Original Article

Timing of stereotactic radiosurgery within the first-line systemic treatment in non-small cell lung cancer brain metastases: a retrospective single-center cohort study

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Background: Stereotactic radiosurgery/radiotherapy (SRS/SRT) and novel systemic treatments, such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), have demonstrated to be effective in managing brain metastases in non-small cell lung cancer (NSCLC). However, the optimal treatment sequence of SRS/SRT and TKI/ICI remains uncertain. This retrospective monocentric analysis addresses this question by comparing the outcomes of patients with NSCLC brain metastases who received upfront SRS/SRT versus those who were initially treated with TKI/ICI.

Methods: All patients treated with SRS/SRT and TKI/ICI for NSCLC brain metastases were collected from a clinical database. The patients who received first-line TKI or ICI for the treatment of brain metastases were then selected for further analysis. Within this cohort, a comparative analysis between upfront SRS/SRT and patients initially treated with TKI/ICI was conducted, assessing key parameters such as overall survival (OS), intracranial progression-free survival (iPFS) and treatment-related toxicity. Both OS and iPFS were defined as the time from SRS/SRT to either death or disease progression, respectively.

Results: The analysis encompassed 54 patients, of which 34 (63.0%) patients received SRS/SRT and TKI/ICI as their first-line therapy. Of the latter, 17 (50.0%) patients received upfront SRS/SRT and 17 (50.0%) were initially treated with TKI/ICI; 24 (70.6%) received SRS/SRT and ICI, and 10 (29.4%) received SRS/SRT and TKI. The cohorts did not significantly differ in the univariable analyses for the following parameters: sex, age, histology, molecular genetics, disease stage at study treatment, performance status, number of brain metastases, treatment technique, tumor volume, target volume, disease progression, radiation necrosis, dosimetry. While no significant differences were found in terms of iPFS and OS

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between patients treated with upfront SRS/SRT and patients initially treated with TKI, upfront SRS/SRT demonstrated significantly superior OS when compared to patients initially treated with ICI (median OS not reached *vs.* 17.5 months; mean 37.8 *vs.* 23.6 months; P=0.03) with no difference in iPFS. No significant differences in treatment-related toxicity were observed among the cohorts.

Conclusions: In this retrospective, single-center cohort study, patients treated with upfront SRS/SRT demonstrated significantly longer OS compared to patients initially treated with ICI in the cohort receiving first-line therapy for brain metastases. However, given the retrospective design and the limited cohort size, definitive conclusions cannot be drawn from these findings. Nevertheless, the results suggest that the timing of SRS/SRT may play an important role in treatment outcomes. Further investigation, preferably through prospective randomized trials, is warranted to provide more conclusive answers to this important question.

Keywords: Checkpoint inhibitors; targeted treatment; tyrosine kinase inhibitors (TKIs); immunotherapy; stereotactic radiosurgery (SRS)

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Introduction

The treatment landscape for metastatic non-small cell lung cancer (NSCLC) has undergone remarkable advancements in recent years. The introduction of tyrosine kinase inhibitors (TKIs) such as the epidermal growth factor receptor (EGFR)-inhibitor osimertinib, the anaplastic lymphoma kinase (ALK)-inhibitor lorlatinib, and the Kirsten-rat-sarcoma (KRAS)-inhibitor sotorasib, alongside immune checkpoint inhibitors (ICIs), such as the programmed-deadth-ligand-1 (PD-L1)-inhibitor pembrolizumab, has substantially enhanced the prognosis of metastatic lung cancer patients harboring respective mutations (1-5). Notably, osimertinib has shown high efficacy in managing brain metastases due to its excellent ability to penetrate the blood-brain barrier (6).

In addition to systemic therapies, advancements in local treatments, particularly stereotactic radiosurgery (SRS), have also progressed significantly. Technical innovations enable the safe treatment of ten or even more metastases using SRS, positioning it as a less toxic alternative to whole-brain radiotherapy (WBRT) for managing this number of metastases (7,8). In the prospective controlled STEREOBRAIN trial, which compared patients receiving SRS for four to ten metastases with a matched historic WBRT cohort, a notable trend towards overall benefit was observed for SRS, demonstrating a median survival of 10.4 months compared to 7.1 months in the historic cohort (P=0.07), approaching statistical significance (9). Some other studies have suggested the feasibility of administering SRS to higher numbers of metastases, such as 15 or 20, in carefully selected patients (10-13).

The combined approach of these treatments has demonstrated advantages, likely due to a synergistic effect (14-19). Consequently, the standard practice involves the utilization of both local and systemic treatments for NSCLC brain metastases (20). One critical question, however, remains unanswered: Is it more effective to address brain metastases initially, preceding systemic treatment, or could there be greater benefit in implementing SRS on demand for non-responsive lesions subsequent to systemic treatment

Highlight box

Key findings

- In patients receiving stereotactic radiosurgery/radiotherapy (SRS/SRT) and immune checkpoint inhibitor (ICI), as first-line treatment of non-small cell lung cancer (NSCLC) brain metastases, upfront SRS/SRT demonstrated significantly longer overall survival (OS) compared to initial ICI treatment.

What is known and what is new?

- The combination of SRS/SRT and ICI/TKI is highly effective in treating NSCLC brain metastases.
- Timing of SRS/SRT has an important impact on treatment outcome.

What is the implication, and what should change now?

- Prospective trials comparing upfront versus delayed SRS/SRT are urgently needed. Until a higher level of evidence is reached, these data should be used to support upfront SRS/SRT in the clinical routine.

(16,21-25)? This retrospective study aims to analyze patients who received both, SRS/stereotactic radiotherapy (SRT) and TKI/ICI for NSCLC brain metastases. Its objective is to identify potential correlations between the timing of these treatments and the resulting outcomes. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-132/rc).

Methods

Data collection

For this monocentric retrospective analysis, the internal data base within MOSAIQ® (Elekta, Stockholm, Sweden) was searched for patients who underwent cranial SRS/SRT in combination with ICI or TKI between 2017 and 2021. Then, patients who received ICI/TKI as their first line therapy for brain metastases were identified. Patients with prior WBRT were excluded from this study. Additionally, patients without any follow-up including imaging, were excluded as well. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The patients gave their approval as part of a broad consent at the LMU University Hospital of Munich. Due to the anonymized analysis and the retrospective nature of this study, no separate ethical approval by a review board was needed.

Radiation treatment

Brain metastases ranging from 0.3 to 2.5 cm in diameter underwent SRS with prescription doses between 18 and 20 Gy (to the 80% isodose line). Conversely, larger metastases or those positioned in critical areas were managed through multi-fraction SRT, employing a dose of 28 Gy distributed across five fractions (to the 80% isodose line). Up to ten metastases were treated simultaneously using single-isocenter dynamic arc therapy. Irregularly shaped metastases were preferably addressed utilizing volumetric arc therapy (26,27). Gross tumor volume (GTV) to planning target volume (PTV) margin was 1 mm.

Data acquisition

General patient characteristics and therapy data were obtained from the patient records, encompassing variables such as sex, age at the time of brain metastasis diagnosis, identified driver mutations, PD-L1 status, control of extracranial disease, prior radiotherapy (RT) for the primary tumor, Karnofsky performance status (KPS), count of treated brain metastases, median GTV, median PTV, use of additional chemotherapy, and subsequent systemic therapies. V10 and V12 for SRS, and V20 for SRT (volumes receiving a specific dose of more or equal than 10, 12 or 20 Gy, respectively) of the unaffected brain tissue (brain volume minus GTV), were collected as risk factors for radiation necrosis (28). Additionally, the disease specific graded prognostic assessment score (dsGPA), initial brain metastasis velocity (iBMV) score and the brain metastasis velocity (BMV) score were assessed.

$$iBMV = \frac{total\ number\ of\ brain\ metastases\ at\ time\ of\ RT}{number\ of\ years\ since\ initial\ primary\ cancer\ diagnosis} \quad [1]$$

$$BMV = \frac{number\ of\ new\ metastases\ since\ initial\ RT}{number\ of\ years\ since\ initial\ RT} \quad [2]$$

Assessment of treatment-related toxicity involved grading adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Neuroradiological evaluation

Baseline cranial magnetic resonance imaging (MRI) was usually conducted no later than 2 weeks before the initiation of treatment, with follow-up assessments routinely performed every three months in most cases. Follow-up imaging was reviewed by two experienced neuroradiologists, according to the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria (29). Consequently, gadolinium-enhanced T1-weighted MRI was utilized to assess irradiated lesions in terms of progression, pseudoprogression, stable disease, partial response, and complete response.

Timing of SRS/SRT and ICI/TKI

This study focuses on patients who received ICIs and TKIs as first-line therapy for the brain metastases. The patients were categorized into two groups based on the timing of their cranial RT. They either received upfront SRS/SRT following ICI/TKI or underwent initial ICI/TKI treatment before initiating RT. Patients treated with ICI or TKI were analyzed separately. To analyze potential advantages of scheduling SRT/SRS with ICI/TKI, patients who underwent initial SRS/SRT were further examined in two subgroups based on whether they received concurrent or sequential ICI/TKI. The concurrent subcohort received ICI/TKI within a 2-week period after SRS/SRT. The

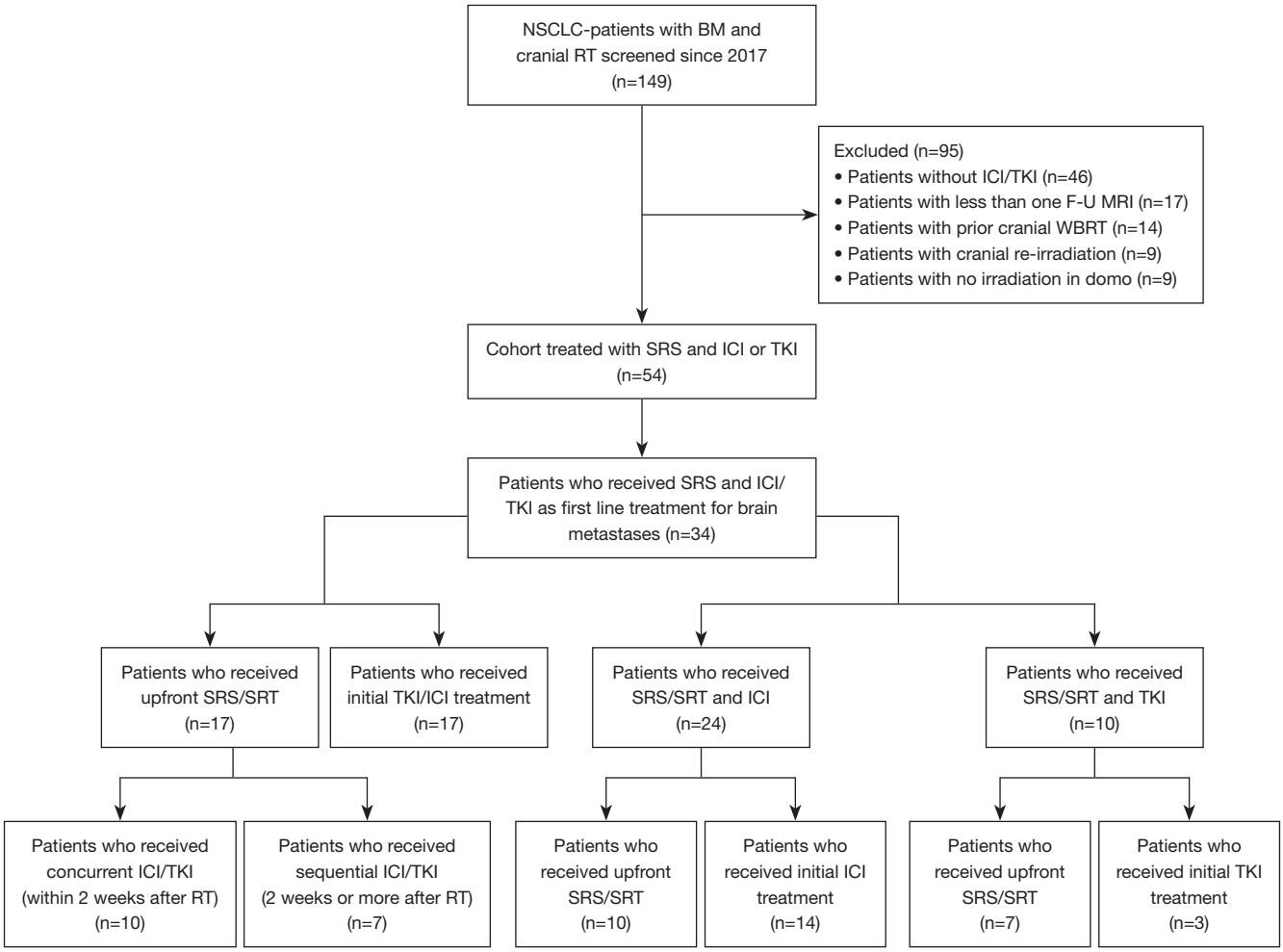

Figure 1 Distribution of the patients in the (sub-)cohorts. NSCLC, non-small cell lung cancer; BM, brain metastases; RT, radiation therapy; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; F-U, follow-up; MRI, magnet resonance imaging; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy.

sequential subcohort received ICI/TKI more than 2 weeks following SRS/SRT. The decision to use this 2-week timeframe was defined analogous to a comparable analysis conducted in the context of melanoma brain metastases, in which a difference between sequential and concomitant treatment was first seen when reducing the usual time frame of 4 weeks to 2 weeks, or even only 1 week (30).

Patient cohort and its subgroups

Following the database evaluation, a total of 54 patients were identified who received SRS/SRT in combination with ICI or TKI. Among them, 34 patients received ICI/TKI as their initial treatment as their first-line therapy for a total of 99 brain metastases. The latter cohort consisted of 17 (50.0%) patients for both upfront SRS/SRT and upfront TKI/ICI, each; 24 (70.6%) received SRS/SRT and ICI, and 10 (29.4%) received SRS/SRT and TKI. From the patients who received TKI (n=10), 7 (70.0%) received upfront SRS/SRT and 3 (30.0%) initial TKI treatment. Conversely, among the patients who received ICI (n=24), 10 (41.7%) patients underwent upfront SRS/SRT and 14 (58.3%) patients were initially treated with ICI. The distribution of the cohort and its subgroups is depicted in *Figure 1*.

Statistical analysis

The data were analyzed using the statistical program IBM

SPSS Statistics version 29.0 (IBM, Armonk, New York, USA). Descriptive statistics involved calculating both relative and absolute frequencies. Patient characteristics across all therapy groups were compared using the Fisher-Yates and Mann-Whitney tests. However, for contingency tables larger than 2×2, the Fisher-Freeman-Halton test was preferred over the Fisher-Yates test. Survival analysis was performed employing Kaplan-Meier analysis along with the log-rank test. Additionally, multiple regression was used to evaluate the impact of various variables on survival times. The survival times considered for analysis were overall survival (OS) since start of treatment (SRS/SRT or ICI/TKI, respectively) and intracranial progression-free survival (iPFS) since start of treatment (SRS/SRT or ICI/TKI, respectively). Radiation necrosis free-survival was calculated from start of SRS/SRT. A significance level of $P \leq 0.05$ was deemed statistically significant.

Results

Patient characteristics

As presented before a total of 54 patients were identified who received SRS/SRT in combination with ICI or TKI. Among them, 34 patients received ICI/TKI as their initial treatment for a total of 99 brain metastases. Within this cohort, 31 (91.2%) patients had adenocarcinoma, and 3 (8.8%) patients had squamous cell carcinoma. The group was divided, with 17 (50.0%) patients each for those receiving upfront SRS/SRT or initial TKI/ICI treatment. The distribution of patients in each cohort is illustrated in *Figure 1*, and specific patient characteristics are outlined in *Tables 1*,*2*.

Notably, the subgroups did not exhibit differences across various parameters except for the dsGPA score. The median dsGPA was 2.5 for upfront SRS/SRT and 2.0 for initial TKI/ICI treatment, yielding a P value of 0.07. However, when analyzed as a binary variable of the scores 0–2 and 2.5–4, the P value was 0.03. The individual components used to determine the dsGPA (such as age, Karnofsky performance score, presence of extracerebral metastases, number of brain metastases and molecular status) showed P values greater than 0.05 (see *Table 2*).

Upfront SRS/SRT versus initial ICI/TKI treatment

Upon comparing upfront SRS/SRT versus initial ICI/TKI treatment, no significant difference was observed OS and iPFS, in spite of a noticeable trend favoring upfront SRS/SRT in the OS curves (*Figure 2*, A1 and A2). Factors impacting survival were assessed in the univariate analysis and detailed in *Table 3*. Extracranial disease control at the time of brain metastasis diagnosis emerged as a significant influencer of OS [hazard ratio (HR) =0.378, 95% confidence interval (CI): 0.149–0.955, P=0.04]. iPFS was solely significantly influenced by the BMV score (P<0.001).

The univariate analysis concerning RNFS, as presented in *Table 4*, revealed a notable impact of V10 (HR =1.193, 95% CI: 1.008–1.411, P=0.04) and V12 values (HR =1.286, 95% CI: 1.018–1.625, P=0.04) specifically for lesions that underwent single-fraction irradiation (n=89, 89.9%). The treatment order (upfront SRS/SRT *vs.* initial ICI/TKI treatment), however, did not show any significant impact on RNFS (HR =0.246, 95% CI: 0.027–2.254, P=0.22).

Subgroup ICI: upfront SRS/SRT vs. initial ICI treatment

In the subset of patients receiving ICI (n=24), the distribution was 10 (41.7%) patients for upfront SRS/SRT and 14 (58.4%) patients for initial ICI treatment (Table S1). With respect to specific ICI regimens 22 (91.7%) patients received pembrolizumab, the other two nivolumab and ipilimumab/nivolumab. Similar to the larger cohort, the groups only differed with regard to dsGPA (P=0.03). Kaplan-Meier analysis revealed a significantly longer OS in the upfront SRS/SRT cohort compared to initial ICI treatment (P=0.03) (*Figure 2*, B1 and B2).

Subgroup TKI: upfront SRS/SRT vs. initial TKI treatment

For the subset of patients receiving TKI (n=10), the distribution was 7 (70.0%) patients for upfront SRS/SRT and 3 (30.0%) patients for initial TKI treatment (Table S2). Three (30.0%) patients received afatinib, 4 (40.0%) osimertinib, 2 (20.0%) crizotinib and 1 (10.0%) gefitinib. The cohorts did not significantly differ from each other. Kaplan-Meier analysis, however, failed to show any significant differences concerning OS and iPFS (P=0.15 and P=0.09, respectively) (Figure S1A,S1B).

Subgroup upfront SRS/SRT: concurrent vs. sequential ICI/TKI treatment

When looking at all patients receiving upfront SRS/SRT

Table 1 The total cohort (n=54) and the patients receiving first line treatment for brain metastases (n=34)

Parameters	Total (n=54)	First line (n=34)
Sex		
Female	25 (46.3)	15 (44.1)
Male	29 (53.7)	19 (55.9)
Age at study RT (years), median [range]	64 [33–82]	64 [33–82]
Histology		
Adenocarcinoma	48 (88.9)	31 (91.2)
Squamous cell carcinoma	3 (5.6)	3 (8.8)
Other	3 (5.6)	0 (0.0)
EGFR	12 (22.2)	8 (23.5)
KRAS	14 (25.9)	10 (29.4)
ALK	1 (1.9)	0 (0.0)
ROS1	3 (5.6)	2 (5.9)
MET	2 (3.7)	1 (2.9)
PD-L1 positive	33 (61.1)	23 (67.6)
Initial brain metastases		
Yes	28 (51.9)	25 (73.5)
No	26 (48.1)	9 (26.5)
Systemic control at diagnosis of BM		
Yes	23 (42.6)	14 (41.2)
No	31 (57.4)	20 (58.8)
RT of primary at study RT		
Yes	9 (16.7)	3 (8.8)
No	45 (83.3)	31 (91.2)
dsGPA		
Median [range]	2 [0.5–4.0]	2 [0.5–4.0]
0–2.0	34 (63.0)	21 (61.8)
2.5–4.0	20 (37.0)	13 (38.2)
iBMV score		
<2	16 (29.6)	8 (23.5)
≥2	38 (70.4)	26 (76.5)
BMV score		
<4	38 (70.4)	24 (70.6)
4–13	8 (14.8)	5 (14.7)
>13	8 (14.8)	5 (14.7)
Intracranial progression	33 (61.1)	21 (61.8)
Extracranial progression	32 (59.3)	20 (58.8)
Adverse events		
No	20 (37.0)	11 (32.4)
Highest CTCAE 1	27 (50.0)	18 (52.9)
Highest CTCAE 2	4 (7.4)	3 (8.8)
Highest CTCAE 3	3 (5.6)	2 (5.9)
Number of BM/patient		
Median [range]	2 [1–9]	2 [1–8]
Single metastases	18 (33.3)	13 (38.2)
2–4 metastases	25 (46.3)	13 (38.2)
5–10 metastases	11 (20.4)	8 (23.5)
Total number of BM	158	99
RT technique		
SRS (No. of lesions)	144 (91.1)	89 (89.9)
SRT (No. of lesions)	7 (4.4)	5 (5.1)
Gross tumor volume (cm^3), median [range]	2.1 [0.1–17.5]	3.3 [0.1–17.5]
Planning target volume (cm^3), median [range]	3.8 [0.3–26.1]	5.1 [0.3–26.1]
Local tumor progression (No. of lesions)	5 (3.2)	3 (3.0)
Radiation necrosis (No. of lesions)	7 (4.4)	5 (5.1)
Dosimetry SRS		
Median V10 (cm^3) [range]	2.6 [0.1–28.1]	2.8 [0.5–20.5]
Median V12 (cm^3) [range]	1.9 [0.3–21.8]	1.9 [0.3–14.7]
Dosimetry SRT, median V20 (cm^3), range	18.9 [2.5–36.7]	13.0 [2.5–25.3]

Data are presented as n (%) unless otherwise specified. RT, radiation therapy; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma virus; ALK, anaplastic lymphoma kinase; ROS1, proto-oncogene tyrosine-protein kinase ROS1; MET, mesenchymal-epithelial transition; PD-L1, programmed death ligand 1; BM, brain metastases; dsGPA, disease specific graded prognostic assessment; iBMV, initial brain metastases velocity; BMV, brain metastases velocity; CTCAE, Common Terminology Criteria of Adverse Events; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; V10, V12, V20: volume which received at least 10, 12 and 20 Gy, respectively.

Table 2 The upfront SRS/SRT and initial ICI/TKI treatment cohort (N=17 each)

Parameters	Upfront RT (n=17)	Upfront ICI/TKI (n=17)	P value
Sex			
Female	8 (47.1)	7 (41.2)	
Male	9 (52.9)	10 (58.8)	>0.99*
Age at study RT (years), median [range]	65 [41–79]	64 [33–82]	0.70***
Histology			
Adenocarcinoma	16 (94.1)	15 (88.2)	
Squamous cell carcinoma	1 (5.9)	2 (11.8)	>0.99*
EGFR	6 (35.5)	2 (11.8)	0.26*
KRAS	4 (23.5)	6 (35.5)	
ALK	0 (0.0)	0 (0.0)	
ROS1	1 (5.9)	1 (5.9)	
MET	1 (5.9)	0 (0.0)	
PD-L1 positive	11 (64.7)	12 (70.6)	>0.99*
Initial brain metastases			
Yes	13 (76.5)	12 (70.6)	
No	4 (23.5)	5 (29.4)	>0.99*
Systemic control at diagnosis of BM			
Yes	8 (47.1)	6 (35.3)	
No	9 (52.9)	11 (64.7)	0.73*
RT of primary at study RT			
Yes	1 (5.9)	2 (11.8)	
No	16 (94.1)	15 (88.2)	>0.99*
KPS at study RT, median [range]	90 [70–100]	90 [60–100]	0.37***
dsGPA			
Median [range]	2.5 [0.5–3.0]	2 [0.5–4]	0.07***
0–2.0	7 (41.2)	14 (82.4)	
2.5–4.0	10 (58.8)	3 (17.6)	0.03*[a]
iBMV score			
<2	4 (23.5)	4 (23.5)	
≥2	13 (76.5)	13 (76.5)	>0.99*
BMV score			
<4	12 (70.6)	12 (70.6)	
4–13	2 (11.8)	3 (17.6)	
>13	3 (17.6)	2 (11.8)	>0.99**
Intracranial progression	12 (70.6)	9 (52.9)	0.48*

Table 2 (*continued*)

Table 2 (*continued*)

Parameters	Upfront RT (n=17)	Upfront ICI/TKI (n=17)	P value
Extracranial progression	11 (64.7)	9 (52.9)	0.73*
Adverse events			
No	8 (47.1)	3 (17.6)	
Highest CTCAE 1	8 (47.1)	10 (58.8)	
Highest CTCAE 2	1 (5.9)	2 (11.8)	
Highest CTCAE 3	0 (0.0)	2 (11.8)	0.21**
Number of BM/patient			
Median [range]	2 [1–7]	2 [1–8]	0.66***
Single metastases	7 (41.2)	6 (35.3)	
2–4 metastases	7 (41.2)	6 (35.3)	
5–10 metastases	3 (17.6)	5 (29.4)	0.82**
Total number of BM	45	54	
RT technique			
SRS (No. of lesions)	42 (93.3)	47 (87.0)	
SRT (No. of lesions)	3 (6.7)	7 (13.0)	
Gross tumor volume (cm^3), median [range]	3.7 [0.1–17.4]	3.1 [0.4–17.5]	0.74***
Planning target volume (cm^3), median [range]	5.2 [0.3–21.9]	5.0 [0.8–26.1]	0.73***
Local tumor progression (No. of lesions)	2 (4.4)	1 (1.9)	0.59*
Radiation necrosis (No. of lesions)	1 (2.2)	4 (7.4)	0.37*
Dosimetry SRS			
Median V10 (cm^3) [range]	3.9 [0.6–20.5]	2.5 [0.5–16.9]	0.40***
Median V12 (cm^3) [range]	2.8 [0.3–14.7]	1.8 [0.3–11.2]	0.38***
Dosimetry SRT, median V20 (cm^3) [range]	6.5 [2.5–18.2]	18.3 [4.6–25.3]	0.20***

Data are presented as n (%) unless otherwise specified. The equal distribution was calculated with the following analyses: *, Fisher-Yates test; **, Fisher-Freeman-Halton test; ***, Mann-Whitney test. [a], P values equal to or below the significance level of 0.05. ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; RT, radiation therapy; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma virus; ALK, anaplastic lymphoma kinase; ROS1, proto-oncogene tyrosine-protein kinase ROS1; MET, mesenchymal-epithelial transition; PD-L1, programmed death ligand 1; BM, brain metastases; KPS, Karnofsky Performance score; dsGPA, disease specific graded prognostic assessment; iBMV, initial brain metastases velocity; BMV, brain metastases velocity; CTCAE, Common Terminology Criteria of Adverse Events; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; V10, V12, V20: volume which received at least 10, 12 and 20 Gy, respectively.

(n=17), 10 (58.8%) patients received ICI/TKI concurrently within 2 weeks after SRS/SRT, and 7 (41.2%) patients sequentially more than 2 weeks after SRS/SRT (Table S3). The analysis unveiled significantly improved OS and iPFS in the sequential cohort compared to the concurrent cohort (P=0.009 and P=0.03, respectively) (*Figure 2*, C1 and C2). Unfortunately, conducting separate analyses for ICI and TKI was not feasible due to the limited number of patients in each subgroup.

Discussion

Despite the advancements in systemic treatments that directly target specific cancer mutations, local therapies

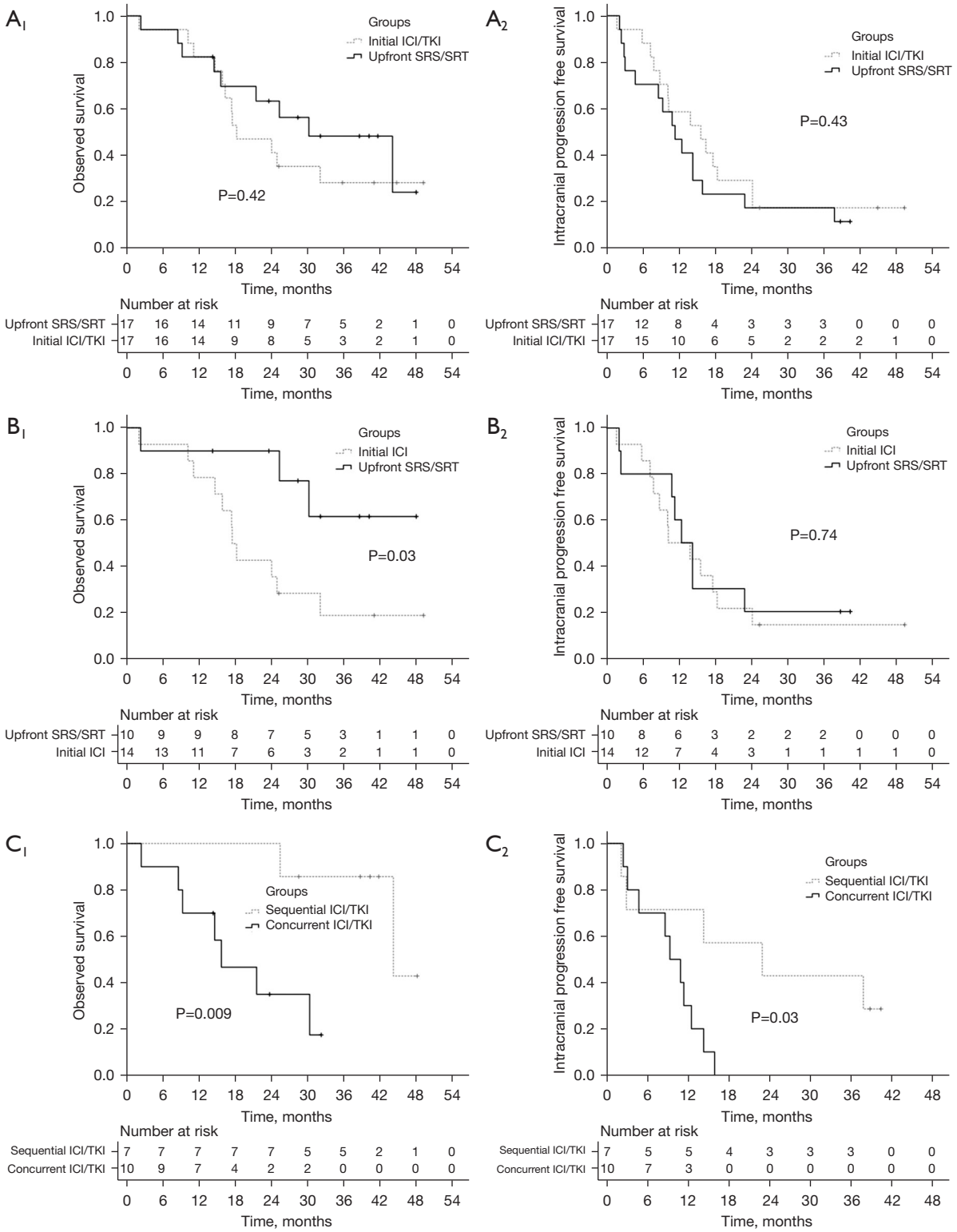

Figure 2 Kaplan-Meier curves of the OS and iPFS regarding initial ICI/TKI treatment *vs.* upfront SRS/SRT (A1,A2), initial ICI treatment *vs.* upfront SRS/SRT (B1,B2), and concurrent (within 2 weeks after RT) ICI/TKI *vs.* sequential (2 weeks or more after RT) ICI/TKI (C1,C2), respectively. SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; ICI, immune checkpoint inhibition; TKI, tyrosine kinase inhibitor; OS, overall survival; iPFS, intracranial progression free survival; RT, radiation therapy.

Table 3 Univariate analysis of OS and iPFS of the main cohort (n=34)

Parameters	Overall survival			Intracranial progression free survival		
	HR	95% CI	P value	HR	95% CI	P value
Median age (years)	1.021	0.980–1.064	0.31	1.019	0.986–1.053	0.26
Initial brain metastases	1.223	0.468–3.199	0.68	1.212	0.530–2.771	0.64
Systemic control at study RT	0.378	0.149–0.955	0.04[a]	0.708	0.333–1.502	0.37
RT of primary tumor at study RT	0.661	0.152–2.881	0.58	0.593	0.140–2.505	0.48
dsGPA	0.475	0.189–1.193	0.11	0.751	0.352–1.601	0.46
iBMV score	1.129	0.412–3.095	0.81	0.705	0.298–1.664	0.43
BMV score						
<4 (ref)	1			1		
4–13	1.293	0.419–3.991	0.66	1.787	0.662–4.824	0.25
>13	2.841	0.902–8.948	0.07	22.566	5.134–99.192	<0.001[a]
BM/patient						
Single metastases (ref)	1			1		
2–4 metastases	1.192	0.458–3.104	0.72	1.138	0.500–2.591	0.76
5–10 metastases	0.767	0.230–2.553	0.67	0.513	0.188–1.403	0.19
Gross tumor volume	1.030	0.946–1.122	0.49	1.002	0.927–1.084	0.96
Planning target volume	1.025	0.964–1.090	0.43	1.004	0.948–1.063	0.89
Upfront RT *vs.* upfront ICI/TKI	0.576	0.241–1.376	0.22	1.036	0.498–2.156	0.92

[a], P values equal to or below the significance level of 0.05. ref, the reference group; OS, overall survival; iPFS, intracranial progression free survival; RT, radiation therapy; dsGPA, disease specific graded prognostic assessment; iBMV, initial brain metastases velocity; BMV, brain metastases velocity; BM, brain metastases; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval.

such as surgery and RT remain integral, particularly in the management of oligometastatic disease. Several trials have highlighted the benefits of improved PFS and/or OS by incorporating focal SRS/SRT alongside systemic treatments for oligometastatic NSCLC (31-33). Due to the high efficacy of EGFR-targeted TKI, the question remains, whether TKI can replace SRS/SRT in patients with EGFR-mutated NSCLC or if patients benefit more from the combination of SRS/SRT and TKI. A retrospective trial by Magnuson *et al.* analyzing 351 patients with EGFR-mutant NSCLC brain metastases treated with TKI demonstrated improved OS when receiving upfront SRS compared to initial TKI treatment and SRS or WBRT at progression (46 *vs.* 25 months, HR 0.39, P<0.001) (15). When looking at extracranial metastases, a recently published trial by Wang *et al.* involving 133 patients with oligometastatic EGFR-mutated NSCLC (without brain metastases) receiving first-line TKI found that those who received upfront focal SRS/SRT to all tumor sites exhibited significantly enhanced OS (25.5 *vs.* 17.4 months, P<0.001) and PFS (20.2 *vs.* 12.5 months, P=0.001) (34). These findings indicate that SRS/SRT influences outcomes even when combined with highly effective systemic treatments like EGFR inhibitors. However, the impact of SRS/SRT in patients receiving the newest generation of EGFR inhibitors, such as osimertinib, remains unclear. Addressing this uncertainty, the NORTHSTAR trial (NCT03410043) aims to investigate the role of SRS/SRT in patients receiving osimertinib, shedding light on its potential impact in this specific treatment context.

In our analysis, upfront SRS/SRT demonstrated a significantly improved OS in the cohort receiving ICI. This

Table 4 Univariate analysis of the RNFS of all metastases in the cohort (n=99)

Parameters	Brain metastases (n=99)	Radiation necrosis free survival		
		HR	95% CI	P value
RT technique				
SRS (ref)	89 (89.9)	1		
SRT	10 (10.1)	2.223	0.248–19.917	0.48
Systemic therapy				
ICI (ref)	68 (68.7)	1		
TKI	31 (31.3)	0.450	0.050–4.034	0.48
Treatment order				
Upfront RT (ref)	45 (45.5)	1		
Upfront ICI/TKI	54 (54.5)	0.246	0.027–2.254	0.22
Dosimetry SRS (n=89)				
Median V10 (cm^3) [range]	2.8 [0.5–20.5]	1.193	1.008–1.411	0.04[a]
Median V12 (cm^3) [range]	1.9 [0.3–14.7]	1.286	1.018–1.625	0.04[a]
Dosimetrics SRT (n=10), median V20 (cm^3) [range]	13.0 [2.5–25.3]	0.974	0.766–1.238	0.83

Data are presented as n (%) unless otherwise specified. [a], P values equal to or below the significance level of 0.05. ref, the reference group; RNFS, radiation necrosis free survival; RT, radiation therapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; V10, V12, V20: volume which received at least 10, 12 and 20 Gy, respectively; HR, hazard ratio; CI, confidence interval.

finding aligns with another retrospective study by Yu *et al.*, indicating that delayed SRS/SRT resulted in poorer OS compared to upfront or concomitant SRS/SRT: within a cohort of 73 NSCLC patients with brain metastases treated with ICI were associated with shorter OS when receiving delayed RT (P=0.003) administration; in a meta-analysis with 254 from four studies parallelly done in the same article, improved OS was shown for concurrent *vs.* delayed RT (HR =0.44, P<0.03) and upfront *vs.* delayed RT (HR =0.32, P<0.01) (17). Guo *et al.* also reported comparable results: while analyzing 461 patients with NSCLC brain metastases receiving ICI, patients with upfront RT showed longer OS (25.4 *vs.* 14.6 months, HR =0.52, P=0.04) (35). The fact that in our study OS is significantly different, but iPFS is not, may appear peculiar at first glance, yet it is a common occurrence in trials involving ICI or TKI: Hess *et al.* specifically analyzed this phenomenon in 192 studies with biological or targeted agents, and concluded that this is not a result of poor study design, but suggested it may be due to still unknown complex mechanisms of action of the biological or targeted agents (36).

Given that 80% of the patients in the subgroup receiving TKI had EGFR mutations, it's plausible to assume that the substantial response of EGFR inhibitors on brain metastases might have minimized the impact of SRS in first-line treatment, consequently impacting the timing as well. It would be intriguing to investigate whether the timing of SRS holds significance in non-EGFR-positive brain metastases treated with TKIs, but due to the limited representation of only two patients, this analysis couldn't be conducted in this cohort. Regarding the comparison between concurrent and sequential application of systemic treatment with RT, patients appeared to benefit more from sequential application, as concurrent treatment of systemic treatment may have a certain impact on toxicity, as it was recently suggested in a study regarding SRS and ipilimumab/nivolumab in melanoma brain metastases (30), a reason herefore may the higher treatment morbidity. However, due to the minimal incidence of radiation necrosis in our study (only one patient in this subgroup), this aspect couldn't be thoroughly analyzed.

In summary, our study suggests that upfront SRS/

SRT may lead to a survival advantage to NSCLC patients undergoing ICI treatment with very low additional treatment toxicity. However, for patients with mutations susceptible to TKIs, the benefits of upfront SRS/SRT appear less pronounced. In these cases, salvage SRS/SRT targeted to persistent or progressing metastases might be sufficient. It is important to note the clear limitations of our study, primarily its retrospective nature and the limited number of patients, which posed challenges in analyzing subgroups comprehensively. Specifically, for the analysis of the TKI cohort, a larger patient cohort would be necessary to draw more definitive conclusions. Besides, the low number of squamous cell carcinoma and relatively high number of EGFR positive patients does not make this cohort representative for all patients. Additionally, a selection bias is very likely due to the fact that patients with a good systemic and intracranial response might not have been treated with SRS/SRT afterwards, and thus were not taken into account in this analysis. Therefore, there is a pressing need for a randomized trial specifically investigating the optimal timing of SRS/SRT in these patient cohorts, which would offer more conclusive and robust insights into treatment strategies.

Conclusions

In this small retrospective cohort, patients treated with ICI (mainly pembrolizumab) and SRS/SRT as first-line treatment for brain metastases of NSCLC, upfront SRS/SRT followed by ICI lead to significantly prolonged OS than initial ICI treatment followed by SRS/SRT. While the difference between patients treated with upfront SRS/SRT and patients initially treated with TKI was not significant, the number of patients in this subcohort was too small to make any meaningful conclusions. Despite of the inherent limitations of this single-center retrospective study, timing of SRS/SRT within multimodal approach for NSCLC brain metastases seems to have a considerable impact on the patients' outcome.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-132/rc

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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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The patients gave their approval as part of a broad consent at the LMU University Hospital of Munich. Due to the anonymized analysis and the retrospective nature of this study, no separate ethical approval by a review board was needed.

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