EGFR Mutation Impact on Definitive Concurrent Chemoradiation Therapy for Inoperable Stage III Adenocarcinoma

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Background: Concurrent chemoradiation therapy (CRT) is the current standard of care for patients with locally advanced lung adenocarcinoma; however, little has been reported about the impact of *epidermal growth factor receptor* (*EGFR*) mutation on CRT efficacy.

Methods: From 2006 to 2013, we retrospectively screened 104 unresectable stage III adenocarcinoma patients who were examined for *EGFR* mutation status and received definitive concurrent CRT consisting of platinum doublet chemotherapy in first-line setting and compared the clinical outcomes and recurrence patterns according to mutation status.

Results: Among 104 patients, *EGFR* mutation was detected in 29 (28%). The overall response rate did not differ between *EGFR*-mutant and wild-type patients (72.4% versus 72.0%, $p = 0.607$). The median progression-free survival in concurrent CRT was significantly shorter in *EGFR*-mutant patients than in wild-type patients (9.8 [95% confidence interval, CI: 7.6–19.0] versus 16.5 [95% CI: 11.8–19.9] months, $p = 0.041$). The 2-year recurrence-free survival rate was 7.7% and 28.1% in *EGFR*-mutant and wild-type patients, respectively ($p = 0.028$). Distant metastases were more frequently identified as the first recurrence site in *EGFR*-mutant patients than in wild-type patients (76% versus 40%, $p = 0.001$). The brain was the most often affected site in *EGFR*-mutant patients (35%). However, locoregional recurrence was less common in *EGFR*-mutant patients than in the wild-type population (14% versus 35%, $p = 0.027$). Overall survival was similar between *EGFR*-mutant and wild-type patients (51.1 [95% CI: 28.2–70.2] versus 42.9 [95% CI: 35.3 to not available] months, $p = 0.637$). Among the *EGFR* wild-type population who were examined for *Kras* mutation, *Kras*-mutant patients had significantly worse overall survival than *Kras* wild-type patients (21.6 versus 49.8 months, $p = 0.024$).

Conclusion: Concurrent CRT resulted in shorter progression-free survival in *EGFR*-mutant stage III adenocarcinoma patients than in wild-type patients, mainly because of distant metastasis relapse, regardless of better local control. Because of these distinct biological features, a different strategy, including EGFR-tyrosine kinase inhibitors for *EGFR*-mutant locally advanced adenocarcinoma patients receiving definitive CRT may be needed.

Key Words: EGFR mutation, Lung adenocarcinoma, Chemoradiation therapy, Locally advanced NSCLC.

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Lung cancer remains the leading cause of cancer-related deaths worldwide, and non—small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers.[1] About one-third of patients present with locally advanced (stage III) NSCLC, the majority of whom have unresectable bulky disease or extensive mediastinal lymphadenopathy, making curative treatment a challenge.[2] The current standard of care for patients with unresectable locally advanced NSCLC is concurrent chemoradiation therapy (CRT). However, most treated individuals develop disease recurrence, with the 5-year survival rate being less than 20%.[3–5]

The discovery of somatic mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) was a paradigm shift in the understanding of the relevance of lung cancer molecular biology to therapeutic strategy and identified a subset of patients with a unique susceptibility to EGFR-specific tyrosine kinase inhibitors (TKIs).[6–8] Several pivotal phase III trials have shown that first-line treatment with EGFR-TKIs, rather than chemotherapy, conferred a progression-free survival (PFS) and quality of life benefit in patients with metastatic NSCLC harboring *EGFR* mutations.[9–12] However, in locally advanced setting, the impact of targeted therapies and the responsiveness of *EGFR*-mutant tumors to CRT have not been established.

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In the present retrospective study, we examined the frequency of *EGFR* mutations among patients with locally advanced lung adenocarcinoma. We also compared the clinical outcomes in concurrent CRT and the recurrence pattern according to mutation status.

PATIENTS AND METHODS

Patients and *EGFR* Analysis

In this retrospective study, we screened the consecutive cases of 113 inoperable stage III adenocarcinoma patients who received definitive concurrent CRT consisting of platinum doublet chemotherapy in first-line setting at Aichi Cancer Center Hospital or Institute of Biomedical Research and Innovation between 2006 and 2013. A total of 104 patients (92%) were examined for *EGFR* mutations by the peptide nucleic acid–locked nucleic acid polymerase chain reaction clamp method or the cycleave polymerase chain reaction method. The remaining nine patients (8%) could not be examined for *EGFR* mutation because they underwent small biopsies. Histological diagnosis was carried out according to the World Health Organization classification. A computed tomography (CT) scan was performed for tumor assessment within 2 months before initiating treatment and was repeated every 2 to 4 months. Enhanced magnetic resonance imaging was performed for central nervous system metastasis assessment within 2 months before initiating treatment and was repeated every 3 to 6 months. Positron emission tomography (PET)-CT was also performed for the initial assessment of hilar/mediastinal lymph node or bone metastases. Clinical responses were defined according to Response Evaluation Criteria in Solid Tumors 1.1. Response was confirmed at least 4 weeks (for a complete or partial response) or 6 weeks (for stable disease) after the first documentation.

Statistical Analysis

Statistical analyses were performed using the JMP statistical software program (9th version, SAS Institute Inc., Cary, NC) to compare clinical outcomes according to *EGFR* mutation status. Comparisons of means and proportions were based on the unpaired *t* test and Fisher's exact test, respectively. Survival curves were estimated by the Kaplan–Meier method, and the differences between the two groups were compared with the log-rank test. PFS was calculated from the date of initiation of concurrent CRT to either the date of recurrence or the date of last contact. Overall survival (OS) was defined as the interval from the date of initiation of concurrent CRT to the date of death from any cause, or the last follow-up. All tests were two-sided, and a p value of less than 0.05 was considered significant.

RESULTS

Patient Characteristics

The clinical characteristics of the 104 patients are shown in Table 1. Sixty-four patients (62%) were female, and 26 (25%) were never-smokers, with an age range of 40 to 77 years (median, 62 years). Forty-seven patients (45%) were diagnosed as stage IIIA, and 57 (55%) were stage IIIB. Forty-six patients (44%) had a performance status (PS) of 0, and 58 (56%) had a PS of 1.

Magnetic resonance imaging of brain was performed on almost all the patients (98%). It was similar in *EGFR*-mutant and wild-type groups (100% and 97%). The timing was also comparable; the median time before treatment was 16 days (95% confidence interval [CI]: 6–31) and 15 days (95% CI: 9–22), respectively. Ninety-one percent of the patients were evaluated with PET-CT before treatment. It was comparable between the two groups (90% and 92%).

Treatment

All patients received 56 to 74 Gy of thoracic radiation therapy concurrently with platinum doublet chemotherapy. Ninety-one patients (87.5%) were irradiated with 60 Gy total delivered in 30 times. There was no significant distribution in both groups as for radiation doses; 27 (93%) and 63 (84%) patients received 60 Gy irradiation in *EGFR*-mutant and wild-type groups, respectively. There were no discontinuations because of radiation side effects. Chemotherapy regimens are shown in Table 1; 54 patients (52%) received carboplatin (CBDCA) and paclitaxel (PTX), 35 (34%) received cisplatin and vinorelbine, and 15 (14%) received other regimens concurrently with radiotherapy. The distribution was comparable between the two groups. No patient received induction or salvage surgery throughout the treatment courses.

Frequency of *EGFR* Mutation

Twenty-nine patients (28%) were *EGFR*-mutated, and 75 (72%) were wild type. Among *EGFR*-mutant patients, 20 patients (69%) were female, and 18 patients (62%) were never-smokers. Thirteen patients (45%) were stage IIIA, and 16 (55%) had a PS of 0. Sixteen patients (55%) had exon 19 deletion, 10 (35%) had L858R, and 3 (10%) had other minor mutations (one with G719S in exon 18 and two with exon 20 insertion). Table 2 shows the distribution of tumor, node, metastasis classification according to *EGFR* mutation status. The *EGFR*-mutant population had the distribution tendency toward smaller T stages compared with the wild-type population.

Tumor Response and Progression-Free Survival

The overall response rate (ORR) was 72.1% for concurrent CRT, as shown in Table 3. There was no discrepancy in the clinical responses to CRT treatment between EGFR-mutant and wild-type patients (ORR, 72.4% versus 72.0%, $p = 0.607$).

Seventy-seven patients (74%) developed tumor recurrence after definitive CRT. The median PFS in concurrent CRT was significantly shorter in *EGFR*-mutant patients than in wild-type patients (9.8 [95% CI: 7.6–19.0] versus 16.5 [95% CI: 11.8–19.9] months, $p = 0.041$), as demonstrated in Figure 1*A*. The 2-year recurrence-free survival rate was also worse in *EGFR*-mutated patients compared with that in wild-type patients (7.7% and 28.1%, $p = 0.028$, Fig. 1*A*).

Recurrence Patterns

Table 4 shows recurrence patterns according to *EGFR* mutation status. Among 29 EGFR-mutant patients, tumor

TABLE 1. Comparison of Patient Characteristics (n = 104)

Characteristics	Total, n = 104	*EGFR* Mutant, n = 29	Wild Type, n = 75
Age, median (range)	62 (40–77)	62 (51–77)	62 (40–74)
Sex, n (%)			
Male	64 (62)	9 (31)	55 (73)
Female	40 (38)	20 (69)	20 (27)
Smoking history, n (%)			
Never	26 (25)	18 (62)	8 (11)
Former/current	78 (75)	11 (38)	67 (89)
Stage, n (%)			
IIIA	47 (45)	13 (45)	34 (45)
IIIB	57 (55)	16 (55)	41 (55)
PS, n (%)			
0	46 (44)	16 (55)	30 (40)
1	58 (56)	13 (44)	45 (60)
Radiation dose (Gy), median (range)	60 (54–74)	60 (60–66)	60 (54–74)
Chemotherapy, n (%)			
CBDCA + PTX	54 (52)	13 (44)	41 (55)
CDDP + VNR	35 (34)	9 (31)	26 (35)
CDDP + DTX	4 (4)	3 (10)	1 (1)
CDDP + S-1	4 (4)	2 (7)	2 (3)
Others[a]	7 (7)	2 (7)	5 (7)
EGFR mutation, n (%)			
Exon 19 deletion	16 (15)	16 (55)	—
L858R	10 (10)	10 (35)	—
Others[b]	3 (3)	3 (10)	—

[a]Three with cisplatin + pemetrexed, three with cisplatin + irinotecan, and one with carboplatin + vinorelbinre.
[b]One with G719S in exon 18 and two with exon 20 insertion.
PS, performance status; EGFR, epidermal growth factor receptor; CBDCA, carboplatin; PTX, paclitaxel; CDDP, cisplatin; VNR, vinorelbine; DTX, docetaxel.

recurrence was identified in 24 patients (83%), whereas 53 out of 75 wild-type patients (71%) had tumor recurrence. Distant metastases were more frequently identified as the first recurrence site in *EGFR*-mutant patients than in wild-type patients (76% versus 40%, $p = 0.001$). The brain was the most individually affected site in *EGFR*-mutant patients (35%, Fig. 2). On the other hand, locoregional recurrence was less common in *EGFR*-mutant patients than in wild-type patients (14% versus 35%, $p = 0.027$).

TABLE 2. TNM Stage Distribution

Clinical Stage	*EGFR* Mutant, n = 29	Wild Type, n = 75
IIIA, n (%)	**13 (45)**	**34 (45)**
T1N2M0	3 (10)	8 (11)
T2N2M0	8 (29)	12 (16)
T3N1M0	0 (0)	0 (0)
T3N2M0	1 (3)	7 (9)
T4N0M0	0 (0)	4 (5)
T4N1M0	1 (3)	3 (4)
IIIB, n (%)	**16 (55)**	**41 (55)**
T1N3M0	6 (21)	12 (16)
T2N3M0	6 (21)	6 (8)
T3N3M0	0 (0)	4 (5)
T4N2M0	2 (7)	14 (19)
T4N3M0	2 (7)	5 (7)

TNM, tumor, node, metastasis; EGFR, epidermal growth factor receptor.

Overall Survival

After a median follow-up of 35.0 months, 46 patients (44%) had died. As shown in Figure 1*B*, no difference was found in OS according to *EGFR* mutation status (51.1 [95% CI: 28.2–70.2] versus 42.9 [95% CI: 35.3 to NA] months, $p = 0.637$). The impact of *Kras* mutations among *EGFR* wild-type population was also evaluated. Fifty-two out of 75 *EGFR* wild-type patients were examined for *Kras* mutations, and seven (13.5%) were positive. Although there was no difference in PFS (17.9 versus 13.1 months, $p = 0.773$), *Kras*-mutant patients had significantly worse OS compared with wild-type patients, as shown in Figure 3 (21.6 [95% CI: 7.6 to NA] versus 49.8 [95% CI: 35.3 to NA] months, $p = 0.024$).

The Outcomes in *Kras*-Mutant Patients

Of seven *Kras*-mutant patients, five were male, and all were current or former smoker, with an age range of 45 to 74 years (median, 68 years). Three patients were diagnosed as stage IIIA, and four were stage IIIB. Six patients had a PS of 1, and one had a PS of 0. Two patients received

TABLE 3. Objective Response Rate (ORR)

RECIST	Total, n = 29	*EGFR* Mutant, n = 104	Wild Type, n = 75
Complete response, n (%)	6 (6)	2 (7)	4 (5)
Partial response, n (%)	69 (67)	19 (66)	50 (67)
Stable disease, n (%)	15 (14)	3 (10)	12 (16)
Progression disease, n (%)	0 (0)	0 (0)	0 (0)
Not evaluable, n (%)	14 (13)	5 (17)	9 (12)
ORR (%)	**72.1**	**72.4**	**72.0**

EGFR, epidermal growth factor receptor, RECIST, Response Evaluation Criteria in Solid Tumors.

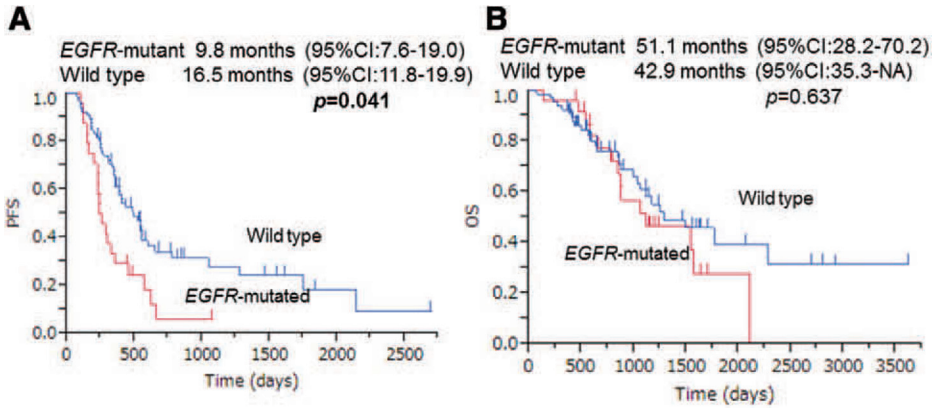

FIGURE 1. Kaplan–Meier survival curves of progression-free survival (PFS) (*A*) and overall survival (OS) (*B*) for concurrent chemoradiation therapy (CRT) according to *epidermal growth factor receptor* (*EGFR*) mutation status.

cisplatin and vinorelbine concurrently with irradiation, and five received CBDCA and PTX. Five patients had tumor recurrence after concurrent CRT; two were identified with brain metastases, two with bone metastases, and one with primary lesion recurrence and pulmonary metastases (data not shown).

The Efficacy of EGFR-TKIs Among *EGFR*-Mutant Patients After Relapse

Twenty-one (87.5%) out of 24 *EGFR*-mutant patients who relapsed after concurrent CRT received EGFR-TKIs. Two received erlotinib and 19 received gefitinib. All patients were treated with EGFR-TKIs as second line, and one patient experienced interstitial pneumonia. The median PFS for EGFR-TKIs was 8.3 months (95% CI: 5.5–14.8 months, Fig. 4).

TABLE 4. Recurrence Patterns According to *EGFR* Mutation

First Site of Recurrence	*EGFR* Mutant, n = 29	Wild Type, n = 75	*P*
Distant, n (%)	**22 (76)**	**30 (40)**	**0.001**
Brain	10 (35)	11 (15)	
Bone	5 (17)	4 (5)	
Others	13 (45)	22 (29)	
Locoregional, n (%)	**4 (14)**	**26 (35)**	**0.027**
Primary	3 (10)	15 (20)	
Lymphnodes	2 (7)	11 (15)	

EGFR, epidermal growth factor receptor.

DISCUSSION

This study on the impact of *EGFR* mutation on definitive CRT efficacy for inoperable stage III adenocarcinoma patients found that PFS was significantly shorter in *EGFR*-mutant patients than in wild-type patients (median PFS, 9.8 versus 16.5 months). In addition, *EGFR*-mutant, locally advanced adenocarcinomas were significantly more prone to development of distant metastases after definitive CRT among lung adenocarcinomas. To the best of our knowledge, this is the first cohort to elucidate these distinct clinical features of *EGFR*-mutant locally advanced adenocarcinoma patients receiving concurrent CRT. In the literature, two previous retrospective studies discussed the impact of *EGFR* mutation on definitive CRT efficacy for inoperable stage III adenocarcinoma patients.[13,14] Both of these studies found better ORR and less locoregional recurrence in the *EGFR*-mutant population, without PFS difference.

Interestingly, there was significantly less relapse in radiation-treated local lesions as the first recurrence site in *EGFR*-mutant patients in this study. In vitro, *EGFR*-mutant NSCLC cell lines exhibit greater sensitivity to radiation.[15,16] A potential mechanism for this greater radiosensitivity is the inability of mutant *EGFR* to translocate to the nucleus and interact with DNA-dependent protein kinase, a key component in repairing DNA.[15] Several clinical studies recently reported that, in locally advanced NSCLC patients with *EGFR* mutation, the locoregional recurrence rate after radiotherapy was lower than in wild-type patients,[13,14,17] and *EGFR* mutation was associated with a better response to CRT.[18] Moreover, T stage was lower in *EGFR*-mutant populations than in wild type. This finding may also correlate with better local control. As mentioned

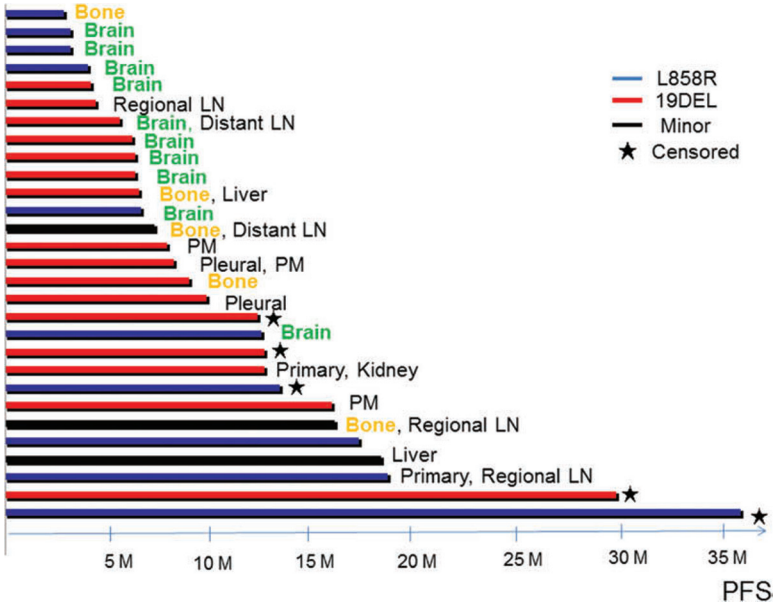

FIGURE 2. Recurrence patterns and progression-free survival (PFS) after concurrent chemoradiation therapy (CRT) in 29 *epidermal growth factor receptor* (*EGFR*)-mutant locally advanced adenocarcinoma patients.

above, two previous studies (demonstrating better ORR and less locoregional recurrence in *EGFR*-mutant populations) support these speculations.[13,14]

Despite better local control, *EGFR*-mutant adenocarcinoma patients relapsed significantly more frequently with distant metastases (75.9%); the brain was the most affected site in *EGFR*-mutant patients. Akamatsu et al.[13] also showed that brain metastases were most frequently observed among the *EGFR*-mutant population after definitive CRT in locally advanced setting. Moreover, a significant association between *EGFR* mutation and risk of brain metastases at the time of diagnosis[19] and follow-up after curative resection[20] in adenocarcinoma was recently reported. Another study demonstrated that *EGFR* mutation was associated with more frequent distant relapse and worse 5-year PFS rate after neoadjuvant CRT followed by surgery in locally advanced mediastinoscopic N2-positive NSCLC.[21] These findings are increasingly important for understanding the biological features of *EGFR*-mutant adenocarcinoma, taken together with the results of this study.

The 2-year recurrence-free survival rate was also significantly worse in *EGFR*-mutant, locally advanced adenocarcinoma (7.7% versus 28.1%, $p = 0.027$), although OS analysis showed no difference between *EGFR*-mutant and wild-type adenocarcinomas. Certainly, EGFR-TKI treatments after recurrence may contribute, in some extent, to preventing disease progression. However, with respect to the curative rate, concurrent CRT with standard platinum doublet chemotherapy did not seem to deliver "definitive" care, especially for *EGFR*-mutant, locally advanced adenocarcinoma. Although *EGFR*-mutant group had more favorable factors (i.e., they were more females, more never-smokers, and had better PS as shown in Table 1), they did not perform better for concurrent CRT. Our finding of more frequent distant recurrence in *EGFR*-mutant patients suggests that systemic control is more important in locally advanced adenocarcinoma patients with *EGFR* mutations. To improve the outcome for these populations, different strategies will be needed to prevent distant metastatic progression. It remains uncertain when, how, and in which populations EGFR-TKIs should be administered in combination with CRT. Two clinical trials are ongoing to evaluate EGFR-TKIs as induction therapy: the Radiation Therapy Oncology Group 1306 trial and the Lung Oncology Group in Kyushu 0902 trial.

Among *EGFR*–wild-type locally advanced adenocarcinoma patients, *Kras* mutation was identified as a statistically

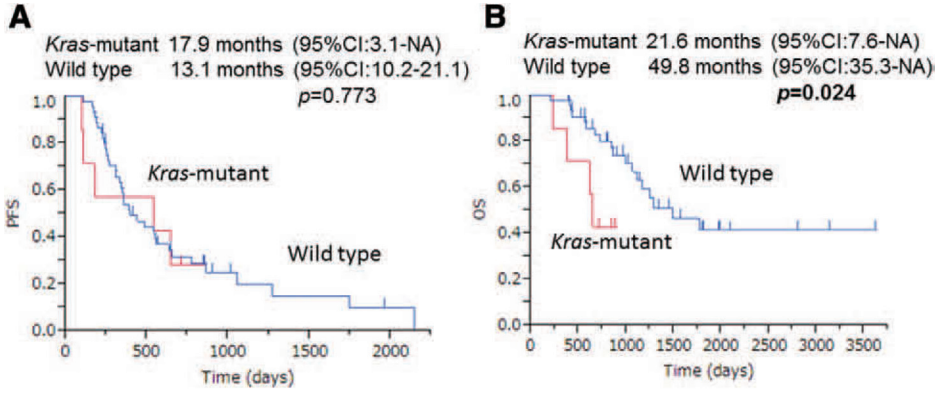

FIGURE 3. Kaplan–Meier survival curves of progression-free survival (PFS) (*A*) and overall survival (OS) (*B*) for concurrent chemoradiation therapy (CRT) among *epidermal growth factor receptor* (*EGFR*) wild-type patients according to *Kras* mutation status.

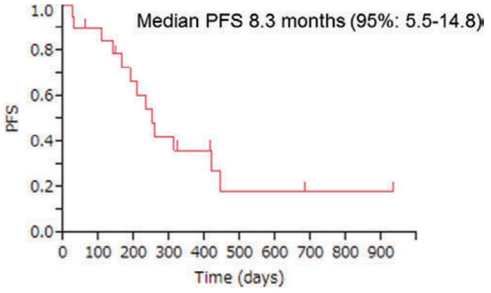

FIGURE 4. Kaplan–Meier survival curve of progression-free survival (PFS) for epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) treatments after relapse in 24 *EGFR*-mutant patients.

significant prognostic factor, although not all patients were examined for *Kras* mutations. Previous reports have demonstrated that *Kras* mutations decrease the efficacy of chemotherapy and/or worsen survival time in advanced-stage NSCLC.[22–24] *Kras*-mutant, locally advanced adenocarcinomas may also have distinct biological features other than those of *EGFR*-mutant or double-negative adenocarcinomas, so further studies are warranted to understand the biological impact of each oncogene.

This study had several limitations; First, it was a retrospective design. ORR and PFS are very soft endpoints, and the interval for the restaging imaging was highly variable, representing a bias for PFS assessment. Second, the clinical indication for surgery (combined with induction chemotherapy/radiotherapy) or concurrent CRT in stage III NSCLC considerably differs according to the institute or doctor, which may have led to selection bias. Third, chemotherapy regimens and radiation doses were diverse. Comparing *EGFR*-mutant and wild-type patients, treatment deviation was quite small: most frequently used chemotherapy was CBDCA + PTX, and the median radiation dose was 60 Gy in each arm. Fourth, most of the patients were diagnosed as stage III adenocarcinoma without lymph node biopsies. The diagnosis of N stage was clinically determined on PET-CT in most patients because the pathological diagnosis was not available in all N1-3 locally advanced NSCLC patients.

In conclusion, concurrent CRT gave shorter PFS in *EGFR*-mutated stage III adenocarcinoma patients compared with wild-type patients, mainly because of distant metastasis relapse, despite better local control. Because of these distinct biological features, a different strategy, including EGFR-TKIs for *EGFR*-mutant, locally advanced adenocarcinoma patients receiving definitive CRT may be needed.

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REFERENCES

1. Parkin DM, Bray FI, Devasa SS. Cancer burden in the year 2000: the global picture. *Eur J Cancer* 2001; 37: 4–66.
2. Blackstock AW, Govindan R. Definitive chemoradiation for the treatment of locally advanced non small-cell lung cancer. *J Clin Oncol* 2007;25:4146–4152.
3. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
4. Pfister DG, Johnson DH, Azzoli CG, et al.; American Society of Clinical Oncology. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–353.
5. Okamoto I. Overview of chemoradiation clinical trials for locally advanced non-small cell lung cancer in Japan. *Int J Clin Oncol* 2008;13: 112–116.
6. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–2139.
7. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497–1500.
8. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A* 2004;101:13306–13311.
9. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
10. Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol* 2005;23:2513–2520.
11. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al.; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
12. Maemondo M, Inoue A, Kobayashi K, et al.; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–2388.
13. Akamatsu H, Kaira K, Murakami H, et al. The impact of clinical outcomes according to EGFR mutation status in patients with locally advanced lung adenocarcinoma who received concurrent chemoradiotherapy. *Am J Clin Oncol* 2014;37:144–147.
14. Yagishita S, Horinouchi H, Taniyama T, et al. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage III nonsquamous non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2015;91:140–148.
15. Das AK, Chen BP, Story MD, et al. Somatic mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) abrogate EGFR-mediated radioprotection in non-small cell lung carcinoma. *Cancer Res* 2007;67:5267–5274.
16. Das AK, Sato M, Story MD, et al. Non-small-cell lung cancers with kinase domain mutations in the epidermal growth factor receptor are sensitive to ionizing radiation. *Cancer Res* 2006;66:9601–9608.
17. Mak RH, Doran E, Muzikansky A, et al. Outcomes after combined modality therapy for EGFR-mutant and wild-type locally advanced NSCLC. *Oncologist* 2011;16:886–895.
18. Li F, Bai H, Li X, et al. [Role of EGFR mutation status in patients with stage III non-squamous non-small cell lung cancer treated with chemoradiotherapy]. *Zhongguo Fei Ai Za Zhi* 2011;14:715–718.
19. Shin DY, Na II, Kim CH, Park S, Baek H, Yang SH. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. *J Thorac Oncol* 2014;9:195–199.
20. Mamon HJ, Yeap BY, Jänne PA, et al. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol* 2005;23: 1530–1537.
21. Ahn HK, Choi YL, Han JH, et al. Epidermal growth factor receptor mutation and treatment outcome of mediastinoscopic N2 positive non-small cell lung cancer patients treated with neoadjuvant chemoradiotherapy followed by surgery. *Lung Cancer* 2013;79:300–306.
22. Huncharek M, Muscat J, Geschwind JF. K-ras oncogene mutation as a prognostic marker in non-small cell lung cancer: a combined analysis of 881 cases. *Carcinogenesis* 1999;20:1507–1510.
23. Mascaux C, Iannino N, Martin B, et al. The role of RAS oncogene in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. *Br J Cancer* 2005;92:131–139.
24. Meng D, Yuan M, Li X, et al. Prognostic value of K-RAS mutations in patients with non-small cell lung cancer: a systematic review with meta-analysis. *Lung Cancer* 2013;81:1–10.

