

Comparison of the Time-to-response Between Radiotherapy and Epidermal Growth Factor Receptor - Tyrosine Kinase Inhibitors for Advanced Non-small Cell Lung Cancer with EGFR Mutation

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Abstract. *Background:* Patients harboring sensitive epidermal growth factor receptor (EGFR) mutations show a dramatic response to treatment with EGFR tyrosine kinase inhibitors (TKIs). However, there have been no clinical reports in lung cancer patients that compare the time-to-response between radiotherapy and EGFR-TKIs. *Patients and Methods:* We reviewed 17 and 32 consecutive patients with inoperable stage III/IV NSCLC who harbored sensitive EGFR mutations and who were treated with thoracic radiotherapy with or without chemotherapy and EGFR-TKIs, respectively. *Results:* There were statistically significant differences in time-to-partial response (PR) with regard to the treatment modalities (radiotherapy vs. EGFR-TKIs, median 57 days vs. 22 days, log-rank test, $p=0.008$). *Conclusion:* EGFR-TKIs elicit tumor shrinkage earlier than does radiotherapy in patients with a sensitive EGFR mutation, suggesting that EGFR-TKIs may be useful for early symptom improvement in these patients.

Lung cancer is the most common cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC)

accounts for approximately 85% of all lung cancers (1). In patients with advanced lung cancer, improvements in the quality of life and disease-related symptoms are key treatment goals. Oncological emergencies arise most commonly in patients who have advanced or metastatic disease. Many of these patients develop symptoms associated with their intrathoracic disease that are directly life threatening or can affect their quality of life.

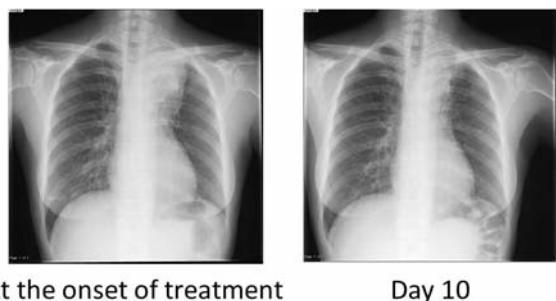
As for the patients with advanced lung cancer, various painful symptoms often develop. These painful symptoms are often due to various causes such as superior vena cava syndrome (SVCs), venous obstruction and airway obstruction and can be relieved by reducing the size of their tumor. Prompt effects of tumor reduction often lead to palliation. Radiotherapy and chemoradiotherapy have been empirically used for reducing the size of tumor. If such treatment is ineffective, therapy directed at the underlying cause should be considered. Symptoms do not usually show rapid improvement if the tumor is unresponsive. Under these circumstances, symptom relief correlates with the magnitude of tumor response (2, 3).

Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), is one of the options for first-line treatment for patients with NSCLC who harbor sensitive EGFR mutations based on the findings of previous clinical trials (4-6). Patients with sensitive EGFR mutations responded dramatically to gefitinib (as shown in Figure 1), demonstrating symptom improvement that correlated with radiographic tumor shrinkage in most cases. Although prompt response is important for patients with oncological emergencies, such as SVC or airway obstruction, the best treatment modality for clinical practice has not yet been established.

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Key Words: Epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib, erlotinib, non-small cell lung cancer; radiotherapy.



At the onset of treatment Day 10

Figure 1. Case of response to Epidermal Growth Factor Receptor - Tyrosine Kinase Inhibitor (gefitinib). A 57-year-old woman with an exon 19 deletion. Time-to-partial response, 10 days.

Despite the correlation of symptom improvement with tumor response in patients with NSCLC receiving gefitinib (2), there have been no clinical reports comparing the time-to-response between radiotherapy and EGFR-TKIs. Therefore, this retrospective study was conducted to compare and clarify the efficacy of radiotherapy compared to EGFR-TKIs for patients with advanced NSCLC harboring sensitive *EGFR* mutations.

Materials and Methods

Patients. The eligibility criteria in this study were as follows: histologically or cytologically proven NSCLC; unresectable stage III/IV disease or recurrent disease after surgery; a tumor that harbors an *EGFR* mutation known to be associated with drug sensitivity (exon 18 G719X, exon 19 deletion, and exon 21 L858R); continuous treatment with an EGFR-TKI or radiotherapy (with or without chemotherapy); age ≥ 20 years; and measurable disease by chest radiography according to the response evaluation criteria in solid tumors (RECIST) ver 1.1 (7). For patients who were treated with radiotherapy and EGFR-TKIs, the first treatment employed was applicable to evaluation. Initial EGFR-TKI therapy was limited to those patients who were receiving first- or second-line chemotherapy. Based on these criteria, we reviewed 17 and 32 consecutive patients with inoperable stage III/IV NSCLC who were treated with thoracic radiotherapy, with or without chemotherapy, and who were treated with EGFR-TKIs (gefitinib or erlotinib), respectively, at Shizuoka Cancer Center between September 2002 and June 2011. The study protocol was approved by the Institutional Review Board of Shizuoka Cancer Center (#.24-J46-24-1-3).

Genomic DNA was extracted from tumor samples, and *EGFR* mutations in exons 18-21 were analyzed as described previously (8, 9).

Medical records and films were cross-reviewed by two principal investigators. To test interobserver variability, each finding was reassessed by the same investigators after completion of the first assessment. The time interval between the first and second assessments was at least four weeks. Intraobserver variability was also determined by comparing the values of the first measurements of each of the two investigators.

Treatment methods. Radiotherapy: Patients had disease at clinical stage III/IV and received definitive thoracic radiotherapy with or

without chemotherapy. Six patients were also treated with combination chemotherapy of cisplatin plus vinorelbine, five patients with cisplatin plus S-1, two patients with carboplatin alone, and two patients with other regimens. Two patients received radiotherapy alone. The prescribed dose was over 60 Gy in 30 fractions. It was ensured that the normal lung volume receiving more than 20 Gy (V20) was equal to or less than 35% of the total lung volume. The maximal dose to the spinal cord did not exceed 45 Gy at any level. All patients were required to undergo chest computed tomography (CT) to facilitate treatment planning.

EGFR-TKIs: Patients received gefitinib (250 mg, orally, once daily) or erlotinib (150 mg, orally, once daily). EGFR-TKIs were continued until disease progression, the appearance of intolerable toxicity, or withdrawal of consent. All patients were EGFR-TKI-naïve.

Response evaluation: Patients were evaluated to determine the disease stage before the start of the treatment and at the time of disease progression or relapse. Disease stage was determined according to complete medical history and a physical examination, including chest radiography, CT of the chest and abdomen, magnetic resonance imaging (MRI) of the head, and additional staging procedures such as bone scintigraphy and positron-emission tomography (PET). Radiographic tumor response was evaluated according to RECIST ver. 1.1 (7), and assessments were performed almost weekly using chest radiography from treatment initiation to the end of the first month. In the second month, chest radiography was performed almost fortnightly. After the third month, chest radiography was performed on the basis of the judgment of the physician. Tumor lesions were accurately measured in at least one dimension (longest diameter) and considered positive for a minimum size of 20 mm by chest radiography. The tumor response was evaluated and classified as follows: complete response (CR), disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of diameters of target lesions, with the baseline sum diameters as reference; progressive disease (PD), at least a 20% increase in the sum of diameters of target lesions, with the smallest sum during the study as reference (this included the baseline sum if that was the smallest during the study); and stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, with the smallest sum of diameters during the study as reference. The time to PR was calculated from the date of starting radiotherapy or administration of the first dose of EGFR-TKI to the date of the occurrence of a PR as confirmed using chest radiography. Progression-free survival (PFS) was calculated from the starting date of treatment to the date of PD or the date of occurrence of death from any cause.

Statistical analyses. To evaluate the differences in the treatment response, the Fisher's exact test was used. A Mann-Whitney *U*-test was used to compare the mean values of the variables of the groups studied. Survival curves were plotted using the Kaplan Meier technique and a log-rank test comparison was performed. In the case of SD or PD, cases were censored at the time of confirmation using chest radiography. PFS was censored at the date of the last visit for those patients who were alive without documented PD. PFS was compared using the log-rank test according to the treatment modality (radiotherapy vs. EGFR-TKI). A *p*-value of 0.05 or less was considered significant for all tests. Statistical analyses were performed using the GraphPad Prism version 5.0 software program for Windows (GraphPad Software, San Diego, CA, USA).

Table I. The baseline characteristics of patients.

	Therapy	
	Radiotherapy	EGFR-TKI
Total	17	32
Gender		
Male/female	10/7	10/21
Median age at treatment (years)	71 (58-80)	62 (33-76)
Performance status		
0/1/2/3/4	12/5/0/0/0	13/15/2/1/1
Smoking status		
Never/former/current	7/8/2	23/8/1
Histology		
Ad/Sq/other	17/0/0	32/0/0
Stage		
IIIA/IIIB/IV	12/4/1	0/0/32
Median tumor size (mm)		
<30/30-50/50-70/>70 (mm)	38 (22-61) 3/11/3/0	37 (23-55) 8/22/2/0
Previous number of chemotherapies		
0/1	17/0	12/20
Mutation status		
Exon 19 del/exon 21 L858R/other	7/8/2*	18/12/2**

Ad: Adenocarcinoma; EGFR-TKI: epidermal growth factor receptor - tyrosine kinase Inhibitor; Sq: squamous cell carcinoma. *exon18 G719X
**exon19 deletion + exon21 L858R.

Results

Patients' characteristics and treatment methods. We reviewed the clinical records of consecutive patients with, unresectable, locally advanced lung cancer, harboring an *EGFR* mutation known to be associated with drug sensitivity, who had received radiotherapy with a prescribed dose of ≥ 60 Gy. Twenty-four patients were identified. Out of 24 patients, 17 had measurable lesions on chest radiography (radiotherapy group). One hundred and thirty-eight patients harboring a sensitive *EGFR* mutation continuously received EGFR-TKIs as first- or second-line treatment. Out of these 138 patients, 32 had measurable lesions on chest radiography (EGFR-TKI group). The baseline characteristics of patients are summarized in Table I. The tumor type in all patients was adenocarcinoma. Among the 17 patients in the radiotherapy group, 12, 4, and one patients had disease of stage IIIA, IIIB, and IV, respectively. All 32 patients in the EGFR-TKI group had disease stage IV. With regard to *EGFR* mutation status, seven and eight patients in the radiotherapy group had an exon 19 deletion and exon 21 L858R mutation, respectively. In the EGFR-TKI group, 18 and 12 patients had an exon 19 deletion and exon 21 L858R mutation, respectively.

Response to therapy. Among the 17 patients of the radiotherapy group, eleven, six and none had PR, SD, and PD, respectively; the response rate was 64.7% and the

Table II. Treatment efficacy.

	Therapy, n (%)	
	Radiotherapy (n=17)	EGFR-TKI (n=32)
CR	0 (0)	0 (0)
PR	11 (64.7)	26 (81.3)
SD	6 (35.3)	5 (15.7)
PD	0 (0)	1 (3)
Response rate (%)	64.7	81.3 p=0.296
Disease control rate* (%)	100	97

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease. *CR+PR+SD.

disease control rate was 100%. In the 32 patients of the EGFR-TKI group, 26, 5, and one had PR, SD, and PD, respectively; the response rate was 81.3% and the disease control rate was 97% (Table II). The differences in the response rate between the two groups were not statistically significant (Fisher's exact test, $p=0.296$).

Time-to-partial response and progression-free survival. Patients treated with EGFR-TKIs had a significantly different median time to PR of 22 days compared with 57 days for patients treated with radiotherapy (radiotherapy vs. EGFR-TKI; log-rank test, $p=0.008$; Figure 2).

When limited to patients with a response, the time-to-PR was significantly shorter in the EGFR-TKI group (Mann-Whitney U-test, $p=0.0001$; Figure 3). The median time-to-PR was 40 days and 20 days for patients who received radiotherapy and those who received EGFR-TKIs, respectively.

Figure 4 shows the Kaplan-Meier curves for PFS. There were no statistically significant differences in PFS with regard to the treatment modality (radiotherapy vs. EGFR-TKIs, log-rank test, $p=0.549$). The median PFS values were 273 days and 295 days for patients who received radiotherapy and those who received EGFR-TKIs, respectively.

Discussion

This is the first study as far as we are aware to evaluate and compare the time-to-response between radiotherapy and EGFR-TKIs for patients with advanced NSCLC who harbor *EGFR* mutations. In the present study, we found that the time to PR was significantly shorter in patients who received EGFR-TKIs than in those treated with radiotherapy. However, no statistically significant differences in response rate or PFS were found with regard to the treatment modalities.

Several prospective clinical trials on gefitinib, and erlotinib for the treatment of patients with NSCLC and *EGFR* mutation have been conducted (10-13). These trials

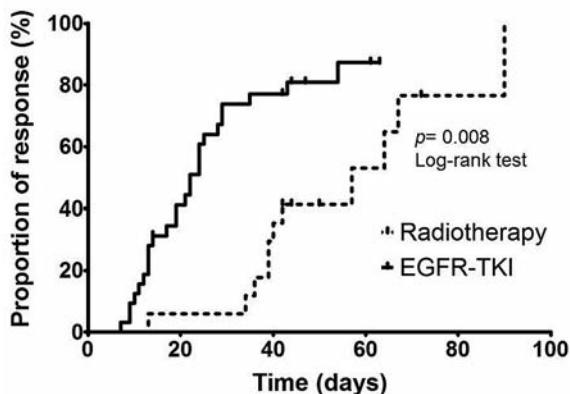


Figure 2. Kaplan-Meier plots showing the time-to-rtial response (49 patients). Median time-to-response: radiotherapy=57 days, EGFR-TKI=22 days. EGFR-TKI: Epidermal growth factor receptor - tyrosine kinase inhibitor.

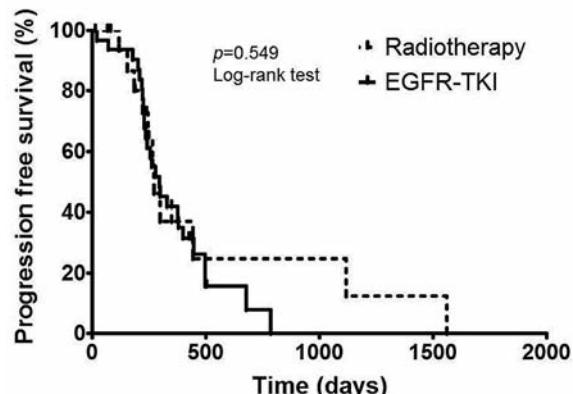


Figure 4. Kaplan-Meier plots showing progression-free survival (PFS) (49 patients) according to the treatment modality. Median progression-free survival time: radiotherapy=273 days, EGFR-TKI=295 days.

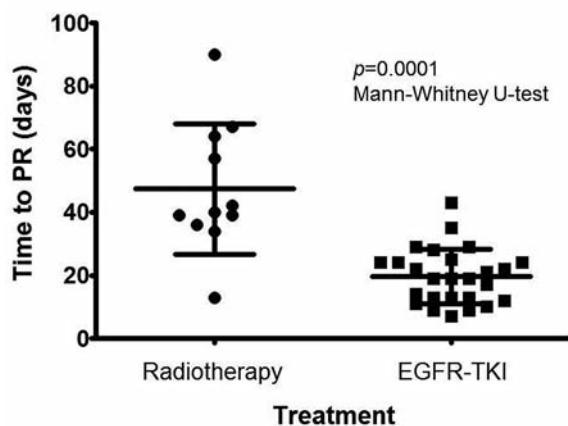


Figure 3. Comparison of the time-to-partial response (PR) between patients treated with radiotherapy and those treated with EGFR-TKIs among patients with PR, as measured on chest radiography. Median time-to-PR: radiotherapy=40 days, EGFR-TKI = 20 days.

demonstrated radiographic response rates ranging from 75% to 90.5%. Our findings are consistent with those of previous studies showing a similar response rate for EGFR-TKI treatment in patients with *EGFR* mutations. To our knowledge, no reports have assessed tumor shrinkage time using chest radiography in patients with NSCLC treated with EGFR-TKIs. However, there are some reports concerning symptom improvement in patients treated with EGFR-TKIs (2, 14-17). For example, median time to improvement with gefitinib was eight days in patients with *EGFR* mutation-positive tumors (14). Celli *et al.* reported that symptom improvement was rapid; the median time to symptomatic relief was less than two weeks (2). Other studies reported that symptomatic improvement was observed in

approximately 40% of patients within three weeks (15, 16). This may support our findings that patients treated with EGFR-TKIs had a median time-to-PR of 22 days. These results suggest that most of the observed improvement in symptoms is correlated with radiographic response.

There are few reports discussing the time-to-response following radiotherapy. Time to a 30% reduction in tumor burden was approximately 40 days in patients with lung adenocarcinoma who received radiotherapy (18), which is consistent with our findings of the median time-to-PR being 40 days in the radiotherapy group. In our study, 15 patients received radiotherapy with chemotherapy. Although one report suggests that a combination of radiotherapy and chemotherapy does not synergistically improve symptomatic relief compared with radiotherapy alone (18), there are no published data comparing radiotherapy and chemoradiotherapy with regard to the assessment of time to response. At any rate, the time-to-PR was significantly shorter in patients who received EGFR-TKIs than in those treated with radiotherapy with/without chemotherapy.

Preclinical studies have shown that NSCLC cells harboring *EGFR* mutations have a predominantly radiosensitive phenotype associated with a delay in the repair of radiation-induced DNA damage, defective radiation-induced arrest of DNA synthesis or mitosis, and a pronounced increase in the frequency of radiation-induced apoptosis (19). Few studies report clinical trials on radiotherapy for treatment of NSCLC with *EGFR* mutations (20-22). A previous study reported that patients with *EGFR*-mutant locally advanced NSCLC achieve better locoregional tumor control after thoracic radiotherapy and chemotherapy than patients with wild-type *EGFR* tumors. However, it is unclear whether radiotherapy has an advantage in patients with TKI-sensitive *EGFR* mutations. Furthermore, no clinical

reports have compared radiotherapy with EGFR-TKIs to assess tumor response.

With regard to reducing symptoms and tumor shrinkage, prompt treatment can lead to a markedly improved quality of life for patients with SVCs or airway obstruction. Our study suggests that the administration of EGFR-TKIs is more useful for tumor shrinkage than radiotherapy to rapidly improve tumor-related symptoms in patients with activating *EGFR* mutations.

This study has several limitations. Firstly, it was a retrospective analysis and the intervals between evaluations in the present study were not as closely monitored as possible in a prospective study. However, all patients were evaluated using chest radiography within similar time frames over the course of treatment, as described in the Materials and Methods section. Although evidence from randomized studies would be very valuable in the management of oncological emergencies regarding the usefulness of treatment modalities, a previous study reported that it is difficult to perform randomized studies in palliative patient groups because of a lack of accrual patient accrual (23). Secondly, the sample size was small. However, because few cases involve tumors measurable on chest radiography, it is difficult to overcome this limitation. Thirdly, although our study evaluates the time-to-response, the time to symptom improvement was not directly evaluated. However, previous studies reported that tumor response and symptom response are related in patients with advanced NSCLC (2, 17). Finally, although this study compared patients with inoperable stage III/IV NSCLC who were treated with definitive radiotherapy and with EGFR-TKIs, the number of patients with stage IV disease with *EGFR* mutations who received thoracic radiotherapy was limited. Therefore, we had no alternative but to compare definitive radiotherapy and systemic therapy with EGFR-TKIs.

In conclusion, EGFR-TKIs lead to earlier tumor shrinkage than radiotherapy in patients with activating *EGFR* mutations. The results of this study indicate that the administration of EGFR-TKIs is more useful for tumor reduction than is radiotherapy to promptly improve tumor-related symptoms in patients with activating *EGFR* mutations. Further pooling of greater numbers of patients and the completion of prospective trials are needed to define the differences in the effects of treatment modalities.

Conflicts of Interest

None of the Authors have financial or personal relationships with other people or organizations that could inappropriately influence this work.

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