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Original Article

Stereotactic Radiosurgery Results in Non-Small-Cell Lung Cancer Patients with Brain Metastases in the Era of Modern Systemic Treatment Agents

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Abstract

OBJECTIVE: This study reports the results of stereotactic radiosurgery and fractionated stereotactic radiosurgery treatment for brain metastasis in non-small cell lung cancer patients treated with modern systemic treatment methods (immunotherapy, targeted agents, and current chemotherapy agents).

MATERIAL AND METHODS: This study retrospectively analyzed patients diagnosed with non-small cell lung cancer and brain metastases who underwent stereotactic radiosurgery/fractionated stereotactic radiosurgery in the Radiation Oncology Clinic of Ankara Bilkent City Hospital between February 21, 2019, and August 15, 2022. The study's primary endpoint was accepted as the lesions' response status after stereotactic radiosurgery/fractionated stereotactic radiosurgery.The secondary endpoint was accepted as the patients' intracranial progression-free survival and overall survival.

RESULTS: This study included 85 patients treated for 174 lesions. Their median follow-up was 6.6 (range: 1-42) months.Their median intracranial progression-free survival after radiotherapy was 5.3 (range: 1-33) months, and their median overall survival was 6.6 (range: 1-42) months. Concurrent immunotherapy was administered to 10 (11%) patients and targeted therapy to 8 (9%). Magnetic resonance imaging indicated that 14 (6%) patients had a complete response, 62 (35.6%) had a partial response, 10 (5.7%) had stable disease, and 23 (13.2%) had progressive disease. The complete response rate was significantly higher in patients receiving targeted therapy ($P < .001$; odds ratio = 0.0025, 95% CI = 0.006-0.109). Intracranial recurrence was observed in 28 (32.9%) patients after stereotactic radiosurgery/fractionated stereotactic radiosurgery: 7 (8.2%) were inside the radiotherapy field, 13 (15.3%) were outside the radiotherapy field, and 8 (9.4%) overlapped the radiotherapy field. Intracranial progression-free survival was higher in patients receiving concomitant immunotherapy ($P = .028$; hazard ratio = 0.107, 95% CI = 0.015-0.783). However, overall survival was higher in patients receiving targeted therapy ($P = .035$; hazard ratio = 0.217, 95% CI = 0.053-0.897).

CONCLUSION: Using current systemic agents with radiotherapy for brain metastasis significantly affected post-radiotherapy intracranial progression-free survival.

KEYWORDS: Lung cancer, radiotherapy, stereotactic radiosurgery, immunotherapy
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INTRODUCTION

Lung cancer is the most common cause of cancer-related deaths worldwide, accounting for 18%.[1] Brain metastases (BMs) are present in 10% of patients with non-small-cell lung cancer (NSCLC) at diagnosis, increasing to 50% during disease progression.[2] Patients with BMs have a poor prognosis, with an average survival time of 3-6 months. However, some studies have reported survival in these patients of up to 2 years, depending on their extracranial disease status, number and prevalence of BMs, general condition, and administered targeted and immunological agents.[3,4]

Together with the historical process, the cornerstones for treating BMs are surgery, systemic therapy, and radiotherapy [RT; stereotactic radiosurgery (SRS) and fractionated SRS (fSRS)].[2,5] Stereotactic radiosurgery/fractionated stereotactic radiosurgery has begun to be used as first-line therapy for BMs, given concerns over neurocognitive decline after whole brain RT (WBRT).[6,7] Surgery, chemotherapy, and RT have been used to treat BMs in patients with NSCLC from the past to the present, but effective and curative treatment remains impossible in many patients. Immunotherapy (IT) has recently begun to be used as a first-line treatment approach in patients with lung cancer, with promising results reported.[8,9] However, there are limited published data on combining SRS/fSRS–IT to treat BMs in patients with lung cancer. It is important to assess the efficacy and safety of combining current systemic treatment agents with SRS/fSRS. Therefore, additional studies on this subject are needed.

This study analyzed the results of patients with NSCLC–BMs treated with SRS/fSRS. It aimed to report the toxicity results and survival data for SRS/fSRS in this patient group.

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MATERIAL AND METHODS

This study retrospectively analyzed patients diagnosed with NSCLC–BMs who underwent SRS/fSRS in the Radiation Oncology Clinic of Ankara Bilkent City Hospital. It examined patient interview information, patient files, and RT planning data. Based on this information, the following patient data were recorded: demographic status, tumor volume, SRS/fSRS total dose and fraction number, planning target volume (PTV), PTV margin, gradient index (GI), conformity index (CI), V12 of brain gross tumor volume (GTV) during treatment, IT agents used concurrently with SRS/fSRS, targeted therapy agents, steroid use and dose, magnetic resonance imaging (MRI)-based response evaluation of lesions, recurrence status and time, and final status.

Patients Selection

This study included patients aged >18 years with a pathologically confirmed NSCLC diagnosis who developed BMs at diagnosis or during follow-up, who received SRS/fSRS at the Ankara Bilkent City Hospital Radiation Oncology Clinic, had complete file information, and had an Eastern Cooperative Oncology Group status of 0-3. Patients without pathological evidence and missing file or follow-up data were excluded. Since the study is a retrospective study, informed consent was not obtained from the patients.

Treatment Planning and Follow-up

Planning computed tomography (CT) images were obtained without contrast with a 1.25 cross-section interval on the GE Discovery brand simulation CT device for the patients' treatment planning. A thermoplastic mask was used for fixation. The obtained images were transferred to the Varian-Aria planning system and fused with contrast-enhanced brain MRI images for GTV determination. For PTV, a 1-5 mm margin was given to the GTV. Treatment plans were made with volumetric modulated arc therapy (VMAT) or hyperarc techniques using the TrueBeam Varian software system. Radiotherapy was given to patients on Varian TrueBeam STX and EDGE devices. The patients' follow-up and RT response evaluations were based on contrast-enhanced, thin-section brain MRIs taken at 3-month intervals after RT. These control brain MRIs were evaluated by comparing them with MRIs at diagnosis. Brain MRI images of the patients at diagnosis and control were evaluated as complete response (CR), partial response (PR), and progressive disease (PD) according to the Response Assessment in Neuro-Oncolog (RANO) criteria.

Primary and Secondary Endpoints

The study's primary endpoint was the lesions' response status after SRS/fSRS. Its secondary endpoint was the patients' intracranial progression-free (iPFS) and overall (OS) survival. Overall survival was the time to death after RT. The RT start date was considered the start date for OS and iPFS. The endpoint for OS was the last control date for surviving patients and the date of death for deceased patients. The endpoint for DFS was the date of the first event for patients with relapse and the date of the last control for patients without recurrence.

Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Continuous (quantitative) variables are expressed as mean, SD, minimum, and maximum values. Categorical variables are expressed as number (n) and ratio (%). The conformity of the variables to the normal distribution was assessed with Kolmogorov–Smirnov tests. The variables were compared using nonparametric tests because they were nonnormally distributed. The patients' categorical demographic characteristics were compared using chi-square and Fisher's exact tests. Univariate correlation analyses used Spearman's rank correlation coefficient (r_s). Kaplan Meier-log rank test were performed for univariate survival analysis. Cox regression analysis was used for multivariate survival analysis. The hazard ratio (HR) and 95% confidence interval (CI) values of the results that were significant in survival values were calculated.The hazard ratio (HR) and 95% confidence interval (CI) values of the results that were significant in survival values were calculated. for multivariate survival analysis.Cox regression analysis was for univariate survival analysis.Kaplan Meier-log rank test were An HR >1 denotes an increased risk relative to the reference category. The significance threshold of this study was set as .05.

Ethics Committee Approval

The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ankara Bilkent City Hospital Ethics Committee 1 with the number E1-22-2874 on September 7, 2022.

MAIN POINTS

- In this study, patients with a diagnosis of non-small cell lung cancer and brain metastases were evaluated according to the Response Assessment in Neuro-Oncolog (RANO) criteria.
- This study is one of the few studies in which the response evaluation of stereotactic radiosurgery/fractionated stereotactic radiosurgery (SRS/fSRS) is according to the RANO criteria.
- It was found that the survival of the patient with a complete response to the RANO criteria was better.
- Intracranial progression-free survival has been observed to increase with SRS/fSRS and immunotherapy.
- Overall survival has been observed to increase with targeted therapies and radiotherapy.

RESULTS

This study included 85 patients who underwent SRS/fSRS in our clinic for lung cancer BMs between February 21, 2019, and August 15, 2022. The total number of BMs that underwent SRS/fSRS was 174. The study's median follow-up period from the start of RT was 6.6 (range: 1-42) months. The patients' median number of BMs was 2.[1-6] The patients' median age was 62 (36-85) years. Seventy-two (85%) patients were male, and 13 (15%) were female. Extracranial metastases were present in 35 (41%) patients and absent in 50 (59%). Concurrent IT was administered to 10 (11%) patients and targeted therapy to 8 (9%). The IT administration was as follows: 6 patients were given pembrolizumab, 3 nivolumab, and 1 atezolizumab. The targeted therapy administered was as follows: 2 patients were given erlotinib, 2 afatinib, 2 alectinib, 1 lorlatinib, and 1 trametinib-dabrafenib. Patient and treatment details are summarized in Table 1.

Table 1. Patient Characteristics and Treatment Parameters

Patient Characteristic		Median
Age		62 (36-85)
Sex	Female	13 (15%)
	Male	72 (85%)
Follow up		6.6 (1-42)
Brain metastases number		2 (1-6)
Systemic agent	Immunotherapy	10 (11%)
	Targeted therapy	8 (9%)
Total lesion		174
Total dose		27 (15-30)
Fraction		3 (1-5)
PTV margin	Yes	125 (71.8%)
	No	49 (28.2%)
WBRT treatment		15 (6.4%)
Tumor diameter and volume		11 mm (0.4-52) and 1 cc (0.1-56.9)
Target parameters	GI	4.61 (1.4-13)
	CI	1.04 (0.6-1.5)
Treatment technique	HA	81 (46.6%)
	VMAT	93 (53.4%)
First response in MRI	CR	14 (6%)
	PR	62 (35.6%)
	SD	10 (5.7%)
	PD	23 (13.2%)
iPFS		6.3 (1-33)
OS		6.6 (1-42)

CI, conformity index; CR, complete response; GI, gradient index; HA, hyperarc; iPFS, intracranial progression-free survival; MRI, magnetic resonance Imaging; OS, overall survival; PD, progressive disease; PR, partial response; PTV, planning tumor volume; SD, stabile disease; VMAT, volumetric arc therapy; WBRT, whole brain radiotherapy.

Stereotactic Radiosurgery/Fractionated Stereotactic Radiosurgery Treatment Parameters

The median total SRS/fSRS dose was 27 (15-30) Gy. The median fraction dose was 9 (5-24), and the median fraction number was 3 (1-5). Treatment was given to 16 (18.8%) patients every other day, and 36 (42.4%) had concomitant steroid use. WBRT was given to 5 (6.4%) patients. WBRT was administered as the primary treatment for 4 patients with multiple brain metastases. In the follow-up of these patients, SRS/fSRS was applied to the progressive lesion. The median time between WBRT and SRS/fSRS was 120 (0-630) days. In 1 patient with multiple brain metastases, SRS was applied to the larger lesion together with WBRT. WBRT was at 30 Gy in 3 (3.5%) patients, 25 Gy for 1 (1.2%), and 20 Gy for 1 (1.2%). Surgery was performed on only 6 (3.4%) lesions.

While SRS/fSRS was applied to 7 (70%) of 11 patients who received IT due to progression, 2 of them were applied SRS/fSRS for both progression and septum control, and 1 (10%) of them was considered as oligometastatic because of metastatic at the time of diagnosis. Stereotactic radiosurgery/fractionated stereotactic radiosurgery was applied to 7 (87%) of 8 patients who received targeted therapy due to progression, and 1 (13%) of them being metastatic at the time of diagnosis, which was accepted as oligometastatic.

In all patients who underwent surgical resection, SRS/fSRS was applied to the cavity after resection. The median long tumor diameter was 11 (0.4-52) mm. The median tumor volume was 1 (0.1-56.9) cc. The median GI was 4.61 (1.4-13). The median CI-Radiation Therapy Oncology Group was 1.04 (0.6-1.5). Hyperarc was used in 81 (46.6%) patients and VMAT in 93 (53.4%). Critical organs within 5 mm of each lesion were evaluated, finding 1 (0.6%) tumor chiasma and 11 (6.3%) tumors close to the brain stem (Table 1). When analyzed according to tumor size, tumors >0.5 cc had lower GIs than tumors ≤0.5 cc ($P < .001$; Z = −7944; Table 2**;** Figure 1).

Stereotactic Radiosurgery/Fractionated Stereotactic Radiosurgery Lesion Response Assessment

Response Assessment in Neuro-Oncolog–brain metastasis criteria are standardized across clinical studies involving BMs and are recommendations for assessing tumor response and progression. The RANO-BM criteria divide treatment responses into 4 groups [CR, PR, stable disease (SD), and PD] based on imaging (MRI or CT) and clinical features.[10] This study used the RANO criteria to evaluate the MRI response. Patients with a CR at their first follow-up after RT had a better OS. Evaluation based on these criteria can predict clinical outcomes.

Of the 174 lesions, 109 (62.6%) had initial MRI controls. According to RANO–BM criteria, 14 (6%) had a CR, 62 (35.6) had a PR, 10 (5.7%) showed SD, and 23 (13.2%) showed PD. The CR rate was higher for lesions in patients who received targeted therapy (Table 3; $P < .001$; odds ratio (OR) = 0.0025, 95% CI = 0.006-0.109). Intracranial recurrence was observed in 28 (32.9%) patients after SRS/fSRS, of which 7 (8.2%) were inside the RT field, 13 (15.3%) were outside the RT field, and

Table 2. Tumor Volume, Gradient Index

Tumor Volume	>0.5 cc	≤0.5 cc
GI_Mean	4.265	7.000
GI_Median	4.000	5.800

GI, gradient index.

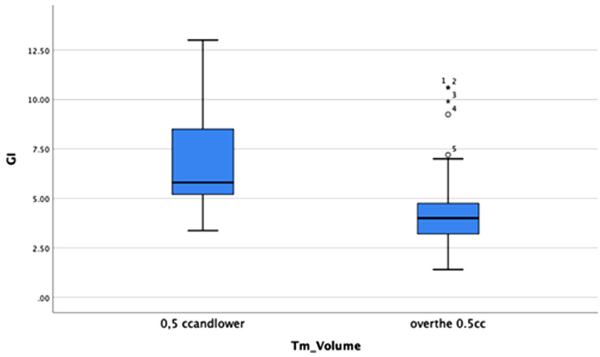

Figure 1. Gradient index and tumor volume box-blot image.

Table 3. Target Therapy and First Magnetic Resonance Imaging Response Relations

Target Therapy	First MRI Response		*P*	OR (95% CI)
	CR	Others		
No	3 (21.4%)	87 (91.6%)	<.001	0.0025 (0.006-0.109)
Yes	11 (78.6%)	8 (8.4%)		

CR, complete response; MRI, magnetic resonance imaging; OR, odds ratio.

8 (9.4%) overlapped the RT field. Patients with CR at their first follow-up had a significantly positive effect on OS compared to the other factors (Figure 2; *P* = .011; HR = 6.32, 95% CI = 1.53-26.01).

Intracranial Progression Free Survival Analysis

The relationships between the patients' response status at their initial control MRI and their OS and iPFS were analyzed. Patients with PD in their first control had a significantly negative effect on iPFS than the others (*P* < .001; HR = 0.116, 95% CI = 0.054-0.251; Figure 3), with a median iPFS of 5.3 (1-33) months. Intracranial recurrence was observed in 28 (32.9%) patients after SRS/fSRS, of which 7 (8.2%) were inside the RT field, 13 (15.3%) were outside the RT field, and 8 (9.4%) overlapped the RT field. Intracranial progression-free survival could be evaluated in 72 patients. While 10 patients who could not be evaluated died before the first control, 3 were excluded from the follow-up. Intracranial progression-free survival was not significantly affected by the number of metastases (*P* = .146), SRS/fSRS total dose (*P* = .576), SRS/fSRS fraction dose (*P* = .476), fraction number (*P* = .993), tumor volume (*P* = .637), longest tumor diameter (*P* = .420), GI (*P* = .878), CI (*P* = .662), RT technique (*P* = .086), sex (*P* = .956), extracranial metastases (*P* = .968), every-other-day treatment scheme (*P* = .361), steroid use (*P* = .348), age (*P* = .789), 5 mm adjacent critical organ (*P* = .554), targeted therapy (*P* = .425), or tumor bed RT status (*P* = .930). However, iPFS was significantly correlated with WBRT dose (*P* = .026; r_s = −0.866) and concurrent IT (*P* = .028; HR = 0.107, 95% CI = 0.015-0.783; Figure 4).

Overall Survival Analysis

Of the included patients, 53 (62.4%) were deceased, and 32 (37.6%) were alive. Their median OS was 6.6 (1-42) months. Overall survival was not significantly affected by the number of metastases (*P* = .900), SRS/fSRS total dose (*P* = .400), SRS/fSRS fraction dose (*P* = .278), fraction number (*P* = .284), tumor volume (*P* = .869), long tumor diameter (*P* = .266), GI (*P* = .751), CI (*P* = .518), WBRT total dose (*P* = .718), the time between WBRT and SRS/fSRS (*P* = .872), sex (*P* = .058), the presence of extracranial metastases (*P* = .9), treatment every other day (*P* = .965), steroid use (*P* = .528), age (*P* = .627), 5 mm adjacent to the critical organ (*P* = .655), concurrent IT status (*P* = .369), and WBRT status (*P* = .972). However, OS was significantly affected by the RT technique (*P* = .011; HR = 1.64, 95% CI = 1.119-2.414) and targeted therapy (*P* = .035; HR = 0.217, 95% CI = 0.053-0.897; Figure 5 and 6). Overall survival was significantly better in patients with CR at the first control than in the others (*P* = .011; HR = 6.32, 95% CI = 1.53-26.01; Figure 2).

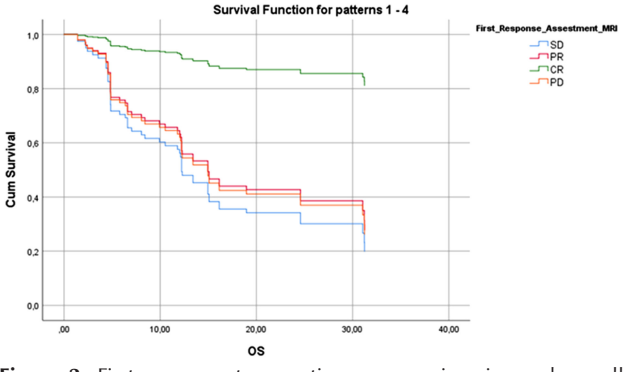

Figure 2. First assessment magnetic resonance imaging and overall survival Cox regression analysis image.

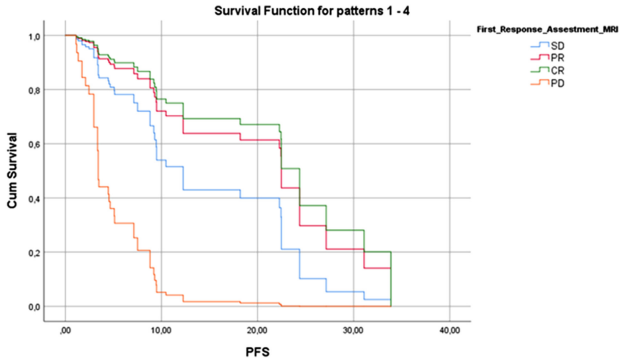

Figure 3. First assessment magnetic resonance imaging and intracranial progression-free survival Cox regression analysis image.

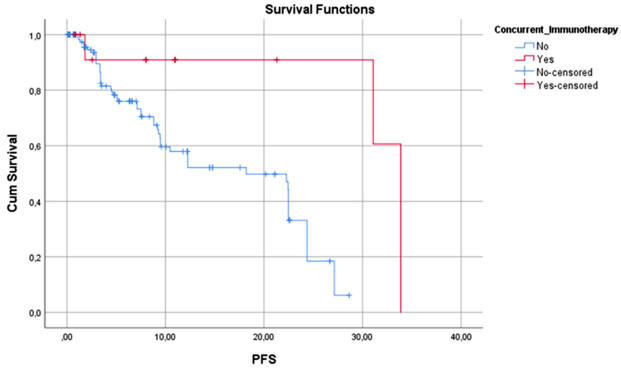

Figure 4. Images of intracranial progression free survival and concurrent immunotherapy Kaplan–Meier analysis images.

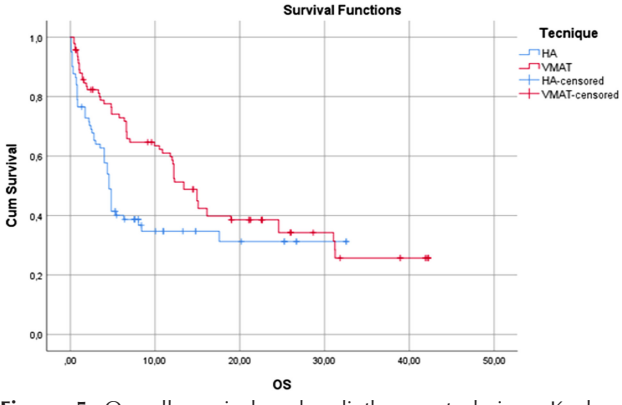

Figure 5. Overall survival and radiotherapy technique Kaplan–Meier analysis images.

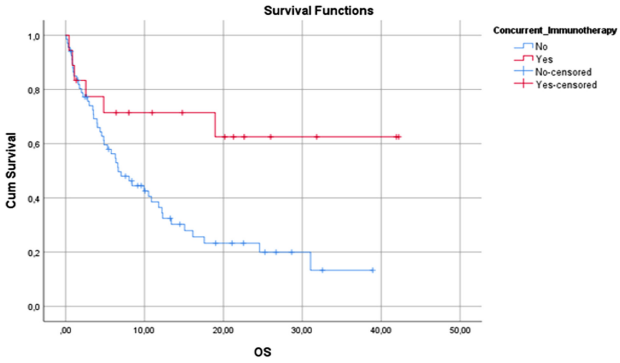

Figure 6. Overall survival and targeted therapy Kaplan–Meier analysis images.

DISCUSSION

This study examined 174 lesions in 85 patients with NSCLC–BM treated with SRS/fSRS. The CR rate was higher in patients receiving the targeted therapy than in others. Patients with a PD response at their first control had a significantly worse iPFS than the others. Patients with a CR response at their first control had a significantly better OS than the others.

In patients with BMs, the reported 7- to 14-month survival rates after SRS/fSRS are similar to surgical resection.[11] Although surgery is indicated for lesions >3 cm that cause a mass effect and are suitable for resection, SRS/fSRS is often preferred in current clinical practice because it is a less invasive and more cost-effective treatment option than resection. Leyrat et al evaluated SRS/fSRS in NSCLC–BM patients, finding a median follow-up period of 12 months and a median OS of 14 months.[12] Minitti et al reported that OS was 15.2 months after SRS/fSRS in NSCLC–BM patients with a median follow-up period of 12 months.[13] In our study, ablative RT doses were applied to lesions considered oligometastatic. Our follow-up period was 6 months, and our median OS was 6.6 months and the iPFS was 5.3 months, and we expect higher OS and iPFS could be obtained by prolonging the follow-up period.

The interactions between immune checkpoint inhibitors (ICIs) and SRS/fSRS must be investigated due to the increasing number of patients with metastatic cancer receiving ICIs. Stereotactic radiosurgery and fSRS act synergistically with immune regulators through many mechanisms, including tumor antigen release, increased antigen-presenting cell activation, increased blood–brain barrier permeability, and cell surface molecule upregulation.[14-16] Clinical data show that combining RT and ICIs increases OS if ICIs are started at least 30 days before and continued throughout RT therapy.[17,18] In our study, there was a significant relationship between IT use and iPFS, consistent with the literature, but not with OS. We believe that this may be due to our small number of patients.

While these combined therapies have survival benefits, there are concerns that combining SRS/fSRS and immune regulators may increase the risk of toxicity. In a retrospective study by Ahmed[19] et al, no additional toxicity was observed after co-administrating SRS/fSRS and anti-PD1/PDL1 treatment in NSCLC patients with BMs. Similarly, there is reassuring data on the safety profile and efficacy of combining anti-PD1/anti-PDL1 agents and various RT regimens (SRS/fSRS and WBRT).[20] There was only a potential warning of increased radionecrosis risk. Unlike these studies, other studies have shown that combined therapy increases side effects such as radionecrosis. A retrospective study evaluating 80 patients with melanoma showed that combining SRS/fSRS with an ICI increases symptomatic radionecrosis risk.[21] Another study by Martin et al[22] observed an increase in symptomatic radionecrosis after combining SRS/fSRS with an ICI in a patient population with NSCLC, melanoma, and renal cell carcinoma. However, most of this patient population comprised melanoma patients. In general practice, 50% of clinicians do not interrupt ICI when applying SRS/fSRS or WBRT to the brain.[23] In our study, no serious side effects were observed during patient follow-up.

The most important limitations of the study are its single-center and retrospective nature. The number of patients was small, the follow-up period was short, and long-term side effects could not be evaluated. Due to the lack of patient files, CT details such as the number of CT courses could not be reached for all patients.

CONCLUSION

This study examined patients who have undergone SRS/fSRS for diagnoses of NSCLC and BMs, evaluating the patients' treatment responses with the RANO criteria. Patients with CR according to the RANO criteria showed better survival. Intracranial progression-free survival increased with SRS/fSRS and IT, and OS increased with targeted agents and RT.

Ethics Committee Approval: This study was approved by Ethics Committee of Ankara Bilkent University City Hospital (Approval No: E1-22-2874, Date: 07.09.2022).

Informed Consent: Since the study is a retrospective study, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.Y.D., T.K.; Design – F.Y.D., T.K.; Supervision – İ.P.A., G.A.İ, Y.T.; Resources – F.Y.D., T.K.; Materials – F.Y.D., T.K.; Data Collection and/or Processing – A.A., A.K.A, B.D., F.B.A., E.G.; Analysis and/or Interpretation – F.Y.D., T.K.; Literature Search – F.Y.D., T.K.; Writing – F.Y.D., T.K.; Critical Review – İ.P.A., G.A.İ, Y.T.

Declaration of Interests: The authors have no conflict of interest to declare.

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