Outcomes and Prognostic Factors of Small Cell Lung Cancer: A Retrospective Study

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Abstract

Background: Small cell lung cancer (SCLC) is a high grade neuroendocrine tumor, and has aggressive nature, so the majority of cases are presented with extensive disease. SCLC was staged into 2 categories: limited-stage disease (LS-SCLC) and extensive disease (ES-SCLC). Despite SCLC is sensitive to radiotherapy and chemotherapy, SCLC has high tendency for rapid dissemination to regional and distant sites. Median survival time ranged from 2 - 4 months in patients with untreated SCLC. Multiagent chemotherapy was the primary treatment for SCLC.

Aim of the work: This retrospective study was conducted to evaluate and analyze clinical features, treatment outcome, survival and prognostic factors affecting survival in patients with SCLC presented to Clinical Oncology and Nuclear Medicine department, Chest department and Medical oncology unit in Mansoura Oncology Centre during the period from 2000-2015.

Methods: Data of patients were collected from their files. The information obtained included demographic features, treatment received; its toxicity and outcome, survival and its prognostic factors. Several factors affecting survival were analysed as age, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), smoking status, stage of disease. Data also included disease presentation and metastatic sites. Strong male predominance (92.1%) was observed; 84.1% of them were smoker.

Results: Sixty-three patients were enrolled in this study. Median age was 56.2 ± 6. Strong male predominance (92.1%) was observed; 84.1% of them were smokers. Thirty six patients (57.2%) were of ECOG-PS of 0 - 1. ES-SCLC was reported in 65% of cases and LDH was high (>1.5 xN) in 47.6%. The most common symptom was chest pain (38.1%) followed by cough (31.8%), weight loss (30%). Fifteen patients had single metastatic site (23.8%) and bone was...
the most common site of metastasis (reported in 8 patients) followed by brain, lung and liver. 2-year overall survival rate was 35% with median survival time of 14 months. On multivariate analysis, there were significantly higher survival in patients aged < 65 years (P = 0.03), female gender (P = 0.04), LD-SCLC (P = 0.03), good performance status (P = 0.04), low LDH level (P = 0.02) and non-smoker (P = 0.04). **Conclusion:** This clinic-co-epidemiologic study provides multiple prognostic factors that have important impact on survival as age, sex, LDH level, stage, smoking and performance status. Larger number of patients and prospective studies are needed to clarify more prognostic factor.

**Keywords**

SCLC, Lung Cancer, LS-SCLC, ES-SCLC

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**1. Introduction**

In both men and women, lung cancer is the most common malignancy and accounts for 18% of deaths worldwide [1]. There are 2 different pathological types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The prevalence of SCLC is 15% - 20% and associated with cigarette smoking [2]. SCLC is a high grade neuroendocrine tumor, has aggressive nature. So the majority of cases are presented by extensive disease [3]. SCLC was staged into 2 categories; limited-stage disease (LS-SCLC) and extensive disease (ES-SCLC). LS-SCLC is confined to one hemithorax, regional mediastinal lymph nodes and ipsilateral supraclavicular lymph nodes [4]. When patients have disease spread beyond supraclavicular areas, they are classified as ES-SCLC [5]. Despite SCLC is sensitive to radiotherapy and chemotherapy, SCLC has high tendency for rapid dissemination to regional and distant sites [6]. Median survival time ranged from 2 - 4 months in patients with untreated SCLC [7]. Multiagent chemotherapy was the primary treatment for SCLC [8]. Because of recurrence at disease site in LS-SCLC, thoracic radiotherapy (TRT) was added to decrease intrathoracic failure [9]. Arriagada et al. [10] reported 3-year survival rate of 8.9% with chemotherapy alone versus 14.3% with chemoradiotherapy. For ES-SCLC combined chemotherapy is the standard treatment and radiotherapy is recommended to cure metastasis or to relieve pain [11] [12]. However, addition of TRT in some patients was suggested as it was found to improve overall survival [13] [14]. Brain is the most common site for distant failure and associated with poor survival ranged from 4 - 6 months only [15] [16]. So in SCLC, prophylactic cranial irradiation (PCI) has been established for patients with complete or partial response to chemotherapy [17] [18] [19].

This retrospective study was conducted to evaluate and analyze clinical features, treatment outcome, survival and prognostic factors affecting survival in patients with SCLC.
2. Patients and Methods

Medical records of all patients with SCLC presented to Clinical Oncology and Nuclear Medicine department, Chest department and Medical oncology unit in Mansoura Oncology Centre, Mansoura University during the period from 2000-2015 were reviewed.

Data of patients were collected from their files. The information obtained included demographic features, treatment received; its toxicity and outcome, survival and its prognostic factors.

Demographic data were: age, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), smoking status, stage of disease. Data also included disease presentation and metastatic sites.

Patients were evaluated through history, physical examination, radiological and laboratory findings and pathological diagnosis.

Radiological investigations were computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and brain and radionuclide bone imaging. Laboratory tests included complete blood picture, liver and kidney function tests, lactic dehydrogenase (LDH). Bone marrow aspirate and biopsy were indicated if there was pancytopenia or high level of LDH. Any detected effusion on chest radiography was evaluated through cytological examination.

Toxic effects of treatment were assessed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) V3.0.

Response to treatment was assessed through Response Evaluation Criteria in Solid Tumors (RECIST) [20].

During follow-up period; all investigations were repeated every 3 months for 2 years then every 6 months thereafter.

Overall survival (OAS) was calculated from date of pathological diagnosis to date of death or last follow-up.

Several factors affect survival were analysed as age, sex, stage, PS, smoking status and LDH.

Statistical methods: IBM SPSS was used for statistical analysis, data expressed as number and percentile, Chi square test used as a test of significance, P < 0.05 considered significant. Kaplan-Meier test was used for survival function.

Ethical consideration: This study was approved by the Medical Ethics Committee.

3. Results

Sixty-three patients were enrolled in this retrospective study. Their demographic features are summarized in Table 1. Median age was 56.2 ± 6. There were strong male predominance (92.1%) and 84.1% of them were smoker. Performance status of the patients was not very poor as 36 patients (57.2%) were of ECOG-PS of 0 - 1, ES-SCLC was reported in 65% of cases and LDH was high (>1.5 xN) in 47.6%.

The most frequent symptom was chest pain (38.1%) followed by cough (31.8%), weight loss (30%) (Table 2).

Fifteen patients had single metastatic site (23.8%). Bone was the most common
Table 1. Demographic features.

<table>
<thead>
<tr>
<th>Character</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range):</td>
<td>56.2 ± 6</td>
<td>(32 - 78) years</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58</td>
<td>92.1</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>7.9</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>53</td>
<td>84.1</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>15.9</td>
</tr>
<tr>
<td>ECOG-PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11</td>
<td>17.5</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>39.7</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>33.3</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>9.5</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD-SCLC</td>
<td>22</td>
<td>34.9</td>
</tr>
<tr>
<td>ES-SCLC</td>
<td>41</td>
<td>65.1</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>33</td>
<td>52.4</td>
</tr>
<tr>
<td>High</td>
<td>30</td>
<td>47.6</td>
</tr>
</tbody>
</table>

Table 2. Presenting symptom.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>24 (38.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>20 (31.8)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>19 (30.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15 (23.8)</td>
</tr>
<tr>
<td>Hoarsness</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Bone ache</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>5 (7.9)</td>
</tr>
</tbody>
</table>

Site of metastasis as reported in 8 patients followed by brain, lung and liver as shown in Table 3.

EP chemotherapy regimen was used in all patients, consisted of cisplatin 80 mg/m² day1 i.v and 100 mg/m² of etoposide days 1 - 3 i.v; cycle was repeated every 3 weeks. After failure of EP, 15 patients needed other regimen of CAV that consisted of cyclophosphamide 1000 mg/m² d1 i.v, adriamycin 45 mg/m² d1 i.v and vincristine 1 mg/m² d1 i.v to be repeated every 3 weeks while 3 patients with poor general condition after EP, received supportive care.

Patients with LD-SCLC received either concurrent chemoradiotherapy in 9 patients (40.9%) or sequential treatment of chemotherapy then radiotherapy in 13 patients (59.1%). Response rate was 36.5% with complete response in 12.7% while disease progression found in 28.6% (Table 4). As shown in Table 5,
leucopenia was the most frequent hematologic toxicity with >grade I in 41.3% followed by thrombocytopenia. Nausea and vomiting > grade I was found in 47.6% as the most common non hematologic toxicity. No reported grade IV toxicity in non hematologic one but reported in 6.4% of hematologic toxicity.

2-year overall survival rate was 35% with median survival time of 14 months (Figure 1).

On multivariate analysis; we found significantly higher survival in patients aged < 65 years (P = 0.03), female gender (P = 0.04), LD-SCLC (P = 0.03), good performance status (P = 0.04), low LDH level (P = 0.02) and non-smoker (P = 0.04).

4. Discussion

Although treatment of lung cancer has much progress, it is still the leading cause of cancer-associated mortality all over the world [21].

### Table 3. Metastatic sites.

<table>
<thead>
<tr>
<th>Site</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One site</td>
<td>15 (23.8)</td>
</tr>
<tr>
<td>≥2 sites</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Bone</td>
<td>8 (12.6)</td>
</tr>
<tr>
<td>Brain</td>
<td>5 (7.9)</td>
</tr>
<tr>
<td>Lung</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Liver</td>
<td>2 (3.2)</td>
</tr>
</tbody>
</table>

### Table 4. Response rate.

<table>
<thead>
<tr>
<th>Response rate</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Partial (PR)</td>
<td>15 (23.8)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>22 (34.9)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>18 (28.6)</td>
</tr>
</tbody>
</table>

### Table 5. Acute toxicity treatment.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>18 (28.6)</td>
<td>6 (9.5)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15 (23.8)</td>
<td>6 (9.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (17.5)</td>
<td>5 (7.9)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>22 (34.9)</td>
<td>8 (12.7)</td>
<td>0</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>10 (15.9)</td>
<td>5 (7.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>7 (11.1)</td>
<td>3 (4.8)</td>
<td>0</td>
</tr>
</tbody>
</table>
In our population study, median age was 56 ± 6 that is similar to literature [22] [23]. As expected 84% of our patients were smokers. It was reported that smoking is the most serious etiology of lung cancer but also current smoking during treatment compromise survival [24] [25].

Males are more smoker than females in our locality; this may explain the more prevalence of SCLC in males.

Multiple features are associated with lung cancer either due to: 1) local disease as chest pain, cough or local spread as hoarseness of voice 2) distant spread as bone ache and weight loss which is a symptom of systemic disease [26]. In our study chest pain was the most frequent complaint followed by cough and weight loss.

Disease was limited in 35% and extensive in 65% comparable to other studies that reported higher incidence of extensive disease [3] [27].

In our patients, about 24% were presented by single site of metastasis while 11% had ≥2 sites and bone was the most common site of metastasis followed by brain similar to what reported by Luan et al. [28]. However, others found that the frequency of metastatic sites were liver then brain and bone [29] [30].

All our patients received EP regimen.

In the European Society for Medical Oncology (ESMO) guidelines patients with small cell lung cancer are advised to receive chemotherapy of cisplatin or carboplatin-based regimen [31].

Although EP is the most widely used regimen; in a randomized trial IP combination (irinotecan-cisplatin) was superior to EP as regard survival rates [32]. However, it was found that IP cause increased gastrointestinal toxicity [33].

Nine patients with limited disease received concurrent chemoradiotherapy which has the advantages of shorter overall treatment time and increase treat-
ment intensity due to synergism between both therapy but it has the disadvantages of increased toxicity [34]. In our study, leucopenia was the most prevalent hematologic toxicity (41.3%) while esophagitis (23.8%) followed by pneumonitis (15.9%) were the most frequent non hematologic one. But Luanz reported incidence of pneumonitis and esophagitis of 1.8% and 1.2% respectively [28]. This can be explained by using 3D conformal TRT for all his patients while only 7.6% of our group treated by 3D conformal TRT. As regard prognostic factors for survival; ECOG of 0 - 1 was associated with significantly higher survival (P = 0.04) comparable to that recorded by Nathan R et al. [35] who explained that by receiving more often full dose therapy in patients with ECOG 0 - 1 than those with ECOG ≥ 2.

High level of LDH was associated with significantly worse prognosis (P = 0.02) consistent with other studies [36] [37]. Smoking was a negative prognostic factor. The mechanism of this finding is unclear. It was found that nicotine protects cancer cells from apoptosis induced by many factors as chemotherapeutic agents, tumor necrosis factors [38] [39]. Studies suggest nicotine possesses angiogenic activities and promote cell migration and invasion [40] [41] [42]. Although Videtic et al. [25] and Chen J et al. [43] showed that continuation of smoking during treatment causes poorer survival rates; Bergnar and Sorenson [44] found no survival difference.

In our study age, male gender and extensive stage disease are poor prognostic factors. That is similar to that encountered in some studies [45] [46] [47] but others not found old age as an adverse prognostic factor [48] [49]. They observed that when older patients with good performance status receive multimodality treatment as younger had the same survival.

2-year survival rate 35% with median overall survival time of 14 months comparable to what reported by Luan Z et al. [28] and Unalmis et al. [29]. While Ramlov A et al. [50] recorded higher median survival time which can be attributed to higher percentage of patients with LD-SCLC in their study (62.7%).

For LD-SCLC; it was found that concurrent chemoradiotherapy with 50 Gy and overdoses radiotherapy provide improvement in overall survival [51]. It was concluded that when radiotherapy started within 30 days of chemotherapy provide better survival rates than if started > 30 days after chemotherapy [52].

5. Conclusion

This clinic-epidemiologic study provides multiple prognostic factors that have important impact on survival as age, sex, LDH level, stage, smoking and performance status. Larger number of patients and prospective studies are needed to clarify more prognostic factors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.
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