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Radiation necrosis risk assessment after stereotactic radiation therapy for brain metastasis

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ABSTRACT

Objective: To investigate factors influencing the occurrence of radiation necrosis (RN) in patients receiving fractionated stereotactic radiotherapy (fSRT) for brain metastases.

Patients and Methods: Forty patients underwent linear accelerator-based fSRT from January 2018 to December 2023. RN and treatment response were monitored using magnetic resonance imaging (MRI), with toxicity graded by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and oncological response was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Results: At a median follow-up of 12 months, RN occurred in 4 (10%) patients. Two patients had asymptomatic grade 1 RN, while two required steroids for grade 2 RN. Univariate analysis showed significant factors for RN: history of repeated fSRT (p=0.020), >1 metastatic lesion (p=0.022), age (p=0.016), and brain V30 (p=0.022). Multivariate analysis confirmed that repeated fSRT (p=0.02) and age (p=0.002) were significant.

Conclusion: Radiation necrosis is a major concern in fSRT for brain metastases. Repeated fSRT, multiple metastatic lesions, age, and higher brain V30 values increase RN risk. Individualized treatment planning, especially considering dose-volume parameters, may help reduce this risk. Larger prospective studies are needed to confirm these findings and optimize RN mitigation strategies.

Keywords: Brain metastasis, Fractionated stereotactic radiotherapy, Radiation necrosis

1. INTRODUCTION

The advancements in systemic treatments and radiotherapy (RT) techniques have led to an increased life expectancy for patients with metastatic disease. Through easier access to radiological methods and their more frequent use, metastases are now being detected more often and at earlier stages [1]. Brain metastasis is seen in 30% of patients diagnosed with cancer and is the most common cause of neurological complications [2]. The three most common tumors that metastasize to the brain are lung, breast, and kidney cancer [3]. The main treatment for brain metastasis is surgery, whole brain RT (WBRT), fractionated stereotactic radiotherapy (fSRT), single fraction stereotactic radiosurgery (SRS), or a combination of these treatments. Currently, guidelines recommend stereotactic RT alone in cases with 1-4 brain metastases [2]. The International Stereotactic Radiosurgery Society (ISRS) recommends stereotactic RT alone in its guideline for one brain metastasis if surgery is not necessary for a single brain metastasis. In cases with 2-4 brain metastases, if surgery is not necessary (if there is a need for urgent surgery according to clinical symptoms, surgery is recommended), it recommends stereotactic RT. In tumors measuring 3 cm and above, surgery is recommended first, and in non-surgical cases, hypofractionated regimens or fSRT are recommended. In patients with 1-4 metastases, it is recommended that WBRT be left as salvage therapy [3].

The use of fSRT for intact brain metastases and surgical cavities is on the rise compared to WBRT. fSRT is favored due to its superior preservation of neurocognitive functions in patients, in addition to the growing availability of advanced technological devices designed for delivering stereotactic RT [4].

Stereotactic RT provides highly effective radiation dose to the target in 1-5 fractions [5]. Although, there are studies conducted with single fraction SRS for brain metastases, the number of studies evaluating radiation necrosis (RN) with the fSRT scheme is low. Studies comparing SRS and fSRT in terms of oncological outcomes have shown no significant difference in local control

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rates but have reported no difference or a slight increase in RN [6-7]. The RN rate in focal brain RT varies between 3-14% [8]. The most important factors affecting the development of RN in focal brain RT are radiation dose, fraction dose and concurrent systemic treatments [9]. Although it is difficult to distinguish and determine the true RN rate from possible tumor recurrence, according to literature, the symptomatic RN rate varies between 5-10% in stereotactic treatments [10,11].

Finding the optimal radiation dose in RT is important in terms of oncological results and side effects. While, the possibility of tumor control increases with high radiation doses, the possibility of normal tissue complications also increases simultaneously. It is important to find an ideal therapeutic index with optimum tumor control and acceptable toxicity. While good oncological results are obtained with fSRT or SRS, serious and symptomatic RN is seen in some cases [12].

In the current study, we aimed to investigate the factors affecting the occurrence of RN in patients who underwent fSRT for brain metastases.

2. PATIENTS and METHODS

Study population

This retrospective study was conducted after obtaining permission from the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University (approval date: 19.03.2024 and decision number: 40). There were 40 adult patients with 60 lesions who underwent fSRT between January 2018 and December 2023 at the Department of Radiation Oncology, Faculty of Medicine, Eskişehir Osmangazi University. Forty cases (with 60 lesions) who were regularly followed and had radiological images were included in the analysis. Patients who underwent fSRT for 1 or more tumors, received 5-9 Gy per fraction in 3-5 fractions, were included in the study. The clinician decided on the fSRT scheme based on the number, volume of the tumors, and their proximity to critical organs. Study patients and disease characteristics are summarized in Table I.

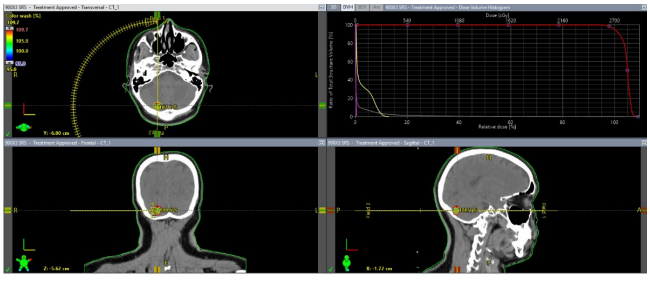


Figure 1. *Representative example of the treatment planning process*

Table I. *Patient and disease characteristics*

Characteristics	
Median age (range)	62 (39-75)
Median KPS (range)	80 (60-100)
	n (%)
Gender	
Female	11 (27.5)
Male	29 (72.5)
Comorbidity	
Yes	20 (50)
No	20 (50)
Smoking history	
Yes	27 (67.5%)
No	13 (32.5%)
Primary tumor site	
Lung	27 (67.5)
GIS	4 (10)
GUS	4 (10)
Gynecological	2 (5)
Breast	2 (5)
Brain	1 (2.5)
Primary tumor histopathology	
Adenocarcinoma	24 (60)
Squamous cell carcinoma	10 (25)
Invasive ductal carcinoma	2 (5)
Renal cell carcinoma	1 (2.5)
Urothelial carcinoma	1 (2.5)
Malignant hemangiopericytoma	1 (2.5)
Serous carcinoma	1 (2.5)

KPS: Karnofsky Performance Status, GIS: Gastrointestinal System, GUS: Genitourinary System

Radiotherapy simulation, target volumes, dose calculations and treatment planning

Planning computer tomography (CT) of the patients was obtained with Siemens Somatom Definition AS® (Siemens Healthineers, Germany) or GE Discovery RT BT® devices (General Electric, United States) at a 1.25 mm slice interval. The patients were immobilized in the supine position with a thermoplastic mask.The gross tumor volume (GTV) was contoured with T1 postgadolinium images after the fusion of contrast-enhanced magnetic resonance imaging (MRI) (Siemens Magnetom Avanto TIM MR, Germany) with the planning CT. A margin of 3 mm (reduced to 1 mm in tumors close to critical structures) was given in all directions for the planning target volume (PTV). The brain contour was obtained up to the

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foramen magnum, including the entire brain. Treatments were planned with megavolt (MV) 6 flattening filter free (6 FFF) photon beam or 6 MV photon beam and volumetric modulated arc therapy (VMAT) technique using partial or full-circle arc according to the location of the tumor with Varian Eclipse System (version 15.6; Varian Medical Systems, Palo Alto, CA, United States). Figure 1 illustrates a representative example of the treatment planning process. The brain volumes receiving 5 Gy (V5), 10 Gy (V10), 15 Gy (V15), 20 Gy (V20), 25 Gy (V25) and 30 Gy (V30) were obtained. In patients with multiple fSRT histories, the fusion of planning CTs was performed in the planning system, plan-sum were obtained, and brain volumes were evaluated based on the total plan.

In cases where WBRT or partial brain irradiation was performed at any stage of their treatment, cumulative biologically effective dose $(BED)_{10}$ and equivalent dose in 2Gy fractions (EQD_2) values were calculated. BED_{10} calculation was obtained using the formula $BED_{10} = n \cdot d\left[1+\frac{d}{\alpha/\beta}\right]$ $(\alpha/\beta=10)$ [16]. EQD_2 was obtained using the formula $EQD_2 = \frac{BED_{10}}{(1+\frac{2}{\alpha/\beta})}$ $(\alpha/\beta=10)$ [13].

The patients were treated with Varian TrueBeam®/Trilogy® linear accelerator device (Varian Medical Systems, Palo Alto, CA, United States). Before and after the treatment, kV cone beam CT images were obtained for each fraction.

Patients follow-up

The follow-up protocol began one month after fSRT and continued every three months, including symptoms and examination. The contrast-enhanced brain MRI, MRI susceptibility weighted imaging (SWI), MRI diffusion-weighted imaging (DWI) and perfusion MRI images were obtained every 3 months. Given the complexity of post-radiotherapy changes in brain tissue, especially pseudoprogression and RN, morphological assessment based on Response Evaluation Criteria in Solid Tumors (RECIST) was supported by advanced MRI techniques, including DWI, and perfusion-weighted imaging (PWI) [14]. In cases with suspected RN or tumor recurrence, MRI was performed more frequently every 6 to 8 weeks and patients were discussed with these images in the oncology board for treatment.

Radiation necrosis assessment was made according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Grade 1: Imaging findings only, asymptomatic, Grade 2: Symptomatic, medical management required, Grade 3: Severe symptoms, hospitalization required, affecting daily life, Grade 4: Life-threatening cerebral edema or neurological compromise, Grade 5: Death due to RN) [15]. fSRT response evaluation was performed using MRI according to RECIST and divided into four groups as complete response, partial response, progressive disease, or stable disease. (Complete Response (CR): Disappearance of all target lesions, Partial Response (PR): ≥30% decrease in the sum of diameters of target lesions, Progressive Disease (PD): ≥20% increase in the sum of diameters or appearance of new lesions, Stable Disease (SD): Neither sufficient shrinkage for PR nor sufficient increase for PD) [16].

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (licensed by Eskişehir Osmangazi University, Eskişehir, Türkiye; IBM Corp., Armonk, NY, United States).Shapiro-Wilk test was used to determine the suitability of the variables for normal distribution. Independent samples t-test and Mann-Whitney U test were used to compare the groups according to their distribution forms. One-way ANOVA and Kruskal-Wallis test were used to compare the groups according to their distribution forms. POST-HOC tests were used to determine the different groups. Chi-square tests were used in the analysis of the created crosstabs. In summarizing the data, number (%) statistics were used for qualitative data and Mean±SD or Median (min/Q1; max/Q3) statistics were used for quantitative data. The Kaplan-Meier method with the log-rank test was used to compare the median survival times between patients with and without necrosis. To evaluate the impact of univariate variables on the presence of necrosis, multivariate logistic regression analysis with the backward stepwise method was performed. $P<0.05$ was considered statistically significant.

3. RESULTS

Treatment characteristics and details are summarized in Table II.

The median tumor size was 15 mm (min: 3 mm, max: 42 mm), while the median tumor number was 1 (min: 1, max: 4). Six patients had a history of surgery for brain tumors (five due to metastasis and one due to primary brain tumor). The median time between primary diagnosis and metastasis is eight (min: 0, max: 108) months. Ten patients had brain metastasis at the time of diagnosis. Twenty-six patients had a history of WBRT, eight patients underwent re-fSRT, and in two patients, GTV localizations were in the same region in re-fSRT.

The median dose of the last applied fSRT was 27 Gy (min: 21 Gy, max: 30 Gy). The median GTV and PTV were 5.5 (min: 0.1 cc, max: 58.7 cc) and 12.5 cc (min: 1 cc, max: 76.9 cc), respectively. The cumulative BED_{10} median was 63 Gy (min: 35.7 Gy – max: 189 Gy), while the cumulative EQD_2 median was 52.5 Gy (min: 29.7 Gy – max: 157.5 Gy). The median cumulative BED_3 was 119 Gy (range: 66.6–392 Gy).

Radiation necrosis was observed in a total of four (10%) patients, two cases were grade 2 requiring steroid treatment and the other two cases were asymptomatic grade 1. An MRI image demonstrating RN is presented in Figure 2. All patients were ≤ 55 years old, and there was a statistically significant difference between RN development and age (p= 0.016). There were no statistically significant relationships between RN and gender, performance status, comorbidity, smoking history, tumor site, BED_3 and histopathology. Statistical analysis was performed to compare necrosis between the small cell lung cancer (SCLC) and non-small

cell lung cancer (NSCLC) groups, and no statistically significant difference was found between the two groups (p = 0.584).

Table II. *Treatment characteristics*

Characteristics	n (%)
WBRT or partial brain RT history	
Yes	14 (35)
No	26 (65)
fSRT history	
Yes	8 (20)
No	32 (80)
	Median (Minimum-Maximum)
GTV (cc)	5.5 (0.1 – 58.7)
PTV (cc)	12.5 (1 – 76.9)
Last fSBRT dose (Gy)	27 (21-30)
Last fSBRT fraction dose (Gy)	9 (5-9)
Last fSBRT BED_{10} (Gy)	51.3 (35.7 – 51.3)
Doses (Gy) received by brain (cc)	
V5	192 (20-607)
V10	71 (8-263)
V15	32 (4-174)
V20	18 (1-115)
V25	8.8 (0-115)
V30	0 (0-63)
Cumulative BED_{10} (Gy)	63 (35.7 – 189)
Cumulative EQD_2(Gy)	52.5 (29.7 – 157.5)

WBRT: Whole brain radiotherapy, RT: Radiotherapy, fSRT: Fractionated stereotactic radiotherapy, BED: Biologically effective dose, GTV: Gross tumor volume, PTV: Planning target volume, EQD2: Equivalent dose in 2Gy fractions

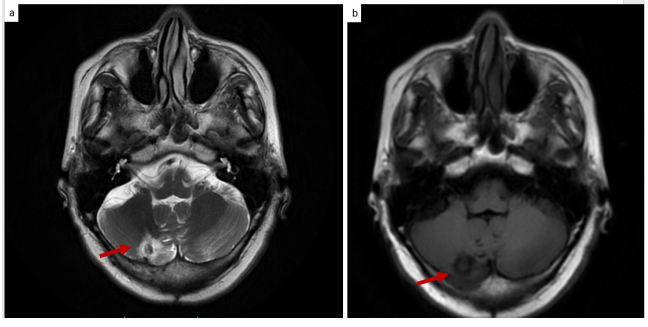


Figure 2. *An MRI image demonstrating radiation necrosis*

a: Post-contrast axial T2-weighted MRI image; b: Axial T1 FLAIR image at the same level. Red arrows indicate the area of radiation necrosis

One patient developed RN with four lesions, two patients had three lesions each, and one patient had a single lesion. The risk of RN increased as the number of metastatic lesions in a patient treated with fSRT increased (p=0.022). RN was observed in 14.3% of patients with a history of WBRT/partial brain RT at any stage of the treatment, while it was observed in 7.7% of patients without a history of WBRT (p=0.602).

There was a history of repeated fSRT in eight cases. RN was identified in three out of eight patients (37.5%) who underwent more than one session of fSRT, whereas RN was observed in only one out of 32 patients (3.1%) treated with a single fSRT session. These findings indicate that multiple fSRT treatments significantly increase the risk of developing RN (p = 0.020).

Table III. *The dosimetric data*

Characteristics	Q1	Median	Q3	p
Brain V5 (cc)				
RN (-)	61.5	172.9	273.0	**0.058**
RN (+)	180.0	391.5	560.1	
Brain V10 (cc)				
RN (-)	23.0	65.0	115.7	**0.053**
RN (+)	77.4	168.0	233.1	
Brain V15 (cc)				
RN (-)	12.2	30.0	60.7	0.079
RN (+)	42.1	69.5	126.9	
Brain V20 (cc)				
RN (-)	5.7	15.7	42.7	0.079
RN (+)	26.5	43.8	90.1	
Brain V25 (cc)				
RN (-)	2.0	6.0	24.5	**0.052**
RN (+)	17.1	27.8	66.3	
Brain V30				
RN (-)	0.0	0.0	0.0	**0.022**
RN (+)	0.0	5.3	32.9	
Cumulative EQD_2 (Gy)				
RN (-)	42.7	42.7	73.5	0.070
RN (+)	56.5	128.3	152.8	
Cumulative BED_3 (Gy)				
RN (-)	51.3	51.3	88.2	0.070
RN (+)	67.8	154.0	183.3	

BED: Biologically effective dose, EQD2: Equivalent dose in 2Gy fractions, RN: Radiation necrosis

No statistically significant difference was observed with the fSRT fraction dose (p=0.282). In patients with RN, cumulative BED_{10} was 43.2, 141.6, 166.5 and 189.0 Gy (p=0.070). Cumulative EQD_2 were 36, 118, 138.7 and 157.5 Gy (p=0.070).

Radiation necrosis was seen in three of 25 cases (12%) with complete and partial response and in one of 15 cases (6.7%) with stable and progressive response (p=1.00). Although the RN rate

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was higher in cases that responded to treatment, it did not reach statistical significance.

Dosimetric results are summarized in Table III. The high dosimetric values seem to be moderately related to RN development, but none reached statistical significance except for brain V30 (p=0.022). While the median GTV volume was 4.7 and 13.6 cc in cases where RN was not observed and observed, the median PTV volume was 10.8 and 27.8, respectively. Although the GTV and PTV volumes were larger in cases where RN was observed, they did not reach statistical significance (p=0.430 and p=0.260). The median tumor diameter in cases with RN was 26.5 mm, while it was 13.5 mm in cases without RN. Although the tumor dia meter was larger in cases with RN, it did not reach statistical significance (p= 0.214).

Multivariate logistic regression analysis was performed using the variables identified as significant in univariate analyses for their association with the development of RN, including history of repeated fSRT, presence of >1 metastatic lesion, age, and brain V30. Among these, history of repeated fSRT (p = 0.02) and age (p = 0.002) were found to be statistically significant.

At a median follow-up of 12 months, 33 (82.5%) cases died. All patients died of disease progression, and no patients died of RN. According to RECIST criteria, the number of patients with complete, partial, stable and progressive responses was 13 (32.5%), 12 (30%), 8 (20%) and 7 (17.5%), respectively. Median overall survival (OS) after fSRT was 10 months (min: 7, max: 58). The median OS in cases with RN was 15.5 months, while it was 9.5 months in cases without RN (Figure 3). RECIST response was found to be associated with tumor diameter (p= 0.011) and PTV volume (p=0.048).

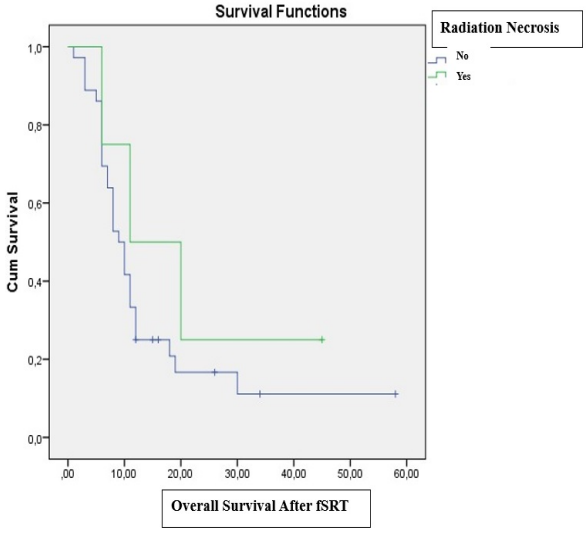


Figure 3. *Radiation necrosis and overall survival curve*

4. DISCUSSION

In the present study, 28 patients had a single lesion, six patients had two lesions, four patients had three lesions, and two patients had four lesions. 5-9 Gy/fr x 3-5 fraction schemes were selected for the patients, considering the number of tumors, tumor locations, and dimensions. In cases with progression, fSRT or WBRT was preferred as salvage therapy, again depending on the number of tumors, tumor size, and location.

In our study, there is a statistically significant relationship between RN and age (cases with RN ≤ 55 years), multiple fSRT history, multiple metastatic lesions and brain V30. In the study conducted by Andruska et al., with 83 patients and 117 brain metastases, 30 Gy fSRT was applied in 5 fractions. There was a previous history of SRS for 21 (18%) lesions. The median follow-up period in the study was 10.3 months and the rate of RN was 15% [17]. As in our study, a statistically significant difference was found between cases that underwent multiple stereotactic RT and RN. It has been shown that high brain V25 and brain V30 dosimetric parameters significantly increase the risk of RN [17]. In our study, brain V30 was also found to be associated with the development of RN. An increase in the risk of RN in cases that underwent multiple fSRT is an expected situation and the risk increases as the radiation dose to which the brain tissue is exposed increases. In studies conducted with cases that underwent multiple SRS to the brain, it has been shown that this multiple SRS application increases RN and the rate of RN in this group is over 20% [18,19].

In a study conducted by Sayan et al., 170 patients and 323 lesions were treated with 12-27.5 Gy stereotactic RT in 1-5 fractions [20]. The symptomatic RN rate was found to be 4% in this study. A large target volume was found to be associated with the development of symptomatic RN. In addition, the application of stereotactic RT in a single fraction, the presence of a diagnosis of diabetes, and high brain V10 and brain V15 were also found to increase the risk of RN [20]. In our current study, the multiple number of metastatic lesions to which fSRT was applied was found to be associated with the development of RN. As expected, as the number of metastatic lesion increases, the target volume also increases. In a study conducted by Blonigen et al., the relationship between irradiated brain volume and RN was investigated [21]. Stereotactic RT was applied to 63 patients and 173 lesions, and 63% of these cases had a history of WBRT. In this study, symptomatic RN was observed in 10% and asymptomatic RN in 4% of the cases. Brain V10 Gy >10.45 cc and brain V12 Gy > 7.85 cc were found to be associated with the development of RN [21]. In a study conducted by Milano et al., it was stated that the risk of RN would decrease to below 10% if brain V18 was below 30 cc and brain V23 was below 7 cc in fSRT applied in 3 fractions [22].

Our findings showed a lower RN incidence (10%) compared to the findings of Andruska et al., (15%) despite a similarly fractionated regimen, which may be attributed to differences in patient selection and lesion volumes [17]. Moreover, the presence of multifocal disease in our cohort seems to contribute more prominently to RN risk, a factor that was less emphasized in previous studies. These discrepancies underline the importance of stratifying patients not only based on dosimetry, but also on metastatic burden and prior treatment history.

In most cases of brain metastasis, tumor control is more important than the risk of developing RN. RN usually presents

as radiographic changes without neurological symptoms, and asymptomatic RN usually does not require any treatment. Symptomatic RN responds to short-term corticosteroids in most cases. In cases that do not respond to/cannot tolerate corticosteroids, symptoms can be reduced with other interventions. Therefore, although it is important to minimize the potential risks for RN, this is not the only concern. When a dose that can treat a metastatic tumor is given, there is a risk of RN at some level in almost all cases [10].

However, the clinical acceptability of RN particularly in asymptomatic cases should be contextualized with quality of life measures. Therefore, even "acceptable" toxicities warrant closer scrutiny, especially in long-surviving patients.

A recent study demonstrated that quality of life was preserved or even improved in most patients who underwent SRS for brain metastases [23]. These findings align with the longer OS observed in patients who developed RN in our study, suggesting that RN may represent an acceptable toxicity in the context of improved oncological outcomes. In the mentioned study, 34% of patients showed improvement in quality of life and 16% remained stable after SRS. These results support the notion that the impact of RN on quality of life may be limited, and that the risk of RN could be considered acceptable in clinical practice to ensure sufficient tumor control [23].

In our current study, the median OS in cases developing RN was 15.5 months, while it was 9.5 months in cases not developing RN. Single-fraction SRS has become frequently used in the treatment of brain metastases due to its increased local control and preservation of neurocognitive functions [9]. However, in these single-fraction treatments, tumor sizes greater than 1 cm and high brain V10 and V12 may cause RN to be seen in 50% of cases [9, 24,25]. Therefore, it is necessary to reduce the dose in large-sized tumors, multiple tumors or tumors with high GTV/PTV volume, which is associated with poor local control. For this reason, the use of fSRT in tumors with these characteristics seems more appropriate, as RN rates decrease to 10-15% and 1-year local control reaches 70-90% [26].

Additionally, a study by Ohguri et al., demonstrated that brain RN was significantly more prevalent in the deep white matter around the lateral ventricles when VMAT-based stereotactic irradiation was used [27]. This finding underscores the potential impact of tumor location on RBN development, suggesting that proximity to critical brain structures may increase susceptibility. In our study, tumor location was not specifically assessed, which represents a limitation and an important consideration for future investigations aiming to refine risk stratification and treatment planning in stereotactic RT.

Our data support the individualized adjustment of fractionation schemes based on lesion size and prior RT history. Specifically, in patients under 55 years with multiple lesions or a history of prior SRS/fSRT, adopting lower per-fraction doses might reduce RN risk without compromising tumor control.

Our study's median follow-up of 12 months provides a relatively long-term perspective on the development of RN, allowing the identification of both asymptomatic and symptomatic cases. This may add to the growing literature on acceptable risks of RN in the context of maintaining tumor control and patient survival. Based on our study results, treatment strategies for patients undergoing fSRT may need to be adapted to individual risk factors, particularly age, number of metastatic lesions, and brain V30 dosimetric parameters. In cases of multiple metastatic lesions, more fractionated schedules may be considered to minimize the risk of RN while maintaining tumor control. Additionally, for those with a longer life expectancy or less extensive brain metastases, higher fSRT doses may be used without significantly increasing the risk of RN. For patients with preexisting neurological conditions or greater sensitivity to RN, dose selection should be made carefully to balance the risk and benefit of treatment. Further prospective studies are needed to determine precise dose-volume constraints that optimize fSRT outcomes in different patient populations.

The biggest limitations of the study are the small number of patients and the heterogeneity of the groups. There are patients who only received fSRT, WBRT + fSRT, WBRT and multiple fSRT, and patients who underwent or did not undergo surgery in these groups. However, considering the increasing life expectancy of the patients, these heterogeneous multiple treatment options will always be encountered, and it is important to find the most appropriate treatment method.

Conclusion

Radiation necrosis remains a significant concern in patients undergoing fSRT for brain metastases. Our findings suggest that repeated fSRT, the presence of multiple metastatic lesions, advanced age, and higher brain V30 values are associated with an increased risk of RN. Careful patient selection and individualized treatment planning, particularly with respect to dose-volume parameters, may help mitigate this risk. Further prospective studies with larger cohorts are warranted to validate these findings and to develop optimized strategies for minimizing RN while maintaining treatment efficacy.

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Compliance with Ethical Standards

Ethical approval: This retrospective study was conducted after obtaining permission from the 'Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University (approval date: 19.03.2024 and decision number: 40).

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Author contributions: MY and DE: Concept and design, MY: Data acquisition, MY and DE:Drafting the manuscript, MY and DE: Critical revision. Both authors read and approved the final manuscript.

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