



Concurrent Chemoradiotherapy for Patients With Postoperative Recurrence of Surgically Resected Non–Small-Cell Lung Cancer

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Abstract

The effect of concurrent chemoradiotherapy (CRT) for recurrent non–small-cell lung cancer has not yet been established. Thirty-five patients received concurrent CRT as an initial treatment in our study. The median progression-free survival and postrecurrence survival after CRT was 13 and 31 months, respectively. The ECOG performance status, surgical procedure, and types of platinum agents used were independent prognostic factors.

Background: A few reports have evaluated the outcomes of concurrent chemoradiotherapy (CRT) for patients with postoperative recurrence of non–small cell lung cancer (NSCLC). **Patients and Methods:** From 2000 through 2011, 1237 consecutive patients with NSCLC underwent pulmonary resection at our institution. Of those, 280 patients had experienced postoperative recurrence by the end of 2012. Thirty-five patients received concurrent CRT as initial treatment of the recurrent disease. We retrospectively reviewed these cases, analyzed the outcomes of concurrent CRT after surgical resection, and examined the factors that predict long-term postrecurrence survival. **Results:** The most common sites of recurrence in this cohort were the lymph nodes in 24 patients, followed by the lung in 5 patients and bone in 6 patients. The median radiation dose given as the initial treatment of recurrence was 60 Gy (range, 30–60 Gy). Chemotherapy included a platinum agent in all cases; cisplatin-based chemotherapy was administered in 23 cases, and a carboplatin-based chemotherapy regimen was administered in 12. The median progression-free and postrecurrence survival after CRT was 13 months (range, 4–127 months) and 31 months (range, 5–127 months), respectively. Seven patients were still alive without evidence of disease for > 3 years after the recurrence diagnosis. The ECOG performance status (PS), surgical procedure, and types of platinum agents used were independent prognostic factors for postrecurrence survival. **Conclusion:** Concurrent CRT for recurrent NSCLC is a promising therapy for selected patients. A poor PS and postpneumectomy state were poor prognostic factors for patients who received concurrent CRT.

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Introduction

Non–small cell lung cancer (NSCLC) continues to be the most frequently occurring type of cancer, with approximately

1.61 million new cases annually worldwide.¹ Although surgery is the best therapeutic modality for patients with early-stage NSCLC, recurrence has been reported to occur in 20% to 50% of all cases.^{2–7}

The treatment of recurrent disease has usually been considered to be similar to that used for advanced disease; however, considering the diversity of recurrent disease and the postoperative state, it remains controversial whether the standard treatment of advanced disease should be the standard for recurrent disease. Although chemotherapy is a commonly accepted option for recurrent lung cancer, some of the local therapies, such as radiotherapy,

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chemoradiotherapy (CRT), and surgical resection, have been shown to improve the prognosis of selected patients with recurrent disease.⁸⁻¹² No standard therapeutic policy for treating recurrent disease has been established. The National Comprehensive Cancer Network guidelines have recommended that mediastinal lymph node recurrence or superior vena cava obstruction be treated using concurrent CRT based on level 2A evidence.¹³ However, the prognosis of patients with recurrent NSCLC treated with concurrent CRT has been examined less often than that of patients with advanced disease.¹¹

The purpose of the present study was to examine the efficacy of concurrent CRT for recurrent NSCLC and to identify the prognostic factors associated with postrecurrence survival.

Patients and Methods

Patients

A total of 1237 consecutive patients who had undergone surgical resection for NSCLC at the National Kyushu Cancer Center from January 2000 to December 2011 formed the initial study cohort. Until the end of 2012, 280 patients were identified as having developed recurrent disease. Of the 280 patients, 90 (32%) had local recurrence, 114 (41%) had distant recurrence, and 76 (27%) had both local and distant recurrence. Of those patients, 35 patients received concurrent CRT as an initial treatment of the recurrent disease.

Postoperative Follow-up and Diagnosis of Recurrence

A follow-up examination was usually performed every 2 to 3 months for the first 2 years after surgery and every 3 to 6 months thereafter. The routine follow-up procedures included physical examinations, hematologic examinations, and chest radiography. In addition, chest and abdominal computed tomography was performed at least annually. When recurrent disease was suspected, additional evaluations, such as brain magnetic resonance imaging, bone scintigraphy, and/or fluorodeoxyglucose-positron emission tomography, were added. Recurrent NSCLC was thus diagnosed through physical examination and the diagnostic finding on imaging of lesions consistent with recurrent disease. Differentiation between a second primary lung cancer and intrapulmonary metastases was generally performed according to the definitions proposed by Martini and Melamed.¹⁴ Histologic confirmation of the diagnosis was made when clinically feasible. The date of recurrence was defined as the date of histologic proof or, in cases diagnosed from clinical evidence, the date of recognition of the recurrent disease by the attending physician. Local recurrence was defined as disease recurrence at the surgical margin, ipsilateral hemithorax, or mediastinum. Distant metastasis was defined as disease recurrence in the contralateral lung or outside the hemithorax and mediastinum.

Data Collection and Extraction

The demographic, clinical, and treatment data were abstracted from an institutional database that included the data from all patients who had undergone thoracic surgery. The histologic diagnosis of the tumors was determined using the criteria proposed by the World Health Organization,¹⁵ and the TNM stage was

determined according to criteria revised in 2009.¹⁶ The Brinkman index is defined as the number of cigarettes smoked per day multiplied by the number of smoking habits. Epithelial growth factor receptor (*EGFR*) mutations were detected using direct sequencing or a highly sensitive polymerase chain reaction-based analysis. A deletion mutation in exon 19 and a point mutation in exon 18 or exon 21 were considered to be *EGFR* mutations in the present study. Each patient provided written informed consent for the use of their medical records. The institutional review board approved the present study.

Statistical Analysis

Progression-free survival (PFS) was defined as the interval from the date of recurrence to documented disease progression. Postrecurrence survival was defined as the interval from the date of recurrence to the date of the last follow-up examination. The probability of survival was estimated using the Kaplan-Meier method. Differences in survival were evaluated using the log-rank test. Significant variables affecting postrecurrence survival identified on univariate analysis were tested by multivariate analysis using a Cox proportional hazards regression model. All the hazard ratios in the present study were derived from the postrecurrence survival data. *P* values < .05 were considered statistically significant.

Results

Patient Characteristics

The patient characteristics are listed in Table 1. The median patient age at the diagnosis of recurrence was 64 years (range, 35-82 years). Of the 35 patients, 25 were male and 10 were female. Thirty-three patients (94%) had an ECOG performance status (PS) of 0 or 1 at the diagnosis of the initial recurrence. Adenocarcinoma accounted for 60% of the cases (*n* = 21), followed by squamous cell carcinoma (*n* = 11, 31%), and other histologic types (*n* = 3, 9%). The resection types performed as the initial treatment included lobectomy (*n* = 28) and pneumonectomy (*n* = 7). The pathologic stage according to the TNM 7th edition was stage I in 11 patients (31%), stage II in 9 (26%), and stage III in 15 patients (43%). The *EGFR* mutation was examined in 26 patients (64%), 9 (35%) of whom were positive. Postoperative chemotherapy was administered to 13 patients (37%). The median disease-free interval from the detection of the first recurrence was 12 months (range, 1-40 months).

The recurrence types and recurrent sites are listed in Table 2. The most commonly involved organs were the lymph nodes, which were affected in 24 patients, followed by the lung in 5 patients and bone in 6. Of the 24 patients with lymph node recurrence, 21 had intrathoracic recurrence and 3 had extrathoracic recurrence. Of all the patients with recurrence, 25 (71%) had local recurrence and 10 (29%) had distant; 21 cases (60%) had multiple lesions. The bone and lung recurrences included in the present study were identified as single lesions.

Treatments and Treatment Toxicity

All patients underwent planned CRT with curative intent. The treatment received is summarized in Table 3. The delivered

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