ORIGINAL ARTICLE

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Clinicopathological Characteristics and Real-life Data of Patients Receiving Tyrosine Kinase Inhibitor in Metastatic EGFR Mutant Non-small Cell Lung Carcinoma

Metastatik EGFR Mutant Küçük Hücreli Dışı Akciğer Karsinomunda Tirozin Kinaz İnhibitörü Alan Hastaların Klinikopatoloik Özellikleri ve Gerçek Yaşam Verisi

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ABSTRACT

Aim: The desired survival times could not be achieved with conventional treatments in lung cancer. Tyrosine kinase inhibitors (TKIs) are used in the treatment of non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations. The aim of this study was to investigate the clinicopathologic features of EGFR mutant NSCLC patients and the effects of TKIs on progression-free survival (PFS) and overall survival (OS).

Materials and Methods: A total of 61 patients who were admitted to Cerrahpaşa Faculty of Medicine, Department of Internal Medicine, Department of Medical Oncology, between 2012 and 2022, who were EGFR mutants with NSCLC and who used TKI as treatment were included in the study. Demographic and pathological characteristics of the patients, treatments used in the patients, progression and death dates were examined retrospectively.

Results: Age at diagnosis, serum creatinine, last visit ECOG score and progression rate were significantly higher in the deceased group. The rate of T790M mutation and osimertinib use was significantly higher in the surviving group. Last visit ECOG score was significantly higher in the progression group. Survival time was significantly shorter in the group with visceral metastasis than in the group without visceral metastases, in the group with a last visit ECOG score II-III-IV compared to those with 0-I, and in the group without the T790M mutation than in the group with the T790M mutation. The progression-free survival time was significantly shorter in the group with ECOG score II-III-IV at the last visit compared to those with 0-I and in the group with visceral metastasis than in the group without. There was no statistically significant difference between erlotinib, afatinib and gefitinib in terms of PFS and OS. PFS calculated as 27.4 months and OS 49.2 months. The median PFS duration of 13 patients receiving osimertinib was calculated as 18.5 months.

Conclusion: Age, diagnosis and ECOG performance score at the last visit, visceral metastasis at the beginning of TKI, T790M mutation and therefore osimertinib use had a significant effect on the OS, while on PFS, the significant effect of the visceral metastasis at TKI initiation, stage at the time of diagnosis, the ECOG performance score at the last visit was seen.

Keywords: Lung cancer, EGFR, tyrosine kinase inhibitors

ÖZ

Amaç: Akciğer kanserinde konvansiyonel tedaviler ile istenen sağkalım süreleri sağlanamamıştır. Epidermal büyüme faktörü reseptörü (EGFR) mutant olan küçük hücreli dışı akciğer kanseri (KHDAK) hastalarının tedavisinde tirozin kinaz inhibitörleri (TKİ) kullanılmaktadır. Çalışmamızda EGFR mutant KHDAK hastaların klinikopatolojik özelliklerinin ve TKİ'lerin progresyonsuz sağkalım (PS) ve genel sağkalım (GS) üzerindeki etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Cerrahpaşa Tıp Fakültesi İç Hastalıkları Medikal Onkoloji Polikliniği'ne 2012-2022 arasında başvurmuş KHDAK tanılı EGFR mutant ve TKİ kullanmış olan 61 hasta çalışmaya alınmıştır. Hastaların demografik ve patolojik özellikleri, kullanılan tedaviler, progresyon ve ölüm tarihleri incelendi.

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Bulgular: Ölen grupta tanı yaşı, serum kreatinini, son vizit ECOG skoru, progresyon oranı anlamlı olarak daha yüksekti. Hayatta olan grupta T790M mutasyonu ve osimertinib kullanım oranı anlamlı olarak daha yüksekti. Progresyon olan grupta son vizit ECOG skoru anlamlı olarak daha yüksekti. TKİ başlandığında visseral metastaz olan grupta olmayana göre, son vizit ECOG skoru II-III-IV olan grupta 0-I olana göre ve T790M mutasyonu olmayan grupta olana göre sağkalım süresi anlamlı olarak daha kısaydı. Son vizit ECOG II-III-IV olan grupta 0-I olana göre ve TKİ başlandığında visseral metastaz olan grupta olmayana göre PS süresi anlamlı olarak daha kısaydı. Erlotinib, afatinib ve gefitinib arasında PS ve GS açısından istatistiksel anlamlı fark saptanmadı, PS 27,4 ay, GS 49,2 ay olarak hesaplandı. Osimertinib kullanan 13 hastanın medyan PS süresi 18,5 ay olarak hesaplandı.

Sonuç: GS üzerinde yaşın, tanıda ve son vizitteki ECOG performans skorunun, TKİ başlandığında visseral metastazın, T790M mutasyonun ve dolayısıyla osimertinib kullanımının anlamlı etkisi görülmüştür. PS üzerinde ise TKİ başlandığında visseral metastazın, tanı anındaki evrenin, son vizitteki ECOG performans skorunun anlamlı etkisi görülmüştür.

Anahtar Kelimeler: Akciğer kanseri, EGFR, tirozin kinaz inhibitörü

INTRODUCTION

Lung cancer is the cancer that causes death most frequently in the world[1]. Lung cancer is divided into two main groups as pathological small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLCs constitute 80% of lung cancers and are divided into 3 groups: large cell lung cancer, squamous cell lung cancer (SCC) and adenocarcinoma. The 5-year survival rate of NSCLCs is considered low (19.1%) despite recent advances in imaging, diagnosis and treatment[1]. Although tobacco and tobacco product use are etiologically leading in the development of lung cancer with the epidemiological increase in non-smoking-related lung cancers, specific molecular and genetic tumor characteristics have been identified. Somatic genomic alterations called driver mutations include epidermal growth factor receptor (EGFR), ALK, ROS-1, BRAF, HER2, MET, RET, KRAS, NTRK mutations[2]. Among the mutations defined as driver mutations in this group, mutations in the Epithelial Growth Factor receptor (EGFR) gene are the most common.[3] The side effect profile of conventional chemotherapy (CT) and radiotherapy treatments in the treatment of lung cancer is wide and that the desired survival times could not be achieved has led to significant advances in treatments. Treatments called tyrosine kinase inhibitors (TKI) are primarily used in the treatment of patients with NSCLC who have a driver mutation in the *EGFR* gene. In addition, PD-1 and PDL-1 expression levels are measured and immunotherapies are used in treatment.

Our study mainly aimed to examine the clinicopathological features of patients with EGFR exon 19 and exon 21 L858R mutations and to investigate to what extent the clinicopathological features and TKI used for treatment affect the progression-free survival (PFS) and overall survival (OS).

MATERIALS AND METHODS

A total of 61 patients who were diagnosed with NSCLC, EGFR mutant, and who used TKI as treatment, who applied to the outpatient clinic of Cerrahpaşa Faculty of Medicine, Department of Internal Medicine. Medical oncology department between 2012 and 202, were included in the study. Patients with non-EGFR driver mutations or EGFR mutant patients who did not use TKIs were excluded from the study.

Patients' age, gender, body mass index (BMI), smoking history, NSCLC diagnosis date, ECOG performance score at diagnosis, NSCLC histological subtype, type of EGFR mutation, stage at diagnosis, brain and visceral metastasis status at diagnosis, serum creatinine and bilirubin values at diagnosis, whether or not they received CT before TKI, the TKI they received, TKI start date, side effect status under TKI, the reason if TKI was discontinued, T790M mutation status, whether they used Osimertinib, last visit dates, ECOG performance scores at the last visit and, if death occurred, death dates were examined retrospectively.

This thesis study was found to be in compliance with medical ethics and the Helsinki Declaration of Human Rights with the decision of the Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee dated 15.02.2023 and numbered E-83045809-604.01.01-620248.

Statistical Analysis

Mean, standard deviation, minimum and maximum median, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. Mann-Whitney U test was used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fisher's test was used when chi-square test conditions were not met. Cox-regression (univariate-multivariate) and Kaplan-Meier were used in survival analysis. Statistical Package for the Social Sciences 28.0 program was used in the analyses.

RESULTS

Sixty-one patients diagnosed with metastatic NSCLC and EGFR mutant who used TKI were included in the study.

The median age at diagnosis of the patients was 63 years. Of the 61 patients, 36 were female (59%) and 25 were male (41%). The median BMI was calculated as 26.12. It was observed that 31 of 61 patients had never smoked (50.8%), 14 of them had

smoked before (23%), 8 of them were still active smokers (13.1%), and 8 patients (13.1%) were smokers. No information was available about whether 8 patients (13.1%) smoked or not. The median serum creatinine values of the patients were calculated as 0.76, and the median total bilirubin values were calculated as 0.46 (Table 1).

It was observed that 60 of 61 patients were histologically in the Adenocarcinoma subtype (98.4%), and 1 patient was in the SCC subtype (1.6%). When the EGFR mutation distribution was examined, it was seen that 40 patients had Exon 19 mutations (65.6%), 16 patients had Exon 21 mutations (26.2%), and 5 patients had non-classical mutations (8.2%) (Table 2).

When we look at the ECOG performance score of the patients at the time of diagnosis, the score was "0" in 13 patients (21.3%), "1" in 41 patients (67.2%), "2" in 4 patients (6.6%), and "3" in 1 patient (1.6%), and "4" (3.3%) in 2 patients.

Table 1. Findings

		Minimum-maximum	Median	Mean±SD / n (%)	
Age at diagnosis		26.00-86.00	63.00	62.25±13.56	
Gender	Female			36	59.0%
	Male			25	410%
BMI		20.23-41.62	26.12	26.45±3.98	
Smoking status					
Non-smoker				31	50.8%
Ex smoker				14	23.0%
Smoker				8	13.1%
Unknown				8	13.1%
Serum creatinine		0.43-1.82	0.76	0.82±0.28	
Total bilirubin		0.17-1.33	0.46	0.48±0.23	
Histological subtype	Adenocarcinoma			60	98.4%
	SCC			1	1.6%
ECOG at diagnosis	0			13	21.3%
	I			41	67.2%
	II			4	6.6%
	III			1	1.6%
	IV			2	3.3%
EGFR mutation					
Exon 19				40	65.6%
Exon 21				16	26.2%
Non-classical				5	8.2%
Stage at diagnosis					
Suitable for surgery				9	14.8%
Local advanced				1	1.6%
Metastatic				51	83.6%
Brain metastasis at diagnosis	(-)			42	68.9%
	(+)			19	31.1%
Visceral metastasis when TKI is started	(-)			44	72.1%
	(+)			17	27.9%
Location of visceral metastasis					
Lung				8	47.1%
Adrenal				8	47.1%
Kidney				1	5.9%
1st line CT	(-)			46	75.4%
	(+)			15	24.6%

CT: Chemotherapy, SD: Standard deviation, BMI: Body mass index, SCC: Squamous cell lung cancer, TKI: Tyrosine kinase inhibitor, EGFR: Epidermal growth factor receptor

At diagnosis, 51 patients were metastatic (83.6%), 1 patient was at a locally advanced stage (1.6%), and 9 patients were suitable for surgery (14.8%). Nineteen of 61 patients had brain metastases at the time of diagnosis (31.1%). All patients were in the metastatic stage when TKI was started.

At the time TKI was started, 17 of 61 patients had visceral metastases (27.9%). It was observed that 47.1% of visceral metastases were in the liver (8 patients), 47.1% in the adrenal gland (8 patients), and 5.9% in the kidney (1 patient).

46 of the patients had not received CT before TKI (75.4%), and 15 had received first-line CT (24.6%). Of the 15 patients who received first-line CT, 14 received TKI treatment as a second-line treatment, while 1 received it as a third-line treatment. The patient who received third-line treatment was found to have SCC as histological subtype.

While 53 patients received erlotinib as TKI (86.9%), 6 patients received afatinib (9.8%) and 2 patients received gefitinib (3.3%). While side effects were observed in 32 patients receiving TKI (52.5%), no side effects were observed in 29 patients (47.5%). While skin rash was seen as a side effect in 28 of 32 patients with side effects (87.5%), liver enzyme elevation was observed in 4 patients (12.5%). Side effects were graded according to the "Common Terminology Criteria of Adverse Effects" classification. When examined, it was observed that there were grade 1 side effects in 5 patients (16.1%), grade 2 side effects in 15 patients (48.4%), and grade 3 side effects in 11 patients (35.5%). It was observed that no patient discontinued TKI due to side effects (Table 3).

The last check date was determined as September 2022. Thus, the median follow-up period was calculated as 39.4 months. It was observed that 52 of 61 patients progressed during the follow-up period (85.2%), and 9 did not progress (14.8%). It was observed that T790M mutation was detected as positive in a total of 13 patients (21.3%), and since it could not be started in the first step in these patients due to SUT rules, osimertinib treatment was started after progression under TKI.

The ECOG performance score at the last visit date was "0" in 11 patients (18%), "1" in 20 patients (32.8%), "2" in 4 patients (6.6%), and "3" in 12 patients (19.7%), it was found to be "4" in 4 patients (6.6%). During the follow-up period, 40 of 61 patients died (65.6%) and 21 were alive (34.4%).

The relationship between the demographic, clinicopathological characteristics and laboratory findings of the patients and mortality was examined.

The age at diagnosis in the deceased group was significantly higher than the surviving group ($p<0.05$). Serum creatinine value in the deceased group was significantly higher than the surviving group ($p<0.05$). The follow-up period in the deceased group was significantly lower than in the surviving group ($p<0.05$).

The relationship between gender, BMI, smoking history, serum total bilirubin level and mortality did not show any significant difference.

Histological subtype distribution between deceased and surviving groups, ECOG score distribution at diagnosis, EGFR mutation type distribution, stage distribution at diagnosis, brain metastasis rate at diagnosis, visceral metastasis rate when

Table 2. Findings

TKI received			
Erlotinib		53	86.9%
Afatinib		6	9.8%
Gefitinib		2	3.3%
The stage of TKI as treatment	I	46	75.4%
	II	14	23.0%
	III	1	1.6%
TKI side effect			
(-)		29	47.5%
(+)		32	52.5%
Elevated liver enzyme		4	12.5%
Rash		28	87.5%
TKI side effect CTCAE grade			
Grade I		5	16.1%
Grade II		15	48.4%
Grade III		11	35.5%
T790M mutation	(-)	48	78.7%
(+)	13	21.3%	
Osimertinib	(-)	48	78.7%
(+)	13	21.3%	
Last visit ECOG	0	11	18.0%
I	20	32.8%	
II	4	6.6%	
III	12	19.7%	
IV	4	6.6%	
Progression	(-)	9	14.8%
(+)	52	85.2%	
Exitus	(-)	21	34.4%
(+)	40	65.6%	

TKI: Tyrosine kinase inhibitor, CTCAE: Common Terminology Criteria of Adverse Effects

Table 3. Follow-up duration

	Minimum-maximum	Median	Mean±SD / n (%)
Follow-up duration (month)	3.30-108.07	39.47	38.65±25.39

SD: Standard deviation

TKI is initiated, 1st line CT rate, distribution of TKI received, which step treatment is TKI and the side effect rate of TKI did not show any significant difference (p>0.05).

The T790M mutation rate and osimertinib rate in the surviving group were significantly higher than the deceased group (p<0.05).

Last visit ECOG performance score in the deceased group was significantly higher than the surviving group (p<0.05).

Progression rate in the deceased group was significantly higher than the surviving group (p<0.05).

The relationship between the patients' demographic, clinicopathological characteristics and laboratory findings and progression was examined.

Age at diagnosis, gender distribution, BMI value, smoking rate, serum creatinine value, total bilirubin value, histological subtype distribution, ECOG score distribution at diagnosis, EGFR mutation distribution, stage distribution at diagnosis, brain metastasis rate at diagnosis between groups with and without progression. Visceral metastasis rate when TKI was started, 1st line CT, TKI received, which TKI was the first-line treatment, TKI side effect rate, T790M mutation rate, osimertinib rate did not show any significant difference (p>0.05).

Last visit ECOG rate in the progression group was significantly higher than the non-progression group (p<0.05).

Cox regression analysis was used to predict OS, and significant variables were examined by the Kaplan-Meier method.

In the univariate model, no significant effect of gender, BMI, smoking, EGFR mutation type, stage at diagnosis, serum creatinine value, total bilirubin value, TKI side effect, first-line CT status, and TKI type received was observed in predicting survival time (p>0.05).

In the univariate model, a significant effect of age, ECOG score at diagnosis, visceral metastasis at TKI initiation, T790M mutation, osimertinib use, ECOG score at last visit and progression was observed in predicting survival time (p<0.05).

In the multivariate reduced model, a significant and independent effect of visceral metastasis at TKI initiation, T790M mutation, and last visit ECOG score was observed in predicting survival time (Table 4).

When the survival times of TKI were examined, the predicted survival time with erlotinib was 47 months, while it was 36.4 months with afatinib. It could not be calculated because there were a total of 2 patients using gefitinib. No significant difference was detected between TKI's in terms of OS (Table 5).

The predicted survival time in the group with visceral metastasis at TKI start (26.2 months) was significantly shorter than the group without visceral metastasis at TKI start (56.0 months) (p<0.05) (Figure 1, Table 6).

The predicted survival time in the group without T790M mutation (40.5 months) was significantly shorter than in the group with T790M mutation (86.8 months) (p<0.05) (Figure 2, Table 7).

Cox regression analysis was used to predict PFS, and significant variables were examined by the Kaplan-Meier method.

In the univariate model no significant effect of age, gender, BMI, smoking, ECOG score at diagnosis, EGFR mutation type, T790M mutation, Osimertinib receipt, serum creatinine value, total bilirubin value, first-line CT status and type of TKi received was observed in predicting PFS time (p>0.05) (Table 8).

In the univariate model, a significant effect of visceral metastasis at TKI initiation, diagnosis stage, TKI side effect, and last visit ECOG score was observed in predicting PFS time (p<0.05).

In the multivariate reduced model, a significant-independent effect of visceral metastasis at TKI initiation and last visit ECOG score was observed in predicting PFS time.

The predicted PFS time in the group with visceral metastasis at TKI initiation (15.1 months) was significantly shorter than in the group without visceral metastasis at TKI initiation (31.2 months) (p<0.05) (Tables 9, 10).

When the PFS durations of TKI were calculated separately, the predicted PFS was calculated as 26 months with erlotinib, 22.9 months with afatinib, and 48.1 months with gefitinib. No statistically significant difference was found between the 3 TKI in terms of PFS.

Progression was observed in 4 of 13 patients using osimertinib during the follow-up period, and the median PFS duration was calculated as 18.5 months. Nine patients continue to use osimertinib.

DISCUSSION

With the development of targeted therapies for driver mutations in NSCLCs, the clinical importance of these mutations has increased. Currently, the most common targetable mutations are mutations in the EGFR gene. In our study, we examined the demographic and clinicopathologic characteristics of NSCLC patients with EGFR exon 19 and exon 21 L858R mutations and the effects of these characteristics on PFS and OS.

Inoue et al.[4] published a study in 2016 in which EGFR mutant NSCLC patients treated with TKI were evaluated and 1660 Japanese patients were evaluated. In the study by Inoue et al.[4], the median OS duration was 30.8 months and the median PFS duration was 11.4 months, while in our study the predicted

Table 4. Overall survival relationship

Overall survival	Univariate model			Multivariate model		
	HR	95% CI	p	HR	95% CI	p
Age at diagnosis	1.03	1.00-1.06	**0.027**			
Gender	1.03	0.54-1.94	0.936			
BMI	0.98	0.88-1.08	0.674			
Smoking	0.82	0.42-1.60	0.553			
ECOG in diagnosis	1.59	1.11-2.29	**0.011**			
EGFR mutant Exon 19	0.87	0.46-1.65	0.665			
EGFR mutant Exon 21	1.24	0.63-2.43	0.541			
EGFR mutant non-classic	0.87	0.27-2.85	0.822			
Stage at diagnosis suitable for surgery	0.38	0.15-1.00	0.050			
Stage metastatic in diagnosis	0.45	0.18-1.09	0.077			
Brain metastasis in diagnosis	1.25	0.62-2.53	0.539			
Serum creatinine in diagnosis	2.00	0.82-4.88	0.130			
Total bilirubin in diagnosis	0.74	0.16-3.45	0.700			
TKI initiation visceral metastasis	2.70	1.35-5.38	**0.005**	2.95	1.33-6.55	**0.008**
TKI side effect	0.93	0.50-1.74	0.813			
1st line CT	0.99	0.49-1.99	0.979			
The TKI received was erlotinib	1.89	0.58-6.15	0.290			
The TKI received was afatinib	0.98	0.30-3.22	0.972			
The TKI received was gefitinib	0.96	0.50-1.85	0.907			
TKi side effect CTCAE grade	0.56	0.22-1.41	0.219			
T790M mutation	0.23	0.07-0.76	**0.015**	0.15	0.03-0.68	**0.013**
Osimertinib	0.23	0.07-0.76	**0.015**			
Last visit ECOG	1.59	1.23-2.05	**0.000**	1.54	1.17-2.03	**0.002**
Progression	29.2	1.04-823.7	**0.048**			

Cox regresyon (forward LR).

CI: Confidence interval, CT: Chemotherapy, BMI: Body mass index, TKI: Tyrosine kinase inhibitor, EGFR: Epidermal growth factor receptor, CTCAE: Common Terminology Criteria of Adverse Effects

Table 5. TKIs-OS periods

	Predicted survival time (month)	95% CI	p
Erlotinib	47.0	36.9-57.0	0.295
Afatinib	36.4	24.0-48.9	
Gefitinib			
Total	49.2	39.4-59.0	

Kaplan-Meier (log-rank).

CI: Confidence interval, TKI: Tyrosine kinase inhibitor

OS duration was 49.2 months and the predicted PFS duration was 27.4 months. Again, the median age at diagnosis was 67 years in the study by Inoue et al.[4]. In our study, the median age at diagnosis was 63 years, the median age at diagnosis of the patients who died was 66 years, while the median age at diagnosis of the survivors was 59 years, and the association of age with mortality was found to be statistically significant ($p<0.05$), and a significant effect of age at diagnosis on the prediction of OS was observed in the Cox regression analysis in accordance with the literature. In the study of Inoue et al.[4] 66.7% of the patients were clinically at stage 4 and there was a statistically significant association between clinical stage and OS and PFS in both univariate and multivariate regression analyses. In our study, 83.6% of the patients were in stage 4 at the time of diagnosis, and the rest progressed to metastatic stage during follow-up. In univariate Cox regression analyses, a significant association of clinical stage with PFS was found in accordance with the literature, but not in multivariate analyses. Also, unlike the literature, the association with GS was not statistically significant. In our study, the fact that TKIs were given only in the metastatic stage was thought to be effective in this situation. In our study, in the Cox regression analysis of the ECOG performance score at the time of diagnosis, the association with GS was statistically significant in the univariate model but not in the multivariate model in accordance with the study of Inoue et al.[4]. However, the association of ECOG performance score at the last visit with both OS and PFS was statistically significant in univariate and

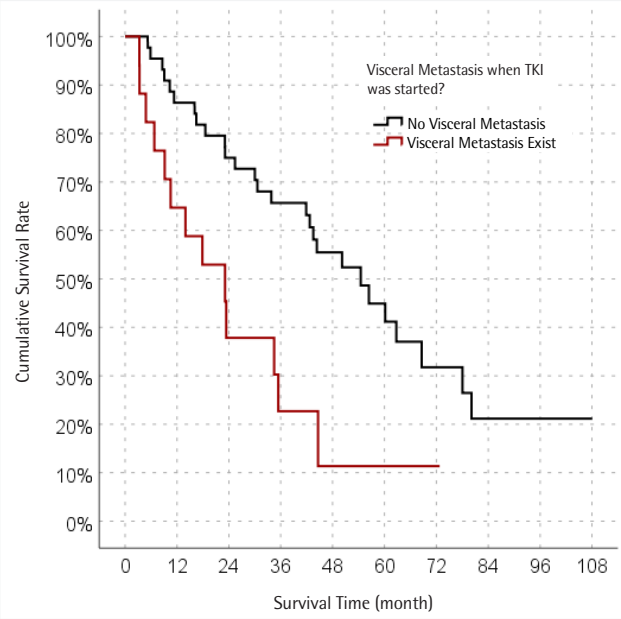

Figure 1. Visceral metastasis-OS relationship
OS: Overall survival, TKI: Tyrosine kinase inhibitor

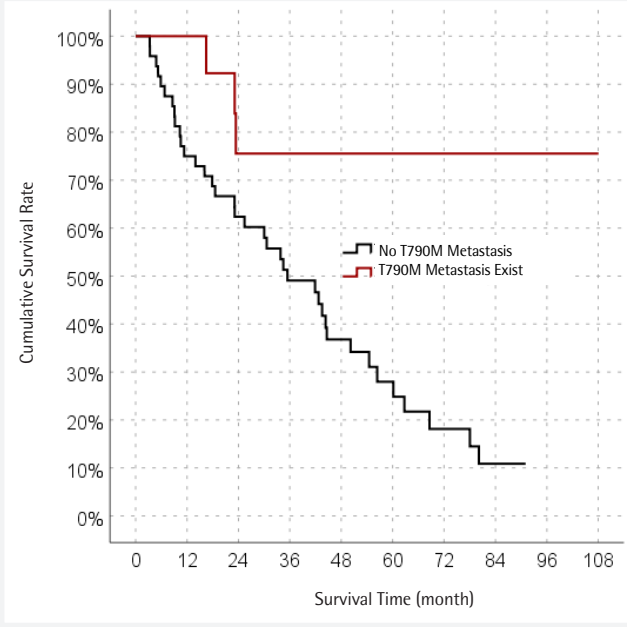

Figure 2. T790M mutation-OS relationship
OS: Overall survival

Table 6. Visceral metastasis-OS relationship

		Predicted survival time (month)	95% CI	p
Was there visceral metastasis when TKI was started?	None	56.0	44.7-67.2	**0.003**
	Yes	26.2	15.3-37.2	
	Total	49.2	39.4-59.0	

Kaplan-Meier (log-rank).
CI: Confidence interval, TKI: Tyrosine kinase inhibitor, OS: Overall survival

Table 7. T790M mutation-OS relationship

		Predicted survival time (month)	95% CI	p
T790M mutation	None	40.5	32.1-48.8	**0.008**
	Yes	86.8	65.8-107.8	
	Total	49.2	39.4-59.0	

Kaplan-Meier (log-rank).
OS: Overall survival, CI: Confidence interval

multivariate analyses. This supports the idea that deterioration in performance score during clinical follow-up can be used as a guide for prognosis.

The gender distribution in the study by Inoue et al.[4] was 64.8% female and 35.2% male. Similarly, the gender distribution of the patients included in our study was 59% female and 41% male. Although lung cancer is more common in men, the fact that patients with driver mutation are mostly from the non-smoking group and the smoking rate of women is lower compared to men and as a result, EGFR mutant NSCLC is more common in women is consistent with the data[5-7]. In the meta-analysis published by Lee et al.[8] in 2015, it was reported that treatment with TKI was more beneficial in women than men and provided 27% longer PFS (10 months vs. 11.8 months). However, in the EURTAC study published in 2012, no significant difference was observed between male and female genders[9]. In our study, the association of female gender with mortality and OS and PSK was not statistically significant.

In a meta-analysis of 3.688 patients published by Ren et al.[10] in 2012, it was reported that EGFR mutation was more common in patients with no smoking history. In a study published by Lee et al.[11] in 2010 with 324 Korean patients, it was reported that EGFR mutation was more common in patients with less than 25 pack-years of smoking and was more common in women. Again, in the study published by Lee et al.[12] in 2010, it was reported that the incidence of EGFR mutation decreased even in passive smokers. In the meta-analysis published by Lee et al.[8] in 2015, it was reported that treatment with TKI provided 36% more benefit in never smokers than in former smokers and current smokers. In our study, 50.8% of the patients were never smokers, 23% had quit smoking, 13.1% were active smokers, and 13.1% had no smoking-related data. The association of smoking with mortality, OS and PFS was not statistically significant. This situation, which differs from the literature, was thought to be due to the patients in our study whose smoking data could not be accessed.

Table 8. Progression-free survival relationship

Progression-free survival	Univariate model			Multivariate model		
	HR	95% CI	p	HR	95% CI	p
Age at diagnosis	1.01	0.99-1.04	0.206			
Gender	1.06	0.61-1.86	0.827			
BMI	0.96	0.87-1.05	0.346			
Smoking	0.97	0.54-1.75	0.929			
ECOG in diagnosis	1.17	0.84-1.63	0.368			
EGFR mutant Exon 19	1.36	0.76-2.44	0.297			
EGFR mutant Exon 21	0.68	0.36-1.28	0.234			
EGFR mutant non-classic	1.11	0.39-3.12	0.843			
Stage operable in diagnosis	0.39	0.17-0.89	**0.024**			
Stage metastatic in diagnosis	0.42	0.19-0.90	**0.026**			
Brain metastasis in diagnosis	1.31	0.71-2.41	0.381			
Serum creatinine in diagnosis	1.46	0.61-3.51	0.398			
Total bilirubin in diagnosis	0.93	0.25-3.44	0.917			
TKI initiation visceral metastasis	2.22	1.19-4.14	**0.012**	2.19	1.12-4.31	**0.022**
TKI side effect	1.11	0.64-1.92	0.705			
1st line CT	0.68	0.35-1.30	0.241			
TKI erlotinib received	1.50	0.60-3.77	0.391			
TKI afatinib received	0.84	0.30-2.34	0.736			
TKI gefitinib received	0.90	0.52-1.55	0.697			
TKI side effect CTCAE grade	0.40	0.16-0.95	**0.038**			
T790M mutation	1.63	0.86-3.07	0.135			
Osimertinib	1.63	0.86-3.07	0.135			
Last visit ECOG	1.38	1.11-1.71	**0.004**	1.37	1.10-1.71	**0.006**

Cox regression (forward LR).

CI: Confidence interval, CT: Chemotherapy, BMI: Body mass index, TKI: Tyrosine kinase inhibitor, EGFR: Epidermal growth factor receptor, CTCAE: Common Terminology Criteria of Adverse Effects

Table 9. TKIs-PFS times

	Predicted survival time (month)	95% CI	p
Erlotinib	26.0	19.6-32.3	0.581
Afatinib	22.9	12.9-32.8	
Gefitinib	48.1	0.0-103.4	
Total	27.4	20.9-33.9	

Kaplan-Meier (log-rank).

CI: Confidence interval, TKI: Tyrosine kinase inhibitor, PFS: Progression-free survival

Table 10. Osimertinib PFS

Discontinuation of osimertinib	Minimum-maximum	Median	Mean±SD / n (%)	
(-)			9	69.2%
(+) Progression			4	30.8%
PFS	3.27-91.03	18.57	24.00±19.21	

PFS: Progression-free survival, SD: Standard deviation

In a study published by Jiang et al.[13] in 2017, it was reported that in KHDAK patients with EGFR-mutant TKI, liver metastases were associated with shorter PFS duration (7.5 months vs. 11.8 months). In a study published by Luo et al.[14] in 2022, it was reported that bone, liver, and surrenal gland metastases increased mortality in EGFR mutant NSCLC patients. In our study, 17 patients had visceral metastases when TKI was initiated (27.9%). Univariate and multivariate Cox regression analyses revealed statistically significant associations between visceral metastases and OS and PFS. The predicted survival time was significantly shorter in the group with visceral metastasis at TKI initiation than in the group without visceral metastasis at TKI initiation (26.2 months vs 56 months). The predicted PFS time was significantly shorter in the group with visceral metastases on TKI than in the group without visceral metastases on TKI (15.1 months vs 31.2 months).

In our study, 31.1% of patients had brain metastases at the time of diagnosis. There was no significant correlation between the presence of brain metastasis at the time of diagnosis and OS and PFS. In a study published by Ouyang et al.[15] in 2020, it

was reported that metachronous brain metastases (occurring >6 months after the diagnosis of the primary tumor) had shorter OS and PFS times than synchronous brain metastases (22.1 months vs. 30.3 months) and brain metastasis was the most important prognostic factor and metachronous brain metastases should be treated more aggressively. In our study, metachronous brain metastases were not analyzed separately; a separate study on this subject is warranted.

In the study published by Maemondo et al.[16] in 2010, it was reported that the most common side effect after TKI use was skin rash with 71.1%. In the LUX-Lung 3 and LUX-Lung 6 studies, skin rash was reported to be the most common side effect in patients (16-15%)[17]. In our study, 52.5% of the patients had side effects related to TKI use, the most common side effects were skin-related side effects (87.5%) and 48.4% of these were grade 2 side effects, consistent with the literature. TKI was not discontinued in any patient due to side effects.

In the meta-analysis published by Lee et al.[8] in 2015, it was reported that treatment with TKI was more beneficial in patients with exon 19 mutation than those with exon 21 mutation, longer OS was detected in patients with exon 19 mutation compared to those with exon 21 mutation after treatment with TKI, and patients with exon 19 mutation who were not treated with TKI had a worse prognosis compared to those with exon 21 mutation. It was reported that patients with exon 21 mutation treated with TKI had shorter PFS than patients with exon 19 mutation treated with TKI. Similarly, many other studies have also reported longer OS in patients with exon 19 mutations compared to those with exon 21 mutations. In the LUX-Lung 3 and 6 studies published in 2015, it was reported that when afatinib and CT use were compared in exon 19 mutant patients, significantly longer OS was obtained in patients receiving afatinib, but no significant difference was found in patients with exon 21 mutants[17-22]. However, in the LUX-Lung 7 study, no significant difference was found between exon 19 and exon 21 in terms of PSK[23]. In our study, 65.6% of patients had exon 19 mutation, 26.2% had exon 21 mutation, 8.2% had other non-classical mutations and no significant difference was found between exon 19 and exon 21 mutations in terms of OS and PFS.

In the OPTIMAL study published in 2011, erlotinib and CT were compared as first-line treatment in EGFR mutant patients and a significantly longer OS was found in the erlotinib group (13.1 months vs. 4.6 months)[18]. In the LUX-Lung 3 and LUX-Lung 6 trials published in 2015, afatinib and pemetrexed-cisplatin treatments were compared and no significant difference was found in terms of OS, but when the exon 19 mutant subgroup was considered separately, it was reported that longer OS was achieved in the group receiving afatinib in both studies[17]. In our study, 75.4% of the patients received TKI as first-line treatment, while 24.6% had received CT previously. There was no significant difference in OS and PFS between the group who received 1st-line CT and the group who did not. This was thought to be due to the fact that most of the patients in the group received CT while waiting for EGFR mutation results and after the mutation was detected, the patients were switched to TKI treatment before the completion of CT.

In a meta-analysis of 1821 patients published by Liang et al.[24] in 2014 comparing the use of erlotinib, gefitinib, afatinib and icotinib in EGFR mutant patients, it was reported that no significant difference was found between these 4 TKIs in terms of OS and PFS. Similarly, no significant difference was found between erlotinib, gefitinib and afatinib in terms of OS and PFS in our study.

In the FLAURA study published in 2021 comparing the use of osimertinib, a 3rd generation EGFR TKI, with 1st generation EGFR TKIs as 1st line treatment in EGFR mutant patients, it was reported that significantly longer PFS (18.9 months-10.2 months) and longer OS (38.6 months-31.8 months) were achieved in the osimertinib group[22]. In the study published by Lee et al.[3] in 2021, it was reported that patients receiving 1st-line osimertinib had a longer OS compared to the other TKI group, no difference was observed in terms of OS, but patients who started treatment with afatinib and switched to osimertinib after progression had similar OS times to those receiving 1st-line osimertinib. In a study published by Luo et al.[14] in 2022, it was reported that the use of osimertinib reduced mortality in EGFR mutant NSCLC patients receiving 1st generation TKI as 1st line treatment with or without T790M mutation. Since osimertinib cannot be used in patients with progression under TKI and not positive for T790M mutation according to SUT rules in our country, there were no patients receiving 1st line osimertinib in our study. In our study, a significant difference was found between patients who received osimertinib and those who did not in terms of mortality and OS, similar to the literature, but no significant difference was found in terms of PFS. Since 1st generation and 2nd generation TKIs do not adversely affect the PFS duration of systemic therapies given after them, and since CT is also used as interim treatment in the use of osimertinib after 1st and 2nd generation TKIs, we found that the PFS duration of osimertinib was shorter than expected.

Study Limitations

The small number of patients receiving osimertinib is one of the limiting parts of our study, and the lack of a significant difference in terms of PS between patients receiving and not receiving osimertinib is at a scientifically low level of evidence and has low reliability when evaluated statistically. In our study, the relatively small number of patients, not using all of the TKIs classically used in the world in primary care and the retrospective nature of our study are the prominent limitations of our study.

CONCLUSION

In conclusion, our study showed that age, ECOG performance score at diagnosis and at the last visit, visceral metastasis at TKI start, T790M mutation and thus osimertinib use had a significant effect on OS, whereas visceral metastasis at TKI start, stage at diagnosis, ECOG performance score at the last visit had a significant effect on PFS.

Ethics

Ethics Committee Approval: This thesis study was found to be in compliance with medical ethics and the Helsinki Declaration of Human Rights with the decision of the Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee dated 15.02.2023 and numbered E-83045809-604.01.01-620248.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.S.D., Design: N.S.D., Data Collection or Processing: B.E., Analysis or Interpretation: B.E., N.S.D., Literature Search: B.E., Writing: B.E.

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