Surgical Intervention for Non–Small-Cell Lung Cancer Patients with Pleural Carcinomatosis

Results From the Japanese Lung Cancer Registry in 2004

Tomohiko Iida, MD, Mitsutoshi Shiba, MD,* Ichiro Yoshino, MD,† Etsuo Miyaoka, PhD,‡ Hisao Asamura, MD,§ Hiroshi Date, MD,‖ Meinoshin Okumura, MD,¶ Hirohito Tada, MD,# Yoichi Nakanishi, MD,** Hirotoshi Dosaka-Akita, MD,†† Hideo Kobayashi, MD,‡‡ Kazuhisa Takahashi, MD,§§ Masayoshi Inoue, MD,¶ and Kohei Yokoi, MD,‖‖ for the Japanese Joint Committee of Lung Cancer Registry*

Introduction: A subset of non–small-cell lung cancer (NSCLC) patients with malignant pleural effusion and/or malignant pleural nodules is now classified as stage IV and is generally considered a contraindication to surgery. However, several reports have demonstrated that the prognosis of patients with pleural carcinomatosis first detected at thoracotomy is relatively favorable. The aim of this study was to describe the results of surgical intervention in NSCLC patients with pleural carcinomatosis in Japan.

Methods: In 2010, the Japanese Joint Committee of Lung Cancer Registry conducted a nationwide registration of lung cancer patients who underwent surgery in 2004. Using this database, we performed a retrospective study focused on pleural carcinomatosis. We examined the clinicopathological features, the current status of therapy, and surgical outcomes in patients with pleural carcinomatosis.

Results: Among the 11,420 registered NSCLC patients, 329 (2.9%) patients had pleural carcinomatosis. The median survival time and 5-year survival rate of 313 patients without other metastatic disease were 34.0 months and 29.3%, respectively. Primary tumor resection was performed in 256 (81.8%) patients, and macroscopic complete resection was achieved in 152 (48.6%) patients, with 5-year survival rates of 33.1% and 37.1%, respectively. Multivariate analysis revealed that Eastern Cooperative Oncology Group performance status ($p < 0.001$), best stage nodal status ($p = 0.002$), and the presence or absence of gross residual tumor ($p = 0.013$) were independent predictors of survival.

Conclusion: In our surgical registry for NSCLC, patients with pleural carcinomatosis accounted for 2.9%, and macroscopic complete resection for them was associated with better survival.

Key Words: Non–small-cell lung cancer, Pleural carcinomatosis, Malignant pleural effusion, Malignant pleural nodule, Surgical treatment.

(*J Thorac Oncol.* 2015;10: 1076–1082)

Pleural carcinomatosis is defined as the progression of the primary cancer to the pleural cavity.[1] In particular, it includes malignant pleural effusion (MPE) and/or malignant pleural nodules (MPN). Generally, non–small-cell lung cancer (NSCLC) patients with pleural carcinomatosis have a poor prognosis and are considered unsuitable candidates for surgery.[2–4] In the 7th edition of the tumor, node, metastasis (TNM) staging system for lung cancer, pleural carcinomatosis was reclassified from T4 to M1a.[5] However, patients with pleural carcinomatosis are very diverse; some have minimal amounts of pleural effusion, which is only detected at thoracotomy, and others have massive amounts of pleural effusion and symptoms. In fact, a number of papers have reported that the postoperative prognosis of patients diagnosed with malignant pleural disease at thoracotomy is relatively favorable.[6–11]

Herein, we aimed to describe the results of surgical intervention in NSCLC patients with pleural carcinomatosis in Japan during 2004.

PATIENTS AND METHODS

Patients

In 2010, the Japanese Joint Committee of Lung Cancer Registry conducted a nationwide registration of lung cancer

*Department of Thoracic Surgery, Kimitsu Central Hospital, Chiba, Japan; †Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba, Japan; ‡Department of Mathematics, Science University of Tokyo, Tokyo, Japan; §Division of Thoracic Surgery, Keio University School of Medicine, Tokyo, Japan; ‖Department of Thoracic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan; ¶Department of General Thoracic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan; #Department of General Thoracic Surgery, Suita Tokushukai Hospital, Osaka, Japan; **Department of Clinical Medicine, Research Institute for Diseases of the Chest, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan; ††Department of Medical Oncology, Hokkaido University Graduate School of Medicine, Sapporo, Japan; ‡‡Division of Respiratory Disease, National Defense Medical College, Tokorozawa, Japan; §§Division of Respiratory Medicine, Juntendo University Faculty of Medicine & Graduate School of Medicine, Tokyo, Japan; and ‖‖Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Disclosure: Asamura has received speaker honoraria from Johnson & Johnson and Covidien Japan. The other authors declare no conflicts of interest.

Address for correspondence: Tomohiko Iida, MD, Department of Thoracic Surgery, Kimitsu Central Hospital, 1010 Sakurai, Kisarazu, Chiba 292–8535, Japan. E-mail: hptiida@hotmail.co.jp

DOI: 10.1097/JTO.0000000000000554

ISSN: 1556-0864/15/1007-1076

patients who underwent surgery in 2004. As described previously, the committee asked the 605 teaching hospitals certified by the Japanese Board of General Thoracic Surgery to join the study, of which 253 (41.8%) participated.[12] From these institutions, clinicopathological data and survival outcomes for 11,663 patients were collected. This registry was approved by the institutional review board of Osaka University Medical Hospital where the registry office is located.

In the registry, the total number of patients with NSCLC was 11,420, but 45 patients had incomplete pleural carcinomatosis data. Thus, we ultimately analyzed 11,375 patients in this study. The TNM staging was reclassified according to the 7th edition of the International Union Against Cancer-TNM staging system published in 2009.[13] Patients did not always have pathological stage records, so we adopted the concept of best stage, which is defined as the pathological stage if available and clinical otherwise.[5] Although, as for pleural carcinomatosis, we selected patients with cytologically proven MPE and/or histologically proven MPN.

Statistical Analysis

We examined the clinicopathological features, the current status of therapy, and survival outcomes in patients with pleural carcinomatosis. Fisher's exact test or χ^2 test for categorical data and *t*-test for continuous data were used to compare differences in clinicopathological variables and treatment modalities. Overall survival was calculated from the date of surgery to the date of last follow-up or death. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to identify prognostic factors after surgery. A significant difference was defined as a p value less than 0.05. Statistical analyses were performed with SPSS 19.0 (IBM Corp, Armonk, NY) and the SAS 9.3 (SAS institute, Inc, Cary, NC).

RESULTS

There were 329 (2.9%) patients with pleural carcinomatosis. Of these patients, 183 had MPE (98 with MPN, 82 without MPN, and 3 with unknown data for MPN), and 244 had MPN (98 with MPE, 136 without MPE, and 10 with unknown data for MPE). Characteristics of patients with pleural carcinomatosis were compared with those of patients without pleural carcinomatosis (Table 1). Elevation of preoperative serum tumor markers (including carcinoembryonic antigen, squamous cell carcinoma-related antigen, cytokeratin 19 fragment, Sialyl Lewis X, neuron-specific enolase, and progastrin-releasing peptide), nonsquamous cell carcinoma histology, larger tumor size, and lymph node involvement were significantly associated with a higher incidence of pleural carcinomatosis.

The treatment modalities are summarized in Table 2. To avoid any impact from another metastasis, we excluded 16 patients with other M1a and/or M1b disease, and therefore, we analyzed 313 patients. Despite the presence of pleural carcinomatosis, the primary tumor was resected in 256 (81.8%) patients. Even in the 81 patients diagnosed with or suspected to have pleural carcinomatosis before thoracotomy, the rate of primary tumor resection was similar, but the rate of pneumonectomy was significantly higher than that in patients who were diagnosed at thoracotomy. Postoperative chemotherapy before disease progression was used in 180 (57.5%) patients.

The median survival time (MST) and 5-year survival rate of all 313 patients were 34.0 months and 29.3%, respectively. The 5-year survival rate for the 92 patients with both MPE and MPN was 16.2%, whereas the 5-year survival rates for the 81 patients only with MPE and the 126 patients only with MPN were 37.6% ($p = 0.001$) and 34.5% ($p < 0.001$), respectively (Fig. 1).

To identify prognostic factors, we performed univariate and multivariate analyses using the Cox proportional hazards model (Table 3). Univariate analyses revealed that women, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, adenocarcinoma histology, tumor size ≤ 3cm, best stage N status (N0 or N1), resection of primary tumor, and absence of gross residual tumor were associated with significantly longer survival. These variables were examined by multivariate analysis, and ECOG performance status ($p < 0.001$), best stage N status ($p = 0.002$), and the presence/absence of gross residual tumor ($p = 0.013$) persisted as independent predictors of survival.

The 5-year survival rate for patients with macroscopic complete resection was 37.1%, compared with 22.7% and 12.2% in patients with macroscopic incomplete resection ($p = 0.009$) and exploratory thoracotomy ($p < 0.001$), respectively (Fig. 2). There was no significant prognostic difference between macroscopic incomplete resection and exploratory thoracotomy ($p = 0.137$).

We also examined the clinicopathological variables of 57 patients subjected to exploratory thoracotomy (Table 4). Although the proportion of patients with a large number of MPN was significantly higher in the exploratory thoracotomy group (52.6%, $p = 0.007$), 86 (33.6%) patients in the primary tumor resection group had a large number of MPN. By contrast, the proportion of patients with N2/N3 was significantly lower in the exploratory thoracotomy group (22.8%, $p = 0.045$).

DISCUSSION

The advantage of this study was that the sample was very large, and that the patients were treated at approximately the same time. According to a recent systematic review of pleural carcinomatosis studies, the number of patients ranged from 5 to 227, and the study duration ranged from 4 to 17 years.[2] Our study had more than 300 patients, and all of them underwent thoracotomy in 2004. The short-term study enables us to eliminate the effect of progress in chemotherapy, diagnosis, etc.

In this study, we had 329 (2.9%) patients with pleural carcinomatosis, but the incidence was slightly lower than that in previous studies.[6,14] Patients with a small amount of MPE may have blended in with the 217 patients with positive pleural lavage cytology in our registry. Because other metastases may have influenced the choice of therapy and the prognosis in patients with pleural carcinomatosis, the analyses of treatment modalities and survival were performed for 313 patients without other M1a and/or M1b disease.