. copy	0 ± 0.0		4 ± 8.9		0.225	X^2
	EBUS	6 ± 18.8		7 ± 15.6		0.952	X^2
Localization	Right up	6 ± 18.8		8 ± 17.8		0.913	X^2
	Right mid.	8 ± 25.0		15 ± 33.3		0.549	X^2
	Right b.	1 ± 3.1		3 ± 6.7		0.634	X^2
	Left up	17 ± 53.1		16 ± 35.6		0.222	X^2
	Left b.	0 ± 0.0		2 ± 4.4		0.505	X^2
PET SU_{Vma}x		15.0 ± 8.6	13.9	13.2 ± 6.4	11.2	0.213	m
T stage	I	8 ± 25.0		10 ± 22.2		0.093	X^2
	II	23 ± 71.9		26 ± 57.8			
	III	1 ± 3.1		9 ± 20.0			
N stage	I	21 ± 65.6		10 ± 22.2		0.000	X^2
	II	11 ± 34.4		35 ± 77.8			
Lymph node	Single	21 ± 65.6		10 ± 22.2		0.000	X^2
	Multiple	11 ± 34.4		35 ± 77.8			
Tumor diameter		4.4 ± 1.6	5.0	4.6 ± 1.5	5.0	0.575	m
Tumor diameter (cm)	≤4	15 ± 46.9		17 ± 37.8		0.425	X^2
	>4	17 ± 53.1		28 ± 62.2			
Local recurrence	No	25 ± 78.1		31 ± 68.9		0.370	X^2
	Yes	7 ± 21.9		14 ± 31.1			
Distance metastasis	No	27 ± 84.4		14 ± 31.1		0.000	X^2
	Yes	5 ± 15.6		31 ± 68.9			
Brain		2 ± 6.3		13 ± 28.9		0.013	X^2
Bone		3 ± 9.4		9 ± 20.0		0.205	X^2
Liver		1 ± 3.1		7 ± 15.6		0.078	X^2
Adrenal		0 ± 0.0		3 ± 6.7		0.136	X^2
Contr. lung		0 ± 0.0		4 ± 8.9		0.137	X^2
Chemotherapy	No	19 ± 59.4		19 ± 42.2		0.138	X^2
	Yes	13 ± 40.6		26 ± 57.8			
Radiotherapy	No	19 ± 59.4		26 ± 57.8		0.889	X^2
	Yes	13 ± 40.6		19 ± 42.2			
Concurrent CRT	No	14 ± 43.8		26 ± 57.8		0.225	X^2
	Yes	18 ± 56.3		19 ± 42.2			
PCI	No	0 ± 0.0		14 ± 31.1		0.000	X^2
	Yes	32 ± 100.0		31 ± 68.9			

[m]Mann-Whitney U-test. [X²] χ^2 test. FOB: Fiber optic bronchoscopy; FNA: Fine-Needle Aspiration; EBUS: Endobronchial ultrasound; Med: Median; PET SUV: Positron emission tomography standardised uptake value; T stage: Tumour stage; N stage: Node stage; CRT: Chemoradiotherapy; PCI: Prophylactic cranial irradiation. χ^2: Significant p-value ≤0.05 according to paired χ^2 test. Bold and italics indicate significant values: p<0.05.

Table 3. Comparison of univariate and multivariate model.

	Univariate model			Multivariate model		
	HR	95%CI	p	HR	95%CI	p
Age	1.34	0.74 – 2.42	0.331			
Sex	4.16	1.00 – 17.28	0.049			
Smoking	2.80	1.17 – 6.71	0.021	3.30	1.33 – 8.21	0.010
Diagnostic method	1.05	0.81 – 1.36	0.712			
Localization	1.05	0.83 – 1.34	0.667			
PET SUV_{max}	0.97	0.93 – 1.02	0.229			
T stage	2.01	1.11 – 3.65	0.022			
N stage	4.69	2.26 – 9.74	0.000	3.24	1.48 – 7.10	0.003
Lymph node multiple	4.69	2.26 – 9.74	0.000			
Tumor diameter		0.91 – 1.36	0.282			
Local recurrence	1.27	0.67 – 2.41	0.459			
Distant metastasis	3.56	1.88 – 6.77	0.000			
Brain	2.85	1.44 – 5.65	0.003			
Bone	1.17	0.56 – 2.44	0.676			
Liver	2.37	1.05 – 5.34	0.037	3.515	1.501 – 8.232	0.004
Adrenal	1.54	0.47 – 5.03	0.473			
Contr. lung	1.47	0.52 – 4.12	0.466			
Chemotherapy	1.95	1.07 – 3.54	0.029			
Radiotherapy	1.15	0.64 – 2.09	0.642			
Concurrent CRT	0.55	0.30 – 1.00	0.049			
PCI	0.11	0.06 – 0.23	0.000	0.13	0.06 – 0.28	0.000

Cox regression (forward likelihood ratio); HR: Hazard ratio; PET SUV: Positron emission tomography standardized uptake value; T stage: Tumour stage; N stage: Node stage; Contr. Lung: Contralateral lung; CRT: Chemoradiotherapy; PCI: Prophylactic cranial irradiation. Bold and italics indicate significant values: p<0.05.

DISCUSSION

SCLC accounts for approximately 15% of all lung cancers and demonstrates a quite aggressive clinical course with a maximum of around 25% of 5-year survival rate even in limited-stage disease (LS-SCLC)[14]. Factors affecting survival in LS-SCLC, therefore, have often been studied. Male gender, old age, African American race, involvement of main bronchus, and poor performance status were reported as poor prognostic factors in LS-SCLC[15,16], while young age, smoking cessation, concurrent CRT, platinum-based chemotherapy, surgical treatment, pulmonary RT procedure, receiving >50 Gy of RT, and PCI were determined to increase survival[17-19]. In our study, gender and concurrent CRT were effective on survival in the univariate analysis while they were not found to be independent prognostic factors in the multivariate analysis. However, we determined that smoking history was an effective factor independently predictive of survival.

N stage is another factor whose relationship with SCLC survival has been examined. Salem et al. reported that the patients without mediastinal LN involvement showed better survival rates in their CRT study in stages 1–2 SCLC patients[20]. Guan and Zhang also found in their study involving 88 LS-SCLC patients that the presence of lymphadenopathy at mediastinal levels 2 and 3 before chemotherapy was associated with SCLC recurrence[21]. In a study in China, tumor size and LN metastasis were determined to be independent prognostic factors in stage 3A SCLC, and tumor size ≤4 cm and single LN metastasis were found to be associated with longer survival[22]. In our study, similar to the literature data, N stage was found to be an independent factor effective on survival in LS-SCLC.

Another independent factor found to be effective on LS-SCLC survival in this study was PCI. Although a study in the literature reports that PCI has no effect on the development time of brain metastasis and overall survival (OS) in SCLC patients

who underwent N0 M0 surgical resection[23], it has been concluded that PCI significantly increased survival in both extensive- and limited-stage diseases[24], extensive-stage elderly patient (≥70 years) group[25], SCLC patients in complete remission[26], LS-SCLC patients who underwent definitive surgery[27], and LS-SCLC patients who underwent definitive CRT[28].

Pre-CRT PET/CTs were analyzed in 120 individuals with LS-SCLC. On univariate analysis, SUV_{max}, SUV_{mean}, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of the primary tumor were not associated with OS, local-regional failure (LRF), or disease-free survival (DFS). On univariate analysis, MTV was substantially associated with DFS (p=0.024), but not on multivariate analysis. In LS-SCLC, pretreatment PET-CT scans and advanced metric measures had no independent prognostic significance[29]. Also in our study, we did not observe a significant difference in PET-CT SUV_{max} values.

Our study is designed to investigate the link between survival and prognostic factors such as tumor size, LN metastasis, and metabolic activity detected on PET-CT in LS-SCLC patients.

In the univariate model, we observed that gender, smoking, T stage, N stage, multiple LNs, distant metastasis, brain metastasis, liver metastasis, sequential chemotherapy, sequential RT, concurrent CRT, and PCI had significant effect on survival time. In the multivariate model, smoking, N stage, liver metastasis, and PCI demonstrated significant independent effect on survival time.

Our findings will provide useful information for especially the management of LS-SCLC patients.

CONCLUSION

Chemoradiotherapy can be used to treat LS-SCLC, and improvements in radiotherapy have greatly increased overall survival. According to the findings of our study and previous research, concurrent CRT is the cornerstone of care for LS-SCLC. In addition, PCI improves OS and DFS and reduces the incidence of cranial metastases. The N stage, smoking, and gender all have a significant impact on survival.

AUTHORS' CONTRIBUTION

FÇ: Conceptualization, Data curation, Writing – original draft. **MA:** Data curation, Writing – original draft. **SD:** Data curation. **AŞ:** Data curation. **ŞA:** Conceptualization. **ÖÖ:** Formal Analysis.

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