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Results of stereotactic radiosurgery in the treatment of radioresistant brain metastases

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ABSTRACT

Aims: The incidence of brain metastases in patients with renal cell carcinoma (RCC) and malignant melanoma (MM) with radioresistant histologies is over 50%. Stereotactic radiodiosurgery (SRS), which delivers high-dose radiation to target volume, may be beneficial in treating radioresistant histologies. The effectiveness of SRS in terms of local control and survival rates in the treatment of patients with radioresistant brain metastases was the focus of our study.

Methods: A retrospective review of RCC and MM brain metastases treated with SRS between 2013 and 2020 was conducted. Local control rates, distant brain metastases free survival, and overall survival (OS) were study endpoints.

Results: 55 brain metastases were detected in 29 patients, 14 of whom were MM and 15 were RCC. The median follow-up time was 13 (1-89) months. The 1-y and 3-y actuarial local control rates were 82.4% and 59%, respectively. Increased size and volume of brain metastases were associated with progressive disease (p=0.041, p=0.002). Local control rates were increased in those receiving whole brain radiotherapy (WBRT) prior to SRS (0.008). The 1-y and 3-y distant brain metastases free survival were 87.7% and 60.2%, respectively, and increased in those receiving WBRT before SRS, but not statistically significant (p=0.403). The median OS was 8 months (HR: 1.79, 95% CI: 4.48-11.51). There was no difference in OS according to whether the primary disease diagnosis was RCC or MM (p=0.482). Patients with 1-2 brain metastases had better OS than patients with 3 or more brain metastases (p=0.029). Recursive partitioning analysis (RPA) and graded prognostic assessment (GPA) prognostic risk scores were significantly related to OS (p=0.001, p<0.001). OS worsened in patients who received WBRT before SRS compared to those who did not (0.035). OS increased statistically in patients who received immunotherapy (p=0.033).

Conclusion: Improvement in local control was found in patients with small tumor diameter and volume. The addition of WBRT to the SRS increased both local control and distant brain metastasis free survival. Regarding OS, multiple metastases, high RPA score, and low GPA score worsened OS. Another crucial observation is that a positive predictive effect on OS was detected in patients in whom immunotherapy was combined with SRS.

Keywords: Brain metastases, malignant melanoma, radiosurgery, radioresistant, renal cell carcinoma

INTRODUCTION

Brain metastases are the most common intracranial malignancy seen in adults.[1] Radiotherapy has pivotal role in the management of brain metastases. While whole brain radiotherapy (WBRT) has traditionally been applied for brain metastases, with the development of modern radiotherapy techniques, stereotactic radiosurgery (SRS) techniques have been used and its effectiveness has been proven with the data accumulated over time. High ablative doses are administered in 1 to 5 fractions by SRS to the target tumor volume. According to the evidence obtained from landmark randomized phase 3 studies, local control is provided at a similar or higher rate with SRS, and at the same time, neurocognitive dysfunction is observed at a lower rate compared to WBRT.[2,3] In the light of these findings, SRS has become the treatment of choice for patients with a limited number of (1-4) brain metastases.[4]

The incidence of brain metastases in patients with renal cell carcinoma (RCC) and malignant melanoma (MM) histologies is over 50%.[5,6] When the treatment responses of patients with these histologies were examined, lower local control rates were

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shown compared to other histologies treated with WBRT.[7,8] These tumors are radiobiologically resistant to radiotherapy and are defined as radioresistant tumors. On the other hand, radioresistant tumors were not typically included in the studies stated above that demonstrated the effectiveness of SRS.2,3 In most retrospective series, higher local control rates and increased survival were seen compared to WBRT, when ablative doses were applied with SRS in brain metastases of RCC and MM.[9-11] It is anticipated that radioresistance lowers through altering hypoxia thanks to ablative doses.9 The local control rates in radioresistant tumors treated with SRS were also observed to be comparable to other histologies in numerous retrospective series.[12-15]

In recent years, prolonged survival in patients with RCC and MM has been reported with targeted agents and immunotherapy treatments.[16,17] It is known that deterioration in neurocognitive functions due to WBRT becomes an important issue in patients with a high survival expectancy.[3] At the same time, since the efficacy of WBRT in these radioresistant tumors is known to be low, SRS can be preferred in patients without a limited number of brain metastases. Since 2013, SRS has been actively applied in the treatment of brain metastases in our clinic, and we intend to share the results of our own experience in brain metastases cases of RCC and MM with radioresistant histology. In this context, it was aimed to determine local control rates, to evaluate the factors that may affect local control, and to report survival rates by retrospectively screening patients who underwent SRS with the diagnosis brain metastases of RCC and MM.

METHODS

The study was carried out with the permission of the Samsun University Clinical Researches Ethics Committee (Date: 12.04.2023, Decision No: 2023/7/10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[18]

Study Population and Data Collection

Patients who underwent SRS with the diagnosis of RCC and MM brain metastases between October 2013 and December 2020 in the Radiation Oncology Clinic of Samsun Training and Research Hospital were retrospectively analyzed. Patients with a primary diagnosis of histopathologically confirmed RCC or MM, or operated for brain metastases and diagnosed with RCC or MM, over 18 years of age were included. Patients who received WBRT alone or received more than 5 fractions for SRS were excluded.

The data of the patients were obtained through the patient file and the automation system. Patient and treatment characteristics, age, gender, date of first diagnosis, date of diagnosis of brain metastases, tumor location of brain metastases, tumor size, tumor volume, number of lesions, presence of extracranial metastases, recursive partitioning analysis (RPA) scores,[19] graded prognostic assessment (GPA) scores for RCC and MM primaries,[20] chemotherapy, targeted agent therapy, immunotherapy, WBRT before and after SRS, WBRT dose and fraction number, SRS dose and fraction number were recorded in detail.

Treatment

The robotic radiosurgery system CyberKnife® (Accuray, Sunnyvale, USA) was utilized for radiosurgery. All patients underwent simulation computed tomography (CT) with a 1 mm slice thickness while being immobilized with a thermoplastic mask. To be used for fusion, a T1-weighted MRI with gadolinium contrast was acquired at a slice thickness of 1 mm. A contrast-enhanced mass was referred to as the gross tumor volume (GTV). Planning target volume (PTV) was produced by an automatic 1 mm enlargement from the GTV. According to the target volume and proximity to eloquent structures, the treatment was performed in a single or multiple (2-4) fractions. Also, the biologically effective dose (BED10), calculated using $a/\beta = 10$ for tumor effects, was used to select the treatment dose and fraction.

Follow-up and Response Assessment

Patients were assessed at the initial follow-up visit 2-4 weeks after SRS. A post-treatment magnetic resonance imaging (MRI) was performed on patients 6–8 weeks after SRS, and after that, imaging was done every two months. According to the Response Evaluation Criteria in Solid Tumors (RECIST),[21] tumor response was divided into categories (complete response, partial response, progressive disease, or stable disease) based on MRI findings.

Endpoints and Statistical Analysis

The primary endpoints were local control rates and distant brain metastases free survival in patients diagnosed with RCC and MM brain metastases, and the secondary endpoint was overall survival rates. Local control was defined as stable disease, partial or complete response according to MRI findings. Enlargements in the SRS area were considered as progression, and lesions observed outside the SRS area in the follow-up were considered as distant brain failure. OS was calculated as the time elapsed between the date of SRS to the date of death or lost to follow-up.

Following a normality test, continuous variables were expressed as medians, and categorical variables were shown as frequency and percentage (%). The groups were compared using the chi-square test or the Fisher exact test. The two-sided paired t-test was used for normally distributed data and Wilcoxon Cox test for non-normally distributed data. OS, local local control rates, and distant brain metastases free survival were calculated by Kaplan Meier method, differences were analyzed by Log-rank test. Univarian and multivariate analysis were performed with Cox regression. SPSS v25 statistical program was used, $p<0.05$ was considered significant.

RESULTS

Patient characteristics and treatment information are shown in **Table 1**. We detected 55 brain metastases in 29 patients, 14 of whom were MM and 15 were RCC. 65.5% of the patients were stage 2-3 at initial diagnosis. Extracranial metastases were present in 23 patients before brain metastases. 4 patients were diagnosed with brain metastases, initially. Single brain metastases were present in 13 patients. The median tumor diameter was 1.6 (0.5-4.9) cm. The median prescription dose was 18 Gy (18-24) in median 1 (1-4) fractions. According to RPA classes, there were 6 patients in RPA I, 18 patients in RPA II, and 5 patients in RPA III. According to GPA classes, there were 4 patients in GPA 0.5, 4 patients in GPA 1, 5 patients in GPA 1.5, 5 patients in GPA 2, 6 patients in GPA 2.5, 3 patients in GPA 3, and 2 patients in GPA 3.5.

Table 1. Baseline clinicopathological characteristics and treatment information of the patients

Characteristic	n
Age	58 (31-77)
Gender	
Female	11 (37.9)
Male	18 (62.1)
Primary diagnosis	
MM	14 (48.3)
RCC	15 (51.7)
Stage at diagnosis	
2-3	19 (65.5))
4	10 (34.5)
Extracranial metastases	
Yes	23 (79.3)
No	6 (20.7)
Number of brain metastases	
1	13 (44.8)
2	9 (31.1)
3	3 (10.3)
≥4	4 (13.8)
Localisation of brain metastases	
Frontal	13 (24.5)
Parietal	10 (18.9)
Occipital	10 (18.9)
Temporal	9 (17)
Cerebellar	10 (18.9)
Brain Stem	3 (5.7)
Surgery for brain metastases	
Yes	8 (27.6)
No	21 (72.4)
Size of brain metastases (cm)	1.6 (0.5-4.9)
Volume of brain metastases (cc)	1.76 (0.18-27.60)
RPA	
I	6 (20.7)
II	18 (62.1)
III	5 (17.2)
GPA	
GPA 0.5-1	8
GPA 1.5-2.5	16
GPA 3-3.5	5
WBRT	
Yes	14 (48.3)
No	19 (51.7)
SRS (dose)	
18	33 (60.1)
20	2 (3.6)
21	15 (27.2)
22	2 (3.6)
24	3 (5.5)
SRS (fraction)	
1	27 (49.1)
2	2 (3.6)
3	25 (45.5)
4	1 (1.8)
BED10	29.75 (21.75-58.67)
Chemotherapy before SRS	
Yes	21 (72.4)
No	8 (27.6)
Chemotherapy after SRS	
Yes	22 (75.9)
No	7 (24.1)
Immunotherapy	
Yes	16 (55.2)
No	13 (44.8)
Targeted agent therapy	
Yes	15 (51.7)
No	14 (48.3)

BED: Biologically effective dose, GPA: Graded prognostic assessment, MM: Malignant melanoma, RCC: Renal cell carcinoma, RPA: Recursive partitioning analysis, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy

The median follow-up time was 13 months, with a range from 1 months to 89 months. Stable disease was observed in 22 lesions, whereas complete response and partial response were observed in 5 lesions and in 22 lesions, respectively. In-field progression was observed in 6 (10.9%) lesions at a median 12 (7-20) months after SRS. Re-irradiation was applied to 3 progressive lesions. In the follow-ups, 5 new lesions were detected outside the SRS area at a median 7 (2-25) months after SRS, 3 of them underwent SRS.

The crude rate of local control rate was 89.1%. The 1-y and 3-y actuarial local control rates were 82.4% and 59%, respectively. 1 y- crude rate of local control and actuarial local control rates were 96.2% and 87.5% for RCC, and 93.2% and 77.8% for MM (**Figure 1a**). There was no difference in local control rate according to whether the primary disease diagnosis was RCC or MM (p=0.455). Increased size and volume of brain metastases were associated with progressive disease (p=0.041, p=0.002) (**Table 2**).

Table 2. Demographic and clinical characteristics of patients with local control and progression

Characteristic	PD	SD/PR/CR	p
Age	56.80+/-9.93	58.29+/-10.68	0.776
Primary diagnosis			0.455
MM	4 (13.7)	25 (82.3)	
RCC	2 (7.3)	24 (92.7)	
Number of brain metastases			0.404
1-2	4 (18.2)	18 (81.8)	
≥3	2 (28.6)	5 (71.4)	
Size of brain metastases (cm)	2.65+/-0.69	1.70+/-1.50	0.041
Volume of brain metastases (cc)	13.48+/-8.03	3.84+/-6.49	0.002
BED10	31.66+/-6.35	37.93+/-14.29	0.082
Coverage (%)	98.50+/-1.36	97.53+/-1.60	0.166
HI	1.13+/-0.05	1.20+/-0.05	0.057
CI	1.32+/-0.19	1.48+/-0.36	0.336
nCI	1.33+/-0.19	1.46+/-0.21	0.161
SRS dose (Gy)	19.2+/-1.5	20.4+/-2.5	0.163
WBRT			0.008
Yes	0 (0)	28 (100)	
No	6 (22.3)	21 (77.7)	
Chemotherapy	5 (22.7)	17 (77.3)	0.547
Immunotherapy	8 (34.8)	15 (65.2)	0.196

BED: Biologically effective dose, CI: Conformity index, CR: Complete response, HI: Homogeneity index, MM: Malignant melanoma, nCI: New conformity index, PR: partial response RCC: Renal cell carcinoma, SD: Stable disease, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy

Although SRS dose and BED10 values were found to be lower in the group with progressive disease, no statistically significant difference was detected (p=0.163, p=0.082). Local control rates were increased in those receiving WBRT prior to SRS (0.008). The rate of 1 y- actuarial local control was 100% in those who received WBRT and 76.9% in those who did not (**Figure 2a**). Also, there was no statistically significant effect on actuarial local control rates between the groups that patients received chemotherapy or immunotherapy (p=0.547, p=0.196). There was no correlation with local control ratio in multivariate analysis, only a trend toward an improved local control ratio was observed in patients with smaller brain metastases (p=0.054).

The crude rate of distant brain failure was 9.1%. The 1-y and 3-y distant brain metastases free survival were 87.7% and 60.2%, respectively. Distant brain metastasis free survival was increased in those receiving WBRT before SRS, but not statistically significant (p=0.403). The rate of 1 y- distant brain metastases free survival was 100% in those who received WBRT and 82.2% in those who did not (**Figure 2b**). There was no correlation with distant brain metastases free survival in multivariate analysis.

At the last follow-up, 5 patients were alive. The median OS was 40 months from the initial diagnosis (HR: 17.49, 95% CI: 5.71-74.28), and the median OS was 8 months (HR: 1.79, 95% CI: 4.48-11.51) after SRS with the diagnosis of brain metastasis.

The 1-y and 3-y OS were 41.4% and 22.3%, respectively. There was no difference in OS according to whether the primary disease diagnosis was RCC or MM (p=0.482) (**Figure 1b**). Patients with 1-2 brain metastases had better OS than patients with 3 or more brain metastases (p=0.029) (**Table 3**). RPA and GPA classes were significantly related to OS (p=0.001, p<0.001).

OS worsened in patients who received WBRT before SRS compared to those who did not (0.035) (**Figure 2c**). While chemotherapy before or after SRS, and targeted therapy were not found to be effective on OS (p=0.361, p=0.063, p=0.951), OS increased statistically in patients who received immunotherapy (p=0.033) (**Figure 3a, 3b, 3c, 3d**). No correlation with OS could be demonstrated in multivariate analysis.

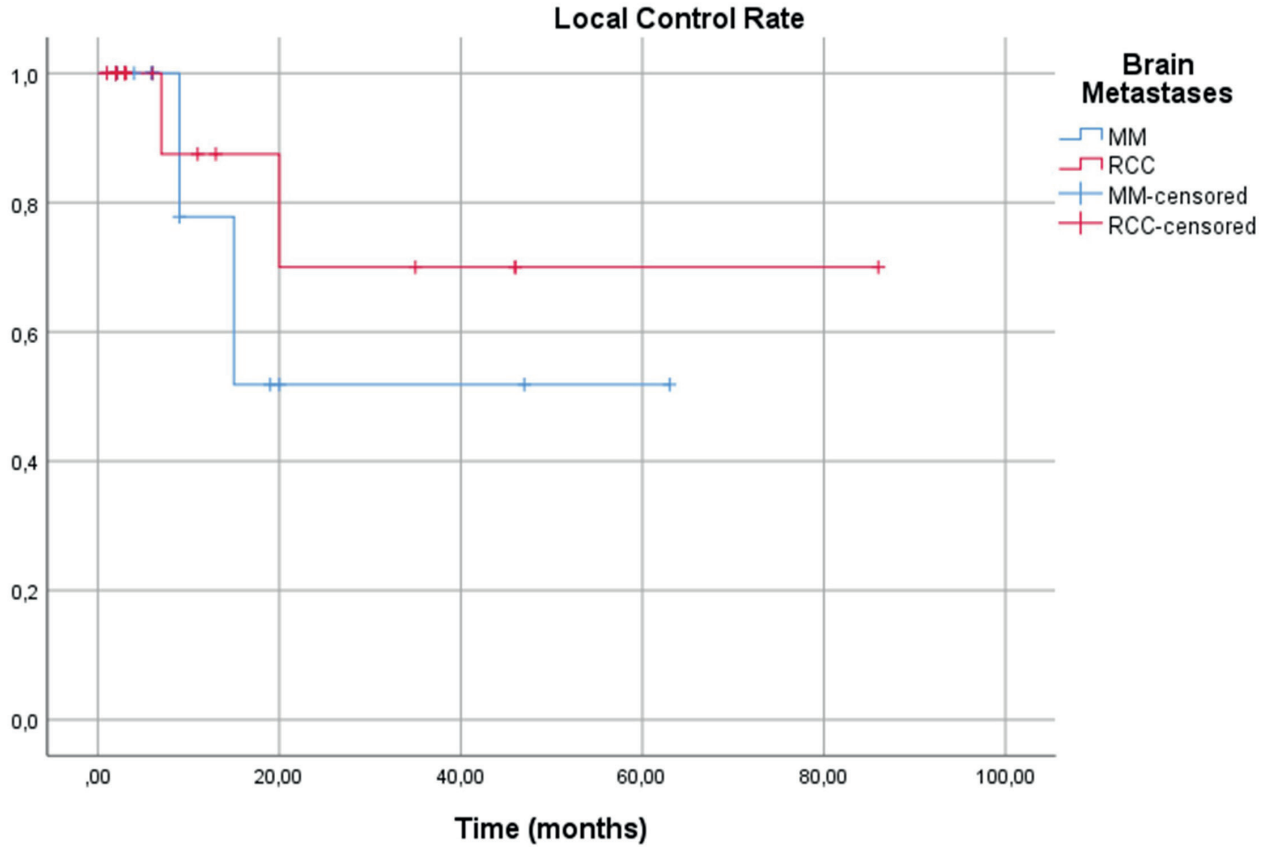

Figure 1a. Kaplan Meier graph on actuarial local control rates for RCC and MM.

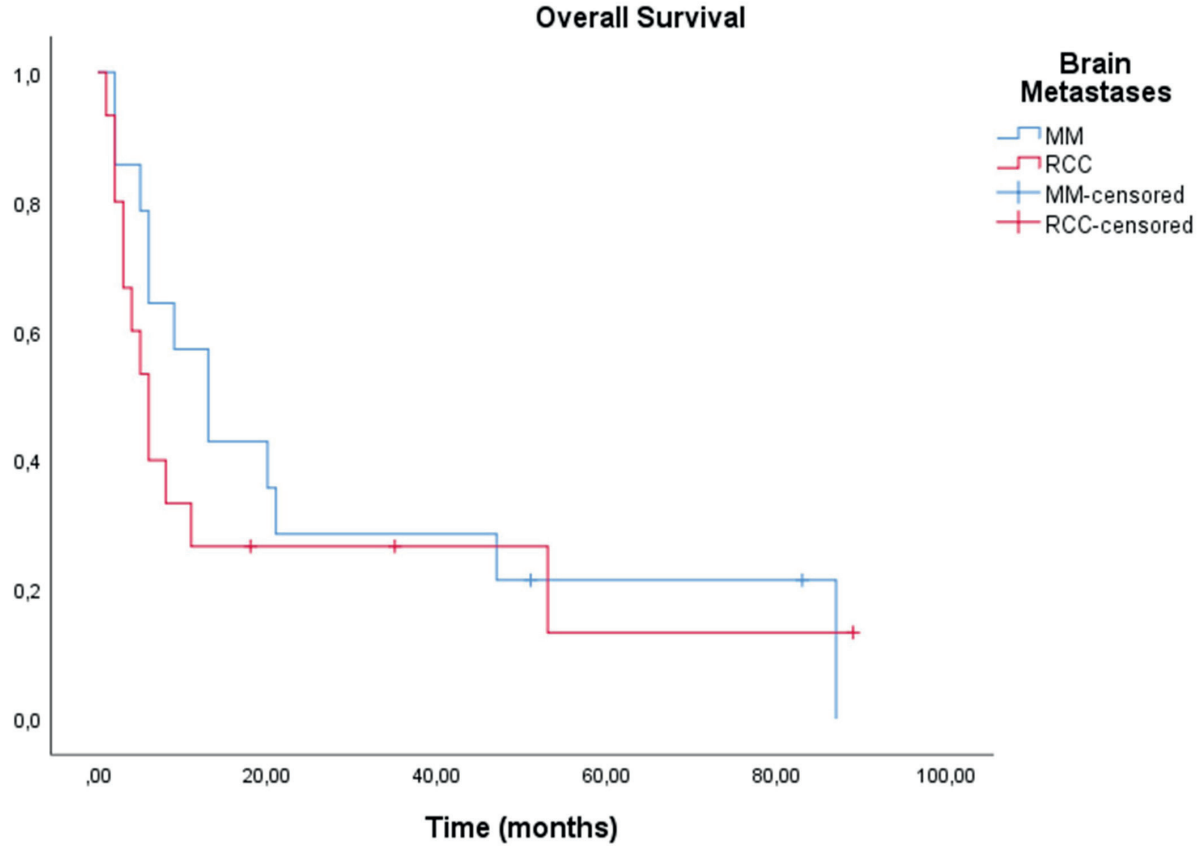

Figure 1b. Kaplan Meier graph on overall survival for RCC and MM.

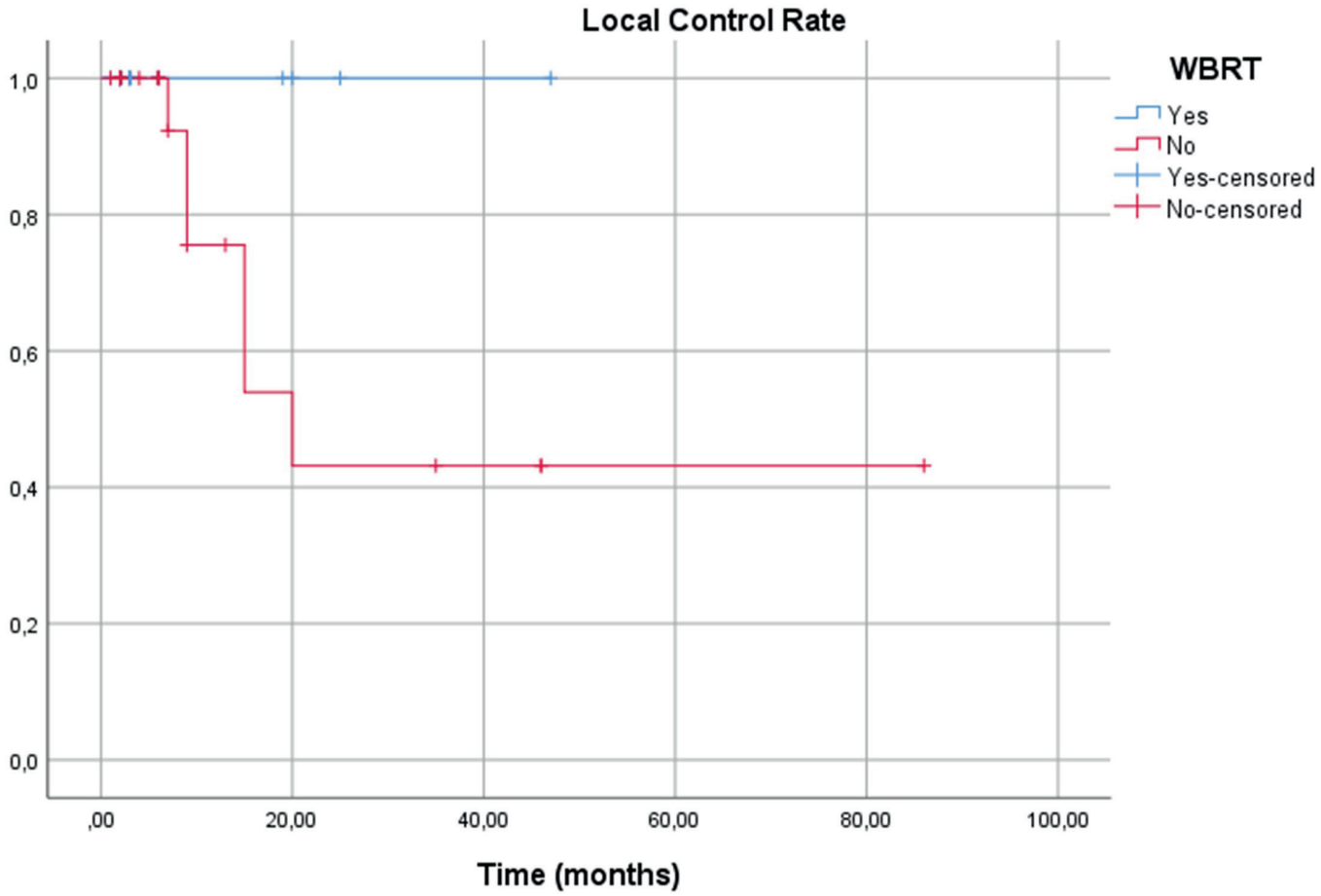

Figure 2a. Kaplan Meier graph on actuarial local control rates for those receiving WBRT and for those who did not.

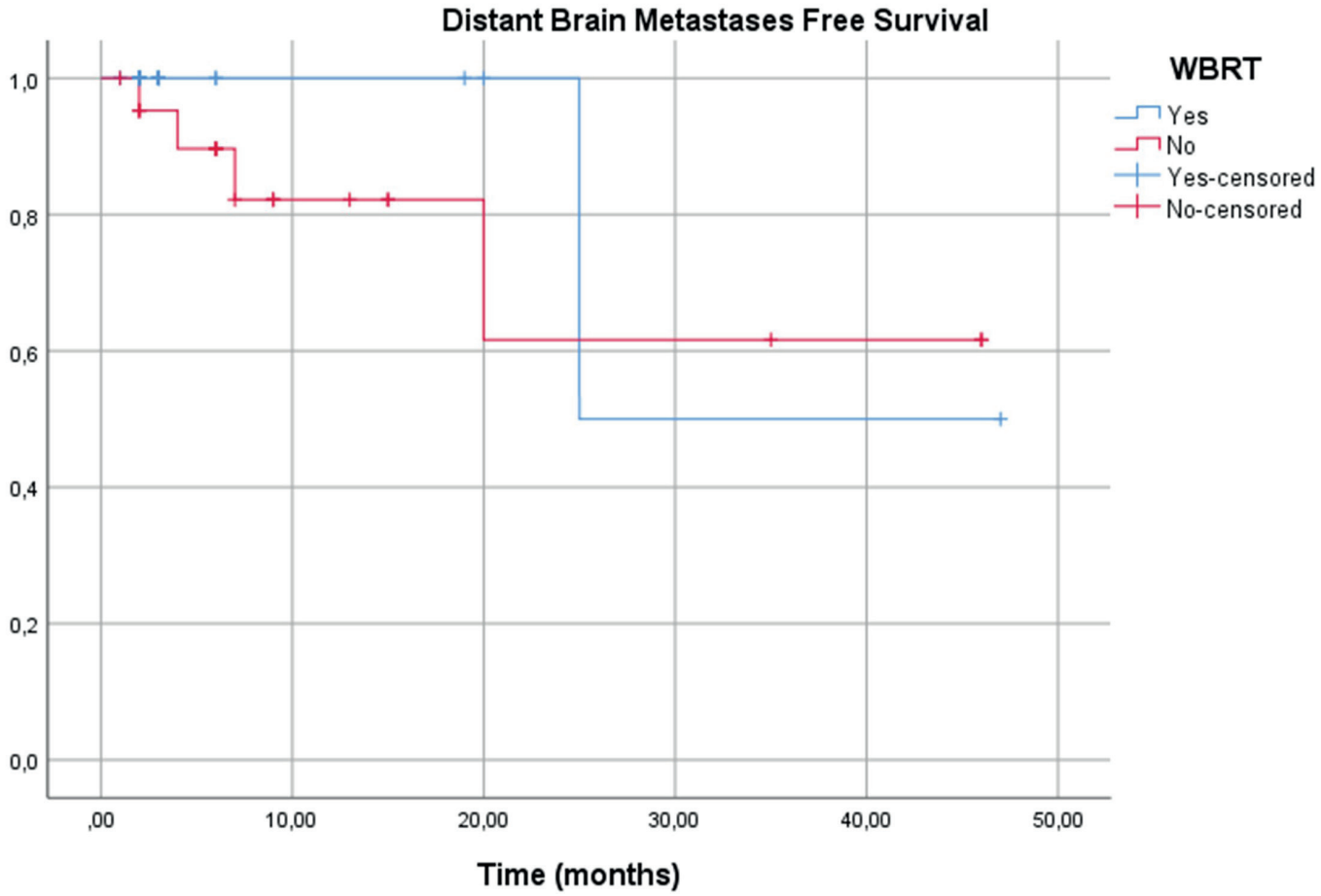

Figure 2b. Kaplan Meier graph on distant brain metastases free survival for those receiving WBRT and for those who did not.

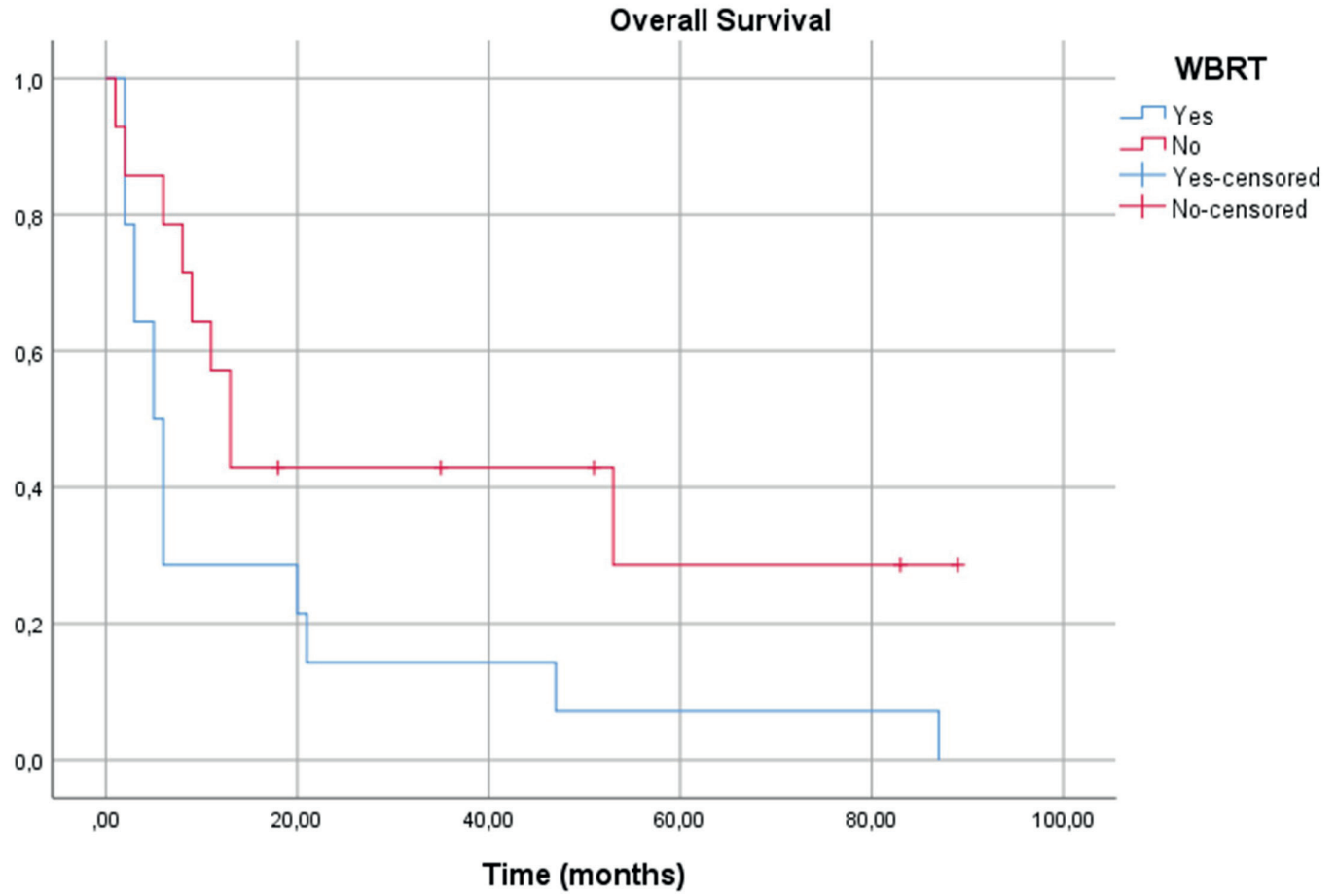

Figure 2c. Kaplan Meier graph on overall survival for those receiving WBRT and for those who did not.

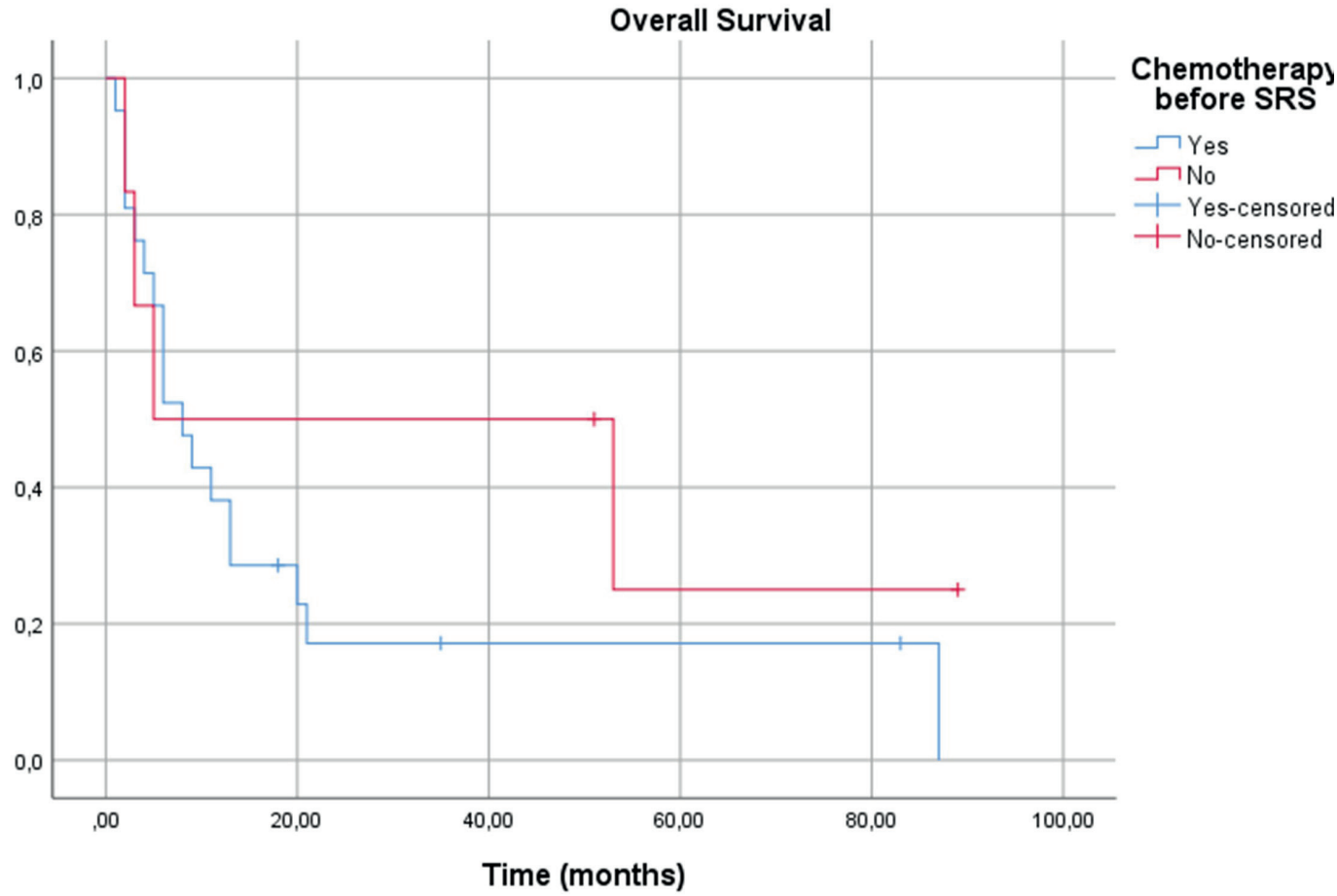

Figure 3a. Kaplan Meier graph on overall survival for those receiving chemotherapy before SRS and for those who did not.

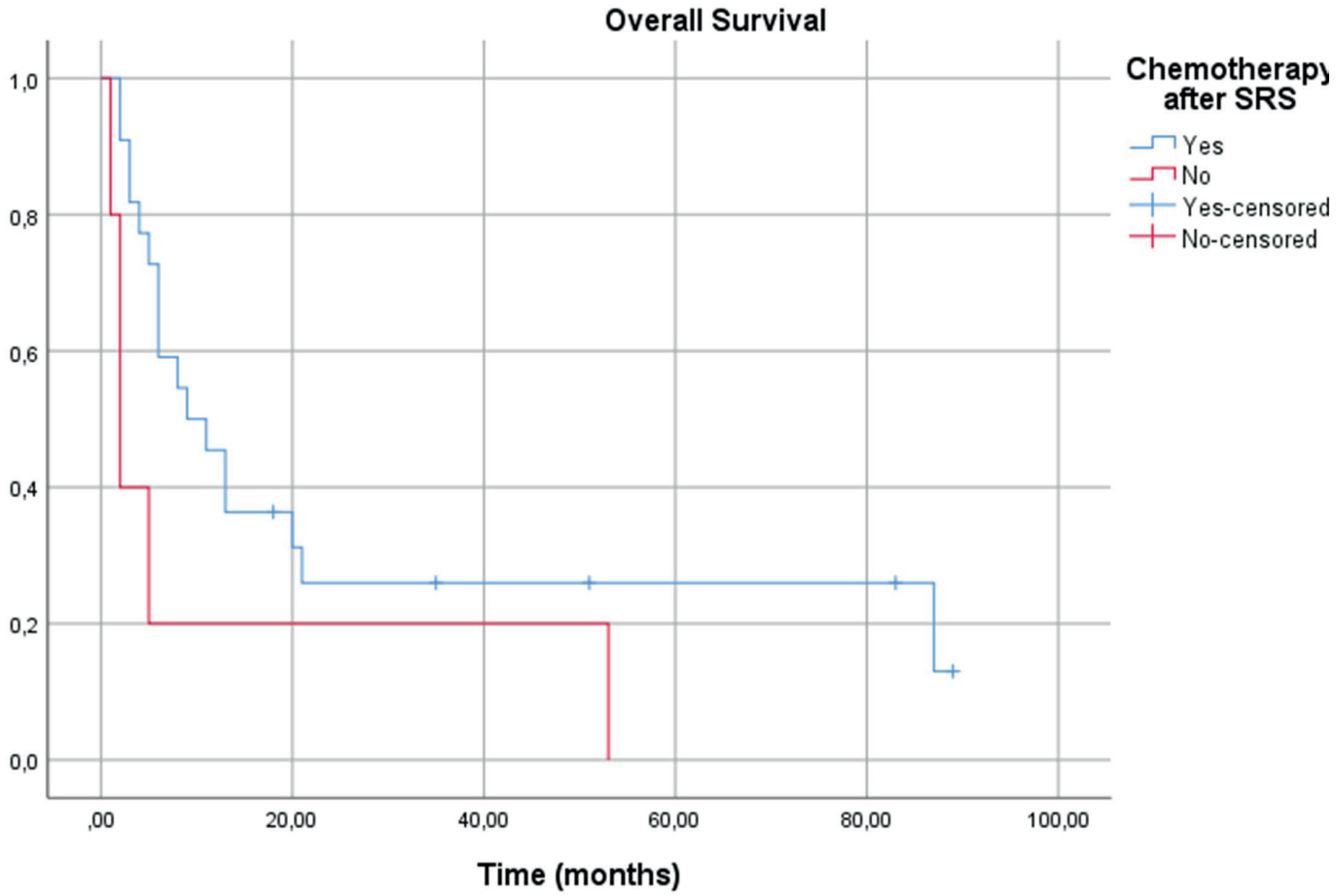

Figure 3b. Kaplan Meier graph on overall survival for those receiving chemotherapy after SRS and for those who did not.

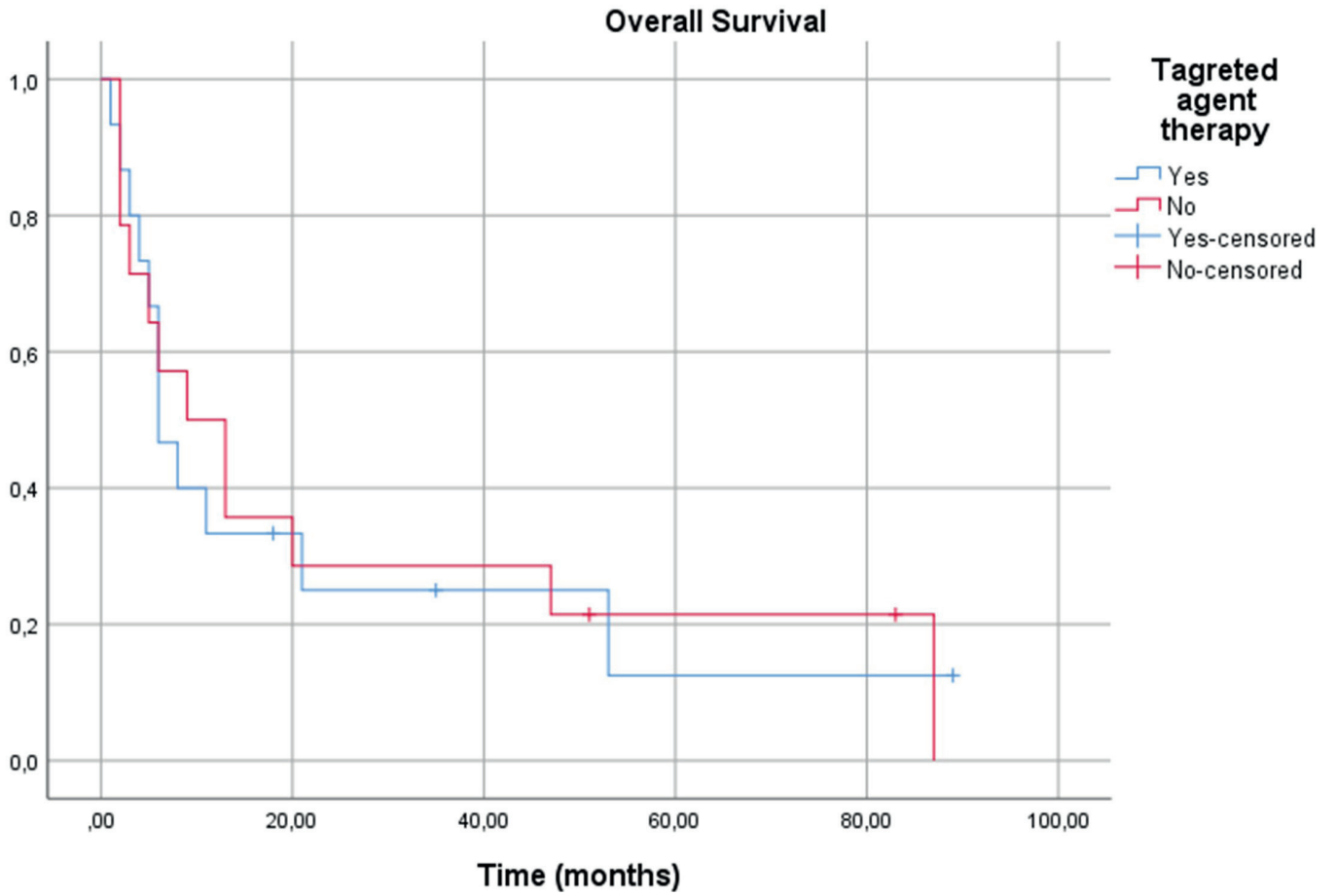

Figure 3c. Kaplan Meier graph on overall survival for those receiving targeted therapy combined with SRS and for those who did not.

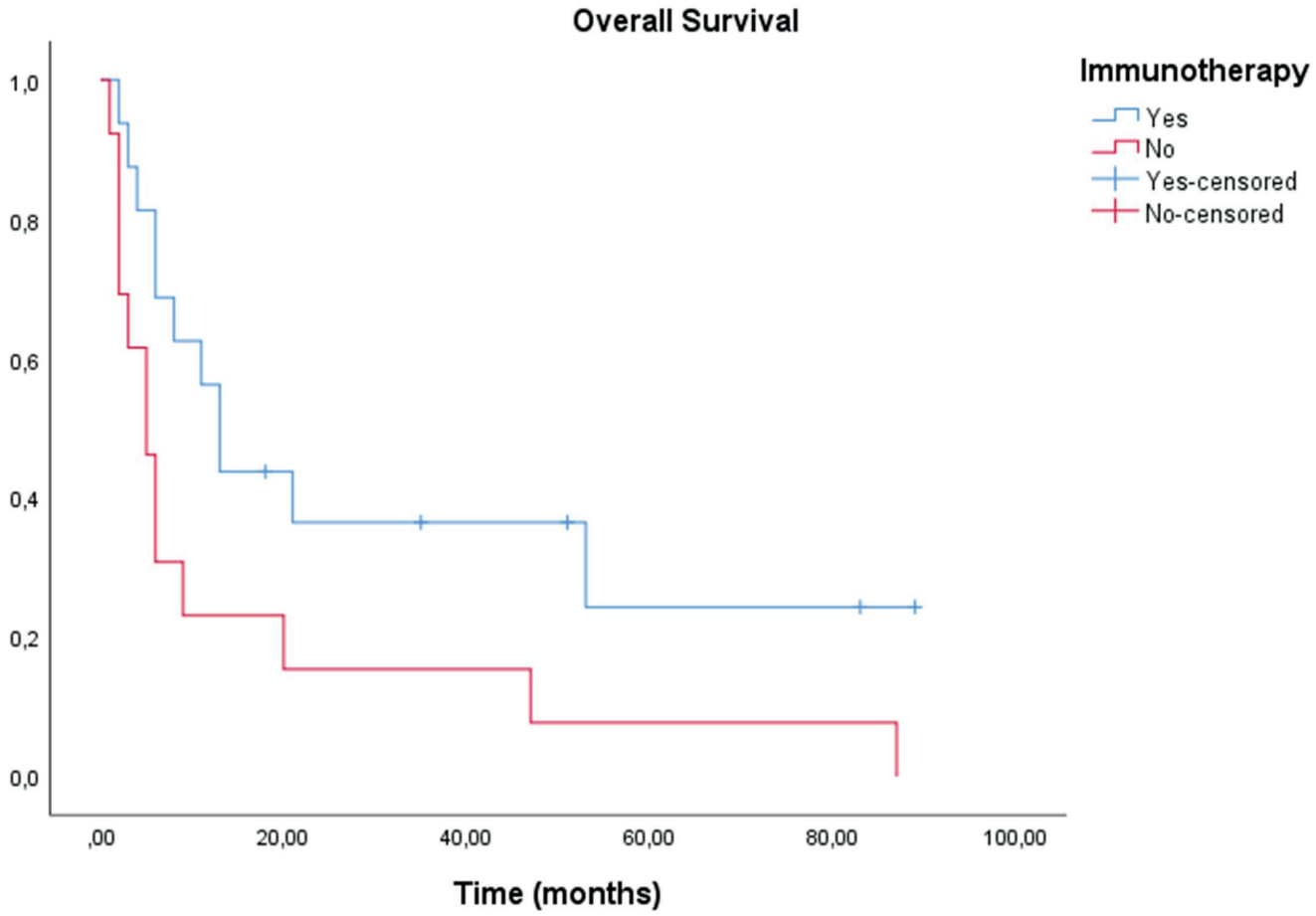

Figure 3d. Kaplan Meier graph on overall survival for those receiving immunotherapy combined with SRS and for those who did not.

DISCUSSION

In our retrospective study, local control rates, distant brain metastases free survival, and OS were evaluated in patients who underwent SRS with the diagnosis of RCC and MM brain metastases. Six patients experienced in-field progression following SRS, which was associated with increased size and volume of brain metastases. It was shown that WBRT contributed significantly to local control rates and distant brain metastases free survival in those who received WBRT before SRS. Regarding OS, there was no difference depending on whether the primary disease diagnosis was BCC or MM, but worsening of OS was found in patients with multiple brain metastases, RPA class 3, GPA 0.5-1, and those receiving WBRT before SRS. In addition, better OS was statistically demonstrated in patients receiving immunotherapy.

An essential part of the treatment for brain metastases utilizing SRS is tumor control. Promising retrospective studies on local control rates in radioresistant tumors treated with SRS have been published.[9-15] Brown et al.[10], in their study in which they compiled 83 brain metastases in 41 patients, reported that they detected in-field recurrence in 12% of the lesions, and the rate of 1 y- actuarial local control was 86%. Lwu et al.[12] found 1 y- and 2 y- actuarial local control rates as 84% and 61% in their study evaluating 36 patients and 103 brain metastases. When we compared our study with the data mentioned above, we found that the 1 y- actuarial local control rates were similar in our study.

Numerous retrospective investigations have revealed further variables that contribute to tumor response following SRS. One of them is size or volume of brain metastases. Smaller tumor diameter and volume are favorable predictors of local local control following SRS, according to one of our study's major findings. Several studies have long supported this conclusion.[12,23,24] For instance, Selek et al.[22] reported that the rate of local control with SRS increased in lesions of 2 cm or less in 153 brain metastases diagnosed with MM. In the series of Lwu et al.[12], the volume of progressive lesions was found to be twice that of the others. Finally, the SABR ORCA meta-analysis published in 2019 included 28 studies of intracranial and extracranial oligometastatic RCC.[23] In 923 patients with brain metastasis, 1 y-local control rate and OS were 90.1% and 49.7%. It has been determined that the ability to achieve local control is due to high SRS doses and small tumor volume. High doses of SRS are an important factor in determining local response.[23,24] Since the doses in our study were relatively lower or more fractionated and had lower BED10 values, no dose-related treatment response advantage could be demonstrated in our study.

A number of studies have discovered variations in the SRS responses of patients with MM and RCC histologies. For example, Lwu et al.[12] reported that the 1-y local control was 91% for RCC and 75% for melanoma, and RCC histology was statistically favorable in terms of tumor response. Similarly, Lo et al.[13], in their series of 38 patients and 66 brain metastases, showed that local control rates were better in patients with primary diagnosis of RCC. Finally, in the study that included 71 BM of 46 patients, those with RCC histology showed better local control rates.[25] On the contrary, Brown et al.[10] reported that they did not detect any difference in terms of local control compared to the primary diagnosis. In our study, although the 1 y- local control rates were 87.5% vs. 77.8% for RCC and

MM, we could not detect a statistically significant difference.

The addition of WBRT to SRS in radioresistant histologies has controversial results in terms of treatment response and OS. Brown et al.[10] determined that while the 6-month local control rate was 100% in those who received WBRT, it was 85% in those who did not, and reported that local control rates increased with WBRT. Lwu et al.[12] reported that there was no difference in treatment response with the addition of WBRT. In a large series including 435 brain metastases with 185 MM, it was shown that WBRT had no effect on local control or distant brain failure.[26] While different outcomes are observed in terms of local control, it is seen that when WBRT is added to SRS, no contribution is made in terms of OS.[10,26,27] In our study, when WBRT was added, both local control and distant brain metastasis-free survival improved, but unlike previous studies, OS worsened. The fact that WBRT was applied mostly in patients with multiple metastases or with a poor prognostic score may be one of the reasons for the worsening of OS in our study.

Prognostic risk scoring was originally developed because of the need to determine prognosis. RPA has long been recognized in the prognostic risk scoring of brain metastases.[19] The GPA for RCC was developed after the RPA and is the currently used and preferred customized prognostic risk scoring.[20] Both prognostic risk scores were demonstrated to have a significant predictive impact on OS in our investigation, which is consistent with the literature.[10,26]

The number of metastases is another factor that positively predicts survival.[4] According to the information obtained from meta-analyses, it is known that a limited number of brain metastases, especially single brain metastases, have a survival advantage.[4] In this data, survival advantage was also shown in patients with single metastasis diagnosed with RCC in subgroup analysis.

The use of targeted agents and immunotherapy in combination with SRS in brain metastases has been a particularly popular topic in recent years. It has been observed that survival times increase with the use of targeted agents and immune checkpoint inhibitors in the management of MM and RCC.[16,17] The main purpose of use of these drugs in patients with brain metastases is to increase treatment response without increasing toxicity. Many studies examining this effect have been published and studies are still ongoing.[28-30] Times for concurrent use vary between studies, including use within 2 weeks, some for up to 3 months. In a study that included 147 brain metastases in 57 patients with RCC, 1 y-OS and 1 y- distant brain metastases free survival were higher in the immune checkpoint inhibitors with SRS arm than in the SRS arm alone, with rates of 66% and 52%. to 38% and 16%.28 In a study of 623 brain metastases in 260 patients with non-small cell lung cancer, RCC, and MM cases, SRS alone was compared with immunotherapy with SRS.[29] In this study, the immunotherapy arm was divided into 2 arms according to timing, and patients were included in the concomitant arm if used within 2 weeks. First of all, it was emphasized that concomitant use does not increase toxicity. The median OS was 12.9, 14.5, and 24.7 months, with the longest in the concomitant arm. It has also been reported to reduce the development of new lesions. The results of a study that included 435 brain metastases in 101 MM patients, which were divided into 3 arms: SRS alone, SRS with concomitant use of immunotherapy drugs, and SRS with non-concurrent use, were recently published.[30] Complete and partial response rates were significantly higher in the concurrent SRS arm than in the other arms. In our study, it was accepted to be within 4 weeks for simultaneous use. OS was prolonged in patients using immunotherapy, without any difference in OS with the use of targeted agents. As in other studies, improvement in terms of local control was not detected in our study.

The strengths of this study are as follows. Despite the small number of patients, our study assessed prognostic risk scores such RPA and GPA, which are known to have a predictive influence on OS, as well as the recently increasing popularity of immunotherapy with SRS, and determined their link with OS. Our study also established the significance of tumor diameter in terms of local control rates.

However, there are limitations to this study, some inherent to a retrospective study design with inherent confounding factors. Another limitation of our study is that we did not evaluate the effect of high-dose SRS on treatment response due to relatively low doses.

CONCLUSION

In conclusion, improvement in local control was found in patients with small tumor diameter and volume. Furthermore, the addition of WBRT to the SRS increased both local control and distant brain metastasis-free survival. Regarding OS, multiple metastases, high RPA score, and low GPA score worsened OS. Another crucial observation is that a positive predictive effect on OS was detected in patients in whom immunotherapy was combined with SRS.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Samsun University Clinical Researches Ethics Committee (Date: 12.4.2023, Decision No: 7/10).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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