# Original Study

# Impact of EGFR Mutation and ALK Translocation on Recurrence Pattern After Definitive Chemoradiotherapy for Inoperable Stage III Non-squamous Non–small-cell Lung Cancer

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## Abstract

We evaluated the failure pattern after definitive chemoradiotherapy in patients with stage III non–small-cell lung cancer harboring epidermal growth factor receptor mutations and/or anaplastic lymphoma kinase translocation. Although the epidermal growth factor receptor-mutant group showed a lower incidence of in-field failure and higher incidence of out-of-field failure, the group with anaplastic lymphoma kinase translocation showed no characteristic in-field or out-of-field failure pattern.

**Introduction:** This study was aimed at clarifying the failure pattern after definitive chemoradiotherapy in patients with stage III non–small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations and/or anaplastic lymphoma kinase (ALK) translocation. **Methods and Materials:** This retrospective study was a single-institution study conducted on patients with unresectable stage III non-squamous NSCLC treated by definitive chemoradiotherapy between January 2006 and March 2016. Only patients with information of EGFR mutations and/or ALK translocation were included. The prognosis and initial recurrence patterns were compared according to the presence/absence of EGFR mutation and/or *ALK* translocation. **Results:** A total of 173 patients (34 with activating EGFR mutations, 13 who were positive for ALK translocation) were enrolled, and the median follow-up duration was 36 months (range, 3-123 months). The 3-year overall survival rate was significantly higher in the EGFR-mutant group than in the wild-type EGFR group (75% vs. 46%; $P = .002$). There was a tendency towards a better overall survival in the ALK-positive group than in the ALK-negative group (68% vs. 44%; $P = .085$). No differences in the 3-year progression-free survival were observed according to the EGFR or ALK status. The EGFR-mutant group showed a significantly lower rate of in-field failure ($P = .027$) and higher rate of out-of-field failure ($P = .029$) as compared with the wild-type EGFR group. There was no significant difference in the rate of in-field failure or out-of-field failure between the ALK-positive and ALK-negative groups. **Conclusions:** Although the ALK-positive group showed no characteristic failure pattern, the EGFR-mutant group showed a lower rate of in-field failure and higher rate of out-of-field failure.

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## Introduction

Lung cancer remains the leading cause of cancer-related death worldwide, and non—small-cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases.[1] Approximately one-third of patients with NSCLC present with locally advanced NSCLC, the majority of whom have unresectable bulky disease or extensive mediastinal lymphadenopathy, making curative treatment a challenge.[2] Recently, the final results of the PACIFIC trial demonstrated that adjuvant immune checkpoint inhibitor (ICI) improved clinical outcomes including progression-free survival (PFS) and overall survival (OS) of unresectable locally advanced NSCLC significantly. Hence, the current standard of care is chemoradiotherapy (CRT) followed by ICI.[3] However, most treated individuals develop disease recurrence, with a median survival time of less than 20 months until approval of ICI as a maintenance therapy after CRT based on the results of the PACIFIC trial.[4]

The finding of mutations in driver genes, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene translocation, brought paradigm shifts in the therapeutic strategy for advanced NSCLC.[5,6] However, there have been no prospective studies and only few retrospective reports regarding the role of EGFR mutations on the clinical outcomes in patients with lung cancer after CRT.[7-10] Reports have suggested that, Although the presence of EGFR mutations is a favorable factor for local control and prognosis, patients harboring these mutations are at a high risk for distant relapse. It was reported from a retrospective review that the local control in response to gamma knife therapy of brain metastases in patients with EGFR mutation- or ALK translocation-positive NSCLC was superior to that in patients with v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation-positive NSCLC.[11] Therefore, similar radiosensitivity to that of tumors carrying EGFR mutations may be expected in tumors with ALK translocation. However, there have been no reports regarding the role of tumor ALK translocation on the clinical outcomes in patients with locally advanced NSCLC in whom CRT is indicated.

The purpose of this study was to clarify the clinical outcomes of patients with unresectable stage III non-squamous NSCLC harboring EGFR mutations or ALK translocations who are eligible for CRT.

## Methods and Materials
### Patient Selection and Treatment

A total of 344 patients with unresectable stage III non-squamous NSCLC underwent definitive CRT between April 2006 and March 2016 at our institution. Among these, information on the EGFR

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**Figure 1  Consort Diagram of the Patients Included for the Analysis in This Study**
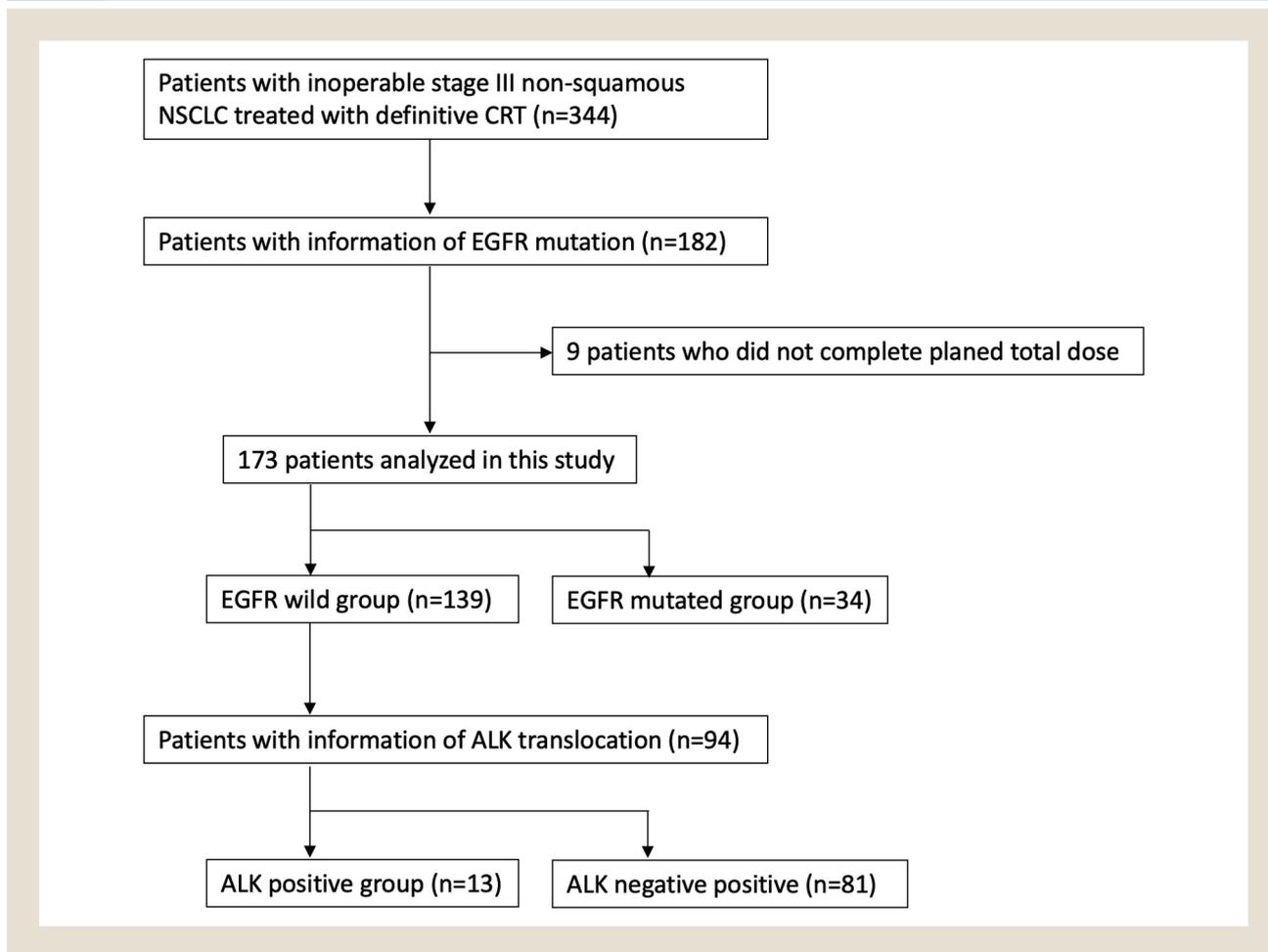


Abbreviations: ALK = anaplastic lymphoma kinase; CRT = chemoradiotherapy; EGFR = epidermal growth factor receptor; NSCLC = non—small-cell lung cancer.

**Table 1** **Patient Characteristics**

| | EGFR Wild-type (n = 139), n (%) | EGFR Mutation (n = 34), n (%) | P Values | ALK Negative (n = 81), n (%) | ALK Positive (n = 13), n (%) | P Values |
|---|---|---|---|---|---|---|
| Age, y | | | | | | |
| Median (range) | 65 (34-81) | 66 (37-77) | .391 | 65 (40-78) | 63 (36-69) | .404 |
| Gender | | | | | | |
| Male | 98 (71) | 11 (32) | <.001 | 55 (68) | 7 (54) | .355 |
| Female | 41 (29) | 23 (68) | | 26 (32) | 6 (46) | |
| ECOG PS | | | | | | |
| 0 | 85 (61) | 27 (79) | .048 | 47 (58) | 12 (92) | .027 |
| 1 | 54 (39) | 7 (21) | | 34 (42) | 1 (8) | |
| Stage | | | | | | |
| IIIA | 76 (55) | 17 (50) | .702 | 44 (54) | 3 (23) | .07 |
| IIIB | 63 (45) | 17 (50) | | 37 (46) | 10 (77) | |
| Histology | | | | | | |
| Adenocarcinoma | 103 (74) | 32 (94) | .01 | 63 (78) | 11 (85) | .728 |
| NOS | 36 (26) | 2 (6) | | 18 (22) | 2 (15) | |
| Treatment | | | | | | |
| CCRT | 123 (88) | 33 (97) | .2 | 66 (81) | 13 (100) | .119 |
| Sequential RT | 16 (12) | 1 (3) | | 15 (19) | 0 (0) | |
| Beam | | | | | | |
| RT | 120 (86) | 27 (79) | .297 | 66 (81) | 10 (77) | .709 |
| PBT | 19 (14) | 7 (21) | | 15 (19) | 3 (23) | |
| Chemotherapy | | | | | | |
| Cisplatin-based | 126 (91) | 32 (94) | .738 | 72 (89) | 13 (100) | .352 |
| Carboplatin-based | 13 (9) | 2 (6) | | 9 (11) | 0 (0) | |

Abbreviations: ALK = anaplastic lymphoma kinase; CCRT = concurrent chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; NOS = not otherwise specified; PBT = proton beam therapy; RT = radiotherapy.

status was available for 182 patients. Figure 1 shows the consort diagram depicting the selection of patients for this study. Nine patients in whom treatment at the planned total dose could not be completed were excluded from this study. Among the remaining 173 eligible patients, information on the EGFR status was obtained using specimens collected before the initial treatment for 125 patients, and using specimens collected after the recurrence for the remaining patients. Among 139 patients with tumors harboring wild-type EGFR, the presence/absence of ALK translocation was examined in 94 cases. The tumor diagnosis was confirmed histologically in all the patients. Clinical staging was performed according to the Seventh Union for International Cancer Control TNM staging system, based on the findings of CT and brain MRI. 18F-fluorodeoxyglucose positron emission tomography/CT was performed as necessary. Data on the following pretreatment patient characteristics were collected from the medical records: age, gender, and Eastern Cooperative Oncology Group performance status (ECOG PS). All the study participants provided informed, written consent of comprehensive study protocol at our institute before initial treatment. The study protocol was approved by the Research Ethics Committee of our institution (reference number: 2017-440). The research was conducted in accordance with the principles laid down in the Declaration of Helsinki 1964 and its subsequent amendments.

### Treatment

The primary treatment approach was determined by discussion among members of a multidisciplinary treatment team at our institution. All patients were treated with a linear accelerator photon beam of 6 MV or a proton beam. The treatment involved radiation at a total dose of at least 60 Gy administered in 2 Gy fractions over a period of 6 weeks to the primary tumor and involved nodes. Our radiation technique was based on elective nodal irradiation at a dose of 40 Gy. The radiation field contained the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal to the subcarinal lymph nodes. The contralateral hilum was not included, and the supraclavicular areas were not routinely treated. Proton beam therapy was used in cases where normal lung V20 < 35% could not achieved with photon beam therapy. The chemotherapy consisted of an intravenous platinum-based regimen.

### EGFR Mutation and ALK Translocation Analysis

Cytologic or paraffin-embedded tumor specimens were assayed for EGFR mutations using polymerase chain reaction-based methods. ALK translocation was determined using immunohistochemistry (IHC) or fluorescence in-situ hybridization.

### Efficacy

After the treatment period, chest CT was performed every 3 months during the first year and at 6- to 12-month intervals thereafter. MRI of

the brain was performed only when clinical signs and symptoms suggestive of possible brain involvement were present. PFS was defined as the time from the date of the start of CRT until detection of the earliest signs of disease progression, as determined from by CT images or MRI using Response Evaluation Criteria In Solid Tumors criteria, or death from any cause. OS was defined as the time from the date of CRT until the date of death from any cause, and was censored at the date of the last follow-up for surviving patients. The first recurrence site was evaluated radiologically. Additional disease sites found on subsequent imaging within 1 month of this event were also defined as initial recurrences. In-field failure was defined as further progression of residual tumors in the irradiated field or appearance of a new radiographic lesion > 80% of the volume of which was covered by the 60% isodose line of elective nodal irradiation. Other new lesions were classified under out-of-field tumor progression.

### Statistical Analysis

Statistical analysis of the data in this study was performed in consultation with a statistician. All the statistical analyses were performed using R software, version 3.4.0 (The R Foundation, Vienna, Austria). Differences in the patient characteristics and clinical results between the EGFR-mutant cases and wild-type EGFR, and also between the ALK-negative and ALK-positive cases were evaluated. Statistical differences in the patient characteristics were compared using the $\chi^2$ test, Fisher exact test, and Wilcoxon signed-rank test. Cumulative incidence curves of recurrence were calculated and compared using the Gray test. Survival curves were constructed using the Kaplan-Meier product limit method and compared by the log-rank test. All the tests were 2-sided, and P values of < .05 were considered as indicative of statistical significance.

## Results

### Patient Characteristics

Among the 173 patients for whom information on the EGFR status was available, EGFR mutation was detected in 34 patients. Among the remaining 139 patients with wild-type EGFR, the presence/absence of ALK translocation was examined in 94 patients, and ALK translocation was detected in 13 (14%) patients. The most frequent type of EGFR mutation was deletion in exon 19 (20 of 34 patients; 59%). The L858R point mutation was observed in 12 patients, and the remaining 2 patients had mutations in exon 18 (G719X). Of 13 patients with ALK translocation, 10 were both fluorescence in-situ hybridization- and IHC-positive, whereas the remaining were only IHC-positive.

The patient characteristics of each group are shown in Table 1. All the patients who had received photon beam therapy received a total radiation dose of 60 Gy in 30 fractions. Nine of the 26 patients who had received proton beam therapy received a total radiation dose of 66 Gy in 33 fractions, and the remaining 17 received a total radiation dose of 60 Gy in 30 fractions. All the patients had received platinum-based chemotherapy. Five patients received daily carboplatin regimen, and all of them completed the planned schedule. Of the remaining patients, 163 (97%) received more than 2 courses of chemotherapy. With regard to differences in the patients' characteristics, there were significant differences in the gender, ECOG PS, and histology (adenocarcinoma vs. not otherwise specified) between the wild-type EGFR group and EGFR-mutant group (P < .001, P = .048, and P = .01, respectively), and in the ECOG PS between the ALK-negative group and ALK-positive group (P = .027).

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**Figure 2** Overall Survival (A) and Progression-free Survival (B) Rates in Groups Stratified by the EGFR Mutation Status
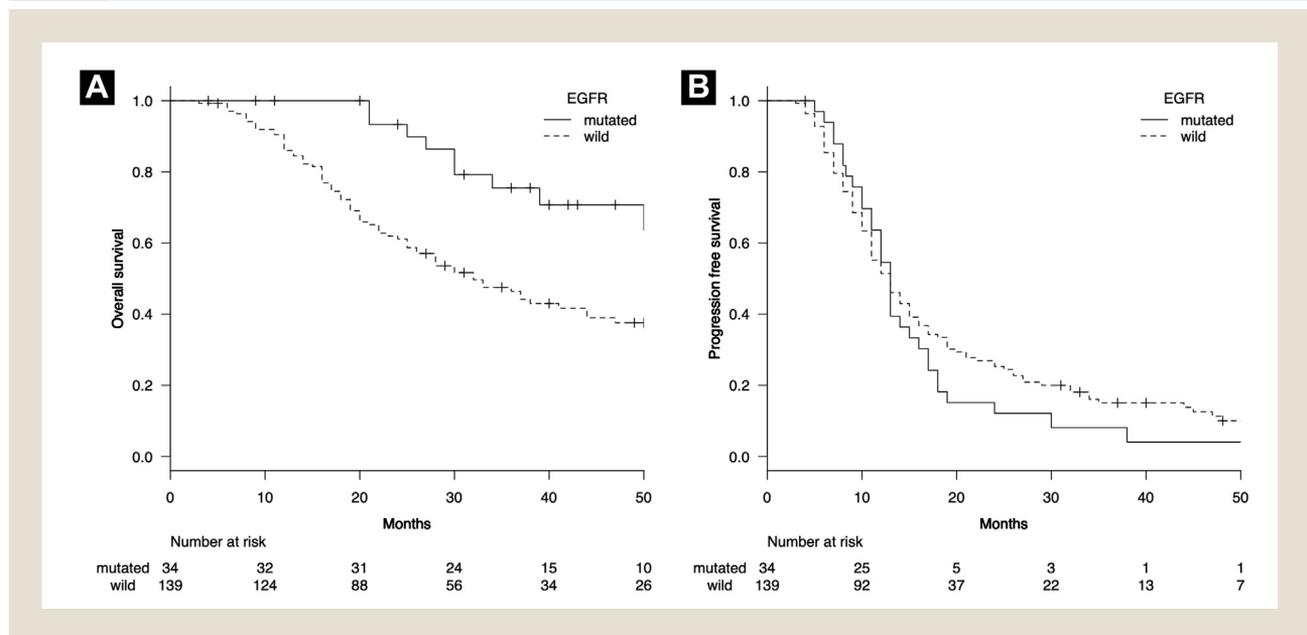


Abbreviation: EGFR = epidermal growth factor receptor.

## Survival

The median follow-up duration of the surviving patients was 36 months (range, 3-123 months). Among the 95 patients who died, 84 patients died owing to disease progression, 8 died owing to other causes, and 3 died of unknown cause. Six of the 13 ALK-positive group patients and 28 of the 34 EGFR-mutant group patients received a tyrosine kinase inhibitor (TKI) for treatment of recurrence. The median period from first recurrence to administration of TKI was 1 month (range, 1-34 months). Eighty of the 126 wild-type EGFR patients (excluding 13 ALK-positive group) received salvage cytotoxic chemotherapy after recurrence. The OS and PFS curves are shown in Figures 2 and 3. The 3-year OS rates in the wild-type EGFR, EGFR-mutant, ALK-negative, and ALK-positive groups were 46% (95% confidence interval [CI], 37%-55%), 75% (95% CI, 55%-88%), 44% (95% CI, 31%-56%), and 68% (95% CI, 36%-87%), respectively. The OS was significantly higher in the EGFR-mutant group than in the wild-type EGFR group ($P = .002$). There was also a tendency towards a better OS in the ALK-positive group as compared with the ALK-negative group ($P = .085$). The 3-year PFS rates in the wild-type EGFR, EGFR-mutant, ALK-negative, and ALK-positive groups were 15% (95% CI, 9%-22%), 8% (95% CI, 2%-21%), 11% (95% CI, 5%-21%), and 12% (95% CI, 1%-38%), respectively. No statistically significant difference in the PFS rate was observed either between the wild-type EGFR and EGFR-mutant groups ($P = .439$) or between the ALK-negative and ALK-positive groups ($P = .722$). However, the OS rates after recurrence were significantly higher in the EGFR-mutant and ALK-positive groups as compared with the wild-type EGFR and ALK-negative groups ($P < .001$ and $P = .022$) (Figure 4).

## Recurrence Patterns

Table 2 shows the pattern of initial failure and the 3-year cumulative incidence rate of failure according to the EGFR and ALK status. The EGFR-mutant group showed significantly lower in-field failure ($P = .027$) and higher out-of-field failure rates ($P = .029$) rates as compared with the wild-type EGFR group. On the other hand, there was no significant difference in either the in-field failure or out-of-field failure rate between the ALK-positive and ALK-negative groups. Analysis by the sites of failure showed that the EGFR-mutant group showed a significantly higher incidence of out-of-field pulmonary metastasis as compared with the wild-type EGFR ($P = .001$) and that the ALK-positive group showed a significantly higher incidence of out-of-field lymph node metastasis as compared with the ALK-negative group ($P = .004$).

## Discussion

This study was conducted to evaluate the impact of EGFR mutations and/or ALK translocation on the clinical outcomes of patients with unresectable stage III non-squamous NSCLC administered definitive CRT. Although the OS was significantly higher in the EGFR-mutant as compared to the wild-type EGFR group and a tendency towards a higher OS was also observed in the ALK-positive as compared to the ALK-negative group, there were no significant differences in the PFS among the groups. Lower in-field failure and higher out-of-field failure rates were observed in the EGFR-mutant as compared with the wild-type EGFR group. On the other hand, although no significant difference was observed in the rates of in-field failure and out-of-field failure between the ALK-positive and ALK-negative groups, the rate of out-of-field lymph node metastasis was significantly higher in the ALK-positive group. This indicated that the ALK translocation and/or EGFR status exert influence on the clinical outcomes, especially the recurrence pattern, after CRT in patients with unresectable stage III non-squamous NSCLC. To the best of our knowledge, this is the first study to evaluate the clinical significance of ALK translocation in patients with stage III NSCLC treated by CRT.

**Figure 3    Overall Survival (A) and Progression-free Survival (B) Rates in Groups Stratified by the ALK Status**
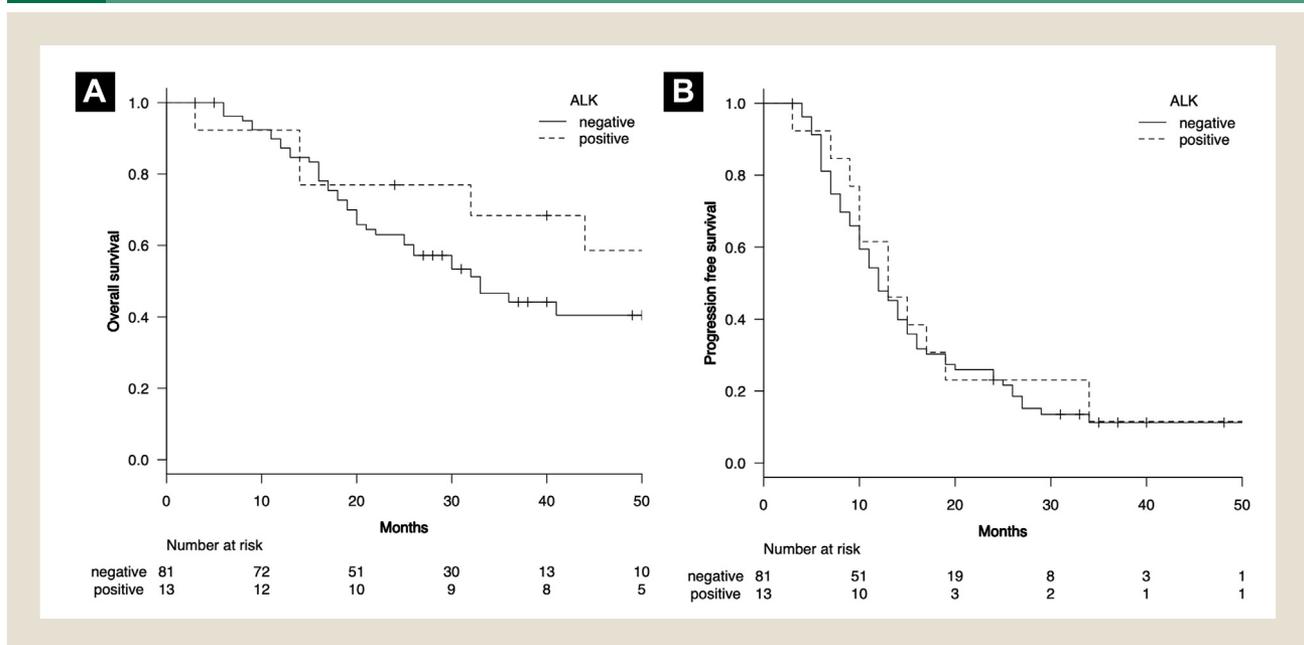


Abbreviation: ALK = anaplastic lymphoma kinase.

**Figure 4** Overall Survival Curves Post Recurrence in Patients Stratified According to the Status of EGFR Mutation (A) and ALK Translocation (B)
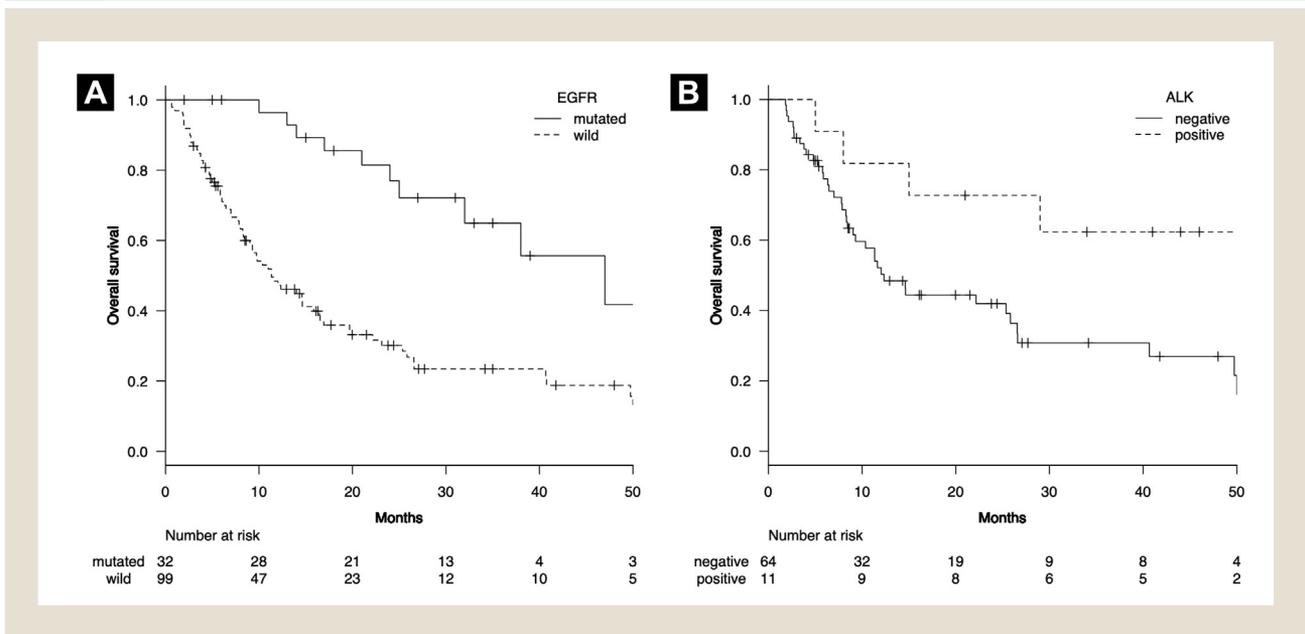


Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor.

Among the 173 patients for whom information on the EGFR status was available, EGFR mutation was detected in 20%, and among the 94 patients for whom information on the ALK status was available, ALK translocation was detected in 14%. The reported prevalence of ALK translocation in Asian patients with NSCLC is 3% to 13%[12] and that of EGFR mutation in patients with lung adenocarcinoma is around 50%.[13] These reports were mainly based on the analysis of patients with stage IV or resectable stage I to II disease. Thus, the incidence of driver gene mutations in patients with stage III NSCLC remains to be fully clarified. Table 3 summarizes the reported results regarding the EGFR gene mutation

status and the recurrence pattern. The reported prevalence of EGFR gene mutations in patients with stage III NSCLC is 17% to 30%,[7-10] lower than the reported prevalence in patients with stage IV NSCLC.

In our study, the OS rate was higher in the EGFR-mutant group than in the wild-type EGFR group and also showed a tendency to be higher in the ALK-positive group as compared with the ALK-negative group. Several previous studies have demonstrated a higher OS in patients with NSCLC harboring EGFR mutations,[7,10] and our results were consistent with these reports. However, Tanaka et al[8] and Yagishita et al[9] showed no significant difference in the OS depending

**Table 2** Three-year Cumulative Incidence of Initial Failure Sites According to the EGFR and ALK Status

| | EGFR Wild-type (n = 139), n (%) | EGFR Mutation (n = 34), n (%) | P Values | ALK Negative (n = 81), n (%) | ALK Positive (n = 13), n (%) | P Values |
|---|---|---|---|---|---|---|
| All failure | 82 (110) | 92 (32) | .192 | 86 (64) | 81 (11) | .43 |
| In-field failure | 39 (51) | 18 (6) | .027 | 34 (26) | 42 (5) | .817 |
| Primary | 30 (39) | 12 (4) | .046 | 25 (19) | 35 (4) | .668 |
| In-field LN | 20 (26) | 15 (5) | .537 | 14 (11) | 15 (2) | .891 |
| Out-of-field failure | 62 (84) | 83 (29) | .029 | 70 (52) | 54 (8) | .315 |
| Brain | 27 (37) | 30 (10) | .781 | 31 (23) | 15 (3) | .278 |
| Out-of-field lung | 10 (14) | 31 (11) | .001 | 14 (10) | 0 (0) | .182 |
| Liver | 8 (10) | 3 (1) | .359 | 12 (9) | 8 (1) | .682 |
| Adrenal gland | 10 (13) | 0 (0) | .065 | 8 (6) | 0 (0) | .303 |
| Out-of-field LN | 8 (11) | 9 (4) | .918 | 5 (4) | 31 (4) | .004 |
| Bone | 11 (15) | 18 (6) | .269 | 15 (11) | 8 (1) | .535 |
| Others | 8 (11) | 3 (1) | .287 | 9 (7) | 8 (1) | .828 |

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; LN = lymph node.

**Table 3** Summary of Reported Results Regarding the EGFR Status and Recurrence Pattern

|  | Akamatsu et al | Yagishita et al | Tanaka et al | Lim et al | Our Study |
|---|---|---|---|---|---|
| **Failure** |  |  |  |  |  |
| EGFR wild-type | 84 (26/31) | 79 (129/164) | 71 (53/75) | NA | 79 (110/139) |
| EGFR mutated | 77 (10/13) | 74 (25/34) | 83 (24/29) | NA | 94 (32/34) |
| ALK positive |  |  |  |  | 85 (11/13) |
| **Locoregional failure** |  |  |  |  |  |
| EGFR wild-type | 32 (10/31) | 33 (54/164)[a] | 35 (26/75) | 45 (31/69)[a] | 45 (63/139) |
| EGFR mutated | 15 (2/13) | 15 (5/34)[a] | 14 (4/29) | 12 (3/26)[a] | 21 (7/34) |
| ALK positive |  |  |  |  | 54 (7/13) |
| **Distant failure** |  |  |  |  |  |
| EGFR wild-type | 58 (18/31) | 63 (102/164)[b] | 40 (30/75) | 39 (27/69)[b] | 61 (85/139) |
| EGFR mutated | 69 (9/13) | 71 (24/34)[b] | 76 (22/29) | 50 (13/26)[b] | 79 (27/34) |
| ALK positive |  |  |  |  | 46 (6/13) |

Data are reported as % (n/N).
Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; NA = not available.
[a]Infield failure.
[b]Out-of-field failure.

upon the EGFR status, indicating that the impact of the EGFR status on the overall survival after CRT still remains to be clearly established in patients with stage III NSCLC, especially because the final OS would also be influenced by the responses to salvage treatments and so on. With regard to the OS after recurrence, Yagishita et al also showed that the survival duration after progression was significantly longer in patients with EGFR mutations than in those with wild-type EGFR. There were no significant differences in the PFS rates depending on the EGFR or ALK status in our study, showing a dissociation between the OS and PFS after CRT depending on the EGFR/ALK status. The OS rates after recurrence were significantly higher in the EGFR-mutant and ALK-positive group than in the wild-type EGFR and ALK-negative group, respectively (Figure 4). After recurrence or disease progression, patients with NSCLC belonging to the wild-type EGFR or ALK-negative group were usually administered salvage chemotherapy, if possible. On the other hand, those in the EGFR-mutant and ALK-positive groups received TKIs based on the type of driver gene mutation after recurrence.[14] The results of a phase III study showed that TKIs were superior to chemotherapy in terms of the PFS in patients with previously treated advanced EGFR-mutant or ALK-positive NSCLC.[15,16] One of the explanations for the dissociation between the OS and PFS described above could be the differences in the response to salvage chemotherapy and TKIs as salvage treatment depending upon differences in the gene mutation status.

Differences in the rates of local control and distant failure according to the driver genes mutation status provides meaningful insights for the development of future therapeutic strategies for locally advanced NSCLC. Ever since CRT using the MVP (mitomycin C, vinblastine and cisplatin) regimen was first established for patients with stage III NSCLC in the latter half of the 1990s,[17] there have been no improvements in the clinical outcomes of CRT in patients with locally advanced NSCLC until approval of ICI as a maintenance therapy after CRT based on the results of the PACIFIC trial.[3,18] The results of several dose-escalation studies demonstrated improved clinical outcomes in patients with locally advanced NSCLC, especially following dose escalation up to the intermediate dose range of around 70 Gy.[19,20] However, further dose escalation beyond 70 Gy did not result in further improvements of the clinical outcome, indicating that other therapeutic approaches or strategies would be needed.[21,22] The results of the current study demonstrated a higher 3-year OS rate and higher in-field control rate, despite a higher out-of-field failure rate, in patients with non-squamous stage III NSCLC, particularly the EGFR-mutant group. Table 3 summarizes the correlation between the EGFR status and the recurrence pattern, especially focusing on the locoregional and distant failure rates. As shown in Table 3, the rates of locoregional and distant failure in patients with EGFR mutations in the current study were almost the same as those reported previously, although locoregional failure does not necessarily imply in-field recurrence. This indicates the possibility that suppression or reduction of out-of-field failure may further improve the clinical outcomes in patients with NSCLC carrying EGFR mutations. Actually, several clinical trials are now under way and are also being planned to introduce EGFR inhibitors for the treatment of locally advanced NSCLC (NCT01822496 and UMIN000005086).

With regard to the recurrence pattern in the ALK-positive group, there have been no reports on the impact of ALK translocation on the recurrence pattern after CRT in patients with stage III NSCLC (Table 3). No significant differences in the in-field or out-of-field failure pattern were observed between the ALK-positive and ALK-negative groups. However, analysis regarding failure sites revealed a significantly higher out-of-field pulmonary metastasis rate ($P = .001$) in the EGFR-mutant group than in the wild-type EGFR group, and a significantly higher out-of-field lymph node metastasis rate ($P = .004$) in the ALK-positive group as compared with the ALK-negative group. Although guidelines suggest that chest CT should be performed every 3 to 6 months for the first 2 years after surgery, the optimal diagnostic imaging modalities and the optimal imaging intervals after CRT have not yet been established.[23,24] As demonstrated in this study, the recurrence patterns after CRT differed significantly according to the tumor genetic status. It is still controversial as to

whether earlier detection of recurrence can improve the clinical outcomes or not; however, it is easily conceivable that early detection of recurrence would enable early initiation of salvage treatment, including chemotherapy, based on the genetic status, and potential prolongation of the survival duration after recurrence.

Recently, a variety of driver gene mutations has been reported in NSCLC.[25] Population analysis of EGFR mutations and ALK translocation is essential for interpretation of the results of dose-escalation trials, and the status of KRAS, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha, v-raf murine sarcoma viral oncogene homolog B1, etc, may also be necessary to determine depending on the results of future analysis. Although genetic diagnosis of NSCLC has been mainly performed in patients with stage IV disease for the purpose of drug selection targeting driver gene mutations, our results indicate that molecular or genetic diagnosis would also be useful and should be applied for patients with locally advanced NSCLC in whom CRT is indicated.

This study has several limitations. First, it was retrospective in nature, and the small sample size may have impacted the validity of the statistical analyses. Second, we adopted elective nodal irradiation at a dose of 40 Gy as a standard technique; however, usage of the involved field technique is widely increasing. It cannot be excluded that the difference described above influenced the recurrence pattern; thus, we need to pay attention to generalize the results of this study. Third, there was a selection bias because genetic information is not routinely obtained before CRT in the patients with locally advanced NSCLC at our institute. For precise and concrete evaluation of the relationship between the recurrence pattern and the tumor genetic status in patients with locally advanced NSCLC, prospective investigations including a sufficient number of cases is needed. However, we believe that the results of this study are important, inasmuch as they indicate the impact of genetic information on the recurrence pattern after definitive CRT in patients with inoperable stage III non-squamous NSCLC.

## Conclusions

EGFR mutation or ALK translocation was detected in 20% and 14% of the patients analyzed in this study, respectively. Neither the EGFR nor the ALK status was predictive of the PFS after CRT, but both exerted an influence on the OS. Although the EGFR-mutant group showed lower in-field and higher out-of-field failure rates, the ALK-positive group showed no characteristic failure pattern in relation to the irradiation field. Analysis by the recurrence sites revealed a higher incidence of out-of-field pulmonary metastasis in the EGFR-mutant group and a higher incidence of out-of-field lymph node metastasis in the ALK-positive group.

### Clinical Practice Points

- The EGFR-mutant group showed a lower incidence of in-field failure and higher incidence of out-of-field failure after definitive CRT in stage III NSCLC.
- There was no significant difference in the rate of in-field failure or out-of-field failure between the ALK-positive and ALK-negative groups.
- Neither the EGFR nor the ALK status was predictive of the PFS after CRT, but both exerted an influence on the OS.

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