Surgery for Small Cell Lung Cancer

A Retrospective Analysis of 243 Patients from Japanese Lung Cancer Registry in 2004

Hidefumi Takei, MD, Haruhiko Kondo, MD,* Etsuo Miyaoka, PhD,† Hisao Asamura, MD,‡ Ichiro Yoshino, MD,§ Hiroshi Date, MD,‖ Meinoshin Okumura, MD,¶ Hirohito Tada, MD,# Yoshitaka Fujii, MD,** Yoichi Nakanishi, MD,†† Kenji Eguchi, MD,‡‡ Hirotoshi Dosaka-Akita, MD,§§ Hideo Kobayashi, MD,‖‖ Noriyoshi Sawabata, MD,¶ and Kohei Yokoi, MD;¶¶ for the Japanese Joint Committee of Lung Cancer Registry*

Introduction: Indications for surgical resection for small cell lung cancer (SCLC) have been very limited. Because early-stage SCLC is a rare presentation of lung cancer, studies comparing surgical resection among a large number of patients are unlikely to be conducted. This study reports the most recent surgical outcomes of a large number of SCLC patients who underwent surgery in 2004.Methods: In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study regarding the prognosis and clinicopathologic profiles of 11,663 patients who underwent resection for primary lung cancer in 2004. Of the 11,663 patients, 243 patients with SCLC (2.1%) were included in this study. The registry data of the patients with SCLC were analyzed, and the clinicopathologic profiles and surgical outcomes of the patients were evaluated.Results: The 5-year survival rate for all cases (n = 243, 213 males, mean age 68.2 years) was 52.6%. The 5-year survival rates by c-stage and p-stage were as follows: IA, 64.3% (n = 132) and 72.3% (n = 93); IB, 45.7% (n = 36) and 61.1% (n = 51); IIA, 50.5% (n =25); and 44.8% (n = 27); IIB, 33.3% (n = 10) and 40.3% (n = 17); IIIA, 30.5% (n = 30) and 23.4% (n = 45); and IV, 0% (n = 7) and 0% (n = 9), respectively. A multivariate analysis showed that the significant prognostic factors were age, gender, c-stage, and surgical curability. A kappa value was moderate conformity between c-stage and p-stage in all cases.Conclusions: Surgical resection in selected patients with early-stage SCLC, especially stage I, had favorable results.

Key Words: Small cell lung cancer, Surgery, Registry

(*J Thorac Oncol*. 2014;9: 1140–1145)

Lung cancer is the leading cause of cancer-related death in the United States and in Japan. Small cell lung cancer (SCLC) represents only 13–20% of all lung cancers.[1] It is distinguished by its rapid growth rate and early dissemination to regional lymph nodes and distant sites. Therefore, SCLC represents less than 5% of cases in large surgical series.[2]

In 1973, the Medical Research Council[3] reported a postoperative survival rate that was as poor as the survival rate for nonsurgical treatment in SCLC patients. In addition, Mountain[4] reported that there was no difference in outcome between resected and non-resected cases in 368 SCLC patients. After those two studies were published, the standard treatment for SCLC became chemotherapy and/or radiation, and surgery was basically contraindicated. In 1983, the Lung Cancer Study Group[5] initiated the only randomized trial of adjuvant surgical resection after induction chemotherapy. This trial failed to show improved survival rates after surgery compared with radiation after neoadjuvant chemotherapy. Thereafter, several authors reported rather favorable surgical results in a relatively small number of patients with early-stage SCLC.[6,7] Shepherd and colleagues[8] reported in 1988 that the postoperative 5-year survival rate was 31% in 77 patients with surgery as the primary treatment for SCLC. In 2005, Japan Clinical Oncology Group reported a 68% 3-year postoperative survival rate in patients with resected clinical stage I SCLC undergoing postoperative adjuvant chemotherapy.[9] Recently, several large cohort studies of surgery for limited disease SCLC have

*Department of General Thoracic Surgery, Kyorin University, Tokyo; †Department of Mathematics, Science University of Tokyo; ‡Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo; §Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba; ‖Department of Thoracic Surgery, Kyoto University Graduate School of Medicine, Kyoto, ¶Department of General Thoracic Surgery, Osaka University Graduate School of Medicine, #Division of General Thoracic Surgery, Osaka City General Hospital, Osaka; **Department of Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Science and Medical School, Nagoya; ††Department of Clinical Medicine, Research Institute for Diseases of the Chest, Faculty of Medical Sciences, Kyushu University, Fukuoka; ‡‡Department of Medical Oncology, Teikyo University School of Medicine, Tokyo; §§Department of Medical Oncology, Hokkaido University Graduate School of Medicine, Sapporo; ‖‖Division of Respiratory Disease, National Defense Medical College, Tokorozawa; and ¶¶Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Hidefumi Takei, MD, Division of General Thoracic Surgery, Kyorin University, 6-20-2, Shinkawa, Mitaka, Tokyo, 181–8611, Japan. E-mail: htakei@ks.kyorin-u.ac.jp

ISSN: 1556-0864/14/0908-1140

been reported.[10,11] An analysis of 205 clinical stage IA SCLC patients from the National Cancer Institute's Surveillance Epidemiology and End Results database who underwent radical lobectomy showed a 5-year survival rate of 50.3% without postoperative adjuvant radiotherapy.[12]

However, optimal indications for surgical resection for SCLC and the efficacy of perioperative chemotherapy have not yet been determined. Because early-stage SCLC is a rare presentation, accounting for 2.4% to 3.4% of resected lung cancer,[13] and a definite preoperative diagnosis of cell type as SCLC is rather difficult, studies prospectively comparing the significance of surgical resection in a large number of cases are unlikely to be conducted.

This study aimed to investigate recent surgical results for SCLC patients retrospectively, based on the large-volume Japanese nationwide registry database.

PATIENTS AND METHODS

Patients

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study regarding the prognoses and clinicopathologic profiles of 11,663 patients who underwent resection for primary lung cancer in 2004. Of those patients, 243 with histologically confirmed SCLC (2.1%) were extracted from the database. The clinicopathologic factors and their relationship to postoperative survival were evaluated.

The following items were included for analysis: gender, age, smoking status, serum tumor markers (carcinoembryonic antigen and proGRP), clinical tumor, node, metastasis (TNM) stage (c-stage), pathological TNM stage (p-stage), surgical procedure, surgical curability (R0 and R1/R2), presence or absence of preoperative and postoperative chemotherapy, and survival time. The Union for International Cancer Control TNM staging, version 7,[14] was adopted in this study.

This study and the Japanese Joint Committee of Lung Cancer Registry registration study adhere to the Ethical Guidelines for Epidemiologic Research imposed by the Japanese Ministry of Health, Labor, and Welfare.[15]

Statistical Analysis

Survival time was defined as the time from the date of the surgery to the date of the last follow-up. Survival curves were estimated by the Kaplan-Meier method. Differences in survival were assessed by the log-rank test. A multivariate analysis by Cox's proportional hazards model was used to test the significance of prognostic factors. Statistical significance was considered to be established when the associated p value was less than 0.05.

A kappa value of conformity between c-stage and p-stage was also determined.[16] A kappa has a maximum of 1 (indicating perfect agreement) and a minimum −1 (indicating worse than chance agreement). A value of 0 indicates an agreement that is no better than chance, values above 0.4 are usually considered indicative of "moderate" agreement, and values higher than 0.6 are considered "good" agreement.

RESULTS

Patient Profiles

The clinicopathologic characteristics of the 243 patients with resected SCLC are summarized in Table 1. Of the 243 patients with resected SCLC, there were 213 (87.7%) men and 30 (12.3%) women. The mean age at the time of operation was 68.2 ± 9.5 years. Preoperative serum proGRP levels were elevated in 58 patients (23.9%) and within normal limits in 185 (76.1%) patients. The major operative mode was lobectomy/bilobectomy (n = 174, 71.6%), followed by segmentectomy/wedge resection (n = 51, 21.0%). More than 60% of patients (n = 169, 68.6%) were diagnosed as c-stage IA or IB. As for the pathologic stage, 93 patients (38.3%) were recognized as p-stage IA, and 51 (21.0%) as p-stage IB. There were 45 (18.5%) patients in p-stage IIIA. Complete resections (R0) were achieved in 214 (88.1%) patients.

Postoperative Survival

The overall postoperative survival curve is shown in Figure 1. The 5-year survival rate of the 243 patients with SCLC was 52.6%. The postoperative survival curves according to c-stage and p-stage are shown in Figure 2. The 5-year survival rates by c-stage and p-stage were as follows: 64.3% in c-stage IA, 45.7% in c-stage IB, 50.5% in c-stage IIA, 33.3% in c-stage IIB, 30.5% in c-stage IIIA, 0% in c-stage IV, 72.3% in p-stage IA, 61.1% in p-stage IB, 44.8% in p-stage IIA, 40.3% in p-stage IIB, 23.4% in p-stage IIIA, and 0% in p-stage IV. The differences in survival were significant between c-stage IA and c-stage IB (p = 0.0423), c-stage IA and c-stage IIB (p = 0.0367), c-stage IA and IIIA (p = 0.0023), p-stage IA and p-stage IIA (p = 0.0074), p-stage IA and p-stage IIB (p = 0.0033), p-stage IA and p-stage IIIA (p = 0.0000), and p-stage IB and p-stage IIIA (p = 0.0006).

The relationship of each factor to survival, determined by univariate analysis, is shown in Table 1. Except for c-stage and p-stage, there was statistical significance in gender (women fared better than men did), serum ProGRP level (worse in elevated cases), and surgical curability (R0 patients fared better than R1/R2 patients did). In a Cox proportional hazards model to predict overall survival, the following factors persisted as significant prognostic factors: gender, age, c-stage, and surgical curability (Table 2).

Clinicopathological Results According to c-Stage

The relationship of p-stage, perioperative chemotherapy, and surgical curability to c-stage is shown in Table 3. In c-stage IA + IB, 39 of 168 cases (23.2%) were upstaged to p-stage, and eight of 30 cases (26.7%) in c-stage IIIA and two (66.7%) of three in c-stage IIIB were downstaged to p-stage I or II. A conformity of c-stage and p-stage was determined to be moderate, with a kappa value of 0.425.

As for surgical curability, in c-stage I (IA + IB), 158 cases (96.3%) underwent R0 resection and only six cases (3.7%) underwent R1/R2 resection. In c-stage II, 32 cases

