Surgical treatment of stage IV non-small cell lung cancer

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Abstract

Most stage IV non-small-cell lung cancer (NSCLC) patients are not amenable to curative treatment. The purpose of this study was to analyse our initial experience with an aggressive surgical strategy for stage IV NSCLC, and to define which patients can benefit from this treatment. Forty-six stage IV NSCLC patients who underwent surgical resection of both primary lung cancer and metastatic sites from April 1989 to December 2010 were included in this study. The record of each patient was reviewed for age, gender, pN status, sites of metastasis, histology, surgical procedure and duration of survival. There were 13 females and 33 males. Their median age was 62.0 years (range, 44–82 years). The overall 5-year survival rate was 23.3% (median, 20.0 months), and the disease-free survival rate was 15.8% at 5 years (median, 16.1 months). Patients with the pN2 status had a significantly worse survival than patients with a pN0 or pN1 status (8.6 versus 33.1%, \( P = 0.0497 \)). According to a multivariate Cox proportional hazards analysis, no independent predictor of survival was identified. The results of our study suggest that surgical treatment can extend the survival in stage IV NSCLC patients if the patients can tolerate surgery.

Keywords: Stage IV • non-small cell lung cancer

INTRODUCTION

Lung cancer is one of the most prevalent malignancies and the leading cause of cancer-related death worldwide. Non-small-cell lung cancer (NSCLC) accounts for nearly 80% of lung cancer cases. Of the patients who will develop NSCLC, ~20–50% will present with metastatic disease. Most of the patients presenting with metastatic disease are not amenable to curative treatment, and they have an overall median survival time of 7–11 months [1]. The most common extrapulmonary sites of distant metastases are the brain, bones, liver and adrenal glands [2]. Approximately 7% of patients with metastatic disease from a NSCLC primary tumour will be found to have a solitary metastasis after full evaluation [3]. There are no clear guidelines about whether NSCLC stage IV patients, or certain subgroup of stage IV NSCLC patients, may benefit from surgical resection. In our institution, when we judged that we can control both primary and metastatic sites, we performed aggressive surgical treatment. The purpose of this study was to analyse our initial experience with this aggressive surgical strategy for stage IV NSCLC, and to define which patients can benefit from this treatment.

MATERIALS AND METHODS

A retrospective review from April 1989 to December 2010 identified 46 stage IV NSCLC patients who underwent surgical resection for primary lung cancer in the Department of Thoracic Surgery at the Clinical Research Institute, National Hospital Organization, Kyushu Medical Center (Fukuoka, Japan). All of these patients also underwent treatments for distant metastases, including surgical resection or cerebral stereotactic radiosurgery (SRS). Preoperative evaluations were performed using chest roentgenograms and computed tomography images, brain MRI, bone scintigraphy and fluorodeoxy glucose positron emission tomography. All patients were staged using seventh edition of the TNM classification of malignant tumours [4]. The record of each patient was reviewed for age, gender, site(s) of metastasis, histology, surgical procedure, date of recurrence and duration of survival. Overall survival was defined as the time from the date of surgery for primary lung cancer until the last date of follow-up. The disease-free survival was defined as the time from the date of surgery for primary lung cancer to recurrence or death. The study was approved by our Institutional Review Board. Informed consent was not required for this retrospective study.

The statistical analyses were carried out with Stat View software program (SAS Institute, Inc, Cary, NC, USA). Overall survival was calculated by the Kaplan–Meier method. The differences between survival curves were analysed using the log-rank test for univariate analyses. A multivariate analysis was performed according to the Cox proportional hazards model to estimate the relative risk with 95% confidence interval. The results of the analysis were regarded as statistically significant at a probability value <0.05.

RESULTS

The characteristics of the patients at the time of resection of their NSCLC primary tumour are shown in Table 1. There were
13 females and 33 males. Their median age was 62.0 years (range, 44–82 years). Sixteen patients had no identified lymph node metastasis, 5 patients were pN1, 20 patients were pN2 and 5 patients had an unknown status. The sites of metastases were the brain (22 patients), contralateral lung (9 patients), bone (7 patients), adrenal grand (4 patients), liver (2 patients), small bowel (2 patients) and chest wall (1 patient). A histological analysis confirmed the presence of adenocarcinoma (26 patients), squamous cell carcinoma (11 patients), adenosquamous cell carcinoma (7 patients) and other types (2 patients) of cancer. All of these 46 patients underwent surgical resection, including a pneumonectomy in 1 patient, bilobectomy in 4 patients, lobectomy in 35 patients, segmentectomy in 1 patient and partial resections in 5 patients.

The overall 5-year survival rate was 23.3% (median, 20.0 months) (Fig. 1). Figure 2 shows that the disease-free survival rate was 15.8% at 5 years (median, 18.1 months). The pN-positive status was not found to correlate with survival (15.4 versus 31.5%, \( P = 0.1062 \)) (Fig. 3a). However, patients with the pN2 status had a significantly worse survival than patients with the pN0 or pN1 status (8.6 versus 33.1%, \( P = 0.0497 \)) (Fig. 3b). Patients who have bone metastasis tended to have a worse outcome than those with metastases at other sites, but the difference was not significant (14.3 versus 30.5%, \( P = 0.0527 \)) (Fig. 4a). Patients who had contralateral lung metastasis tended to have a better outcome than those with other sites of metastasis, but again, the difference was not significant (55.6 versus
Chemotherapy is commonly administered for patients with stage IV NSCLC. However, at our institution, when we judge that we can control both the primary tumour and metastatic site(s), we perform aggressive surgical treatment. The overall 5-year survival rate in our surgically treated patients was 23.2%, and median survival from the date of pulmonary resection was 20.0 months. The disease-free 5-year survival rate was 15.8%, and median survival from the date of pulmonary resection was 16.1 months. However, there were patients who achieved long-term survival after treatment for recurrence. This is in contrast to chemotherapy with gemcitabine and carboplatin, which provide time to progression of 5.6–5.7 months, and median survival of 10.3–10.6 months [5]. Our results show a better outcome for surgery compared with these studies. There were two octogenarian patients in our study. One patient had adenocarcinoma with brain metastasis, and underwent cerebral SRS and segmentectomy. The other patient had squamous cell carcinoma with contralateral lung metastasis, and underwent a lobectomy without diagnosing the contralateral lung nodule as the metastasis. Afterward, a partial resection was performed because the contralateral nodule had gradually increased in size. These patients survived 18 months and 57 months, respectively.

In our study, most patients had not received adjuvant chemotherapy, because there was no evidence of any benefit to using adjuvant chemotherapy for stage IV NSCLC. However, various new drugs have been shown to provide favourable outcomes, especially in patients with adenocarcinoma. For example, EGFR tyrosine kinase inhibitors (EGFR TKI) led to progression-free survival of 9.7–14 months among patients with EGFR mutations [6], and platinum-based chemotherapy in combination with bevacizumab led to progression-free survival of 6.5–7.8 months in non-squamous NSCLC [7, 8]. We may be able to provide a better outcome for our surgically treated patients in the future by adding these agents as adjuvant chemotherapy.

We performed surgical resection after obtaining informed consent, when we judge that we could control both the primary tumour and metastatic site(s) even for N2 cases. Billing et al. [9] reported that the presence of thoracic lymph node metastases was an independent predictor of a worse prognosis for primary lung cancer with synchronous brain metastases. Bonnette et al. [10] reported that the presence of thoracic lymph node metastases was not an independent predictor of a worse prognosis for primary lung cancer with synchronous brain metastases. In our study, the pN status was not found to correlate with survival; however, patients with the pN2 status had a significantly worse survival than patients with the pN0 or pN1 status. However, in our multivariate Cox proportional hazards analysis, the pN2 status was not identified as a significant independent predictor of adverse survival, although there was a trend for it to be a predictor. We believe that the lack of significance may be due to the use of systematic and en-block lymph node dissection (ND2a) at our institution.

Without treatment, the development of brain metastases is usually a fatal event in the natural history of NSCLC, and the median survival after discovery of brain metastasis is a dismal 1–2 months [11]. The 5-year survival rate is 14.5% in patients who have had brain metastasis. This is identical to the previous reports indicating that the 5-year survival rate is 11–23.5% in patients who were treated by surgical resection for synchronous brain metastas
metastases [9, 12]. An alternative approach to cerebral resection is cerebral SRS. Although SRS and neurosurgery are local treatment options, no randomized trials have examined the local recurrence-free survival and overall survival of patients receiving radiosurgery versus conventional surgery. While retrospective data are not conclusive, there so far does not appear to be a better clinical outcome with neurosurgery compared with SRS [13].

Patients who develop intrapulmonary metastasis in the same lobe are, according to the seventh edition of the IASLC, considered to have T3 disease. If the metastasis is located within an ipsilateral non-primary lobe, the cancer is then classified as T4. The presence of pulmonary metastases in a contralateral lobe is considered to indicate M1a disease [4]. We utilized the criteria described by Martini and Melamed [14] to distinguish a metastasis in the contralateral lung from a second primary carcinoma. Leyn et al. [15] reported that the 5-year survival rate was 38%, after complete surgical resection of synchronous multiple contralateral lung cancers. In our present study, the 5-year survival rate was 55.6% in patients who had contralateral lung metastasis. Based on these findings, even patients with contralateral lung metastases should be considered for curative surgical resection.

There was no significant difference in the survival for partial resection versus other procedures (20.0 versus 24.4%, \(P = 0.7752\)). This may have been due to the fact that partial resection had been performed for only five patients. These patients had poor pulmonary function, but no lymph node metastases. This finding suggests that local control for primary lung cancer should be considered if the patient's pulmonary function is poor. Recently, minimally invasive procedures for the local treatment of primary tumours, for example radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT), have been performed in patients with high surgical risk or poor lung functional reserve.

In conclusion, surgical treatment can extend the survival in stage IV NSCLC patients, because surgery remains the only potentially curative treatment. If the affected organ is one which is easily compromised by the presence of metastasis, such as the brain or small bowel, we recommend that to resect the metastatic site(s) prior to the lung cancer. We believe that aggressive surgical treatment should be provided if patients can tolerate surgery, but certain subgroup of patients, including those with bone metastasis, should be treated using other modalities. Local control for primary lung cancer, such as via partial resection, RFA or SBRT, should be considered in cases with high surgical risk or poor lung functional reserve, and in cases with less favourable sites of M1 disease.

Conflict of interest: none declared.

REFERENCES