Combined SCLC clinical and pathological aspects

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Abstract

Combined small cell lung carcinoma (C-SCLC) is rare and accounts for 1-3% of all lung cancer cases. Although its incidence has increased recently, there are limited studies on it. The records of patients admitted to our hospital between January 2015 and December 2019 and diagnosed with histologically proven combined small cell were scanned retrospectively and reviewed. 31 patients were analyzed. The average follow-up time was 10 months. The radiotherapy (RT) rate, surgery rate, and large cell malignancy rate were significantly lower in the ex group than in the living group (p=0.024, p=0.023, p=0.015). The rates of extensive disease, metastasis, and thyroid transcription factor 1 (TTF1) were significantly higher in the old group than in the living group (p=0.000, p=0.000, p=0.029, respectively). In the univariate model, sequential RT, fatigue, lactate dehydrogenase (LDH), stage, metastasis, contralateral lung metastasis, chemotherapy were observed to be significantly effective in predicting survival time (p=0.000, p=0.050, p=0.011, p=0.004, p=0.004, p=0.045, p=0.009). In the multivariate model, independent (p=0.015, p=0.022, p=0.049) efficacy of RT, stage, and chemotherapy in predicting survival was observed. C-SCLC is a specific mixed carcinoma and reports evaluating this type are still scarce. The stage of the disease, radiotherapy and chemotherapy are extremely important in predicting survival.

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Introduction

Lung cancer is one of the leading causes of cancer-related death for both genders worldwide. About 15% of all lung cancers are small cell lung carcinoma (SCLC) cases [1].

Combined small cell lung carcinoma (CSCLC) is a histopathological variant of SCLC. Approximately 10-25% of SCLC cases are combined SCLC. The World Health Organization (WHO) defines CSCLC as small cell carcinoma with an extra component of any non–small cell histologic type. [2]. While adenocarcinoma (ADC), squamous cell carcinoma (SCC), large cell carcinoma (LCC), large cell neuroendocrine carcinoma (LCNEC) components are more common among C-SCLC constituents, these are observed less frequently with giant cell carcinoma (GC) [3]. C-SCLC is diagnosed when ADC, SCC, or sarcomatoid cancer are coupled with SCLC, regardless of cell numbers. For C-SCLC diagnosis, however, at least 10% LCC (or LCNEC) is required. The World Health Organization/International Association for the Study of Lung Cancer (WHO/IASLC) has divided SCLC into three subgroups as pure, mixed and combined small cell carcinomas [4].

In contrast to the recent advances in diagnostic techniques, the incidence of C-SCLC has had an increasing trend [5]. C-SCLC contains various NSCLC components. Therefore, it has significant differences from pure SCLC in terms of biological, clinical, molecular and pathological aspects. Overall, SCLC is the most aggressive of the major types of lung cancer, with the worst long-term prognosis and survival rates [6]. C-SCLC staging, treatment and follow- up are similar to those of SCLC. Currently, C-SCLC is treated with surgery, radiotherapy, and chemotherapy according to SCLC guidelines. Follow-up without treatment quickly results in

death. C-SCLC cases have a better prognosis compared to individuals with pure small cell type cancer who benefit from surgery.

Due to the small number of studies and reports on C-SCLC; clinical aspects, optimized treatment model and prognostic factors are not yet clear. Currently, studies evaluating combined small cell lung carcinoma (C-SCLC) are relatively few and limited. Our study aimed to investigate the clinical aspects and prognostic factors of C-SCLC, as well as the role of multimodality therapy.

Materials and Methods

After Ethics Committee approval, hospital records of histologically combined small cell lung cancer patients over 18 years of age admitted between January 2015 and December 2019 were retrospectively analyzed at Ankara Atatürk Chest Diseases and Chest Surgery Training and Research Hospital starting from January 2020. The demographic, clinical and laboratory parameters, staging status, treatment methods and prognostic data of the patients were reviewed retrospectively. Between these years, 313 patients were diagnosed with small cell lung cancer, while 31 patients were diagnosed with combined small cell lung cancer. Staging includes positron emission tomography (PET) or PET/CT. Brain metastasis was assessed using magnetic resonance imaging (MRI) or computed tomography (CT).

As recommended by the International Association for the Study of Lung Cancer, limited stage TNM is equivalent to stages I-III and comprehensive-stage TNM is equivalent to stage 4 [7]. The requirement for informed consent from the patients was waived off due to the retrospective nature of the study. Confidentiality of patient data was maintained throughout the study.

Statistical analysis

In the descriptive statistics of the data, mean, standard deviation, median minimum-maximum, frequency and ratio values were used. The distribution of variables was measured with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data. Chi-square test was used for the analysis of qualitative independent data, and Fischer test was used when the chi-square test conditions were not met. Cox-regression (univariate-multivariate) and Kaplan Meier were used for survival analysis. SPSS 27.0 program was used in the analysis.

Results

The male/female ratio of our patients was 24/7, and the mean age was 59. The most common symptoms were shortness of breath, cough, chest pain and fatigue. Most of the cases were diagnosed by bronchoscopic biopsy. In the histopathological examination, 15 cases were diagnosed with small cell + squamous cell, 9 cases with small cell + large cell, and 7 cases with small cell+adenocarcinoma (Table 1). Table 1 shows the patients' age, gender, smoking history, symptoms, type of tumor, diagnosis methods, laboratory and

Table 1. Patient baseline data.

			Min-Max	Median	Mean±SD	n-%
Age			44.0-81.0	59.0	60.4±8.4	
Sex	Female	7				22.6%
	Male	24				77.4%
Chemoteraphy	(-)	6				19.4%
	(+)	25				80.6%
Radioterphy	(-)	12				38.7%
	(+)	19				61.3%
Simultaneous KRT	(-)	28				90.3%
	(+)	3				9.7%
Additional malignancy	SCC	15				48.4%
	Large cell	9				29.0%
	Adeno	7				22.6%
Family history	(-)	28				90.3%
	(+)	3				9.7%
Smoking history	(-)	9				29.0%
	(+)	22				71.0%
Cigarette pack (year)			0.0-100.0	40.0	41.0±31.3	
Diagnostic method	FOB	14				45.2%
	FNA	3				9.7%
	EBUS	4				12.9%
	VATS biopsy	2				6.5%
	Wedge resection	8				25.8%
Symptom						
Hemoptysis		2				6.5%
Cough		9				29.0%
Dispne		25				80.6%
Weakness		5				16.1%
		5				16.1%
NLR			0.1-14.3	3.4	4.2±3.1	
CRP			0.0-133.5	3.0	13.0±25.7	
LDH			1.0-2646.0	200.0	381.6±601.9	

treatment methods. The location of the tumor was predominantly the central and right upper lobe. 11 cases had limited disease and the remaining 20 cases had extensive disease. Areas of metastasis at diagnosis were contralateral lung (n=7), bone (n=6), brain (n=5), and liver (n=5). The mean follow-up period of the patients was 10 months (Table 2). Table 2 shows tumor characteristics, location, tumor stages, molecular and pathological aspects, treatments applied, and survival durations. Age, gender distribution, chemotherapy (CT) and concomitant chemoradiotherapy CRT ratio did not differ significantly between the ex and the living groups (p>0.05). The radiotherapy (RT) rate of the ex group was significantly (p=0.024) lower than that of the living group (Table 3). The rate of SCC, adeno additional malignancy did not differ significantly between the ex and the living groups (p>0.05). The large cell malignancy rate of the ex group was significantly (p=0.015) lower than that of the living group (Table 3). There was no significant difference between the family history and smoking history ratio, smoking habit, diagnosis method, symptom distribution, neutrophil to lymphocyte ratio (NLR) , C-reactive protein (CRP) and lactate dehydrogenase (LDH) values (p>0.05) of the ex and living groups (Table 3). Tumor central/peripheral ratio, tumor location, tumor SUV max value, tumor diameter and metastasis area distribution did not differ significantly between the ex and surviving groups (p>0.05) (Table 4). The rate of extensive disease and

Table 2. Tumor characteristics.

			Min-Max	Median	Mean ± SD	n-%
Tumor	Central Peripheral	22 9				71.0% 29.0%
Tumor site	Right up Right mid. Right b. Left up. Left b.	9 8 5 6 3				29.0% 25.8% 16.1% 19.4% 9.7%
Tumor diamater (cm)			1.0-9.0	5.0	4.9±2.3	
Tumor SUV max			6.5-28.3	11.5	12.3±4.7	
Stage	Extensive disease Limited disease	20 11				64.5% 35.5%
Metastazis	(-) (+)	11 20				35.5% 64.5%
Opp. lung		7				22.6%
Liver		5				16.1%
Bone		6				19.4%
Brain		5				16.1%
Pleura		4				12.9%
Pericard		1				3.2%
Spleen		1				3.2%
Abdomen		2				6.5%
Adrenal		4				12.9%
Pleural effusion	(-) (+)	21 10				67.7% 32.3%
EGFR	(-) (+) Not done	24 2 5				77.4% 6.5% 16.1%
ALK	(-) Not done	24 7				77.4% 22.6%
ROS	(-) Not done	24 7				77.4% 22.6%
TTF		18				58.1%
CD 56		19				61.3%
Cytoceratin		0				0.0%
Chromogranin		12				38.7%
Napsin		1				3.2%
Surgery		10				32.3%
Surgery technique	Wedge resection Lobectomy	7 3				22.6% 9.7%
Chemoteraphy	(-) (+)	4 27				12.9% 87.1%
Targeted theraphy	(-) (+)	28 3				90.3% 9.7%
Latest status	Live Exitus	10 21				32.3% 67.7%
Following time (month)			1.0-96.0	10.0	17.5±20.5	

metastasis of the ex group was significantly higher (p=0.000, p=0.000) than that of the living group (Table 4). The rates of pleural effusion, epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), reactive oxygen species (ROS), and CD 56 did not differ significantly (p>0.05) between the ex group and the living group. The thyroid transcription factor 1 (TTF1) rate of the ex group was significantly (p=0.029) higher than that of the living group. The ratio of cytokeratin, chromogranin and napsin did not differ significantly between the ex and the living groups (p>0.05) (Table 4). The surgical rate of the ex group was significantly (p=0.023) lower than that of the living group. Surgical technique distribution, chemotherapy and targeted therapy rates did not differ significantly between the ex and the living groups (p>0.05) (Table 4). In predicting the survival duration in the univariate model; no significant efficacy (p>0.05) of age, gender, sequential chemotherapy, concomitant chemoradiotherapy (CRT), additional malignancy, family history, smoking, diagnostic method, hemoptysis, cough, dyspnea, chest pain, NLR, crp, tumor distribution, tumor location, tumor diameter, tumor SUV max, liver metastases, bone metastases, brain metastases, pleural metastases, pericardial metastases, spleen metastases, abdominal metastases, adrenal metastases, pleural effusion, EGFR, ALK, ROS, TTF1, CD 56, chromogranin, napsin, surgery, surgical technique and targeted therapy were observed. In the univariate model, sequential RT, fatigue, LDH, stage, metastasis, contralateral lung metastasis, chemotherapy were observed to be significantly efficient in predicting survival time (p=0.000, p=0.050, p=0.011, p=0.004, p=0.004, p=0.045, p=0.009 respectively) (Table 5). Significant-independent efficacy of sequential RT, stage, and chemotherapy in predicting survival duration was observed in the multivariate model (p=0.015, p=0.022, p=0.049) (Table 5).

Discussion

Combined SCLCs constitute 10% to 25% of all SCLC cases and are defined by a mixture of pure SCLC and adenocarcinoma, squamous cell, large cell, or sarcomatoid (spindle or giant cell) carcinoma, regardless of the amount of NSCLC [4,8]. The mean age of patients with C- SCLC, which is a histopathological variant of SCLC, is 59-64 [9,10]. The mean age of our patient group was 59, which is in line with this.

C-SCLC patients are predominantly male, with rates ranging from 43% to 82.5% [11,12]. Similarly, the rate was 77.4% for our patient group. Smoking history is obvious in the etiology of C-SCLC. In the analysis performed by Luo *et al*., smoking history was 77.5%, which is similar to the rate in our analysis [10]. NSCLC components in C-SCLC are mainly squamous cell carcinoma and adenocarcinoma [13]. In our study, however, the predominant type was the squamous cell component. SCLC and large cell neuroendocrine carcinoma (LCNEC) include components of other types of lung cancer often described as combined SCLC. Large cell neuroendocrine carcinomas (LCNECs) and small cell lung carcinomas (SCLCs) are high-grade neuroendocrine carcinomas of the lung with very aggressive behavior and poor prognosis [14]. However, in our study, the large cell malignancy rate of the ex group was significantly (p=0.015) lower than that of the living group.

Diagnosis in C-SCLC is mostly made with small samples obtained by bronchoscopic biopsy, transthoracic fine needle aspiration, and cytology. The reason for the low case rates may be

Table 3. Comparison of baseline data ex and living groups.

			Live			Ex		p
		Mean±SD	n-%	Median	Mean±SD	n-%	Median	
Age		63.9±9.6		63.5	58.7±7.4		58.0	0.144*
Sex	Female	3	30.0%		4	19.0%		0.495#
	Male	7	70.0%		17	81.0%		
Chemoteraphy		9	90,0%		16	76.2%		0.634#
Radioteraphy		9	90,0%		10	47.6%		**0.024#**
Simultaneous KRT		1	10.0%		2	9.5%		1.000#
Additional malignancy	SCC	4	40.0%		11	52.4%		0.704#
	Large cell	6	60.0%		3	14.3%		**0.015#**
	Adenocarcinoma	0	0.0%		7	33.3%		0.066#
Familiy history	(-)	8	80.0%		20	95.2%		0.237#
	(+)	2	20.0%		1	4.8%		
Smoking	(-)	2	20.0%		7	33.3%		0.445#
	(+)	8	80.0%		14	66.7%		
Cigarette packs (year)		41.5±30.8		37.5	40.7±32.3		40.0	0.898*
Diagnostic method	FOB	2	20.0%		12	57.1%		0.067#
	FNA	1	10.0%		2	9.5%		1.000#
	EBUS	1	10.0%		3	14.3%		1.000#
	VATS biopsy	1	10.0%		1	4.8%		1.000#
	Wedge resection	5	50.0%		3	14.3%		0.074#
Symptom								
Hemoptysis		1	10.0%		1	4.8%		1.000#
Cough		3	30.0%		6	28.6%		0.935#
Dyspnea		8	80.0%		17	81.0%		1.000#
Weakness		0	0.0%		5	23.8%		0.147#
Chest pain		1	10.0%		4	19.0%		1.000#
NLR		4.0±2.4		4.0	4.2±3.4		3.4	0.833*
CRP		8.3±16.4		2.6	15.2±29.2		5.0	0.583*
LDH		255.8±110.6		228.5	441.6±725.4		200.0	0.735*

due to the small sample size and limited cytological materials. In their study, Fraire *et al.* [15] concluded that the diagnosis rate of C-SCLC is affected by the size and integrity of the biopsy specimen, and the number of pathological sections. Our patient group was mostly diagnosed with bronchoscopic biopsy. The main clinical symptoms of C-SCLC are cough, dyspnea and hemoptysis [16]. In our study, dyspnea was the most prominent symptom. C-SCLC is usually centrally located (59.1%-86.4%). Luo *et al.* [5], found the imaging aspects of the central mass in 86.4% of cases. In our patient group, the central location rate was 71%.

Due to the excellent agreement between the prognosis of SCLC and TNM stage, the International Association for the Study of Lung Cancer recommended the use of the TNM classification system for NSCLC and SCLC in the 7th issue of AJCC [17]. At admission, 60-70% of C-SCLC patients are in the extensive stage [18]. The rate of common disease was 64.5% in our patient group. In our study, the rate of extensive disease and metastasis in the ex group was significantly higher (p=0.000, p=0.000) than that of the living group. Prognostic factors for C-SCLC are primarily stage [15] and type of non-SCLC component [13]. PET-CT has a high sensitivity for staging SCLCs [19]. Although SCLC is sensitive to chemoradiotherapy, survival rates are extremely low due to its high spread rates. When Luo *et al*. [5] summarized the clinical data of 88 patients with C-SCLC, they found the median OS of Stage III and IV patients to be 10 months and 7.8 months, respectively. Similarly, 64.5% of our patients were in the extensive disease group and the mean follow-up period was 10 months.

A number of studies have been conducted to measure the prognostic value of TTF-1 for patients with SCLC. Disease-free survival and overall survival were found to be poor for patients with SCLC TTF-1 expression. The study by Yan *et al*. showed that TTF-1 predicted lower survival in SCLC, which strengthened the prognostic value of TTF-1 [20]. In our study, this result was similar to the literature. The TTF1 rate in the ex group was significantly (p=0.029) higher than that of the living group. Epidermal growth factor receptor (EGFR) mutations are found in NSCLC. Such mutations are rarer in SCLC. Combined SCLC/adenocarcinoma may

Table 4. Comparison of tumor characteristics and treatment ex and living groups.

			Live			Ex		p
			Mean±SD	n-%	Median	Mean±SD	n-%	Median	
Tumor	Central	6		60.0%		16	76.2%		0.353#
	Peripheral	4		40.0%		5	23.8%		
Tumor site	Right up	2		20.0%		7	33.3%		0.677#
	Right mid.	3		30.0%		5	23.8%		1.000#
	Right b.	2		20.0%		3	14.3%		1.000#
	Left up	2		20.0%		4	19.0%		1.000#
	Left b.	1		10.0%		2	9.5%		1.000#
Tumor diamater (cm)			4.6±2.7		4.5	5.0±2.1		5.0	0.591*
Tumor SUV MAX			14.6±6.7		12.6	11.2±3.0		11.0	0.254*
Stage	Extensive disease	2		20.0%		18	85.7%		**0.000**#
	Limited disease	8		80.0%		3	14.3%		
Metastasis	(-)	8		80.0%		3	14.3%		**0.000**#
	(+)	2		20.0%		18	85.7%		
Opp. lung		1		10.0%		6	28.6%		0.248#
Liver		1		10.0%		4	19.0%		0.522#
Bone		1		10.0%		5	23.8%		0.634#
Brain		0		0.0%		5	23.8%		0.147#
Pleura		0		0.0%		4	19.0%		0.277#
Pericard		0		0.0%		1	4.8%		1.000#
Spleen		0		0.0%		1	4.8%		1.000#
Abdomen		0		0.0%		2	9.5%		1.000#
Adrenal		0		0.0%		4	19.0%		0.277#
Pleural effusion		1		10.0%		9	42.9%		0.067#
EGFR		0		0.0%		2	11.8%		0.529#
ALK		0		0.0%		0	0.0%		0.248#
ROS		0		0.0%		0	0.0%		0.248#
TTF1		3		30.0%		15	71.4%		**0.029**#
CD 56		5		50.0%		14	66.7%		0.373#
Cytoceratin		0		0.0%		0	0.0%		1.000#
Chromogranin		4		40.0%		8	38.1%		0.919#
Napsin		0		0.0%		1	4.8%		1.000#
Surgery		6		60.0%		4	19.0%		**0.023**#
Surgery technique	Wedge resection	5		50.0%		2	9.5%		0.500#
	Lobectomy	1		10.0%		2	9.5%		
Chemoteraphy		10		100.0%		17	81.0%		0.277#
Targeted theraphy		0		0.0%		3	14.3%		0.274#

*Mann-Whitney U test; #chi-square test; bold indicate significant values: p<0.05.

include EGFR mutations in patients with a slight smoking history. In some studies, EGFR mutations were found to be 15% in C-SCLC [21]. In our study, a positivity rate was found in 2 patients (7.6%) out of 26 patients whose EGFR was analyzed. Pleural effusion rate, EGFR rate, ALK rate, ROS rate, CD 56 rate did not differ significantly (p>0.05) between the ex group and the living group in our study.

Although C-SCLC is very sensitive to chemotherapy and radiotherapy, it relapses very quickly and becomes resistant to treatment within 1-2 years. C-SCLC is treated according to SCLC guidelines with commonly used multimodality therapy (surgery, radiotherapy, and chemotherapy). Patients in the limited stage are usually treated with combined treatment modalities, while chemotherapy is used in the extensive stage. Platinum-based regimens are preferred because of their long survival and high response rates. While the SCLC component of C-SCLC responds well to

Table 5. Univariate *vs* multivariate model comparison.

	Univariate model			Multivariate model		
	HR	%95 GA	p	HR	%95 GA	p
Age	0.964	0.912-1.019	0.196			
Sex	1.094	0.362-3.304	0.873			
Chemoteraphy	0.356	0.121-1.049	0.061			
Radioteraphy	0.135	0.045-0.406	**0.000**	0.241	0.076-0.762	**0.015**
Simultaneous KRT	1.244	0.280-5.521	0.774			
Additional malignancy	1.717	0.958-3.078	0.070			
Family history	0.444	0.059-3.350	0.431			
Smoking	0.585	0.229-1.495	0.263			
Cigarette packs (year)	0.993	0.978-1.008	0.354			
Diagnostic method	0.832	0.620-1.118	0.223			
Hemoptysis	1.296	0.170-9.884	0.802			
Cough	1.330	0.502-3.520	0.566			
Dyspneae	0.552	0.176-1.726	0.307			
Weakness	2.864	1.002-8.185	**0.050**			
Chest pain	2.674	0.851-8.400	0.092			
NLR	1.023	0.880-1.189	0.767			
CRP	1.004	0.990-1.019	0.545			
LDH	1.001	1.000-1.002	**0.011**			
Tumor distribution	0.804	0.287-2.250	0.678			
Tumor site	0.895	0.629-1.272	0.535			
Tumor size (cm)	1.099	0.908-1.329	0.334			
Tumor SUV MAX	0.910	0.805-1.030	0.135			
Stage	0.051	0.007-0.392	**0.004**	12.02	1.42-101.64	**0.022**
Metastasis	19.638	2.548-151.332	**0.004**			
Opp. lung	2.801	1.022-7.681	**0.045**			
Liver	1.790	0.591-5.427	0.303			
Bone	2.014	0.720-5.628	0.182			
Brain	2.642	0.936-7.453	0.066			
Pleura	2.558	0.811-8.070	0.109			
Pericard	1.651	0.216-12.595	0.629			
Spleen	3.447	0.431-27.584	0.244			
Abdomen	2.312	0.520-10.277	0.271			
Adrenal	2.944	0.944-9.185	0.063			
Pleural effusion	1.926	0.776-4.781	0.158			
EGFR	1.433	0.843-2.436	0.184			
ALK	1.495	0.913-2.446	0.110			
ROS	1.495	0.913-2.446	0.110			
TTF1	2.177	0.831-5.705	0.113			
CD 56	2.103	0.752-5.884	0.157			
Chromogranin	0.837	0.333-2.103	0.704			
Napsin	3.447	0.431-27.584	0.244			
Surgery	0.293	0.085-1.007	0.051			
Surgical technique	1.194	0.108-13.167	0.885			
Chemoteraphy	0.205	0.063-0.668	**0.009**	0.269	0.072-0.998	**0.049**

Cox-regression (forward LR); bold indicate significant values: p<0.05.

chemotherapy, the NSCLC component increases. For this reason, C-SCLC is considered to be resistant to chemotherapy [22]. Studies have shown that surgical treatment, especially lobectomy, results in local control, and the survival rate is higher for these patients [23,24]. In line with this, the surgical rate in the ex group was significantly (p=0.023) lower than that of the surviving group in our study.

Lactate is up regulated by LDH by tumor cells. It is known that a high LDH level is a poor prognostic factor in small cell lung carcinoma. Elevated LDH levels can be associated with tumor mass and amount. For our patients, LDH levels were high in the ex group and provided a poor prognosis. These results are consistent with previous reports [25].

In our study, significant efficacy of sequential RT, fatigue, LDH, stage, metastasis, contralateral lung metastasis, and chemotherapy in predicting survival time in a univariate model was observed (p=0.000, p=0.050, p=0.011, p=0.004, p=0.004, p=0.045, p=0.009, respectively). In our study, significant-independent efficacy of sequential RT, stage, and chemotherapy was observed in predicting survival duration in a multivariate model (p=0.015, p=0.022, p=0.049).

Combined SCLC histology is uncommon, accounting for 10% to 25% of all SCLC cases. C-SCLC is a kind of mixed carcinoma that has received little research attention. It's critical to figure out what type of mixed histology you have because it can alter your chances of survival.

Small cell lung cancer is treated similarly to mixed type small cell lung cancer in terms of diagnosis, treatment, and follow-up. High TTF1 and LDH levels, as indicated in our study, are poor prognostic markers, as are advanced stage and the existence of metastases. Survival is highly dependent on the stage of the disease, radiation, and chemotherapy. To better understand clinical behavior and prognosis, multicenter researches are required.

Our study has several limitations, including a single-center design, retrospective analysis, and a small sample size. However, these observations should be developed in larger scale studies.

In the future, we expect that novel chemotherapeutic medications and targeted agents will have an impact on response rates and survival in this patient group.

Referances

1. Jackman DM, Johnson BE. Small-cell lung cancer. Lancet 2005;366:1385-96.
2. Travis WD. Update on small cell carcinoma and its differentiation from squamous cell carcinoma and other non-small cell carcinomas. Mod Pathol 2012;25:S18–30.
3. Travis WD. The 2015 WHO classification of lung tumors. Pathologe 2014;35:s188.
4. Trawis WD, Brambilla E, Müler-Hermelink K, et al. Tumors of the lung. In: World Health Organization classifications of tumors, pathology and genetics, tumors of the lung, pleura, thymus and heart. Lyon: IARC; 2004. p. 9-124.
5. Luo J, Ni J, Zheng H. Clinical analysis of 88 cases with combined small cell carcinoma. Zhong Liu 2009;29:156–9.
6. Travis WD, Travis LB, Devesa SS. Lung cancer. Cancer 1995;75:s191-202.
7. van Meerbeeck JP, Fennell DA, De Ruysscher DKM. Small-cell lung cancer. Lancet 2011;378:1741–55.
8. Travis WD, Brambilla E, Burke AP, et al. WHO Classification of tumours of the lung, pleura, thymus and heart. 4th Ed. Geneva: WHO; 2015.
9. Babakoohi S, Fu P, Yang M, et al. Combined SCLC clinical and pathologic characteristics. Clin Lung Cancer 2013;14:113–9.
10. Luo Y, Hui Z, Yang L, et al. [Clinical analysis of 80 patients with combined small-cell lung cancer].[Article in Chinese]. Zhongguo Fei Ai Za Zhi 2015;18:161–6.
11. Zhang C, Yang H, Zhao H, et al. Clinical outcomes of surgically resected combined small cell lung cancer: a two-institutional experience. J Thorac Dis 2017;9:151–8.
12. Wallace AS, Arya M, Frazier SR, et al. Combined small-cell lung carcinoma: an institutional experience. Thorac Cancer 2014;5:57–62.
13. Lvu X, Sun LN, Zhan ZL, et al. [Clinicopathological characteristics and prognosis of combined small cell lung cancer].[Article in Chinese]. Zhongguo Zhong Liu Lin Chuang 2011;38:769–72.
14. Lantuejoul S, Fernandez-Cuesta L, Damiola F, et al. New molecular classification of large cell neuroendocrine carcinoma and small cell lung carcinoma with potential therapeutic impacts. Transl Lung Cancer Res 2020;9:2233.
15. Fraire AE, Johnson EH, Yesner R, et al. Prognostic significance of histopathologic subtype and stage in small cell lung cancer. Hum Pathol 1992;23:520–8.
16. Men Y, Hui Z, Liang J, et al. Further understanding of an uncommon disease of combined small cell lung cancer: clinical features and prognostic factors of 114 cases. Chin J Cancer Res 2016;28:486–94.
17. Goldstraw P. IASLC staging handbook in thoracic oncology. Editorial Rx Press; 2009.
18. Fushimi H, Kikui M, Morino H, et al. Histologic changes in small cell lung carcinoma after treatment. Cancer 1996;77: 278-83.
19. Bradley JD, Dehdashti F, Mintun MA, et al. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. J Clin Oncol 2004;22:3248-54.
20. Yan L, X Liu, YH Li, et al. Prognostic value of delta like protein 3 combined with thyroid transcription factor-1 in small-cell lung cancer. Oncol Lett 2019;18:2254-61.
21. Tatematsu A, Shimizu J, Murakami Y, et al. Epidermal growth factor receptor mutations in small cell lung cancer. Clin Cancer Res 2008;14:6092–6.
22. Cooper S, Spiro SG. Small cell lung cancer. Treatment review. Respirology 2006;11:241-8.
23. Schreiber D, Rineer J, Weedon J, et al. Survival outcomes with the use of surgery in limited-stage small cell lung cancer: should its role be re-evaluated? Cancer 2010;116:1350–7.
24. Varlotto JM, Recht A, Flickinger JC, et al. Lobectomy leads to optimal survival in early-stage small cell lung cancer: a retrospective analysis. J Thorac Cardiovasc Surg 2011;142:538–46.
25. Maestu I, Pastor M, Gomez-Codina J, et al. Pretreatment prognostic factors for survival in small-cell lung cancer: a new prognostic index and validation of three known prognostic indices on 341 patients. Ann Oncol 1997;8:547-53.