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ORIGINAL ARTICLE

Early treatment response of breast cancer brain metastases to gamma knife stereotactic radiosurgery

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Summary

Introduction: Brain metastases represent the most common intracranial malignancy in the adult population, while breast cancer represents the leading cause of brain metastases among women. Brain metastases have increased in recent years due to improved therapeutic control of systemic disease and better diagnostic tools. Stereotactic radiosurgery (SRS) is used in patients with brain tumors to achieve local disease control, preserve the quality of life, and extend patient survival. This study aimed to evaluate the effects of SRS in patients with brain metastases from breast cancer through analysis of magnetic resonance imaging (MRI) parameters of the brain.

Methods: Brain MRI was conducted in 30 adult female patients before and 3-6 months after SRS treatment. Radiological analysis was used to estimate lesion volumes before and after SRS.

Results: Patients were categorized into four groups based on therapeutic response: 1 - complete response (CR) with loss of the lesion, 2 - partial response (PR) with more than 50% reduction in lesion volume, 3 - disease progression (PD) with more than 25% increase in lesion volume, 4 - stable disease (SD) if the patient did not display PR or PD. Among all patients, it was found that CR was present in 0 (0%), PR in 15 (50%), PD in 1 (3%), and SD in 14 (47%) patients. Following the SRS treatment, a statistically significant reduction in tumor volume was observed ($p<0.001$).

Conclusion: Radiological volumetric analysis of brain metastases after SRS showed a statistically significant reduction in lesion volume, demonstrating effective local disease control.

Keywords: brain metastases, breast cancer, stereotactic radiosurgery, magnetic resonance imaging

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INTRODUCTION

Brain metastases represent the most common intracranial malignancy in the adult population, while breast cancer represents the leading cause of brain metastases among women (1, 2). Brain metastases from breast cancer occur in 20-40% of cases during the disease, with a higher risk in patients older than 41 years, those with human epidermal growth factor receptor 2 (HER2) positive or triple-negative breast cancer subtypes, and those with existing metastases at 2-3 extracranial sites (1-3). Approximately 50% of brain metastases from breast cancer are solitary, while multicentric lesions occur in the remaining cases (1). The increase in brain metastases over the last decade can be attributed to advancements in therapeutic modalities, longer patient survival, improved lesion detection, and more frequent use of magnetic resonance imaging (MRI) of the brain (1, 4, 5).

Stereotactic radiosurgery (SRS) is currently the method of choice for the non-invasive treatment of brain metastases, providing local disease control with minimal toxicity to the surrounding brain structures (4). It involves delivering a high dose of focal Gamma radiation to a precisely defined volume, typically in a single fraction, in patients with 1-10 brain metastases totaling less than 15 ml in volume. Assessing the effect of SRS on brain metastatic lesions is crucial for planning further local and systemic therapies for patients, with MRI of the brain being a pivotal method both for diagnosis and for therapeutic planning and post-therapy monitoring of patients.

In recent years, various research groups have proposed different criteria to achieve more objective measures for evaluating the post-therapy response of brain tumors (6-18). Many authors, including the leading RANO (The Response Assessment in Neuro-Oncology) working group, advocate for linear 1-dimensional (1D) or 2-dimensional (2D) models of analysis by measuring 1 or 2 largest diameters of the lesion (6-12) while volumetric 3-dimensional (3D) analysis has been performed in fewer individual studies (13-20). Given that brain metastasis is treated with SRS based on its volume, volumetric analysis is the most objective method for evaluating tumor response to applied therapy (21, 22).

Although the number of studies confirming the significance of volumetric measurements of lesions is increasing, most focus on analyzing metastases regardless of their primary origin (13-20). To date, only two studies have specifically addressed the volumetric analysis of metastatic lesions from breast cancer (23, 24). Therefore, this study aimed to assess the early therapeutic effect of SRS in local disease control of brain metastases originating from breast cancer through MRI volumetric analysis, thereby contributing to the scientific literature in this field.

MATERIALS AND METHODS

A retrospective study was conducted at the Department of Magnetic Resonance Imaging at the Center for Radiology of the University Clinical Center of Serbia (UCCS) involving 30 adult female patients with solitary brain metastases originating from breast cancer. The study was approved by the Ethics Committee of UCCS (number 1264/12).

From 2023 to 2024, all patients underwent stereotactic radiosurgery (SRS) treatment at the Department of Stereotactic Neurosurgery—Gamma Knife Center for Neuro-oncology, Clinic of Neurosurgery, UCCS. The average dose of focused SRS radiation delivered was 20 Gy.

MRI of the brain was performed for all patients before and 3-6 months after SRS using a 3 Tesla MRI with a 32-channel head coil. The MRI protocol for intracranial examination included: axial and sagittal T2-weighted imaging (T2WI) [time of echo/time of recovery (TE/TR) = 5000/98 ms, slice thickness/gap = 5/1 mm, field of view (FOV) = 23 cm], axial T1-weighted imaging (T1WI) [TE/TR = 220/4.8 ms, slice thickness/gap = 5.1 mm, FOV = 23 cm], coronal T2-weighted FLAIR (fluid-attenuated inversion recovery) sequence [TE/TR = 9000/97 ms, time of inversion (TI) = 2500 ms, slice thickness/gap = 5/1 mm, FOV = 23 cm], and diffusion-weighted imaging (DWI) [TR/TE = 3800/68 ms, slice thickness/gap = 5/1 mm, FOV = 23 cm] with b-values of 0 and 1000 s/mm^2, along with calculation of apparent diffusion coefficient (ADC) maps.

Following intravenous administration of gadolinium-based contrast agent (0.1 mmol/kg body weight; gadobutrol; Gadovist, Bayer, UK), a three-dimensional T1-weighted MPRAGE (magnetization-prepared rapid acquisition gradient-echo) sequence [TE/TR = 2400/3.6 ms, TI = 1000 ms, slice thickness/gap = 5/1 mm, FOV = 24 cm] was acquired.

Brain MRI findings were analyzed using commercial software (Syngo Via, Siemens, Germany). Lesion dimensions were measured on post-contrast T1-weighted images, calculating the anteroposterior (d1), laterolateral (d2), and craniocaudal (d3) diameters in millimeters. Lesion volume was calculated using the formula:

$$V = \frac{3}{4} \pi \times d1/2 \times d2/2 \times d3/2.$$

Figure 1 shows a representative MRI image of the brain in a patient with brain metastasis before and after SRS.

Statistical analysis

Descriptive and analytical statistical methods were used in this study. Central tendency measures (mean) and dispersion measures (standard deviation, SD) were used for continuous numerical variables. Categorical variables

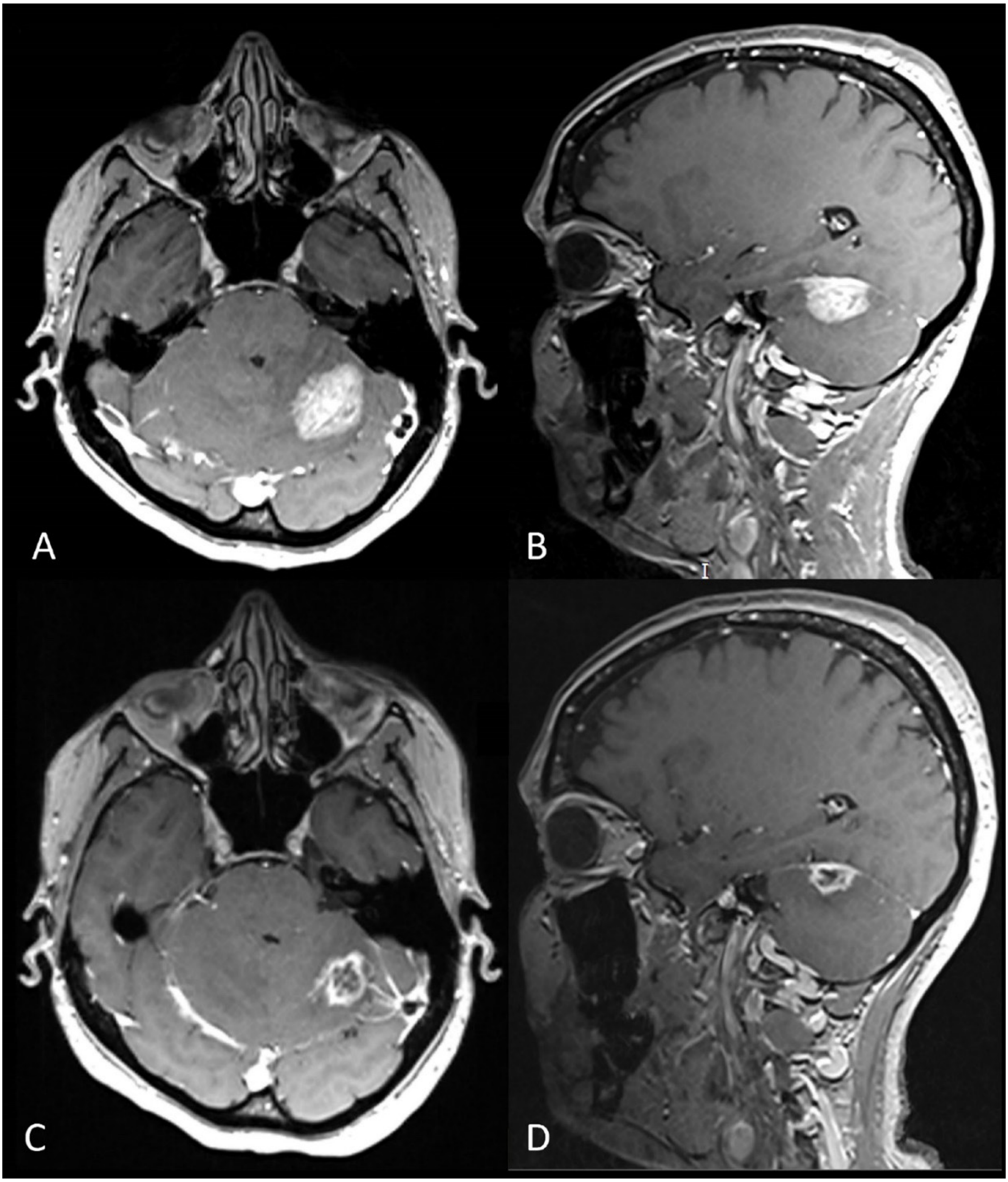


Figure 1. MRI of brain metastasis before and 3 months after SRS in a 57-year-old patient with breast carcinoma. (A) Axial postcontrast T1WI before SRS, (B) sagittal postcontrast T1WI before SRS, (C) axial postcontrast T1WI after SRS, (D) sagittal postcontrast T1WI after SRS. Expansive lesion in the left cerebellar hemisphere with inhomogeneous postcontrast enhancement and edema, with partial response (PR) after SRS.

were presented as absolute numbers with percentages. Results were presented in tables and graphs. All data were analyzed using SPSS 20.0 (IBM Corp., Armonk, NY) and R 3.4.2 (R Core Team, Vienna, Austria) statistical software packages. A value of less than 0.05 for type-1 statistical error was considered statistical significance (alpha) for hypothesis testing.

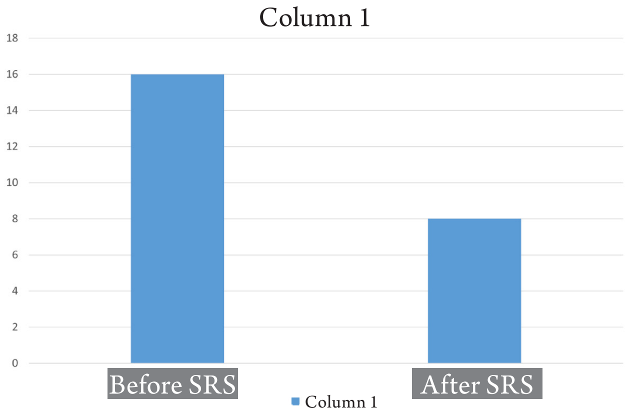
RESULTS

The study included a total of 30 female patients with solitary brain metastases originating from breast cancer. The average age of the participants was 60 (ranging from 46 to 64 years).

Table 1. Arithmetic mean value and standard deviation (SD) of lesion diameter and volume before and after SRS size (statistically significant change - p<0.001).

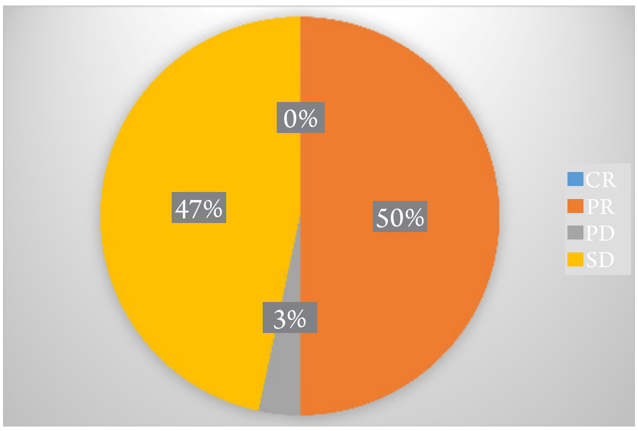
	AP1 (mm)	AP2 (mm)	LL1 (mm)	LL2 (mm)	CC1 (mm)	CC2 (mm)	V1 (cm3)	V2 (cm3)	%
Mean	13.53	10.87	12.77	9.53	12.43	9.30	1.57	0.77	46.87
SD	8.48	8.61	8.55	7.59	8.55	5.76	2.81	1.58	23.81

Following the SRS treatment, a statistically significant change in tumor volume was observed, indicating a significant reduction in lesion size (p<0.001). The mean with standard deviation of lesion diameters and volumes before and after SRS is presented in **Table 1**, and the change in brain metastasis volume values before and after SRS expressed in cm^3 is shown in **Graph 1**.



Graph 1. Volume changes of brain metastasis before and after SRS in cm3 size (statistically significant change – p<0.001).

By calculating the percentage change in lesion volume values before and after SRS, patients were categorized into 4 groups based on therapeutic response: 1 - Complete Response (CR), 2 - Partial Response (PR) with more than 50% reduction in lesion volume, 3 - Progressive Disease (PD) with more than 25% increase in lesion volume, 4 - Stable Disease (SD) if the patient's condition did not meet PR or PD criteria. Among the total number of patients, it was found that CR was present in 0 patients (0%), PR in 15 patients (50%), PD in 1 patient (3%), and SD in 14 patients (47%).



Graph 2. Therapeutic response of brain metastasis after SRS in percentages.

CR – complete response, PR – partial response, PD – progressive disease, SD – stable disease

The distribution of therapeutic responses in patients with solitary brain metastases from breast cancer after SRS, expressed in percentages, is illustrated in **Graph 2**.

DISCUSSION

In this study, we analyzed changes in brain metastasis volumes before and 3-6 months after SRS therapy in patients with primary breast cancer. By evaluating brain MRI parameters, the study enabled the assessment of lesion size changes and therapeutic responses to SRS. Radiological and statistical analyses confirmed a significant reduction in metastatic lesion volume shortly after SRS, validating its effectiveness in local disease control of brain metastases.

SRS is a preferred therapeutic modality for treating brain metastases, used either as monotherapy or adjunctive therapy alongside whole-brain radiotherapy (WBRT) or surgical resection (1, 4, 25, 26). WBRT, known for its significant neurotoxic effects, can lead to long-term neurocognitive decline and cerebellar dysfunction in treated patients. Furthermore, due to these potential side effects, its clinical use has been limited to palliative care settings (1).

In contrast, SRS delivers a high dose of focal Gamma radiation to a precisely defined volume, achieving local disease control with minimal toxicity to surrounding healthy brain structures. It is typically recommended for patients with a good clinical status and up to 4 brain metastases or up to 10 lesions with a total volume not exceeding 15 ml (1, 4, 25, 26). SRS is most commonly delivered as a single radiation fraction ranging from 15 to 24 Gy. In contrast, 2-5 fractions are recommended for larger lesions (>3 cm in diameter), lesions near critical structures like the brainstem, optic nerves, or optic chiasm, or in patients who have previously received cranial radiation therapy (1, 4, 25). The primary goals of SRS are long-term local tumor control, improved quality of life, and extended patient survival. As a result, the use of SRS for treating brain metastases has significantly increased.

In local disease control, SRS and surgical treatments are competitive therapeutic approaches. Neurosurgical tumor resection favors scenarios such as unknown primary tumors, unreliable neuroradiological lesion diagnosis, large cystic or necrotic lesions, the need for high-dose corticosteroid therapy, significant compressive effects of the lesion on surrounding structures, or the necessity for lesion molecular profiling for therapeutic purposes. Despite studies demonstrating the benefits of surgical resection, many patients are not optimal candidates due to their poor overall medical condition, other medical comorbidities, inaccessible tumor locations, or multiple intracranial metastases, with some patients declining surgical treatment due to high risks.

Assessing the effect of SRS therapy on brain metastases is crucial for planning both local and systemic therapies for patients, with MRI of the brain being the most precise method for evaluating post-therapeutic findings. Over the recent years, several working groups have proposed various criteria to achieve more objective, quantitative radiological assessments of tumor response post-therapy. These models typically include analyzing brain tumor responses on post-contrast T1W MRI sequences. The World Health Organisation (WHO), McDonald's, The Response Evaluation Criteria In Solid Tumors (RECIST), and The Response Assessment in Neuro-Oncology (RANO) working groups have developed linear models for analyzing brain tumor response post-therapy. In contrast, volumetric analysis has been conducted in fewer individual studies (6-11, 13-18). By measuring one (unidimensional, 1D) or two (bidimensional, 2D) maximum tumor diameters on post-contrast T1W MRI sequences, 1D RECIST and 2D RANO analyses define CR as complete absence of the lesion post-therapy, PR as at least a 30% reduction in the largest diameters of the lesion, PD as at least a 20% increase in the largest diameters of the lesion, and SD as a state not classified as PR or PD (8-10, 27). According to the WHO and McDonald working groups, 2D tumor analysis defines CR as a complete absence of the lesion post-therapy, PR as at least a 50% reduction in the largest diameters of the lesion, PD as at least a 25% increase in the largest diameters of the lesion, and SD as a state that is not classified as PR or PD (7, 9, 27). While the aforementioned authors performed 1D or 2D measurements of brain metastasis size, the authors of this study conducted 3D measurements with lesion volume calculation, followed by therapeutic response classification according to the WHO and McDonald working groups.

Follwell et al. were among the first to analyze the volume of 178 brain metastases of various primary origins in 70 patients treated with SRS (18). They compared the therapeutic response of brain metastases based on 1D RECIST criteria and 3D lesion volume, defining PD as a condition with a 71.5% increase in lesion volume, PR as a 58.5% decrease in lesion volume, and SD for those lesions that were neither PD nor PR. Over a two-year follow-up, they found that assessing brain metastasis therapeutic response to SRS based on changes in lesion volume was more accurate than using 1D RECIST criteria. Popat et al. emphasize the importance of calculating brain metastasis volumes as a prerequisite for assessing the feasibility of SRS, as reflected in the mandatory analysis for evaluating the therapeutic effect of SRS applied in this study (21).

The significance of volumetric measurements of metastatic lesions has increased in recent years, although most studies have focused on analyzing metastases regardless of their primary origin (13-20). Only two studies have been published and examining the volume of brain metastases originating from breast cancer (23, 24).

Maucevic et al. studied the volume of solitary and multiple brain metastases originating from breast cancer after SRS in 151 patients (23). However, the authors of this study did not clearly define tumor response based on changes in lesion volume after SRS was applied. In contrast to the Maucevic study, the authors of this study analyzed brain metastases originating from breast cancer with a more complex classification of therapeutic responses.

Consistent with the results of this study, Kowalchuk et al. demonstrated that SRS of solitary and multiple brain metastases significantly reduces lesion volume after therapy in patients with triple-negative breast cancer (24). The authors explained that the low overall survival during the seven-month follow-up of these patients could be explained by systemic disease progression rather than a local progression of intracranial metastasis after SRS treatment. Given the advancements in systemic therapy development for this triple-negative breast cancer subtype, greater effectiveness of SRS in treating brain metastases in these patients is expected in the future (1, 24). In contrast to the aforementioned study, the authors of this study analyzed only solitary brain metastases regardless of the histopathological subtype of breast cancer.

This current study has several limitations. The sample size was small, and the study included patients with metastases originating from primary breast tumors regardless of their histopathological subtype. The study was limited to analyzing conventional MRI parameters, while advanced MRI techniques such as diffusion, susceptibility, MR spectroscopy, and perfusion were not applied. Lastly, clinical evaluation of patient performance status, progression-free survival, quality of life, and overall survival was not analyzed.

Further research on the changes in brain metastasis volume before and after SRS in a more significant number of patients, grouped by histopathological subtypes of primary tumors, with analysis of multiple parameters of conventional and advanced MRI techniques and longer patient follow-up, would facilitate the development and clinical application of radiological methods in post-therapeutic monitoring of patients with brain metastases.

CONCLUSION

This study has demonstrated that SRS therapy in patients with brain metastases originating from breast cancer leads to a statistically significant reduction in lesion volume in the early post-therapy period, confirming the validity of SRS application in local control of metastatic disease. The findings of this study should be further validated by larger studies examining the significance of volumetric measurements of lesions.

Ethical Statement: The study was conducted by the Declaration of Helsinki and was approved by the Ethics Committee of the University Clinical Center of Serbia.

Conflict of interest: None to declare.

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RANI TERAPIJSKI ODGOVOR NA GAMA NOŽ STEREOTAKSIČNU RADIOHIRUGIJU U SLUČAJU METASTAZA NA MOZGU KOD PRIMARNOG KARCINOMA DOJKE

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Sažetak

Uvod: Metastaze mozga su najučestaliji intrakranijalni malignitet adultne populacije, a u ženskoj populaciji najčešće potiču od primarnog karcinoma dojke. Incidencija metastaza mozga raste poslednjih godina usled bolje terapijske kontrole sistemske bolesti i bolje dijagnostike stanja pacijenta. Primena stereotaksične radiohirurgije (stereotactic radiosurgery, SRS) kod pacijenata sa tumorima mozga ima za cilj da obezbedi kako lokalnu kontrolu bolesti, tako i očuvanje kvaliteta života i duže preživljavanje pacijenata. Cilj ovog rada je da proceni efekat SRS kod pacijentkinja sa metastazama mozga kod primarnog karcinoma dojke analizom parametara magnetno-rezonantnog prikaza (magnetic resonance imaging, MRI) mozga.

Metode: Kod 30 adultnih pacijentkinja načinjen je MRI endokranijuma pre i 3-6 meseci nakon SRS tumora. Radiološkom analizom izračunati su volumeni lezija pre i nakon SRS.

Rezultati: Pacijentkinje su svrstane u četiri grupe prema terapijskom odgovoru: 1 – kompletni terapijski odgovor (CR) kod potpunog gubitka lezije, 2 – parcijalni terapijski odgovor (PR) u slučaju smanjenja volumena lezije za više od 50%, 3 – progresija bolesti (PD) kod povećanja volumena lezije za više od 25%, 4 – stabilna bolest (SD) ukoliko stanje pacijenta nije označeno kao PR ili PD. Od ukupnog broja pacijentkinja, CR je bi prisutan kod 0 (0%), PR kod 15 (50%), PD kod 1 (3%), a SD kod 14 (47%) pacijentkinja. Nakon primenjene SRS utvrđena je statistički značajna razlika u promeni volumena tumora ($p<0.001$).

Zaključak: Radiološkom volumetrijskom analizom metastaza mozga nakon SRS ustanovljena je statistički značajna redukcija u volumenu lezija i time lokalna kontrola bolesti.

Ključne reči: metastaze mozga, karcinom dojke, stereotaksična radiohirurgija, magnetnorezonantni prikaz

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