Strahlentherapie und Onkologie (2025) 201:645–655
https://doi.org/10.1007/s00066-024-02360-1

ORIGINAL ARTICLE

Efficacy and toxicity of stereotactic radiotherapy combined with third-generation EGFR-TKIs and immunotherapy in patients with brain metastases from non-small cell lung cancer

Xiaoxuan Tao[1] · Qichang Gao[2] · Yiyang Chen[1] · Nannan Cai[1] · Chuncheng Hao[1]

Received: 19 May 2024 / Accepted: 23 December 2024 / Published online: 26 February 2025

Abstract

Objective Stereotactic radiotherapy (SRT) is fast gaining attention as a preferred treatment alternative for patients with brain metastases (BM) from non-small cell lung cancer (NSCLC). In this study, we examined the efficacy and safety of combining SRT with immunotherapy (IT) and targeted therapy (TT), either separately or concurrently with the aim to formulate an optimal therapeutic regimen for patients with NSCLC BM.

Methods The combination therapy were comprised of IT and TT agents. For the SRT-combined TT agents group, TT was limited to third-generation EGFR-TKIs. The administration of these drugs within 30 days before or after SRT was defined as combination therapy. The primary endpoint was 1-year progression-free survival (PFS), which was evaluated by a blinded independent review committee and categorized into local recurrence at the radiation site and the emergence of new distant intracranial metastases. Secondary endpoints included confirmed intracranial objective response rate (IORR) and intracranial disease control rate in the overall population. Post-treatment grading was performed according to CTCAE, and the levels of radiation necrosis were differentiated.

Results The 266 patients with NSCLC BM were categorized into the following four groups based on their treatment methods: SRT alone, SRT combined with IT, SRT combined with third-generation EGFR-TKIs, and SRT combined with both IT and TT. For the local radiation range, the 1-year PFS of these four groups were 77.89% ($P=0.239$), 88.75% ($P=0.266$), 88.01% ($P=0.210$), and 91.97% ($P=0.057$), respectively. For new intracranial metastases outside of the radiotherapy site, the corresponding values were 63.96% ($P=0.039$), 74.17% ($P=0.258$), 88.70% ($P=0.024$), and 87.81% ($P=0.015$), respectively. By the end of the study period, the IORR increased from 32% with SRT alone to 46% in the IT group, 58% in the TT group, and 61% in the SRT combined with both the IT and TT groups. However, the group that received SRT in combination with IT and TT exhibited a higher occurrence rate of grade 3 adverse events, and a statistically significant difference was observed in grade 3 radiation necrosis.

Conclusion For NSCLC BM, IT, TT, or both together with SRT increased the distant intracranial tumor control. Nonetheless, combining SRT with both IT and TT increased the occurrence rate of acute adverse events. Thus, while SRT provided good local control independently, the incidence of symptomatic RN was low.

Keywords Stereotactic radiosurgery (SRT) · Immunotherapy (IT) · Targeted therapy (TT) · Non-small cell lung cancer (NSCLC) · Brain metastases (BM)

XT and QG contributed equally to this work. XT conducted statistical analysis of data and wrote the manuscript; QG calculated radiological statistics and plotted the curve; YC collected radiological data; NC collected clinical data. HC revised the manuscript.

Xiaoxuan Tao
x1173239378@163.com

✉ Chuncheng Hao
HaoChuncheng1980@163.com

[1] Department of Radiation Oncology, Harbin Medical University Cancer Hospital, Harbin, China

[2] The 1st Affiliated Hospital of Harbin Medical University, Harbin, China

Introduction

Primary lung cancer is a common tumor type with hypermalignancy and occupies the second position globally in terms of incidence and mortality rates [1]. Non-small cell lung cancer (NSCLC) with brain metastases (BM) occurs in 30–64% of advanced NSCLC cases [2, 3]. The central nervous system (CNS) is a common location for NSCLC metastases in the late stages [4, 5]. Without timely treatment, the median survival is only 1–5 months [6, 7]. The primary treatments for NSCLC BM include whole-brain radiation therapy (WBRT), stereotactic radiotherapy (SRT) [8], targeted therapy (TT), and immunotherapy (IT) [4]. When compared with WBRT, SRT offers advantages such as higher precision, rapid dose fall-off, fewer cognitive side effects, and better preservation of healthy tissues [9, 10]. SRT is usually used to treat patients with ≤4 BM. However, recent studies evaluated the therapeutic effect of SRT in treating patients with ≥15 BM [11]. Radiation primarily causes cell death via DNA damage, as well as facilitates antitumor immunity by releasing tumor antigens, enhancing antigen presentation, and releasing proinflammatory signals [12]. Furthermore, SRT may alter the tumor microenvironment to enhance the invasion of activated T cells [13]. Owing to this immunomodulatory effect, the combined application of radiation therapy and IT has become an attractive option [14]. Although SRT has demonstrated efficacy, systemic treatments continue to face considerable challenges. Because of the presence of the blood-brain barrier (BBB), several systemic agents cannot reach intracranial blood levels, which makes the CNS a refuge for metastases [15]. This barrier limits the effectiveness of systemic therapies for BM. Recently, EGFR-TKIs were identified as an efficient treatment for patients with NSCLC BM in the AURA3 and FLAURA studies [16]. Osimertinib has great BBB penetrability into the CNS [17] and could prolong the median overall survival by 6.8 months and reduce the risk of mortality by 20% [18]. In addition to the survival benefit, TT can enhance the modulation of tumor-adaptive immunity [19, 20]. However, there is a dearth of research on the efficacy and adverse reactions of combining SRT with IT and TT for NSCLC BM. Therefore, this study focused on NSCLC BM treatment efficacy and the safety of patients treated with SRT combined with different treatment modalities.

Methods

Patient sample

Detailed patient characteristics are presented in Table 1. In this study, data were retrospectively collected and analyzed from 645 patients diagnosed with NSCLC-related BM at the Harbin Medical University Affiliated Cancer Hospital from February 2020 to March 2024. In accordance with the inclusion criteria, 266 patients with a total of 501 brain lesions were enrolled in the study, and the main pathological subtype was identified to be lung adenocarcinoma. The major exclusion criteria are illustrated in Fig. 1. Patients included in the study did not exhibit any signs of herniation, had an anticipated survival period of at least 3 months, had not undergone surgical treatment for cerebral metastatic lesions, and had a Karnofsky Performance Status score of ≥70. All patients had primary histologic

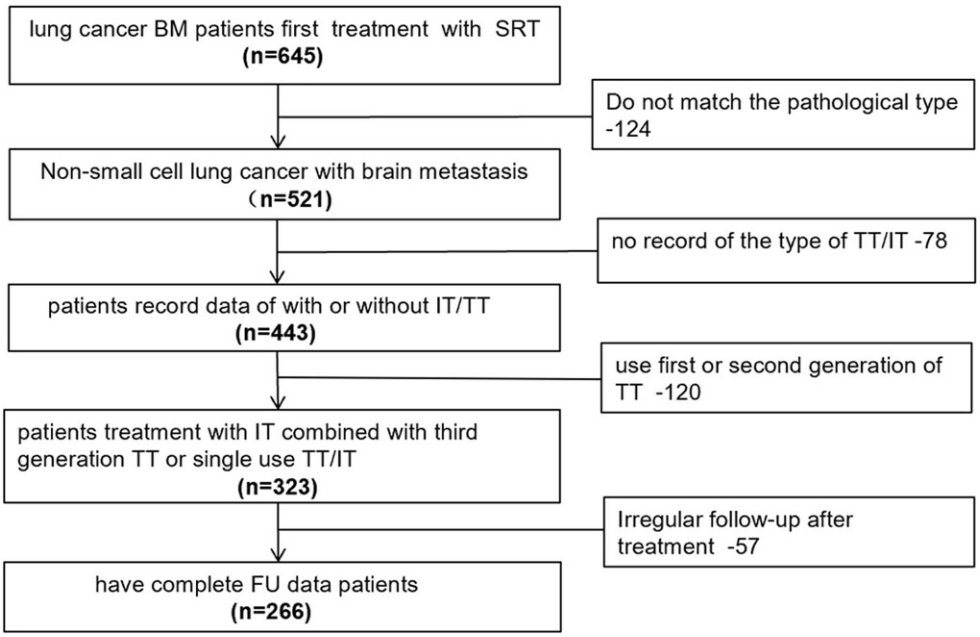

Fig. 1 Exclusion criteria

Table 1 Characteristics of patients in different groups

	Patients treated by SRT without TT/IT ($n=73$)	Patients treated by SRT with IT ($n=65$)	Patients treated by SRT with TT ($n=62$)	Patients treated by SRT with IT and TT ($n=66$)
Age	60	58	56	62
In years median	(43–79)	(43–79)	(47–63)	(53–70)
Female/male ratio	36:37	30:35	30:32	41:25
KPS in %	81 (70–93)	81 (71–96)	79 (70–90)	80 (70–94)
Pathological type				
Adeno carcinoma	45	47	45	42
Squamous	9	3	10	10
Neurendocrine	10	7	2	4
Large cell lung cancer	6	4	2	6
Adenosquamous carcinoma	3	4	3	4
Number of brain metastases				
Single metastases	18	15	14	18
Multiple metastases	55	50	48	48
Multiple other metastases	6	15	8	26
Size of brain metastases(cc)				
0 ~ 1	18	12	15	13
1 ~ 2	18	10	8	10
2 ~ 3	19	17	19	22
3 ~ 4	51	26	17	14
4 ~ 10	10	53	62	45
> 10	4	9	12	17
Location of brain metastases				
Frontal	23	30	25	39
Parietal	21	23	20	23
Occipital	21	19	15	25
Temporal lobe	15	21	33	26
Basal ganglia	12	7	10	9
Brainstem	6	4	7	6
Parencephalon	10	16	25	10
EGFR mutation				
EGFR-wt	34	16	2	5
EGFR-mut	23	9	54	50
Unknown/NA	16	40	6	11
Diagnosis-specific, DS-GPA				
3 ~ 4	23	16	14	16
2 ~ 3	12	23	29	19
1.5 ~ 2	18	14	10	11
1 ~ 1.5	14	9	4	12
0 ~ 1	6	3	5	8

types limited to NSCLC. The patients were accordingly categorized into the following four groups depending on the treatment modalities: SRT-alone, SRT combined with IT, SRT combined with TT, and SRT combined with both IT and TT. Concomitant medication was defined as drugs administered during SRT or within 30 days before or after SRT.

Figure 1 shows the exclusion criteria for patients—a total of 645 patients first treatment with SRT. Among these patients, 124 patients did not match the pathological type of NSCLC; 78 patients had no medication records; 120 patients had not applied third-generation EGFR-TKIs; 57 patients lost follow-up data.

Table 1 describes the details of characteristics of the four groups including those with patients treated with SRT and SRT combining IT or TT and those who were treated with a combination of SRT and IT with TT. Diagnosis-specific, DS-GPA: Regarding the GPA scoring system for lung cancer BM, the scores were assigned as follows: age: >60 years: 0 points; 50–60 years: 0.5 points; <50 years: 1 point; Karnofsky Performance Status (KPS): <70: 0 points; 70–80: 0.5 points; 90–100: 1 point; number of BM: >3: 0 points; 2–3: 0.5 points; 1:1 point; Extracranial Metastases: Present: 0 points; Absent: 1 point. The total score of these parameters constitutes the DS-GPA score.

Stereotactic radiotherapy

A novel fixation method was adopted for SRT, which included a thermoplastic mask, a headrest, and a shield adjuster that connected the mechanical interface to the therapy device (all provided by Elekta). The patients were positioned using the mask on a 1.5-Tesla magnetic resonance imaging (MRI) scanner, and gadolinium-enhanced T1-weighted MRI sequences were used to acquire localization images. After determining the BM treatment plan, CBCT was performed in Leksell Gamma Plan® to obtain stereotactic references during the treatment and for planning purposes, ensuring 100% coverage of the lesion. The treatment was administered using the Leksell Gamma Knife® Icon™. The BMs were planned on isodose lines at 50% (SRT: 50, 40–90%; IT: 50, 40–90%; TT: 50, 40–90%; TT + IT: 50, 40–90%). The median prescribed dose was 18 Gy (SRT: 18, 10–20 Gy; TT: 18, 8–20 Gy; IT: 18, 8–20 Gy; TT + IT: 18, 6–21 Gy), and the median central dose was 36 Gy (SRT: 30, 20–42 Gy; TT: 36, 24–60 Gy; IT: 36, 24–60 Gy; TT + IT: 36, 28–70 Gy). Selection criteria for single-fraction treatment included total lesion volume <25 cc, good patient condition, minimal edema, the target being distant from critical structures (e.g., brainstem, optic nerve), and total treatment time <30 min. The prescribed dose ranged from 18 to 21 Gy. For other patients, multi-fraction SRT was used, with regimens such as 10 Gy for 2 days consecutively, 9 Gy for 3 fractions with 1-day intervals, 8 Gy for 4 fractions, or 6 Gy for 5 fractions, with a 1-day interval.

Follow-up and assessment results

Endpoint analysis included the assessment of progression-free survival (PFS), which were comprised of progression at the local radiation site and distant intracranial progression outside the irradiated area. Death was a reason to censor in the K-M curve. The next endpoints were the IORR and intracranial disease control rate (IDCR). IORR denoted the proportion of patients achieving complete response (CR) or partial response (PR) in the intracerebral lesions after treatment. On the contrary, IDCR signified the proportion of patients achieving CR, PR, and stable disease (SD) in the intracerebral lesions after treatment. Both endpoints were applied to evaluate the response of the intracerebral lesions to treatment. Following SRT, patients underwent a brain MRI every 3 months. Using a 3D-slicer, post-treatment tumor volumes were calculated from the MRI images acquired 3 months after SRT and then compared with the pretreatment volumes documented in the Leksell Gamma Plan®. All CNS scans were evaluated by an independent neuroradiologist (CNS BICR) according to the revised RECIST 1.1 guidelines. The treatment efficacy was assessed by comparing the tumor volume changes after 3 months of SRT-alone, SRT combined with IT, SRT combined with TT, and SRT combined with both IT and TT. The intracranial objective response rate (IORR) were comprise of the following four key components: CR: complete regression of the tumor, which lasted ≥4 weeks; PR: the summation of the target lesion diameters decreased by ≥30%, which was maintained for at least 4 weeks; SD: between the range of PR and PD; progressive disease (PD): the summation of the target lesion diameters increased by ≥20% or new lesions appeared. Patient status was decided according to CTCAE v4.03.

Statistical analysis

Descriptive statistics were applied to analyze the patients in different groups, including the median and range of successive variates or the count and percentage of categorical variates. The Kaplan-Meier method was employed to compute the time from the diagnosis of BM to progression. Patients without progression, those who were lost to follow-up, and deaths due to reasons other than SRT were censored. Univariate analysis was performed using the Cox proportional hazards model, and clinically relevant variables were included in the multivariate Cox proportional hazards model. Furthermore, rank tests were performed to assess otherness between different groups. SPSS version 22 was used for the analysis. Waterfall plots were used to compare the IORR, and statistical significance was defined as $p < 0.05$.

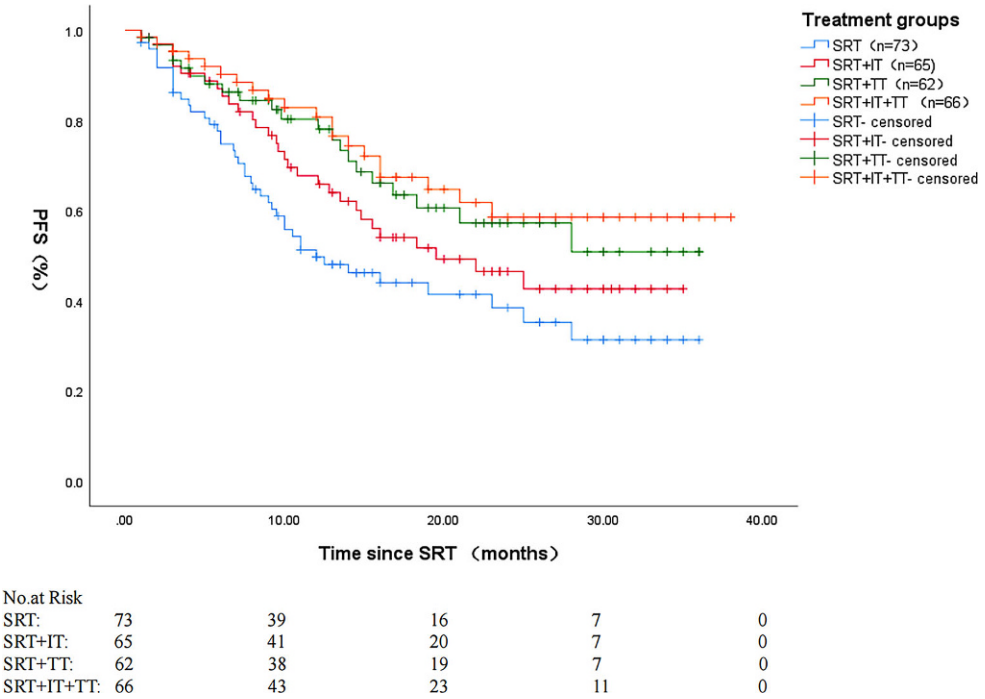

Fig. 2 Intracranial PFS

Results

Patients

Initially, the 266 included patients were categorized into four groups based on their treatment methods. The median time from first diagnosis of BM to treatment was 1 month (0–9 months). There were 42/501 lesions of >10 cc, 645 patients with lung cancer BM in the institution, and 124 patients who did not match the pathological type of NSCLC. Moreover, there were 78 patients with no records of immunologic or targeted drug use, 120 patients who were still on first-generation or second-generation EGFR-TKIs, 57 patients who were lost to follow-up, and 266 patients who were eligible for the study. A total of 73 (27%) patients were treated with SRT-alone; 65 (24%) were treated with SRT combined with IT, 62 (23%) were treated with SRT combined with TT, and 66 (25%) were treated with SRT combined with IT and TT. The SRT combined IT and TT treatment group included two subgroups: one receiving first-line combined IT and TT before SRT and the other receiving oral TT before SRT followed by IT. However, there was no significant difference in the recurrence rates between the two subgroups. ($P=0.059$).

Progression-free survival

A total of 42% (113/266) of patients included in the study developed intracranial progression, which included 76 patients who developed intracranial progression within 1 year, accounting for 67% of the patients who relapsed at the study endpoint. Of these, 35.5% (27/76) patients developed progression locally at the irradiated sites within 1 year and 64.5% (49/76) developed intracranial progression at distant sites without radiation within 1 year. Thirty-five patients who were newly diagnosed with BM underwent SRT therapy again, and the median follow-up time for PFS was 10.50 (0–36) months in SRT-alone group, 13.50 (0–35) months in SRT combined with IT group, and 13.75 (0–36) months in SRT combined with TT group. The median follow-up time in SRT combined with the IT and TT group was 14.75 (0–38) months. For these four different groups, SRT-alone, SRT combined with IT, SRT combined with TT, and SRT combined with IT and TT, the overall 12-month PFS was 49.73%, 65.89% (HR, 0.63 [95% CI: 0.32–1.24]. $P=0.183$), 78.05% (HR, 0.38 [95% CI: 0.18–0.76]; $P=0.007$), and 80.76% (HR, 0.32 [95% CI: 0.16–0.65]; $P=0.001$) (Fig. 2). The 1-year PFS of the local intracranial radiation site in these four groups were 77.89% ($P=0.239$), 88.75% (HR: 0.607, 95% CI [0.251–1.465], $P=0.266$), 88.01% (HR: 0.556, 95% CI [0.221–1.394], $P=0.210$), and 91.97% (HR: 0.366, 95% CI [0.130–1.029], $P=0.057$) (Fig. 3), respectively. The 1-year PFS of new intracranial (distant intracranial failure outside of the radiotherapy site) BM in the respective groups were 63.96% ($P=0.039$), 74.17% (HR: 0.726, 95% CI [0.417–1.264], $P=0.258$), 88.70% (HR: 0.480, 95% CI [0.253–0.908], $P=0.024$), and 87.81% (HR: 0.459, 95% CI [0.246–0.858], $P=0.015$) (Fig. 4). Patients treated with SRT combined with IT

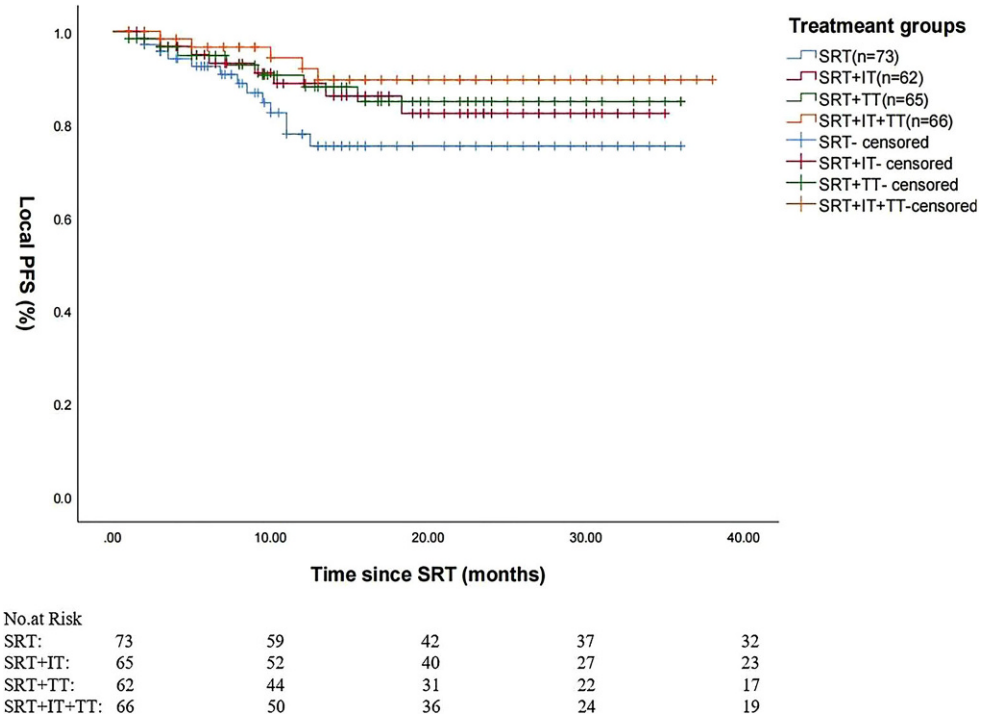

Fig. 3 Local PFS

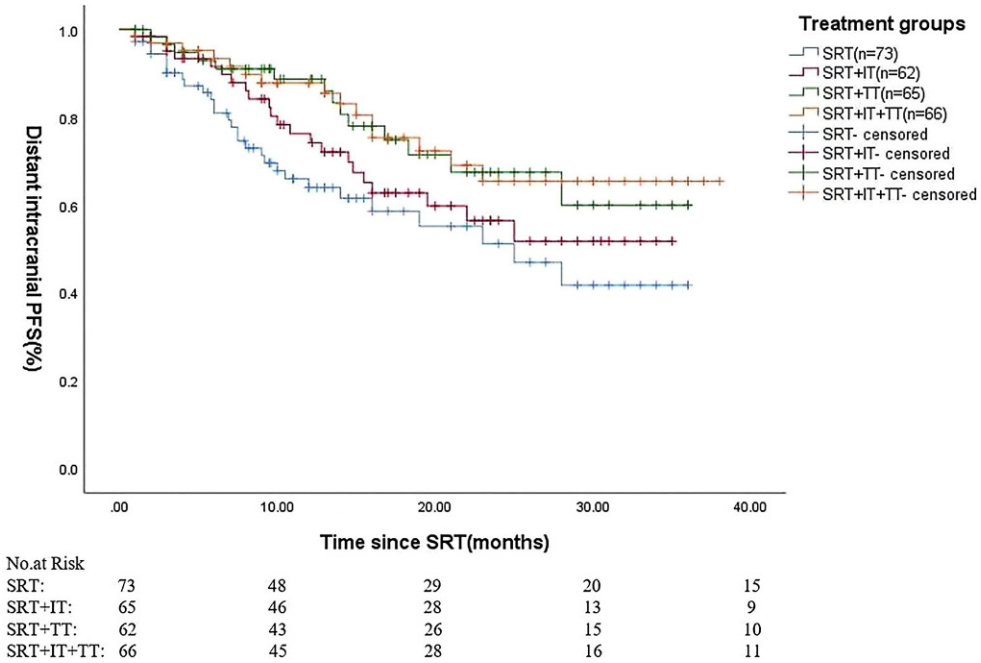

Fig. 4 Distant intracranial PFS

and TT displayed better PFS than those treated with SRT-alone, SRT combined with IT, and SRT combined with TT.

Figure 2 shows the overall intracranial PFS. The 1-year PFS rate for SRT-alone was 49.73%, that for SRT combined with IT group was 65.89% (HR 0.63 [95% CI: 0.32–1.24]; $P=0.183$), that for SRT combined with TT group was 78.05% (HR 0.38 [95% CI: 0.18–0.76]; $P=0.007$), and that for SRT combined with both IT and TT was 80.76% (HR 0.32 [95% CI: 0.16–0.65]; $P=0.001$).

Figure 3 depicts local radiation-range recurrence in different treatment modalities. The 1-year PFS for local recurrence at the radiation site was 77.89% for SRT-alone ($P=0.239$); 88.75% for SRT combined with IT (HR: 0.607, 95% CI [0.251–1.465], $P=0.266$); 88.01% for SRT combined with third-generation EGFR-TKIs (HR: 0.556, 95% CI [0.221–1.394], $P=0.210$), and 91.97% for SRT combined with both IT and third-generation EGFR-TKIs (HR: 0.366, 95% CI [0.130–1.029], $P=0.057$).

Table 2 BM response of different treatments assessed by BICR

	SRT($n=73$)	IT + SRT($n=65$)	TT + SRT($n=62$)	IT + TT + SRT($n=66$)
Best objective response, No. (%)	23 (32)	30 (46)	36 (58)	40 (61)
CR	4	8	15	17
PR	19	22	21	23
IORR, % (95%CI)	32 (21 to 42)	46 (34 to 59)	58 (45 to 71)	61 (49 to 73)
OR (95%CI)	–	0.54 (0.27 to 1.07)	0.33 (0.16 to 0.67)	0.32 (0.16 to 0.64)
P	–	0.08	0.002	0.001
IDCR, % (95%CI)	44 (32 to 55)	52 (40 to 65)	66 (54 to 78)	71 (60 to 82)
OR (95%CI)	–	0.71 (0.36 to 1.39)	0.40 (0.20 to 0.81)	0.34 (0.17 to 0.68)
P	–	0.321	0.010	0.002

CR Complete Response, *PR* Partial Response, *IORR* Intracranial Objective Response Rate, *OR* Odds Ratio, *IDCR* Intracranial Disease Control Rate

Figure 4 depicts distant intracranial recurrence beyond the local radiation range. For new intracranial metastases, the 1-year PFS was 63.96% for SRT-alone ($P=0.039$); 74.17% for SRT combined with IT (HR: 0.726, 95% CI [0.417–1.264], $P=0.258$); 88.70% for SRT combined with third-generation EGFR-TKIs (HR: 0.480, 95% CI [0.253–0.908], $P=0.024$); 87.81% for SRT combined with both IT and third-generation EGFR-TKIs (HR: 0.459, 95% CI [0.246–0.858], $P=0.015$).

Tumor intracranial objective response rate

Only 5% of the patients in the SRT-alone group achieved CR at a median time of 8.9 (3–13.5) months, 12% of the patients in the SRT combined with IT group achieved CR at a median time of 6.25 (2–16) months, and 24% of the patients in the SRT combined with TT group achieved CR at a median time of 8.2 (1–17) months. In addition, 26% of the patients in the SRT combined with IT and TT group achieved CR, and the median time to CR was 14 (1–22) months, which was longer than that in the other treatment groups. This difference could be attributed to the higher

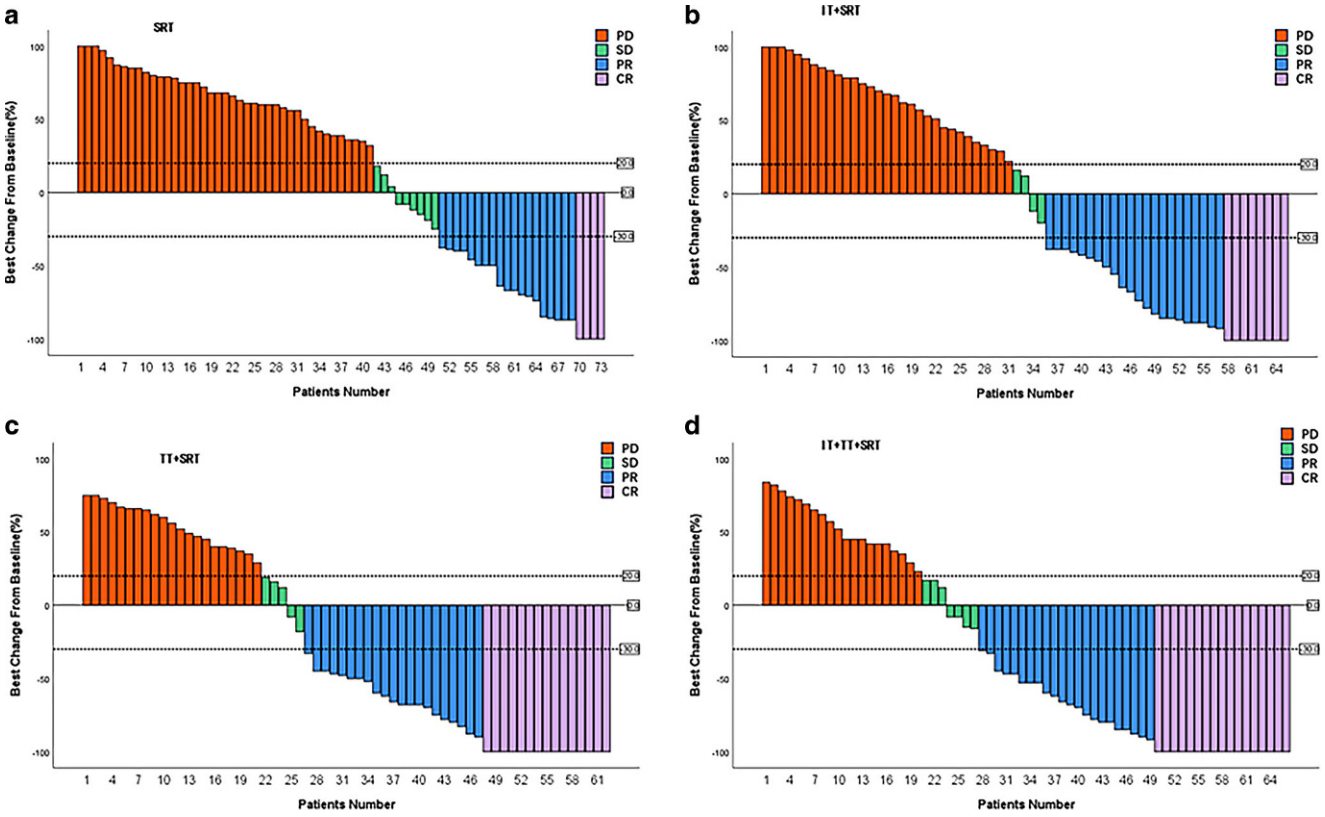

Fig. 5 Objective response rate of intracranial tumors

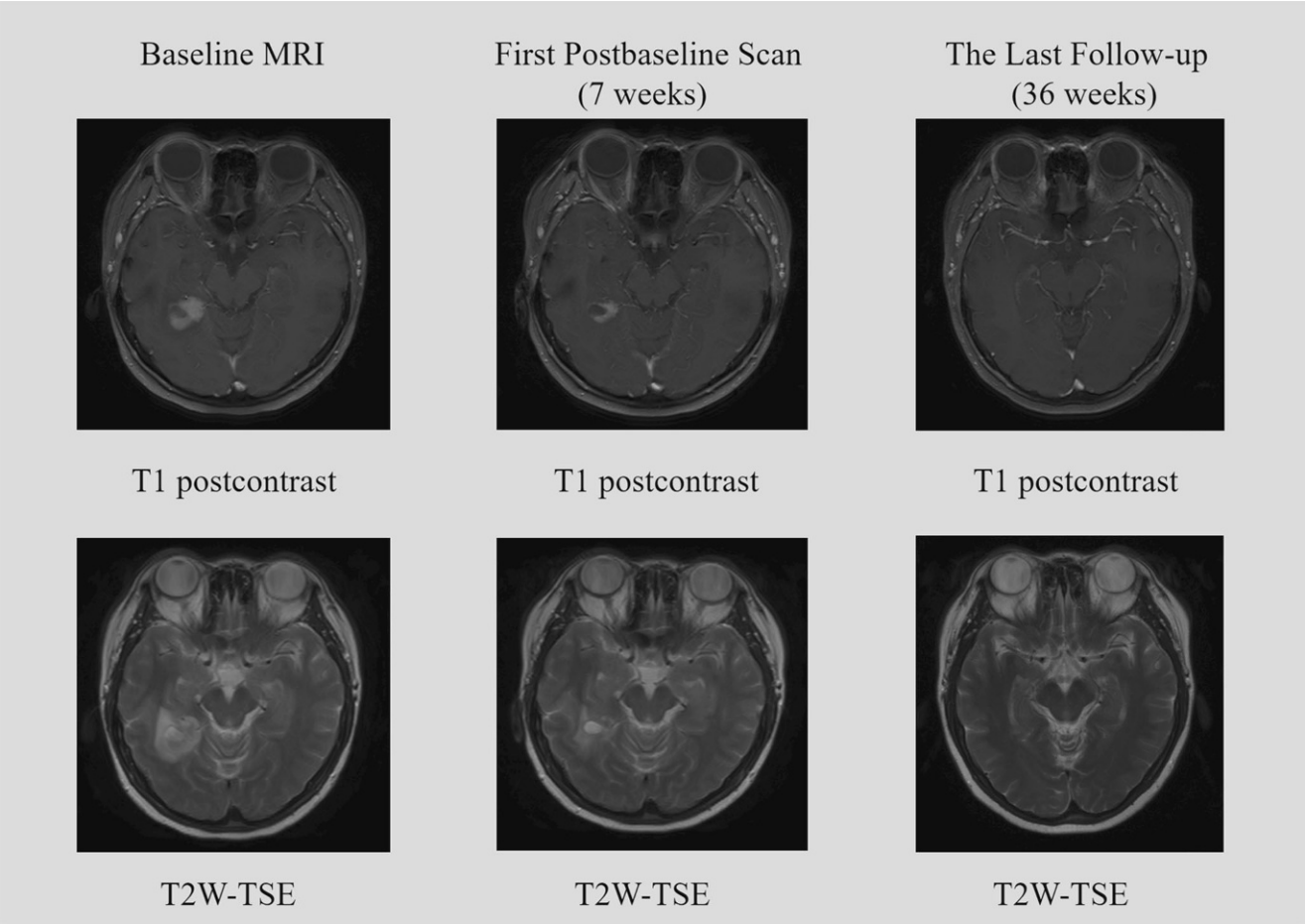

Fig. 6 Actual case

baseline tumor volume in the SRT combined with the dual therapy group. The tumor IORR in the SRT-alone group was 32% (95% CI: 21–42) (Fig. 5a); in the SRT combined with IT group, the IORR was 46% (95% CI: 34–59, OR 0.54 [95% CI: 0.27–1.07], $P=0.08$) (Fig. 5b); in the SRT combined with TT group, the IORR was 58% (95% CI: 45–71, OR 0.33 [95% CI: 0.16–0.67], $P=0.002$) (Fig. 5c); and in the SRT combined with IT and TT group, the IORR was 61% (95% CI: 49–73, OR 0.32 [95% CI: 0.16–0.64], $P=0.001$) (Fig. 5d). The IORR of patients treated with SRT combined with IT and TT was higher than that of patients in the other groups, which indicated that the combination therapy markedly increased the IORR of the tumor (Table 2). Figure 6 provides the image of a patient in whom CR was recorded at the last follow-up.

Figure 5 presents the IORR of four different treatments, including a visual comparison of CR PR SD PD of every group. (a) The application of SRT-alone; (b) SRT combined with IT monotherapy; (c) SRT combined in the application of third-generation EGFR-TKIs; (d) SRT combined with both IT and TT.

Figure 6 illustrates a patient with BM associated with NSCLC. Following the initial discovery of BM via MRI, SRT was promptly administered. The patient subsequently commenced regular oral administration of osimertinib in conjunction with treatment with the IT agent, avelumab. At the 7-week follow-up, a reduction in tumor volume and a decrease in the peritumoral edema were recorded. By the 36-week follow-up, the tumor had completely regressed with no residual lesions, and the peritumoral edema had subsided, achieving a CR.

Disease control rate of BM

IDCR was defined as the proportion of intracranial lesions that achieved CR, PR, and SD after treatment. In those treated with SRT-alone, IDCR was 44% (95% CI: 32–55), whereas patients treated with SRT combined with IT achieved an IDCR of 52% (95% CI: 40–65, OR 0.71 [95% CI: 0.36–1.39], $P=0.321$). In patients treated with SRT combined with TT, the IDCR was 66% (95% CI: 54–78, OR 0.40 [95% CI: 0.20–0.81], $P=0.010$) and in those simultaneously treated with SRT combined with IT

Table 3 Radiation-related adverse reactions

		SRT($n=73$)	SRT + IT($n=65$)	SRT + TT($n=62$)	SRT + IT + TT($n=66$)	*P* value
Radionecrosis	Total	10	14	11	17	$P=0.324$
	Mild	5	6	9	4	$P=0.336$
	Moderate	5	7	3	10	$P=0.190$
	Severe	0	0	0	3	$P=0.026$
Grade of adverse reaction	Grade 1–2	60	54	41	35	$P<0.001$
	Grade 3	12	8	15	17	$P<0.01$
	Grade 4	1	3	5	10	
	Grade 5	0	0	0	0	

and TT, the IDCR was 71% (95% CI: 60–82, OR 0.34 [95% CI: 0.17–0.68], $P=0.002$). Furthermore, the IDCR in the SRT combined with IT and TT group surpassed that of patients treated with SRT-alone or SRT combined with either IT or TT (Table 2).

Safety

In the enrolled patients, brain MRI was reviewed every month during the first 3 months after SRT and then every 3 months to monitor the radiation reactions at the brain treatment site. Symptomatic and asymptomatic radionecrosis was mainly observed, which was classified into three grades based on its severity, and the observation of toxicity and side effects was categorized into radiation-related reactions directed at SRT. According to the CTCAE grading standard, the classification included grade 1–2 and grade ≥ 3 adverse reactions. Grade ≥ 3 adverse effects encompass severe coma, generalized seizures, delirium, hypertensive crises, ataxia impairing self-care, cognitive impairment affecting daily activities, and intracranial hemorrhage. Adverse symptoms after combined use are shown in Table 3. A statistically significant difference was not noted in the overall occurrence of radionecrosis among the four groups, but three cases of severe occurred in the SRT combined with IT and TT group ($P=0.026$). No severe radionecrosis occurred in the other groups. According to the CTCAE scores, grade 1–2 patients in various groups presented obvious differences, and there were also significant statistical differences in ≥ grade 3 adverse reactions.

Discussion

This retrospective study was conducted to contrast the therapeutic effect and safety of SRT-alone, SRT combined with either IT or TT and SRT combined with both IT and TT. On Kaplan-Meier analysis, SRT combined with IT, TT, and SRT combined with IT and TT was associated with reduced distant intracranial metastases outside of the radiotherapy site. For local recurrence, SRT provided good local control independently, but it did not remain statistically significant among the four study groups, possibly because of the fewer numbers of patients with local relapses. In terms of safety, SRT, when combined with the third-generation EGFR-TKIs, exhibited a favorable safety profile in the occurrence of radionecrosis and radiation-related adverse events.

Radiotherapy, while killing tumor cells with high-energy radiation, promotes the release of tumor-associated antigens (TAAs) [21, 22]. However, it has not been proven whether SRT + IT has a synergistic (or additive) effect [23, 24]. In our research, the 1-year PFS of the local irradiated site in SRT combined with IT was 88.75% (HR: 0.607, 95% CI: [0.251–1.465], $P=0.266$). The 1-year PFS in cases of distant intracranial metastases outside of the radiotherapy site was 74.17% (HR: 0.726, 95% CI [0.417–1.264], $P=0.258$), which was higher than that of SRT-alone, albeit there was no statistical significance. This observation can be attributed to IT resistance. Some patients exhibited drug resistance after the initial administration of immune drugs. Subsequently, IT was discontinued or the regimen was switched to other immune drugs. This result may also be associated with the radiotherapy dosage.

The incidence of BM in patients with oncogene-driven NSCLC had increased (29–35% at the time of diagnosis) [25]. Nonetheless, most chemotherapy agents and effective targeted agents cannot cross the BBB and enter the CNS [26]. In this study, the 1-year PFS of local irradiated sites in patients with NSCLC BM treated using SRT and third-generation EGFR-TKIs was 88.01% (HR: 0.556, 95% CI [0.221–1.394], $P=0.210$), which suggest a trend effect, but did not reach statistical significance. This finding can be ascribed to the characteristics of the patients included in this group. The number of tumors treated was not limited, and the focus was on their total volume. In this patient cohort, only a few patients presented with multiple BM in relative proximity, accompanied by moderate to severe cerebral edema, which resulted in the reduction of the central dose. This implies an increased risk of local recurrence, and further research is warranted on this hypothesis [27]. How-

ever, for distant intracranial metastases, the 1-year PFS was 88.70% (HR: 0.480, 95% CI [0.253–0.908], $P = 0.024$), and the safety profile was good. The third-generation EGFR-TKI targeting drugs displayed better penetration [28]. And specifically designed to overcome resistance caused by the T790M mutation and exhibit significantly improved blood-brain barrier (BBB) penetration compared to earlier generations. These agents are particularly effective for treating non-small cell lung cancer (NSCLC) patients with brain metastases due to their higher CNS efficacy [29, 30].

Past studies have shown that targeted agents can modulate different components of the antitumor immune response by suppressing the innate immune-escape program of the tumor cells or by enhancing their antigenicity [31]. Furthermore, targeted agents act directly on immune effector and immunosuppressor cells; hence, combined targeting and IT may improve drug action. STR, TT, and IT were simultaneaously applied to patients with NSCLC BM receiving SRT in this study, and the median time to reach CR was 14 months. This result can be attributed to the larger baseline tumor volume in the SRT and dual-drug combination group. However, in this group, the 1-year local radiation site PFS of SRT combined with IT and TT was 91.97% (HR: 0.366, 95% CI [0.130–1.029], $P = 0.057$) and the distant intracranial metastases 1-year PFS was 87.81% (HR: 0.459, 95% CI [0.246–0.858], $P = 0.015$), thereby achieving good clinical effect. In terms of safety, severe radionecroses occurred, which may be related to the larger SRT dose administered to the dual drug combination group. In terms of safety, severe radionecroses did not occur in SRT combined with single drug therapy, and the incidence of grade ≥ 3 adverse reactions was also low. However, significant adverse reactions were noted in the SRT combined with dual drug therapy group, which could be due to the cumulative toxicity of the drugs when SRT was combined with dual drug therapy.

Conclusions

For patients with NSCLC BM, IT or TT combined with SRT increased the distant intracranial tumor control while maintaining a favorable safety profile. When SRT was combined with both IT and TT, good control over distant and unirradiated areas was observed, albeit the incidence of adverse reactions had increased. The control rate at locally irradiated sites was similarly effective; SRT provided good local control independently. The incidence of symptomatic RN was low. However, no significant statistical differences were observed among the different treatment modalities, which may be attributed to the fewer numbers of patients with local relapses. Hence, further large-scale studies are required to establish the optimal radiation dose in relation to the tumor volume for SRT combined with IT or TT. This dose standardization is essential for developing individualized treatment protocols involving SRT combined with drug therapy for different patients.

Funding This research was funded by the Beijing Medical Award Foundation No.YXTL-2023-726-0158 and the Shanghai Zhenghao Charity Foundation No. ZH-YXJK-34

Author Contribution XT and QG contributed equally to this work. XT conducted statistical analysis of data and wrote the manuscript; QG calculated radiological statistics and plotted the curve; YC collected radiological data; NC collected clinical data. HC revised the manuscript.

Declarations

Conflict of interest X. Tao, Q. Gao, Y. Chen, N. Cai and C. Hao declare that they have no competing interests.

Ethical standards This study was performed in line with the principles of the Declaration of Helsinki. The Ethics Committee of Harbin Medical University reviewed and approved this study. The included patient treatment details and imaging photographs were accompanied by written informed consent, signed by either the patients themselves or their relatives.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209–249
2. Molina-Arcas M, Moore C, Rana S, van Maldegem F, Mugarza E, Romero-Clavijo P, Herbert E, Horswell S, Li LS, Janes MR et al (2019) Development of combination therapies to maximize the impact of KRAS-G12C inhibitors in lung cancer. Sci Transl Med. https://doi.org/10.1126/scitranslmed.aaw7999
3. Hattori A, Suzuki K, Takamochi K, Wakabayashi M, Sekino Y, Tsutani Y, Nakajima R, Aokage K, Saji H, Tsuboi M et al (2024) Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer with radiologically pure-solid appearance in Japan (JCOG0802/WJOG4607L): a post-hoc supplemental analysis of a multicentre, open-label, phase 3 trial. Lancet Respir Med 12(2):105–116
4. Kahraman S, Karakaya S, Kaplan MA, Goksu SS, Ozturk A, Isleyen ZS, Hamdard J, Yildirim S, Dogan T, Isik S et al (2024)

Treatment outcomes and prognostic factors in patients with driver mutant non-small cell lung cancer and de novo brain metastases. Sci Rep 14(1):5820
5. Mithoowani H, Febbraro M (2022) Non-small-cell lung cancer in 2022: a review for general practitioners in oncology. Curr Oncol 29(3):1828–1839
6. Khalifa J, Amini A, Popat S, Gaspar LE, Faivre-Finn C (2016) Brain metastases from NSCLC: radiation therapy in the era of targeted therapies. J Thorac Oncol 11(10):1627–1643
7. Rutkowski J, Saad ED, Burzykowski T, Buyse M, Jassem J (2019) Chronological trends in progression-free, overall, and post-progression survival in first-line therapy for advanced NSCLC. J Thorac Oncol 14(9):1619–1627
8. Chang EL, Wefel JS, Maor MH, Hassenbusch SJ 3rd, Mahajan A, Lang FF, Woo SY, Mathews LA, Allen PK, Shiu AS et al (2007) A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. Neurosurgery 60(2):277–283 (discussion 283–274)
9. Holikova K, Selingerova I, Pospisil P, Bulik M, Hynkova L, Kolouskova I, Hnidakova L, Burkon P, Slavik M, Sana J et al (2024) Hippocampal subfield volumetric changes after radiotherapy for brain metastases. Neurooncol Adv 6(1):vdae40
10. Kuntz L, Le Fèvre C, Jarnet D, Keller A, Meyer P, Thiery A, Cebula H, Noel G, Antoni D (2023) Changes in the characteristics of patients treated for brain metastases with repeat stereotactic radiotherapy (SRT): a retrospective study of 184 patients. Radiat Oncol 18(1):21
11. Hartgerink D, Swinnen A, Roberge D, Nichol A, Zygmanski P, Yin FF, Deblois F, Hurkmans C, Ong CL, Bruynzeel A et al (2019) LINAC based stereotactic radiosurgery for multiple brain metastases: guidance for clinical implementation. Acta Oncol 58(9):1275–1282
12. Hudson WH, Olson JJ, Sudmeier LJ (2023) Immune microenvironment remodeling after radiation of a progressing brain metastasis. Cell Rep Med 4(6):101054
13. Jeon SH, Jang BS, Kim DY, Kim JH, Shin EC, Kim IA (2024) Dynamic responses of circulating T cells after stereotactic body radiation therapy for bone metastasis in patients with breast cancer. Int J Radiat Oncol Biol Phys 118(3):790–800
14. Mansouri A, Padmanaban V, Aregawi D, Glantz M (2021) VEGF and immune checkpoint inhibition for prevention of brain metastases: systematic review and meta-analysis. Neurology 97(15): e1484–e1492
15. Tian W, Chu X, Tanzhu G, Zhou R (2023) Optimal timing and sequence of combining stereotactic radiosurgery with immune checkpoint inhibitors in treating brain metastases: clinical evidence and mechanistic basis. J Transl Med 21(1):244
16. Ogimoto T, Ozasa H, Tsuji T, Funazo T, Yamazoe M, Hashimoto K, Yoshida H, Hosoya K, Ajimizu H, Nomizo T et al (2024) Combination therapy with EGFR tyrosine kinase inhibitors and TEAD inhibitor increases tumor suppression effects in EGFR mutation-positive lung cancer. Mol Cancer Ther 23(4):564–576
17. Popat S, Ahn MJ, Ekman S, Leighl NB, Ramalingam SS, Reungwetwattana T, Siva S, Tsuboi M, Wu YL, Yang JC (2023) Osimertinib for EGFR-mutant non-small-cell lung cancer central nervous system metastases: current evidence and future perspectives on therapeutic strategies. Target Oncol 18(1):9–24
18. Vaid AK, Gupta A, Momi G (2021) Overall survival in stage IV EGFR mutation-positive NSCLC: comparing first-, second- and third-generation EGFR-TKis (review). Int J Oncol 58(2):171–184
19. Liu Z, Han C, Dong C, Shen A, Hsu E, Ren Z, Lu C, Liu L, Zhang A, Timmerman C et al (2019) Hypofractionated EGFR tyrosine kinase inhibitor limits tumor relapse through triggering innate and adaptive immunity. Sci Immunol. https://doi.org/10.1126/sciimmunol.aav6473
20. Kleczko EK, Le AT, Hinz TK, Nguyen TT, Navarro A, Hu CJ, Selman AM, Clambey ET, Merrick DT, Lu S et al (2023) Novel EGFR-mutant mouse models of lung adenocarcinoma reveal adaptive immunity requirement for durable osimertinib response. Cancer Lett 556:216062
21. Gagliardi F, De Domenico P, Snider S, Roncelli F, Pompeo E, Barzaghi LR, Bulotta A, Gregorc V, Lazzari C, Cascinu S et al (2021) Role of stereotactic radiosurgery for the treatment of brain metastasis in the era of immunotherapy: a systematic review on current evidences and predicting factors. Crit Rev Oncol Hematol 165:103431
22. Scoccianti S, Olmetto E, Pinzi V, Osti MF, Di Franco R, Caini S, Anselmo P, Matteucci P, Franceschini D, Mantovani C et al (2021) Immunotherapy in association with stereotactic radiotherapy for non-small cell lung cancer brain metastases: results from a multicentric retrospective study on behalf of AIRO. Neuro Oncol 23(10):1750–1764
23. Uezono H, Nam D, Kluger HM, Sznol M, Hurwitz M, Yu JB, Chiang VL (2021) Outcomes of stereotactic radiosurgery and immunotherapy in renal cell carcinoma patients with brain metastases. Am J Clin Oncol 44(9):495–501
24. Butterfield LH, Najjar YG (2024) Immunotherapy combination approaches: mechanisms, biomarkers and clinical observations. Nat Rev Immunol 24(6):399–416
25. Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, Kim SW, Sugawara S, Yu Y, Fan Y, Geater SL et al (2023) Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC. N Engl J Med 389(21):1935–1948
26. Moraes FY, Taunk NK, Marta GN, Suh JH, Yamada Y (2016) The rationale for targeted therapies and stereotactic radiosurgery in the treatment of brain metastases. Oncologist 21(2):244–251
27. Loo M, Clavier JB, Attal Khalifa J, Moyal E, Khalifa J (2021) Dose-response effect and dose-toxicity in stereotactic radiotherapy for brain metastases: a review. Cancers. https://doi.org/10.3390/cancers13236086
28. Pardridge WM (2005) The blood-brain barrier: bottleneck in brain drug development. NeuroRx 2(1):3–14
29. Yin W, Zhao Y, Kang X, Zhao P, Fu X, Mo X, Wang Y, Huang Y (2020) BBB-penetrating codelivery liposomes treat brain metastasis of non-small cell lung cancer with EGFR(T790M) mutation. Theranostics 10(14):6122–6135
30. Colclough N, Chen K, Johnström P, Strittmatter N, Yan Y, Wrigley GL, Schou M, Goodwin R, Varnäs K, Adua SJ et al (2021) Preclinical comparison of the blood-brain barrier permeability of osimertinib with other EGFR TKis. Clin Cancer Res 27(1):189–201
31. Bergholz JS, Wang Q, Kabraji S, Zhao JJ (2020) Integrating immunotherapy and targeted therapy in cancer treatment: mechanistic insights and clinical implications. Clin Cancer Res 26(21): 5557–5566