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근치적 방사선 치료 후 재발한 상피성장인자 수용체 돌연변이 비소세포폐암 환자에서 상피성장인자 수용체 티로신 키나아제 억제제의 효과

Efficacy of EGFR tyrosine kinase inhibitor in EGFR mutant non-small cell lung cancer patients who recurred after definitive radiotherapy

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이 논문을 석사 학위 논문으로 제출함

2020년 2월

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2019 년 12 월

감사의 글

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Abstract

Background For patients with recurrent EGFR mutant non-small cell lung cancer (NSCLC), EGFR tyrosine kinase inhibitor (TKI) is the standard therapy. In this study, we evaluated efficacy of EGFR TKI in EGFR mutant NSCLC patients who recurred after definitive radiotherapy (RT) or concurrent chemo-radiation therapy (CCRT) by comparing with those who recurred after surgical resection.

Methods Patients with diagnosis of EGFR mutant NSCLC who received EGFR TKI after recurrence to definitive treatment (RT vs. surgery) at Asan Medical Center, Seoul, Korea were included. Survival curves between two groups were estimated by Kaplan-Meier method and compared using log-rank test. Overall survival (OS) was defined as from the initiation of EGFR TKI to any cause of death, and progression-free survival (PFS) was defined as from the initiation of EGFR TKI to objective disease progression or any cause of death.

Results Total 56 patients were included in analysis (21 in RT group vs. 35 in surgery group). Clinical characteristics were similar between two groups, including disease status at recurrence (Logo-regional vs. distant metastasis). Median OS was significantly shorter in the RT group compared to the surgery group (15.6 vs. 47.2 months, P=0.001). This remained significant in multivariate analysis including potential prognostic factors (HR 3.03, 95% CI 1.45-6.25, P=0.003). Median PFS was also significantly shorter in the RT group compared to the surgery group (8.5 vs. 14.5 months, P=0.045), but adjusted HR was not statistically significant (P=0.138).

Conclusion In patients with EGFR mutant NSCLC who received EGFR TKI after recurrent to definitive RT or CCRT, OS and PFS was significantly shorter compared to those who received EGFR TKI after recurrence to surgery.

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Introduction

Lung cancer is malignant neoplasm deriving from bronchus and alveoli. In Korea, lung cancer is the 4th most common cancer and the leading cause of death among cancers (1). There has been progress in the treatment of lung cancer, but survival outcomes are still dismal with 5 years overall survival of 18% (2). Targeted therapy improved survival outcomes of stage 4 or recurrent NSCLC patients with actionable mutations and molecular testing is mandatory for newly diagnosed NSCLC patients (3, 4).

EGFR mutation is most commonly found driver mutation among NSCLC patients and certain EGFR gene mutations are known to be sensitive to EGFR tyrosine kinase inhibitor (TKI) (5, 6). First and second generation EGFR TKIs, including gefitinib, erlotinib, and afatinib has shown survival benefit and was approved for first-line treatment in advanced NSCLC patients with targetable EGFR mutations (7-9).

Irrespective of EGFR mutation status, locally advanced unresectable NSCLC patients are treated with definitive radiotherapy (RT) or concurrent chemo-radiation therapy (CCRT) (10, 11). In patients with early stage NSCLC with inoperable medical conditions or who refuse to have surgery, conventional RT or hypofractionated RT, also known as stereotactic radiosurgery (SRS), could be a curative treatment option (12). NSCLC patients harboring targetable EGFR mutations who recur after definitive RT or CCRT are treated with EGFR TKI.

There are several studies comparing outcomes of definitive CCRT in EGFR mutant locally advanced NSCLC with EGFR wild-type (WT) disease and the data showed similar response rates in both groups, shorter recurrence-free interval and more systemic recurrence in EGFR mutant disease, although these were retrospective observational studies and results varied in between studies (13-16). Meanwhile, several in vitro studies showed that somatic mutation of EGFR is associated with increased sensitivity to ionizing radiation by attenuation of DNA repair mechanisms in NSCLC cell lines (17, 18). However, the efficacy of EGFR TKI in patients who received RT is not well established. In this study, we

evaluated efficacy and survival outcomes of EGFR TKI in EGFR mutant NSCLC patients who recurred after definitive RT by comparing with those who recurred after surgery.

Materials and Methods

1. Patients

Patients with histologic diagnosis of NSCLC harboring targetable EGFR mutation from July 21th, 2009 to June 11th, 2015 at Asan Medical Center were screened. Among these patients, those who received EGFR TKI as first-line treatment after recurrence to curative treatment were included in this study. Patients were divided in to two treatment groups according to initial curative treatment (definitive RT vs. surgical resection).

Clinical data were extracted from electronic medical records including patient's demographics, initial stage, initial curative treatment, type of recurrence, treatment after recurrence, and outcomes. Patient's initial stage was re-assessed according to American Joint Committee on Cancer (AJCC) staging system, 8th edition.

2. Initial treatment

Definitive RT was given to patients who had locally advanced un-resectable disease, medically not feasible for surgical resection, or patients who refused surgery. Type of RT given was decided by treating radiation oncologist among concurrent chemo-radiation therapy (CCRT), conventional definitive RT without chemotherapy, or SRS.

For patients with resectable disease and operable medical condition, surgical resection of primary lesion with mediastinal LN dissection was performed. Adjuvant treatment with chemotherapy, radiotherapy, or sequential chemo-radiation therapy was given as indicated, with shared-decision making among treating medical oncologist, radiation oncologist, and patients.

After completion of curative treatment, patients were evaluated every 3 to 6 months by chest computed tomography (CT) until recurrence. Disease-free survival (DFS) was defined as from the completion of definitive treatment do the date of recurrence confirmation. Loco-regional recurrence was defined as ipsilateral lung and lymph node (LN) metastasis.

3. Treatment after recurrence

After recurrence, additional testing of biopsy or resected tumor tissue including EGFR mutation, anaplastic lymphoma kinase (ALK) immunohistochemistry, and ALK fusion fluorescence in situ hybridization (FISH) was done in patients with non-squamous histology. Patients with targetable EGFR mutation (exon 18 p.G719X, exon 19 deletions and insertions, exon 20 p.S768I, and exon 21 p.L858R) were treated with first or second generation EGFR TKIs including gefibinib, erlotinib, or afatinib. In patients with symptomatic metastatic lesions such as brain or bone metastasis, palliative surgical resection or RT of the disease site could be performed prior to EGFR TKI administration.

After initiation of EGFR TKI treatment, response was evaluated every 6 to 12 weeks with CT scans of known sites of disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Unlike cytotoxic chemotherapy, patients can benefit from continued EGFR TKI beyond objective progression and discontinuation may even lead to rapid progression of the tumor in some patients (19). Hence, initial EGFR TKI could be continued beyond objective progression with treating physicians' discrete. In patients with symptomatic or rapid progression, re-biopsy and subsequent treatment was decided by shared decision making with patients and treating physician.

4. Efficacy of EGFR TKI and statistical analysis

Efficacy outcomes of EGFR TKI between the two treatment groups were compared. Overall survival (OS) was defined as from the initiation of EGFR TKI to any cause of death. Progression-free survival (PFS) was defined as from the initiation of EGFR TKI to objective disease progression according to RECIST 1.1 or any cause of death in patients without recorded objective progression. As many patients continued EGFR TKI beyond progressive disease (PD), time-to treatment discontinuation (TTD) was also assessed as efficacy outcome, which was defined as from the initiation of EGFR TKI to discontinuation of any cause.

Time-to progression (TTP) and duration of response (DoR) was also assessed, which were defined as from the initiation of EGFR TKI to objective PD, and from the date of best response to objective PD according to RECIST 1.1. Objective response rate (ORR) was defined as proportion of patients who showed complete response (CR) or partial response (PR) as best response according to RECIST 1.1 among patients who had at least one objective disease evaluation. Disease control rate (DCR) was defined as proportion of patients with CR, PR or stable disease (SD) as best response according to RECIST 1.1 among patients who had at least one objective disease evaluation.

Chi-square test or Fisher's exact test was performed to compare categorical variables between the two treatment groups as appropriate. Survival curves were estimated by Kaplan-Meir methods and compared using log-rank test. Clopper-Pearson interval was used to estimate confidential intervals of ORR and DCR, and compared using Chi-square test or Fisher's exact test as appropriate. Multivariate analysis using Cox proportional hazards model was performed to adjust effects of clinical variables on survival outcomes other than initial curative treatment. A two-sided p value of less than 0.05 was considered statistically significant and all statistical analyses were performed using Statistical Package for the Social Sciences (IBM Corp, Armonk, NY, USA) 21.0.

Results

1. Baseline characteristics

Patients diagnosed with NSCLC from July 21st, 2009 to June 11th, 2015 and treated in Asan Medical Center were screened. We identified 56 patients who received EGFR TKI treatment after recurrence to curative treatment and divided into two groups according to curative treatment modality (RT group vs. Surgery group). Study outline is summarized in figure 1. Median age was 66 years (range, 38-83), 16 patients (28.6%) were male, and 41 patients (73.2%) were never smokers.

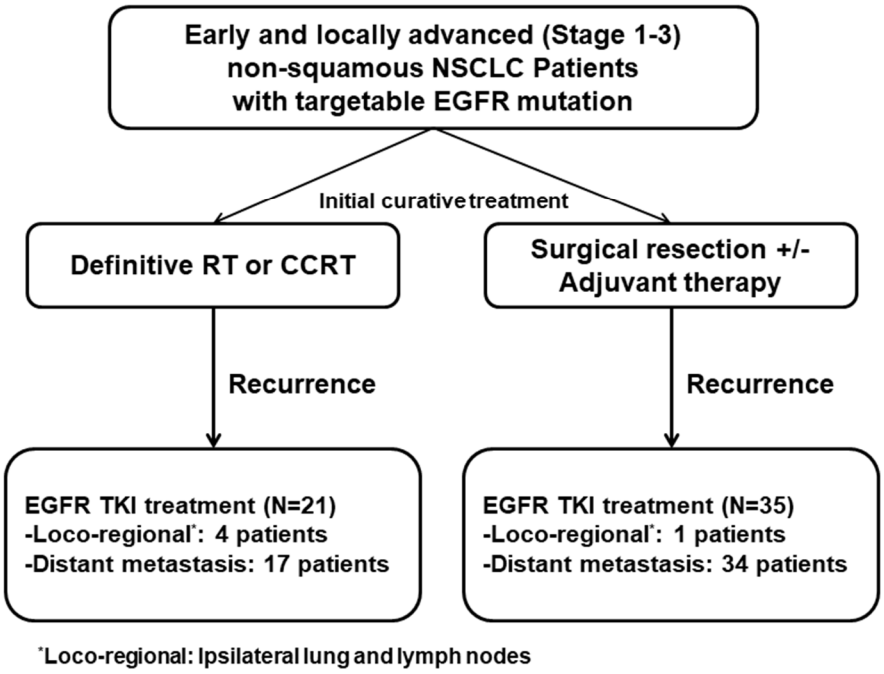

Figure 1. Study Outline

Among the patients, 21 patients recurred after definitive RT or CCRT, and 35 patients recurred after surgical resection. Comparison of baseline characteristics between the two groups is shown in table 1. Clinical characteristics including age, sex, and comorbid status were similar between the two groups. Although there were significantly more patients with initial clinical stage 1-2 in the surgery group compared to the RT group, disease status at recurrence (Loco-regional recurrence vs. distant metastasis) were similar between the two groups. Histologic subtype was adenocarcinoma in all patients except one in surgery group, who had adeno-squamous cell carcinoma.

Table 1. Baseline Characteristics

	RT Group (N=21)	**Surgery Group (N=35)**	**P**
Median age, years (range)	62 (38-77)	67 (43-83)	
Age			0.184
≥ 60 years	12 (57.1%)	26 (74.3%)	
< 60 years	9 (42.9%)	9 (25.7%)	
Sex			0.541
Male	7 (33.3%)	9 (25.7%)	
Female	14 (66.7%)	26 (74.3%)	
Smoking status			0.391
Current or past smoker	7 (33.3%)	8 (22.9%)	
Never smoker	14 (66.7%)	27 (77.1%)	
Histology			
Adenocarcinoma	21 (100%)	34 (97.1%)	
Adeno-squamous cell carcinoma	0	1 (2.9%)	

Table 1. Continued			
Initial Stage			
IA3	1	5	
IB	2	6	
IIA	1	7	
IIB	2	11	
IIIA	0	6	
IIIB	15	0	
Initial Stage (I-II vs. III)			< 0.001
IA3-IIB	6 (28.6%)	29 (82.9%)	
IIIA-IIIB	15 (71.4%)	6 (17.1%)	
Disease status at recurrence			0.060
Loco-regional (Ipsilateral lung and LN)	4 (19.1%)	1 (2.9%)	
Distant metastasis	17 (80.9%)	34 (97.1%)	
Comorbidities other than lung disease			0.24
Yes	8 (38.1%)	19 (54.3%)	
No	13 (61.9%)	16 (45.7%)	
Chronic lung disease (COPD, ILD, TB destroyed lung)			0.165
Yes	7 (33.3%)	6 (17.1%)	
No	14 (66.7%)	29 (82.9%)	

2. Initial treatment

In the RT group, 13 patients (61.9%) received CCRT and 6 patients (28.6%) received hypo-fractionated SRS. Median sum of RT dose was 6380 cGy (range, 4800-6900) and platinum-based doublet chemotherapy was used in all patients who had CCRT. In the surgery group, 22 patients (62.8%) had stage 3 disease according to pathologic staging confirmed after resection. Fourteen patients (40.0%) received post-operative adjuvant treatment. Initial curative treatment details of the two groups are summarized in table 2 and 3.

Table 2. Initial treatment in the RT group

	RT group (n=21)
Type of definitive RT	
CCRT	13 (61.9%)
Definitive RT	2 (9.5%)
Stereotactic radiosurgery	6 (28.6%)
Sum of RT dose (cGy), median (range)	6380 (4800-6900)
Concurrent chemotherapy regimen	N=13
Paclitaxel + Cisplatin	10 (76.9%)
Paclitaxel + Carboplatin	2 (15.4%)
Irinotecan + Cisplatin	1 (7.7%)

Table 3. Initial treatment in the surgery group

	Surgery group (n=35)
Pathologic stage (AJCC 8th edition)	
IB	4 (11.4%)
IIA	1 (2.9%)
IIB	8 (22.9%)
IIIA	18 (51.4%)
IIIB	4 (11.4%)
Adjuvant therapy	
Chemotherapy	2 (5.7%)
Radiotherapy	9 (25.7%)
Sequential chemo-radiation	3 (8.6%)
None	21 (60.0%)

3. Recurrence

From the completion of initial treatment, median DFS was 13.4 months (95% CI 11.1-15.8) and 41 patients (78.6%) recurred as distant metastasis. Clinical characteristics at the time of recurrence are compared between the two groups in table 4. There were no statistically significant differences between the two groups in terms of Eastern Cooperative Oncology Group (ECOG) performance status at recurrence and type of EGFR mutations. Most common sites of metastasis were lung followed by LN, brain, and bone. Most patients in both groups received gefitinib as first-line EGFR TKI, with 19 patients (90.5%) in the RT group and 32 patients (91.4%) in the surgery group. There was no statistically significant difference between the two groups in terms of DFS with median DFS of 9.7 months (95% CI 7.7-11.9) in the RT group and 14.0 months (95% CI 9.7-18.3) in the surgery group (P=0.838, figure 2).

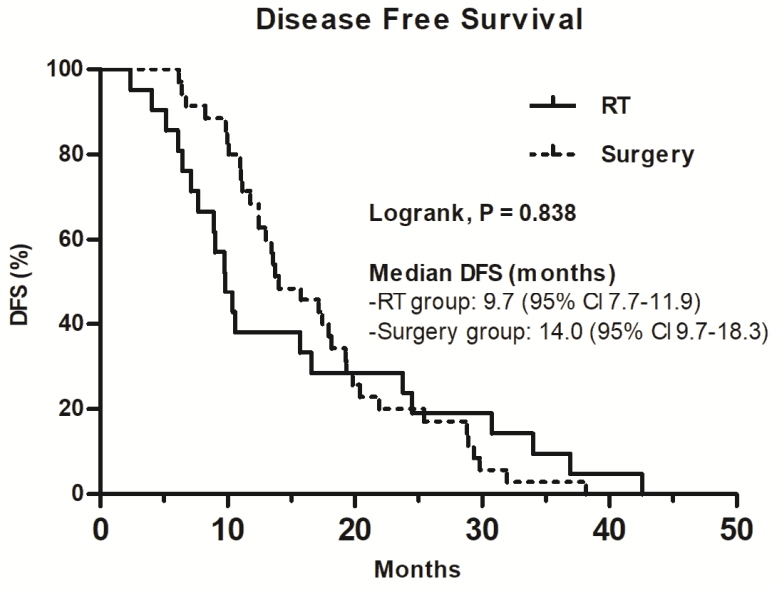

Figure 2. Disease-free survival in the two groups

Table 4. Recurrence after curative treatment

	RT group (N=21)	Surgery group (N=35)	P
Location of metastasis	**N=17**	**N=34**	
Lung	9	22	
LN	7	9	
Pleura	6	14	
Brain	6	5	
Bone	6	5	
Adrenal	0	1	
Other	2	2	
Number of metastasis	**N=17**	**N=34**	
1	7 (41.2%)	17 (50.0%)	
2	5 (29.4%)	10 (29.4%)	
≥ 3	5 (29.4%)	7 (20.6%)	
ECOG PS at recurrence			0.857
0-1	17 (58.6%)	29 (82.9%)	
2-4	4 (41.4%)	6 (17.1%)	
Type of EGFR mutation			
Exon 19 deletion	13 (61.9%)	19 (54.3%)	
Exon 21 L858R	8 (33.3%)	13 (37.1%)	
Others	1 (4.8%)	3 (8.6%)	
Type of EGFR TKI			
Gefitinib	19 (90.5%)	32 (91.4%)	
Erlotinib	2 (9.5%)	2 (5.7%)	
Afatinib	0	1 (2.9%)	

4. Efficacy of EGFR TKI after recurrence

In the whole study population, median follow-up duration from the initiation of EGFR TKI was 59.3 months (95% CI 53.6-65.0), median OS and PFS was 26.7 months (95% CI 17.0-36.4) and 13.1 months (95% CI 9.6-16.7), respectively. Treatments after recurrence and response to first-line EGFR TKI in both groups are summarized in table 5 and there was no statistically significant difference between the two groups including proportion of patients who received local palliative control after recurrence and patients who received subsequent treatment after progression. Response rates showed no significant difference between the two groups in terms of ORR (P=0.334) and DCR (P=0.641).

In the RT group, median OS and PFS were 15.6 months (95% CI 2.6-28.7) and 8.5 months (95% CI 3.1-14.0), respectively. ORR was 63.2% (95% CI 38.4-83.7) and DCR was 94.7% (95% CI 91.3-96.4). Twelve patients out of 21 patients in the RT group discontinued EGFR TKI due to disease progression and 2 patients discontinued owing to treatment toxicity. Seven patients received subsequent therapy after progression to first-line EGFR TKI.

When compared with the surgery group, survival outcomes were significantly worse in the RT group compared to the surgery group in terms of OS (log-rank P=0.001, figure 3A). Multivariate Cox proportional hazards model analysis results with potential prognostic factors were consistent with adjusted hazard ratio (HR) of 3.03 (95% CI 1.45-6.25, P=0.003) for the RT group compared to the surgery group (table 6). PFS was also significantly shorter in the RT group compared to the surgery group (log-rank P=0.045, figure 3B), but multivariate analysis result showed no significant survival difference with adjuster HR of 1.64 (95% CI 0.86-3.13, P=0.138) in the RT group compared to the surgery group (table 7). Type of recurrence (Logo-regional vs. distant metastasis) was not associated with survival outcomes of EGFR TKI from Cox proportional hazards model in terms of OS (P=0.840) and PFS (P=0.504). Median TTD, DoR, and TTP were shorter in the RT group compared to the surgery group, but the differences were not statistically significant (figure 4).

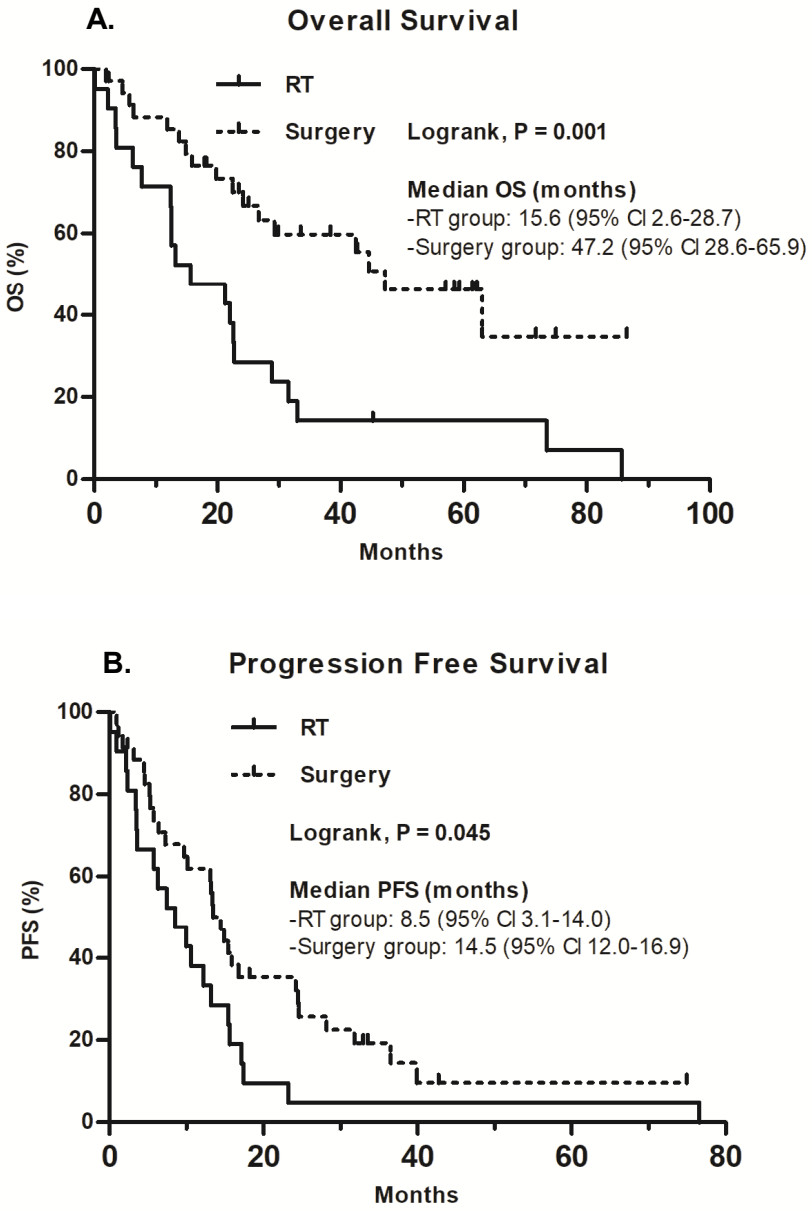

Figure 3. Survival comparison from the initiation of first-line EGFR tyrosin kinase inhibitor. A. Overall survival B. Progression-free survival

Table 5. Treatment after recurrence and response to EGFR TKI

	RT group (N=21)	Surgery group (N=35)	P
Best response to EGFR TKI	**N=19**	**N=33**	
CR	0	0	
PR	12	25	
SD	6	4	
PD	1	4	
ORR (CR+PR) (95% CI)	63.2% (38.4-83.7)	75.8% (74.0-77.0)	0.334
DCR (CR+PR+SD) (95% CI)	94.7% (91.3-96.4)	87.9% (86.0-89.0)	0.641
Local control after recurrence			0.139
Yes	8 (38.1%)	7 (20.0%)	
No	13 (61.9%)	28 (80.0%)	
Treatment beyond PD	**N=15**	**N=26**	0.837
Yes	7 (46.6%)	13 (50.0%)	
No	8 (53.4%)	13 (50.0%)	
Reasons for EGFR TKI discontinuation	**N=21**	**N=31**	
Disease progression	12 (57.1%)	22 (72.0%)	
Treatment toxicity	2 (9.5%)	2 (6.5%)	
Patient's will	1 (4.8%)	1 (3.2%)	
Follow-up loss	6 (28.6%)	6 (18.3%)	
Subsequent treatment			0.362
Yes	7	16	
No	14	19	

Table 5. Continued

Type of subsequent treatment	**N=7**	**N=16**
Osimertinib	1 (14.3%)	3 (18.8%)
Cytotoxic chemotherapy	6 (85.7%)	13 (81.2%)

Table 6. Univariate and multivariate analysis of potential prognostic factors in terms of overall survival

	Univariate analysis		**Multivariate analysis**	
	HR (95% CI)	**P**	**Adjusted HR (95% CI)**	**P**
Curative treatment				
Surgery				
RT	2.78 (1.45-5.26)	0.002	3.03 (1.45-6.25)	0.003
Age				
< 60 years				
≥ 60 years	1.64 (0.80-3.36)	0.174		
Sex				
Male				
Female	0.33 (0.17-0.65)	0.001	0.60 (0.21-1.74)	0.351
Smoking status				
Yes				
Never	0.37 (0.18-0.73)	0.005	0.73 (0.28-1.89)	0.517
Initial clinical stage				
Stage IA3-IIB				
Stage IIIA-IIIB	1.17 (0.60-2.29)	0.653		

Table 6. Continued

Chronic lung disease				
Yes				
No	0.21 (0.10-0.43)	< 0.001	0.337 (0.11-1.04)	0.059
Type of recurrence				
Logo-regional				
Metastatic	0.68 (0.26-1.81)	0.441		
CNS metastasis				
Yes				
No	0.55 (0.25-1.22)	0.146		
ECOG PS at recurrence				
0-1				
2-4	3.15 (1.37-7.23)	0.007	2.88 (1.00-8.28)	0.49
Local disease control after recurrence				
Yes				
No	0.86 (0.42-1.74)	0.668		
Objective response to EGFR TKI				
Yes				
No	2.70 (1.30-5.61)	0.008	1.06 (0.41-2.77)	0.903

Table 7. Univariate and multivariate analysis of potential prognostic factors in terms of progression-free survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**P**	**Adjusted HR (95% CI)**	**P**
Definitive treatment before recurrence				
Surgery				
RT	1.79 (1.01-3.23)	0.048	1.64 (0.86-3.13)	0.138
Age				
< 60 years				
≥ 60 years	1.10 (0.60-2.04)	0.751		
Sex				
Male				
Female	0.43 (0.23-0.81)	0.008	1.19 (0.48-2.97)	0.712
Smoking status				
Yes				
Never	0.32 (0.17-0.62)	0.001	0.29 (0.11-0.75)	0.011
Initial clinical stage				
Stage IA3-IIB				
Stage IIIA-IIIB	1.10 (0.62-1.96)	0.752		
Chronic lung disease				
Yes				
No	0.37 (0.19-0.72)	0.003	0.92 (0.37-2.27)	0.851
Type of recurrence				
Logo-regional				
Metastatic	1.35 (0.48-3.78)	0.565		

Table 7. Continued.

CNS metastasis				
Yes				
No	0.66 (0.32-1.36)	0.262		
ECOG PS at recurrence				
0-1				
2-4	1.889 (0.90-3.98)	0.095		
Local disease control after recurrence				
Yes				
No	1.05 (0.56-1.95)	0.879		
Objective response to EGFR TKI				
Yes				
No	2.24 (1.17-4.26)	0.014	2.01 (0.89-4.54)	0.093

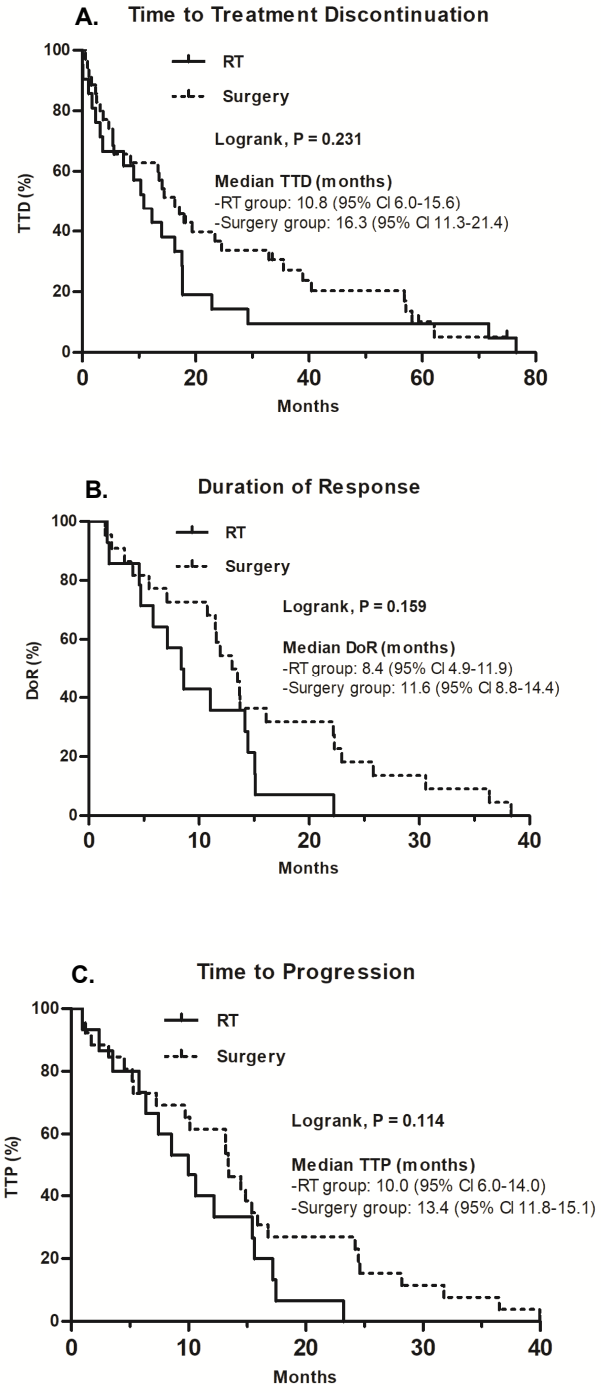

Figure 4. Outcome differences of EGFR tyrosine kinase inhibitor treatment between the two groups. A. Time to treatment discontinuation B. Duration of response C. Tim to progression

Discussion

In this study, median OS and PFS with first-line EGFR TKI treatment after recurrence to definitive RT or CCRT was 15.6 months and 8.5 months, respectively. Survival outcomes of EGFR TKI were significantly shorter in the RT group compared to the surgery group in terms of OS and PFS. This result was consistent in terms of OS with Cox proportional hazards model adjusting potential prognostic factors of the study population (adjusted HR 3.03, P=0.003). The difference in OS is much greater than PFS between the two groups, which may implicate shorter post-progression survival in the RT group compared to the surgery group. Other efficacy outcomes including TTD, DoR, TTP, and ORR were better in the surgery group although there were no statistical significance. Clinical characteristics, especially disease status at recurrence (Logo-regional vs. distant metastasis) were similar between the two groups.

To our knowledge, our study is first to evaluate efficacy of EGFR TKI in patients who recurred after definitive RT or CCRT as primary outcome. Although there are several analyses providing survival data after recurrence to definitive CCRT in EGFR mutant NSCLC, the primary objectives were to evaluate impact of EGFR mutational status on efficacy of definitive CCRT. In an observational study with stage 3 unresectable NSCLC patients who recurred after definitive CCRT with platinum-based doublet chemotherapy, 29 patients with EGFR mutations showed median PFS of 8.3 months (95% CI 5.5-14.8) on EGFR TKI treatment which is similar with our results (14). Another study on stage 3 NSCLC patients who had CCRT or sequential chemo-radiation therapy, 29 patients who harbored EGFR mutation relapsed after definitive RT and more than half of the patients receiving EGFR TKI, median OS from the recurrence was 18.1 months (95% CI 0-43.7) which is comparable with our results (median OS 15.6 months, 95% CI 2.6-28.7 in the RT group) (13). A single center study in Korea with unresectable NSCLC patients who recurred after definitive CCRT, median OS from the definitive CCRT was 34.6 months for 36 patients who harbored EGFR mutation (29 patients used EGFR TKI) (15). In another retrospective study, 15 patients with EGFR mutant unresectable stage 3 NSCLC who

recurred after definitive CCRT showed median post-recurrence survival of 29.9 months, which is longer than our result (16). This difference may be due to several clinical characteristics at the time of recurrence or after progression to EGFR TKI, although it is hard to compare as the lack of further data on their results.

According to our results, responses and survival outcomes of EGFR TKI after recurrence to RT were shorter, compared to the results of pivotal phase 3 studies of EGFR TKIs for palliative first-line treatment in initially metastatic NSCLC patients. In the RT group, ORR was 63.2% with median OS and PFS of 15.6 months and 8.5 months, respectively. Phase 3 trial comparing the efficacy of gefitinib with carboplatin plus paclitaxel for advanced NSCLC patients resulted in ORR of 71.2% in the EGFR mutated subgroup (7). In the phase 3 trial comparing erlotinib with cytotoxic chemotherapy, median PFS was 9.7 months and in the LUX-LUNG3 trial which compared afatinib with cisplatin plus pemetrexed, median PFS was 11.4 months (8, 9). In a pooled analysis of 6 studies with 84 patients harboring EGFR mutations who received erlotinib or gefitinib as first-line treatment, ORR was 67% and median OS was 23.9 months (95% CI 19.5-34.4) (20).

Retrospective analysis on EGFR mutant NSCLC patients who recurred after surgical resection showed similar survival outcomes to our results with median survival time after recurrence of 46.7 months (21). This result conjoined with our analysis showed longer overall survival with EGFR TKI in patients who recurred after surgery, compared to the median OS of 23.9 months in the pooled analysis results of palliative EGFR TKI treatment (20). These may implicate that the shorter survival of the RT group could have been overstated in our study by comparing with the surgery group. However, considering that patients in the RT group received EGFR TKI in recurrent setting, it is reasonable to compare with the surgery group as control group, which also received definitive treatment prior to EGFR TKI and showed similar clinical characteristics. Also, survival outcomes and response rates of the RT group is lower even compared with other study results including the pivotal phase 3 trials which patients' with initially metastatic disease received EGFR TKI as first-line palliative treatment (7-9, 20).

The efficacy of EGFR TKI in patients who recurred after definitive RT is not well established. According to our results, prior RT may cut back the effect of EGFR TKI to NSCLC. This could be explained by ionizing radiation-induced de novo mutations of the tumor cells and increased heterogeneity. RT induces double-strand DNA breakage in the tumor cells which is repaired by homologous recombination (HR) and non-homologous end joining repair (NHEJ). Base substitutions, insertions, deletions, and even translocations occur during NHEJ which could lead to increase in tumor mutational burden (TMB) (19). In a study with 153 patients with EGFR mutant stage 4 NSCLC who received EGFR TKI treatment, high tumor mutational burden (TMB) estimated by MSK-IMPACT, one of the targeted next-generation sequencing platform developed by Memorial Sloan Kettering Cancer Center (MSKCC), was associated significantly lower TTD (HR 0.46, P=0.0008) and OS (HR 0.495, P=0.0248) (20). However, a study recently presented at 2019 American Society of Clinical Oncology (ASCO) showed no difference in TMB measured with Illumina NextSeq platform between radiation naïve tissue and post-RT samples (21).

Notably, high TMB group had more p53 mutations which were associated with poor outcomes in the subgroup analysis from the MSKCC study previously mentioned (23). Another study on p53 mutation status and EGFR TKI efficacy with 136 patients showed lower DCR compared to p53 wild type (88.2% vs. 70.3%, p=0.019) and also shorter survival in patients with specific p53 exon 8 mutation, although no statistical significance was found (25). One of the mechanisms of ionized radiation induced tumor cell death is apoptosis by activated p53 and abundancy of p53 protein is somewhat associated, too (26). Accordingly, p53 mutated clones may avoid apoptosis and undergo DNA repairing including NHEJ which could lead to increased TMB.

Another possible explanation is that RT could alter the resistance mechanism to EGFR TKI treatment. Some in vitro studies showed that ionizing-radiation results in cMET amplification and activation of alternative pathway through PI3K –AKT-mTOR, rather than MAP kinase-ERK pathway (27). However, there is lack of evidences in the response of EGFR mutant NSCLC tumor cells to ionizing radiation and association with the efficacy of EGFR TKI treatment. Previous in vitro studies showed increased sensitivity to ionizing-radiation via decreased activity of NHEJ or microhomologous end joining (MHEJ) in EGFR mutant NSCLC cell lines, but these studies did not perform analyses on efficacy of EGFR TKI or mutational profiles after exposure to ionizing-radiation (17, 18). Analysis with re-biopsy tissue after recurrence to RT with further investigations including in vitro studies is needed to reveal the actual relationship of prior RT and EGFR TKI efficacy and its mechanism which could lead to better understanding and management of NSCLC patients.

As previously discussed, our results showed that exposure to RT might reduce the efficacy of EGFR TKI in recurred NSCLC patients. As so, it could be better to use EGFR TKI in the neoadjuvant settings to achieve down-staging and even potential surgical resection for locally advanced EGFR mutant NSCLC rather than upfront definitive CCRT. Recently, phase 2 neoadjuvant erlotinib trial compared to gemcitabine plus cisplatin in stage 3A with N2 positive patients failed to meet the primary endpoint (ORR 54.1% vs. 34.3%, P=0.092). However, PFS in the erlotinib group was significantly better compared to cytotoxic chemotherapy group with median PFS of 21.5 months (HR 0.39, P<0.001) which is promising result compared with outcomes of standard therapy with definitive CCRT in stage 3 NSCLC patients. In observational studies evaluating impact of EGFR mutation status on efficacy of definitive CCRT in locally advanced NSCLC, patients with EGFR mutant tumors showed shorter median recurrence-free survival ranging from 6.3 to 12.1 months compared to EGFR wild-type tumors (13-16). Efficacy of EGFR TKI in adjuvant treatment is proved in a phase 3 trial with 222 patients who had surgically resected stage 2 or 3A EGFR mutant NSCLC showed better DFS in adjuvant gefitinib group compared to vinorelbine plus cisplatin (HR 0.6, P=0.054) (28). Further studies are needed to investigate the role of EGFR TKI as neoadjuvant treatment for locally advanced disease.

Our study inherits several limitations. First, our patients did not receive durvalumab treatment after definitive CCRT, which was recently approved according to PACIFIC trial which showed superiority of adjuvant durvalumab after CCRT compared to placebo (median PFS 16.8 vs. 5.6 months, P<0.001) (29). Interestingly, EGFR positive subgroup did not show significant benefit (HR 0.76, 95% CI 0.35-1.64) compared to the other subgroups (29). Also, none of our patients used osimertinib as initial EGFR TKI treatment which showed superiority compared to gefitinib or erlotinib in the first-line setting (median PFS 18.9 vs. 10.2 months, P<0.001) (30).

Another limitation could be that patients who received EGFR TKI after recurrence to surgery may not be appropriate control group. However, compared to other reports on efficacy of EGFR TKI as initial treatment, RT group showed inferior outcomes. Most patients had distant metastasis rather loco-regional recurrence and some of the metastatic tumors may not have been influenced by radiation. Some cancer cells may have already been in the systemic circulation during RT or micro-metastasis may have been present during curative treatment. Disease-specific survival rate was not evaluated in our study and this could also be additional limitation. Lastly, this is a single center retrospective study with small number of patients. However, considering the small proportion of patients with EGFR mutant NSCLC who recurred after definitive CCRT, our analysis provide valuable real-world data.

Conclusion

In conclusion, patients with EGFR mutant NSCLC who recurred after definitive RT or CCRT showed significantly worse survival outcomes in terms of OS and PFS from the initiation of EGFR TKI treatment compared to those who recurred after surgical resection.

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국문요약

배경 상피성장인자수용체 (EGFR) 돌연변이 비소세포폐암 환자 중 재발한 경우에는, EGFR 티로신 키나아제 (TKI) 억제제가 표준 치료이다. 본 연구에서는, 수술 후 재발한 경우와 비교하여 근치적 방사선 치료를 받은 EGFR 돌연변이 비소세포폐암 환자 중 재발한 경우에서 EGFR TKI 억제제의 효능에 대하여 분석하였다.

연구 방법 서울아산병원에서 EGFR 돌연변이 비소세포폐암 환자 중 근치적 치료 후 재발하여 EGFR TKI를 투여 받은 환자를 대상으로 진행하였다 (방사선 대 수술). 카플란-마이어 방법을 통해 양 군의 생존 곡선을 추정하였고, 이를 로그 순위법을 통해 비교하였다. 전체생존기간은 EGFR TKI 투여로부터 모든 원인으로 인한 사망까지로 정의하였으며, 무진행생존기간은 EGFR TKI 투여로부터 객관적 질병 진행이 확인된 시점 혹은 모든 원인으로 인한 사망까지로 정의하였다.

결과 총 56명의 환자가 분석에 포함되었으며 (방사선군 21명, 수술군 35명), EGFR TKI 투여로부터의 중앙 추적기간은 59.3 개월이었다 (95% 신뢰구간 53.6-65.0). 재발 당시 질병 상태 (국소재발 대 원격전이)를 포함하여 양 군간의 임상적 특성에 유의한 차이는 없었다. 중앙전체 생존 기간은 방사선군에서 유의하게 짧았다 (47.2개월 대 15.6개월, P=0.001). 이 것은 잠재적 예후인자들을 포함한 다인자 분석에서도 유의하였다 (위험비 3.03, 95% 신뢰구간 1.45-6.25, P=0.003). 중앙 무진행생존기간 또한 수술군에 비해 방사선 군에서 유의하게 짧았으나 (14.5개월 대 8.5개월, P=0.045), 다인자 분석에서는 유의하지 않았다 (P=0.138).

결론 근치적 방사선치료 후 재발한 EGFR 돌연변이 비소세포폐암환자에서 EGFR TKI를 사용한 경우, 수술군에 비하여 생존기간이 유의하게 짧았다.