Evaluation of concurrent chemoradiotherapy for locally advanced NSCLC according to EGFR mutation status

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Abstract. Concurrent chemoradiotherapy (cCRT) is the standard treatment for patients with locally advanced non-small cell lung cancer (LA-NSCLC). However, the efficacy and safety of this treatment has not been compared between patients who possess epidermal growth factor receptor (EGFR) mutations and patients with wild-type EGFR. The objective of the present study was to evaluate the effect of the presence of EGFR gene mutations in patients with LA-NSCLC receiving cCRT. Between January 2007 and December 2013, the records of 64 patients were reviewed retrospectively. The data were statistically analyzed to evaluate the efficacy of cCRT according to EGFR mutation status. In total, 15/64 were revealed to possess EGFR mutations, 23%, and comprised the mutant EGFR group. The progression-free survival time was significantly shorter in the mutant EGFR group compared with the patient group with tumors exhibiting wild-type EGFR, 6.3 and 9.5 months, respectively (P<0.001). The overall survival rate was longer in the mutant EGFR group compared with the wild-type EGFR group, although the difference was not statistically significant, 37.1 and 21.1 months, respectively (P=0.26). The disease recurred in all of the patients of the mutant EGFR group, whilst the recurrence rate in the wild-type EGFR group was 89%. The frequency of distant metastasis was significantly higher in the mutant EGFR group compared with the wild-type EGFR group. In conclusion, these data suggest that additional studies are required to identify strategies for reinforcing the efficacy of cCRT, with a focus on the potential use of EGFR tyrosine kinase inhibitors for patients exhibiting an EGFR mutation.

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Introduction

Lung cancer is a leading cause of cancer-associated mortality worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 80% of all cases of lung cancer, and ~30% of patients with NSCLC present with locally advanced lung cancer. The standard treatment for patients with locally advanced NSCLC (LA-NSCLC) possessing a good Eastern cooperative oncology group performance status (ECOG-PS) (0 or 1) and adequate organ function is thoracic radiotherapy (TRT) combined with chemotherapy (2,3). Previous randomized trials demonstrated that concurrent cytotoxic chemoradiotherapy (cCRT) with a third-generation regimen, a combination of a platinum compound with novel agents, is more effective compared with second-generation regimens (4,5). However, the majority of treated individuals developed disease recurrence, with a 5-year survival rate of 15-20% (3,5). The identification of somatic gene mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) (6,7) led to the development of a novel treatment strategy for patients with advanced NSCLC (8-11). Molecular profiling has become essential for the treatment of patients with advanced NSCLC to predict the response to specific molecular targeted agents such as EGFR tyrosine kinase inhibitors (TKIs). Despite the developments in this area of molecular biology, and the discovery of EGFR mutation, there have been no additional improvement in the treatment of LA-NSCLC in the previous decade. In this context, additional research is required to understand the biological behavior of the population of patients with LA-NSCLC with EGFR mutations. The objective of the present study was to evaluate and validate the frequency of EGFR mutations among patients with LA-NSCLC, and the clinical efficacy of cCRT in patients with LA-NSCLC according to EGFR mutation status.

Patients and methods

Patient selection. The patients enrolled in the present retrospective cohort study were diagnosed with unresectable LA-NSCLC and received cisplatin-based chemotherapy with cCRT at the Kitasato University Hospital (Sagamihara, Japan) between January 2007 and December 2013. All patients were histologically or cytologically diagnosed with NSCLC, and received a thoracic radiotherapy (TRT) dose of 50-60 Gy. Medical records were reviewed to collect patient data and data associated with the tumors including the age, gender, tumor EGFR mutation status, clinical disease stage, ECOG-PS, smoking history and presence or absence of a history of EGFR-TKI therapy in each patient. The patients were classified according to their smoking status as non-smokers, <100 cigarettes in a lifetime, or current/former smokers. All patients with unknown EGFR mutation status and patients who underwent induction chemoradiotherapy followed by definitive surgery were excluded. The present study was carried out with approval from the Institutional Review Board at Kitasato University School of Medicine (Sagamihara, Japan).

Response analysis. Tumor response was classified according to the Response Evaluation Criteria in Solid Tumors (version 1.1) (12). Patients were evaluated to identify the evaluable lesions prior to chemoradiotherapy. If chest radiography suggested disease progression or recurrence, additional detailed examination was performed by computed tomography (CT) scans of the chest and abdomen, and other imaging techniques such as magnetic resonance imaging of the head and fludeoxyglucose positron emission tomography.

Analysis for detecting EGFR mutations. Cytologic or histologic specimens were examined for the presence or absence of EGFR mutations by the peptide nucleic acid (PNA)-locked nucleic acid (LNA) polymerase chain reaction (PCR) clamp method or Cycleave method as previously described (13,14).

Treatment methods. All patients were treated with TRT and 2 cycles of cCRT. TRT was administered in 2 Gy daily standard fractionation using 6 or 10 MV X-rays, depending on the position and size of the individual tumors. The total target dose of radiation was fixed at 60 Gy. A CT-based treatment-planning system was mandatory to define the planning target volume. Dose distribution was calculated with tissue heterogeneity correction. The radiation field was reduced around the primary tumor and involved the lymph nodes, subsequent to exposure to 40 Gy using adequate fields to limit the dose to the spinal cord, which received a maximum dose ≤50 Gy. The planned percentages of lung volume receiving >20 Gy (V20) was <35%. cCRT consisted of 80 mg/m^2 cisplatin on day 1 and 20 mg/m^2 vinorelbine on days 1 and 8. Subsequently, the patients received 2 cycles of consolidation chemotherapy with 80 mg/m^2 cisplatin on day 1 and 25 mg/m^2 vinorelbine on days 1 and 8.

Statistical analysis. The differences in the response rates and recurrence patterns according to the tumor EGFR mutation status were compared using the χ^2 test. Progression-free survival (PFS) was measured from the date of start of cCRT to the date of documentation of treatment failure; death, disease progression or appearance of unacceptable toxicity, or the date of censoring at the last follow-up examination. Overall survival (OS) was defined as the interval between the date of start of cCRT and date of death from any cause or the date of censoring. Post-progression survival (PPS) was measured from the date of documentation of disease progression to the date of death from any cause or the date of censoring. The survival curves were plotted using the Kaplan-Meier method, and the differences between the survival times were analyzed using the log-rank test. The variables, including gender, smoking status, PS, status of EGFR mutation, histology and clinical stage were used as variables in a Cox's proportional hazards model to determine the hazard ratios for OS and PPS. $P<0.05$ was considered to indicate a statistically significant difference, and statistical analysis was performed using SPSS, version 17.0 (SPSS, Inc., Chicago, IL, USA) for Windows.

Results

Patient characteristics. The data of 64 patients with unresectable LA-NSCLC who received cCRT with cisplatin-based chemotherapy were examined. The median follow-up time was 27.4 months. The main clinical characteristics of the patients are summarized in Table I. Amongst the 64 patients, 15 (23%) patients possessed EGFR mutations in the tumor. EGFR mutations in the tumors were observed predominantly in non-smokers. All the patients possessed an ECOG-PS of 0-1, and the distribution of the clinical stage was not statistically different between the mutant and wild-type EGFR groups.

Response and survival. The objective tumor responses are summarized in Table II. The overall response rate was 73.4%. The response rates (RRs) in the patient groups with mutant and wild-type EGFR in the tumors were 66.7 and 75.5%, respectively, and no statistically significant difference was observed. The median time to achieve the objective response was not significantly different between the mutant and wild-type EGFR groups, 1.25 and 1.28 months, respectively. The crude recurrence rates in the mutant and wild-type EGFR groups were 100 (15/15) and 89% (44/49), respectively. The frequency of distant metastasis was significantly higher (P=0.01) in the mutant EGFR group compared with the wild-type EGFR group (Table III).

The survival data are demonstrated in Fig. 1. A significantly shorter PFS was observed in the mutant EGFR group compared with the wild-type EGFR group, median PFS 6.3 and 9.5 months, respectively (P<0.001). Conversely, there was no significant difference in OS observed between the two groups, although OS tended to be longer in the mutant EGFR group, median OS 37.1 and 21.1 months, respectively (P=0.26). The PPS data are demonstrated in Fig. 2. Amongst the patients who exhibited disease relapse, the PPS was significantly longer in the mutant EGFR group compared with the wild-type EGFR group, median PPS 29.9 and 11.2 months, respectively (P=0.015).

The results of multivariate analysis are summarized in Table IV. The presence of EGFR mutation and diagnosis of clinical stage were independent prognostic factors of short PFS. Additionally, the presence of EGFR mutation tended to be a predictor of a long PPS.

Table I. Patient characteristics.

Characteristics	EGFR mutation (%)		
	Mutant (n=15)	Wild type (n=49)	
Age			
Median, range	61, 52-72	60, 34-74	
Gender			
Male	10 (67)	38 (78)	
Female	5 (33)	11 (22)	
Smoking status			
Non-smoker	8 (53)	6 (12)	
Current/former smoker	7 (47)	43 (88)	P<0.001
ECOG-PS			
0-1	15 (100)	49 (100)	
2-4	0	0	
Clinical stage			
IIIA	7 (47)	22 (45)	
IIIB	8 (53)	27 (55)	
Chemotherapy regimen			
Platinum based regimen	15 (100)	49 (100)	
Presence of EGFR-TKI therapy	15 (100)	3 (0.12)	P<0.0001

WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Table II. Tumor response.

Variables	All patients (n=64)	EGFR mutation		P-value[a]
		Mutant (n=15)	Wild type (n=49)	
Complete response	2	0	2	
Partial response	45	10	35	
Stable disease	12	5	7	
Progressive disease	4	0	4	
Not evaluable	1	0	1	
Response rate (%)	73.4	66.7	75.5	0.84

[a]χ^2 test; Mutant vs. Wild type; EGFR, epidermal growth factor receptor. Response rate = complete response + partial response.

Table III. Recurrence rate and recurrence pattern.

Variables	EGFR mutation		P-value
	Mutant (n=15)	Wild type (n=49)	
Crude recurrence rate (%)	15 (100)	44 (89)	
Loco-regional recurrence	1	15	0.06
Distant recurrence	14	29	0.01

EGFR, epidermal growth factor receptor.

Discussion

The present study evaluated the effect of EGFR mutation in patients with LA-NSCLC who underwent cCRT with definitive radiotherapy. In the present study, PFS was revealed to be significantly shorter in the EGFR mutant group compared with the wild type group. Disease recurrence was revealed to occur more frequently in the EGFR mutant group compared with the wild type group, particularly more frequently in the distant site from the primary region.

Other studies have reported on the association between EGFR status and treatment outcomes subsequent to cCRT in

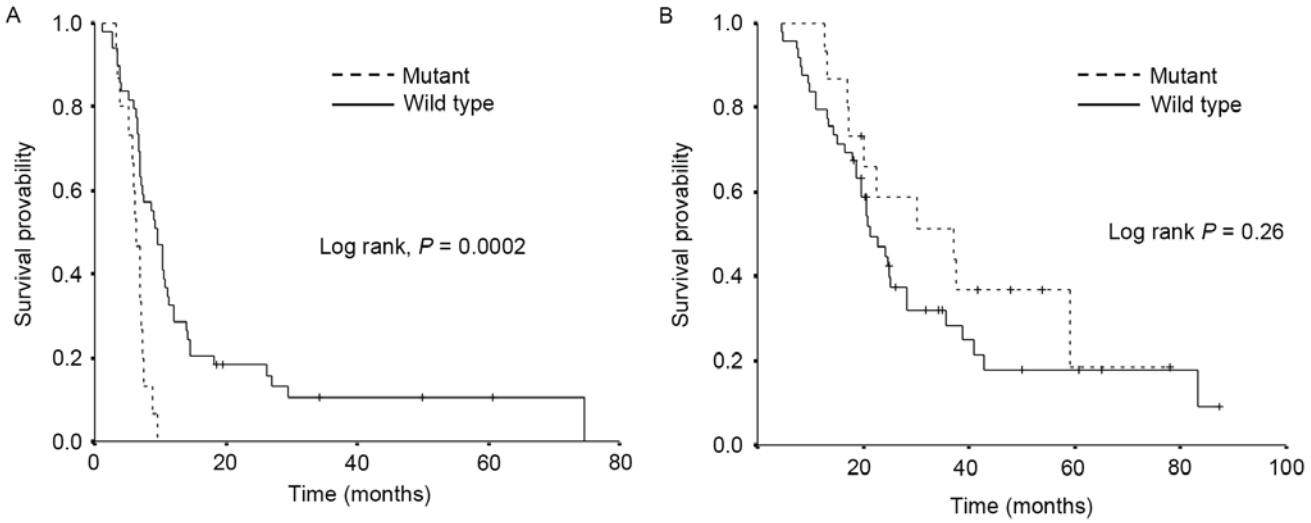

Figure 1. Kaplan-Meier plots of the (A) progression-free survival and (B) overall survival in patients with (EGFR) mutations in the tumor vs. patients with wild-type EGFR in the tumor. EGFR, epidermal growth factor receptor; bold line, EGFR mutation group; dashed line, EGFR wild type.

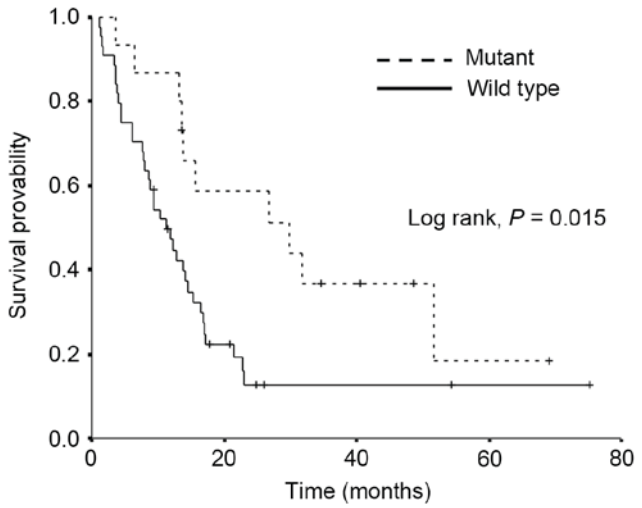

Figure 2. Kaplan-Meier plots of the post-progression survival in patients with EGFR mutations in the tumor vs. patients with wild-type EGFR in the tumor. EGFR, epidermal growth factor receptor; bold line, EGFR mutation group; dashed line, EGFR wild type.

patients with LA-NSCLC. Amongst these studies, the majority of groups reported that PFS and recurrence rate were not statistically different (15-17) between the two groups. In the present study PFS was shorter and recurrence rate was higher in the EGFR mutant group, which was inconsistent with data from previous studies. Only one study, Tanaka *et al* (18), demonstrated that the PFS was shorter and 2-year recurrence-free survival rate was poorer in the EGFR mutant group.

Notably, the recurrence patterns in these studies subsequent to cCRT in LA-NSCLC setting were similar to those of the present study, which demonstrated that the EGFR mutant groups exhibited lower loco-regional recurrence rate (15,16,18). Preclinical studies have demonstrated that NSCLC cell lines with EGFR mutations exhibit greater radiosensitivity compared with those without EGFR mutation. The assumed mechanism underlying this observation is the delayed repair of radiation-induced DNA damage in these cells (19,20). These preclinical studies may measure the aforementioned clinical observations, better local control of the cCRT for EGFR mutant patients, as the anticancer effect for irradiated field is superior for the EGFR mutant tumors.

Although these observations promote the expectation that cCRT is a potentially more favorable treatment in patients with LA-NSCLC that possess EGFR mutations, these studies do not demonstrate that cCRT is more beneficial compared with PFS. Additionally, the PFS was significantly shorter in the EGFR mutant group in the present study. To explain this discrepancy, the recurrence rate in the distant site was a focus of the present study. It was significantly higher in the EGFR mutant group compared with the wild type (P=0.01). Therefore, it may be hypothesized that the EGFR mutant tumors were more likely to result in distant metastasis. These data regarding recurrence patterns are considered important as it suggests that the improvement of the treatment strategy for patients with EGFR mutant LA-NSCLC is required.

Regarding OS, the present study demonstrated a tendency towards a longer median OS and a significantly longer median PPS in the mutant EGFR group compared with the wild-type EGFR group. Previous studies have revealed that in patients with metastatic NSCLC who possess EGFR mutations, EGFR-TKI therapy was associated with higher response rates and a longer PFS compared with standard chemotherapy (8-11). Therefore, the present study hypothesized that the addition of EGFR-TKI therapy alongside standard chemotherapy may account for the longer OS and PPS in the mutant EGFR group compared with the wild-type EGFR group in the groups of the present study. The multivariate analysis of PPS performed in the present study supports this hypothesis. Several studies have reported that EGFR inhibition enhances the antitumor activity of ionizing radiation *in vitro* (21-23). Accordingly, it may be appropriate to suggest that a combined therapy of EGFR inhibitor and TRT may improve the probability of a cure in patients with LA-NSCLC who possess an EGFR mutation. However, few clinical trials have been able to demonstrate a clear benefit of combined EGFR-TKI therapy with TRT in patients with

Table IV. Multivariate analysis using a Cox's proportional hazards regression model.

A, PFS

	Multivariate analysis	
Variables	HR (95% CI)	P-value
Gender	1.07 (0.50-2.25)	0.87
ECOG-PS (0 vs. 1)	0.95 (0.51-1.77)	0.87
Smoking (current/former smoker vs. non-smoker)	0.79 (0.35-1.76)	0.56
EGFR (mutant vs. wild type)	3.23 (1.51-6.88)	<0.01
Clinical stage (IIIA vs. IIIB)	1.94 (1.07-3.52)	0.03
Histology (Sq. vs. Non-Sq.)	1.06 (0.48-2.30)	0.89

B, PPS

	Multivariate analysis	
Variables	HR (95% CI)	P-value
Gender	1.45 (0.64-3.26)	0.38
ECOG-PS (0 vs. 1)	1.15 (0.55-2.40)	0.72
Smoking (current/former smoker vs. non-smoker)	0.93 (0.35-2.46)	0.89
EGFR (mutant vs. wild type)	0.41 (0.16-1.03)	0.06
Clinical stage (IIIA vs. IIIB)	0.79 (0.43-1.45)	0.44
Histology (Sq. vs. Non-Sq.)	1.17 (0.50-2.78)	0.71

PFS, progression-free survival; PPS, post-progression survival; ECOG-PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Sq, squamous cell carcinoma; HR, hazard ratio; CI, confidence interval.

LA-NSCLC (24-29). In an attempt to obtain an answer to this question, the WJOG6911L trial is currently in progress in Japan, which is a multicenter phase II trial of gefitinib administration in combination with radiotherapy in patients with LA-NSCLC who possess sensitizing EGFR mutations (trial no., UMIN000008366).

The data of the present study demonstrated a higher recurrence rate in the EGFR mutant and wild type groups compared with historical control data of phase III studies of cCRT (3,4). It is hypothesized that two of the eligibility criteria of the patients may have caused this difference. Firstly, the result of the EGFR mutation analysis was required for the present study, which was possibly absent if a patient survived without disease recurrence. Secondly, patients who were treated with induction chemoradiotherapy followed by definitive surgery (CRT+S) were excluded. In Kitasato University Hospital (Sagamihara, Japan), CRT+S was performed for the patients in which the tumors were nearly resectable stage IIIA tumors that had been successfully downgraded in stage, and had become resectable with a good response for the induction chemoradiotherapy. It is suggested that exclusion of these patient groups who exhibited better prognoses caused the higher recurrence rate.

There were several limitations to the present study. First, as a retrospective study the results cannot be regarded as definitive. Secondly, the sample size may not have been sufficient. Thirdly, there was no pharmacokinetic validation for the differences in the efficacy of chemotherapy according to the tumor EGFR mutation status in the present study. In addition, the eligibility criteria of the patients included a result of the EGFR mutation status, which may have introduced some bias during patient selection. The absence of EGFR mutation analysis was most commonly due to the histological diagnosis of the patients, such as squamous cell carcinoma.

In conclusion, the present study confirmed that conventional cCRT using platinum based regimen may not be the most effective type of treatment for patients with LA-NSCLC who possess EGFR mutations. The results of ongoing studies including the WJOG6911L trial are required to identify novel strategies for improving the efficacy of cCRT, with special consideration given to the potential use of EGFR-TKIs.

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