Concurrent afatinib and stereotactic body radiotherapy in patient with oligometastatic *EGFR*-mutated non-small cell lung cancer: a case report and literature review

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Background: Epidermal growth factor receptor (*EGFR*)-mutated patients treated with target therapy are inevitable to develop resistance to tyrosine kinase inhibitors (TKIs). It has been proved that concurrent stereotactic body radiotherapy (SBRT) and the first-generation TKIs can prolong both progression-free survival (PFS) and overall survival (OS) of *EGFR*-mutated patients with limited metastases. However, the efficacy and safety of concomitant second-generation TKIs and SBRT is still unknown.

Case Description: We for the first time present a stage IVA patient with mutation of both *EGFR* G719X and L861Q, who after initial response, had developed intracranial progression during afatinib monotherapy. With local treatment for the brain metastasis, she continued to receive afatinib and then a concurrent consolidative lung SBRT. Until January 2023, the patient had achieved a PFS of 24 months and OS of 32 months without serious adverse events except for a grade 1 radiation pneumonitis after the lung SBRT.

Conclusions: With this case and a literature review, we aim to demonstrate that concurrent afatinib and consolidative SBRT can bring prognostic benefits to oligometastatic NSCLC patients with uncommon *EGFR* mutations with good tolerance. However, larger studies with longer follow-up, including randomized controlled trials, are needed to better define the response rates, survival outcomes, and toxicity profiles of this combined therapy. Additionally, further research is required to determine the optimal timing for introducing SBRT in conjunction with afatinib.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); afatinib; stereotactic body radiotherapy (SBRT); case report

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Introduction

Lung cancer is the most common malignant tumor in China and has the highest mortality rate (1). From 2012 to 2016, the five-year survival rate for patients with stage IV lung cancer was only 8% (2). Since 2013, the mortality from non-small cell lung cancer (NSCLC) has declined remarkably due to the routine use of gene tests for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations,

along with targeted therapies in clinical practice (3). Patients receiving EGFR-TKIs (tyrosine kinase inhibitors) typically experience longer progression-free survival (PFS) and overall survival (OS) than those without targetable genetic mutations. However, the development of resistance to TKIs seems unavoidable, necessitating alternative therapeutic strategies. Recently, the use of stereotactic radiotherapy (SRT) to both primary tumors and metastatic sites before resistance develops has shown promising results in improving PFS and OS. Interim results from the SINDAS trial (NCT02893332) demonstrated that upfront concurrent stereotactic body radiotherapy (SBRT) combined with first-generation TKIs significantly improve the prognosis of patients with *EGFR*-mutated oligometastatic NSCLC (4). The more recent phase II LUNG-SORT trial (NCT04764214) demonstrated improved PFS with consolidative SBRT in metastatic NSCLC (mNSCLC) patients with oligo-residual disease after first-line treatment with third-generation EGFR-TKIs (5). While the third generation TKIs are well-recognized for their prognostic advantages over earlier generations (6,7), the second-generation TKI afatinib exhibited superior PFS compared to osimertinib (11.0 *vs.* 7.0 months) in patients with uncommon *EGFR* mutations (8). Nevertheless, the efficacy and safety of combining afatinib with SBRT remain unclear, as most existing evidence has been derived from studies involving the first- and third-generation TKIs. Meanwhile, this combined treatment has not been widely accepted due to concerns about the potentially increased risk of radiation-induced toxicity, such as radiation pneumonitis (RP), particularly when thoracic radiotherapy (RT) is administered concomitantly with TKIs (9). We present, for the first time, a case study of a stage IV NSCLC patient with both *EGFR* G719X and L861Q mutation. After treatment with afatinib and concurrent SBRT, has reached a long PFS and OS without any clinically significant adverse events. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-174/rc).

Highlight box

Key findings

- Concurrent stereotactic body radiotherapy (SBRT) and afatinib prolong both progression-free survival (PFS) and overall survival (OS) of epidermal growth factor receptor (*EGFR*)-mutated patients with limited metastases.

What is known and what is new?

- Concurrent SBRT and the first-generation tyrosine kinase inhibitors (TKIs) can prolong both PFS and OS of advanced *EGFR*-mutated non-small cell lung cancer (NSCLC).
- Here, we present a patient who got benefit in PFS and OS from concurrent SBRT and the second-generation TKIs afatinib with tolerable adverse effects.

What is the implication, and what should change now?

- Concurrent the second-generation TKIs afatinib and SBRT can bring prognostic benefits to oligometastatic NSCLC patients with uncommon *EGFR* mutations with good tolerance.

Case presentation

A 65-year-old female patient came to our department with a pulmonary mass in the right middle lobe. She denied any symptoms such as cough, hemoptysis, chest pain, or headache. Past history revealed no comorbidity and tobacco use. Physical examination found no positive signs with an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Chest computed tomography (CT) showed a lobulated and irregular-shaped 2.6 cm × 3.4 cm mass in the middle lobe of the right lung (*Figure 1A*). Brain magnetic resonance imaging (MRI) revealed a 2.3 cm × 2.5 cm metastasis with a narrow edema zone in the left frontal lobe (*Figure 1B*). The pulmonary mass was metabolically active with a maximum standardized uptake value (SUV) value of 9.8 as shown by Positron emission tomography-CT (PET/CT) (*Figure 1C*). A lung puncture biopsy was performed, and a pathological diagnosis of adenocarcinoma was confirmed (*Figure 1D*). Gene test revealed both 18 exon G719X (mutation abundance 15.24%) and 21 exon L861Q (mutation abundance 15.24%) in the EGFR gene at the same time. The clinical stage was cT2aN0M1b IVa according to American Joint Committee on Cancer (AJCC) 8th edition pathological staging system.

First-line TKI target therapy with afatinib 40 mg once a day has been administered since April 30, 2020. One month later, a thorax CT scan and brain MRI were repeated and revealed partial remission of both the lung tumor and brain metastasis (Figure S1A). Because the patient preferred a non-surgical treatment, we administrated hypofractionated SRT to the brain metastasis with 30 Gy in 5 fractions, 6 Gy/fraction/day (Figure S1B). One month after RT, the brain tumor showed a minor increase in size while no neurological symptoms were reported (Figure S1C). We considered this change might be a treatment effect of radiation instead of progression.

Seven months later, the patient gradually developed a headache. The brain MRI revealed that the metastasis grew

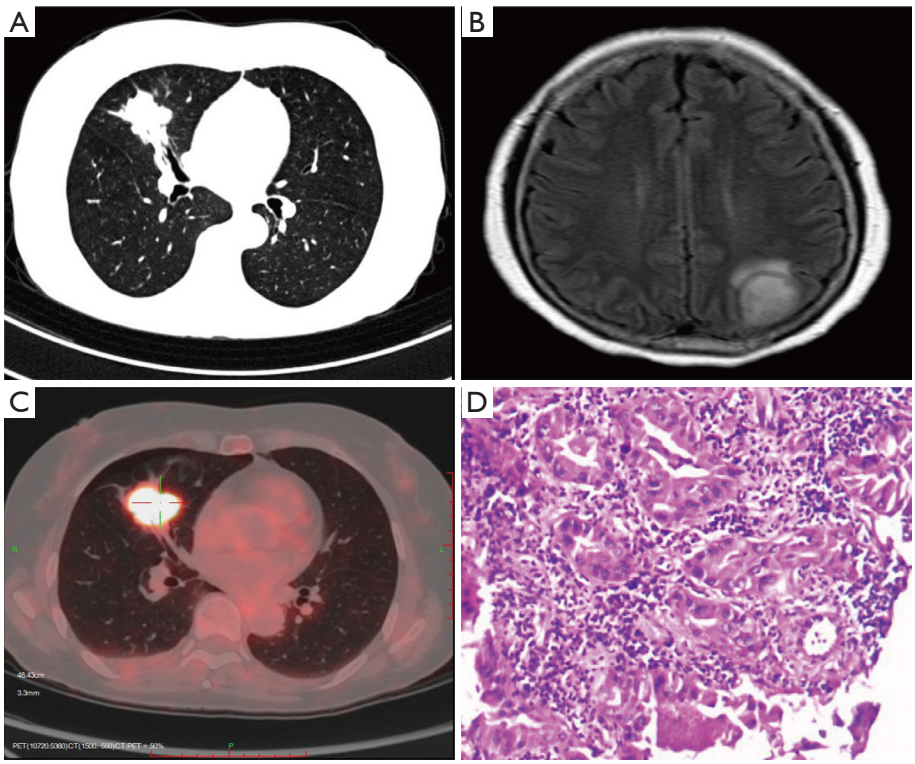

Figure 1 Imaging and pathological studies of the patient at initial diagnosis. (A) Chest CT scan (lung window) before treatment showed a 2.6 cm × 3.4 cm mass in the middle lobe of the right lung. (B) Brain MRI (T2 FLAIR) before treatment showed 2.3 cm × 2.5 cm metastasis with surrounding edema in the left frontal lobe. (C) PET/CT showed the metabolically active mass (maximum SUV value 9.8) in the right lung. (D) Hematoxylin and eosin staining of the lung biopsy (magnification, ×100). CT, computed tomography; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; PET, positron emission tomography; SUV, standardized uptake value.

from 1.5 cm × 1.4 cm to 2.1 cm × 1.8 cm (Figure S2A). Meanwhile, the right pulmonary tumor remained unchanged as shown by the subsequent thorax CT scans. Considering that the patient was going through a symptomatic intracranial oligo-progression, surgical resection was performed followed by a postoperative SRT thereafter (Figure S2B-S2F). Due to the large resection cavity volume (46 cc) and the previous irradiation history of this brain lesion, the constraints of the organs at risk could not be met if treated with a high-dose regimen of SRT. To achieve tolerable toxicity and an acceptable local control, a relatively low dose regimen of SRT, 25 Gy in 5 fractions over 1 week, was applied to this patient. The gene test of the resected brain metastasis remained the same as the initial lung tumor with both exon 18 G719X (mutation abundance 5.8%) and exon 21 L861Q (mutation abundance 6.5%) in the *EGFR* gene. Seven months later, the patient received a concurrent afatinib with SBRT with 50 Gy/5 fractions, 10 Gy/fraction/day, to the primary lung tumor (conformity index =0.98, gradient index =3.17, homogeneity index =1.48; lung V5 =17.52%, lung V20 =4.58%, lung V30 =2.59%, Dmean =412 cGy, V12 =241.03 cc) (*Figure 2*). Three months after completion of thorax RT, a grade 1 RP was detected during a routine follow-up chest CT scan (Figure S3). Up to January 2023, the patient was still alive, continued to use afatinib with good tolerance, and remained a stable disease.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

We reported a case of an oligometastatic NSCLC patient with

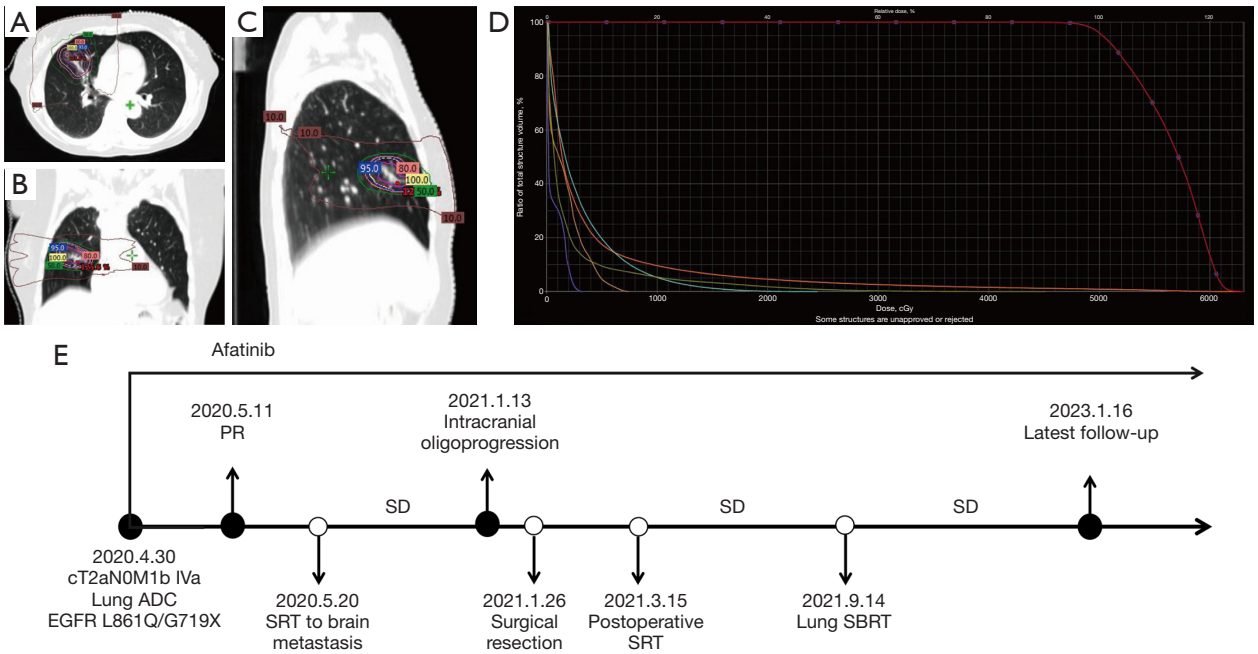

Figure 2 SBRT plan of right lung and timeline of treatment. (A-C) Isodose curve (A: axial, B: sagital, C: transverse). (D) Dose volume histogram (red: PTV, blue: heart, orange: lungs, yellow: esophagus, green: chest wall, purple: spinal cord). (E) Timeline of treatment. ADC, adenocarcinoma; PR, partial response; SD, stable disease; SBRT, stereotactic body radiotherapy; SRT, stereotactic radiotherapy.

both the *EGFR* G719X and L861Q mutations. Following first-line targeted therapy with afatinib combined with concurrent SRT to the brain metastasis and primary lung tumor, the patient achieved a PFS of 24 months and OS of 32 months. These outcomes are longer than the previously reported median PFS (8.2–13.8 months) and OS (12.1–26.9 months) of stage IIIb–IV NSCLC patients with *EGFR* G719X/L861Q mutations treated with afatinib (10). Furthermore, the patient showed good tolerance during the concurrent treatment of afatinib and SRT/SBRT. To our knowledge, this is the first case study of concurrent second-generation TKI afatinib and SBRT for *EGFR*-mutated NSCLC.

Retrospective studies and phase II randomized clinical trials (RCTs) have shown that local consolidative surgical resection and RT offer additional prognostic benefits for oligometastatic NSCLC patients beyond effective systemic treatment. This includes *EGFR*-mutated patients who are on target therapy (11-14). Despite high response rates, acquired resistance to TKIs is unavoidable for these patients. A real-world study found that 76.2% of disease progression occurred in original oligo-residual lesions in patients who did not receive local consolidative therapy before osimertinib treatment failed (15). Therefore, instead of being used as a salvage treatment after local progression on TKIs, upfront or consolidative local RT could suppress potentially resistant clones while still controlling sensitive clones which have not developed resistance yet (16). As early as 2011, a prospective study first uncovered the favorable outcomes of concurrent treatment with gefitinib or erlotinib and thoracic RT in mNSCLC patients (17). In recent years, several investigations have analyzed the efficacy and safety of concurrent treatment with TKIs and local RT, primarily focusing on mNSCLC (*Table 1*) (4,5,14,17-20). In a single-arm phase II study published in 2019, patients with mNSCLC received concurrent erlotinib/gefitinib and conventionally fractionated thoracic RT (14). The 1-year PFS rate (57.1%) and median PFS (13 months) were numerically higher than those observed in the ENSURE study, where patients receiving erlotinib monotherapy had a 1-year PFS rate of 43% and a median PFS of 11.0 months (21). Compared to conventionally fractionated or hypofractionated RT, SBRT demonstrates superior efficacy and safety, along with a shorter treatment duration. This approach reduces the risk of disease flare cause by discontinuing TKIs and minimizes the overlap of thoracic RT with simultaneous TKI treatment (22,23). Consequently, SBRT is being increasingly used as a local therapy for mNSCLC (24). Subsequent clinical trials have shown that EGFR-TKIs combined with concurrent

Table 1 Efficacy and toxicity of concurrent radiotherapy and EGFR-TKI treatment

Author	Year	Study design	TKI	RT regimen	Groups [n]	Median follow-up (months)	mPFS (months)	mOS (months)	≥ grade 3 toxicity
Zhou (5)	2024	Phase II single arm	Osimertinib, almonertinib	SBRT (25–50 Gy/≤5 F) to primary tumor and all metastases	61	21.1	29.9	not reached (80% CI, 33.6–NA)	Pneumonitis (1.6%), esophagitis (1.6%), leukopenia, cranial radiation necrosis (1.6%)
Peng (18)	2023	Phase II RCT	Gefitinib, erlotinib, icotinib	SBRT (30–50 Gy/5 F) to primary tumor and all metastases	TKI [31]	29.4	9.0	23.2	None
					SBRT + TKI [31]		17.6	33.6	
Wang (4)	2023	Phase III RCT	Gefitinib, erlotinib, icotinib	SBRT (25–40 Gy/≤5 F) to primary tumor and all metastases (patients with brain metastases were excluded)	TKI [65]	23.6	12.5	17.5	Skin rash (15.4%), RP (12.3%)
					SBRT + TKI [68]		20.2	25.5	Skin rash (14.7%), RP (7.4%)
Zheng (14)	2019	Phase II single arm	Erlotinib, gefitinib	Thoracic RT (54–60 Gy/27–30 F)	10	19.8	13	NA	RP (20%), skin rash (10%)
Borghetti (19)	2019	Retrospective	Gefitinib, erlotinib, afatinib, crizotinib osimertinib	SRT/HRT (30 Gy/10 F, 20 Gy/5 F, 8 Gy/1 F) to primary tumor and metastases	106	9.1	NA	23	None from thoracic RT group
Xu (20)[†]	2018	Retrospective	Gefitinib, erlotinib, icotinib	SRT (21–27 Gy/1 F, 26.5–33 Gy/3 F, 30–37.5/5 F), EBRT (60 Gy/30 F, 45 Gy/15 F), WBRT (30 Gy/10 F) to primary tumor and metastases	All-LAT [51]	38	20.6	40.9	RP (7.7%), radiation esophagitis (16.9%)
					Part-LAT [55]		15.6	34.1	
					Non-LAT [39]		13.9	30.8	
Wang (17)	2011	Prospective	Gefitinib, erlotinib	Thoracic RT with CRT, IMRT, γ-SBRT (42–82 Gy)	25	10.2	10.2	21.8	RP (4%), radiation esophagitis (4%)

[†], all-LAT group: consolidative LAT to all oligometastatic sites; part-LAT group: consolidative LAT to either primary tumor or oligometastatic sites; non-LAT group: did not receive any consolidative LAT. CI, confidence interval; CRT, chemoradiotherapy; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; EBRT, external beam radiation therapy; HRT, hypofractionated radiotherapy; IMRT, intensity-modulated radiation therapy; LAT, local ablative therapy; mPFS, median progression-free survival; mOS, median overall survival; NA, not available; RT, radiotherapy; RCT, randomized clinical trial; RP, radiation pneumonitis; SBRT, stereotactic body radiation therapy; SRT, stereotactic radiotherapy; WBRT, whole brain radiation therapy.

Table 2 Incidence of ≥3 grade RP in concurrent thoracic RT and TKI treatment

Author	Year	Study design	TKI	RT regimen	Cases [n]	Median follow-up (months)	Median time to develop RP (months)	≥3 grade RP
Jia (35)	2020	Retrospective	Osimertinib	Conventional fractionated RT and SBRT (30–64 Gy, 2–5 Gy/F)	IIIB–IVB [11]	7.8	3.0	45.4%
Jia (22)	2021	Retrospective	Gefitinib, erlotinib, icotinib	Conventional fractionated RT and SBRT (39–72 Gy, 2–12 Gy/F)	IIIB–IVB [67]	15.3	3.5	8.96%
Xu (36)	2021	Retrospective	Gefitinib, icotinib, erbtinib	Conventional fractionated RT (50–60 Gy, 2 Gy/F)	IIIA–IIIB [45]	62.7	2.5	6.7%
Akamatsu (37)†	2021	Prospective	Gefitinib	Conventional fractionated RT (64 Gy, 2 Gy/F)	IIIA–IIIB [28]	51.8	2.4	0%
Yang (38)	2022	Retrospective	Gefitinib, erlotinib, icotinib, afatinib (55.4%)	Conventional fractionated RT (50–66 Gy, 2 Gy/F)	III–IV [85]	6	NA	16.5%
Banla (34)	2023	Retrospective	Osimertinib	Conventional fractionated RT and SBRT (24–66 Gy, 2–12 Gy/F)	III–IV [22]	10.2	2.2	4.5%

†, 16 patients (59%) developed grade 1 and 8 patients (30%) developed grade 2 RP, 8 patients had discontinued treatment because of RP. NA, not available; RP, radiation pneumonitis; RT, radiotherapy; SBRT, stereotactic body radiotherapy; TKI, tyrosine kinase inhibitor.

SBRT to metastases and primary tumor significantly improved PFS and OS in *EGFR*-mutated oligometastatic NSCLC compared to TKI alone (4,5,18). This finding is supported by retrospective studies that noted a more marked survival benefit from local consolidative treatment to all residual diseases (19,20). For patients with synchronous brain metastasis, the role and timing of brain RT have been debated (25-27), especially since third-generation TKIs have notably improved intracranial control (28). A recent real-world study showed that combining TKIs with brain RT as first-line treatment leads to prolonged intracranial PFS compared to TKIs alone (16.0 *vs.* 9.0 months, P<0.001) (29). Retrospective analysis has revealed that upfront craniocerebral RT improves both OS and PFS in osimertinib-treated patients with oligo-brain metastases (30). The ongoing NCT03769103 and completed NCT03497767 phase II trials are both designed to compare the use of osimertinib with and without stereotactic radiosurgery (SRS) in patients with brain metastasis.

Afatinib is now widely used in mNSCLC patients harboring uncommon *EGFR* mutations, thanks to the efforts of LUX-LUNG 2/3/6 studies (10). Despite its unique advantages for this patient group, the clinical efficacy and safety of combining afatinib with concurrent local RT have not been thoroughly examined, as most patients in previous studies and ongoing clinical trials (NCT05089916, NCT03667820, NCT06014827) have received first- or third-generation TKIs (4,5,18,31). In 2014, Akin Atmaca *et al.* reported a case of concurrent afatinib and conventional fractionated thoracic RT to relieve upper vena cava compression, leading to a partial response of the irradiated tumor and pulmonary metastases (32). Eze *et al.* reported a case of concomitant afatinib and whole brain radiotherapy (WBRT) in a NSCLC patient with *EGFR* 19del mutation, resulting in near-complete regression of neurological symptoms (33). Both cases did not report any clinically significant toxicities.

Pneumonitis has been a major obstacle limiting the application of concurrent thoracic RT and TKI treatment (22,34-38) (*Table 2*). While the toxicities associated with concurrent TKIs and SBRT are generally tolerable, RP and skin rash caused by target therapies are the most common severe adverse events (*Table 1*). Compared to conventionally fractionated thoracic RT, SBRT is associated with a lower risk of RP (6.7% with grade ≥2, 0.4% with grade 3 RP) (39). For the present case, we chose SRT rather than WBRT as the initial consolidative therapy for brain metastasis, as WBRT can result in cognitive deterioration, especially among long-term survivors. Previous studies have also

found that WBRT fails to provide OS or intracranial PFS benefits (25,40). However, it has been reported that patients on TKIs have an elevated risk of radiation cerebral necrosis after stereotactic radiosurgery than those who are not on TKIs (41).

We speculated that this new mode of concurrent afatinib and SBRT may offer a promising strategy to further prolong PFS and OS in mNSCLC patients with uncommon *EGFR* mutations. Our case is the first one to demonstrate the efficacy and safety of concurrent thoracic SBRT and afatinib, as far as we know. Nonetheless, we acknowledge the limitations of our treatment strategy. The patient failed to receive an upfront surgical resection of the brain metastasis out of personal preference, which may preclude the risk of late onset brain necrosis potentially induced by the re-irradiation of brain.

Conclusions

We present the first case of a patient who, after concurrent treatment with the second-generation TKI afatinib and thoracic SBRT, has achieved a sustainable PFS of 24 months and OS of 32 months with good tolerance. Due to the scarcity of clinical data, the exact response rate, long-term survival outcome, and toxicity profile of this combined therapy remain to be further clarified. Moreover, a large-scale randomized control study is also needed to determine the optimal time for adding SBRT to afatinib treatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-24-174/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-24-174/prf

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-174/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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