



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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ARTICLE INFO

Article history:

Received 23 September 2014

Received in revised form 20 January 2015

Accepted 31 January 2015

Keywords:

SCLC
CT screening
Radiographic survey
Prognosis
Lung cancer
Health screening

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: 11.7–26.3) 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.

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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

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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 \pm 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

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	16:8	21:16	30:56
(LD %)	(67)*	(57)**	(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.

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