ORIGINAL ARTICLE

Survival Analysis of Lung Adenocarcinoma Patients with Exon 19 Del and 21 L858R Mutations Receiving EGFR-TKI Treatment

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ABSTRACT

Introduction: Patients with lung adenocarcinoma with a common epidermal growth factor receptor (EGFR) mutation, the exon 19 del mutation, survive better than those with the exon 21 L858R mutation. This study examined whether there is a significant difference in prognosis between two common EGFR mutations, namely exon 19 del and 21 L858R. This study compared overall survival (OS) and progression-free survival (PFS) in non–small cell lung cancer (NSCLC) patients with exon 19 del and exon 21 L858R mutations who received EGFR tyrosine kinase inhibitors (EGFR-TKI) targeted therapy at Haji Adam Malik Hospital, Medan.
Methods: This study used a retrospective cohort design to evaluate the OS and PFS of NSCLC patients who underwent EGFR-TKI precision medicine at Haji Adam Malik Hospital, Medan, between 1 January 2017 and 31 December 2020 and had exon 19 del and exon 21 L858R alterations.
Results: A total of 88 people were sampled. The majority of study subjects were males (60.2%). Median OS was 11 months (95% CI:9,594-12,406). According to the study, eight people (9.1%) survived until the end. The median OS of exon 19 del common mutation was 11 months (95%CI 9,064-12,936). The exon 21 L858R group had ten months (95%CI 4,546-15,454). The log-rank test identified no statistical difference in median OS between mutation types (p = 0.562).
Conclusion: This study revealed that subjects with exon 19 Del mutations had a longer median OS and PFS than those with exon 21 L858R variants. Nevertheless, there was no significant difference in median OS and PFS between study subjects with mutation of exon 19 del and exon 21 L858R who received the targeted medication.

INTRODUCTION

Lung cancer cases are increasing worldwide, along with rising deaths.[1] The main culprit of cancer death in the United States (US) in 2021 was lung cancer, the third most widely diagnosed malignancy after breast and prostate cancer.[2]

Histologically, lung cancer is classified into two categories, small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). NSCLC is the most frequently diagnosed cancer, accounting for 85% of pulmonary cancer cases, and includes several subtypes such as adenocarcinoma (38.5%), squamous carcinoma (epidermoid carcinoma) (20%), and large cell carcinoma (2.9%). Meanwhile, NSCLC is the highest malignant tumor originating from cells similar to neuroendocrine and accounts for 15% of lung cancer cases.[3]

Treatment modalities for patients suffering from lung adenocarcinoma include chemotherapy, surgery, targeted therapy, radiotherapy, and immunotherapy.[4] In particular, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) therapy can deal with patients with mutations in EGFR. A previous study by

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Yoshioka, *et al*. (2019) reported that EGFR-TKI targeted therapy with gefitinib was superior to chemotherapy and could increase the progression-free survival (PFS) of NSCLC patients with alterations in EGFR.[5] Jackman, *et al*. (2006) reported that NSCLC patients with exon 19 del mutations treated with gefitinib or erlotinib have more prolonged survival than exon 21 mutation L858R.[6] A study in Korea by Won, *et al*. (2011) reported no significant difference in overall survival (OS) among NSCLC patients with exon 19 del and exon 21 L858R mutations.[7] However, PFS in exon 19 del mutations is longer than in exon 21 L858R mutation. The study is in line with the study by Jiang, *et al*. (2019), who reported a significant difference between mutations of exon 19 del and exon 21 L858R in terms of PFS, but not with OS.[8] Nonetheless, this study described that patients with exon 19 mutations del have a response rate value (75.7 vs. 51.4%; p = 0.032), disease control rate (DCR; 89.2 vs. 68.6%; p = 0.031), modified median PFS (13.2 vs. 10.8 months; p = 0.030), and OS (30.2 vs. 25.6 months; p = 0.030) which were higher than the exon 21 mutation L858R.

Several studies have been conducted regarding the prognostic factors between targeted therapy and chemotherapy or survival rate analysis in adenocarcinoma patients receiving EGFR-TKI therapy. However, no data in Medan specifically compares the survival rate of OS and PFS of adenocarcinoma patients with EGFR alterations, exons 19 del and 21 L858R. Therefore, this study compared OS and PFS between both variants, exon 19 del and exon 21 L858R mutations receiving EGFR-TKI medication, not only as a study to characterize and analyze the survival of lung adenocarcinoma patients with common mutations but as prognostic education and a springboard for the next generation of EGFR-TKI research.

METHODS

Study Design

An analytical study with a retrospective cohort study design was performed to assess PFS and OS in NSCLC patients who have mutations throughout exons 19 Del and 21 L858R that received first-generation EGFR-TKI (gefitinib or erlotinib) targeted therapy at Haji Adam Malik Hospital, Medan. Data were collected by reviewing medical records and followed up from when the patient started treatment until the end of the study phase or death.

Populations and Samples

The study population included all patients who obtained EGFR TKI and were diagnosed with adenocarcinoma with exon 21 L858R and exon 19 Del mutations between 1 January 2017 and 31 December 2020. The study samples were part of the population who met the inclusion criteria but were not included in the exclusion criteria. The sampling method was selected by non-probability sampling with a consecutive sampling technique. From January 2017 to December 2020, all medical records from participants treated at the Pulmonary Oncology Polyclinic, Haji Adam Malik Hospital, Medan, were recruited as subjects until the required samples were obtained by meeting the inclusion and exclusion criteria.

Research Subject Criteria

Research participants were determined based on inclusion and exclusion criteria. Patients must be over 18 years old and had cytological and histopathological proven lung adenocarcinoma with exon 21 L858R and exon 19 del mutations previously receiving targeted therapy. Exclusion criteria were incomplete medical record data and patients with primary cancer other than lung (double primary malignancy).

Data Analysis

After the data had been recorded, it proceeded to statistical analysis by Statistical Package for Social Science (SPSS) software version 25. The relationship between the characteristics of the subjects and the EGFR mutation was analyzed using the Chi-Square test or the Likelihood Ratio test if the Chi-Square test conditions were not met. Then univariate analysis was conducted to determine each group's survival rate, presented in the frequency distribution table. This analysis was continued using the Kaplan-Meier curve. If the log-rank test was significant with $p < 0.05$ and the proportional hazard ratio assumption was fulfilled, as evidenced by the absence of intersecting curves, then the multivariate analysis was continued with the Cox regression model.

Ethical Clearance

The Ethical Clearance Committee of the Faculty of Medicine, Universitas Sumatera Utara, with the registered number 1310/KEP/USU/2021, approved this study.

RESULTS

The total subjects were 88 patients, namely lung cancer patients diagnosed cytologically/histopathologically at Haji Adam Malik Hospital, Medan, with the type of adenocarcinoma with EGFR common mutation. Most of the study subjects were males, namely 53 people (60.2%). The oldest age was 40-60 years old, with a total of 43 people (48.9%). The highest ethnicity in this study was Batak, with 51

people (58%), followed by the Javanese, as many as 21 people (23.9%). Based on smoking status, the highest number was former smokers, with 43 people (48.9%), followed by passive smokers, with 34 people (38.6%).

The number of study subjects with a previous history of pulmonary tuberculosis (TB) was 22 people (25%), while subjects without a previous history of pulmonary TB were 66 people (75%). Most of the study subjects (83%) had no family history of cancer. Most specimens were histopathological specimens, with 49 people (55.7%). Based on staging, the highest number found in this study was IVA staging, with as many as 57 people (64.8%), followed by IVB staging, with 13 people (14.8%). Based on the performance status score, most of the study subjects with PS 1 status were 66 people (75%) with the most metastatic lesions in the pleura, with a total of 50 people (56.8%). Based on the EGFR mutation, the highest number of subjects was the exon 19 del mutation, with as many as 57 people (64.8%). Meanwhile, 82 subjects (93.2%) were treated with gefitinib, while erlotinib was used to treat six subjects (6.8%). Table 1 shows an overview of the characteristics of the subjects.

Table 1. Characteristics of the subjects

No.	Characteristics	n	%
1.	Sex		
	Male	53	60.2
	Female	35	39.8
2.	Age (years old)		
	18-40	8	9.1
	41-60	43	48.9
	>60	37	42
3.	Ethnicity		
	Batak	51	58
	Jawa	21	23.9
	Minang	3	3.4
	Melayu	9	10.2
	Aceh	1	1.1
	Padang	2	2.3
	Mandailing	1	1.1
4.	Smoking status		
	Non-smoker	10	11.4
	Current smoker	1	1.1
	Former smoker	43	48.9
	Passive smoker	34	38.6
5.	History of lung TB		
	Yes	22	25
	No	66	75
6.	Family cancer history		
	Lung	3	3.4
	Other	12	13.6
	No history	73	83
7.	Specimen		
	Histopathology	49	55.7
	Cytology	39	44.3
8.	Staging		
	IIIA	6	6.8
	IIIB	8	9.1
	IIIC	4	4.5
	IVA	57	64.8
	IVB	13	14.8
9.	Performance status		
	0	2	2.3
	1	66	75
	2	20	22.7
10.	Metastatic lesions		
	No	33	37.5
	Pleura	50	56.8
	Brain	4	4.5
	Pleura and brain	1	1.1
11.	EGFR mutation		
	Exon 19 del	57	64.8
	Exon 21 L858R	31	35.2
12.	EGFR-TKI		
	Gefitinib	82	93.2
	Erlotinib	6	6.8

Survival Analysis of Adenocarcinoma Patients that Obtained EGFR-TKI Medication

Patients with lung adenocarcinoma taking EGFR-TKI treatment had their survival time calculated using the Kaplan-Meier method. In this study, eight individuals (9.1%) made it until the assessment's conclusion, with a median OS of eleven months (95% CI: 9,594-12,406). Figure 1 shows the survival curves for all patients taking EGFR-TKI during the trial period (the maximum survival period is 38 months).

The Median OS of Patients Based on Mutation Type

The median OS of the study subjects according to the variety of common EGFR alterations, with the largest in exon 19 del around 11 months (95% CI: 9.064-12.936). On the other hand, the median OS of the mutation group exon 21 L858R was ten months (95% CI: 4,546-15,454). The log-rank test revealed no statistical difference in median OS between both groups ($p = 0.562$). It can be seen from the curves in Figure 2 intersect that there was no strong relationship between the kind of EGFR mutation and the survival time of adenocarcinoma patients. The Proportional Hazard assumption was not met, meaning the survival rate was not constant between the two variants of EGFR alterations.

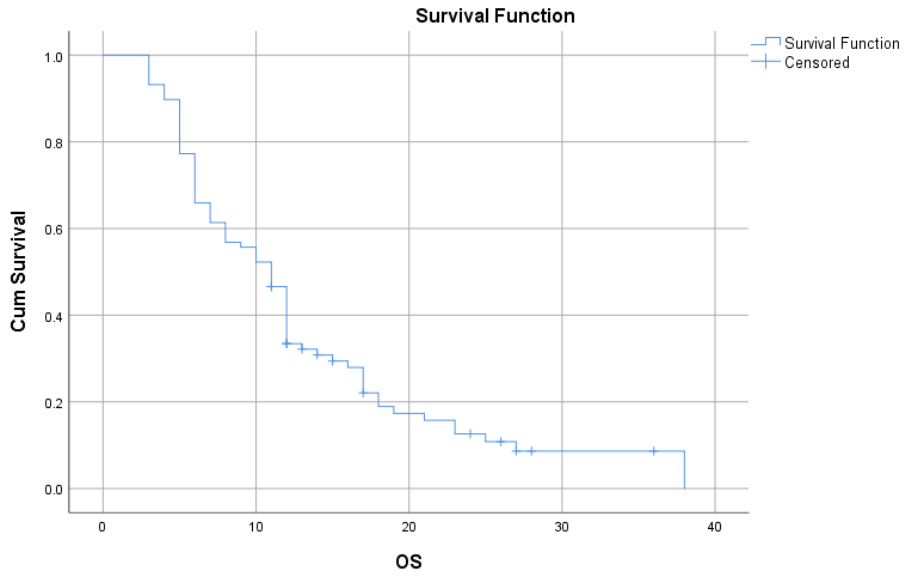

Figure 1. Survival analysis of adenocarcinoma patients that obtained EGFR-TKI medication

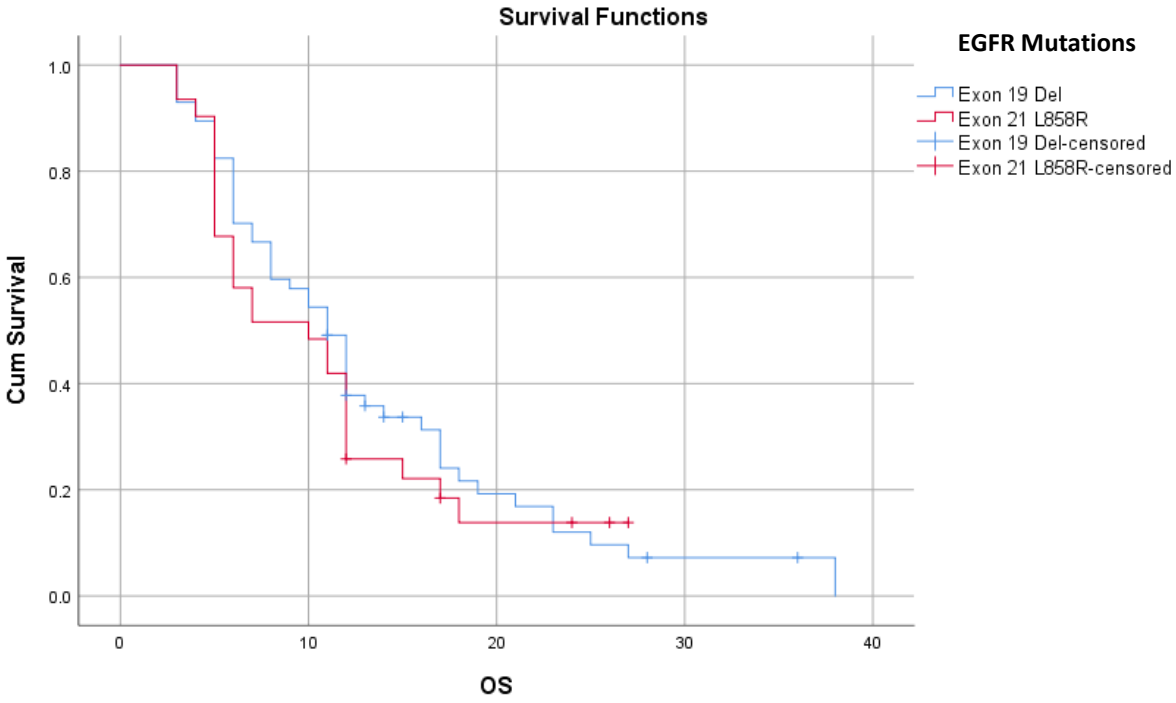

Figure 2. The median OS of patients based on mutation type

PFS of Adenocarcinoma Patients that Obtained EGFR-TKI

Figure 3 shows the PFS curves for all subjects with pulmonary adenocarcinoma who got EGFR-TKI treatment during the study period (the longest survival duration was 38 months). In this study, the median PFS was six months, with a 95% confidence interval of 4,958 to 7,042.

Median PFS of Patients Based on Mutation Type

The median PFS of the study subjects, depending on the EGFR common mutation variety, was six months (del of exon 19) (95% CI: 5,097-6,903). Meanwhile, the mutation group exon 21 L858R was five months (95% CI: 3,280-6,720). The log-rank test found no discernible difference in median PFS between the two categories of mutations ($p = 0.645$). Figure 4 indicates no meaningful correlation between the kind of common EGFR mutation and the number of patients with PFS for lung adenocarcinoma. The PFS ratio between the two groups of mutations was not constant because the proportional hazard assumption was not satisfied.

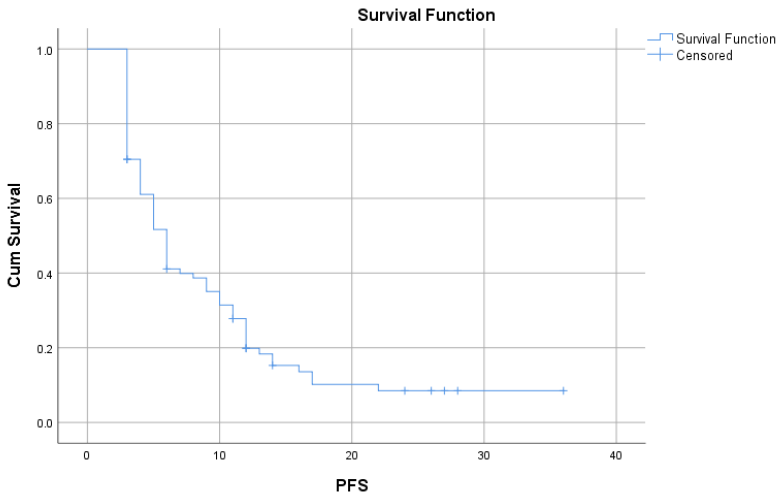

Figure 3. PFS of adenocarcinoma patients that obtained EGFR-TKI

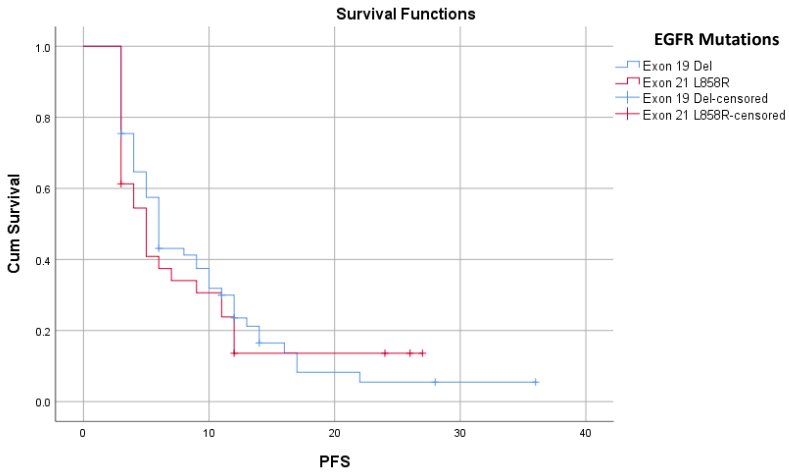

Figure 4. Median PFS of patients based on mutation type

DISCUSSION

The duration of the follow-up period from the defined start point to the occurrence of a specific event, from the start of the remission phase to its conclusion, or from the time of disease diagnosis, is measured using overall survival analysis.[9–17] Any event that can happen to a person can be of interest, including death, the development of an illness, its recurrence or recurrence after it has been treated, convalescence, or anything else.[18–23]

In the analysis of resilience, censored data always occurs. There is information about the endurance time at the individual level. However, it is still unclear how long it takes.[9,22] The reason for the occurrence is that the desired event has not appeared, has suffered circumstances unrelated to the substance under construction, or has vanished from public view until the end of the works. Censored cases were not eliminated. Instead, they were still considered since, at the most basic level, it can still be demonstrated that they have not been subjected to an event. It is assumed that censorship events happen equally throughout a particular period. It is called censorship if, for example, a study ends. Still, the desired event does not appear, the subject under study leaves without a message, the subject resigns for some reason, or the subject can also get an event that is not the focus of the study.[9,18–23] The censored data can also be divided into types I, II, and III[9,22] or by three based on when the event occurred with survival time, namely right-censoring, left-censoring, and interval-censoring.[9] There were 13 censored data in this study, of which eight people (9.1%), five men (5.7%) and three women (3.4%), were still alive after the study period with a median OS of 11 months, and five people (5.7 %) were lost to follow-up. The maximum period of survival was 38 months. This is slightly different from the results of a previous study also conducted at Haji Adam Malik Hospital, Medan, by Kasuma, *et al*. (2020) who reported that six patients survived with a median OS of seven months during the 30 months of the study period.[24] These differences may

be due to individual factors that differ from one patient to another.

Based on the EGFR type of common mutation, the median OS of the study subjects was the largest with mutations in exon 19 del, 11 months with a value of 95%CI 9,064-12,936. In contrast, the mutation group exon 21 L858R was ten months with a value of 95%CI was 4,546-15,454. The median value of PFS of the study subjects depending on the type of EGFR common mutation, was six months (del of exon 19) with a value of 95%CI 5,097-6,903. In comparison, the mutation group exon 21 L858R was five months. The value of 95%CI was 3,280-6,720. Median OS and PFS log-rank tests showed no difference significantly between both types of EGFR common mutations (p = 0.562 for OS; p = 0.645 for PFS). This differs from a study conducted by Agustina in 2017, where the median PFS value in exon 19 mutations was higher than exon 21, which was statistically significant (p = 0.049). This study also reported that the median OS value in exon 19 mutations was greater than in exon 21, although there was no significant difference (p = 0.526).[25] Yu, *et al*. (2023) also reported different results where the median OS in exon 19 del mutations was better than exon 21 L858R with a very significant difference (mOS 32.4 vs. 24.83, p = 0.0013).[26] As previously explained, the OS and PFS curves based on the EGFR common mutation type intersect, meaning there was no significant relationship between both types. The Proportional Hazard assumption was not met, meaning that the survival rate and PFS ratio between the two types of mutations were not constant.

The multivariate analysis with Cox regression form could not be performed because the Proportional Hazard assumption needed to be met. This indicates that the PFS comparison between EFGR common mutations was not constant. This study demonstrated that at the very least, median OS and PFS were higher in study subjects with the exon 19 del mutation rather than the exon 21 L858R, even though there was no statistical difference in median OS or PFS between study subjects with exon 21 L858R and exon 19 del mutations whom EGFR-TKI treated. This outcome was consistent with several earlier studies that were performed.[8,27-36]

This study has limitations because the patients only got first-generation therapy from EGFR-TKI (Social Security Agency on Health/BPJS insurance) and did not get a change in treatment like second or third-generation EGFR-TKI if they are already experiencing disease progression. In general, the prognosis of patients with exon 19 del mutations is better than exon 21 L858R if given EGFR-TKI monotherapy, either first, second, or third generation. However, a different prognosis may result if a combination therapy or dose modification is given, as in the study reported by Li, *et al*.(2020).[37]

CONCLUSION

This study showed no statistical difference between the two groups who got EGFR-TKI. However, the median of OS and PFS was higher in the study subjects with the del mutation of exon 19 than exon 21 L858R. This eventual result is consistent with several previous studies that have been performed.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conceptualizing and validating data: SJP. Checking grammar: NNS. Investigating data: SPT and NNF. Analyzing data: NNS and EM. Preparing manuscript: SJP, NNS, SPT, NNF, and EM. All authors contributed and approved the final version of the manuscript.

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