



Original Article

EGFR Mutation–Positive Unresectable Stage III Non-Squamous Lung Cancer Is Associated with a High Incidence of Brain Metastasis

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Purpose The impact of epidermal growth factor receptor (*EGFR*) mutation in locally advanced non-small cell lung cancer (NSCLC) remains controversial. This study was conducted to investigate the clinical outcomes and recurrence patterns after definitive chemoradiotherapy (CRT) in patients with unresectable stage III non-squamous-cell lung cancer according to *EGFR* mutation status.

Materials and Methods We retrospectively reviewed 604 patients with pathologically confirmed stage III NSCLC who were treated with definitive CRT and were examined for *EGFR* mutation at Samsung Medical Center, Korea, from January 2013 to December 2018. Among them, we identified 236 patients with stage III non-squamous-cell lung cancer who were treated with definitive CRT and were examined for *EGFR* mutation status. We analyzed the frequency of *EGFR* mutation, progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and recurrence pattern.

Results Among 236 patients, *EGFR* mutation was detected in 71 patients (30.1%) and the median follow-up duration was 41.7 months. There were no significant differences in PFS (9.9 vs. 10.9 months, $p=0.236$), and ORR to CRT (93.0% vs. 90.3%, $p=0.623$) according to *EGFR* mutation status. However, the *EGFR* mutant group showed significantly higher recurrence (88.7% vs. 75.2%, $p=0.022$), distant metastasis (76.1% vs. 61.2%, $p=0.036$) rates, especially brain (38.0% vs. 12.7%, $p < 0.001$), and better median OS (59.2 vs. 41.3 months, $p=0.037$) compared with patients without *EGFR* mutation.

Conclusion Patients with *EGFR* mutation–positive unresectable stage III non-squamous lung cancer exhibited higher recurrence and distant metastasis rates, especially brain metastasis.

Key words Non-small-cell lung carcinoma, *EGFR* mutation, Chemoradiotherapy, Metastasis, Survival

Introduction

Approximately 85% of lung cancer patients have non-small cell lung cancer (NSCLC) and about one-third of patients with NSCLC present with locally advanced NSCLC [1,2]. The majority of locally advanced NSCLC patients have unresectable disease or extensive mediastinal lymphadenopathy. Concurrent chemoradiotherapy (CRT) is the standard treatment for these patients [3,4].

Recently, the PACIFIC trial demonstrated that consolidation with durvalumab following CRT, in unresectable stage III NSCLC patients whose disease has not progressed, significantly prolonged progression-free survival (PFS) and overall survival (OS) [5]. Therefore, the current standard treatment is CRT followed by durvalumab. Despite the good outcomes of the new treatment strategy, the majority of patients treated with CRT followed by durvalumab developed disease progression and died [6]. Therefore, there is a need for a predictive biomarker that appropriately selects the

best treatment for patients individually.

The findings of driver mutations in metastatic NSCLC patients, such as epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) gene translocation, brought paradigm shifts in the therapeutic strategy for metastatic NSCLC [7,8]. However, there have been no prospective studies and only a few retrospective studies are available that reported an association of *EGFR* mutation with clinical outcomes including PFS, OS, and recurrent patterns in locally advanced NSCLC patients treated with CRT [9-12]. Given the small sample sizes and heterogeneous patient populations, the role of *EGFR* mutation in locally advanced NSCLC remains controversial. In this study, we investigated the frequency of *EGFR* mutations and clinical outcomes in patients with unresectable stage III non-squamous-cell lung cancer after definitive CRT according to *EGFR* mutation status.

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Materials and Methods

1. Patients

We retrospectively reviewed 604 patients with pathologically confirmed stage III NSCLC who were treated with definitive CRT and were examined for *EGFR* mutations at Samsung Medical Center, Korea, from January 2013 to December 2018. NSCLC stage evaluation was based on the American Joint Committee on Cancer 8th Edition Cancer Staging Manual. A total of 262 patients diagnosed with squamous cell carcinoma were excluded from the analysis. Among 342 remaining patients, 102 who were treated with definitive CRT due to metachronous oligorecurrence after surgical resection and four who did not complete planned radiation were also excluded (Fig. 1). The baseline clinicopathologic characteristics were reviewed with their medical records. All *EGFR* mutational status was analyzed from tumor specimens using a peptide nucleic acid clamp kit and polymerase chain reaction-based methods at the time of first diagnosis. The Institutional Review Board (IRB No. 2022-06-022) at the Samsung Medical Center approved this study and the need for informed consent was waived because of the retrospective nature of this study.

2. Treatment and outcomes

All 236 patients received 60-74 Gy of thoracic radiation therapy concurrently with platinum doublet chemotherapy. Chemotherapy regimens included paclitaxel plus cisplatin,

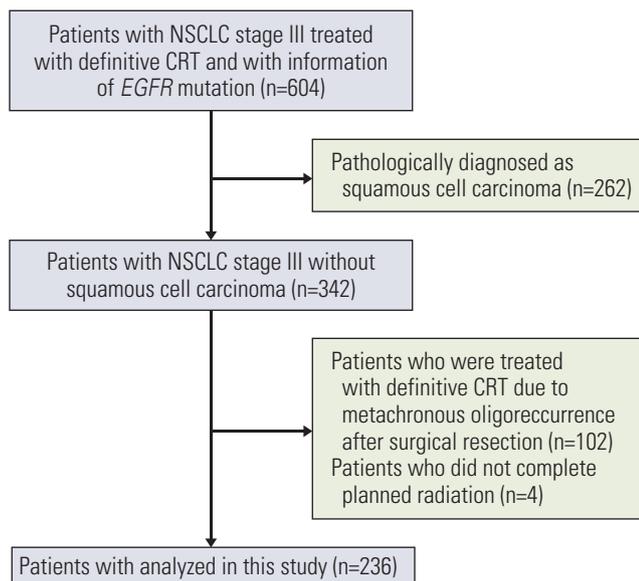


Fig. 1. Flow diagram of the study population. CRT, chemoradiotherapy; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

paclitaxel plus carboplatin, docetaxel plus cisplatin, etoposide plus cisplatin, and etoposide plus carboplatin. Among 236 patients, seven received consolidation with durvalumab following CRT. All patients were evaluated radiologically for clinical outcomes including objective response rate (ORR), disease control rate (DCR), PFS, and OS according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 through computed tomography (CT) or magnetic resonance imaging (MRI). The first follow-up and response evaluation were scheduled 1 month after completion of CRT with chest CT scan. Subsequent follow-up evaluations were conducted at 3-4-month intervals thereafter. The brain MRI was performed only when clinical signs and symptoms suggestive of possible brain involvement were present. The recurrence was evaluated radiologically and defined as documentation of disease progression. PFS was defined as the time from CRT start date until the date of documented disease progression or death from any cause. OS was defined as the time from the CRT start date until death from any cause. According to the RECIST, ORR was defined as the proportion of patients with a complete response (CR) or partial response (PR) to treatment, and DCR was defined as the proportion of patients with a CR, PR, or stable disease to treatment.

3. Statistical analyses

The cutoff date for data collection was December 31, 2021. Descriptive statistics were used to summarize patient and tumor characteristics and treatment history and were reported as proportions and medians. Data are presented as numbers (%) for categorical variables. Correlations of response rates and recurrence patterns according to *EGFR* mutation status were analyzed by Fisher's exact test. Survival analyses were performed with the Kaplan-Meier method, and differences were analyzed with the log-rank test. Hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) were calculated with the Cox proportional hazards model. All p-values were two-sided, and statistical significance was set at $p < 0.05$. Univariate analysis of prognostic factors was performed using Cox proportional hazards models for PFS and OS. Multivariate analysis was used in factors that were significant ($p < 0.05$) on univariate analysis. Statistical analyses were performed with the Statistical Package for the Social Sciences software program ver. 25 (IBM Corp., Armonk, NY).

Results

1. Patient characteristics

All 236 patients were retrospectively reviewed in this study. *EGFR* mutation test was conducted for all patients. *EGFR* mutation was detected in 71 patients (30.1%). The

Table 1. Patient characteristics

Characteristic	EGFR mutation (n=71)	EGFR wild-type (n=165)	p-value
Median age (yr), median (range)	60 (45-79)	62 (28-80)	0.688
Sex			
Male	33 (46.5)	125 (75.8)	< 0.001
Female	38 (53.5)	40 (24.2)	
Smoking status			
Never smoker	44 (62.0)	47 (28.5)	< 0.001
Current/Former smoker	27 (38.0)	118 (71.5)	
ECOG performance status			
0-1	70 (98.6)	160 (97.0)	0.671
2	1 (1.4)	5 (3.0)	
Clinical T category			
T1-2	55 (77.5)	98 (59.4)	0.007
T3-4	16 (22.5)	67 (40.6)	
Clinical N category			
N1-2	5 (7.0)	35 (21.2)	0.008
N3	66 (93.0)	130 (78.8)	
Clinical stage			
IIIA	2 (2.8)	15 (9.0)	0.054
IIIB	57 (80.3)	108 (65.5)	
IIIC	12 (16.9)	42 (25.5)	
Histology			
Adenocarcinoma	71 (100)	153 (92.7)	0.020
NOS	0	12 (7.3)	
EGFR mutation			
Exon 19 deletion	37 (52.1)		
L858R	23 (32.4)		
Uncommon	11 (15.5)		
Chemotherapy			
Cisplatin-based	68 (95.8)	154 (93.3)	0.562
Carboplatin-based	3 (4.2)	11 (6.7)	
Radiation dose (Gy), median (range)	6,600 (6,000-7,040)	6,600 (6,000-7,400)	0.879
Durvalumab consolidation	2 (2.8)	5 (3.0)	> 0.99

Values are presented as median (range) or number (%). ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NOS, not otherwise specified.

most frequent type of EGFR mutation was a deletion in exon 19 (37 patients, 52.1%). L858R point mutation was detected in 23 patients (32.4%) and uncommon mutations (exon 20 insertion, G719X, S768I, T790M) were detected in 11 patients (15.5%).

Table 1 presents the clinical characteristics of patients with and without EGFR mutation. All patients received 60-74 Gy of radiation therapy concurrently with platinum doublet chemotherapy. The EGFR mutation group had a statistically higher proportion of females (53.5%), never smokers (62.0%), low T category (77.5%), high N category (93.0%), and adenocarcinoma (100.0%) ($p < 0.05$).

2. Survival

The median follow-up duration was 41.7 months (2.8 to 106.3 months). Overall, 140 patients died and 204 patients experienced disease progression. Median PFS was 9.9 months for the EGFR mutation versus 10.9 months for EGFR wild type. Median OS was 59.2 months for the EGFR mutation versus 41.3 months for EGFR wild type. There was no statistically significant difference in PFS according to EGFR mutation status ($p=0.236$) (Fig. 2A). There was a statistically significant difference in OS according to EGFR mutation status ($p=0.037$) (Fig. 2B). The 52 patients (82.5%) with EGFR mutation were treated with EGFR tyrosine kinase inhibitors (TKIs) (gefitinib, n=19; erlotinib, n=7; afatinib, n=25; olmuti-

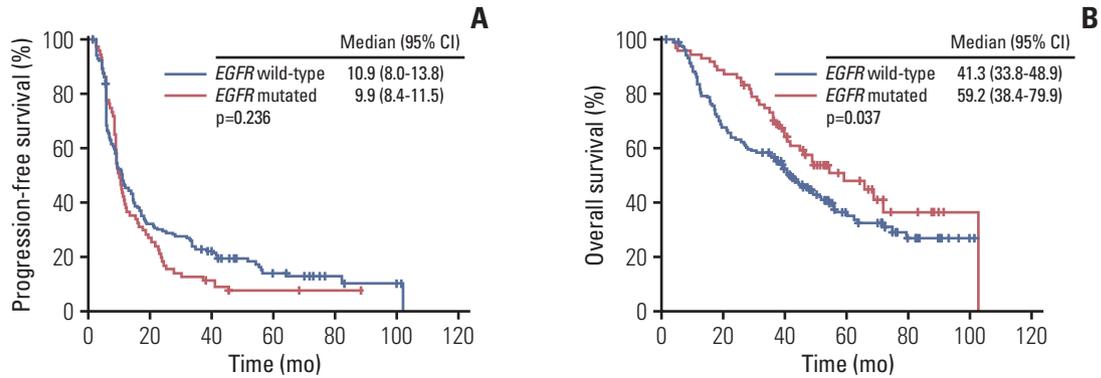


Fig. 2. Kaplan-Meier curves of progression-free survival (A) and overall survival (B) according to epidermal growth factor receptor (*EGFR*) mutation status. CI, confidence interval.

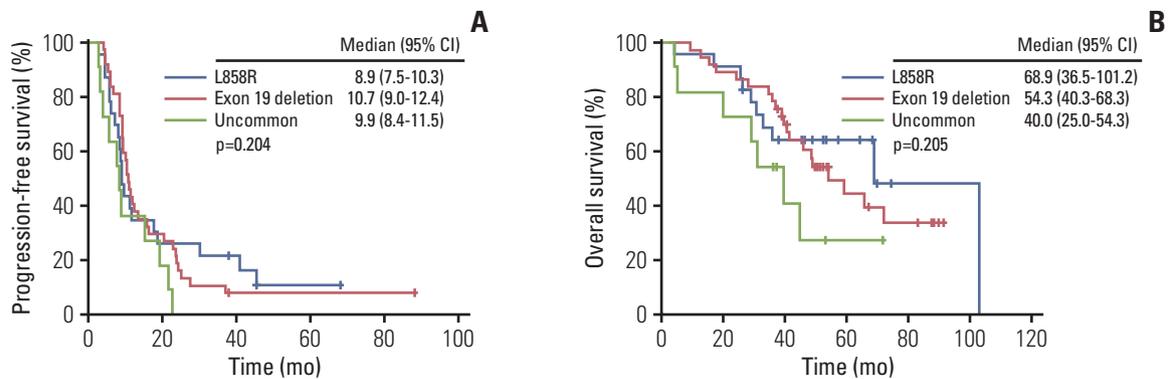


Fig. 3. Kaplan-Meier survival curves of progression-free survival (A) and overall survival (B) according to epidermal growth factor receptor (*EGFR*) mutation subtypes. CI, confidence interval.

nib, n=1) after recurrence. On the other hand, most patients (77/124, 62.1%) with *EGFR* wild-type were treated with cytotoxic chemotherapy. Also, those patients (10/124, 8.1%) in the *EGFR*-wild type and *ALK*-positive were treated with *ALK* TKIs based on the driver gene mutation after recurrence.

Among 71 patients harboring *EGFR* mutations, we analyzed survival according to the *EGFR* mutation subtype, but there were no statistically significant differences in PFS and OS according to *EGFR* mutation subtype ($p=0.204$ and $p=0.205$, respectively) (Fig. 3A and B). We additionally conducted survival analyses for PFS and OS according to *EGFR* mutation. *EGFR* mutation also was not an independent factor in univariate analysis for PFS ($p=0.237$) (Table 2). Univariate analysis for OS revealed age ($p=0.031$), and *EGFR* mutation ($p=0.039$) as significant factors (Table 3). Multivariate analysis for OS showed age ($p=0.037$), and *EGFR* mutation ($p=0.045$) as significant independent prognostic factors (Table 3).

3. Response to CRT

We compared the tumor response to CRT according to *EGFR* mutation status. ORR and DCR were 93.0% and 97.2%, respectively, in patients with *EGFR* mutation and 90.3% and 93.3%, respectively, in patients with wild-type *EGFR*. ORR and DCR according to *EGFR* mutation status were not significantly different ($p=0.623$ and $p=0.354$, respectively) (Table 4).

4. Recurrence patterns

Table 5 shows the initial recurrence patterns according to *EGFR* mutation status. Among 71 patients with *EGFR* mutation, 63 (88.7%) developed tumor recurrence without death and 54 patients (76.1%) had distant metastasis. Among 165 patients with wild-type *EGFR*, 124 patients (75.2%) developed tumor recurrence without death and 101 patients (61.2%) had distant metastasis.

The *EGFR* mutant group showed significantly higher recurrence rates (88.7% vs. 75.2%, $p=0.022$) and distant metastasis rates (76.1% vs. 61.2%, $p=0.036$) compared with

Table 2. Univariate analysis of progression-free survival

	Progression-free survival	
	HR (95% CI)	p-value
Age (yr)		
< 65	1	0.230
≥ 65	0.84 (0.62-1.12)	
Sex		
Male	1	0.119
Female	1.26 (0.94-1.68)	
Smoking status		
Never smoker	1	0.046
Current/Former smoker	0.75 (0.57-0.99)	
Clinical T category		
T1-2	1	0.991
T3-4	1.00 (0.75-1.34)	
Clinical N category		
N1-2	1	0.319
N3	1.21 (0.83-1.76)	
Clinical stage		
IIIA	1	
IIIB	1.10 (0.63-1.90)	0.746
IIIC	1.33 (0.73-2.42)	0.349
EGFR mutation		
Mutant type	1	0.237
Wild type	0.84 (0.62-1.13)	

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio.

the EGFR wild-type group. In contrast, loco-regional recurrence incidence was not significantly different according to EGFR mutation status ($p > 0.99$). The most common distant metastasis site in the EGFR mutant group was the brain (38.0%) followed by lung-to-lung (36.6%), bone (14.1%), pleura (8.5%), liver (5.6%), distant lymph node (4.2%), and adrenal gland (4.2%). The EGFR mutant group showed a significantly higher incidence of brain metastasis compared with the EGFR wild-type group (38.0% vs. 12.7%, $p < 0.001$).

Discussion

In our study, we identified the frequency of EGFR mutation and the clinical outcomes in patients with stage III non-squamous-cell lung cancer after definitive CRT according to EGFR mutation status. We found that 30% of patients with unresectable stage III non-squamous-cell lung cancer treated with CRT harbor an EGFR mutation, which is consistent with previous studies [9,10,12]. Intriguingly, EGFR mutation was associated with higher recurrence rates and distant metastasis, especially in the brain, compared with patients without

EGFR mutation. The association between EGFR mutation and brain metastasis from metastatic NSCLC has been reported in previous studies. These studies have consistently reported that the risk of brain metastasis increased in metastatic NSCLC with EGFR mutation [12-14]. Based on these results, EGFR mutation may impact the pattern of distant metastasis. Despite higher recurrence rates and distant metastasis, the OS was significantly higher in patients with EGFR mutation than patients with EGFR wild-type. After recurrence or disease progression, most patients (82.5%) with EGFR mutation were treated with EGFR TKI. On the other hand, most patients (62.1%) with EGFR wild-type were treated with cytotoxic chemotherapy and those patients (8.1%) in the EGFR-wild type and ALK-positive were treated with ALK TKIs. Therefore, the dissociation between the high recurrence rate and OS could be due to the response to salvage treatment based on the driver gene mutation after recurrence.

The impact of EGFR mutation on clinical outcomes after definitive CRT in stage III NSCLC remains controversial. Nakamura et al. [10] and Yagishita et al. [11] reported no significant difference in PFS according to EGFR mutation status. Alternatively, Park et al. [9] and Tanaka et al. [12] reported significantly shorter PFS in patients with EGFR mutation compared with the wild-type EGFR. These different results indicate that the impact of EGFR mutation on PFS after CRT remains unestablished. However, these studies have consistently demonstrated that the incidence of distant metastasis and disease progression is high and that the brain was the most frequent site of distant metastasis in patients with EGFR mutation, which were consistent with our results. The high incidence of recurrence with distant metastases, including those in the central nervous system (CNS), highlights the need for regular brain MRI follow-up and CNS-penetrant targeted therapy as consolidation in patients with EGFR mutation.

Several clinical trials of EGFR TKIs in unresectable stage III EGFR-mutated NSCLC are evaluated [15,16]. These phase-II studies reported that gefitinib and erlotinib showed improved clinical outcomes, however, they have less penetration of the blood-brain barrier and lower CNS activity than osimertinib. Also, these studies did not include regular brain image follow-up.

Recently, the ADAURA phase III trial demonstrated that osimertinib, a CNS active third-generation EGFR TKI, significantly improved disease-free survival in patients with completely resected, EGFR-mutated stage II to -IIIA NSCLC after completing standard adjuvant chemotherapy (HR, 0.17; 95% CI, 0.1 to 10.26). Furthermore, adjuvant osimertinib treatment was associated with a marked reduction in CNS recurrence or death (HR, 0.18; 95% CI, 0.10 to 0.33) [17]. These results suggest that osimertinib might be a good candidate

Table 3. Univariate and multivariate analysis of overall survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)				
< 65	1	0.031	1	0.037
≥ 65	1.47 (1.04-2.08)		1.45 (1.02-2.05)	
Sex				
Male	1	0.350		
Female	0.84 (0.59-1.21)			
Smoking status				
Never smoker	1	0.349		
Current/Former smoker	1.18 (0.83-1.68)			
Clinical T category				
T1-2	1	0.163		
T3-4	1.29 (0.90-1.82)			
Clinical N category				
N1-2	1	0.409		
N3	0.83 (0.53-1.30)			
Clinical stage				
IIIA	1			
IIIB	1.10 (0.54-2.26)	0.796		
IIIC	1.42 (0.66-3.09)	0.372		
EGFR mutation				
Mutant type	1	0.039	1	0.045
Wild type	1.49 (1.02-2.19)		1.48 (1.01-2.16)	

CI, confidence interval; *EGFR*, epidermal growth factor receptor; HR, hazard ratio.

Table 4. Response rate according to *EGFR* mutation

	<i>EGFR</i> mutation (n=71)	<i>EGFR</i> wild-type (n=165)	p-value
Complete response	8 (11.3)	19 (11.5)	
Partial response	58 (81.7)	130 (78.8)	
Stable disease	3 (4.2)	5 (3.0)	
Progressive disease	2 (2.8)	10 (6.0)	
Not evaluable	0	1 (0.6)	
Objective response rate	66 (93.0)	149 (90.3)	0.623
Disease control rate	69 (97.2)	154 (93.3)	0.354

Values are presented as number (%). *EGFR*, epidermal growth factor receptor.

for consolidation therapy following CRT in patients with locally advanced *EGFR*-mutated NSCLC. Currently, the phase-III LAURA trial is underway to assess the efficacy and safety of consolidation with osimertinib following CRT in patients with stage III unresectable *EGFR*-mutated NSCLC [18]. This included patients with locally advanced, unresectable stage III *EGFR*-mutated NSCLC after completing CRT who were randomly assigned to receive osimertinib or placebo until disease progression. The primary endpoint of the study was PFS in patients with locally advanced, unresect-

able stage III *EGFR*-mutated NSCLC. Secondary endpoints include time to CNS PFS and cumulative incidence at 12 and 24 months, OS, PFS by mutation status, time to death or distant metastasis, and safety. How well osimertinib consolidation can reduce recurrence rate, especially brain metastasis will be an important insight from the LAURA trial. Our results provide a strong rationale to investigate CNS-penetrant *EGFR* TKI as consolidation in unresectable locally advanced NSCLC with *EGFR* mutation.

In the era of immune checkpoint inhibitors (ICI), the PACI-

Table 5. Initial recurrence pattern according to *EGFR* mutation

	<i>EGFR</i> mutation (n=71)	<i>EGFR</i> wild-type (n=165)	p-value
Recurrence rate	63 (88.7)	124 (75.2)	0.022
Loco-regional recurrence	9 (12.7)	23 (13.9)	> 0.99
Primary	4 (5.6)	8 (4.8)	
Lymph nodes	5 (7.0)	15 (9.1)	
Distant metastasis	54 (76.1)	101 (61.2)	0.036
Brain	27 (38.0)	21 (12.7)	< 0.001
Pleura	6 (8.5)	18 (10.9)	0.645
Lung to lung	26 (36.6)	32 (19.4)	0.008
Distant lymph nodes	3 (4.2)	32 (19.4)	0.002
Bone	10 (14.1)	21 (12.7)	0.834
Liver	4 (5.6)	8 (4.8)	0.756
Adrenal gland	3 (4.2)	15 (9.1)	0.286
Other	0	8 (4.8)	0.109

Values are presented as number (%). *EGFR*, epidermal growth factor receptor.

FIC trial demonstrated that consolidation with durvalumab following CRT significantly improved clinical outcomes in unresectable stage III NSCLC patients whose disease has not progressed. However, the PACIFIC trial subgroup analysis of prognostic factors for PFS showed that patients with *EGFR* mutation may benefit less from CRT followed by durvalumab (HR, 0.84; 95% CI, 0.40 to 1.75) [5,6]. Also, a meta-analysis demonstrated that patients with *EGFR*-mutated metastatic NSCLC exhibited poor survival when treated with ICIs [19], but the reason is not clear. Previous studies have suggested that *EGFR* mutant tumors generate an immunosuppressive tumor microenvironment with less programmed death-ligand 1 expression, reduced tumor mutational burden and neoantigen presentation, and decreased tumor infiltrating lymphocyte infiltration, all of which decrease ICI efficacy [20].

The optimal treatment in unresectable stage III *EGFR*-mutated NSCLC patients remains unclear. Results with *EGFR* TKIs showed improved clinical outcomes when given concurrently or induction to CRT in unresectable stage III *EGFR*-mutated NSCLC patients [11,16]. However, they should be confirmed in the phase III trial. Also, in the PACIFIC trial, only 6% of patients had *EGFR* mutation [5]. Given the *post-hoc* analysis and small sample size, further evaluation is needed to evaluate the role of durvalumab consolidation in *EGFR*-mutant patients. Currently, the phase III LAURA trial is ongoing. This study will evaluate the role of *EGFR* TKI to improve clinical outcomes and suggest a new treatment strategy, which is the definitive CRT followed by *EGFR* TKI.

This study has several limitations. First, it is a single-center retrospective study, which can lead to bias. Second, only Asian patients with NSCLC were analyzed, and this limits its generalizability because of differences in molecular profiles

and clinical features between Western and Eastern patients with NSCLC. Nevertheless, to the best of our knowledge, this study is one of the largest with a long-term follow-up analysis of the impact of *EGFR* mutation in patients with unresectable stage III non-squamous-cell lung cancer after definitive CRT.

In conclusion, patients with *EGFR* mutation-positive unresectable stage III non-squamous lung cancer exhibited higher recurrence and distant metastasis rates, especially in the brain.

Ethical Statement

This study was approved by the Institutional Review Board (IRB No. 2022-06-022) at Samsung Medical Center and the need for individual consent for this retrospective analysis was waived.

Author Contributions

Conceived and designed the analysis: Kim H, Ahn MJ.

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Contributed data or analysis tools: Kim H, Park S, Jung HA, Sun JM, Lee SH, Ahn JS, Ahn MJ.

Performed the analysis: Kim H, Ahn MJ.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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