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ORIGINAL ARTICLE

Upfront thoracic radiotherapy to primary lesion improves outcomes in patients with stage IV non-small cell lung cancer harboring EGFR mutations

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Summary

Purpose: *The role of thoracic radiotherapy in the treatment of metastatic EGFR mutant non-small cell lung cancer (NSCLC) patients in literature data are insufficient.The purpose of this study was to examine the effectiveness of upfront thoracic radiotherapy in metastatic EGFR mutant NSCLC patients treated with chemotherapy or tyrosine kinase inhibitors (TKI).*

Methods: *This study was designed as a hospital-based retrospective observational case-series study. A total of 141 patients with metastatic EGFR mutant NSCLC who were followed in two different oncology centers in Turkey between 2014 and 2019 have been included into this study.*

Results: *The median patient age was 63 years (range 35-91). EGFR mutation results of exon 19 deletion, exon 21 mutation and exon 18 mutation were found in 82 (58.2%), 56 (39.7%) and 3 (2.1%) patients, respectively.The median follow-up time was 22 months and 94 (33.3%) patients died during follow-up. Median overall survival (OS) was 26 months and progression free survival (PFS) (for first line treatment) was 10 months for the whole cohort, respectively. Radiotherapy was given to the primary tumor site in 32 (22.6%) patients. Patients receiving radiotherapy to primary tumor site had better OS than those who had not (31 versus 23 months respectively, p=0.02). Survival advantage was also seen for patients group taking TKI at upfront setting (33 versus 23 months respectively, p=0.05).*

Conclusion: *In this study, we have shown that upfront thoracic radiotherapy to primary lesion as combination with EGFR-TKI treatment may improve the outcome in advanced stage IV NSCLC patients harboring EGFR mutations.*

Key words: *NSCLC, EGFR mutations, thoracic radiotherapy, upfront treatment*

Introduction

Non-small cell lung cancer (NSCLC) is the first most common type of lung cancer worldwide (accounting for 85 to 90% of lung cancers) and the leading cause of cancer-related deaths [1,2]. Historically, treatment for advanced NSCLC was limited to platinum-based chemotherapy at first-line. A new era in NSCLC treatment has evolved with the discovery of targetable driver oncogenic mutations, such as rapid advances in understanding the molecular pathogenesis of NSCLC which have shown that it is a heterogeneous group of diseases. After the discovery of driver mutations such as EGFR, anaplastic lymphoma kinase (ALK) and ROS-1 gene, molecular targeted drugs have been used therapeutically and a new era has evolved in personalized treatment for NSCLC patients. EGFR mutations located in the tyrosine kinase domain result in increased kinase activity of EGFR, and

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lead to continued activation of signaling pathways and continue cell proliferation and carcinogenesis [3,4]. The most commonly seen EGFR mutations are deletions in exon 19 (Ex19del) and exon 21 L858R point mutation [5]. Nowadays, the current standard of treatment recommended for EGFR-mutant NSCLC is epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) monotherapy [6,7]. The EURTAC study of erlotinib and the IPASS study of gefitinib showed that the median progression-free survival (PFS) was around 10 months and the median overall survival (OS) was around 23 months [8,9]. Median PFS and OS have increased to 18 months and 30 months, respectively with the 3rd generation osimertinib in the FLAURA study [10].

Radiotherapy is used to improve local control or palliation as a combined treatment with TKIs during progression at metastatic sites in advanced lung cancer harboring EGFR active mutations. Local radiotherapy is shown to be associated with PFS in oligoprogressive disease with EGFR-mutant advanced lung cancer [11]. In particular, several studies have shown that local brain radiotherapy is effective in the presence of brain metastasis and in these patients EGFR-TKI treatment can be continued without systemic therapy changes [12,13]. To the best of our knowledge, the effectiveness of upfront thoracic radiotherapy in metastatic EGFR mutant NSCLC patients is not well established. In addition, data on the radiotherapy techniques and dosage are also insufficient. In this study, we aimed to examine the effect of upfront thoracic radiotherapy on the primary lesion with EGFR-TKI treatment on survival outcomes.

Methods

This study was designed to evaluate the prognostic role of upfront thoracic radiotherapy to primary sites in metastatic EGFR mutant NSCLC patients. This study was a hospital-based retrospective observational case-series. Included were 141 patients from Radiation Oncology and Medical Oncology Departments of Baskent Univeristy and Dr. Ersin Arslan Research and Training Hospital between 2014-2020. Demographic features and treatment modalities were recorded from patient electronic files. All results were presented as rates for categorical values or means and medians for continuous variables.

Statistics

All results were presented as rates for categorical values or means and medians for continuous variables. OS was defined by the time from the date of death and last control minus the first day of chemotherapy. Survival curves were estimated according to Kaplan-Meier method, and log-rank test was used for univariate statistical comparisons. Adjusted hazard ratio (HR) and 95% confidence intervals (95% CIs) were used for estimation. All statistical data were analyzed using the SPSS version 17.0, and a p value<0.05 was considered statistically significant.

Results

Study patients

The median age of the patients was 63 years (range 35-91). There were 78 (55.3%) female patients. All of the patients (n:147) were stage 4 and all of them had EGFR mutation. Of the patients, 58 of 141 (41.1%) had active smoking history. Histopathological diagnosis of adenocarcinoma, squamous cell carcinoma and adeno-squamous carcinoma were found in 138 (97.9%), 2 (1.4%) and 1 (0.7%) patients, respectively. While 127 (90.1%) patients had *de novo* metastatic disease, 14 (9.9%) were found later with metastatic disease. EGFR mutation results of exon 19 deletion, exon 21 mutation and exon 18 mutation were found in 82 (58.2%),

Table 1. Patient and tumor characteristics

Characteristics	*n (%)*
Median age, years	63 (35-91)
Gender	
Men	63 (44.7)
Women	78 (55.3)
Smoking	
Yes	58 (41.1)
No	83 (58.9)
Diagnosis	
Adenocarcinoma	138 (97.9)
Squamous cell carcinoma	2 (1.4)
Adenosquamous cell carcinoma	1 (0.7)
Metastasis time	
De novo metastasis	127 (90.1)
Later metastasis	14 (9.9)
EGFR mutation	
Exon 19	82 (58.2)
Exon 21	56 (39.7)
Exon 18	3 (2.1)
Brain metastasis	
Yes	41 (29.1)
No	100 (70.9)
Bone metastasis	
Yes	71 (50.4)
No	70 (49.6)
Lymph node metastasis	
Yes	106 (75.2)
No	35 (24.8)

56 (39.7%) and 3 (2.1%) patients, respectively. Forty-one (29.1%) patients had brain metastasis, 71 (50.4%) had bone metastasis and 106 (75.2%) had lymph node metastasis. Patient characteristics are shown in Table 1.

Radiotherapy techniques

Thirty-two (22.6 %) patients received thoracic radiotherapy with different doses and techniques. Computed tomography (CT)-based simulation, three-dimensional (3D) conformal radiotherapy and stereotactic body radiotherapy (SBRT) were used. The types of thoracic radiotherapy applied were 3D conformal and SBRT in 15 (46.9%) and 17 (53.1%) patients, respectively. The daily radiation dose with 3D conformal regimen ranged from 2 to 8 Gy, while that with SBRT regimen ranged from 6 to 20 Gy. The radiation dose prescribed to the tumor was converted into biologically effective dose using α/β=10 (BED10) according to the linear quadratic modeling method. The BED10 value ranged from 14.4 to 180 Gy with a mean value of 77.3 Gy. Patients were divided into 2 groups according to BED10 values (group 1 <100 and group 2 >100).

Treatment and outcomes

The median follow-up time was 22 months and 94 (33.3%) patients haddied during follow-up. Median OS was 26 months (95%CI, 23.2-28.8) and PFS (for first line treatment) was 10 months (95%CI, 5.4-12.6) for the whole study group, respectively (Figure 1 and Figure 2).Nine (6.4%) of the patients in the later metastatic group received adjuvant

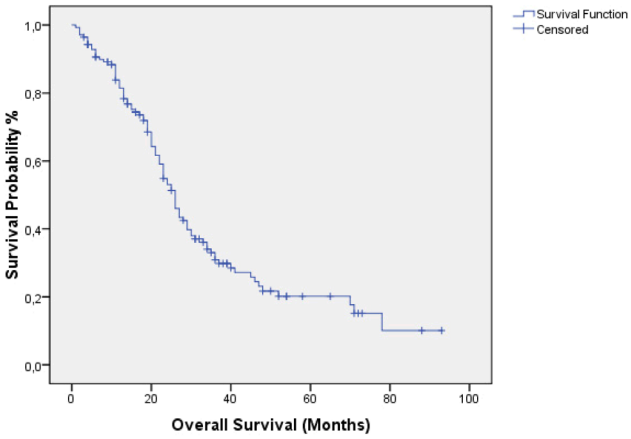

Figure 1. Kaplan-Meier estimates of overall survival (OS) of the whole patient cohort.

Table 2. Treatment modalities

Treatment options	*n (%)*
Adjuvant chemotherapy	9 (6.4)
First line treatment	
Chemotherapy (CT)	36 (25.5)
Tyrosine kinase inhibitor (TKI)	86 (61.0)
Chemotherapy switch TKI[a]	19 (13,5)
Thoracic radiotherapy type	
3D-CRT	15 (46.9)
SBRT	17 (53.1)
BED10 values	
<100	20 (62,5)
>100	12 (37.5)
Final status	
Died	94 (33.3)
Alive	47 (66.7)

[a]Switching to TKI after 2 cycles of chemotherapy, 3D-CRT: Three-dimensional conformal radiotherapy, SBRT: Stereotactic body radiotherapy, IMRT: Intensive modulated radiotherapy

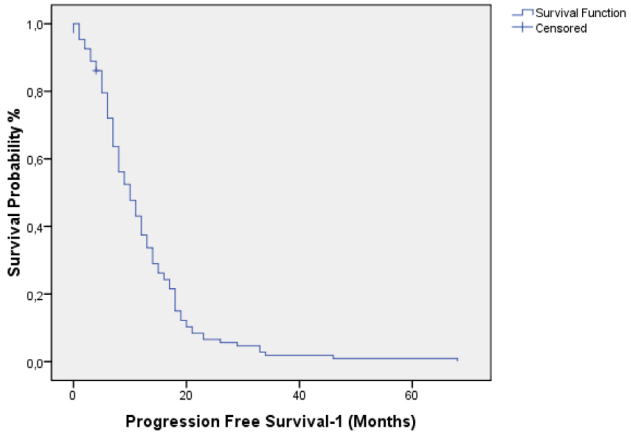

Figure 2. Kaplan-Meier estimates of progression-free survival (PFS) for first line treatment of the whole patient cohort.

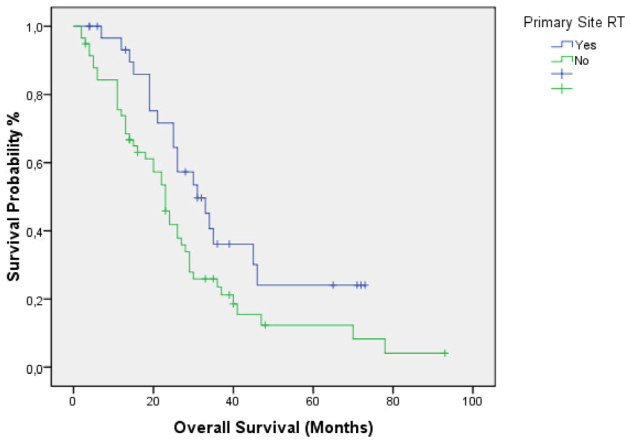

Figure 3. Patients receiving radiotherapy to primary tumor site had better overall survival than those who had not (31 versus 23 months respectively, p=0.02).

chemotherapy. Eighty-six (61%) patients received TKI treatment in the upfront setting. Either erlotinib or gefitinib were used as TKI treatment. In contrast, 36 (25.5%) patients received systemic chemotherapy in the first line setting and after progression switched to TKI. Nineteen (13.5%) patients had chemotherapy switch from TKI (without progression). Treatment outcomes are shown in Table 2.

Patients receiving radiotherapy to primary tumor site had better OS than those who had not (31 versus 23 months respectively, p=0.02) (Figure 3). However, this statistically significant difference was not seen in terms of median PFS between patients receiving radiotherapy to primary tumor site and those who had not (11 versus 10 months respectively, p=0.68). There was also statistically significant relationship between radiotherapy to primary tumor site and median OS in the group of patients taking TKI at upfront setting (33 versus 23 months respectively, p=0.05) (Figure 4). Also, there was no statistically significant difference in terms of median PFS between patients receiving radiotherapy to primary tumor site and those not in the group of patients taking TKI at upfront setting (12 versus 13 months respectively, p=0.75). The OS of patients who received SBRT was statistically significantly better than the patients who received 3D-CRT (46 versus 26 months respectively, p=0.05) (Figure 5). Statistically significant difference in median survival and radiotherapy BED10 values were found. The OS of patients who had BED10 value>100 was statistically significantly

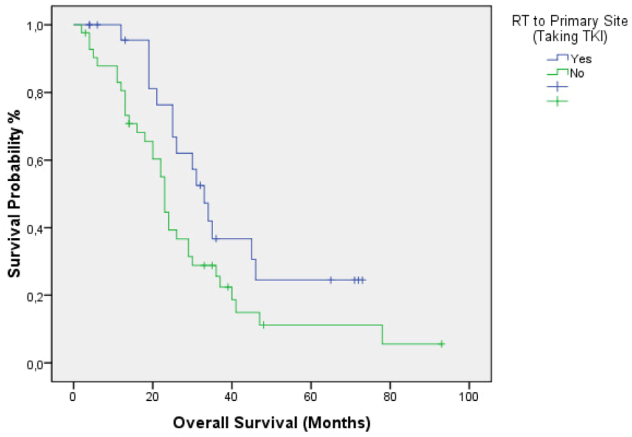

Figure 4. Patients (taking TKI at upfront setting) receiving radiotherapy to primary tumor site had better overall survival than those who had not (33 versus 23 months respectively, p=0.05).

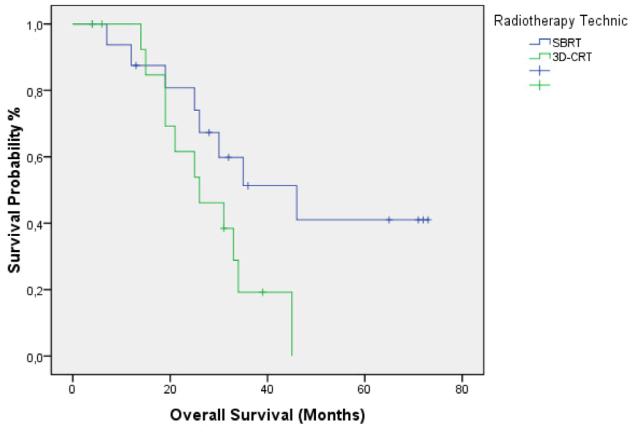

Figure 5. The overall survival of patients who received SBRT was significantly better than the patients who received 3D-CRT (46 versus 26 months respectively, p=0.05).

Table 3. Relationship between radiotherapy with survival parameters

Variables	*Median OS*		*Median PFS*	
	Months	*p*	*Months*	*p*
Thoracic RT		0.02[a]		0.68
Yes	31		11	
No	23		10	
Thoracic RT (taking TKI)		0.05[a]		0,75
Yes	33		12	
No	23		13	
Thoracic RT Technique		0.05[a]		0.34
SBRT	46		11	
3D-CRT	26		8	
BED10 values		0.004[a]		0.13
>100	NR		11	
<100	26		8	

OS: overall survival, PFS: progression-free survival, RT: radiotherapy, TKI: tyrosine kinase inhibitor, NR:not reached, [a]statistically significant

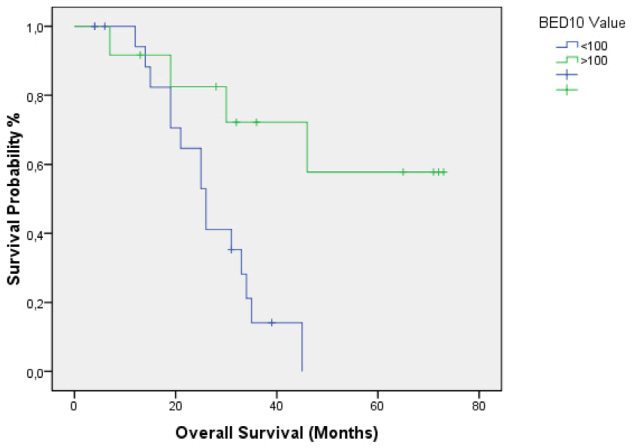

Figure 6. The overall survival of patients who had BED10 value>100 was significantly better than the patients who had BED10 value<100 (not reached and 25 months respectively, p=0.004).

better than in the patients who had BED10 value<100 (not reached and 25 months respectively, p=0.004) (Figure 6). It was seen that BED10 value and RT techniques (SBRT or 3D-CRT) had no statistically significant effects on PFS. Six patients had grade 1-2 radiation-related pneumonia and 1 patient required short-term steroid therapy for this reason. Grade 1 esophagitis occurred in one patient There were no other treatment related adverse events observed. Relationships with radiotherapy localization and survival parameters are shown in Table 3.

Discussion

EGFR was shown to be associated with radioresistance in translational studies in early 1990s [14,15]. On the other hand, some synergistic effects of EGFR inhibitors and radiotherapy and prospect in the combination of these modalities were shown in several preclinical studies [15]. Continued studies have shown that NSCLCs, which harbored EGFR mutation, exhibited enhanced sensitivity to radiation but the mechanism of radiosensitization with EGFR inhibitors is complex. EGFR's role in DNA repair, the activation of pro-survival pathways, and enhanced cell proliferation are distinct phases of EGFR's role in the radiation response [16-18]. Additionally, several studies have shown that EGFR-TKIs (EGFR-TKI) combined with radiation have synergistic effect [10]. It was also known that EGFR-TKI could increase radiosensitivity and that radiotherapy could reduce EGFR-TKI resistance [19]. Therefore, the combination of EGFR-TKI and radiotherapy could be a strategy for treating patients with advanced NSCLC. Palliative local radiotherapy is often applied to metastatic sites (especially brain and bone metastasis) for advanced NSCLC patients harboring EGFR mutations [20,21], however upfront thoracic radiotherapy to primary site is used rarely for locally advanced or metastatic patients.

Mıng-Hsıen Li et al investigated the association between tumor response to thoracic radiotherapy and EGFR mutation status in patients with lung adenocarcinoma in 48 patients in 2018 and they showed that EGFR mutations were associated with reduction of residual tumor burden after radiotherapy and patients with EGFR mutations had longer median OS (31.1 vs 26.6 months) [22]. But the radiotherapy in this study was given to the residual tumor site and it was not at upfront setting. In 2018 Yu-Chun Yen et al showed that thoracic radiotherapy reduces the incidence of death and can improve the OS in EGFR mutant lung adenocarcinomas who received and responded to EGFR-TKI treatment in their study [23]. However, radiotherapy was also initiated to the patients who responded to the TKI treatment in this study. In 2019, Lınpeng Zheng et al investigated the effectiveness of combination treatment of EGFR-TKI with thoracic radiotherapy as first line in stage IV non- NSCLC harboring EGFR mutations. Outcomes of 10 patients were evaluated in this phase 2 study and each patient received EGFR-TKI (erlotinib or gefitinib) plus thoracic radiotherapy (54-60 Gy/27-30 F/5.5-6 w). This study showed that thoracic radiotherapy contributes to survival outcomes and objective response rates [19]. But there were only 10 patients in this trial and all of them had oligometastatic disease. Apart of these studies there are no other similar studies in the literature investigating the effectiveness of thoracic radiotherapy for metastatic EGFR mutant NSCLC patients. Additionally, no prospective study has been reported on combined EGFR-TKI and thoracic radiotherapy to primary lung lesions for advanced stage EGFR mutant NSCLC.

In the present study,we included 141 EGFR mutant NSCLC patients the number of which was higher than in radiotherapy studies in the literature. As we mentioned before, the median survival was around 23 months with gefıtınıb and erlotınıb treatment in metastatıc EGFR mutant NSCLC. In our study, the median OS was similar in the group that received only EGFR-TKI treatment. We showed that the patients receiving radiotherapy to primary tumor site had better OS than those who had not. The survival difference between two groups were 10 months,which was statistically significant. And this difference was much more pronounced in the upfront TKI taking group. Additionally, we found that SRS was better than 3D-CRT in terms of survival outcome and high dose radiotherapy (BED10>100) is better than low dose radiotherapy (BED10<100). Thus, we found a relationship between the radiotherapy localization and survival parameters. Our results indicate that upfront thoracic radiotherapy may add additional survival benefit to patients with advanced lung adenocarcinomas with EGFR mutations. There was no other study with more patients in the literature than our study examining the effectiveness of thoracic radiotherapy in EGFR mutant NSCLC patients.

Limitations of our study were reported at two centers with limited patient numbers with a retrospective design. The gold standard of TKI treatment at upfront setting is osimertinib nowadays. But at the time interval in our study osimertinib was not approved treatment in our country. So, none of our patients had used osimertinib. But we

know that survival benefit of osimertinib is much more better than the other first and second generation TKIs. Therefore, the effect of thoracic radiotherapy in combination with osimertinib is not known. Maybe future clinical studies will show this effect and additional survival benefit to osimertinib therapy alone.

In conclusion, upfront thoracic radiotherapy in combination with EGFR-TKI treatments may positively affect survival outcomes for advanced stage NSCLC patients who have EGFR mutations.

Ethics

The study protocol was reviewed and approved by our Institutional Ethics Committee before collection of patients' data (project no.e-94603339-604.01.02-5766. Baskent University Ethics Committee.

Conflict of interests

The authors declare no conflict of interests.

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