Appropriate delay of primary tumour radiotherapy may lead to better long-term overall survival for non-small cell lung cancer treated with EGFR-TKIs

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Abstract

Purpose The most appropriate time of primary tumor radiotherapy in non-small cell lung cancer(NSCLC) with EGFR-TKIs remains unclear. The aim of this study was to investigate the effect of the time factor of primary tumor radiotherapy on long-term overall survival(OS)and provide a theoretical basis for further clinical research.

Patients and methods In total, 238 patients with EGFR-TKIs and OS ≥ 12 months were statistically analysed. Patients were grouped: the D group without primary tumor radiotherapy and the R group with it.The R group were divided into three groups according to the interval between the start of EGFR-TKIs and the start of primary tumor radiotherapy: R_{0-30}(<30 days), R_{30-PD}(≥ 30 days and disease stable), and R_{PD}(radiotherapy after disease progression). The Kaplan-Meier method and log-rank test were used for survival analyses. Exploratory landmark analyses were investigated.

Results The OS rates at 1, 2, 3, 5 years for the R group and D group were 96.8%, 62.9%, 38.3%, 17.1%, and 95.6%, 37.7%, 21.8%, 2.9%, respectively; the corresponding MST was 29 months(95% CI: 24.3–33.7) for the R group and 22 months(95% CI: 20.4–23.6) for the D group ($\chi^2 = 13.480$, $p<0.001$). Multivariate analysis revealed that primary tumor radiotherapy was independent predictors of prolonged OS.Among the four groups, The R_{30-PD} appeared to have the best OS (D, $\chi^2 = 19.307$, $p<0.001$;R_{0-30}, $\chi^2 = 11.687$, $p = 0.01$; R_{PD}, $\chi^2 = 4.086$, $p = 0.043$). Landmark analyses(22 months) showed the R_{30-PD} group had a significant long-term OS.The incidence of radiation pneumonitis ≥ grade 2 was17.3%($n = 19$)and radiation esophagitis ≥ grade 2 was observed in 32 patients(29.1%).

Conclusions Our results showed that primary tumour radiotherapy may prolong long-term OS with acceptable toxicities. Appropriate delay(R_{30-PD})of primary tumour radiotherapy may be the best choice.Premature radiotherapy(R_{0-30}) and radiotherapy after disease progression (R_{PD})may not be reasonable for long-term OS.

Keywords Time, Non-small cell lung cancer (NSCLC), EGFR-TKIs, Primary tumor radiotherapy, Overall survival

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Introduction

Non-small cell lung cancer (NSCLC) accounted for 86% of newly diagnosed lung cancer, and approximately 60% of them had metastatic lesion in initial diagnosis [1]. For such patients, Systemic treatment is the mainstay of treatment and has entered the era of precision medicine according to result of Genetic testing [2, 3]. Epidermal growth factor receptor (EGFR) mutation is the most common gene mutation, especially in Asian population [4]. EGFR-Tyrosine Kinase Inhibitors (EGFR-TKIs) has become the first-line treatment for metastatic NSCLC due to better objective response rates (ORR)and progression-free survival (PFS) compared with systemic chemotherapy [5–8].

However, the fatal drawback of EGFR-TKIs is the inevitable disease progression because of drug resistance [9, 10]. Tumor progression mainly occurred in the original disease sites, and this failure pattern suggested that radiotherapy may delay disease progression and prolong overall survival(OS) [11, 12]. Numerous studies have confirmed that primary tumor radiotherapy can significantly prolong progression-free survival (PFS)and OS on the basis of EGFR-TKIs [13–18]. Unlike traditional chemotherapy, EGFR-TKIs is a long-term treatment that is continued by oral administration until extensive disease progression [2, 3]. In the interim, when is radiation therapy most appropriate? Experts have explored and researched it, but it is only limited to theoretical analysis [19, 20]. The aim of this study was to investigate the effect of the time factor of primary tumor radiotherapy on long-term OS, and to provide a theoretical basis for further clinical research.

Materials and methods

Patients

Our research subjects were patients with NSCLC who had EGFR-mutation(EGFR-M) from January 2014 to December 2021 at Affiliated Cancer Hospital of Guizhou Medical University (the 7th edition of the American Joint Committee on Cancer staging system).We hunted out potential cases in the electronic medical record system. Keywords included Gefitinib, Icotinib, Erlotinib, Osimertinib and Almonertinib, which were available EGFR-TKIs in our hospital. These patients who met the following criteria were enrolled: (1) histologically or cytologically confirmed NSCLC and molecular testing confirmed EGFR-M (2) EGFR-TKIs as first line therapy; (3)≥18 years old (4) no previous thoracic radiotherapy or surgery; (5) no previous malignancy or other concomitant malignant diseases; (6) OS≥12 months [21–24].

We collected data from the electronic medical records and the department of epidemiology, including age at initial diagnosis, sex, smoking status, histology, TNM stage, EGFR-M types, metastasis status, radiotherapy data, and

so on. This study was approved by the ethics committee of the affiliated cancer Hospital of Guizhou medical university.

According to primary tumor radiotherapy, patients were grouped: the D group without primary tumor radiotherapy (primary tumor, lymph nodes) and the R group with it.The R group were divided into three groups: R_{0-30} group with the interval between the start of EGFR-TKIs and the start of radiotherapy<30 days, R_{30-PD} group with that ≥30 days and without disease progression, R_{PD} group with primary tumor radiotherapy after disease progression.The start of radiotherapy was defined as the time of Simulation Computed Tomography Scan(SCTS) in order to perform primary tumor radiotherapy.

Radiotherapy

Primary tumor radiotherapy

Primary tumor radiotherapy was not mandatory for any patient, but it was performed when patient had signed an informed consent form. The treating radiotherapist made the radiotherapy regime. The plans were evaluated as 100% of the prescription dose line including 100% of the GTV and 90% of the prescription dose including 98% of the PTV. The percentage of total lung volume receiving≥20 Gy (V20) was kept to ≤32%, the maximum point dose to the spinal cord was ≤50 Gy, the mean oesophageal dose was ≤35 Gy, and the mean heart dose was ≤30 Gy for all individual treatment plans. The prescribed dose was to be at least 30 Gy and given according to the tolerance of the organ at risk. One hundred and twenty-four patients received external beam radiation therapy for primary tumor(30 Gy≤dose≤54 Gy, n=34;dose>54 Gy, n=90). Radiotherapy toxicities were recorded and graded according to Common Terminology Criteria for Adverse Events (CTCAE, version4.0).

Metastases radiotherapy

Radiotherapy for metastatic lesions should meet two conditions at the same time.First, patient suffered from brain metastasis or bone metastasis with cancer pain or risk of fracture, and so on. Second, patient had signed an informed consent form. Brain metastases radiotherapy included whole brain radiotherapy (WBRT) (30 Gy/10 fractions or 40 Gy/20 fractions), simultaneous integrated boost of intensity modulated radiation therapy(SIB-IMRT)(Boost, 47–48 Gy/10–12 fractions, WBRT 30 Gy/10–12 fractions), and fractionated stereotactic radiotherapy (FSRT) (50 Gy/10fractions). Bone metastases radiotherapy was given in 3 Gy per fraction, 5 days per week, to a total dose of 30–45 Gy.

Statistical analysis

The study employed SPSS software (version 26.0) for statistical analysis. Dichotomous variables were presented

as counts and analyzed using Pearson's chi-square or Fisher's exact test. Overall survival(OS) [25] was defined as the period from the date of treatment commencement to the last follow-up date or death from any cause.The Kaplan-Meier method and log-rank test were used for survival analyses. Using the Cox proportional hazards model, the hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. To investigate the impact of radiation time on long-term survival, landmark analysis of OS was performed.Because the MST for patients with stage IV NSCLC who receive first-generation EGFR-TKIs was approximately 22 months [21–24], we chose 22 months from the start of treatment as the time point for landmark analyses.All statistical tests were 2-sided, and P values < 0.05 were considered statistically significant.

Results

Patient characteristics

In total, 238 patients with EGFR-TKIs and OS ≥ 12 months were statistically analysed, including 114 cases in the D group and 124 in the R group (R_{0-30} group, $n = 44$; R_{30-PD} group, $n = 47$; R_{PD} group, $n = 33$; Figure 1). The patient characteristics are presented in Table 1. The majority of patients had histology of adenocarcinoma($n = 223$, 93.7%)
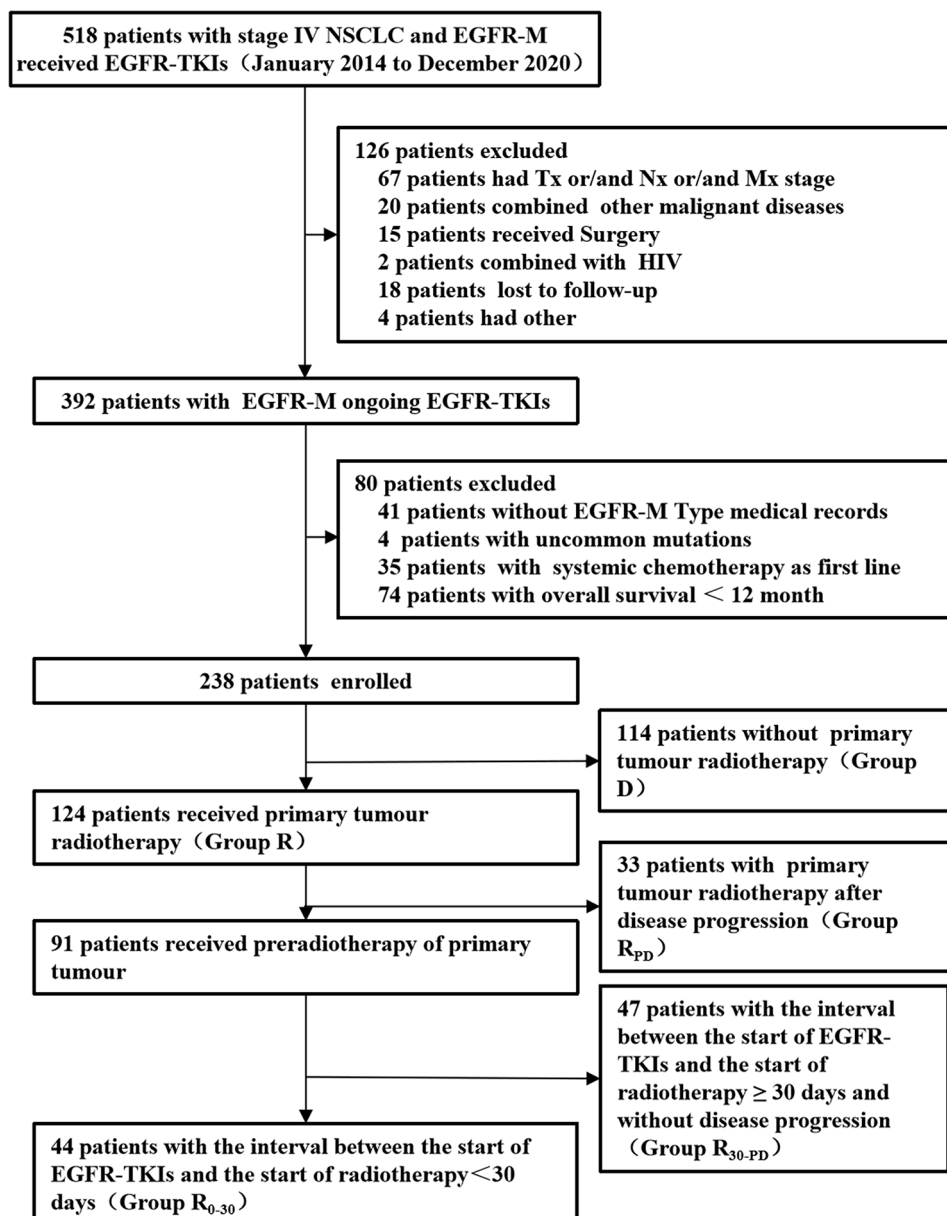
Fig. 1 Flowchart of patient cohort. HIV: human immunodificiency virus; NSCLC: Non-small cell lung cancer; EGFR-M: Epidermal growth factor receptor mutation;TKIs: Tyrosine kinase inhibitors.The start of radiotherapy; the time of Simulation Computed Tomography Scan in order to perform primary tumor radiotherapy

Table 1 Patient characteristics

characteristic		All	D group	R group			P(reference, R_{30-PD})		
		(n = 238)	(n = 114)	R_{0-30}(n = 44)	R_{30-PD}(n = 47)	R_{PD}(n = 33)	Group D	Group R_{0-30}	Group R_{PD}
Sex	Male	100	52	18	16	14	0.220	0.523	0.488
	Female	138	62	26	31	19			
Age (years)	<59	119	55	25	24	15	0.863	0.675	0.656
	≥59	119	59	19	23	18			
Histology*	LUAD	223	106	40	45	32	0.725	0.425	>0.999
	Other	15	8	4	2	1			
EGFR mutation type	Exon 19	132	58	29	30	15	0.164	>0.999	0.115
	Other**	106	56	15	17	18			
Smoking	Yes	74	38	14	10	12	0.136	0.342	0.203
	No	164	76	30	37	21			
T stage	T_{1-2}	77	35	16	16	10	0.712	0.830	0.811
	T_{3-4}	161	79	28	31	23			
N stage	N_{0-2}	93	49	12	16	16	0.377	0.505	0.248
	N_3	145	65	32	31	17			
M stage	IVA	55	24	12	9	10	0.834	0.457	0.292
	IVB	183	90	32	38	23			
Metastases									
Bone	Yes	137	62	30	26	19	>0.999	0.281	>0.999
	No	101	52	14	21	14			
Brain	Yes	82	47	5	21	9	0.728	<0.001	0.160
	No	156	67	39	26	24			
Lung	Yes	88	44	14	19	11	0.860	0.513	0.640
	No	150	70	30	28	22			
Liver	Yes	30	18	5	6	1	0.642	>0.999	0.230
	No	208	96	39	41	32			
Adrenal	Yes	22	8	4	9	1	0.044	0.234	0.041
	No	216	106	40	38	32			
Other	Yes	42	21	9	9	3	>0.999	>0.999	0.341
	No	196	93	35	38	30			
Oligometastasis***	Yes	73	29	17	13	14	0.844	0.372	0.230
	No	165	85	27	34	19			
Concurrent or Sequential Systematic chemotherapy	Yes	83	39	17	8	19	0.036	0.033	<0.001
	No	155	75	27	39	14			
EGFR-TKIs(Third generation)	Yes	108	54	13	23	18	0.864	0.086	0.656
	No	130	60	31	24	15			
Metastases radiotherapy	Yes	125	29	35	36	25	<0.001	0.803	>0.999
	No	113	85	9	11	8			

LUAD*,lung adenocarcinoma; *, Exon 18 or T790M ; ***,Involving organ≤3 and Involving lesions≤5

and stage IVB (n = 183, 76.9%) and non-oligometastases (n = 165, 69.3%).The ratio of males to females was 0.725; the median age was 59 years (28–84 years, age≤60 years in 128 patients). The T and N stages were as follows: 37 cases with $T_{1-2}N_{0-2}$, 40 with $T_{1-2}N_3$, 56 with $T_{3-4}N_{0-2}$, and 105 with $T_{3-4}N_3$. The common site of metastatic disease at initial diagnosis was the bone (57.6%), lung (37.0%), and brain (34.5%).Most patients (n = 155, 65.1%) underwent simple EGFR-TKIs during the course of the disease. There was no significant difference between the three groups with respect to gender, age, histology, smoking status, EGFR mutation type, metastases number, the types of EGFK-TKIs, and.
subsequent treatment.

Radiotherapy

Of the 238 patients, 38.2% (91 patients) received pre-radiotherapy of primary tumour, 13.9%(33 patients)following disease progression, and 47.9% (114 patients) did not receive primary tumor radiotherapy (Table 1). Of the 91 patients with pre-radiotherapy of primary tumour, 49.5% (n = 44) received it within 30 days after EGFR-TKIs,

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50.5% ($n=47$) received it beyond 30 days after EGFR-TKIs and without disease progression. One hundred and twenty-five patients underwent metastases radiotherapy, including 29 in the D group, 35 in the R_{0-30} group, 36 in the R_{30-PD} group, and 25 in the R_{PD} group.

The median interval between the start of EGFR-TKIs and the start of radiotherapy was 32 days(range 0-281 days). The median interval between the SCTS and the execution of radiotherapy was 7 days.

Survival outcomes and OS analysis

The final follow-up was in July 2023, with a median follow-up of 23.3 months (range 12–74.3 months). At the last follow-up visit, 61 of 238 patients were still alive. The median survival time(MST) for all patients was 24.2 months (95% CI: 22.6–25.8), and the OS rates were 96.2% at 1 year, 50.3% at 2 years, 30.0% at 3 years, and 10.7% at 5 years. The OS rates at 1, 2, 3, 5 years for the R group and D group were 96.8%, 62.9%, 38.3%, 17.1%, and 95.6%, 37.7%, 21.8%, 2.9%, respectively; the corresponding MST was 29 months (95% CI: 24.3–33.7) for the R group and 22 months(95% CI: 20.4–23.6) for the D group ($\chi^2=13.480$, $p<0.001$) (Fig. 2). Univariate analysis results are shown in Table 2.Multivariate analysis revealed that primary tumor radiotherapy, Stage IVA, Adenocarcinoma, Oligometastasis, and Third generation EGFR-TKIs were independent predictors of prolonged OS(Table 3).

Landmark survival analyses

Among the four groups, The R_{30-PD} appeared to have the best OS (D group, $\chi^2=19.307$, $p<0.001$;R_{0-30} group, $\chi^2=11.687$, $p=0.01$; R_{PD} group, $\chi^2=4.086$, $p=0.043$; Figure3; Supplement Table 1).In the landmark analysis using 22 months time point, patients in the group R_{30-PD} had the most excellent long-term survival (D group, $\chi^2=14.254$, $p<0.001$; R_{0-30} group, $\chi^2=12.414$, $p<0.001$; R_{PD} group, $\chi^2=8.897$, $p=0.003$; Supplement Table 2; Fig. 1).

Radiation toxicity

The majority of lung radiation toxicities were grade 1. According to our observation, patients did not exhibit Grade 4–5 radiation toxicities. In 110 evaluable patients, there were 19 (17.3%) and 32 (29.1%) cases of grade≥2 radiation pneumonitis and esophagitis, respectively.

Discussion

Stage IV non-small cell lung cancer accounts for more than half of all cases [26]. Both National Comprehensive Cancer Network(NCCN)and European Society for Medical Oncology (ESMO) guidelines recommend systemic therapy as the cornerstone of comprehensive treatment according to result of Genetic testing [2, 3]. EGFR positive mutations are the most common mutation type for non-small cell lung cancer.The first-line treatment of Stage IV non-small cell lung cancer with EGFR positive
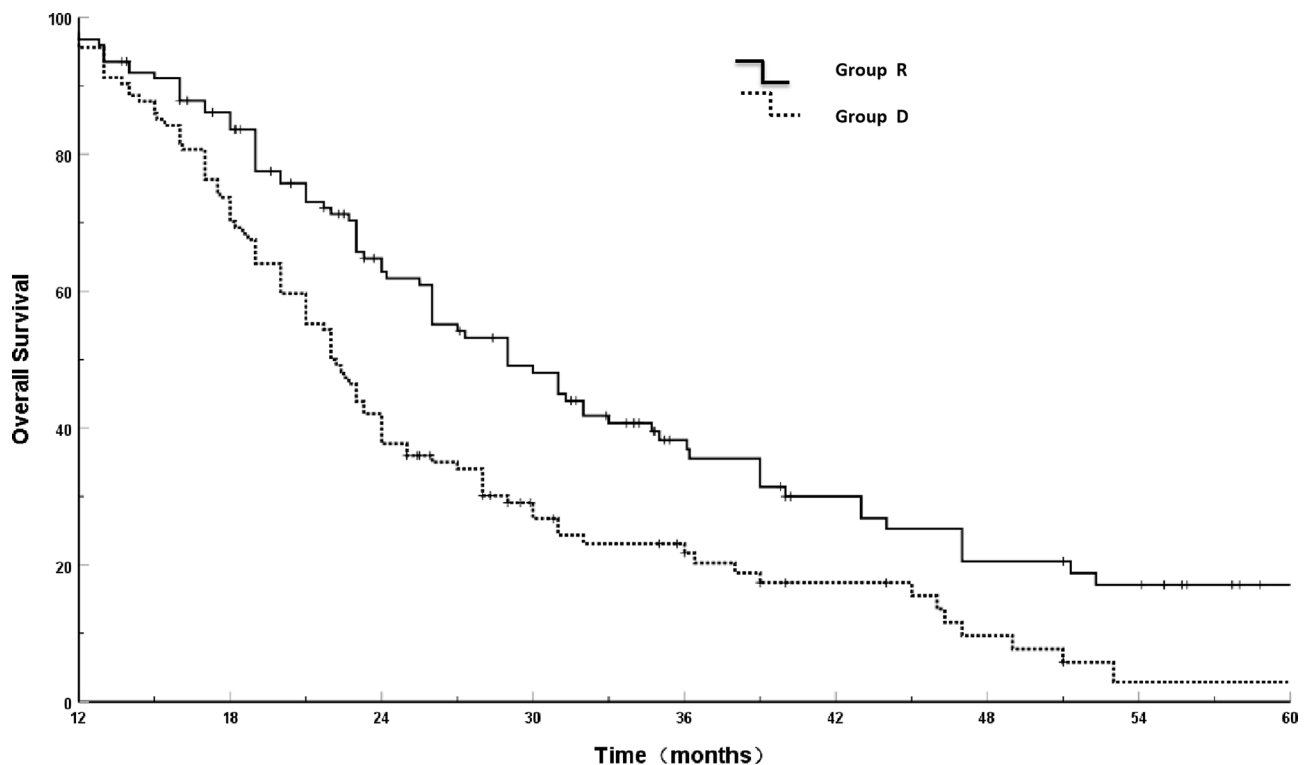
Fig. 2 Overall survival for Group R and D group
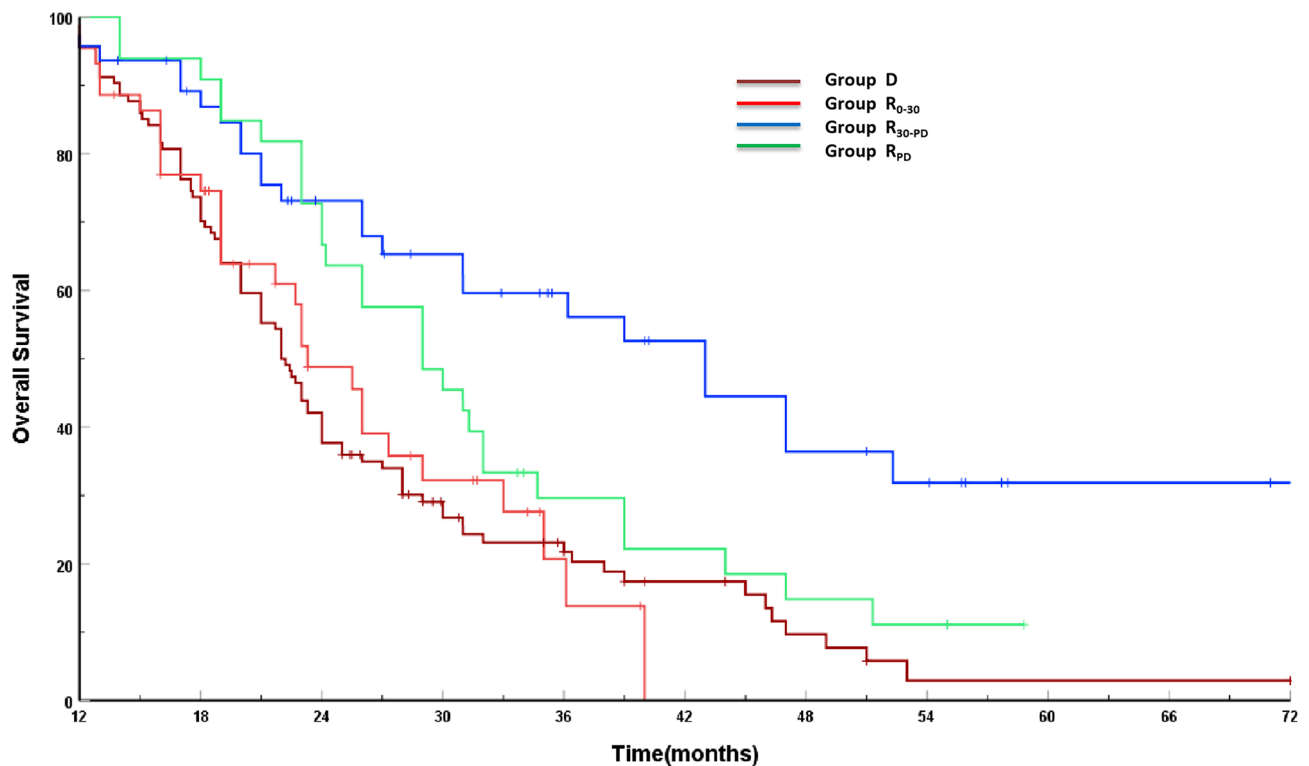
Fig. 3 Overall survival for Group R_{0-30}, R_{30-PD}, R_{PD} and D

mutations is undoubtedly EGFR-TKIs, due to better ORR and PFS, but ultimately it did not bring better overall survival [27, 28]. The main limiting factor is acquired drug resistance [15]. Studies have found that the most common failure of EGFR-TKIs is in the initial involved lesions, especially in the primary tumor [11, 12]. This failure pattern suggested the necessity of local radiotherapy intervention, which can not only improve local control [15, 29] but may also reduce the systemic reseeding of distant metastasis [11]. A number of studies have suggested that primary tumor radiotherapy before disease progression can significantly prolong PFS and OS [13–18, 30]. Radiotherapy also confered a survival benefit for non-small cell lung cancer with oligoprogression [18, 31, 32]. Our study also showed that the primary tumor radiotherapy significantly prolonged overall survival, as compared with such patients treated with EGFR-TKIs alone.

The overall survival of concurrent chemoradiotherapy was significantly better than sequential chemoradiotherapy for locally advanced non-small cell lung cancer [33]. Similar results have been obtained in studies related to Stage IV non-small cell lung cancer [34, 35]. However, compared with traditional systemic chemotherapy, EGFR-TKIs has no limit on the number of cycles and needs to be taken orally at all times. Radiotherapy performance before disease progression should always be a reasonable choice. A Study [36] performed byYen YC, et al. showed that the time between TKI initiation and

thoracic RT initiation was not uniform, 1–3 months in 29 patients(9.83%),4–6 months in 127 patients (43.05%), 9–12 months in 109 patients (36.95),and 10-12months in 30 patients (10.17%). Tang Y et al [19] suggested that local therapy can be adopted after two months after TKI initiation due to considerable shrinkage for TKI therapy. A radiotherapy timing analysis [20] based on tumour volume change recommended that the 40th day after targeted therapy may be a reasonable time to start radiotherapy for stage IV NSCLC with EGFR-positive mutations. Our study showed that patients receiving primary tumor radiotherapy from 30 days after EGFR-TKIs to pre-progression had better long-term OS than those with primary tumor radiotherapy within 30 days. The median interval between the SCTS and the execution of radiotherapy was 7 days.The data of our study showed that the majority of patients (n=201,84.5%) had stage T_{3-4} and/or N_{2-3}, which was similar to the data of previous studies [37–39]. Due to the relatively large gross tumour volume, premature radiotherapy may fail to achieve the radical radiation dose, so as to prolong OS. The incidence of radiation toxicities in EGFR-TKIs combined with radiotherapy was relatively common [25, 40–42]. If the radiation dose is increased blindly, it may lead to severe heart and lung injury, which may affect the quality of life and even endanger the life [20, 43]. Targeted therapy has a high ORR, and the primary tumor volume gradually shrinked after EGFR-TKIs to achieve the purpose of

Table 2 Univariable Analysis of Overall Survival

Variable		n	OS rates(years)%				Mean survival time (months)	Value	
			1	2	3	5		X^2	p
Sex	Male	100	96.0	49.5	27.9	8.4	24.0	0.549	0.459
	Female	138	96.4	50.9	31.7	12.3	25.0		
Age	<59	119	95.0	49.9	31.7	12.6	24.0	0.073	0.787
	≥59	119	97.5	49.7	28.3	9.1	24.2		
Histology	Adenocarcinoma	223	96.0	51.7	31.3	11.5	25.5	6.156	0.013
	other	15	86.7	26.0	8.7	0	21.0		
Smoking	Yes	174	94.6	45.8	24.2	6.0	24	2.558	0.110
	No	164	97.0	52.3	32.7	12.9	26		
T stage	T_{1-2}	77	97.4	57.1	35.1	5.6	27	0.647	0.421
	T_{3-4}	161	95.7	47.0	27.5	12.9	24		
N stage	N_{0-2}	93	95.7	50.4	34.1	15.4	25	0.653	0.419
	N_3	145	96.6	50.0	26.3	5.9	24.2		
M stage	IVA	55	98.2	59.0	45.5	17.2	30	6.504	0.011
	IVB	183	95.6	47.7	25.4	8.7	24		
Oligometastasis*	Yes	73	97.3	62.0	39.1	20.5	30	8.356	0.004
	No	165	95.8	45.3	26.1	6.4	23		
Bone metastases	Yes	137	94.9	50.9	26.0	4.4	25	3.401	0.065
	No	101	98.0	49.3	35.9	19.7	24		
Brain metastases	Yes	82	96.3	39.1	29.1	8.5	22	3.559	0.059
	No	156	96.2	56.2	30.2	11.8	26		
Lung metastases	Yes	88	97.7	46.5	31.1	12.9	23	0.004	0.948
	No	150	95.3	52.5	29.5	9.3	26		
Liver metastases	Yes	30	90.0	24.9	8.9	0	20	12.819	<0.001
	No	208	97.1	53.9	33.1	12.5	26		
Adrenal metastases	Yes	22	90.9	50.0	25.0	0	22.2	1.573	0.210
	No	216	95.8	50.3	30.7	11.5	24.2		
Other metastases	Yes	42	97.6	45.0	26.0	10.4	23	1.095	0.295
	No	196	95.9	51.5	30.9	11.2	25		
EGFR- mutation types	Exon 19	132	96.2	53.2	32.4	12.0	26	0.424	0.515
	Other**	106	96.2	46.8	27.1	8.9	24		
Systematic chemotherapy	Yes	83	97.6	58.3	31.3	7.8	28	0.954	0.329
	No	155	95.5	45.8	29.5	12.0	23		
Third generation EGFR-TKIs	Yes	108	96.3	61.7	39.1	15.5	31	11.014	0.001
	No	130	93.1	40.6	22.3	7.1	23		
Radiotherapy	Yes	153	96.7	58.5	36.4	14.6	28	12.105	0.001
	No	85	95.3	36.5	18.9	2.8	22		
Primary radiotherapy	Yes	124	96.8	62.9	38.3	17.1	29	13.480	<0.001
	No	114	95.6	37.7	21.8	2.9	22		
Metastases radiotherapy	Yes	125	96.0	55.4	33.7	11.0	26	1.449	0.229
	No	113	96.5	44.7	26.0	10.3	23		

*,Involving organs (≤3)and leisons (≤); **, Exon 18, Exon 21, T790M

Table 3 Multivariate analysis of overall survival

Variable	HR	95% CI	P
Primary tumor radiotherapy (yes vs. no)	0.574	0.422–0.781	<0.001
IVA vs. IVB	0.541	0.361–0.809	0.003
Adenocarcinoma vs. Other	0.449	0.250–0.808	0.008
Liver(no vs. Yes)	0.561	0.369–0.851	0.007
Third generation EGFR-TKIs (yes vs. no)	0.531	0.390–0.724	<0.001

HR, hazard ratio; CI, confidence interval

low damage and high radiation dose [19, 20]. Therefore, appropriate delay of primary tumour radiotherapy may be a better choice and premature radiotherapy may not be reasonable.

Acquired resistance is an inevitable defect of EGFR-TKIs. Studies showed that radiotherapy can prolong overall survival for patients with oligoprogressive disease in EGFR-mutated non-small cell lung cancer [18, 31, 32]. Our study suggested that primary tumor radiotherapy after disease progression(R_{PD}) similarly prolonged overall

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survival, but appeared to be detrimental to long-term OS compared with R_{30-PD}. Acquired resistance means that radiotherapy may miss the best opportunity to kill potential metastatic tumor cells [11, 44]. At this time, more metastatic lesions may occur except for that detected by systemic imaging due to the sensitivity and specificity of current examination. The volume of primary tumors increases after disease progression, and low damage and radical radiotherapy dose may not be achieved [20]for such patients. Previous studies of concurrent chemoradiotherapy in stage IV NSCLC have suggested that radiotherapy may have a greater survival benefit on the basis of chemotherapy effectivity [45, 46].Therefore, similar benefits may have been limited to EGFR-TKIs resistance. Some studies have confirmed the enhanced anti-tumor activity of EGFR-TKIs [47–49], and radiotherapy reduces EGFR-TKIs acquired resistance [50, 51]. However, whether these mechanisms between radiotherapy and EGFR-TKIs still exist is not clear while acquired resistance occurs. There may be many other unknown factors affecting this result, which need to be further explored.

In order to achieve high-quality long-term OS, the radiation toxicity is one of the focuses that must be paid attention to. A number of previous studies [25, 40–43] have showed that most of toxicity are grade 1–2 for NSCLC with comprehensive treatment of EGFR-TKIs and primary tumors radiotherapy and special attention should be paid to the occurrence of fatal radiation pneumonitis(RP).Our study showed the incidence of RP≥grade 2 was17.3% ($n=19$) and radiation esophagitis≥grade 2 was observed in 32 patients (29.1%). There were no fatal toxicity in our study.

Although the results of our study are very interesting and may have clinical implications for the appropriate timing of primary tumors radiotherapy, there are several limitations. First of all, the sample included only hospitalized patients, which may lead to selection bias. Second of all, the advantage of this research was a population of our hospitalized patients, single institution study is a non-negligible disadvantage. Third of all, the majority of patients received only first generation EGFR-TKIs($n=130,54.6\%$)and did not receive systemic chemotherapy ($n=155,65.1\%$). Finally, this was a retrospective study with inevitable bias. Therefore, randomized controlled trials are necessary to validate the findings of this study.

Conclusions
Our results showed that primary tumour radiotherapy may prolong long-term OS with acceptable toxicities. Appropriate delay(R_{30-PD})of primary tumour radiotherapy may be the best choice.Premature radiotherapy(R_{0-30}) and radiotherapy after disease progression (R_{PD}) may not be reasonable for long-term OS.

Potential biases should not be neglected: further randomized controlled trials are necessary to confirm this result.

Supplementary Information

Acknowledgements

Author contributions

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
This study was reviewed by the ethical review boards in China (Ethics Committee of Affiliated Cancer Hospital of Guizhou Medical University, GuiYang, China).

Competing interests
The authors declare no competing interests.

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