Preoperative Chemoradiotherapy Using Cisplatin plus S-1 Can Induce Downstaging in Patients with Locally Advanced (Stage III) Non-Small-Cell Lung Cancer

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Abstract. Background: About 30% of patients with non-small cell lung cancer (NSCLC) have locally advanced cancer (stage IIIA or IIIB) at the time of presentation. Many institutions have reported treatment with preoperative chemoradiotherapy (PCRT) followed by curative resection in patients with stage III NSCLC, but the optimal therapeutic protocol for this group has not been established. Patients and Methods: Nineteen patients with stage III NSCLC were treated with PCRT, followed by surgery at the Hamanomachi Hospital, Fukuoka, Japan from May 2000 to November 2011. We evaluated the effectiveness of PCRT for inducing downstaging using mainly three chemoradiotherapy regimens; cisplatin plus Tegafur-Gimeracil-Oteracil Potassium (S-1), cisplatin plus Tegafur-Uracil (UFT), or 1,1’cyclobutanedicarboxylate (Carboplatin, CBDCA) plus paclitaxel, with concurrent radiation therapy in 19 patients with stage III NSCLC. Results: The overall 5-year survival rate was 57.1%, which is higher than the average survival rate for patients with stage III NSCLC in Japan. Among the regimens used, only cisplatin plus S-1 with concurrent radiation therapy significantly induced downstaging. There was a significant difference in survival time between the downstaged and non-downstaged groups. However, there was no significant difference in survival time between the S-1 plus cisplatin group and the other groups combined, because of the short observation period for the S-1 plus cisplatin group. Conclusion: PCRT using cisplatin plus S-1 with concurrent radiation therapy is useful for inducing downstaging in patients with locally advanced stage III NSCLC.

Lung cancer is difficult to diagnose at an early stage. The prevalence of lung cancer is increasing, and so is the resulting mortality. Among patients with non-small cell lung cancer (NSCLC), 25%-30% have locally advanced cancer (stage IIIA or IIIB) at the time of initial diagnosis (1, 2). Most patients will develop local recurrence or distant metastasis shortly after the primary treatment (3). The optimal treatment approach for stage III NSCLC has yet to be determined. Patients with stage IIIB or IV NSCLC have a poor prognosis even if they undergo surgery. In Japan, patients with stage IIIA, or lower, NSCLC are indicated for surgery. Downstaging to stage IIIA or lower is essential for curative resection. In a randomized phase III study, the West Japan Lung Cancer Group and Radiation Therapy Oncology Group have shown that patients with stage III NSCLC have a superior survival rate after surgery if they undergo concurrent chemoradiotherapy (4, 5). Downstaging by preoperative chemoradiotherapy (PCRT) has been shown to allow for curative surgery in patients with locally advanced cancer (3, 6, 7). In patients with N2 disease, PCRT followed by surgery has been shown to improve survival compared with surgical treatment alone (8, 9). Higgins et al. reported that PCRT was associated with a higher rate of mediastinal pathological complete remission, but not with improved survival, compared with preoperative chemotherapy (10). Uy et al. reported that radiation therapy with concurrent chemotherapy using cisplatin plus etoposide can lead to improved overall and disease-free survival of patients with stage IIIA NSCLC (11). Kunitoh et al. reported that radiation therapy with concurrent chemotherapy using mitomycin, vindesine, and cisplatin is safe and effective for the treatment of patients with superior sulcus tumors (12). Kaya et al.
reported that PCRT using weekly cisplatin and docetaxel followed by surgery is effective and well-tolerated in patients with locally advanced NSCLC (13). However, the optimal protocol for chemotherapy regimens has not been established.

Cisplatin is a central drug used in combination chemotherapy because it does not often induce bone marrow suppression and is easy to use in combination with other drugs. In Japan, cisplatin plus Tegafur-Gimeracil-Oteracil Potassium (S-1) is currently standard therapy for advanced relapsed gastric cancer (14), and cisplatin plus 5-fluorouracil (5-FU) is standard therapy for advanced esophageal cancer (15, 16). Bleiberg et al. reported a response rate of 35% to cisplatin plus 5-FU and 19% to cisplatin-alone in patients with esophageal cancer (15). However, the effectiveness of chemotherapy using cisplatin plus S-1 in patients with lung cancer, especially stage III NSCLC, has not been reported yet. In the present study, we retrospectively evaluated our experience with PCRT using mainly three chemoradiotherapy regimens; cisplatin plus S-1, cisplatin plus Tegafur-Uracil (UFT), and 1,1’cyclobutanedicarboxylate (Carboplatin, CBDCA) plus paclitaxel with concurrent radiation therapy for inducing downstaging in 19 patients with locally advanced NSCLC.

### Patients and Methods

**Patients.** Nineteen patients with stage III NSCLC underwent PCRT prior to surgical treatment at the Hamanomachi Hospital, Fukuoka, Japan from May 2000 to November 2011. Patients' characteristics are shown in Table I. The hospital’s Ethics Committee approved the study protocol. All patients were given full explanations and gave their written informed consent before treatment.

**Chemoradiation protocol.** All patients underwent radiation therapy (30-45 Gy, in daily fractions of 1.8 Gy, 5 times per week). Chemotherapy regimens were as follows. Seven patients received 1-2 cycles of cisplatin (80 mg/m² on day 1) plus S-1 (60-120 mg daily for 14 days), five patients received 1 cycle of CDDP (60 mg/m² on day 1) plus UFT (400-600 mg/m² daily for 14 days), five patients received 1-3 cycles of CBDCA (ACU-6) plus paclitaxel (200 mg/m² on day 1), one patient received 1 cycle of cisplatin (80 mg/m² on day 1) plus docetaxel (60 mg/m² on day 1) every 3 weeks, and one patient received 2 cycles of cisplatin (80 mg/m² on day 1) plus irinotecan (60 mcg/m² on days 1, 8, and 15 every 3 weeks). The histological response to PCRT was classified into four categories as follows (17): Ef0: no histological response, Ef1: more than one-third of the tumor cells viable, Ef2: less than one-third of the tumor cells viable, Ef3: no viable tumor cells. Severe treatment-related toxicity (grade 3-5) did not occur in any patient.

**Statistical analysis.** Cumulative survival time was calculated using the Kaplan–Meier method and analyzed using the log-rank test. Survival time was calculated from the time of operation to the time of death or the last follow-up. A two-tailed *p*-value of <0.05 was considered to be significant.

### Results

**Downstaging by PCRT improved 5-year survival rate.** The overall 5-year survival rate of all 19 patients was 57.1%, which is higher than the average survival rate of about 30%,
reported in Japan (Figure 1) (18). Downstaging was induced in nine patients, who had a 5-year survival rate of 85.7%. The 5-year survival rate in patients who were not downstaged was 33.3%, which is almost the same as the average reported survival time in Japan. Survival time was significantly longer in patients who were downstaged than those who were not (Figure 2). However, the histological response to PCRT was not associated with the likelihood of downstaging (Table II). PCRT using cisplatin plus S-1 induced downstaging. Nineteen patients with stage III NSCLC underwent PCRT at our hospital during the study period. The chemotherapy regimens are given in Table I. Among these regimens, only cisplatin plus S-1 significantly induced downstaging (Table II). The 5-year survival rate for patients who received cisplatin plus S-1 was 64.3%, and for patients treated by other regimens was 55.6% (Figure 3). Survival time was longer in patients treated with cisplatin plus S-1 than the average survival time of stage III lung cancer patients. However, there was no significant difference in survival time between the CDDP plus S-1 group and the other groups combined. Histological response (Ef1 vs. Ef2+3, Figure 4), tumor histology (adenocarcinoma vs. squamous cell carcinoma, Figure 5), gender (data not shown), and age (data not shown) were not associated with survival time. Details of a representative case treated using cisplatin plus S-1 are shown in Figure 6. The huge tumor in the right lung decreased significantly in size after PCRT (Figure 6A). Histological examination showed a degenerative component of squamous cell carcinoma and scar-like fibrous tissue, with no evidence of viable carcinoma cells (Ef3; Figure 6B).

Discussion

In our treatment protocol, patients with T3 or N2 stage III NSCLC underwent PCRT. In patients with T3 stage III NSCLC, we expected that PCRT would induce a decrease in tumor size. In patients with N2 stage III NSCLC, we expected that PCRT would induce downstaging. Patients with clinical stage N2 have the worst prognosis among all patients (19, 20). A smaller tumor size and lower clinical stage allows for curative resection with less need for resection or reconstruction of the great vessels and vertebral bodies. The overall 5-year survival rate of all 19 patients was 57.1%, which is higher than the previously reported average survival rate for stage III patients (Figure 1). This may be the result of a skilled surgeon performing surgery at one institute. From this point of view, we recognize that the current cohort study is relatively small, but the results are still worth analyzing.

Downstaging was significantly induced in six out of the seven patients in the cisplatin plus S-1 group, whereas downstaging

![Figure 1. Kaplan–Meier analysis of overall survival of patients with stage III non-small cell lung cancer who were treated at our hospital.](image)

![Figure 2. Kaplan–Meier analyses of overall survival of patients who were downstaged and those who were not.](image)

Table II. Statistical analysis in the induction of downstaging.

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*Statistically significant as evaluated by chi-square test. CDDP: cisplatin; UFT: tegafur uracil; S-1: tegafur gimeracil oteracil potassium; Ef: effect.
was not significantly induced in patients in the cisplatin plus UFT or CBDDCA plus paclitaxel groups. As expected, survival time was significantly longer in patients who were downstaged than in those who were not (Figure 2). Unexpectedly, however, survival time was not longer in the cisplatin plus S-1 group than the other groups (Figure 3). One reason for this is the small number of patients in this study. Another reason is that the observation period was shorter in the cisplatin plus S-1 group than the other groups. Interestingly, the histological response to PCRT was not associated with survival time (Figure 4). One reason for this is that distant metastasis may not be controlled, even if the primary tumor has decreased in size. These results suggest that the histological response to PCRT may not accurately reflect control of systemic disease by chemotherapy (3). Thomas et al. reported that mediastinal downstaging was an independent predictor of overall survival of patients with stage III NSCLC, but that histopathological response was not (3). Cisplatin plus UFT did not induce downstaging in our series, even though UFT is also a FU group drug. Postoperative chemotherapy might be a confounding factor in this series, as patients in good condition underwent adjuvant chemotherapy (without radiation therapy) after surgical treatment, using the regimen that had been effective preoperatively.

Complications of chemoradiation also need to be addressed. After PCRT, curative resection is more technically challenging because of inflammation and scarring. Adhesiolysis between the tumor tissue and the pulmonary artery or vein should be performed with particular care, and lymph node dissection may be difficult because of adhesions between nodes and vessels. Reynolds et al. reported that neoadjuvant chemoradiotherapy increases the risk of respiratory complications and sepsis after transthoracic esophagectomy (21). An operative mortality rate of 26% has been reported in patients undergoing pneumonectomy (22). The European Organization for Research and Treatment of Cancer (EORTC) trial reported an overall surgical mortality rate of 4%, with a mortality rate of 7% in patients who underwent pneumonectomy and 0% in patients who underwent lobectomy (23). We mainly performed lobectomy after PCRT, which may have contributed to the low mortality rate at our hospital. As our prognosis is better than the average, lobectomy is thought to be an appropriate surgical treatment for our patients. However, the leak rate after sleeve resection tends to be higher after PCRT. We therefore covered the anastomosis with pericardial fat and thymus after sleeve resection.

Our results suggest that their preoperative chemoradiotherapy regimen of S-1 plus cisplatin may be useful in patients with stage III NSCLC because it can induce downstaging and allow for subsequent curative resection.

Conflicts of Interest

The Authors declare no conflicts of interest.
Acknowledgements

This study was supported by a General Scientific Research Grant (23592065) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We thank Ms Kaori Nomiyama for skilful technical assistance.

References

