Clinical outcomes in patients with small cell lung cancer in a single institute: comparative analysis of radiographic screening with symptom-prompted patients

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Abstract

Objectives

The present study was performed to evaluate the differences in clinical characteristics and survival outcomes of patients with small cell lung cancer (SCLC) according to methods used for detecting the disease: radiographic screening or symptomatically prompted.

Materials and Methods

The clinical findings and actual treatment outcomes were estimated according to three means of detection of SCLC: computed tomography (CT), radiographic test, and symptom-prompted cases.

Results

We identified 147 patients (male/female ratio: 127/20; mean age: 68.1 years old) between 2000 and 2011. The patients were divided into three categories according to method of detection: chest CT (CT; n = 24), radiographic screening (CXR; n = 37), and symptom-prompted cases (symptom; n = 86). There was no significant shift to early TNM stage distribution in the CT or CXR group compared with the symptom group. However, the rates of limited disease (LD)-SCLC were significantly higher in the CT and CXR groups than the symptom group. Median survival times were 17.0 months (95% confidence interval (CI): 11.6 – 22.4) in the

CT group, 19.0 months (95%CI: 11.7 – 126.3) in the CXR group, and 12.0 months (95%CI: 9.6 – 14.4) in the symptom group. There were statistically significant differences in overall survival between CT and symptom groups ($P < 0.05$) and between CXR and symptom groups ($P < 0.001$). However, there was no significant difference in survival between CT and CXR groups.

Conclusions

Radiographic (CT plus CXR) testing contributes to better clinical outcome in patients with SCLC.

Key words: SCLC, CT screening, radiographic survey, prognosis

1.Introduction

Lung cancer is the leading cause of cancer mortality worldwide [1], including Japan [2]. Small cell lung cancer (SCLC) represents 10% – 15% of all lung cancers and shows a high grade of malignancy with rapid growth and early widespread metastasis [3 – 7]. Approximately two thirds of patients with SCLC present with extensive disease (ED), and less than 5% of those with ED-SCLC survive for over 3 years. The median survival for patients with ED-SCLC is around 8 – 13 months, while that for patients with limited disease (LD)-SCLC is approximately 15 – 18 months with a 2-year estimated survival rate of 13% – 38% [4 – 7]. It has been reported that the overall incidence of SCLC is declining in the USA, probably due to a decrease in smoking prevalence over the last several decades [3]. However, there have been few therapeutic advances despite the improvement of therapeutic modalities, including combination chemotherapy, hyperfractionated thoracic radiation, and prophylactic cranial irradiation [4 – 10]. Therefore, it is important for clinicians to search for novel therapeutic and preventive strategies for improving clinical outcomes in patients with SCLC.

The National Lung Screening Trial (NLST), a large randomized controlled trial designed to evaluate low-dose computed tomography (CT) screening for lung cancer in heavy smokers, demonstrated a decrease in lung cancer-specific mortality in a CT screening population [11]. In addition, there have been many reports that CT can detect more of these lesions at an earlier stage than chest radiography [12 –

15]. Recently, Austin et al. [16] presented a summary of 48 subjects with SCLC detected by the International Early Lung Cancer Action Program (I-ELCAP) [17] and reported that CT screening identified a shift toward early stage and away from late stage disease. We initially began a low-dose CT screening trial using a mobile CT unit in Japan [13,14,18], and CT screening for lung cancer has now been extended in Nagano Prefecture, Japan. Previously, we reported 12 cases of SCLC detected by CT screening in Nagano Prefecture and showed that LD stage was prominent (9 cases), including 5 cases of early stage SCLC suitable for thoracic surgery [18]. Thus, radiographic screening, including CT, may influence the clinical characteristics and outcome in patients with SCLC, although SCLC is usually considered a systemic disease at the time of diagnosis.

In the present study, we performed a retrospective review of SCLC patients treated at our institute. We analyzed patients' clinical characteristics and treatment outcomes according to the initial presentations or reasons for detecting the diseases into the following three categories: chest CT (CT group), radiographic test group (CXR group), and symptom-prompted cases (symptom group). Furthermore, we examined and analyzed survival to determine differences in clinical outcome among the three categories.

2. Materials and Methods

2.1. Patients

We retrospectively reviewed consecutive SCLC patients admitted and treated at Shinshu University Hospital from January 2000 to December 2011. Clinical records were reviewed and patients were divided into three categories according to the initial clinical presentation or means of detection of the disease. The information was recorded by the investigator in a manner in which subjects were anonymized and de-identified prior to analysis to protect patient privacy. Eastern Cooperative Oncology Group (ECOG) performance status (PS) at the time of diagnosis was estimated. Clinical staging was evaluated by standard examination. All patients underwent physical examination, complete blood cell count, biochemistry examination, chest radiograph, CT scans of the thorax and abdomen, bone scintigraphy, and magnetic resonance imaging (MRI) scan of the brain as pretreatment evaluation. Routine integrated positron emission tomography (PET)/CT scan was added to assess regional lymph node involvement and distant metastasis from 2005. Clinical staging was performed according to the 6th edition of the TNM classification of lung cancer [19]. The classification of LD and ED was based on the International Association for the Study of Lung Cancer (IASLC) criteria [20]. Cases of mixed with non-SCLC (large cell neuroendocrine carcinoma, squamous cell carcinoma) components were not included in the present analysis. CT and radiographic (CXR) test groups included patients who were detected by annual health screening and incidentally detected and diagnosed during follow-up of other non-pulmonary diseases. They had no specific respiratory symptoms at the time of CT or CXR examination. In general, therapy consisted of

chemoradiotherapy for LD and chemotherapy for ED. Platinum compound with VP-16 in LD-SCLC and with CPT-11 in ED-SCLC were used as chemotherapy regimens. Cisplatin or carboplatin was selected by clinicians based on the patient's renal function, PS, and age. In certain cases of early stage SCLC, thoracic surgery was initially performed followed by at least two cycles of chemotherapy. Prophylactic cranial irradiation was performed in LD-SCLC patients who showed complete response (CR) to initial treatment.

All of the patients were followed up periodically, consisting of a monthly checkup. The patients underwent routine blood examination and chest radiography. Chest CT and brain MRI were performed every 3 months or as necessary. The survival rates of patients were calculated from the date on which treatment was started until the time of death. Survival was recorded up for all patients to 31 December 2013.

2.2. Statistical analysis

Data are expressed as means ± SD. Category data were analyzed using the chi-square test and Mann-Whitney U test. The actual overall survival rates after treatment were calculated using the Kaplan–Meier method, and differences in the resulting distributions were compared between groups by the log-rank test. Prognostic factors for overall survival were examined by the Cox proportional hazards model with adjustment for covariates, including sex, age (≦74 vs ≧75), PS (0-1 vs. ≥ 2), surgery or non-surgery, clinical stage (LD vs. ED), and modes of

detection (CT, CXR, and symptom). Statistical calculations were performed using SPSS Statistics 19 (IBM). In all analyses, $P < 0.05$ was taken to indicate statistical significance.

3. Results

3.1. Clinical characteristics

The mean age of all patients was 68.1 years old (range: 39 – 86 years old). The study population consisted of 127 men (85.8%) and 20 women. Thirteen patients were never smokers, but the others were smokers with a mean number of pack years of 52.3 ± 34.1. The clinical characteristics according to three modes of the detection are shown in Table 1. Twenty-four patients were detected with CT, 37 with CXR, and 86 were prompted by symptoms. Age, sex, and PS distribution were similar between the three modes of detection. According to TNM stage, patients presenting early stage including Ⅰ and Ⅱ showed a tendency to be observed in CT and CXR. Furthermore, a half of patients detected by symptom-prompted group had stage IV. However, there was no significant distribution shift toward early from late stage in the CT or CXR group compared with the symptom-prompted group. Based on the classification of LD and ED, there were significantly more LD cases in the CT and CXR groups compared with the symptom group.

The initial treatments according to the three modes of detection are summarized in Table 2. As initial therapy, thoracic surgery was performed in 8 patients in the CT group, 6 in the CXR group, and 3 in the symptom group; thus, a total of 17 (11.6%) patients were treated with surgery. The frequency of patients treated with surgery in the CT group was significantly higher than that in the symptom group. There were no significant differences in patient populations treated with

chemoradiotherapy or chemotherapy among the three groups. One patient in the CXR group and two patients in the symptom group were treated only with thoracic radiotherapy because of advanced age and poor PS. In addition, there were several cases in each group that were unsuitable for treatment with cytotoxic agents because of poor PS or comorbidities, including cardiovascular disease and interstitial pulmonary fibrosis. Of the two cases in the CT group, one patient refused chemotherapy and the other was of advanced age and had many complications, such as liver cirrhosis and diabetes mellitus.

3.2. Survival analysis

Survival curves according to the three modes of detection in patients with SCLC are shown in Figures 1 and 2. The median survival times (MST) were 17.0 months (95%CI: 11.6 – 22.4) in the CT group, 19.0 months (95%CI: 11.7 – 126.3) in the CXR group, and 12.0 months (95%CI: 9.6 – 14.4) in the symptom group. The survival rates at three years were 24.3% (95%CI: 6.0% – 42.0%) in the CT group, 30.6% (95%CI: 16.0% – 46.0%) in the CXR group, and 9.1% (95%CI: 2.0% – 16.0%) in the symptom group. There were significant differences in overall survival between the CT and symptom groups ($P < 0.05$) and between the CXR and symptom groups ($P < 0.001$) (Figure 1). Thus, survival in SCLC patients detected by radiographic (CT plus CXR) testing was significantly superior to that in symptom-prompted patients (Figure 2). However, there was no significant difference in survival between CT and CXR groups.

We also analyzed survival according to LD/ED, surgery/non-surgery, PS 0 – 1/PS 2 – 4, age ≦74/≧75, and male/female. There were significant differences in survival between LD and ED (MST: 19.0 vs. 12.0 months, respectively, $P < 0.001$), surgery and non-surgery (MST; 51.0 vs. 14.0 months, respectively, $P < 0.001$), PS 0 – 1 and ≥ 2 (MST; 16.0 vs. 6.0 months, respectively, $P < 0.001$), age≦74 vs ≧75 (MST; 15.0 vs. 14.0 months, respectively, $P < 0.05$) (data not shown). There were no significant differences in survival between male and female patients.

CT and CXR groups included patients detected incidentally by radiographic examinations and those who were detected by annual screening tests. There were no statistically significant differences in survival between incidentally detected patients and those detected by annual screening in CT [MST; 19.0 months in screening (n = 12) vs.16.0 months in non-screening (n = 12)] and CXR [MST; 19.0 months in screening (n = 12) vs. 15.0 months non-screening (n=12)] groups (data not shown).

4. Discussion

We summarized consecutive patients with SCLC who were treated at our hospital and analyzed the clinical characteristics and outcomes according to the initial means of detection of the disease. We found that subjects detected by chest CT and radiography (CT and CXR) groups had better survival than those prompted by symptoms. In addition, CT detected early stage SCLC suitable for thoracic surgery, but did not shift the early stage distribution of SCLC and failed to improve survival compared with others.

A prospective study by NLST for lung cancer screening using chest CT demonstrated a decreased lung cancer-specific mortality rate in heavy smokers [11,12]. Although survival analysis according to histological type was not described in the NLST study, there were no significant differences in detection of patients with SCLC in each stage between CT and radiographic screening groups [11]. Indeed, Cuffe et al. [21] summarized the survival and stage of 10 cases with SCLC detected by CT screening and concluded the ineffectiveness of CT screening for altering the stage distribution and survival, consistent with the present results. These data suggest that SCLC is an inappropriate screening target due to its aggressive natural biology and early dissemination. However, Austin et al. [16] reported that CT screening identified a shift toward early stage and away from late stage disease. Although the present study was performed in a non-randomized manner and evaluated prospectively, our data reflect clinical practices related to

preventing lung cancer in Japan. The present results suggest that radiographic screening, including CT, can better detect LD-SCLC compared with symptom-prompted cases.

The present study also focused on comparison of survival in patients with SCLC according to CT and CXR or symptoms. We found that CT had no better survival benefit compared with CXR screening and symptom-prompted patients. In view of the survival results, our observations were consistent with those of Cuffe et al. [16]. However, patients detected by CT and radiography (CT plus CXR) had better survival compared with the symptom group. In addition, LD in radiographic screening groups was significantly predominant compared to the symptom group. Thus, we believe that CT and radiographic survey can find SCLC in the relatively early stages and contribute to improving survival even in patients with SCLC.

Seventeen patients with early stage SCLC underwent thoracic surgery as initial treatment. These surgical patients showed MST of 27.0 months (95%CI: 0.0 – 62.0 months) and a 5-year survival rate of 35.0% (95%CI: 13.0% – 58.0%). Several recent retrospective analyses have described improved or favorable survival rates in patient with resected SCLC [22 – 24]. Lim et al. [22] recently reported excellent results with a 5-year survival rate of 52% in patients with stage I – III disease who underwent lung resection. In Japanese subjects with resected SCLC, 5-year survival rate was 43% and the survival has improved over the past several decades [23]. Among the 48 patients with SCLC detected in the I-ELCAP study, 16 had

stage I disease and were treated with both surgery and additional therapy. The estimated cure rate (5-year survival rate) was reported to be 69% [16]. Thus, good results can be achieved in selected patients with complete resection throughout the spectrum of UICC from stage I to II. In our series, surgery could have an important role in the treatment strategies in patients with early stage LD-SCLC. Therefore, detection in the early stage of SCLC can contribute to mortality benefit in patients with SCLC.

The present study had several limitations. First, analysis was performed retrospectively in a single institute. The numbers of patients in each group were small, which adversely affected evaluation of the clinical characteristics and outcomes. Second, CT and CXR groups included patients who were detected by annual health screening and incidentally detected and diagnosed during follow-up of other diseases. However, we found that there were no statistically significant differences in survival between incidentally detected patients and those detected by screening in the CT and CXR groups. Although none of the patients had respiratory symptoms, concomitant diseases in incidentally detected patients may affect the subsequent treatment strategy and/or prognosis of SCLC. Thus, we were unable to draw definite conclusions regarding the roles of CT or radiographic screening in patients with SCLC.

5. Conclusions

Retrospective analysis of serial patients with SCLC at our institute suggested that

annual CT and/or radiographic examination contributed to detection of LD stage SCLC, and could be related to improved clinical outcome in patients with SCLC compared to those presenting with cancer-related symptoms.

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Figure Legends

Figure 1

Overall survival curves according to the three modes of detection in patients with small cell lung cancer. The median survival times were 17.0 (95%CI: 12.0 – 22.0) months in the computed tomography (CT) group, 19.0 (95%CI: 12.0 – 126.0) in the chest radiography (CXR) group, and 12.0 (95%CI: 10.0 – 14.0) in the symptom group.

Figure 2

Comparative analysis of overall survival curves between radiographically detected [computed tomography (CT) and chest radiography (CXR)] small cell lung cancer patients and symptom-prompted patients. The median survival times were 18.0 months (95%CI: 14.6 – 21.4 months) in the radiographic group and 12.0 (95%CI: 10.0 – 14.0) in the symptom group. The difference between the two groups was statistically significant ($P < 0.001$).

・Small cell lung cancer shows a widespread metastasis.
・There have been few therapeutic advances in small cell lung cancer.
・Utility of chest radiographic screening remains unclear.
・CT screening demonstrated a decrease in lung cancer-specific mortality.

Table 1

Clinical characteristics of patients with small cell lung cancer according to the three modes of detection

	CT (*n* = 24)	**CXR** (*n* = 37)	**Symptom** (*n* = 86)
Mean age (range)	**69 (51 – 83)**	**70.3 (51 – 81)**	**66.8 (39 – 86)**
Sex (M: F)	**21 : 3**	**33 : 4**	**73 : 13**
PS (0/1/2/3)	**17 / 2 / 5 / 0**	**21 / 12 / 4 / 0**	**25 / 44 / 11 / 6**
stage (I/II/III/IV)	**8 / 4 / 8 / 4**	**6 / 6 / 18 / 7**	**0 / 5 / 41 / 40**
Stage LD:ED (LD %)	**16 : 8 (67) ***	**21 : 16 (57) **:**	**30 : 56 (35)**

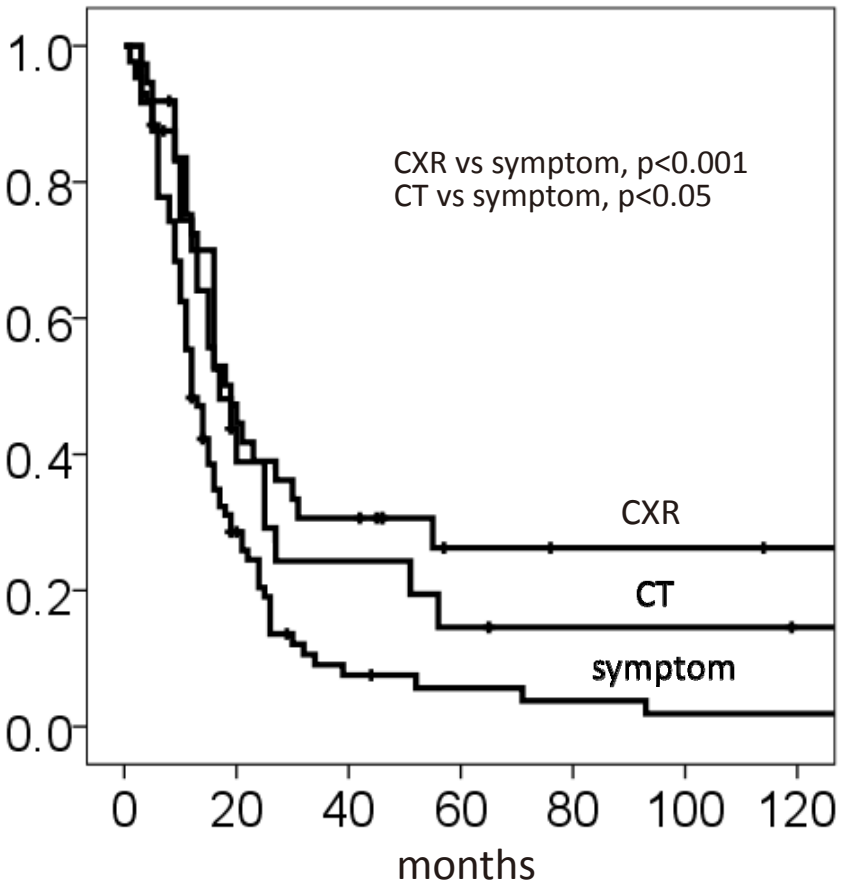
*$P < 0.01$ and ** $P < 0.02$ vs. symptom group.

Table 2

Initial treatments in patients with small cell lung cancer according to the three modes of detection

Initial Treatments	CT (n=24)	CXR (n=37)	symptom (n=86)
Thoracic surgery	8 (33%)*	6 （16%）**	3 （3%）
Chemo + radiation	3 （13%）	11（30%）	26 （31%）
Chemotherapy	11 （46%）	18 （48%）	51 （60%）
Thoracic radiotherapy only	0 （0 %）	1 （3 %）	2 （2 %）
Best supportive care	2 （8 %）	1 （3 %）	4（4 %）

*$P < 0.0001$ vs. symptom group, ** $P < 0.01$ vs. symptom group.


1.0
0.8
0.6
0.4
0.2
0.0
CXR vs symptom, p<0.001
CT vs symptom, p<0.05
CXR
CT
symptom
0
20
40
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80
100
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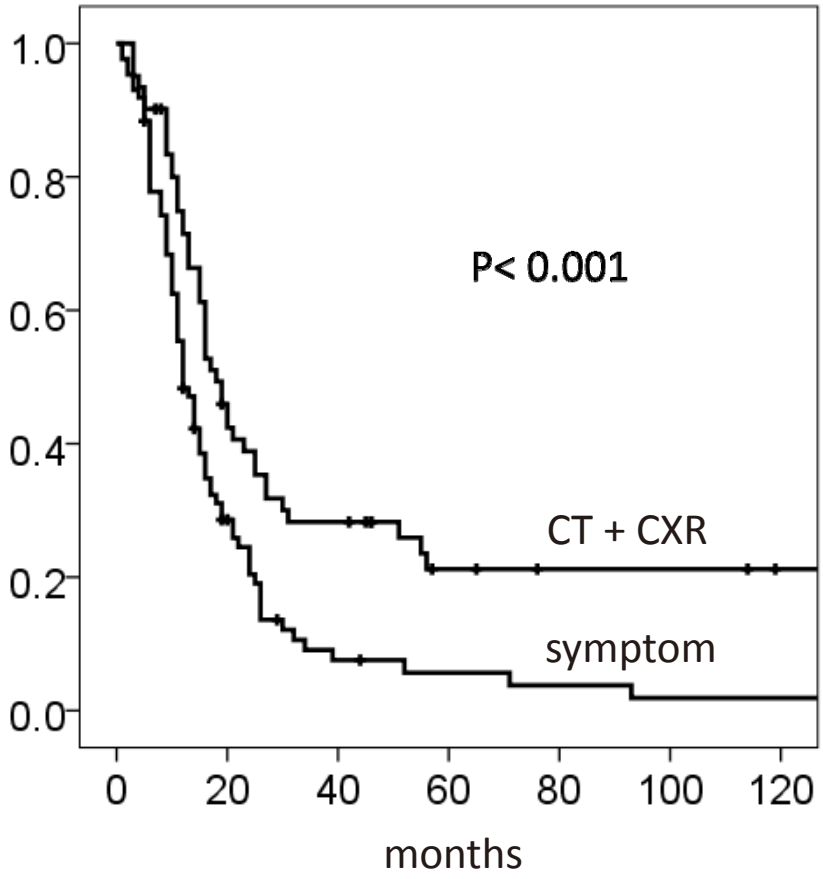
months


1.0
0.8
0.6
0.4
0.2
0.0
P< 0.001
CT + CXR
symptom
0
20
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100
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months