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Original Article

A Retrospective Study of Epidemiology and Prognostic factors of Small cell lung cancer

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ABSTRACT

Background: Lung cancer has been the most common cancer overall for several decades. According to the last data of GLOBOCAN series of the International Agency for Research on Cancer there were estimated 1.8 million new cases in 2012 of which 1.2 million cases estimated to occur in males with lower incidence rate in females about 583,000 cases.
Aim of the work: This study aims to ascertain retrospectively the epidemiology and prognostic factors of small cell lung cancer (SCLC) and also highlights the outcomes in the terms of overall survival (OS) and progression free survival (PFS) among Egyptian patients at clinical oncology and nuclear medicine department, Ain Shams university hospitals
Results The files of 56 patients with SCLC were reviewed. 17 patients were excluded from analysis due to insufficient data in the files. Among the 39 patients in the study, 32 patients received active treatment, while 2 patients received only WCI as palliative intent, 2 patients received best supportive care treatment as they were not fit for treatment (PS: 3-4) and 3 patients didn't receive treatment as they lost follow up before starting treatment.
Conclusion: SCLC is usually diagnosed in advanced stage and No great improvement in survival over the past years, so, health care centres should monitor the efficacy of their management plans by comparing survival outcomes with other centres. Prognostic factors are essential in better understanding the treatment outcome in terms of OS and PFS.

Keywords
Small cell lung cancer,
Neuroendocrine tumors,
Prognostic factors

INTRODUCTION

Lung cancer has been the most common cancer overall for several decades. According to the last data of GLOBOCAN series of the International Agency for Research on Cancer there were estimated 1.8 million new cases in 2012 of which 1.2 million cases estimated to occur in males with lower incidence rate in females about 583,000 cases [1].

More than sixty percent of diagnosed lung cancer cases occur at the age of 65 or older. Less than two percent of cases occur in people under the age of 45 years. The average age of lung cancer diagnosis is at the age of 70[2].

Egypt was completely lacking incidence rates at national level till the national population based cancer registry program was offered. Lung cancer occupied third or fourth rank representing 5-7%of cancers [3].

About 37.8 million people smoke cigarettes in the United states [4]. Smoking is responsible for more than 480,000 deaths per year. This is about 1,300 deaths every day. Smoking is the main risk factor for lung cancer. About 80% of all lung cancer deaths are thought to result from smoking [5].

Second hand smoking, radon, outdoor air pollution, cooking oil fumes, coal fumes, and asbestos play a role in carcinogenesis of lung cancer in non smokers[6].

Typically SCLC presents as a huge hilar mass and bulky mediastinal lymphadenopathy that cause dyspnea and cough. Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss,, bone pain, and neurological compromise[7].

Diagnosis

is essential for treatment planning, and tissue diagnosis is required to assess whether the tumour is a primary malignancy, a pulmonary metastasis from another site, or possibly a non-malignant growth [87].

SCLC treatment remains challenging. The prognosis is still unfa-

vorable, with the median survival time ranging from 15 to 20 months for limited disease (LD) SCLC and 8 to 13 months for extensive disease (ED) SCLC [9].

LD SCLC is a potentially curable disease when it is aggressively and rapidly treated with concurrent chemo-radiotherapy. Surgery is rarely indicated, because most patients present in advanced stages or with extensive disease. In retrospective studies patients with stage I (T1–2N0M0) that undergo lobectomy, and with no mediastinal and supraclavicular lymphadenopathy, long-term overall survival (OS) is forty to sixty percent[10].

SCLC is sensitive to chemotherapy with rapid response to treatment. Even in emergency situations with superior vena cava syndrome rapid start of chemotherapy is preferred over radiological intervention [9].

The incidence of brain metastases is high (around 50%) in patients with small-cell lung cancer and therefore Prophylactic Cranial Irradiation (PCI) should be considered in patients who have achieved a partial or complete response to treatment to reduce the risk of cerebral metastases and improve overall survival [4]. With prophylactic cranial irradiation the risk of brain metastases can be reduced from 59% to 33% at 3 years and is accompanied by a survival benefit (21% *versus* 15%) [4].

Most patients relapse with relatively resistant disease, these patients have a median survival of only 4 to 5 months when treated with further systemic therapy[11].

Subsequent systemic therapy provides significant palliation in many patients, although the likelihood of response is highly dependent on the time from initial therapy to relapse if this interval is less than 3 months (refractory or resistant disease), response to most agents or regimens is poor (≤10%). If more than 3 months have elapsed (sensitive disease), expected response rates are approximately 25%. If patients relapse more than 6 months after first-line treatment, then treatment with their original regimen is recommended[12].

PATIENTS AND METHODS

Study design and Data selection: The study involved 39 patients with histologically confirmed Non-small cell lung cancer of any stage, aged 18 years or above, treated between January 1, 2014 and June 31, 2017, in thoracic oncology and chemotherapy units, department of clinical oncology and nuclear medicine, Ain Shams University hospitals, Cairo, Egypt. Patients were retrospectively reviewed to ascertain the epidemiology and prognostic factors of SCLC and also highlights the outcomes in the terms of overall survival (OS) and progression free survival (PFS). The clinical records of the patients were revised for epidemiological factors (sex, residence),patient factors (age, smoking and co morbidities),tumor factors (VALSG staging system),treatment factors (type of treatment) and examined outcome parameters will include (response to treatment according to RESIST response criteria after 2 weeks of last cycle chemotherapy and 6 weeks after last radiotherapy fraction, progression free survival, and overall survival. The study was approved by the Ethics Board of Ain Shams University and an informed written consent was taken from each participant in the study. *Data Analysis:* Statistical Analysis Software (IBM SPSS, version 20) was used for data analysis. First, descriptive analysis for the whole study population was done using count and percentage for categorical variable and mean ±SD for quantitative variables. Univariate frequency analysis was performed using Chi-square test and Fisher exact test for categorical variables and independent-t test and paired-t test for numerical variables. Statistical significance was established at a p-value of less than 0.05.

RESULTS

Descriptive analysis

The files of 56 patients with SCLC were reviewed. 17 patients were excluded from analysis due to insufficient data in the files.

I-Patients' Characteristics

Table 1. Patients descriptive characteristics.

	Frequency	Percent
Age		
Mean	61.69	
Median	62.00	
Gender		
Males	35	89.7
Females	4	10.3
Residency		
Urban	34	87.2
Rural	5	12.8
Smoking		
Yes	33	84.6
No	6	15.4
Performance		
1	21	53.8
2	16	41
3	1	2.6
4	1	2.6
Co morbidities		
DM	8	20.5
Hypertension	7	17.9
IHD	5	12.8
No co morbidities	28	71.8

IHD: ischemic heart disease, DM: diabetes milletus

II-Disease characteristics:

All patients were staged according to VALSG staging system and it was found that 10 patients had limited stage disease meanwhile 29 patients had extensive stage

Table 2. Disease distribution among patients

	Frequency	Percent
Extensive	29	74.4
Limited	10	25.6

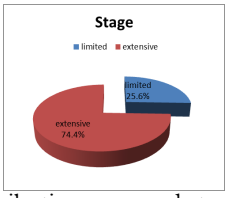


Fig.1. Disease's distribution as regard stage

III- treatment details:

All patients were treated by multi disciplinary approach according to patient's and disease's characteristics.

Among the 39 patients in the study, 32 patients received active treatment, while 2 patients received only WCI as palliative intent, 2 patients received best supportive care as they were not fit for treatment (PS: 3-4) and 3 patients didn't receive any treatment as they lost follow up before starting treatment.

Regarding the primary chemotherapy agents,23 patients received vepsid- cisplatin (8 patients were limited stage and 15 patients were extensive stage), meanwhile 9 patients received vepsid- carboplatin (2 patients were limited and 7 patients were extensive).

Seven patients with limited stage disease received thoracic with total dose 60 Gy. Five patients only received PCI following the thoracic irradiation, the total dose was 25Gy.

Table 2. Response to treatment

	Frequency	Percent
CR	2	6.3
PD	9	28.1
PR	11	34.4
SD	1	3.1
Unknown	9	28.1

CR: complete response - **PR**: partial response - **SD**: stable disease- **PD**: progressive disease. N.B: Patients with unknown response lost follow up before evaluation.

Regarding second line chemotherapy which used in patients with disease progression, only 5 patients received second line treatment only, as the rest of the patients with disease progression had lost follow up.

Table 3. Secondary chemotherapeutic agents type

	Frequency	Percent
Irinotecan	1	2.6
Paclitaxel	1	2.6
Docetaxel	3	7.7
None	34	87.1

Response to the second line treatment was recorded in 3 patients with disease progression and the rest of patients did not do evaluation and lost follow up.

Regarding palliative radiotherapy, 4 patients received palliative bone radiotherapy, 2 patients received mediastinal radiotherapy, 4 patients received whole cranial irradiation.

Table 4. Palliative radiotherapy

	Frequency	Percent
None	29	74.3
Bone	4	10.2
Mediastinum	2	5.1
WCI	4	10.2

Statistical analysis

I-Progression free survival (PFS)

For the 32 patients the median progression free survival (PFS) was 10.6 months and the mean was 10.4 months (95% confidence interval: 7.92-13.05) **Fig(2).**

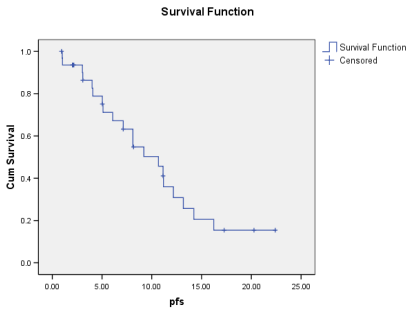


Fig. 2. PFS of patients group who received primary treatment.

Relation between PFS in months and significant variables

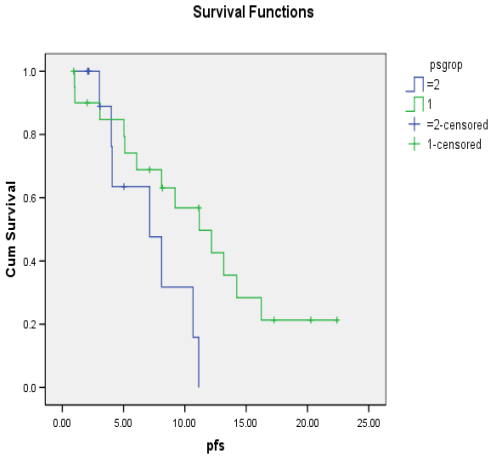
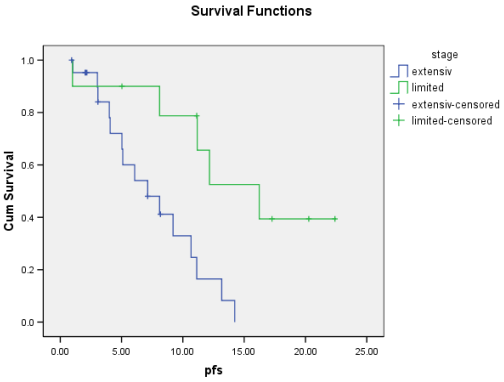


Fig. 3. Relation between performance and PFS in months.



II– I

Fig. 4. Relation between stage and PFS in months

Table 5. The relation between patients' variables and PFS in months

Variable	PFS in months (95% CI)			p value
	Group	Mean	Median	
Age (years)	≤ 60	10.359	8.100	.993
	> 60	10.297	11.130	
Gender	Females	13.887	16.230	.441
	Males	10.065	8.100	
Smoking	Yes	10.007	8.100	.449
	No	12.575	11.170	
Co morbidities	Yes	10.879	11.130	.589
	No	9.980	8.100	
Performance status	1	11.689	11.170	**.045**
	2	7.239	7.130	
Stage	Limited	15.025	16.230	**.005**
	Extensive	7.639	7.130	
1ry chemotherapy type	vep-cis	10.751	10.670	.783
	vep-carb	9.264	5.100	
Thoracic irradiation for	Yes	15.621	16.230	.963
	No	11.847	not reached	

Chi-Square test was used to assess the relationship between the different patients' variables and overall survival and progression free survival

II- Overall survival (OS):

For the 39 patients (whole group), the median OS 11.17 (95% CI: 4.3-18) and the estimated mean was 14.5 months (95% CI: 11.3-17.6).

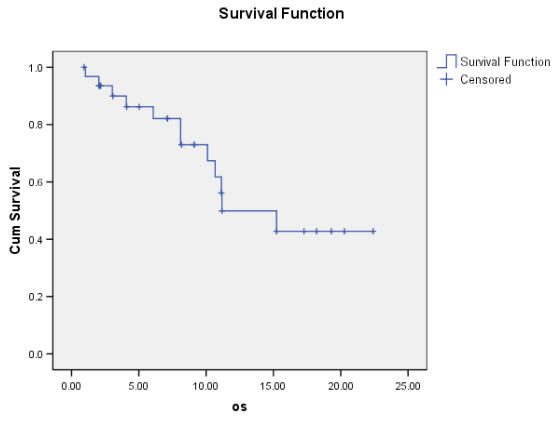


Fig.5. OS in months for the whole group.

Table 6. Relation between different patients' variables and OS in months

Variable	OS in months (95% CI)			p value
	Group	Mean	Median	
Age (years)	≤ 60	16.460	Not reached	.250
	> 60	12.1	10.6	
Sex	Females	15.235	11.170	.419
	Males	14.038	11.130	
Smoking	Yes	13.550	11.130	.20
	No	16.590	Not reached	
Co morbidities	Yes	11.5	11.1	0.75
	No	14.8	15.2	
Performance status	1	16.8	Not reached	**.01**
	2	8.4	10.5	
Stage	Limited	19.0	not reached	**.002**
	Extensive	10.2	10.6	
1ry chemotherapy type	vep-cis	14.0	11.1	.72
	vep-carb	13.0	Not reached	
Thoracic irradiation for limited stage	Yes	20.6	not reached	.41
	No	12.1	not reached	

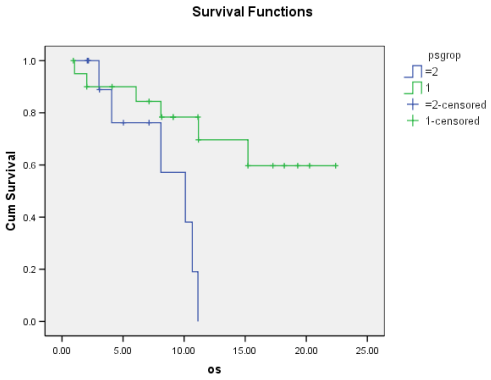


Fig.6. Relation between PS and OS in months

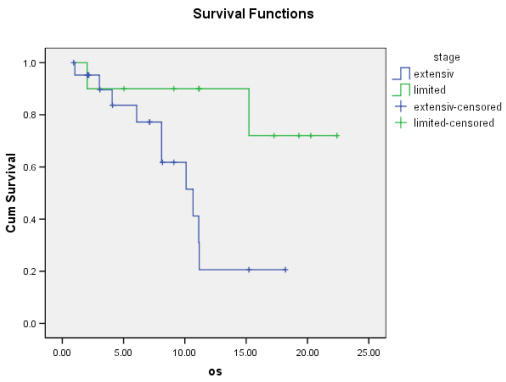


Fig.7. Relation between stage and OS in months

DISCUSSION

Our retrospective study was conducted to study the epidemiology of SCLC and different factors that affect prognosis. It was conducted over 39 patients diagnosed with SCLC presented to clinical oncology department at Ain-shams university hospitals. All patients records were reviewed from January 2014 to June 2017 .

In our study the mean age at diagnosis of the study population was 61 years. As compared to UK, in 2013-2015, annually more than 44% of new cases of lung cancer were in people aged 75 and over **(11).**

In the USA, Lung cancer mainly occurs in older people. Most people diagnosed with lung cancer are 65 or older, while a very small number of people diagnosed are younger than 45. The average age at the time of diagnosis is about 70 **(12).**

Smokers were more prone to lung cancer in our study, in which 84% of the patients were smokers and the smoker: non-smoker ratio was 5.5:1.This ratio was higher than that reported by Akl *et al.* (13), a study in Cairo with smoker to non smoker ratio 3:1. Rawat et al. (14) in India estimated the ratio as 4.5:1. Higher ratio was also reported by Agarwala *et al.* (15) (7.8:1).

The percentages of SCLC represented by limited- and extensive -stage subtypes in relation to each other have not changed significantly. The increase in overall percentage of staged patients is a reflection of the increased use of staging investigations in 2002 compared with in 1973. In 1973, 32.5% of SCLC patients had limited-stage disease, 49.5% of patients had extensive-stage disease, and 17.9% of patients were un-staged. In 2002, a similar pattern emerged: 39.6% of patients were staged with limited -stage disease and 56.6% of patients were staged with extensive -stage disease, and only 3.8% of patients were left un-staged **(16).**

Regarding staging, in our study all patients were staged according to VALSG staging system and it is found that 26% patients were limited stage disease meanwhile 74% patients were extensive stage. Neal *et al.* (17), reported that the proportion of SCLC patients diagnosed with ES-SCLC increased from 50% to 75%, which is explained by using the modest staging tools (PET-CT and MRI brain).

In our study the majority of the patients (about 74%) presented with extensive disease and this may be due to lack of patients' education or lack of clinical suspicion in healthcare professionals with poor referral to speciality centres.

As SCLC is a systemic disease, chemotherapy plays an important role in the treatment. Four to six cycles of a platinum-based chemotherapy doublet is recommended usually, and many studies have demonstrated that less than 4 cycles of chemotherapy could incur a poor prognosis **(18).**

Among our patients, 32 patients received 1ry chemotherapeutic agent in which about 32% were limited disease and 68% were extensive disease, with 100% of limited disease patients and 75% of extensive patients received chemotherapy. However, these proportions are relatively different from one observational study**(19)** in which 81% of patients with limited disease and 77% of patients with extensive disease received chemotherapy. This discrepancy may be due to small sample size of our study .

Once the diagnosis of LD-SCLC is established the standard treatment for fit patients will be concurrent chemo-radiotherapy **(20).** Unfortunately in our study only 7 patients with limited disease received radiotherapy as most of the patients were unfit or extensive disease at presentation.

Turrisi *et al.* **(21)**, reported a 5-year overall survival benefit of 10% with four cycles of EP and concurrent twice-daily (1.5 Gy twice daily, 45Gy/30 fractions) when compared to once-daily radiotherapy (1.8 Gy, 45Gy/25 fractions).

Since then, the radiotherapy doses used in standard fractionation have increased to ~60–66 Gy and a direct comparison between the higher dose standard fractionation and the twice-daily schedule was missing. The potential inconvenience of twice-daily administration and the significantly increased rates of transient grade 3 esophagitis were the main concerns that explain why the twice-daily regimen was not universally adopted **(22).**

With prophylactic cranial irradiation (PCI), the risk of brain metastases can decrease from 59% to 33% at 3 years and is accompanied by a absolute survival benefit 6% (21% versus 15%) **(4).**PCI should be considered part of standard treatment in patients with LD-SCLC with partial or complete response to ini-

tial treatment .

Only five patients in our study received PCI following the thoracic irradiation and the rest of the patients didn't receive. This may be explained by disease progression and losing follow up.

The PCI standard dose is 25 Gy in 10 fractions. Higher doses do not improve outcome, but increase mortality and chronic **neurotoxicity [23].**

Also Péchoux *et al.* [24]reported that the preferred dose for PCI is 25 Gy in 10 daily fractionation, and patients receiving a dose of 36 Gy had higher mortality and higher chronic neurotoxicity compared to patients treated with 25 Gy.

Regarding the response rate for treatment, 6.3% of patients achieved CR,34.4% of patients achieved PR, 3.1% of patient achieved SD and 28.1% of patients achieved PD, in contrast to a Japanese retrospective study which revealed that 68% of patients had a PD following treatment **[19].**

The rest of the patients (28.1%) unfortunately lost follow up post chemotherapy without radiological evaluation. This is considered a drawback in our study.

Only 5 patients (12.9%) in our study received second line treatment, in contrast to **Seigo *et al.*** [19] that revealed 55% of the patients received second line treatment, and that's due to most of the patients lost follow up in our study.

Sixty percent of the patients who received second line treatment achieved PD, in contrast to the same study that held in Japan that showed 90% of the patients had disease progression **[19].** This may be attributed to the small sample size of our study.

SCLC has a poor prognosis because it tends to metastasize very rapidly. Brain metastases are common in patients with SCLC. About 15%-20% of SCLC patients had detectable brain metastases at the time of initial diagnosis. During the course of the disease the occurrence of brain metastasis is even higher with a cumulative risk around 50% at 2 year **[25].**

But this data was different in our study, in which at time of diagnosis there was only 3 patients out of 39 (about 7%) presented with brain metastasis, and during the course of the disease only 1 patient (about 2%) developed brain metastases. This may be due to our policy in our department which doesn't necessitate doing brain imaging for all patients at time of diagnosis .

In our study, the median OS for limited stage was not reached due to censored data and for extensive stage it reached 10.6 months with better OS survival in limited disease patients and significant p value:0.002. Meanwhile, the estimated median PFS was better in patients with limited disease (16 months) than those who are extensive(7.1 months) (95% confidence interval 9.6-22.8) with a significant P value 0.005.

In comparison to a study held in China, the median survival was 26.2 months and progression free survival time was 13.7 months in limited stage **[4].**

CONCLUSION

SCLC is usually diagnosed in advanced stage and no great improvement in survival over the past years was achieved. Health care centres should monitor the efficacy of their management plans by comparing survival outcomes with other centres . Prognostic factors are essential in better understanding the treatment outcome in terms of OS and PFS.

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