Clinical Manifestation and Survival of Patients with Small-Cell Lung Cancer

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Objective: *To assess the clinical manifestation, diagnostic investigation, treatment, and survival of patients with small-cell lung cancer (SCLC).*
Design: *Retrospective study.*
Material and Method: *Patients with histologically and/or cytologically proven SCLC, adequate medical record for clinical history, and survival between January 1, 1999 and December 31, 2003, were reviewed. The stage of disease at presentation was based on the Veterans' Administration Lung Cancer Study Group (VALSG) staging system of limited-stage and extensive-stage disease.*
Results: *One hundred and sixteen evaluative SCLC patients were enrolled in the present study. SCLC was common in elderly men who smoked. Major symptoms were cough 81%, weight loss 72%, and dyspnea 67%. Hoarseness and superior vena cava syndrome (SVC syndrome) were present in 18% and 17% respectively. Forty-nine patients (42%) presented with limited-stage disease and 67 (58%) with extensive-stage disease. Thirty patients (26%) received chemotherapy alone, 23 patients (20%) received radiotherapy alone, 33 patients (28%) received combined chemoradiotherapy, and 30 patients (26%) received supportive treatment. A chemotherapy regimen of cisplatin combined with etoposide was used in 61 of 63 patients (97%). The overall response to chemotherapy was complete remission in 12 cases (19%), and partial response in 20 cases (32%). The median survival of limited-stage disease was significantly better than those with extensive-stage disease (44 weeks vs. 22 weeks). Patients with chemotherapy treatment had significantly improved median survival in both limited-stage and extensive-stage disease.*
Conclusion: *More than half of the SCLC patients presented in extensive-stage disease. The majority of the patients were treated with systemic chemotherapy. Patients with limited-stage disease had better response to chemotherapy and better survival than those with extensive-stage disease.*

Keywords: *Small-cell lung cancer, Treatment, Prognosis*

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Lung cancer is currently the leading cause of cancer deaths worldwide. In Thailand, data on the incidence of cancer between 1995-1997 showed that lung cancer was the second leading cancer in males, after liver cancer, and the fourth in females, after cervical, breast, and liver cancer[1]. The report of lung cancer in Songkhla province from the Cancer Registry of Prince of Songkla University in 1996 shows that lung cancer was the most common cancer in males and the sixth in females. The estimated incidence rate was 25.9 per 100,000 in men and 10.0 per 100,000 in women. Among lung cancer, the proportion of small-cell lung carcinoma (SCLC) accounted for approximately 20-25% of all new cases. In Thailand, the proportion of SCLC accounted for 10% of lung cancer[2]. SCLC is the most aggressive of lung cancer subtypes. Although most patients'

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tumors respond to chemotherapy, more than 95% of patients eventually died from the cancer[3]. Cigarette smoking is the major cause of lung cancer. Patients with SCLC typically present with disseminated disease. Symptoms are related either to bulky, intrathoracic disease, or to distant metastasis. Cough and dyspnea are the most common findings. SCLC tends to be centrally located, with hilar masses and hilar and mediastinal adenopathy. Patients with SCLC more often have paraneoplastic syndromes such as hyponatremia, Cushing's syndrome, and Lambert-Eaton myasthenic syndrome.

In the pre-chemotherapy days, when treatment for SCLC was usually palliative radiotherapy, the median survival for patients with limited-stage disease was just 12 weeks, while for those with extensive-stage disease just 6 weeks. With current therapeutic approaches, the median survival for all patients is approximately 11 months[4]. The clinical response to chemotherapy was dependent on good performance status, limited-stage disease, being female, and normal level of serum lactic dehydrogenase (LDH)[5].

There are few reports on the clinical history and survival of patients with SCLC in Thailand. This retrospective study was performed to investigate the clinical manifestation, diagnostic investigation, treatment, and survival of patients with NSCLC.

Material and Method

Eligibility

The patients with SCLC in Songklanagarind Hospital were identified through the database maintained by the Cancer Registry of Prince of Songkla University between January 1, 1999 and December 31, 2003. Patient selection was restricted to cases with histologically and/or cytologically proven SCLC, adequate medical records for clinical history and survival.

Patient evaluation

The medical records were reviewed for clinical history, chest roentgenographic findings, and diagnostic investigations. Choice of therapy was based on the initial intention to treat. The stage of disease at presentation was based on Veterans' Administration Lung Cancer Study Group (VALSG) staging system of limited and extensive-stage disease.[6] Limited-stage disease includes patients with disease restricted to one hemithorax, with regional lymph node metastasis including hilar, ipsilateral or contralateral mediastinal lymph node, and ipsilateral supraclavicular lymph node involvement. Patients with cytologically positive or negative ipsilateral pleural effusions are also in limited-stage disease. Extensive-stage disease includes all patients with disease beyond the confines of limited-stage disease. The response to chemotherapy treatment was based on World Health Organization (WHO) criteria.[7] Measurement of tumor size was made using chest x-ray or CT scan after two courses of chemotherapy. Overall survival time was defined as the time between the date of diagnosis and the date of death. Date of death was collected from the medical record in case of death occurring in hospital or death certificate in case of death occurring at home.

Statistical analysis

The Kaplan Meier method was used to calculate survival, which was reported as 1-year, 2-year survival, and median survival time. The log-rank test was employed to compare the survival of different groups[5]. A value of $p < 0.05$ was considered statistically significant.

Results

There were 116 evaluative cases of SCLC during the present study period. One hundred and eight (93.1%) were men and eight (6.9%) were women. The characteristics of patients are listed in Table 1. The age of these 116 patients ranged from 42-87 years with a mean of 63.36 years (standard deviation = 10.47 years). One hundred and nine (94.0%) were smokers. Forty-nine (42.2%) presented with limited-stage disease and 67 (57.8%) with extensive-stage disease.

Major symptoms related to cancer were cough 81.0%, weight loss 72.4%, and dyspnea 67.2%. Chest pain and hemoptysis were present in 29.3% and 26.7% respectively. Hoarseness and superior vena cava syndrome (SVC syndrome) were present in 18.1% and 17.2% respectively. Neurological symptoms due to metastatic disease were present in 13.8%. Syndrome of inappropriate antidiuretic hormone (SIADH) and Cushing's syndrome were found in 11.2% and 2.6% respectively (Table 2). Abnormal chest roentgenography showed a mass lesion in 93 cases (80.2%), infiltrative lesion in 23 cases (19.8%), and pleural effusion in 34 cases (29.3%). Common sites of lesion were right hilar (25.9%), left hilar (23.3%), left upper lobe (20.7%), and right upper lobe (16.4%) (Table 3). Diagnosis of SCLC used bronchoscopy with biopsy, transthoracic needle aspiration, lymph node biopsy, bronchial wash cytology, pleural fluid cytology, and pleural biopsy in 59 (50.9%), 28 (24.1%), 22 (19.0%), 6 (5.2%), 3 (2.6%) and 1case (0.9%), respectively.

Table 1. Demographic data of the 116 patients with SCLC

	n = 116
Mean age ± SD (years)	63.36 ± 10.47
(range)	(42-87)
Sex (%)	
Male	108 (93.1)
Female	8 (6.9)
Smoking (%)	109 (94)
Stage	
Limited-stage disease	49 (42.2)
Extensive-stage disease	67 (57.8)

Table 2. Clinical manifestation of patient with SCLLC

Symptoms and signs	N (% of total 116 cases)
Cough	94 (81.0)
Weight loss	84 (72.4)
Dyspnea	78 (67.2)
Chest pain	34 (29.3)
Hemoptysis	31 (26.7)
Massive hemoptysis	2 (1.7)
Hoarseness	21 (18.1)
SVC syndrome	20 (17.2)
Cushing's syndrome	3 (2.6)
SIADH	13 (11.2)
Neurological symptom	16 (13.8)

Table 3. Chest roentgenography of patients with SCLC

	N (%)
Mass	93 (80.2)
Infiltration	23 (19.8)
Effusion	34 (29.3)
Site	
Right upper lobe	19 (16.4)
Right middle lobe	14 (12.1)
Right lower lobe	17 (14.7)
Right hilar	30 (25.9)
Left upper lobe	24 (20.7)
Left lower lobe	11 (9.5)
Left hilar	27 (23.3)
Mediastinum	18 (15.5)

Table 4. Treatment modalities of SCLC

Treatment	N (%)
Chemotherapy alone	30 (25.9)
- Limited-stage disease	18 (15.5)
- Extensive-stage disease	12 (10.3)
Chemoradiotherapy	33 (28.4)
- Limited-stage disease	15 (12.9)
- Extensive-stage disease	18 (15.5)
Radiotherapy alone	23 (19.8)
Supportive treatment	30 (25.9)

Thirty patients (25.9%) received chemotherapy alone, 18 cases (15.5%) of limited-stage disease and 12 cases (10.3%) of extensive-stage disease. Thirty-three patients (28.4%) received combined chemoradiotherapy, 15 cases (12.9%) of limited-stage disease and 18 cases (15.5%) of extensive-stage disease. Twenty-three patients (19.8%) received radiotherapy alone. The last 30 patients received supportive treatment (Table 4). A chemotherapy regimen of cisplatin combined with etoposide was used in 61 of 63 patients (96.8%). Mean chemotherapy cycles were 3.79 courses, 4.15 courses for limited-stage disease and 3.40 courses for extensive-stage disease. The overall response to chemotherapy was complete response in 12 cases (19.03%), partial in 20 cases (31.7%), stable disease in eight cases (12.7%), and progressive disease in ten cases (15.9%). Fourteen cases (22.2%) were not evaluated. Patients with limited-stage disease tended to have more complete response to chemotherapy than extensive-stage disease (Table 5).

Table 6 summarizes the survival data with 95% confidence interval (CI) of the 116 patients with SCLC limited- and extensive-stage disease. One-year and 2-year survival, and median survival time of limited-stage disease without chemotherapy treatment were 27.1%, 6.8%, and 11.7 weeks, respectively. The corresponding survivals for limited-stage disease with chemotherapy treatment were 48.5%, 15.2%, and 49.7 weeks, of extensive-stage disease without chemotherapy treatment 18.9%, 0%, and 9.3 weeks, and of extensive-stage disease with chemotherapy treatment 26.7%, 6.7%, and 32.0 weeks, respectively. Overall median survival of patients with limited-stage disease was better than that of patients with extensive-stage disease (44.4 weeks vs. 21.9 weeks, $p = 0.0131$). Median survival, one-year and two-year survival, were more favorable in patients who received chemotherapy compared with those without chemotherapy patients ($p = 0.0001$) (Table 6).

Discussion

The present study showed that SCLC patients are mostly elderly, male, and smokers. There were 14 times more males than females among the presented

Table 5. The results of chemotherapy of limited-versus extensive-stage SCLC

	Limited-stage disease	Extensive-stage disease	Overall
Total cases, N	33	30	63
Courses of chemotherapy, mean ± SD	4.15 ± 2.03	3.40 ± 1.90	3.79 ± 2.02
Response, N (%)*			
Complete response (CR)	8 (24.2)	4 (13.3)	12 (19.0)
Partial response (PR)	11 (33.3)	9 (30.0)	20 (31.7)
Total response (CR + PR)	19 (57.6)	13 (43.3)	32 (50.8)
Stable	3 (9.1)	5 (16.7)	8 (12.7)
Progression	5 (15.2)	5 (16.7)	10 (15.9)
Not evaluable	6 (18.2)	7 (23.3)	14 (22.2)

* No significant difference in response between limited-stage and extensive-stage disease
$p > 0.05$

Table 6. Survival data of the 116 patient with SCLC

Treatment	N	1-year survival (95%CI)	2-year survival (95%CI)	Median survival (week)	
Limited-stage disease	49	41.2 (27.8-55.1)	12.5 (5.1-23.5)	44.4	
Limited-stage disease without chemotherapy	16	27.1 (8.4-50.2)	6.8 (0.4-26.4)	11.7	*
Limited-stage disease with chemotherapy	33	48.5 (30.8-64.1)	15.2 (5.5-29.2)	49.7	*
Extensive-stage disease	67	22.4 (13.3-32.9)	3.0 (0.6-9.3)	21.9	**
Extensive-stage disease without chemotherapy	37	18.9 (8.3-32.8)	0	9.3	***
Extensive-stage disease with chemotherapy	30	26.7 (12.6-43.0)	6.7 (1.2-19.2)	32.0	***

* Limited-stage disease: chemotherapy vs. no chemotherapy, $p = 0.0096$
** Overall limited vs. extensive-stage disease, $p = 0.0131$
*** Extensive-stage disease: chemotherapy vs. no chemotherapy, $p = 0.0259$

patients. More than half of the patients (57.8%) presented with extensive-stage disease. Most common presenting symptoms of SCLC were cough, weight loss, and dyspnea. Unlike the previous reports of Chulalongkorn University Hospital[8], the symptoms of dyspnea, hoarseness and SVC syndrome are more frequent in the present report compared to Chulalongkorn Hospital: 67% vs. 26%, 18% vs. 9%, and 17% vs. 11% respectively. Because SCLC tends to be centrally located, approximately 20% of patients presented with hoarseness and/or SVC syndrome. Eleven patients developed SIADH and 2.6% were associated with Cushing's syndrome, comparable to the other reports of 15% and 2 to 5%, respectively[9,10]. SCLC usually presents with a mass at the hilar or upper lobes. One-third of patients have pleural effusion. Diagnosis is usually documented by histological analysis of a bronchoscopic biopsy, transthoracic needle aspiration, or lymph node biopsy.

The mainstay of treatment is combination systemic chemotherapy with the goal of achieving the highest response rate and long-term disease-free survival. In the prechemotherapy days, the median survival for patients with limited-stage disease was only 12 weeks, whereas those with extensive-stage disease was 6 weeks[4]. In patients with limited-stage disease, response rates of 70% to 90% are expected with concurrent platinum plus etoposide and thoracic radiotherapy. In extensive-stage disease, a response rate of 60% to 70% is achievable with combination chemotherapy alone[11]. Median survival rates were only 14 to 20 months and 9 to 11 months for patients with limited-stage and extensive-stage disease, respectively. With appropriate treatment, the 2-year survival rate was 40% in patients with limited-stage disease, but less than 5% in those with extensive-stage disease[3,12]. Almost all patients in the present report (96.7%) received cisplatin combined with etoposide. The overall clinical response in the present report was 50%, which is lower than other reports. Two-year survival

of patients with limited-stage disease who received chemotherapy was much lower than in other reports (15% vs. 40%), but similar 2-year survival of patients with extensive-stage disease. The poor prognosis in limited-stage disease in the present report may be due to under staging in some of the patients or poor response to chemotherapy in Thai patients. Further investigation of chemotherapy in Thai patients is warranted. Thoracic radiotherapy for limited-stage disease reduces a 25% to 30% local failure and a corresponding 5% to 7% improvement in 2-year survival[13]. In the present report, about half of the patients with limited-stage disease who received chemotherapy did not receive thoracic radiotherapy.

The survival of patients with limited-stage disease is significantly better than that of patients with extensive-stage disease. Chemotherapy can significantly improve the survival both in patients with limited- and extensive-stage disease compared to those patients without chemotherapy treatment. In general practice, patients with poor performance status and old age are not given chemotherapy due to poor prognosis. Thus, the survival improvement in the chemotherapy group may be somewhat overestimated. However, this result is in concordance with reports in Western countries. There are no available data on the natural history of SCLC in Thailand for comparison with the present report. Compared to non-small cell lung cancer in Songklanagarind Hospital[14], patients with small-cell lung cancer have shorter median survival whether they receive chemotherapy treatment or supportive treatment.

Conclusion

The clinical characteristics of 116 patients with SCLC are reported. More than half of the patients presented with extensive-stage disease. Survival in limited-stage disease was lower than in other reports, but that of extensive-stage disease was comparable. Radiotherapy was commonly used for palliative treatment. Chemotherapy was used in half of the patients. The response to chemotherapy was about 50% and median survival was significantly better than in patients without chemotherapy for both limited- and extensive-stage patients.

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อาการทางคลินิกและการพยากรณ์โรคของผู้ป่วยมะเร็งปอดชนิด small-cell lung cancer

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วัตถุประสงค์: *เพื่อศึกษาผู้ป่วยที่เป็นมะเร็งปอดชนิด small-cell lung cancer (SCLC) ในด้านอาการทางคลินิก วิธีการวินิจฉัยโรค การรักษา และการพยากรณ์โรค*

ระเบียบวิจัย: *เป็นการศึกษาแบบย้อนหลัง*

วัสดุและวิธีการ: *ได้ศึกษาผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งปอดชนิด SCLC จากการตรวจทาง histology และ/หรือ cytology ที่มีประวัติการรักษาและประวัติการเสียชีวิตที่ชัดเจน ในช่วงมกราคม พ.ศ. 2542 ถึง ธันวาคม พ.ศ. 2546 การแบ่งระยะของโรคเป็น limited-stage และ extensive-stage disease ใช้ระบบ Veterans' Administration Lung Cancer Study Group (VALSG) staging system*

ผลการศึกษา: *มีผู้ป่วย SCLC จำนวน 116 คน ที่ได้รับการศึกษา ผู้ป่วยส่วนใหญ่อายุมากและสูบบุหรี่ อาการสำคัญที่พบคือไอร้อยละ 81.0 น้ำหนักลดร้อยละ 72.4 และหอบเหนื่อยร้อยละ 67.2 มีผู้ป่วยมาด้วยเสียงแหบและ superior vena cava syndrome (SVC syndrome) ร้อยละ 18.1 และ 17.2 ตามลำดับ ผู้ป่วยอยู่ในระยะ limited-stage disease ร้อยละ 42.2 และ extensive-stage disease ร้อยละ 57.8 ผู้ป่วย 30 ราย (25.9%) ได้รับยาเคมีบำบัด ผู้ป่วยได้รับยาเคมีบำบัดร่วมกับการฉายแสง 33 ราย (28.4%) ผู้ป่วย 23 ราย (19.8%) ได้รับการฉายแสงอย่างเดียว มีผู้ป่วย 30 ราย ได้รับการรักษาแบบประคับประคอง ผู้ป่วยได้รับยาเคมีบำบัดสูตร cisplatin ร่วมกับ etoposide จำนวน 61 ราย คิดเป็นร้อยละ 96.8 ของผู้ได้รับยาเคมีบำบัดทั้งหมด การตอบสนองต่อยาเคมีบำบัดเป็น complete response 12 ราย (19.0%) และ partial response 20 ราย (31.7%) การพยากรณ์โรคผู้ป่วย limited-stage disease มี median survival ดีกว่า extensive-stage disease อย่างมีนัยสำคัญทางสถิติ (44.4 สัปดาห์ เปรียบเทียบกับ 21.9 สัปดาห์) ผู้ป่วยได้ยาเคมีบำบัดจะมีการพยากรณ์โรคดีกว่าผู้ป่วยที่ไม่ได้ยาเคมีบำบัด*

สรุป: *ผู้ป่วยมะเร็งปอดชนิด SCLC มากกว่าครึ่งจะมาในระยะ extensive-stage disease การรักษาผู้ป่วยส่วนมากได้รับยาเคมีบำบัด พบว่าผู้ป่วยกลุ่ม limited-stage disease จะตอบสนองต่อยาเคมีบำบัดได้ดีและมีการพยากรณ์โรคดีกว่าผู้ป่วย extensive-stage disease*