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Original Article

Resistance patterns of non-small cell lung cancer treated with third-generation epidermal growth factor receptor-tyrosine kinase inhibitors

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Abstract: The third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are the preferred therapy for patients with EGFR mutant non-small cell lung cancer (NSCLC); however, the therapy faces resistance challenges. We aimed to clarify the resistance patterns of EGFR-TKIs in patients with EGFR mutant NSCLC. In this retrospective study, we analyzed 104 patients with advanced EGFR mutant NSCLC who experienced treatment failure of third-generation EGFR-TKIs. Resistance models were classified as 1) original site failure (OF), distant site failure (DF), and combined failure (ODF) based on the failure site or 2) oligo-progression (OP) and non-oligoprogression based on the disease progression (PD) pattern. Among the patients, 58.7% (n = 61 of 104) developed OF, while 25 (24.0%) and 18 (17.3%) developed DF and ODF, respectively. A high OP rate (76.9%, n = 80) was observed, with primary progression accounting for 30.8%. OF was related to sex (odds ratio = 3.961, 95% confidence interval: 1.629-9.631, P = 0.002). Over 50% of patients with third-generation EGFR-TKI treatment failure developed OF. Sex, central nervous system metastases, and disease stage influenced the resistance patterns of the EGFR-TKI therapy.

Keywords: Non-small cell lung cancer, EGFR-TKI, resistance patterns

Introduction

The leading cause of tumor death in China remains lung carcinomas, including small-cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for 85% of lung carcinomas and has a 5-year survival rate of only 18%; approximately 75% of patients with NSCLC are diagnosed at advanced stages [1-3].

In Asian patients with advanced adenocarcinoma, the percentage of epidermal growth factor receptor (EGFR) mutations is 51.4% and reaches 60.7% in patients without a smoking history [4]. The major EGFR mutation types are exon 19 deletion mutation (19del) and exon 21 L858R point mutation (L858R), which account for nearly 85% of cases [5, 6]. For patients with EGFR-sensitive mutant NSCLC, EGFR-tyrosine kinase inhibitors (EGFR-TKIs) are the standard treatment. The third-generation EGFR-TKIs have shown superior progression-free survival (PFS) and overall survival (OS) over first-generation EGFR-TKIs and chemotherapy in EGFR mutant NSCLC. According to the FLAURA experiment, the median PFS was 18.9 months with third-generation EGFR-TKI osimertinib vs. 10.2 months with first-generation EGFR-TKI gefitinib or erlotinib, and the median OS was 38.6 months (95% confidence interval (CI): 34.5-41.8) with osimertinib vs. 31.8 months (95% CI: 26.6-36.0) with gefitinib or erlotinib in advanced EGFR mutant NSCLC [7, 8]. In the AURA trial, the median PFS was distinctly advantageous with osimertinib compared with chemotherapy (10.1 vs. 4.4 months; P < 0.001) as a subsequent therapy for patients with T790M mutant NSCLC [9].

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However, almost all patients receiving the third-generation EGFR-TKIs developed acquired resistance. The median time to resistance onset was 18.9 months for first-line therapy and 10.1 months for subsequent therapy [7, 9]. Most patients with resistance to EGFR-TKIs developed disease progression (PD) in original sites and experienced oligo-progression (OP). A study showed that original site failure (OF) accounted for 47% of failed treatments, and the most common sites of progression were the lungs in patients with first- or second-generation EGFR-TKI resistance [10]. Another study showed that young patients and those without baseline brain metastases are more likely to experience progression in the original sites after erlotinib failure [11]. Additionally, half of the patients experienced resistance in the original sites, and 70% developed OP after osimertinib failure [12].

Identifying the resistance patterns of third-generation EGFR-TKIs is crucial. Thus, this study aims to explore resistance patterns, the potential predictive factors of resistance patterns, and survival.

Materials and methods

This retrospective study was approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University and Dongying People's Hospital. The study was conducted according to the tenets of the Declaration of Helsinki.

Patients

We retrospectively analyzed 197 patients with radiographically confirmed stage IIIB/IIIC to IV NSCLC who experienced third-generation EGFR-TKI failure between October 2016 and August 2023, including 115 patients with The First Affiliated Hospital of Shandong First Medical University and 82 patients with Dongying People's Hospital. NSCLC was cytologically or pathologically confirmed, and PD was evaluated according to the response evaluation criteria in solid tumors (version 1.1, RECIST 1.1). All patients had 19del, L858R, or EGFR exon 20 T790M point mutation (T790M mutation) with at least one measurable lesion for radiologic evaluation and complete imaging data. Baseline characteristics were sex, age, smoking history, pathological type, EGFR mutation type, treatment lines, Eastern Cooperative Oncology Group Performance Status score, initial central nervous system (CNS) metastasis, clinical stages, the number of organs with metastasis, and the number of oligo-progression.

Treatment and follow-up

Oral osimertinib (80 mg) or almonertinib (110 mg) was administered once daily until PD or intolerable toxicity. All patients underwent contrast-enhanced computed tomography (CECT) of the chest, abdomen, bones, and pelvis at baseline. When EGFR-TKIs were administered, CECT was conducted every 6 weeks for 18 months and subsequently every 12 weeks until PD.

Definition

According to Al-Halabi, the resistance patterns were divided into OF, distant site failure (DF), and combined failure (ODF) [10]. PD at original sites (primary/metastatic) was categorized as OF, and progression at new sites was defined as DF. Concurrent OF and DF were considered ODF. Resistance patterns were divided into oligo-progression (OP) and non-oligoprogression (NOP), with OP defined as ≤ 5 metastasis sites and ≤ 3 organs [13].

Responses to third-generation EGFR-TKIs were classified as complete response (CR), partial response (PR), stable disease (SD), or PD. Objective response rate (ORR) was classified as the percentage of patients who obtained CR and PR, and disease control rate (DCR) was the percentage of patients who obtained CR, PR, and SD.

PFS was recorded as the time between the initiation of third-generation EGFR-TKI therapy and clinical progression or death (whichever occurred first). OS indicated the time between the initiation of third-generation EGFR-TKI therapy and death from any cause.

Statistical analysis

PFS and OS were analyzed using the Kaplan-Meier method and the log-rank test in GraphPad Prism 8. The logistic regression model was used to estimate the relationship between resistance patterns and clinical characteristics, including the EGFR mutation type (L858R

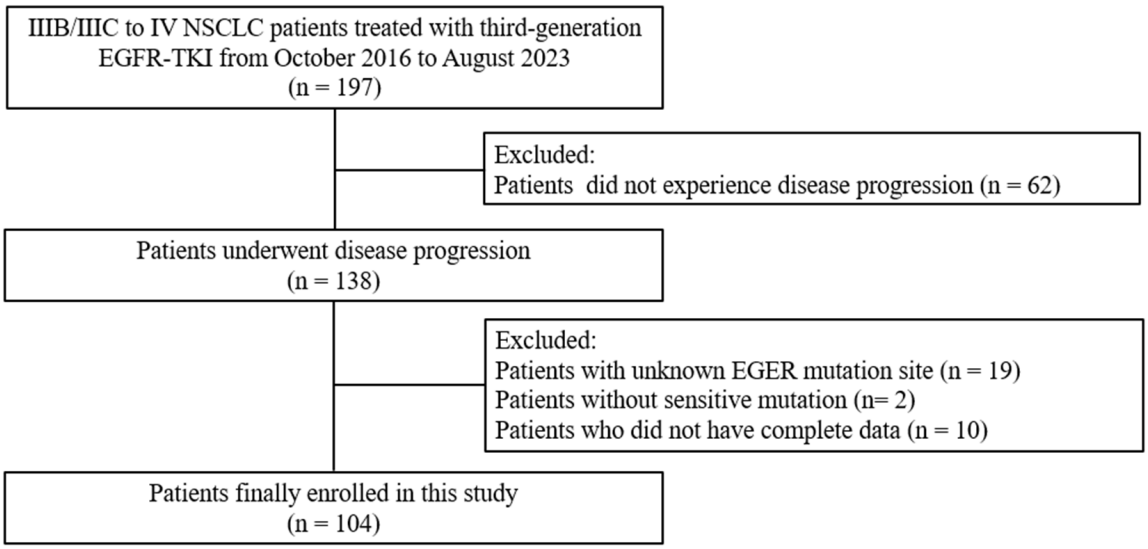

Figure 1. Flowchart of patient enrollment.

vs. 19del), age (≥ 65 vs. < 65 years), sex (female vs. male), smoking history (yes vs. no), best response evaluation (PR vs. SD and PD vs. SD), initial oligometastatic status (yes vs. no), initial CNS metastasis (yes vs. no), treatment line (subsequent line vs. first line), and disease stage (IV vs. IIIB/IIIC). For each resistance pattern (OF, DF, or ODF), the rest of the models were treated as competing events. The multivariate logistic regression model was used for further analysis to identify predictive factors of resistance patterns and evaluate the odds ratios (ORs) and 95% CI. The multivariate analysis included all clinical characteristics with $P < 0.2$ in the univariate analysis. All statistical analyses were conducted using SPSS Statistics version 26.0 (IL, Armonk, NY, USA). All *p*-values were two-sided, with $P < 0.05$ being considered statistically significant.

Results

Baseline characteristics

In total, 197 patients treated with third-generation EGFR-TKIs were screened, and 104 who experienced PD and were followed up constituted the study population (**Figure 1**). The mean age was 60 (range: 34-85) years. There were 68 women (65.4%) and 56 non-smokers (82.7%). Similarly, 46 participants had 19del mutations, and 58 had L858R mutations. In addition, 38 patients (36.5%) received first-line therapy, and 66 (63.5%) received subsequent treatment. The lymph nodes (74.0%) experienced PD the most, followed by the lungs (54.8%), bones (52.9%), and other sites. Most patients (n = 53, 51.0%) had ≤ 3 organ metastases, and 41 (39.4%) had oligo-metastases. Twenty-three patients had previously undergone radical surgery. Detailed baseline characteristics of the patients before the initiation of EGFR-TKI treatment are provided in **Table 1**.

Resistance patterns

Primary progression accounted for 30.8% of PD (n = 32 of 104). The lungs (45.2%) were the most common organs with PD, followed by the brain (22.1%), lymph nodes (20.2%), and bone (18.3%). For different treatment lines, OF remained the most common PD pattern. However, for patients with subsequent-line treatment, 65.2% (n = 43 of 66) developed OF, while 47.4% (n = 18 of 38) of patients with first-line treatment had OF. The progression sites are listed in **Table 2**. After PD, 13 patients were treated with radiotherapy, 49 received chemotherapy, and 32 continued the original EGFR-TKI therapy.

Furthermore, 58.7% of patients experienced OF (n = 61 of 104), while 25 (24.0%) and 18 (17.3%) developed DF and ODF, respectively. The most common organs with OF were the lungs (n = 25 of 61, 41.0%), brain (n = 14 of 61, 23.0%), and bone (n = 8 of 61, 13.1%).

Table 1. Baseline characteristics of 104 patients

Variable	Number	Percent
Gender		
Male	36	34.6
Female	68	65.4
Age (year)		
≥ 65	41	39.4
< 65	63	60.6
Smoking history		
Former	18	17.3
Never	86	82.7
Disease stage		
IIIB	12	11.5
IV	92	88.5
EGFR mutation		
19del	46	44.2
21exon	58	55.8
Treatment Lines		
First line	38	36.5
Second line	66	63.5
Oligo-metastasis before initiation TKI		
Yes	41	39.4
No	63	60.6
Number of organs with metastases per patient		
≤ 3	53	51.0
> 3	51	49.0
Central nervous system metastasis		
Yes	44	42.3
No	60	57.7
Surgery		
Yes	23	22.1
No	81	77.9
Distribution of metastases before TKI initiation		
Lymph nodes	77	74.0
Lung	57	54.8
Bone	55	52.9
Brain	43	41.3
Pleura	14	13.5
Liver	9	8.7
Others	40	38.5

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Similarly, the lungs (n = 11 of 25, 44.0%), brain (n = 6 of 25, 24.0%), and bone (n = 6 of 25, 24.0%) were the most common sites of DF. While the lungs (n = 11 of 18, 61.1%), lymph nodes (n = 9 of 18, 50.0%), and bone (n = 5 of 18, 27.8%) were the most common organs with ODF.

Most patients had OP (n = 80 of 104, 76.9%), while 24 (23.1%) developed NOP. Among patients with OP, 31.3% developed primary progression, and most experienced OF (n = 54 of 80, 67.5%). In a subgroup of patients with OP, the most common organ was the lungs (n = 30 of 80, 37.5%), followed by the brain (n = 17, 21.3%), bones (n = 12, 15.0%), and lymph nodes (n = 8, 10.0%).

Predictors of OF

In the univariate analysis, sex, initial CNS metastases, and treatment line were selected for further analysis. The multivariate analysis revealed sex (OR = 3.961, 95% CI: 1.629-9.631, P = 0.002) and initial CNS metastases (P = 0.044) as independent predictors of OF (**Table 3**). Female patients and those with initial CNS metastases tended to develop OF.

Predictors of DF

In the univariate analysis, age, sex, smoking history, initial CNS metastases, and treatment line were selected for further analysis. The multivariate analysis indicated initial CNS metastases (OR = 0.191, 95% CI: 0.058-0.635, P = 0.007) as an independent predictor of DF (**Table 4**). Therefore, patients with initial CNS metastases were more likely to develop DF.

Predictors of ODF

In the univariate analysis, sex and initial oligometastatic status were selected for further analysis. In the multivariate analysis, no factors were identified as predictors of ODF (**Table 5**). Similarly, no predictors were found for ODF.

Predictors of OP

In the univariate analysis, sex, initial oligometastatic status, and disease stage were used for

Table 2. Characteristics of 104 patients after disease progression

Variable	OF		DF		ODF		Overall	
	n	%	n	%	n	%	n	%
Oligo-progression	54	67.5	20	25	6	7.5	80	76.9
Primary progression	24	23.1	3	2.9	5	5.8	32	30.8
First line	18	47.4	13	34.2	7	18.4	38	36.5
Subsequent line	43	65.2	12	18.2	11	16.6	66	63.5
Organs harboring progression								
Lung	25	41.0	11	44.0	11	61.1	47	45.2
Brain	14	23.0	6	24.0	3	16.7	23	22.1
Others	13	21.3	4	16.0	7	38.9	24	23.1
Bone	8	13.1	6	24.0	5	27.8	19	18.3
Lymph nodes	8	13.1	4	16.0	9	50.0	21	20.2
Adrenal glands	3	4.9	3	12.0	1	5.6	7	6.7
Liver	2	3.3	2	8.0	3	16.7	7	6.7
Number of organs with progression								
1	51	49	18	17.3	5	4.8	74	71.2
2	7	6.7	5	4.8	6	5.8	18	17.3
3	2	1.9	1	1.0	6	5.8	9	8.7
4	0	0	1	1.0	2	1.9	3	2.9

OF, original site failure; DF, distant site failure; ODF, combined failure.

Table 3. Logistic regression model for predictors of original site failure

Variable	Univariate analysis			Multivariate analysis		
	ORs	95% CI	*P* value	ORs	95% CI	*P* value
EGFR mutation type (L858R vs. 19del)	1.375	(0.626, 3.017)	0.428			
Age (≥ 65 vs. < 65)	1.387	(0.619, 3.107)	0.427			
Sex (female vs. male)	4.246	(1.802, 10.005)	0.001	3.961	(1.629, 9.631)	0.002
Smoking history (yes vs. no)	0.654	(0.236, 1.813)	0.414			
Best response evaluation (PR vs. SD)	0.967	(0.399, 2.340)	0.940			
Best response evaluation (PD vs. SD)	1.050	(0.341, 3.236)	0.932			
Initial Oligometastatic status (yes vs. no)	1.172	(0.526, 2.613)	0.698			
Initial CNS metastasis (yes vs. no)	2.851	(1.237, 6.567)	0.014	2.480	(1.024, 6.008)	0.044
Treatment line (subsequent line vs. first line)	2.077	(0.921, 4.686)	0.078	1.855	(0.766, 4.490)	0.171
Disease stage (IV vs. III)	1.015	(0.300, 3.439)	0.981			

CNS, central nervous system; 95% CI, confidence interval; EGFR, epidermal growth factor receptor; ORs, odds ratios; PR, partial response; PD, progressive disease; SD, stable disease.

further analysis. The multivariate analysis revealed disease stage (OR = 3.912, 95% CI: 1.062-14.408, P = 0.040) as an independent predictor of OP (**Table 6**). Patients with Stage IV disease tended to show OP.

Response

CR, PR, SD, and PD were discovered in 0, 50, 34, and 20 patients, respectively. The ORR was 48.1% (n = 50 of 104), and the DCR was 80.8% (n = 84 of 104). Fifty patients achieved PR, including OF in 58.0% (n = 29), DF in 26.0% (n = 13), and ODF in 16.0% (n = 8). Thirty-nine patients (78.0%) who achieved PR experienced OP, while 11 had NOP. Thirty-four patients achieved SD, including OF in 58.8% (n = 20), DF in 20.6% (n = 7), and ODF in 20.6% (n = 7). Of the patients who achieved SD, 26 (76.5%) showed OP, and 8 (23.5%) showed NOP. Twenty patients achieved PD, including OF in 60.0% (n = 12), DF in 25.0% (n = 5), and ODF in 15.0%

Table 4. Logistic regression model for predictors of distant site failure

Variable	Univariate analysis			Multivariate analysis		
	ORs	95% CI	*P* value	ORs	95% CI	*P* value
EGFR mutation type (L858R vs. 19del)	0.662	(0.268, 1.634)	0.371			
Age (≥ 65 vs. < 65)	0.515	(0.193, 1.372)	0.184	0.427	(0.147, 1.238)	0.117
Sex (female vs. male)	0.379	(0.151, 0.954)	0.039	0.548	(0.157, 1.917)	0.347
Smoking history (yes vs. no)	2.404	(0.816, 7.084)	0.112	1.422	(0.315, 6.416)	0.647
Best response evaluation (PR vs. SD)	1.355	(0.477, 3.850)	0.568			
Best response evaluation (PD vs. SD)	1.286	(0.347, 4.764)	0.707			
Initial Oligometastatic status (yes vs. no)	1.592	(0.642, 3.947)	0.316			
Initial CNS metastasis (yes vs. no)	0.186	(0.058, 0.590)	0.004	0.191	(0.058, 0.635)	0.007
Treatment line (subsequent line vs. first line)	0.427	(0.171, 1.069)	0.069	0.480	(0.176, 1.311)	0.152
Disease stage (IV vs. III)	1.667	(0.340, 8.172)	0.529			

CNS, central nervous system; 95% CI, confidence interval; EGFR, epidermal growth factor receptor; ORs, odds ratios; PR, partial response; PD, progressive disease; SD, stable disease.

Table 5. Logistic regression model for predictors of combined failure

Variable	Univariate analysis			Multivariate analysis		
	ORs	95% CI	*P* value	ORs	95% CI	*P* value
EGFR mutation type (L858R vs. 19del)	0.990	(0.356, 2.751)	0.984			
Age (≥ 65 vs. < 65)	1.285	(0.460, 3.586)	0.632			
Sex (female vs. male)	0.347	(0.123, 0.978)	0.045	0.389	(0.135, 1.117)	0.079
Smoking history (yes vs. no)	0.547	(0.114, 2.621)	0.450			
Best response evaluation (PR vs. SD)	0.735	(0.239, 2.260)	0.591			
Best response evaluation (PD vs. SD)	0.681	(0.155, 2.997)	0.611			
Initial Oligometastatic status (yes vs. no)	0.378	(0.115, 1.244)	0.110	0.439	(0.130, 1.477)	0.183
Initial CNS metastasis (yes vs. no)	1.111	(0.399, 3.093)	0.840			
Treatment line (subsequent line vs. first line)	0.886	(0.312, 2.518)	0.820			
Disease stage (IV vs. III)	0.584	(0.141, 2.415)	0.458			

CNS, central nervous system; 95% CI, confidence interval; EGFR, epidermal growth factor rece,ptor; ORs, odds ratio; PR, partial response; PD, progressive disease; SD, stable disease.

Table 6. Logistic regression model for predictors of oligo-progression

Variable	Univariate analysis			Multivariate analysis		
	ORs	95% CI	*P* value	ORs	95% CI	*P* value
EGFR mutation type (L858R vs. 19del)	1.683	(0.672, 4.216)	0.266			
Age (≥ 65 vs. < 65)	1.795	(0.670, 4.809)	0.245			
Sex (female vs. male)	2.333	(0.919, 5.927)	0.075	2.277	(0.852, 6.086)	0.101
Smoking history (yes vs. no)	0.737	(0.233, 2.329)	0.604			
Best response evaluation (PR vs. SD)	1.091	(0.387, 3.078)	0.869			
Best response evaluation (PD vs. SD)	0.923	(0.255, 3.338)	0.903			
Initial Oligometastatic status (yes vs. no)	2.333	(0.838, 6.497)	0.105	1.740	(0.595, 5.086)	0.311
Initial CNS metastasis (yes vs. no)	0.830	(0.331, 2.078)	0.690			
Treatment line (subsequent line vs. first line)	1.055	(0.411, 2.711)	0.911			
Disease stage (IV vs. IIIB/IIIC)	4.111	(1.186, 14.253)	0.026	3.912	(1.062, 14.408)	0.040

CNS, central nervous system; 95% CI, confidence interval; EGFR, epidermal growth factor receptor; ORs, odds ratio; PR, partial response; PD, progressive disease; SD, stable disease.

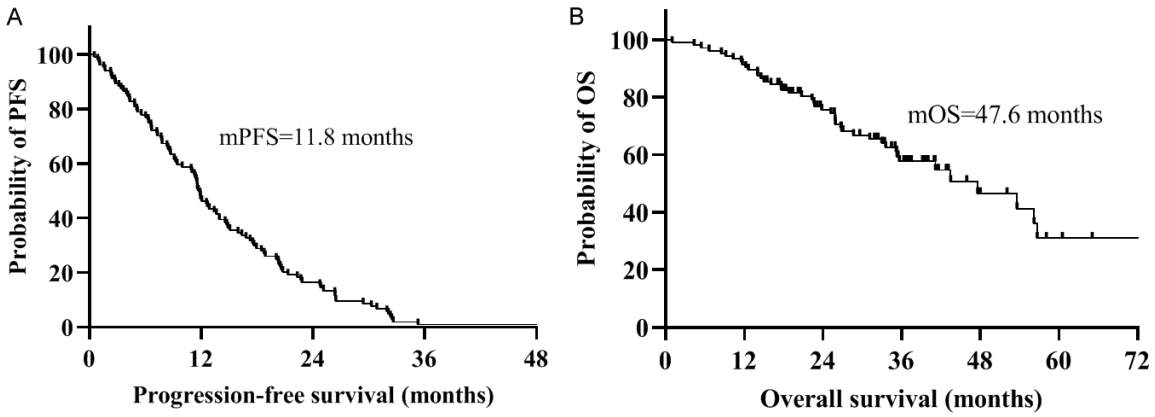

Figure 2. Survival curves of all patients. A. Progression-free survival. B. Overall survival.

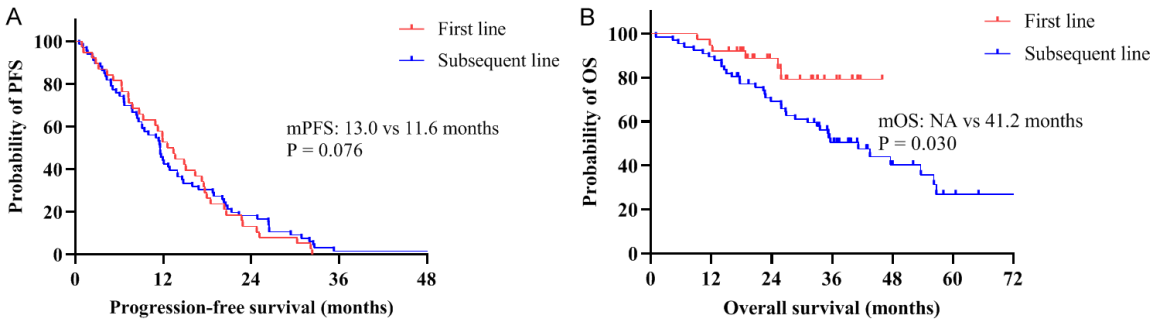

Figure 3. Survival curves of first-line and subsequent line patients. A. Progression-free survival. B. Overall survival.

(n = 3). Of these, 15 (75.0%) showed OP, and 5 (25.0%) had NOP. The ORR of OF, DF, and ODF were 47.5% (n = 29 of 61), 52.0% (n = 13 of 25), and 44.4% (n = 8 of 18), respectively. The DCR of OF, DF, and ODF were 80.3% (n = 49 of 61), 80% (n = 20 of 25), and 83.3% (n = 15 of 18), respectively. The ORR of OP vs. NOP was 49% vs. 46% (P = 0.802), and the DCR was 81% vs. 79% (P = 0.776). The resistance patterns of OF, DF, and ODF were not significantly different among patients with and without PR (P = 0.880), similar to the resistance patterns of OP and NOP (P = 0.802).

Survival analysis

As of the last follow-up on July 31, 2024, with a median follow-up time of 39.3 (range: 11.7-95.9) months. All patients developed PD. The median PFS was 11.8 (range: 0.5-55.1) months, and the median OS was 47.6 (range: 0.97-77.20) months (**Figure 2**). We compared the PFS and OS of EGFR-TKIs as first- and second-line treatments and found no statistically significant difference in the median PFS (13.0 vs. 11.6 months, P = 0.746); however, there was a significant difference in the median OS (NA vs. 41.2 months, P = 0.030) (**Figure 3**). There was no statistically significant difference in the median PFS among the three groups (11.9 vs. 11.6 vs. 14.1 months, P = 0.755). However, a significant difference was observed in the median OS (33.6 vs. NA vs. 53.6 months, P = 0.007) (**Figure 4**). In addition, we compared the median PFS and OS between patients with OP and those with NOP. No significant difference was observed in the median PFS (11.6 vs. 14.0 months, P = 0.059) or OS (43.5 months vs. NA, P = 0.173) (**Figure 5**).

Discussion

Our study revealed that approximately 58.7% (n = 61) of patients with third-generation EGFR-TKI resistance experienced failure in the original sites, and 76.9% (n = 80) developed OP. Primary site failure accounted for 30.8%, and the lungs were the most affected organs con-

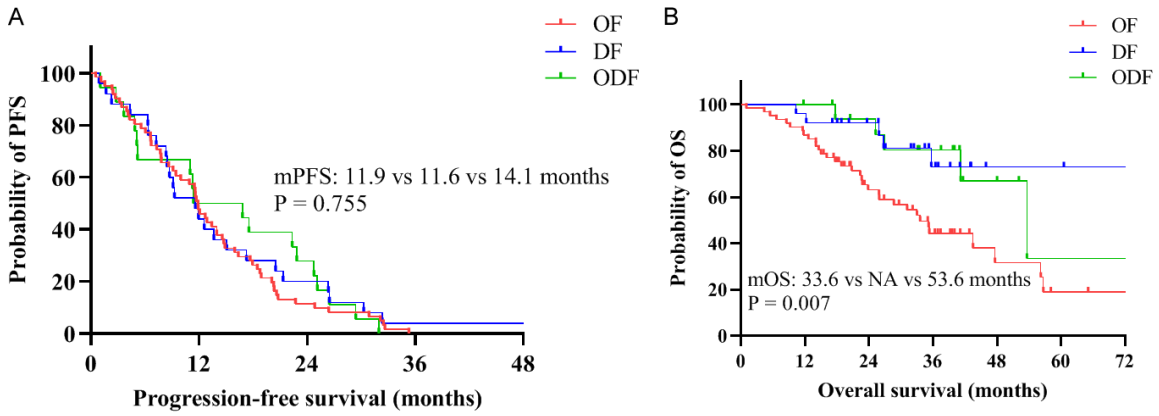

Figure 4. Survival curves of OF, DF and ODF patients. A. Progression-free survival. B. Overall survival.

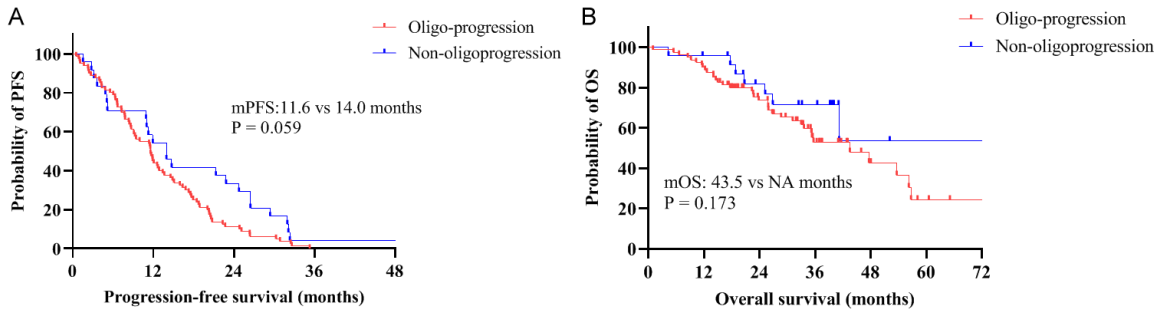

Figure 5. Survival curves of oligo-progression and non-oligoprogression patients. A. Progression-free survival. B. Overall survival.

cerning PD. These patients may obtain survival benefits from local treatment. The female was more likely to develop failure in the original sites. Additionally, the third-generation EGFR-TKIs as first-line treatment had significantly longer OS than as subsequent-line treatment, and patients with ODF had a better survival benefit.

Over 50% of patients experienced OF (n = 61, 58.7%), followed by DF (24.0%) and ODF (17.3%). Our results are similar to those of previous studies on first- and second-generation EGFR-TKIs [10, 11]. Tang et al. showed that OF, DF, and ODF accounted for 41.25%, 42.5%, and 16.25%, respectively, in patients with advanced NSCLC who experienced icotinib failure [14]. Patel et al. showed that OF accounted for 60.2% of resistance in patients with EGFR mutant NSCLC who experienced erlotinib failure, and lungs (60%) were the most common metastatic organs [11]. In our study, 76.9% of patients developed OP. Similarly, we observed that OF accounted for 30.8% of failure, and the distribution of PD lesions was as follows: lungs (45.2%), brain (22.1), lymph nodes (20.2%), and bone (18.3%). A Swiss cohort study reported that 77% of patients developed OP, and 23% developed NOP; the metastatic sites included the lungs (62%), brain (30%), lymph nodes (30%), and bone (27%) [15]. Guo et al. reported that 50% (n = 25 of 50) of patients developed OF, 22% (n = 11 of 50) developed DF, and 28% (n = 14 of 50) experienced ODF among those with osimertinib treatment failure [12]. Additionally, 70% of patients experienced OP [12].

The female was more likely to develop OF. Tang et al. observed that individuals with 19del were more likely to develop OF after icotinib failure [14]. Takeyasu et al. indicated that patients with 19del mutation are likely to develop primary progression, while those with L858R mutation tend to develop CNS metastasis after osimertinib failure [16]. Patel et al. found that patients without baseline brain metastasis and the younger population are more likely to devel-

op OF after erlotinib failure [11]. Additionally, Al-Halabi et al. revealed that the size of the primary tumor was closely related to OF in the resistance pattern of afatinib, erlotinib, or gefitinib [10]. The factors influencing the resistance patterns include EGFR-TKI therapy, the physical condition of the patients, sample size, and the EGFR mutation type. These predictors require further investigation involving larger sample sizes.

Furthermore, we compared survival between different subgroups after third-generation EGFR-TKI failure. The median PFS did not differ markedly between first- and subsequent-line treatments (13.0 vs. 11.6 months, P = 0.746). However, the median OS was improved with first-line therapy compared with that of subsequent-line therapy. Additionally, we observed no statistical difference in the median PFS between the three patterns; however, ODF had the highest OS. The death percentages associated with OF, DF, and ODF were 54%, 20%, and 28%, respectively. The lower mortality rate in patients with ODF may have contributed to this difference. Tang et al. found no statistical differences in the median PFS or OS among OF, DF and ODF [14]. Wei et al. indicated that patients with OF had the shortest median PFS (6 vs. 11 vs. 10 months, P = 0.0084) [17]. Our study revealed no statistically significant differences in the median PFS or OS between patients with OP and NOP.

Studies have shown that original site progression is the primary resistance pattern after EGFR-TKI failure. Additionally, some research reported that new distant metastases may be caused by residual tumor lesions of original resistant clones [10, 11]. The local ablative therapy at the original tumor sites before PD may result in good survival, decreased tumor cell clones of original sites, and decreased distant metastasis. Under extensive CNS involvement, patients should receive whole-brain radiotherapy combined with systemic therapy with high blood-brain barrier penetration as an adjunct [18]. A phase II study showed that for patients with advanced NSCLC, combined first-generation EGFR-TKIs and stereotactic body radiotherapy (SBRT) improve survival ratio and delay acquired resistance development compared with the effects of first-generation EGFR-TKIs alone [19]. Similarly, the study suggested that radiotherapy to original sites alone may be preferable to metastatic lesions [19]. An observational cohort study indicated that patients treated with the first-generation EGFR-TKI + SBRT targeting original sites had a longer PFS than did those treated with the first-generation EGFR-TKI alone (15.50 vs. 9.33 months, P < 0.0020), and the treatment primarily caused a new site failure, particularly 19del, rather than an original site failure [20]. Keane et al. suggested that targeting SBRT to residual lesions reduces the occurrence of disease metastasis in patients treated with the first-generation EGFR-TKIs as the first-line therapy [21].

Patients with OP who undergo local therapy, such as microwave ablation and SBRT, achieve favorable results [22-24]. Some studies reported that patients with OP who received local therapy had at least 6 months of extra disease stabilization [23, 25, 26]. In individuals experiencing OP with NSCLC treated with the third-generation EGFR-TKIs as the first-line therapy, EGFR-TKI + SBRT caused a significantly longer PFS than did EGFR-TKI alone (Hazard Ratio: 0.46, 80% CI: 0.20-0.61; P = 0.002) [27]. A study indicated that patients with oligo-progressive advanced NSCLC treated with third-generation EGFR-TKIs combined with SBRT experienced delayed disease development and prolonged PFS [28]. A Swiss cohort study showed that patients with OP who received local ablative treatment had more favorable outcomes than did those without local treatment [29]. Furthermore, the combination of EGFR-TKI and SBRT notably hinders PD in patients with oligo-metastatic NSCLC experiencing EGFR-TKI resistance, significantly extending their PFS [30].

As a retrospective analysis, our study has certain limitations, including a relatively small sample size, potential selection bias in obtaining data from patients with PD, and inconformity in the timing of TKI initiation. Compared with those of previous studies, our cohort had no CR and few PR cases, possibly because some patients received chemotherapy or local treatment before TKI therapy, which may have reduced their response to TKI [28, 31-33].

Conclusion

In patients with advanced NSCLC who received third-generation EGFR-TKIs, the major resis-

tance was OF. Factors such as sex, CNS metastases, and the disease stage were associated with the resistance patterns. However, the predictors of resistance patterns require substantial investigation using larger sample sizes.

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Disclosure of conflict of interest

None.

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References

[1] Blandin Knight S, Crosbie PA, Balata H, Chudziak J, Hussell T and Dive C. Progress and prospects of early detection in lung cancer. Open Biol 2017; 7: 170070.

[2] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.

[3] Wu YL, Zhong WZ, Li LY, Zhang XT, Zhang L, Zhou CC, Liu W, Jiang B, Mu XL, Lin JY, Zhou Q, Xu CR, Wang Z, Zhang GC and Mok T. Epidermal growth factor receptor mutations and their correlation with gefitinib therapy in patients with non-small cell lung cancer: a meta-analysis based on updated individual patient data from six medical centers in mainland China. J Thorac Oncol 2007; 2: 430-9.

[4] Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Heeroma K, Itoh Y, Cornelio G and Yang PC. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014; 9: 154-62.

[5] Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J and Haber DA. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004; 350: 2129-39.

[6] Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE and Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304: 1497-500.

[7] Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y and Ramalingam SS; FLAURA Investigators. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018; 378: 113-125.

[8] Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, Shah R, Cobo M, Lee KH, Cheema P, Tiseo M, John T, Lin MC, Imamura F, Kurata T, Todd A, Hodge R, Saggese M, Rukazenkov Y and Soria JC; FLAURA Investigators. Overall survival with Osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 2020; 382: 41-50.

[9] Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Theelen WS, Lee CK, Sebastian M, Templeton A, Mann H, Marotti M, Ghiorghiu S and Papadimitrakopoulou VA; AURA3 investigators. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017; 376: 629-640.

[10] Al-Halabi H, Sayegh K, Digamurthy SR, Niemierko A, Piotrowska Z, Willers H and Sequist LV. Pattern of failure analysis in metastatic egfr-mutant lung cancer treated with tyrosine kinase inhibitors to identify candidates for consolidation stereotactic body radiation therapy. J Thorac Oncol 2015; 10: 1601-7.

[11] Patel SH, Rimner A, Foster A, Zhang Z, Woo KM, Yu HA, Riely GJ and Wu AJ. Patterns of initial and intracranial failure in metastatic EGFR-mutant non-small cell lung cancer treated with erlotinib. Lung Cancer 2017; 108: 109-114.

[12] Guo T, Ni J, Yang X, Li Y, Li Y, Zou L, Wang S, Liu Q, Chu L, Chu X, Li S, Ye L and Zhu Z. Pattern of recurrence analysis in metastatic EGFR-mutant NSCLC treated with osimertinib: implications for consolidative stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2020; 107: 62-71.
[13] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.
[14] Tang Y, Xia B, Xie R, Xu X, Zhang M, Wu K, Wang B and Ma S. Timing in combination with radiotherapy and patterns of disease progression in non-small cell lung cancer treated with EGFR-TKI. Lung Cancer 2020; 140: 65-70.
[15] Schuler A, Huser J, Schmid S, Schär S, Scherz A, Gautschi O, Mauti L, von Briel T, Waibel C, Wannesson L, Pankovics J, Mark MT, Rothschild SI, Addeo A, Janthur WD, Siano M, Boos L, Britschgi C and Früh M. Patterns of progression on first line osimertinib in patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC): a Swiss cohort study. Lung Cancer 2024; 187: 107427.
[16] Takeyasu Y, Yoshida T, Masuda K, Matsumoto Y, Shinno Y, Okuma Y, Goto Y, Horinouchi H, Yamamoto N and Ohe Y. Distinct progression and efficacy of first-line osimertinib treatment according to mutation subtypes in metastatic NSCLC harboring EGFR mutations. JTO Clin Res Rep 2024; 5: 100636.
[17] Wei Y, Shen K, Lv T, Wang X, Li C, Fan H, Lv Y, Liu H and Song Y. Three new disease-progression modes in NSCLC patients after EGFR-TKI treatment by next-generation sequencing analysis. Lung Cancer 2018; 125: 43-50.
[18] Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Muñoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M and Paz-Ares L; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13: 239-46.
[19] Peng P, Gong J, Zhang Y, Zhou S, Li Y, Han G, Meng R, Chen Y, Yang M, Shen Q, Chu Q, Xia S, Zhang P, Zhang L, Chen Y and Zhang L. EGFR-TKIs plus stereotactic body radiation therapy (SBRT) for stage IV Non-small cell lung cancer (NSCLC): a prospective, multicenter, randomized, controlled phase II study. Radiother Oncol 2023; 184: 109681.
[20] Xu H, Qi R, Zhou C, Yu Y, Lin L, Wu X and Lv D. Early stereotactic body radiation therapy improves progression-free survival of first-generation EGFR tyrosine kinase inhibitors in EGFR-mutated lung cancer: an observational cohort study. Ther Adv Med Oncol 2024; 16: 17588359241290133.
[21] Keane FK, Yeap BY, Khandekar MJ, Lin JJ, Dagogo-Jack I, Sequist LV, Piotrowska Z and Willers H. Phase 2 trial of consolidative stereotactic body radiation therapy in patients with metastatic oncogene-driven non-small cell lung carcinoma treated with tyrosine kinase inhibitors. Int J Radiat Oncol Biol Phys 2025; 121: 975-979.
[22] Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L and You C. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol 2015; 26: 1877-1883.
[23] Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L and You C. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12: 735-42.
[24] Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S and Nukiwa T; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362: 2380-8.
[25] Campo M, Al-Halabi H, Khandekar M, Shaw AT, Sequist LV and Willers H. Integration of stereo-

tactic body radiation therapy with tyrosine kinase inhibitors in stage IV oncogene-driven lung cancer. Oncologist 2016; 21: 964-73.
[26] Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA Jr, Aisner DL, Gaspar LE, Kavanagh BD, Doebele RC and Camidge DR. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thorac Oncol 2012; 7: 1807-1814.
[27] Zhou Y, Peng L, Liang F, Chu L, Chu X, Yang X, Zhang J, Guo T, Jiang S, Pang Y, Wang Z, Zhang L, Ni J and Zhu Z. Safety and efficacy of consolidative stereotactic radiotherapy for oligoresidual EGFR-mutant non-small cell lung cancer after first-line third-generation EGFR-tyrosine kinase inhibitors: a single-arm, phase 2 trial. EClinicalMedicine 2024; 76: 102853.
[28] Zhao X, Zhang S, Sun X, Lin Y, Capone L, Ko EC, Kann BH, Li Y and Wang X. Narrative review of stereotactic body radiation therapy combined with tyrosine kinase inhibitors for oligometastatic EGFR-mutated non-small cell lung cancer: present and future developments. Transl Lung Cancer Res 2024; 13: 1383-1395.
[29] Di Noia V, D'Aveni A, D'Argento E, Rossi S, Ghirardelli P, Bortolotti L, Vavassori V, Bria E and Ceresoli GL. Treating disease progression with osimertinib in EGFR-mutated non-small-cell lung cancer: novel targeted agents and combination strategies. ESMO Open 2021; 6: 100280.
[30] Franceschini D, De Rose F, Cozzi S, Franzese C, Rossi S, Finocchiaro G, Toschi L, Santoro A and Scorsetti M. The use of radiation therapy for oligoprogressive/oligopersistent oncogene-driven non small cell lung cancer: state of the art. Crit Rev Oncol Hematol 2020; 148: 102894.
[31] Schmid S, Klingbiel D, Aeppli S, Britschgi C, Gautschi O, Pless M, Rothschild S, Wannesson L, Janthur W, Foerbs D, Demmer I, Jochum W and Früh M. Patterns of progression on osimertinib in EGFR T790M positive NSCLC: a swiss cohort study. Lung Cancer 2019; 130: 149-155.
[32] Ni Y, Bi J, Ye X, Fan W, Yu G, Yang X, Huang G, Li W, Wang J, Han X, Ni X, Wei Z, Han M, Zheng A, Meng M, Xue G, Zhang L and Wan C. Local microwave ablation with continued EGFR tyrosine kinase inhibitor as a treatment strategy in advanced non-small cell lung cancers that developed extra-central nervous system oligoprogressive disease during EGFR tyrosine kinase inhibitor treatment: a pilot study. Medicine (Baltimore) 2016; 95: e3998.
[33] Yu HA, Sima CS, Huang J, Solomon SB, Rimner A, Paik P, Pietanza MC, Azzoli CG, Rizvi NA, Krug LM, Miller VA, Kris MG and Riely GJ. Local therapy with continued EGFR tyrosine kinase inhibitor therapy as a treatment strategy in EGFR-mutant advanced lung cancers that have developed acquired resistance to EGFR tyrosine kinase inhibitors. J Thorac Oncol 2013; 8: 346-51.