

## Survival of Small-cell Lung Cancer and its Determinants of Outcome in Singapore

Chee-Keong Toh,<sup>1</sup>MBBS, MRCP (UK), Siew-Wan Hee,<sup>2</sup>BSc, MSc, Wan-Teck Lim,<sup>1</sup>MBBS, MRCP (UK),  
Swan-Swan Leong,<sup>1</sup>MBBS, MMed, MRCP (UK), Kam-Weng Fong,<sup>3</sup>MBBS, FRCR (Clin Oncol), FAMS,  
Swee-Peng Yap,<sup>3</sup>MBBS, MRCP (Int Med), FRCR (Clin Oncol), Anne AL Hsu,<sup>4</sup>MBBS, MMed (Int Med), FRCP (UK),  
Philip Eng,<sup>4</sup>MBBS, MMed (Int Med), FAMS, Heng-Nung Koong,<sup>5</sup>MBBS, MMed (Surg), FRCS,  
Thirugnanam Agasthian,<sup>5</sup>MBBS, MMed (Surg), FRCS, Eng-Huat Tan,<sup>1</sup>MBBS, MMed (Int Med), MRCP (UK)

### Abstract

**Introduction:** The survival and epidemiology of small-cell lung cancer (SCLC) in Singapore has not been described. We aim to present the characteristics as well as determine the survival outcome and important prognostic factors for SCLC patients. **Materials and Methods:** A retrospective analysis of SCLC patients diagnosed from 1999 to 2002 was conducted at the Outram campus, Singapore. Clinical characteristics and treatment data were obtained from case records and survival data were checked with the registry of births and deaths on 30 May 2005. **Results:** One hundred and eleven patients were analysed. There were 38 (34.2%) limited-disease (LD) patients and 73 (65.8%) extensive-disease (ED) patients. The majority were current or former smokers (94.7% among LD and 94.5% among ED). More patients with LD had good performance status (92% versus 63%,  $P = 0.0003$ ) and were treated with combined chemotherapy and radiotherapy (82% versus 48%,  $P = 0.012$ ). The median survival time of LD patients treated with curative chemoradiotherapy was 14.2 months (95% CI, 10.96 to 17.44). Those given prophylactic cranial irradiation had a median survival time of 16.9 months (95% CI, 11.83 to 21.97). For ED patients, the median survival time was 8.17 months (95% CI, 5.44 to 10.89). None of the factors analysed were significant prognostic factors for LD patients while performance status and type of treatment given were significant among ED patients. **Conclusions:** We found that the characteristics and survival of SCLC patients in Singapore are fairly similar to that of other countries.

Ann Acad Med Singapore 2007;36:181-8

**Key words:** Epidemiology, Prognostic factors, Survival

### Introduction

Lung cancer is the leading cause of cancer mortality around the world.<sup>1</sup> Small-cell lung cancer (SCLC) constitutes about 15% to 25% of all lung cancer cases in North America and Europe.<sup>2,3</sup> In contrast, SCLC constitutes a smaller percentage of lung cancer cases in Asian countries. In a Taiwanese hospital, 8.1% of lung cancer cases seen were SCLC<sup>4</sup> while in Singapore, the percentage of SCLC among all lung cancer cases diagnosed from 1998 to 2002 was 10.8%.<sup>5</sup> The lower incidence of SCLC in some Asian countries probably reflects the lower smoking rates among

these populations as SCLC occurs almost exclusively in smokers.

SCLC is an aggressive disease with a median survival time of 2 to 4 months when left untreated.<sup>6</sup> Over the past decades, survival times of patients with SCLC have improved modestly for both limited-stage (LD) and extensive-stage (ED) disease. The median survival time of patients with LD SCLC has increased from 12 months to 17 months while the 5-year survival time has improved from 5.2% to 12.1%.<sup>7</sup> Although not as dramatic, analysis of the National Cancer Institute Cancer Therapy Evaluation

<sup>1</sup> Department of Medical Oncology

<sup>2</sup> Division of Clinical Trials and Epidemiological Sciences

<sup>3</sup> Department of Therapeutic Radiology

<sup>4</sup> Department of Surgical Oncology

National Cancer Centre, Singapore

<sup>5</sup> Department of Respiratory and Critical Care Medicine

Singapore General Hospital, Singapore

Address for Correspondence: Dr Chee-Keong Toh, Department of Medical Oncology, National Cancer Centre, 11 Hospital Drive, Singapore 169610.

Email: dmotck@nccs.com.sg

Programme and Surveillance, Epidemiology, and End Results database of patients with ED SCLC showed a 2-month prolongation in median survival time.<sup>8</sup> Factors contributing to the improvement in survival time seen over the years include possible stage migration with improved imaging technologies, changes in patient and disease demographics, as well as better therapy.

The studies that demonstrated improvements in outcome over the decades and identified important prognostic factors were made possible with good existing databases in the various countries. As disease burden differs across continents, it is imperative that each country has a good grasp of the epidemiology of SCLC within its population. Furthermore, the survival outcome of SCLC may differ between countries solely because of differences in patient and disease characteristics. To date, there have been no reports of the demographics and survival outcome of SCLC patients treated in Singapore, which is a multiracial Asian country. We thus carried out a retrospective analysis of SCLC patients treated at the Outram campus, which includes the National Cancer Centre, National Heart Centre and Singapore General Hospital.

## Materials and Methods

This study included patients from the Singapore General Hospital, National Heart Centre and National Cancer Centre, Singapore. All 3 centres are located within the Outram campus and all treatments (chemotherapy and/or radiotherapy) are given at the National Cancer Centre only. Study subjects had SCLC diagnosed between 1 January 1999 and 31 December 2002. The study received the approval of the institutional review boards of all centres.

All patients diagnosed consecutively with available case records were reviewed. Certain patients were excluded because their case records were missing or irretrievable. Selected epidemiological characteristics, investigation results, and performance status as defined by Eastern Cooperative Oncology Group (ECOG) classification were recorded. Staging procedure at diagnosis included computed tomographic (CT) scan of the brain and thorax, ultrasound or CT scan of the abdomen and radionuclide scan of the bone.

The presence of weight loss, co-morbidities, and type of treatment given were also reviewed. Weight loss was recorded in kilograms (kg) and significant weight loss was defined as more than 5 kg (taking an average weight of 50 kg, this will be equivalent to 10% of baseline body weight). The presence of co-morbidities included one or more of the following conditions: diabetes mellitus, ischaemic heart disease, hypertension, asthma, chronic obstructive lung disease and pulmonary tuberculosis. Treatment given was recorded as supportive care/no treatment, radiotherapy

alone, chemotherapy alone or a combination of chemotherapy and radiotherapy. In our analysis, we have grouped the patients into LD and ED based on the initial stage at diagnosis. For patients with LD treated with curative intent, radiotherapy was given concurrently and started with the second or third cycles of chemotherapy. Radical radiotherapy was given at 200 cGy daily on weekdays, up to a minimum dose of 5400 cGy and a maximum dose of 6400 cGy. Palliative radiotherapy was given for symptom control and was given sequentially to chemotherapy at disease progression.

Smoking data included pack-years smoked and quit time for former smokers. Smokers who were smoking during diagnosis or had quit for less than 2 years were classified as current smokers. Those who had quit for more than 2 years were classified as former smokers. A never-smoker was defined as one who had never smoked before. Data regarding passive exposure to environmental tobacco smoke were not consistently available in the medical records.

Overall survival for each patient was measured from the date of diagnosis till the date of death or till the date the patient was last known to be alive for censored observation. The patients' death data were checked with the Singapore Registry of Births and Deaths on 30 May 2005.

The Kaplan-Meier method was used to estimate the survival function and log-rank statistic test to test for survival difference by subgroups. Due to the small numbers of patients with significant weight loss, this variable was not included in the univariate survival analysis. A *P* value of less than 0.05 was considered statistically significant. The unadjusted hazard ratio was estimated by using Cox's proportional hazards method. All analyses were performed using SPSS 11.5 for Windows.

## Results

A total of 113 patients were reviewed. However, one patient had unknown stage at diagnosis while another had missing date of diagnosis. Hence, only 111 patients were analysed (Table 1).

There were 38 (34.2%) LD and 73 (65.8%) ED SCLC. The majority of the patients were current or former smokers (94.7% among LD and 94.5% among ED). There were 2 never-smokers with one having LD and another ED. Both never-smokers were females but unfortunately, the information on environmental tobacco exposure was not available. Most of the patients with LD (92%) had good performance status of ECOG 0 to 1 compared to 63% of those with ED (*P* = 0.0003). As expected, more patients diagnosed with LD (82%) were treated with combined chemotherapy and radiotherapy compared to 48% with ED (*P* = 0.012). The other characteristics were not significantly different between the 2 groups.

Table 1. Patient and Disease Characteristics of 111 Patients by Stage of Disease

Characteristics	Limited-disease (n = 38)		Extensive-disease (n = 73)		P
	No.	%	No.	%	
Sex					0.386
Male	28	73.7	59	80.8	
Female	10	26.3	14	19.2	
Race					0.067†
Chinese	36	94.7	60	82.2	
Malay	1	2.6	13	17.8	
Others	1	2.6	0	0.0	
Smoking status					1.000
Never-smoker	1	2.6	1	1.4	
Current and former smoker	36	94.7	69	94.5	
Age					0.253
<70	21	55.3	32	43.8	
≥70	17	44.7	41	56.2	
Performance status (ECOG*)					0.003
0 and 1	35	92.1	46	63.0	
2, 3 and 4	3	7.9	23	31.5	
Co-morbidities					0.276
No	18	47.4	26	35.6	
Yes	20	52.6	45	61.6	
Haemoglobin					0.476
<11g/dL	4	10.5	12	16.4	
≥11g/dL	30	78.9	58	79.5	
Albumin					0.435
<36	14	36.8	33	45.2	
≥36	19	50.0	32	43.8	
Sodium					0.128
<135	7	18.4	24	32.9	
≥135	27	71.1	44	60.3	
Treatment					0.006‡
Supportive/no treatment	1	2.6	8	11.0	
Radiotherapy only	1	2.6	5	6.8	
Chemotherapy only	4	10.5	19	26.0	
Combined (ChemoRT)	31	81.6	35	47.9	
Defaulted	1	2.6	5	6.8	

\* ECOG: Eastern Co-operative Oncology Group

† Chinese against non-Chinese

‡ Supportive care/Radiotherapy only against chemotherapy only against combined treatment

### Limited-disease SCLC

Out of the 38 patients with LD, 4 patients had chemotherapy only while 31 patients had combined chemotherapy with radiotherapy. Among the 31 patients, 25 (81%) were treated with curative intent and 5 (16%) with palliative intent. Combining those patients (n=9) who were treated with palliative chemotherapy or

chemoradiotherapy, their one-year survival rate was 56% (SE = 0.1656) and the median survival time was 12.4 months (95% CI, 0.00 to 30.65). In contrast, those patients (n = 25) who were treated with curative intent had a 1-year survival rate of 67% and median survival time of 14.2 months (95% CI, 10.96 to 17.44) (Fig. 1). Although the median survival time of those who were treated with

Table 2. One-year Survival Rate and Median Survival Times by Kaplan-Meier Method and Estimated Hazard Ratio by Cox's Proportional Hazards of 25 Patients Presenting with Limited-disease Treated with Curative Intent Chemoradiotherapy

Characteristics	1-year survival rate (%) (SE)	Median survival	
		Time (mo) (95% CI)	Unadjusted hazard ratio (95% CI)
Overall survival	67 (0.0950)	14.20 (10.96 - 17.44)	
Sex			
Male (n = 19)	68 (0.1066)	13.90 (12.90 - 14.90)	1.000
Female (n = 6)	67 (0.1925)	17.53 (0.00 - 35.76)	0.977 (0.358 - 2.666)
Age			
<70 (n = 15)	86 (0.0911)	16.90 (11.48 - 22.32)	1.000
≥70 (n = 10)	40 (0.1549)	10.23 (7.60 - 12.87)	1.958 (0.827 - 4.636)
Performance status (ECOG)			
0 and 1 (n = 24)	66 (0.0980)	13.90 (9.67 - 18.13)	1.000
2, 3 and 4 (n = 1)		14.20 Only 1 patient	1.377 (0.178 - 10.637)
Co-morbidities			
No (n = 12)	58 (0.1423)	13.73 (3.83 - 23.63)	1.000
Yes (n = 13)	76 (0.1206)	14.20 (13.04 - 15.36)	0.827 (0.362 - 1.885)
Haemoglobin			
<11g/dL (n = 1)		14.20 Only 1 patient	1.000
≥11g/dL (n = 21)	76 (0.0941)	16.90 (11.67 - 22.13)	0.589 (0.074 - 4.670)
Albumin			
<36 (n = 8)	75 (0.1531)	14.20 (9.81 - 18.59)	1.000
≥36 (n = 13)	77 (0.1169)	16.23 (11.50 - 20.97)	1.171 (0.465 - 2.951)
Sodium			
<135 (n = 3)	100 NA	16.90 (12.10 - 21.70)	1.000
≥135 (n = 19)	73 (0.1024)	16.23 (11.07 - 21.40)	0.749 (0.208 - 2.703)

95% CI: 95% confidence interval; ECOG: Eastern Co-operative Oncology Group; SE: standard error

curative intent was higher, the difference was not significant with an unadjusted HR = 1.420 (95% CI, 0.630 to 3.199).

Among the 25 patients who were treated with curative intent, 4 (16%) were given prophylactic cranial irradiation (PCI). The median survival time of the 4 patients given PCI was 16.9 months (95% CI, 11.83 to 21.97) while the other 21 patients not given PCI had a median survival time of 13.9 months (95% CI, 10.96 to 16.84). On univariate analysis for the 25 LD patients treated with curative

chemoradiotherapy, none of the prognostic factors analysed were statistically significant (Table 2).

The chemotherapy given for the 25 patients treated with curative intent included etoposide/cisplatin (60%), etoposide/carboplatin (20%), gemzar/cisplatin (4%), paclitaxel-based treatment (8%) and unknown (8%).

#### Extensive-disease SCLC

Out of the 73 ED patients, 8 (11%) were on supportive

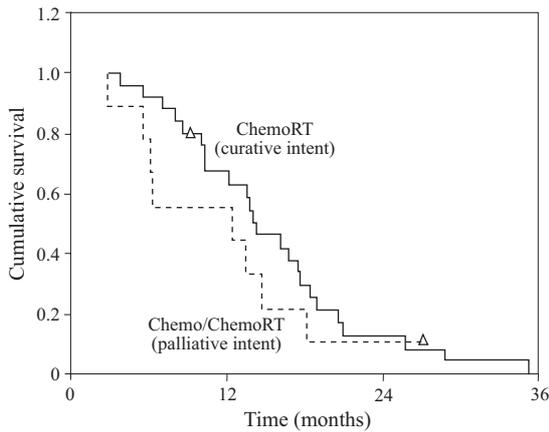


Fig. 1. Estimated survival curves of 34 limited-stage small-cell lung cancer patients treated with either curative intent chemoradiotherapy (chemoRT) or palliative intent chemotherapy/chemoradiotherapy. (r) represents a censored observation.

care, 5 (6.8%) had radiotherapy alone, 19 (26%) had chemotherapy alone, 35 (47.9%) had combination of palliative chemotherapy and radiotherapy and 5 (6.8%) defaulted. The median survival of ED patients was 8.17 months. Univariate analysis for the 73 ED patients found that poor performance status of ECOG 2 to 4 was associated with a significantly poorer outcome (HR = 1.745, 95% CI, 1.023 to 2.974) (Table 3).

In addition, treatment affected survival outcome (Table 3). The survival of those who were treated with radiation therapy was not significantly different from those who had best supportive care only. Patients treated with chemotherapy alone did not have significantly different survival compared to those who were on best supportive care or radiotherapy alone (HR = 0.70; 95% CI, 0.33 to 1.50). However, patients treated with the combination of chemotherapy and radiation therapy had a lower risk of dying (HR = 0.27; 95% CI, 0.13 to 0.56) (Fig. 2). Further analysis found that the importance of treatment was mainly limited to those with good ECOG of 0 to 1 (results not shown).

Among the 54 patients who received at least one line of chemotherapy, the first-line regime included etoposide/cisplatin (40.7%), etoposide/carboplatin (27.8%), paclitaxel-based treatment (13.0%), carboplatin (7.4%), oral VP-16 (5.5%) and unknown (5.5%).

**Discussion**

The characteristics of patients with SCLC in our population are similar to those of other countries. Almost all patients have a history of active smoking exposure. Most of them are males and the majority present with extensive disease. The survival of SCLC patients in Singapore is also fairly similar to that in other countries. The median survival of LD SCLC treated with curative

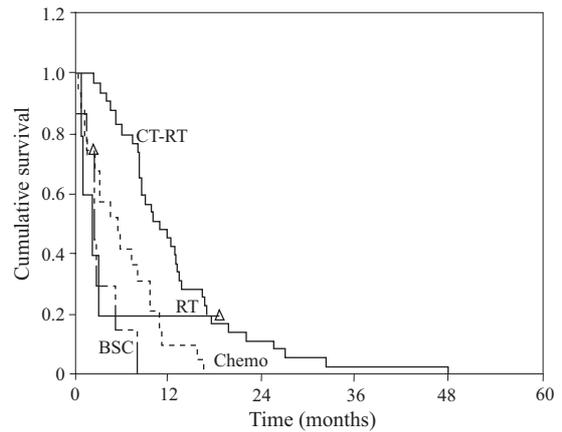


Fig. 2. Estimated survival curves of 67 patients presenting with extensive-disease small cell lung cancer. (r) represents a censored observation; BSC: best supportive care; RT: radiotherapy; chemo: chemotherapy; chemoRT: combination of chemotherapy and radiotherapy

chemoradiotherapy is 14.2 months. Based on the analysis of phase III trials for LD SCLC in North America, the median survival was 17 months (range, 11 to 20) for studies conducted between 1982 and 1992.<sup>7</sup> However, when compared to more recent studies using concurrent chemoradiotherapy with etoposide and cisplatin, the survival of our patients with LD would seem inferior.

In a study by Turrisi et al,<sup>9</sup> the median survival was 23 months for the experimental arm given twice-daily thoracic radiotherapy, compared to 19 months for the control arm given once-daily radiotherapy. One of the reasons for our inferior results could be the timing of concurrent radiotherapy. Ideally, radiotherapy should start concurrently with the first or second cycle of chemotherapy. Murray et al<sup>10</sup> reported that cisplatin-etoposide combination with radiotherapy beginning with cycle 2 was superior to radiotherapy starting with cycle 6 while Takada et al<sup>11</sup> also found starting radiotherapy concurrently with chemotherapy gives better results than beginning radiotherapy after completion of chemotherapy. In our patient population, radiotherapy was often started with the second cycle of chemotherapy but at times, it was given concurrently with the third cycle of chemotherapy. Another reason could be the choice of chemotherapeutic agents as not all our patients received etoposide/cisplatin (60% of LD patients given curative chemoradiotherapy). Although most investigators would prefer etoposide/cisplatin as the chemotherapy of choice, carboplatin/etoposide has been shown to be as effective as cisplatin/etoposide with less toxicity, at least in patients with ED.<sup>12</sup>

As PCI has been shown to improve overall survival and disease-free survival,<sup>13</sup> we examined the survival of those patients who were given PCI within the LD patients who were treated with curative intent. The median survival time

Table 3. One-year Survival Rate and Median Survival Times by Kaplan-Meier Method and Estimated Hazard Ratio by Cox's Proportional Hazards of 73 Patients Presenting with Extensive-disease

Characteristics	1-year survival rate (%) (SE)	Median survival time (months) (95% CI)	Unadjusted hazard ratio (95% CI)
Overall survival	26 (0.0520)	8.170 (5.44-10.89)	
Sex			
Male (n = 59)	28 (0.0588)	8.330 (7.14-9.53)	1.000
Female (n = 14)	21 (0.1097)	4.230 (0.00-8.94)	1.405 (0.779-2.534)
Age			
<70 (n = 32)	34 (0.0840)	8.430 (7.19-9.68)	1.000
≥70 (n = 41)	20 (0.0636)	6.07 (2.63-9.50)	1.208 (0.752-1.940)
Performance status (ECOG)			
0 and 1 (n = 46)	30 (0.0678)	8.40 (7.77-9.03)	1.000
2, 3 and 4 (n = 23)	19 (0.0837)	3.23 (2.14-4.32)	1.745 (1.023-2.974)
Co-morbidities			
No (n = 26)	0.3217 (0.0935)	8.17 (6.71-9.63)	1.000
Yes (n = 45)	0.2222 (0.0620)	7.40 (3.59-11.21)	1.139 (0.690-1.879)
Haemoglobin			
<11g/dL (n = 12)	17 (0.1076)	5.20 (0.00-13.63)	1.000
≥11g/dL (n = 58)	28 (0.0597)	8.17 (5.71-10.62)	0.652 (0.342-1.244)
Albumin			
<36 (n = 33)	22 (0.0735)	7.43 (3.41-11.46)	1.000
≥36 (n = 32)	31 (0.0819)	8.23 (7.86-8.60)	0.768 (0.464-1.270)
Sodium			
<135 (n = 24)	17 (0.0761)	6.07 (1.83-10.31)	1.000
≥135 (n = 44)	33 (0.0716)	8.33 (7.01-9.65)	0.801 (0.479-1.337)
Treatment			
Supportive/no treatment (n = 8)	0 (0)	2.63 (2.22-3.04)	1.000
Radiotherapy only (n = 5)	20 (0.1789)	2.30 (0.00-4.80)	0.323 (0.088-1.187)
Chemotherapy only (n = 19)	11 (0.0704)	5.50 (2.09-8.91)	0.400 (0.160-1.003)
Combined (Chemoradiotherapy) (n = 35)	46 (0.0842)	11.03 (7.13-14.94)	0.151 (0.060-0.378)
Treatment			
Supportive care/Radiotherapy only (n = 13)	9 (0.0836)	2.63 (2.10-3.16)	1.000
Chemotherapy only (n = 19)	11 (0.0704)	5.50 (2.09-8.91)	0.702 (0.328-1.501)
Combined (Chemoradiotherapy) (n = 35)	46 (0.0842)	11.03 (7.13-14.94)	0.274 (0.134-0.560)

95% CI: 95% confidence interval; ECOG: Eastern Co-operative Oncology Group; SE: standard error

of the patients given PCI was 16.9 months while the patients not given PCI had a median survival time of 13.9 months. Unfortunately, the number of patients in our study given PCI was very small. This may be due to the fact that PCI was not that established during the period of our study and was not routinely recommended. Thus, the low number of patients given PCI in our study could explain the inferior results compared to other studies.

The median survival of our patients with ED was 8.17 months. The analysis of phase III trials for patients with extensive disease was 8.9 months for trials conducted between 1982 and 1990. Since the 1990s, there have not been many advances in the treatment of extensive SCLC. The Hoosier Oncology Group evaluated the addition of ifosfamide to cisplatin and etoposide in a phase III trial of 171 patients with ED. The median survival times were 7.3 months and 9.0 months for the control and experimental arm respectively. However, the small improvement in survival was achieved at the expense of increased toxicities.<sup>14</sup> Newer chemotherapeutic agents such as irinotecan was shown by the Japanese to be better than etoposide, when combined with cisplatin. The median survival time was 12.8 months versus 9.4 months for the experimental and control arm respectively.<sup>15</sup> However, the superior results were not replicated in a North American study, where the median survival remained at around 10 months.<sup>16</sup> Maintenance chemotherapy has also not been shown to benefit these patients.<sup>17</sup>

Other than stage, many studies have put forward patients and disease factors that could improve the prognostication of patients with SCLC.<sup>18,19</sup> We did not find any significant prognostic factors on univariate analysis of our patients with LD. Among our patients with ED, ECOG performance status and treatment given were important prognostic factors. Performance status is a known important prognostic factor in many other studies. In addition, we found that patients who were treated with a combination of chemotherapy and radiotherapy fared better than those who had no treatment or had chemotherapy or radiotherapy alone. On further subset analysis, we found that the superiority of combination of chemotherapy and radiotherapy was limited to those patients with good performance status. Thus, the finding of a lower risk of death with combination of chemotherapy and radiotherapy may be the result of more aggressive treatment within a subset of patients with good performance status. None of the other prognostic factors that were important in other studies bore out significance in our study. We did not include serum lactate dehydrogenase level in the analysis, as there were many patients with missing values. One must bear in mind that the analysis of prognostic factors in a small group of patients has definite limitations.

The biology of SCLC is likely to be similar across continents as the aetiological agent is almost exclusively cigarette smoke. This is unlike that of non-small-cell lung cancer where the epidemiological characteristics of patients may differ in Western and Asian countries. More novel therapies need to be developed for this disease, as improvements in outcome with chemotherapy have been very modest. The burden of the disease is unlikely to decrease over the next decade given the prevalence of cigarette smoking worldwide. However, one should continue to propagate anti-smoking messages in order to curb this dreadful disease.

#### REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74-108.
2. Page NC, Read WL, Tierney RM, Arquette MA, Piccirillo JF, Govindan R. The epidemiology of small cell lung carcinoma. *Proc Am Soc Clin Oncol* 2002;21:305a.
3. Levi F, Franceschi S, La Vecchia C, Randimbison L, Te VC. Lung carcinoma trends by histologic type in Vaud and Neuchatel, Switzerland, 1974-1994. *Cancer* 1997;79:906-14.
4. Chen KY, Chang CH, Yu CJ, Kuo SH, Yang PC. Distribution according to histologic type and outcome by gender and age group in Taiwanese patients with lung carcinoma. *Cancer* 2005;103:2566-74.
5. Seow A, Koh WP, Chia KS, Shi LM, Lee HP, Shanmugaratnam K. Trends in cancer incidence in Singapore 1968-2002. Singapore: Singapore Cancer Registry, 2004. Report No. 6:110-1.
6. Simon GR, Wagner H; American College of Chest Physicians. Small cell lung cancer. *Chest* 2003;123(suppl):259S-271S.
7. Janne PA, Freidlin B, Saxman S, Johnson DH, Livingston FA, Johnson BE. Twenty-five years of clinical research for patients with limited-stage small cell lung carcinoma in North America. *Cancer* 2002;95:1528-38.
8. Chute JP, Chen T, Feigal E, Simon R, Johnson BE. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. *J Clin Oncol* 1999;17:1794-801.
9. Turrisi AT 3rd, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265-71.
10. Murray N, Coy P, Pater JL, Hodson I, Arnold A, Zee BC, et al. (The National Cancer Institute of Canada clinical trials group). Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. *J Clin Oncol* 1993;11:336-44.
11. Takada M, Fukuoka M, Furuse K, Ariyoshi Y, Ikegami H, Kurita Y, et al. Phase III study of concurrent versus sequential thoracic radiotherapy (TRT) in combination with cisplatin (C) and etoposide for limited-stage (LS) small cell lung cancer (SCLC): preliminary results of the Japan Clinical Oncology Group (JCOG). *Proc Am Soc Clin Oncol* 1996;15:372 (abstract).
12. Brahmer JR, Ettinger DS. Carboplatin in the treatment of lung cancer. *Oncologist* 1998;3:143-54.
13. Auperin A, Arriagada R, Pignon JP, Pechoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *N Engl J Med* 1999;341:476-84.
14. Loehrer PJ Sr, Ansari R, Gonin R, Monaco F, Fisher W, Sandler A, et al.

- Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study. *J Clin Oncol* 1995;13:2594-9.
15. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, et al; Japan Clinical Oncology Group. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85-91.
  16. Hanna NH, Einhorn L, Sandler A, Langer C, Hariharan S, Ansari R, et al. Randomized, phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated, extensive-stage small cell lung cancer (SCLC). *J Clin Oncol* 2005;23 (Suppl):LBA7004 (abstract).
  17. Sculier JP, Berghmans T, Castaigne C, Luce S, Sotiriou C, Vermylen P, et al. Maintenance chemotherapy for small cell lung cancer: a critical review of the literature. *Lung Cancer* 1998;19:141-51.
  18. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. *J Clin Oncol* 1990;8:1563-74.
  19. Osterlind K, Anderson PK. Prognostic factors in small cell lung cancer: a multivariate model based on 778 patients treated with chemotherapy with or without irradiation. *Cancer Res* 1986;46:4189-94.
-