Pulmonary Resection for Synchronous M1b-cStage IV Non-Small Cell Lung Cancer Patients

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Background. We wanted to assess the efficacy of curative intent pulmonary resection for non-small cell lung cancer (NSCLC) patients with synchronous M1b-distant metastases in a single organ or lesion.

Methods. Between 1995 and 2015, 23 consecutive synchronous M1b-cStage IV NSCLC patients who underwent any treatment for metastases and curative intent pulmonary resection were retrospectively analyzed.

Results. Sixteen patients were men and 7 were women, with a median age of 56 years (range: 41 to 76 years). There were 17 adenocarcinoma, 4 large-cell carcinoma, 1 large-cell neuroendocrine cancer, and 1 carcinosarcoma. Thirteen patients had no lymph node metastasis. Fourteen patients received preoperative chemotherapy, and 10 received postoperative chemotherapy. The metastatic sites were the brain in 13 patients; bone in 3 patients; adrenal glands and extrathoracic lymph nodes in 2 patients each; and the liver, small intestine, and subcutaneous tissue in 1 patient each. Nineteen patients underwent lobectomy, and the other 4 patients underwent pneumonectomy. Seventeen patients experienced recurrence as follows: local recurrence in 3 patients, distant recurrence in 13 patients, and both in 1 patient. The 5-year progression-free survival rates in the 23 patients was14.5% (95% confidence interval: 0% to 30.6%), and the 5-year overall survival rate was 41.7% (95% confidence interval: 19.6% to 63.8%).

Conclusions. Some M1b-cStage IV NSCLC patients achieved longer survival than others with the same stage disease by using local treatment for distant metastases and curative intent pulmonary resection. Oligometastatic patients might have been inadvertently included in the present cohort. However, at present, the optimum method for patient selection remains unclear.

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The principle treatment strategy for non-small cell lung cancer (NSCLC) patients with distant metastasis is chemotherapy as a systemic treatment [1, 2]. Local treatment modalities, such as radiotherapy, are commonly used with palliative intent for cancer-associated symptoms [3], and surgical intervention is seldom indicated. Moreover, with the recent remarkable advances in chemotherapy drugs and strategies, the reported survival of NSCLC patients with distant metastasis has been improving [4], especially for the patients with adenocarcinoma that harbors sensitive driver oncogene mutation or fusion, such as epidermal growth factor receptor (EGFR) [5] and anaplastic lymphoma kinase [6]. Indeed, the patients treated with the EGFR-tyrosine kinase inhibitor afatinib showed a median overall survival (OS) of 23.1 to 28.2 months in phase III trials [7, 8], which was almost more than twice as long as the OS previously reported with chemotherapy using cytotoxic drugs [9].

Recently, the concept of isolated metastasis, that is, oligometastasis, has been widely recognized. The basic concept of oligometastasis involves one or a small number of distant metastases, generally with an indolent nature, that can be controllable by local therapy such as radiotherapy or surgical resection, thereby curing or extending the survival of patients [10]. However, no method of determining which patients have oligometastasis at the time of diagnosis has been developed. With the increasing attention being focused on this concept, some retrospective analyses for NSCLC patients with synchronous solitary brain metastasis [11, 12] or adrenal metastasis [13, 14] have shown comparatively better prognoses for cStage IV disease with simultaneous local treatment for metastasis and pulmonary resection. In addition, surgical resection both for the primary site and

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metastasis in the contralateral lung in M1a-cStage IV patients has been reported to improve survival in some retrospective analyses [15, 16]; however, being able to distinguish pulmonary metastasis from synchronous multiple primary lung cancer has up to now been difficult, with diagnoses made based on the criteria established in 1975 [17].

We therefore evaluated the potential benefit to OS of curative intent pulmonary resection for M1b-cStage IV NSCLC patients with their distant metastases in a single organ or lesion treated with curative intent pulmonary resection as a single-institute experience.

Patients and Methods

We retrospectively reviewed the medical charts of 1829 consecutive NSCLC patients who underwent curative intent pulmonary resection by lobectomy or greater lung parenchymal resection between January 1995 and August 2015 at the Department of Thoracic Oncology, National Kyushu Cancer Center, Japan. We analyzed 23 synchronous M1b-cStage IV NSCLC patients with their distant metastases in a single organ or lesion treated with curative intent pulmonary resection.

The patients with contralateral pulmonary metastases were eliminated, because the differentiation of pulmonary metastasis from multiple primary lung cancer can be difficult, especially for patients without lymph node metastasis, even in the retrospective setting. All of the 23 M1b-cStage IV NSCLC patients were cytologically or histologically confirmed to have NSCLC before any treatment, and 22 of 23 patients underwent stereotactic, conventional radiation therapy or surgical removal of the metastatic site; the remaining patient received chemotherapy alone followed by curative intent pulmonary resection.

A histologic analysis of the tumor was conducted according to the World Health Organization classification for cell types [18]. The clinical or pathologic stage of the disease was defined based on the general rules for the *TNM Classification of Malignant Tumors* (7th edition) [19]. The eligibility for surgical resection in this series of patients was determined based on clinical practice; basically, the patients with an Eastern Cooperative Oncology Group performance status (PS) of 0 to 1, an estimated postoperative forced expiratory volume in 1 second greater than 600 mL/m^2 of the body surface area, and adequate preserved organ functions expected to tolerate chemotherapy radiotherapy or both were considered to be eligible. Chest radiography, computed tomography (CT) of the chest and upper abdomen, CT or magnetic resonance imaging of the brain, a bone scan or fluorodeoxyglucose positron emission tomography, and flexible optical bronchoscopy were routinely performed for all patients. The patients who had other concomitant uncontrolled malignancies or serious comorbidities, such as clinically significant cardiac disease, active infection, or neurologic or psychiatric disorders, were excluded. The principles of surgical resection were en bloc removal of the affected lobe or lung parenchyma with adjacent structures and, if necessary, systemic hilar and mediastinal lymph node dissection.

The statistical analyses were conducted using the χ^2 test and two-tailed Student's t test for comparison of the variables. The Kaplan-Meier method was used to determine the OS and disease-free survival curves. The progression-free survival (PFS) was defined as the time from the starting date of any treatment until disease progression or death from any cause. The OS was defined as the time from the starting date of any treatment until death from any cause. The median follow-up time was 37.8 months (range, 5.7 to 192.5 months) for all patients, 58.2 months (range, 7.9 to 192.5 months) for the living patients, and 24.0 months (range, 5.7 to 97.8 months) for the deceased patients at the time of the analysis. All of the statistical analyses were performed using the IBM SPSS Statistics 18 software package (SPSS Japan, Tokyo, Japan).

The institutional review board and ethics committee reviewed and approved the protocol of this retrospective analysis. Written informed consent was obtained from all patients.

Results

The characteristics of the 23 patients are listed in Table 1. The median age of the patients was 56 year (range, 41 to 76 years). There were 16 men and 7 women. At the time of the initial treatment, 17 patients (73.9%) were Eastern Cooperative Oncology Group PS 0, and 6 (26.1%) were PS 1. The pathologic diagnosis of the primary tumor was mandatory, and the major histologic type was adenocarcinoma in 17 patients (73.9%), followed by large-cell carcinoma in 4 patients (17.4%) and large-cell neuroendocrine carcinoma and carcinosarcoma in 1 each. Four patients each had a tumor status of cT1a and b, 9 had cT2a, 1 had T2b, and 5 had cT3, and 13 had a lymph node status of cN0, 5 had N1, 3 had cN2, and 2 had cN3 at the time of diagnosis.

Table 2 lists the characteristics of the metastatic site and its treatment. Eighteen patients had single metastatic lesion and 5 patients had two or more metastatic lesions. The most frequent metastatic site in this series of patients was the brain in 13 (56.5%) patients, including 4 with multiple metastatic lesions; 5 patients with single brain metastasis underwent surgical removal of the metastatic tumor, and 1 patient with two metastases underwent surgical resection followed by stereotactic radiotherapy. Two patients had single adrenal gland metastasis, and both underwent surgical resection of the metastasis. Of the three patients with bone metastasis, one with rib metastasis underwent simultaneous resection with the pulmonary resection, and the other two with vertebral metastases received radiotherapy at the metastatic site. One patient with single liver metastasis experienced complete remission of the liver metastasis after chemotherapy before pulmonary resection. One patient with a single but bulky metastasis in the small intestine, two