Background

Lung cancer is the most common type of cancer, both worldwide and in Japan [1]. Non-small cell lung cancer (NSCLC) accounts for 80-85% of lung cancer cases, and approximately 30% of patients have unresectable, locally advanced disease at diagnosis [2]. In the 1990's, radiotherapy alone was recognized as the standard treatment, but its efficacy was insufficient [3]. Sause et al., reported that adding chemotherapy to radiotherapy brought further survival benefit [4]. A recent meta-analysis concluded that concurrent chemoradiotherapy (CRT) is state-of-the art treatment in this population [5,6].

The goal of CRT in locally advanced NSCLC (LA-NSCLC) is to cure. In the early period of treatment, tumor shrinkage is an indicator of efficacy. Although concurrent CRT provides a high rate of tumor response (60–70%), we should take into account that it does not always mean cure. Recent phase III trials of concurrent CRT reported that two-thirds of patients who experienced complete, or partial response eventually relapsed [7,8]. Another indicator of efficacy is progression-free survival (PFS). The Kaplan-Meier curves of PFS in LA-NSCLC showed the "infant mortality" type. This means that most progression occurred in the first 2 to 3 years. Therefore, we speculate that PFS rate at 2 years could be another candidate surrogate for cure.

Overall survival (OS) is the gold standard endpoint in phase III trials. However, it requires long-term follow-up, and a large number of patients. Overall response rate (ORR), median PFS, and PFS rate at specific time points were commonly adopted primary endpoints in phase II trials. However, their surrogacy for cure has not been fully investigated. The aim of this study is to search for the optimal surrogate marker of the 5-year survival rate in patients with LA-NSCLC treated with CRT.

Methods

Patient selection and treatment methods

We collected the clinical records of LA-NSCLC patients treated with concurrent CRT at Shizuoka Cancer Center between Sep. 2002 and Dec. 2009. The eligibility criteria of this study was as follows: (1) histologically or cytologically proven NSCLC; (2) chemoradiotherapy naïve; (3) age < 75 years; (4) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2; and (5) treated with curative thoracic radiotherapy over 50Gy concurrent with platinum doublet chemotherapy.

Treatment comprised concurrent CRT and subsequent consolidation chemotherapy. Chemotherapy regimen was selected at investigator's discretion. The doses and schedules were in accordance with the published reports [7,9-12]. All patients were treated with a linear accelerator photon beam of 4 MV or more. The primary tumor and involved nodal disease were to receive at least 60 Gy in 2-Gy fractions over 6 weeks. Our radiation technique was based on elective nodal irradiation. The radiation fields contained the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal to subcarinal lymph nodes. The contralateral hilum was not included, and the supraclavicular areas were not routinely treated.

Assessment of outcomes and statistical analysis

Tumor response was classified in accordance with the Response Evaluation Criteria for Solid Tumors (RECIST), ver. 1.1. In almost all patients, tumor response was assessed every 2 courses of chemotherapy. After the treatment period, chest computed tomography (CT) was done every 2 to 3 months during the first year and at 3 to 6 month intervals thereafter. Positron emission tomography (PET) or PET-computed tomography (PET-CT) using 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) was performed at 6 to 12 month intervals if available. Magnetic resonance imaging (MRI) of the brain was performed only when clinical signs and symptoms suspicious for brain involvement were present. PFS was assessed from the first day of treatment with CRT to the earliest signs of disease progression as determined by CT or MRI imaging using RECIST criteria, or death from any cause.

The primary outcome of this study was to evaluate the surrogacy of ORR and PFS rate at 3-month intervals (from 9 to 24 months after the initiation of treatment) for the 5-year survival rate. Landmark analyses were performed to assess the association of these outcomes with the 5-year survival rate.

A p value of < 0.05 indicated statistical significance. The Kaplan-Meier method was used to estimate survival as a function of time. All the analyses were performed using JMP ver. 7 (SAS Institute Inc, USA) or R ver. 2. 15. 1. This retrospective analysis was approved by the institutional review board of Shizuoka Cancer Center.

Results

A total of 159 consecutive patients were enrolled in this retrospective study. Baseline characteristics of the patients are summarized in Table 1. Median age was 64 years, 79% of patients were male, 75% were heavy smokers, 56% had an ECOG PS of 0, 53% had adenocarcinoma, and 54% were stage IIIB. Treatment characteristics are shown in Table 2. The most common regimens were carboplatin (CBDCA) plus paclitaxel, and cisplatin (CDDP) plus S-1 (46 patients each), and the third most frequent regimen was CDDP plus vinorelbine (VNR) (41 patients). The median radiation dose was 60 Gy (range, 52–74). The median follow-up time for censored patients was 57 months. At the time of analysis, 89 patients (56%) had died and 114 patients (72%) showed disease progression.

Table 1 Baseline characteristics

Characteristic	N = 159	
Age-year		
Median	64	
Range	40-75	
Sex-no. (%)		
Male	126	(79)
Female	33	(21)
Smoking status		
Non or light smoker	25	(16)
Heavy smoker	119	(75)
Unknown	15	(9)
ECOG performance status-no. (%)		
0	90	(57)
1	67	(42)
2	2	(1)
Histology-no. (%)		
ad	84	(53)
sq	54	(34)
Other	21	(13)
Clinical stage-no. (%)		
IIIA	86	(54)
IIIB	73	(46)

Abbreviations: ECOG Eastern Cooperative Oncology Group, *ad* adenocarcinoma, *sq* squamous cell carcinoma.

Complete response was observed in 6 patients, and 107 patients had partial response. Then, ORR was 72% (95% confidence interval [CI]: 65–78). Figure 1 shows Kaplan-Meier curves of PFS and OS. Median PFS was 12 months (95% CI: 10–14), and median OS was 39 months (95% CI: 30–46). Among 110 first relapse sites, 29 were loco-regional, 66 were distant, and 15 were

Table 2 Treatment characteristics

Treatment	N = 159	
Chemothrapy regimen-no. (%)		
CBDCA + PTX	46	(29)
CDDP + S-1	46	(29)
CDDP + VNR	41	(26)
MVP	14	(9)
CBDCA + CPT-11	5	(3)
CDDP + VP-16	4	(2)
CDDP + VNR + DE-766	3	(2)
RT dose-Gy		
Median	60	
Range	52-74	

Abbreviations: CBDCA carboplatin, *PTX* paclitaxel, *CDDP* cisplatin, *VNR* vinorelbine, *MVP* mitomycin, vindesine, and cisplatin, *CPT-11* irinotecan, *VP-16* etoposide, *RT* radiation therapy.

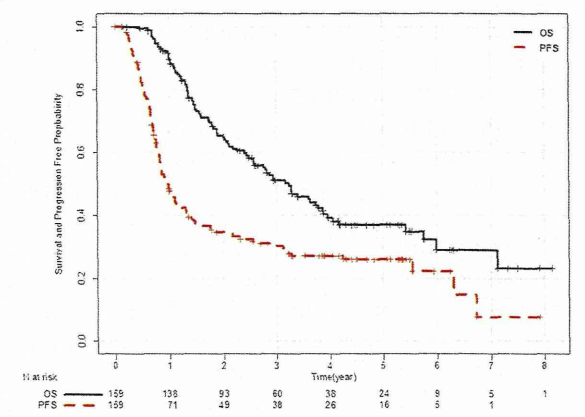

Figure 1 Kaplan-Meier-estimated PFS (dashed line) and OS curve (bold line) in LA-NSCLC patients treated with concurrent CRT (n = 159).

both. Of 114 relapsed patients, 89 (78%) received subsequent chemotherapy, and 58 (51%) received third line chemotherapy. Six patients had *epidermal growth factor receptor (EGFR)* mutation, and they all were treated with gefitinib in a subsequent line. Six other patients demonstrated durable progression-free intervals (≥ 6 months) with EGFR-tyrosine kinase inhibitors, but their *EGFR* mutation status could not be assessed for lack of a sufficient specimen.

One hundred and forty-eight, 138, 121, 106, 101, 93, 87, and 79 patients who were alive at 9, 12, 15, 18, 21, 24, 27, and 30 months were included in the respective landmark analysis. The hazard ratio (HR) of patients who achieved progression-free to those who progressed at each landmark analysis is described in Figure 2. HR gradually decreased in accordance with progression-free interval extended, and reached the lowest level at 24

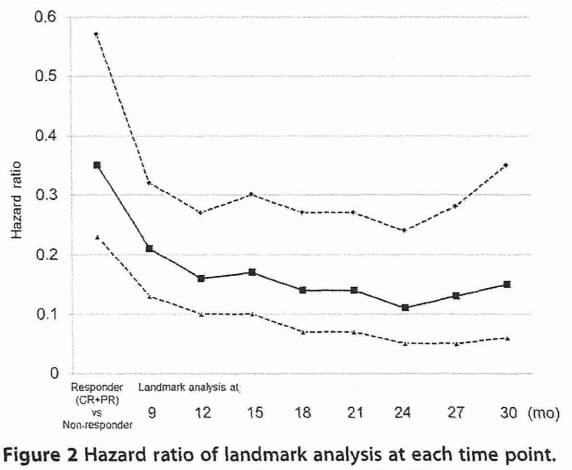

Figure 2 Hazard ratio of landmark analysis at each time point. Dashed lines indicate 95% confidence intervals. Abbreviations: CR, complete response; PR, partial response.

months (0.11; 95% CI: 0.05-0.24). Figures 1 and 2 suggest that an observational period of about 24 months is sufficient to detect almost all recurrences.

Next, we examined the 5-year survival rates of patients who achieved response or progression-free at each time point. Among patients with complete response, or partial response, the 5-year survival rate was 45% (95% CI: 35–55) (Figure 3). The 5-year survival rates of patients who were progression free at each time point (3-months intervals from 9 to 30 months) were 53% (95% CI: 42–64), 69% (95% CI: 57–79), 75% (95% CI: 62–84), 82% (95% CI: 68–90), 84% (95% CI: 70–91), 89% (95% CI: 76–95), 90% (95% CI: 77–96), and 90% (95% CI: 77–96), respectively. The rate gradually increased in accordance with progression-free interval extended, and finally reached a plateau at 24 months. Patients who maintained progression-free intervals longer than 24 months had a 5-year survival rate of about 90%.

Discussion

In this study, 159 LA-NSCLC patients treated with concurrent CRT were analyzed to evaluate the surrogacy of ORR and PFS rate at 3-month intervals for the 5-year survival rate. Kaplan-Meier curve of progression-free survival (Figure 1) and HR of landmark analysis at each time point (Figure 2) suggest that most of progression occurred in the first 2 years. Patients who maintained progression-free intervals longer than 2 years had a 5-year survival rate of approximately 90%, and the rate did not increase thereafter (Figure 3).

Although ORR could be assessed in the early period of CRT, its surrogacy for the 5-year survival rate has not been fully evaluated. McAleer et al., did a combined analysis of two RTOG studies with CRT [13]. They reported that response to induction chemotherapy was a possible predictor of long survival (p = 0.06). Kim et al., also reported that responders demonstrated 5-fold long term survival compared with non-responders among LA-NSCLC patients treated with CRT [14]. However, in McAleer's report, Kaplan-Meier curves of OS revealed that 90% of responders died within 4 years. Furthermore, Kim's report was premature because the median follow-up time was only 489 days. Our analysis, with a longer follow up period, demonstrated that the ORR was not a favorable surrogate marker for the 5-year survival rate.

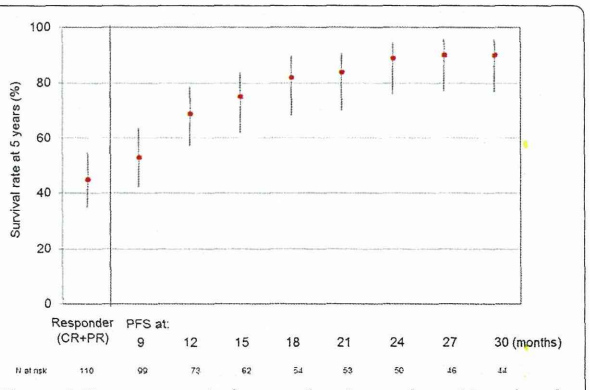

Figure 3 Five-year survival rates of patients who achieved each outcome. The bars indicate 95% confidence intervals.

With regard to median PFS, Mauguen et al., conducted a meta-analysis of LA-NSCLC. They found a very good correlation between median PFS and OS both at the individual level and trial level (ρ^2 range; 0.77-0.85, R2 range; 0.89-0.97, respectively) [15]. However, it is worth noting that their analysis contained relatively old trials. The median survival time of 15 months reported by Mauguen et al. was much shorter than that in a recent phase III trial, which reported a median survival time of 29 months [16]. This prolongation of survival may account for the development of post progression therapy, as the median PFS did not differ between the 2 reports. This might be a cause for concern about the relationship between median PFS and OS. In fact, our analysis showed that the 5-year survival rates in patients who were disease free at 9–12 months were only 53-69%. The rate gradually increased in accordance with progression-free interval extended, and reached a plateau at 90% after 24 months. This suggests that longer progression-free period, not median PFS, is required to identify cured patients.

The present study has several limitations. First, this study contained various chemotherapy regimens, and the timing of evaluatton depended on investigators because this was a retrospective study. Second, efficacy results were slightly better than previous reports. In our analysis, about 70% of patients were screened with PET (or PET-CT) at diagnosis, and 3-dimensional conformal radiation therapy was adopted in all cases. These contributed to accurate staging, and proper radiation therapy. In addition, the proportion of patients who received post progression therapy was very high (approximately 80%).

Conclusion

Our study suggests that PFS at 2 years could be a reliable surrogate endpoint for 5-year survival rate in LA-NSCLC patients treated with concurrent CRT. Further analysis is warranted using prospective datasets.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

HA contributed to the drafting of this manuscript and data collection, and KM, and TN contributed to the study design and statistical analysis. HI, TS, TT, HK, HM, ME, HH, TT, and NY contributed to analysis of the data and interpretation of the findings. All authors have read and approved of the submission of the final manuscript.

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The Impact of Clinical Outcomes According to *EGFR* Mutation Status in Patients with Locally Advanced Lung Adenocarcinoma Who Recieved Concurrent Chemoradiotherapy

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Objectives: Among patients with locally advanced lung adenocarcinoma, the frequency of epidermal growth factor receptor (*EGFR*) and *KRAS* mutations was unknown. In addition, it has not been fully evaluated about the role of these mutations treated with concurrent chemoradiotherapy (CCR).

Methods: The clinical records of locally advanced lung adenocarcinoma patients treated with CCR at Shizuoka Cancer Center between September 2002 and December 2009 were reviewed.

Results: Forty-four patients were eligible for this study. *EGFR* mutation was detected in 13 (29.5%) of 44 patients, and *KRAS* mutation was detected in 2 (6.5%) of 31 patients. Among *EGFR* mutation status known patients, overall response rate, median progression-free survival (PFS), and median survival time were 52.3%, 11.5 months, and 35.8 months, respectively. Overall response rate was significantly higher in *EGFR* mutant group than in *EGFR* wild-type group (76.9% vs. 41.9%, $P=0.02$), but this difference did not translate into a significant PFS benefit (9.6 vs. 13.2 mo, $P=0.78$). Locoregional relapse occured less frequently in patients with *EGFR* mutation than those with *EGFR* wild-type, but not significant (15.4% vs. 32.3%, $P=0.46$). Brain was the most frequent metastatic site of relapse in *EGFR* mutant group.

Conclusions: Among locally advanced lung adenocarcinoma, *EGFR* mutation was detected in 29.5% and *KRAS* mutation was detected in 6.5%. We were not able to detect a difference in PFS or overall survival between *EGFR* mutant and wild-type patients treated with conventional CCR. Locoregional relapse was approximately half in the *EGFR* mutant group compared with the *EGFR* wild-type group; however, this finding did not reach statistical significance.

Key Words: non–small cell lung cancer (NSCLC), locally advanced, chemoradiotherapy, epidermal growth factor receptor (*EGFR*) mutation

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Lung cancer is the leading cause of cancer-related death in the world. Approximately 30% of patients with non–small cell lung cancer (NSCLC) have an unresectable locally advanced disease.[1,2] Although concurrent chemoradiotherapy (CCR) is the standard treatment in patients with unresectable, locally advanced NSCLC (LA-NSCLC), its outcome was not satisfactory. Recent randomized phase III trials have documented that the CCR with third generation regimens was effective for the treatment of unresectable LA-NSCLC as compared with that with second generation regimens, demonstrating no statistically significant difference in the overall survival (OS).[3,4] However, there have been still no established regimens for the treatment of CCR, therefore, further study is warranted.

In East Asians, epidermal growth factor receptor (*EGFR*) and *KRAS* mutations were detected in 30% and 10% of lung adenocarcinoma, respectively.[5] *EGFR* mutation is a powerful predictive marker for advanced NSCLC treated with *EGFR*-tyrosine kinase inhibitor (TKI),[6–8] whereas *KRAS* mutation is a negative predictive marker and they are mutually exclusive.[9] Recently, very favorable outcomes in 2 phase III studies of gefitinib as first-line therapy compared with platinum-based chemotherapy have been described in patients with advanced NSCLC harboring *EGFR* mutations.[8,9] The patients treated with gefitinib had promising outcomes, median survival time of 30.5 months, and 2-year survival rate of 61.4%. Therefore, selected NSCLC patients, most of them adenocarcinoma, may survive >2 years. Recent in vitro study demonstrated the radiosensitivity in NSCLC cell lines harboring *EGFR* mutation.[10] Clinically, it remains unknown whether CCR is effective for the treatment of locally advanced lung adenocarcinoma with *EGFR* mutation as compared with that with *EGFR* wild-type. There is still no data about the frequency of *EGFR* mutation and the outcome after CCR in patients with locally advanced lung adenocarcinoma. Therefore, we conducted a retrospective study to examine the clinical outcome after CCR according to *EGFR* mutation status in locally advanced lung adenocarcinoma.

MATERIALS AND METHODS

Patient Selection

Between September 2002 and December 2009, we reviewed the clinical records of 90 consecutive, unresectable, locally advanced lung adenocarcinoma patients treated with

CCR at Shizuoka Cancer Center. The eligibility criteria of this study was as follows: (1) histologically or cytologically proven adenocarcinoma; (2) chemoradiotherapy naive, with measurable target legion on physical examination, chest x-ray, and computed tomography (CT) of the chest; (3) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1; (4) received curable thoracic radiotherapy over 50 Gy; and (5) with adequate specimens for *EGFR* mutation analysis. Of 90 patients who received CCR, 44 were eligible for this study. Most common reason for exclusion was lack of adequate samples to analyze *EGFR* mutation (45 patients). One patient was excluded due to his general condition (ECOG PS of 2).

EGFR and *KRAS* Mutations Analysis

EGFR mutation analysis of cytologic or histologic specimens was screened by the PNA-LNA PCR clamp method (untill March 2010) or Cycleave method (between April and December 2010) as previously described.[11,12] *KRAS* mutation analysis of histologic specimens was screened by pyrosequencing method as previously described.[13]

Treatment Methods

Treatment was composed of CCR and subsequent consolidation chemotherapy. Chemotherapy regimen was selected at investigator's discretion. All patients were treated with a linear accelerator photon beam of 4 MV or more. The primary tumor and involved nodal disease was planned to receive at least 60 Gy in 2 Gy fractions over 6 weeks. Our radiation technique is based on elective nodal irradiation. The radiation fields contain the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal to subcarinal lymph nodes. The contralateral hilum was not included, and the supraclavicular areas were not to be treated routinely.

Evaluation of Response and Statistical Analysis

Tumor response was classified in accordance with the Response Evaluation Criteria for Solid Tumors (RECIST), version 1.0. In almost all patients, tumor response was assessed for every 2 courses of chemotherapy. After the treatment period, chest CT was performed every 2 to 3 months during the first year and at 3- to 6-month intervals thereafter. Positron emission tomography (PET) or PET-CT using 2-[^{18}F]-fluoro-2-deoxy-D-glucose was favorable at 6 to 12-month intervals if available. Magnetic resonance imaging of the brain was performed only when clinical signs and symptoms suspicious for brain involvement were present. Progression-free survival (PFS) was assessed from the first day of treatment with CCR to the earliest signs of disease progression as determined by CT or magnetic resonance imaging using RECIST criteria, or death from any cause. Probability values of <0.05 indicated a statistically significant difference. Differences between covariates in patients with *EGFR* mutation and wild-type were analyzed using the Fisher exact tests and χ^2 tests. The Kaplan-Meier method was used to estimate survival as a function of time, and survival difference were analyzed by the log-rank test. All the analyses were performed using JMP version 7 (SAS Institute Inc.).

RESULTS

Patient Characteristics

Patient's characteristics are listed in Table 1. The median follow-up time for the 19 censored patients was 37.7 months (range, 8.3 to 75.6 mo). Fifty-seven percent of patients had died and 84% of patients had disease progression at the time of this analysis. Forty-four samples were available for *EGFR* mutation analysis and 31 were available for *KRAS* mutation analysis.

TABLE 1. Patient's Characteristics

Characteristics	*EGFR* Mutation [N (%)] Mutant (N=13)	Wild-type (N=31)	*P*
Age (y)			0.05
Median	68	64	
Range	55-80	40-76	
Sex [n (%)]			0.29
Male	8 (61.5)	24 (77.4)	
Female	5 (38.5)	7 (22.6)	
Smoking status			<0.05
Non or light smoker	6 (46.2)	5 (16.1)	
Heavy smoker	7 (53.8)	24 (77.4)	
Unknown	0	2 (6.5)	
ECOG performance status [n (%)]			0.68
0	10 (76.9)	22 (71.0)	
1	3 (23.1)	9 (29.0)	
Clinical stage [n (%)]			0.32
IIIA	9 (69.2)	15 (48.4)	
IIIB	4 (30.8)	16 (51.6)	
Chemotherapy regimen [n (%)]			0.57
Platinum-based regimen	11 (84.6)	29 (93.5)	
Monotherapy	2 (15.4)	2 (6.5)	
RT dose (Gy)			0.76
Median	60	60	
Range	60-74	56-74	

ECOG indicates Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; RT, radiation therapy.

Among 44 patients, 32 were male and 12 were female. The median age was 65 years (range, 40 to 80 y). Thirty-two (72.8%) patients were with ECOG PS of 0, and 24 (54.5%) patients were clinical stage IIIA. Forty (90.9%) patients received platinum-based regimen and the other patients received monotherapy. Fifteen patients were treated with cisplatin plus S-1, 13 patients with cisplatin plus vinorelbine, and 9 patients with carboplatin plus paclitaxel. The median radiation doses were 60 Gy (range, 56 to 74 Gy).

EGFR mutation was detected in 13 patients (29.5%). No statistically significant difference in the age, sex, ECOG PS, and disease stage was observed between the groups. Only smoking status yielded a statistically significant difference ($P<0.05$). Most frequent type of mutation was L858R in exon 21 (9 patients). Deletion in exon 19 was observed in 2 patients and the rest site of mutation was detected in exon 18. T790M mutation in exon 20 was not detected. *KRAS* mutation was detected in 2 patients (6.5%). Both of them are codon 12 mutations. *EGFR* and *KRAS* mutations were mutually exclusive.

Efficacy and Survival Analysis

Among *EGFR* status known patients (n=44), overall response rate (ORR), median PFS, and median OS were 52.3%, 10.8 months, and 30.9 months, respectively. The ORR was significantly higher in *EGFR* mutant group than *EGFR* wild-type group (76.9% vs. 41.9%, $P=0.02$). However, this difference did not translate into a significant PFS benefit (9.6 vs. 13.2 mo, $P=0.78$, Fig. 1). The median OS seemed to be longer in *EGFR* mutant group than *EGFR* wild-type group

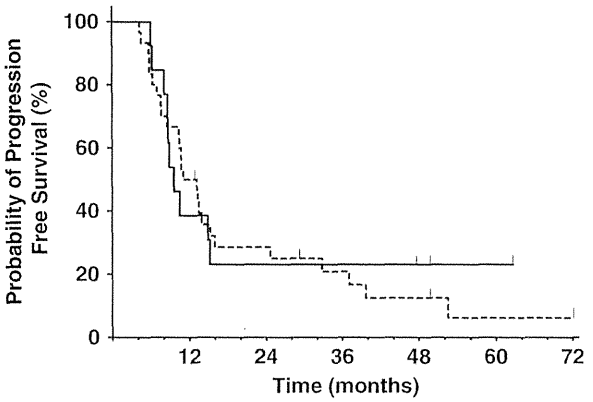

FIGURE 1. Kaplan-Meier–estimated PFS curve in patients with *EGFR* mutation (bold line, 9.6 mo) and *EGFR* wild-type (dash line, 13.2 mo). Significant difference in the PFS was not observed by *EGFR* mutation status; hazard ratio 0.90; 95% confidence interval, 0.41-1.82; $P=0.78$. *EGFR* indicates epidermal growth factor receptor; PFS, progression-free survival.

(57.9 vs. 30.7 mo, Fig. 2). Relapse pattern after initial treatment is listed in Table 2. Thirty-six (81.8%) patients demonstrated disease progression during the follow-up period (median, 28.8 mo). Twenty-four patients developed distant metastasis, 9 patients locoregional relapse, and 3 patients developed both. Locoregional relapse was observed only in 2 patients (15.4%) in *EGFR* mutant group, whereas 10 patients (32.3%) demonstrated locoregional relapse in *EGFR* wild-type group. Brain was the most frequent metastatic site (6 patients) in *EGFR* mutant group. Salvage therapy was also reviewed. Twenty-seven (75.0%) of 36 relapsed patients received second-line chemotherapy. All relapsed patients with *EGFR* mutation were treated with *EGFR*-TKI at any subsequent lines.

DISCUSSION

This is a retrospective study to evaluate the clinical significance of *EGFR* mutation in patients with unresectable, locally advanced lung adenocarcinoma who received CCR. *EGFR* and *KRAS* mutations were detected in 29.5% and 6.5%,

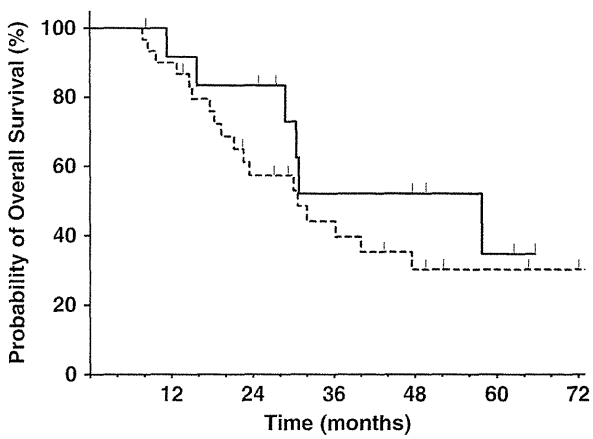

FIGURE 2. Kaplan-Meier–estimated overall survival curve in patients with *EGFR* mutation (bold line, 57.9 mo) and *EGFR* wild-type (dash line, 30.7 mo). *EGFR* indicates epidermal growth factor receptor.

TABLE 2. Relapse Pattern After Chemoradiotherapy in Each Group

Variables	*EGFR* Mutation [N (%)] Mutant (N=13)	Wild-type (N=31)	*P*
Overall recurrence	10 (76.9)	26 (83.9)	0.68
Locoregional only	1 (7.7)	8 (25.8)	0.24
Locoregional + distant	1 (7.7)	2 (6.5)	1.00
Distant only	8 (61.5)	16 (51.6)	0.55
Brain	6 (46.2)	4 (12.9)	0.04
Pulmonary metastasis	2 (15.4)	2 (6.5)	0.57

EGFR indicates epidermal growth factor receptor.

respectively, and they are mutually exclusive. ORR was significantly higher in *EGFR* mutant group than *EGFR* wild-type group, but this difference did not translate into a significant PFS benefit. Locoregional relapse occurred less frequently in patients with *EGFR* mutation than those with *EGFR* wild-type, but not significant.

There were few reports described about the frequency of *EGFR* mutation among stage III LA-NSCLC. Kosaka et al[14] reported that the prevalence of *EGFR* mutation was not different according to disease staging (stage I vs. stage II to IV, $P=0.34$). Mak et al[15] reported that *EGFR* mutation was detected in 24.8% of NSCLC patients treated by curative thoracic radiation. Recent phase II trial for LA-NSCLC has documented that *EGFR* mutation was detected in 28.9% of NSCLC patients.[16] This is corresponding to the result of our study. As the frequency of *EGFR* mutation is detected in approximately 30% of stage IIIB/IV adenocarcinoma, no significant difference in the positive rate of *EGFR* mutation seems to be recognized between stage III and metastatic adenocarcinoma patients. Only 2 patients were found to have *KRAS* mutation in our analysis. Because of this limited sample numbers, it was difficult to evaluate the patient's demographics and prognosis according to *KRAS* mutation in the present study.

Our survival analysis demonstrated that the median PFS was not significantly different between patients with or without *EGFR* mutation. The median OS seemed to be longer in *EGFR* mutant group than *EGFR* wild-type group, because all relapsed patients with *EGFR* mutation were treated with *EGFR*-TKI at any subsequent lines. In the pivotal phase III trials for metastatic NSCLC patients with *EGFR* mutation, *EGFR*-TKI demonstrated higher ORR and longer PFS than platinum doublets.[8,9] However, we should keep in mind that patients were never cured once they relapsed. Okamoto et al[17] reported a feasibility study of gefitinib and thoracic radiation therapy for stage III LA-NSCLC. As 5 of 9 patients did not complete the planned treatment due to disease progression or pneumonitis, they concluded gefitinib and thoracic radiation therapy was not feasible for unselected population. However, 2 patients with *EGFR* mutation completed treatment without interruption. Both of them lived for >5 years and their initial site of relapse was brain. Niho et al[18] conducted another feasibility study of gefitinib and concurrent thoracic radiotherapy for unresectable LA-NSCLC. As patients were highly selected, most of them were Japanese, had adenocarcinoma, and never or light smokers. In this trial, the toxicity was acceptable, taking into account the incidents of pneumonitis (2 of 38 patients). Thus, further study is warranted for evaluating the

therapeutic possibility of CCR including gefitinib or erlotinib according to *EGFR* mutation status in stage III LA-NSCLC.

In the phase III trial, locoregional relapse was observed in approximately 40% of LA-NSCLC patients treated with CCR.[4] Recently, Mak et al[15] described that *EGFR* mutation was an independent factor of locoregional relapse (hazard ratio = 0.45) among LA-NSCLC. However, their analysis contained various types of treatment modalities such as curative radiation only or induction CCR followed by surgery. In the present study, locoregional relapse was observed in 15.4% among *EGFR* mutant group, whereas 32.3% among *EGFR* wild-type group. Although we could not demonstrate statistically significant difference, this finding was concordant with the study by Mak and colleagues, and supports the preclinical data that *EGFR* mutant cells were radiosensitive. Further investigation is warranted for confirming these results.

The present study has several limitations. Our population was small sample size. This may bias the comparison of outcomes after CCR between patients with *EGFR* mutation and *EGFR* wild-type. Because of the low accrual rate of available specimens, 44 of 90 (47.8%) adenocarcinoma patients were screened for the analysis of *EGFR* mutation. Therefore, 46 patients had an unknown status of *EGFR* mutation.

In conclusion, *EGFR* mutation was detected in 29.5% and *KRAS* mutation was detected in 6.5% among locally advanced lung adenocarcinoma. *EGFR* mutation did not predict PFS after CCR but it could predict locoregional control. Our preliminary study suggests that conventional CCR may not be the most recommended treatment for stage III LA-NSCLC patients with *EGFR* mutation. Further studies may be considered for evaluating the therapeutic possibility of CCR adding *EGFR*-TKI in this population.

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