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Brain metastases in non-small cell lung cancer: Prevalence, high-risk factors, and overall survival prognosis

Research Article

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Abstract: **Introduction:** This study assesses brain metastases (BM) in non-small cell lung cancer (NSCLC) – its prevalence, risk factors, overall survival, and influencing aspects.

Materials and methods: A retrospective observational study was conducted at Nghe An Oncology Hospital in Vietnam. We assessed 895 patients diagnosed with NSCLC between June 2019 and June 2023. We used univariate and multivariate logistic regression models to assess the association of BM with factors. We evaluated the overall survival (OS) time using the Kaplan–Meier method and assessed differences using the log-rank test. In addition, we determined the association between OS time and factors using the Cox regression model.

Results: The prevalence of BM in NSCLC at the time of diagnosis was 13.1%. BM were associated with non-squamous carcinoma (odds ratio [OR] = 2.04, 95% confidence interval [95% CI]: 1.01–4.14), lymph node stage N3 (OR = 1.77, 95% CI: 1.15–2.72), and serum carcinoembryonic antigen (CEA) ≥5 ng/ml (OR = 1.81, 95% CI: 1.05–3.13). The median OS time for patients with BM was lower than in those without BM (15.3 vs. 18.3 months, $p = 0.005$). When analyzing multivariable Cox regression, the OS time of patients with BM was associated with positive *EGFR*/*ALK* gene mutation status (hazard ratio [HR] = 0.38, 95% CI: 0.20–0.70) and number of brain metastatic in 1–3 lesions (HR = 0.56, 95% CI: 0.33–0.96).

Conclusions: The prevalence of BM at the time of diagnosis in NSCLC was 13.1% and was associated with non-squamous carcinoma, node stage, and serum CEA. *EGFR*/*ALK* gene mutation status and the number of brain metastatic lesions were independent prognostic factors for OS of BM NSCLC.

Keywords: *Brain metastases • non-small cell lung cancer • Vietnam*

1. Introduction

Brain metastases (BM) in non-small cell lung cancer (NSCLC) at the time of diagnosis are quite common, occurring in about 10%–20% of cases[1,2]. Risk factors associated with the frequency of BM in NSCLC include non-squamous carcinoma, elevated serum carcinoembryonic antigen (CEA) levels, lymph node metastases (especially metastasis to multiple mediastinal lymph nodes), and *EGFR/ALK* gene mutations[3]. Chinese authors have also observed that lesion diameter, calcium concentration, and CEA level are independent risk factors for brain metastasis[4]. Increased lymph node size is also linked to asymptomatic BM[5].

The primary treatments for NSCLC with BM used to be surgery, radiosurgery, and whole-brain radiotherapy. Chemotherapy had limited effectiveness due to the presence of the blood–brain barrier. However, now there are numerous treatment options, and the effectiveness has greatly improved with the emergence of targeted drugs[6].

Although immunotherapy is an emerging option for increasing treatment options in NSCLC, its benefits in BM are unclear and require further study[7,8]. The median

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overall survival time for patients with BM is approximately 12 months[9]. Factors such as performance status, gene mutation status, and histopathology play an important role in predicting the survival time of NSCLC with BM[9,10].

Overall assessment of BM in NSCLC will assist clinicians in gaining an overview, thereby contributing to diagnosis and treatment strategies. In Vietnam, no comprehensive studies have evaluated this situation thoroughly. Our study aimed to determine the incidence of brain metastasis, evaluate overall survival time, and assess factors influencing these outcomes in the NSCLC population in Vietnam.

2. Materials and Methods

2.1. Study locations and patients

This study was conducted at Nghe An Oncology Hospital in Vietnam. The study protocol received approval from the ethics committee of Nghe An Oncology Hospital.

This study included patients over 18 years old diagnosed with NSCLC by histopathology according to World Health Organization (WHO) 2015 standards[11]. Patients were staged according to AJCC 8th edition, 2017[12]. Diagnosis of BM relied on magnetic resonance imaging (MRI) or computed tomography (CT) results. *EGFR* mutation testing was conducted using real-time polymerase chain reaction (PCR) or next-generation sequencing (NGS), while *ALK* testing was performed using NGS. The patient's physical condition was assessed using the Eastern Cooperative Oncology Group (ECOG) scale[13].

All patients were regularly monitored and assessed following clinical guidelines. This involved documenting the time of death or the date of the last update, as well as the conclusion of the study.

We excluded patients with unidentified histopathology, multiple cancers, or an inaccessible status of brain metastasis at diagnosis.

2.2. Study design and size samples

This is a retrospective observational study evaluating NSCLC patients from June 2019 to June 2023.

The sample size was calculated using the one-proportion estimation formula, ensuring absolute accuracy as recommended by the WHO[14]. We chose a significance level of 0.05, an absolute precision of 0.02, and estimated the brain metastasis rate to be 10.4% (based on a previous study)[1].

We randomly recruited 895 patients who met the criteria for inclusion in the analysis.

2.3. Study variables

The outcome variable of this study was BM (Yes hoặc No). Overall survival (OS) was defined as the time from treatment to death from any cause. Patients alive at the last follow-up or with missing information were censored.

Dependent variables included age group (<60 and ≥60), sex (male and female), histopathology (non-squamous or squamous), performance status (0–1 or 2–4), tumor stage (T1–T2, T3–T4), nodal stage (N0–2, N3), extracranial metastasis (yes or no), tumor size (<3 cm, ≥3 cm), short axis of **mediastinal node** (<1.5 cm or ≥1.5 cm), *EGFR/ALK* gene mutation (positive or negative/unknown), serum CEA (<5 ng/ml or ≥5 ng/ml), number of brain metastatic lesions (1–3 or >3), size of brain metastatic lesions (<3 cm or ≥3 cm), and whole-brain radiotherapy (yes or no).

2.4. Statistical analysis

Quantitative variables are presented as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-normally distributed data. Qualitative variables are presented as frequency and percentage (%).

The chi-squared test or Fisher's exact test was used to compare differences between groups. Univariate and multivariate logistic regression models were used to assess the association of BM with factors. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Survival curves were estimated using the Kaplan–Meier method and compared with the log-rank test. The association with factors was evaluated using the Cox regression model. Results are reported as hazard ratios (HRs) with 95% CIs.

All analyses were performed using International Business Machine Statistical Package for the Social Sciences 25.0. A *p*-value <0.05 was considered statistically significant.

3. Results

Table 1 presents the characteristics of the study participants. The median age of the study participants was 63 ± 13 years, The majority of patients were male, with non-squamous carcinoma, older than 60 years, and

Table 1: Characteristics of patients participating in the study.

Variable	*n* (%)
Age (years) Median (±IQR)	63 ± 13 (range: 24–88)
Age group (years)	
<60	306 (34.2)
≥60	589 (65.8)
Sex	
Male	666 (74.4)
Female	229 (25.6)
Histopathology	
Squamous carcinoma	159 (17.8)
Non-squamous carcinoma	736 (82.2)
PS ECOG	
0–1	734 (82.0)
2–4	161 (18.0)
Tumor stage	
T1	129 (14.4)
T2	192 (21.5)
T3	207 (23.1)
T4	367 (41.0)
Node stage	
N0	201 (22.5)
N1	30 (3.4)
N2	310 (34.6)
N3	354 (39.6)
Tumor size (cm)	
<3	217 (24.2)
≥3	678 (75.8)
Short axis of mediastinal node (cm)	
<1.5	638 (71.3)
≥1.5	257 (28.7)
EGFR/*ALK* mutation	
Positive	250 (27.9)
Negative/unknown	645 (72.1)
CEA (ng/ml)	
<5	251 (28.0)
≥5	644 (72.0)
Extracranial metastasis	
Yes	506 (56.5)
No	389 (43.5)

Note: ECOG: Eastern Cooperative Oncology Group, *EGFR*: epidermal growth factor receptor, *ALK*: anaplastic lymphoma kinase, CEA: carcinoembryonic antigen, PS: performance status, IQR: interquartile range

Table 2. Prevalence of brain metastases in non-small cell lung cancer according to factors.

Variable	n (%)	p-Value
Total	(117) 13.1	-
Age group (years)		
<60	45 (14.7)	0.347
≥60	72 (12.2)	
Sex		
Male	88 (13.2)	0.910
Female	29 (12.7)	
Histopathology		
Squamous carcinoma	10 (6.3)	0.006
Non-squamous carcinoma	107 (14.5)	
PS ECOG		
0–1	91 (12.4)	0.245
2–4	26 (16.1)	
Tumor stage		
T1–T2	40 (12.5)	0.757
T3–T4	77 (13.4)	
Node stage		
N0–2	51 (9.4)	<0.001
N3	66 (18.6)	
Tumor size (cm)		
<3	25 (11.5)	0.488
≥3	92 (13.6)	
Short axis of mediastinal node (cm)		0.028
<1.5	73 (11.4)	
≥1.5	44 (17.1)	
EGFR/*ALK* mutation		
Positive	41 (16.4)	0.077
Negative/unknown	76 (11.8)	
CEA (ng/ml)		0.001
<5	18 (7.2)	
≥5	99 (15.4)	
Extracranial metastasis		
Yes	76 (15.0)	0.057
No	41 (10.5)	

Note: ECOG: Eastern Cooperative Oncology Group, *EGFR*: epidermal growth factor receptor, *ALK*: anaplastic lymphoma kinase, CEA: carcinoembryonic antigen, PS: performance status

with PS ECOG 0–1. Approximately one-third of cases had positive *EGFR/ALK* gene mutations.

Table 2 shows a brain metastasis prevalence of 13.1%. It is high in non-squamous carcinoma subgroups, lymph node stage N3, short axis of **mediastinal node** ≥1.5 cm, and CEA ≥5 ng/ml.

Table 3 shows the association of BM in NSCLC with several factors: BM are associated with non-squamous carcinoma (OR = 2.04, 95% CI: 1.01–4.14), lymph node stage N3 (OR = 1.77, 95% CI: 1.15–2.72), and CEA status ≥5 ng/ml (OR = 1.81, 95% CI: 1.05–3.13).

Figure 1 shows the overall survival time for NSCLC patients with and without BM. The median overall survival time of patients with BM was lower than that of patients without BM (15.3 vs. 18.3 months, $p = 0.005$). The 1-year and 2-year overall survival rates for patients with NSCLC and BM are 55.0% and 27.6%, respectively.

Table 4 presents a multivariable Cox regression analysis of the association between overall survival time in patients with brain metastatic NSCLC and various factors. Overall survival time is associated with positive *EGFR/ALK* gene mutation status (HR = 0.38, 95% CI: 0.20–0.70) and the number of 1–3 BM lesions (HR = 0.56, 95% CI: 0.33–0.96).

Figure 2 shows that the median overall survival time is higher in the group with 1–3 BM (19.5 vs. 9.3 months, $p = 0.004$) (Figure 2A) and in the *EGFR/ALK* gene mutation positive group (20.3 vs. 8.7 months, $p = 0.001$) (Figure 2B).

Table 3. Some factors associated with brain metastases in non-small cell lung cancer: Univariate and multivariate logistic regression.

Variable	Brain metastases in non-small cell lung cancer			
	Crude OR (95% CI)	*p*-Value	Adjustment OR (95% CI)	*p*-Value
Age group (years)				
<60	1.24 (0.83–1.85)		1.21 (0.80–1.83)	
≥60	1	0.297	1	0.370
Sex				
Male	1.05 (0.67–1.65)		1,17 (0.73–1.90)	
Female	1	0.832	1	0.513
Histopathology	1			
Squamous carcinoma	2.53 (1.29–4.97)		1	
Non-squamous carcinoma		0.007	2.04 (1.01–4.14)	0.049
PS ECOG	1			
0–1	1.36 (0.85–2.18)		1	
2–4		0.202	1.51 (0.92–2.50)	0.102
Tumor stage	1		1	
T1–T2	1.09 (0.72–1.64)		0.98 (0.62–1.53)	
T3–T4		0.685		0.925
Node stage				
N0–2	1		1	
N3	2.20 (1.49–3.26)	< 0,001	1.77 (1.15–2.72)	0.009
Tumor size (cm)				
<3	1		1	
≥3	1.21 (0.75–1.93)	0.436	1.33 (0.79–2.22)	0.286
Short axis of mediastinal node (cm)				0.224
<1.5				
≥1.5	1		1	
	1.60 (1.07–2.40)	0.023	1.32 (0.84–2.05)	
EGFR/*ALK* mutation				
Positive	1.47 (0.97–2.22)		1.34 (0.85–2.11)	
Negative/unknown	1	0.067	1	0.206
CEA (ng/ml)	1			
<5	2.35 (1.39–3.97)		1	
≥5		0.001	1.81 (1.05–3.13)	0.034
Extracranial metastasis				
Yes	1.50 (1.00–2.25)	0.050	1.11 (0.72–1.71)	
No	1		1	0.626

Note: ECOG: Eastern Cooperative Oncology Group, OR: odds ratio, 95% CI: 95% confidence interval 95%, *EGFR*: epidermal growth factor receptor, *ALK*: anaplastic lymphoma kinase, CEA: carcinoembryonic antigen, PS: performance status

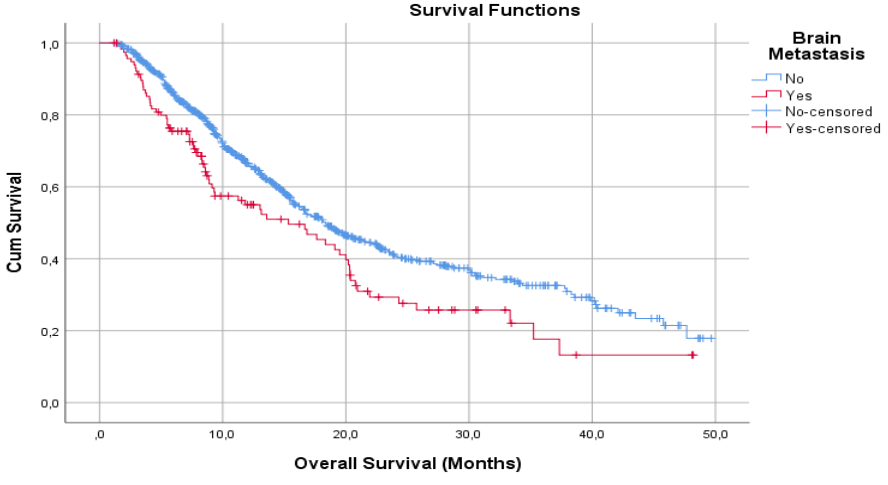


Figure 1: Overall survival time for non-small cell lung cancer patients with and without brain metastases: Kaplan–Meier analysis.

Table 4. Association of overall survival time in patients with brain metastases in non-small cell lung cancer with various factors: Multivariable Cox regression analysis.

Variable (N = 117)	HR (95% CI)	p-Value
Age group (years)		
<60	0.86 (0.50–1.46)	0.569
≥60	1	
Sex		
Male	0.95 (0.50–1.80)	0.862
Female	1	
Histopathology		
Squamous carcinoma	1	0.296
Non-squamous carcinoma	0.63 (0.26–1.50)	
PS ECOG		
0–1	0.60 (0.32–1.11)	0.103
2–4	1	
Tumor stage		
T1–T2	1	0.281
T3–T4	0.71 (0.38–1.32)	
Node stage		
N0–2	1	0.262
N3	0.73 (0.41–1.27)	
Tumor size (cm)		
<3	0.71 (0.35–1.43)	0.332
≥3	1	
Short axis of mediastinal node (cm)	0.80 (0.48–1.35)	0.404
<1.5	1	
≥1.5		
EGFR/ALK mutation		
Positive	0.38 (0.20–0.70)	0.002
Negative/unknown	1	
CEA (ng/ml)		
<5	0.78 (0.34–1.80)	0.554
≥5	1	
BM lesions		
1–3 lesions	0.56 (0.33–0.96)	0,036
>3 lesions	1	
Size of BM lesions		
<3 cm	1	0.996
≥3 cm	0.99 (0.52–1.91)	
WBRT		
Yes	0.98 (0.55–1.81)	0.970
No	1	
Extracranial metastasis		
Yes	1	0.830
No	0.93 (0.51–1.72)	

Note: ECOG: Eastern Cooperative Oncology Group, HR: hazard ratio, 95% CI: 95% confidence interval, *EGFR*: epidermal growth factor receptor, *ALK*: anaplastic lymphoma kinase, BM: brain metastases, PS: performance status.

4. Discussion

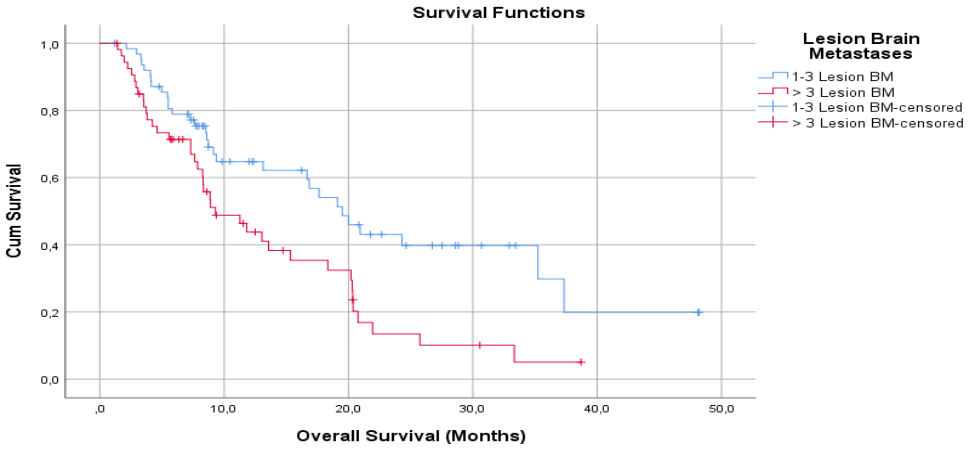
In Vietnam, this is the first study to evaluate BM in NSCLC. We observed a high prevalence of BM at the time of diagnosis, and it was closely linked to several factors. In addition, BM limit the overall survival time of patients with NSCLC. We also found some prognostic factors for overall survival in this group of patients. Our findings will assist clinicians in gaining a comprehensive perspective on patients with brain metastatic NSCLC during diagnosis and treatment.

The presence of BM was typically detected using CT scan or *MRI* of the brain at the time of diagnosis. We observed that the prevalence of BM at the time of diagnosis was 13.1%, consistent with findings from other studies[1,15], but lower than in India, where the prevalence was 21%[2]. Our study was conducted with a large sample size at the largest oncology center in central Vietnam. Therefore, this result can be considered representative of the NSCLC population in central Vietnam.

In this study, when analyzing univariate and multivariate logistic regression, we found that BM are closely associated with non-squamous carcinoma, lymph node stage N3, and serum CEA status ≥5 ng/ml. In an analysis from the US National Cancer database, factors such as younger age, glandular and large cell histology, histological grade >II, tumor size >3 cm, and lymph node positivity were associated with BM in NSCLC[1]. In addition, distant metastases to the liver/bone/lymph nodes, tumor stage, and higher node stage also showed a higher likelihood of BM[16]. Lesion diameter >5.505 cm, calcium concentration >2.295 mmol/l, and CEA >11.160 ng/ml are also prognostic factors for this condition[4]. In Mexico, age, serum CEA, and genetic mutation status are recognized as high-risk factors for BM[17]. Previous studies indicate a high incidence of BM in patients with positive *EGFR/ALK* gene mutations[18,19]. However, we did not find an association of BM with *EGFR/ALK* gene mutations in multivariate analysis. Perhaps due to limited economic resources, a certain proportion of patients do not have access to diagnostic testing for *EGFR/ALK* gene mutations, which thus affects these results when analyzed.

BM are a factor that affects the quality of life as well as the overall survival of patients with NSCLC. Our study found that the median overall survival time in the group of patients with BM was lower than in those without BM (15.3 vs. 18.3 months, $p = 0.005$). A previous study found that the median overall survival in patients with NSCLC with BM was approximately 12 months[9]. Real-life data of patients with BM in Japan showed a median overall survival of 14.3 months[10]. In the present circumstances, the overall survival time for this group of patients has significantly improved due to the use of new local and systemic treatments. A study in the USA revealed that the median overall survival for patients with BM from NSCLC was 17.0 months[20]. The results of our study are quite similar to those of other studies around the world. With the combination of multimodality treatment, in particular, the effectiveness of targeted

2A. Number of brain metastases lesions



2B. EGFR/ALK mutation

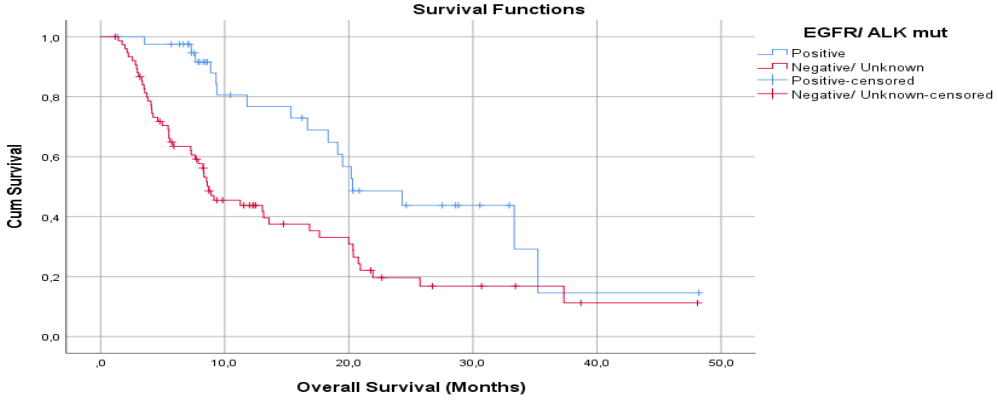


Figure 2: Overall survival time of patients with NSCLC with brain metastases in subgroups: Kaplan–Meier analysis, log-rank test.

treatment drugs on patients with NSCLC with BM has improved and significantly prolonged the overall survival time.

When analyzing multivariable Cox regression, we noted a benefit in overall survival time in patients with BM with *EGFR/ALK* gene mutations compared to patients with *EGFR/ALK*-negative/unknown (HR = 0.38, 95% CI: 0.20–0.70, $p = 0.002$), thereby proving the clear benefits of targeted drugs on patients with BM. This observation is completely consistent with previous reports[21,22]. In our study, we observed a survival benefit among patients with 1–3 BM (HR = 0.56, 95% CI: 0.33–0.96, $p = 0.036$). Previously reported prognostic factors include PDL1 status, *EGFR/ALK* gene mutation, performance status, age, number of BM, and extracranial metastases[23]. For patients with BM, brain radiotherapy is one of the recommended local treatment methods. In cases of limited metastases, radiosurgery (SRS) is recommended as an alternative to surgery or as an adjunct after brain tumor surgery[24,25]. In cases of multiple BM, whole-brain radiotherapy is indicated[26]. Currently, due to limited local resources, the main treatment at our center is steroid or whole-brain radiation therapy. In some cases, the ability of *EGFR/ALK* tyrosine kinase inhibitor drugs to penetrate the brain supports the decision to delay brain radiotherapy in selected patients without negatively impacting treatment outcomes[27]. Whole-brain radiotherapy is performed at our unit for BM that are symptomatic and do not benefit from targeted drugs. In our analysis, whole-brain radiotherapy did not improve survival benefits for patients with NSCLC with BM (HR = 0.98, 95% CI: 0.55–1.81, $p = 0.970$). This result is also consistent with previous reports[28].

The limitations of this study include its retrospective design and the fact that it was conducted at a single center. The collection of data, particularly regarding

the smoking variable, was somewhat affected. Limited resources may have resulted in some patients lacking access to new treatment options, such as targeted therapies and immunotherapy, which could influence the results. Nevertheless, this study provides valuable information on the treatment of NSCLC in Vietnam. Future research should aim to evaluate the effectiveness of new medications, like targeted therapies and immunotherapy, specifically for patients with NSCLC who have BM.

5. Conclusions

Our study indicates a high prevalence of BM in NSCLC in Vietnam. The application of new treatment methods has improved treatment effectiveness.

This study offers an overview of BM in NSCLC, aiming to enhance diagnostic and treatment effectiveness in real-life settings in Vietnam.

Ethical approval

The Ethics Committee of Nghe An Oncology Hospital approved the study proposal. In addition, patient records were anonymized and de-identified before undergoing analysis. Informed consent was waived due to the retrospective nature of this study.

Availability of data and material

We agree to publish the research article according to the guidelines.

Data Availability Statement

Data will be provided upon reasonable request.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author contributions

NVL, NKT, NTTU, and LVT developed the idea and study design, analyzed and interpreted the data, and wrote the article. NVL, PTH, NTTU, LVT, TTTH, BVT, and NTT contributed to data collection. All authors read and approved the final article.

Acknowledgments

This article represents the authors' personal views and does not represent the views of other organizations with which the authors are affiliated.

Abbreviations

ALK: anaplastic lymphoma kinase
CEA: carcinoma embryonic antigen
CI: confidence interval
CT scan: computed tomography scan
EGFR: epidermal growth factor receptor
ECOG: Eastern Cooperative Oncology Group
IQR: interquartile range
HR: hazard ratio
MRI: *magnetic resonance imaging*
NGS: next-generation sequencing
TKI: tyrosine kinase inhibitor
OR: odds ratio
PCR: polymerase chain reaction
PS: performance status
WHO: World Health Organization

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