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ORIGINAL ARTICLE

Hippocampal Sparing in Stereotactic Radiotherapy for Multiple Brain Metastases: A Comparison of Intensity-modulated Arc Therapy, CyberKnife, and Helical Radiotherapy

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OBJECTIVE

In this study, we performed a plan study to evaluate brain and hippocampal doses with hippocampal sparing in the treatment of multiple brain metastases with stereotactic radiosurgery (SRS). For this purpose, treatment plans prepared using intensity-modulated arc therapy (IMAT), CyberKnife radiosurgery, and helical tomotherapy techniques. The results were compared and evaluated according to their superiority to each other.

METHODS

Fifteen patients with multiple brain metastases who had a tumor diameter of <3.5 cm were included in this study. IMAT, CK, and HT plans were separately created for each patient. The dose prescription was defined as 18 Gy in the single fraction.

RESULTS

The D40% of hippocampal (in Gy) averaged 1.63, 1.69, and 0.52 for IMAT, CyberKnife, and Tomotherapy, respectively. The median hippocampal D_{max} (in Gy) averaged 2.81, 4.63, and 1.98, respectively. Some plans were statically different in terms of critical organ doses, but the results were clinically acceptable. The mean values of V_{12} (cc) were found to be 12.6, 38.23, and 37.46 for IMAT, CyberKnife, and Tomotherapy, respectively, when evaluating the doses taken by healthy brain tissue.

CONCLUSION

Brain radiotherapy is a treatment modality for primary and metastatic lesions. However, after radiotherapy (even with SRS) damage especially in the hippocampus may cause cognitive impairment and a decrease in patients' quality of life. Therefore, when the hippocampus is outlined as organs of risk, it can be protected without compromising PTV coverage. We saw this result in all of three treatment platforms used in this study.

Keywords: CyberKnife; helical tomotherapy; IMAT; multiple brain lesions; stereotactic radiosurgery.

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INTRODUCTION

Brain lesions are one of the most common brain tumors. It also occurs when cancer that develops in different organs spreads to the brain tissue. Brain metastases are seen in 20–40% of cancer patients and the incidence of brain metastases is increasing.[1] More than one metastasis is seen in 75% of patients.[2] While determining the treatment option for patients with brain metastases, variables such as the patient's age, Karnofsky performance score which is an indicator of the patient's general condition, number of metastases, size of metastases, and prevalence of the primary disease are important.[3,4]

Surgery, whole-brain radiation therapy (WBRT), hippocampal avoidance WBRT, stereotactic radiosurgery (SRS), chemotherapy, and various combinations of these treatment techniques are used in the treatment of brain lesions.[5] WBRT adversely affects quality of life and neurocognitive function due to both early and late brain toxicity. The aim of SRS is to give a high dose to the lesion and to protect the surrounding healthy tissues as much as possible while minimizing the side effects in the brain tissue. It also ensure that an extremely sharp dose gradient in the surrounding area.[6] When comparing SRS and WBRT, SRS allows as much normal brain tissue to be preserved as possible, thereby preserving cognitive function and quality of life.[7]

Recently, more attention has been paid to the quality of life of the patient folowing cancer treatment and efforts have been made to reduce the negative effects of treatment. Irradiation of the brain, especially the hippocampus region, can lead to more cognitive deficits, and as a result the quality of life of patients is significantly affected. These cognitive functions include basic functions such as thought, memory, attention, association, and imagination. Any impairment in cognitive functions in oncological patients can significantly affect quality of life after completion of treatment and may lead to deepening of low mood and the emergence of depressive episodes.[8] So far, researchers have applied different tests to examine the effect of this condition. For instance, the RTOG 0941 study examined 449 patients with multiple brain metastases who received both hypofractionated (30 Gy/10 fraction) and conventional (40 Gy/20 fractions) WBRT therapy. Two and 3 months after the completion of radiotherapy, it was revealed that there was a significant deterioration in cognitive functions in both groups. Another phase III trial based on 401 patients with brain metastases treated with WBRT (30 Gy/10 fraction) revealed a significant reduction in cognitive function in patients assessed on the verbal fluency test (COWA, controlled oral word association) 4 months after radiotherapy.[8] Therefore, in general, the group of patients with SRS would be expected to have a significantly better prognosis than patients requiring WBRT. Therefore, it is expected to benefit long-term cognitive and quality-of-life with hippocampal protection.[9]

Nowadays, SRS treatments are performed by means of Intensity-Modulated Arc Therapy (IMAT), CK, or HT methods. These techniques can provide a high level of local control with lower normal tissue exposure than conventional radiotherapy and provide sharp dose reductions at target volume limits. IMAT is a radiation technique that uses multiple density-modulated arcs to give the target volume a highly compatible dose of radiation. Conformal doses can be obtained by combining treatment field size aperture, variation of gantry rotation speed, and dose rate. Noncoplanar radiotherapy uses a series of radiotherapy beams, but does not share the same geometric plane.[10] IMAT also has the potential to offer additional benefits, such as shorter treatment times than other treatment techniques.[11] CyberKnife and helical tomotherapy are used to deliver SRS treatments noninvasively, while providing highly conformed dose distribution to targets with complex shapes. The performances that both systems can provide are different in spite of the high-dose conformity. Tomotherapy plans can ensure both homogeneous and typical radiosurgical dose distributions to the target, while CyberKnife plans are characterized by inhomogeneous highly conformal dose distribution to the target.[12]

Therefore, in this retrospective study, we performed hippocampus-protected SRC plans on different treatment platforms using a single isocenter in patients with 2–5 brain metastases. We evaluated the plan parameters, brain, and other critical organ doses in these treatment platforms and tried to determine their superiority over each other. This study was found ethically appropriate in Istanbul University Institute of Oncology with the file number 2017/1355 on October 27, 2017.

MATERIALS AND METHODS

Patient Characteristics

We evaluated 15 patients with 2–5 brain metastases previously treated with SRS at our institution and compared the feasibility of hippocampal preservation without compromising target volume coverage in this patient population using three separate platforms.

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Table 1 Patient characteristics

Patient number	Sex	Number of lesions	Average lesion diameter (cm)	Average lesion volume (cc)	Total lesion volume (cc)
1	F	2	2	4.95	9.9
2	M	2	2.315	5.2	10.4
3	F	2	1.875	2.2	4.4
4	M	2	2.41	4.8	9.6
5	M	2	2.535	5.1	10.2
6	M	2	2.925	7.35	14.7
7	F	2	1.8	3.85	7.7
8	M	2	1.66	3.05	6.1
9	F	3	2.023	4.26	12.8
10	F	3	2.373	7.6	22.8
11	M	3	1.526	1.63	4.9
12	M	3	1.52	2.06	6.2
13	F	3	1.57	1.93	5.8
14	F	3	1.713	2.63	7.9
15	F	5	2.328	4.82	24.1

DICOM sets of 15 patients with multiple brain lesions were obtained from the archives of our institute. Treatment volumes and critical organs were drawn by a radiation oncologist on CT images of patients, and hippocampal volumes were added by a radiologist. There was a median of two metastases per plan, with a mean single tumor volume of 4.05 cc (range, 1.63–7.6 cc) and total tumor volume of 10.5 cc per plan (range, 4.4–24.1 cc). The mean tumor diameter was 2.03 cm (range, 1.14–3.5 cm). Detailed patient characteristics are given in Table 1.

Target Volume Definitions

All patients were treated with CK from 2013 to 2018. A total of 45 plans were evaluated with IMAT and HT, which were planned separately for each patient. PTV was created with 0.2 cm margin on GTV. Image sets for treatment planning were made on Philips Big Bore 4DCT (Philips Healthcare, Cleveland, OH) using 1 mm slice thickness.

Treatment Plans for IMAT, CK, and HT

6 MV photon beams were used for all treatment methods. The same PTV and OAR volumes have been created for all the plans; thus, in all the plans, the same tumor volumes have been irradiated. As an example of the plan for all treatment models, the axial sections of the same patient's IMAT, CK, and HT plans are given in Figure 1.

For each plan, a total of 18 Gy dose were given to planning target volume (PTV) in 1 fraction using a dose of 18 Gy per fraction. Plans were made so that at least 95% of the PTV volume was treated with a dose of 18 Gy and at least 100% of the GTV was received a treatment dose of 18 Gy. For each treatment modality, initial plans were created with the goal of tumor coverage without hippocampal dose concerns. Later, plans were re-optimized according to the maximum point dose D_{max} and dose to 40% of the hippocampi $D_{\%40}$. If the D40 of either hippocampus was greater than 4.50 Gy or maximum hippocampal point dose (D_{max}) was

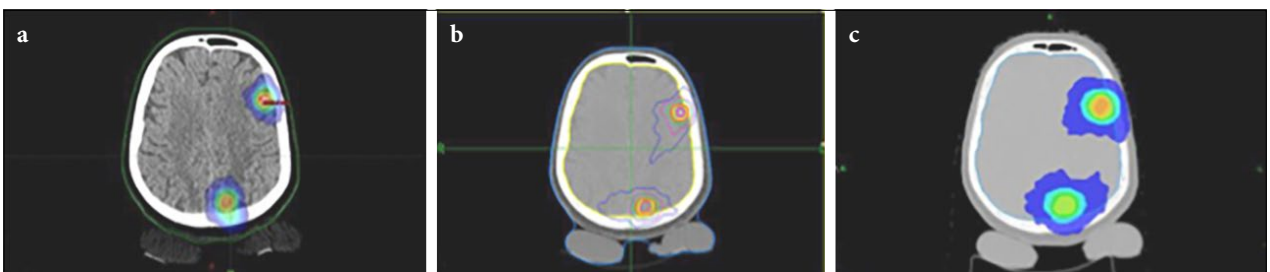

Fig. 1. Axial sections of plans in the same patient; (a) IMAT, (b) CK, and (c) HT.
IMAT: Intensity-modulated Arc Therapy; CK: CyberKnife; HT: Helical radiotherapy.

Table 2 Critic organ dose constraints used in treatment planning

Critic organs	Dose max (Gy)
Brain stem	10 [13]
Hippocampus	6.6 [14]
Pituitary	D_{mean} <9 [15]
Optic nerves	10 [13]
Chiasm	10 [13]
Spinal cord	14 [13]
Cochlea	9 [13]
Lenses	1.5 [16]
Eye	8 [16]

Gy: Gray

greater than or equal to 6.60 Gy, replanning was performed. These doses constrain were selected based on RTOG 0933.[14] PTV coverage was prioritized when both the PTV coverage and the hippocampal restrictions were not made. All other critical organs were preserved based on the constraints shown in Table 2. Critical organ dose constraints for the brainstem, optic nerves, chiasm, spinal cord and cochlea were made according to the values specified in the AAPM Task Group 101 report.[13] The dose restriction for pituitary was based on the study by Palmisciano et al.[15] Dose constraints for the lens and eye are based on the UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy.[16]

One of the limitations of our study was the nature of brain tumors that can form different shapes and sizes in various parts of the brain. The location of the PTV and distance from the hippocampus varied among patients. The closest distance of the tumor to the hippocampus was 0 cm, and the farthest distance was 8.19 cm. Since hippocampus and PTV intersect in 2 of the study patients, hippocampus protection did not occur in these patients.

Treatment Plans for IMAT

Single isocentric IMAT plans were planned on Varian Eclipse TPS (Varian Medical Systems, Version 15.1, Palo Alto, CA, USA) using four non-coplanar arcs (1 full, 3 half arc). The dose rate was selected at 600 MU/min. In IMAT optimization, the algorithm "Photon Optimizer" was used and in dose calculation Anisotropic Analytical Algorithm was used and grid size was selected to 1 mm. Multiple shell volumes have been created to ensure strict coverage of the 9 Gy volume around PTV. A single isocenter was placed at the center of the mass of all targets.

Treatment Plans for CK

CK plans were prepared using Multiplan version 4.0 (Accuray Inc., Sunnyvale, CA, USA) treatment planning system. The plans were prepared using two fixed collimators depending on PTV size. 6D-skull selected as tracing method. The dose rate was selected at 600 MU/min.

Treatment Plans for HT

HT plans were performed in the planning system of the HDA (Accuracy Inc., Sunnyvale, CA, USA). Plans were performed using pitch=0.143 and modulation factor=2. The field width was prepared by selecting 1048 and 2512 depending on the tumor size. The dose calculations for the HT plans were done using the convolution/superposition algorithm.

Treatment Plan Parameters for PTV

The minimum dose in PTV is Dmin, the maximum dose in PTV is D_{max}, and the average dose for PTV is D_{mean}. The dose of any percentage of organ volume is indicated by $D_{n\%}$. Vn is volume of brain receiving at least n Gy of radiation dose.

$D_{2\%}$, $D_{50\%}$, and $D_{98\%}$ were analyzed in evaluation of PTV volumes as described in ICRU 83 guidelines. The homogeneity index (HI) is calculated as follows: $HI=(D_{2\%}- D_{98\%})/D_{50\%}$. For Conformity Index (CI), CI=Vri/TV formula was used (Where Vri is the volume of reference isodose and TV is the treatment volume covered by reference isodose line). The treatment plan criteria for PTV we found are given in Table 3.

Brain Dose Parameters

In a study by Minniti et al.,[17] researchers found that all of the brain V_{10} Gy and V_{12} Gy are the most predictable independent risk factors for radioecrosis, and that V_{10} Gy >12.6 cm^3 and V_{12} Gy > 10.9 cm^3 have a radioecrosis risk of 47%. In addition, for patients with brain metastases in a single fraction SRS treatment, brain volumes receiving 12 Gy of 5 cc, 10 cc, and >15 cc were associated with risks of symptomatic radionecrosis nearly 10%, 15%, and 20%, respectively.[18] Therefore, in this study, both the maximum dose and the doses of 8%, 10%, and 12% volumes of Brain-PTV were evaluated as both percent and cc. Brain dose parameter values and statistical results for three treatment techniques are given in Table 4.

OAR Dose Parameters

In this study, although the plans focus on preserving the hippocampus and healthy brain tissue, other critical organ doses are also important. Therefore, in this study, the doses of all organs in the brain were calculated in detail and are given in Table 5.

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Table 3 D_{max}, $D_{2\%}$(Gy), $D_{95\%}$ (Gy), $D_{98\%}$ (Gy), $D_{100\%}$ (Gy) HI, CI, and MU values for PTV and their statistical results (The values are the average data of 15 patients)

Parameters	IMAT	CK	HT	IMAT vs. CK p*	IMAT vs. HT p*	CK vs. HT p*
PTV D_{max} (Gy)	22.03	20.61	19.41	0.001	0.001	0.001
PTV $D_{95\%}$ (Gy)	18.14	18.41	18.28	0.001	0.021	0.02
PTV $D_{2\%}$ (Gy)	21.31	20.35	19.27	0.002	0.001	0.001
GTV $D_{98\%}$ (Gy)	19.77	18.92	18.64	0.001	0.001	0.005
GTV $D_{100\%}$ (Gy)	19.25	18.43	18.53	0.001	0.001	0.549
HI	1.21	1.15	1.08	0.001	0.002	0.001
CI	1.04	1.38	1.34	0.001	0.001	0.033
MU	4894	15576	38362	0.001	0.001	0.02

p*: Significance is found when variables are compared to IMAT-CK, IMAT-HT, and CK-HT, p-value<0.05 determines significance. HI: Homogeneity index; CI: Conformity index; MU: Monitor unit; PTV: Planning target volume; IMAT: Intensity-modulated arc therapy; CK: CyberKnife; HT: Helical radiotherapy; Gy: Gray; GTV: Gross tumor volume

Table 4 Brain dose parameter values and their statistical results for three treatment techniques (The values are the average data of 15 patients)

Brain parameters	IMAT	CK	HT	IMAT vs. CK p*	IMAT vs. HT p*	CK vs. HT p*
Brain-PTV D_{max} (Gy)	20.41	20.69	19.19	0.03	0.001	0.001
Brain-PTV V_8 (%)	2.42	5.29	6.07	0.003	0.001	0.663
Brain-PTV V_8 (cc)	30.32	76.74	84.76	0.002	0.001	0.548
Brain-PTV V_{10} (%)	1.51	3.83	4.1	0.001	0.001	0.885
Brain-PTV V_{10} (cc)	18.66	49.75	56.04	0.001	0.001	0.950
Brain-PTV V_{12} (%)	0.97	2.94	2.77	0.001	0.001	0.494
Brain-PTV V_{12} (cc)	12.6	38.23	37.46	0.001	0.001	0.545

p*: Significance is found when variables are compared to IMAT-CK, IMAT-HT, and CK-HT, p-value <0.05 determines significance. IMAT: Intensity-modulated arc therapy; CK: CyberKnife; HT: Helical radiotherapy; PTV: Planning target volume; Gy: Gray

Statistical Analysis

In the SPSS, the first step was a normalization test to analyze, whether the data were normally distributed. For normally distributed parameters, a one-way analysis of variance was used to find significance. Bonferroni test was applied for double comparison when "p" value was smaller than 0.05 as a result of this test. When the distribution was not normal, Kruskal–Wallis was used to find significance, then a "Mann–Whitney U"-test was used to find the significance between the subjects. The limit of significance was set at 0.5 for p-value. IBM SPSS version 24.0 (SPSS Inc., IL, USA) was applied for statistical comparison.

RESULTS

Evaluation of Treatment Plan Parameters for PTV

In all plans, treatment plans were made by preserving critical organs (especially the hippocampus). Results of the PTV comparison of three different techniques are shown in Table 3. When PTV volume was evaluated concerning $D_{2\%}$, $D_{95\%}$, and D_{max} values, significantly differences were observed between these techniques ($p<0.05$). HT is superior to other techniques when evaluating $D_{2\%}$ for PTV. Better results were obtained with CK when $D_{95\%}$ was evaluated for PTV.

Evaluation of Brain Dose Parameters

For each plan, the dose values and statistical results of the Brain-PTV volume are given in Table 4. While there was no significant difference between CK and HT for V_8 (%), V_8 (cc), V_{10} (%), V_{10} (cc), V_{12} (%), and V_{12} (cc), which was examined to evaluate healthy brain tissue, there was significant difference between IMAT and other techniques. Better results were obtained by IMAT.

Evaluation of OAR Doses Parameters

For each plan, dose values and statistical results of hippocampus, optic nerve, chiasm, brain stem, eye, lens, cochlea, pituitary, and spinal cord are given in Table 5. When the maximum point dose of the right hippocampus was evaluated, there was no significant difference

Table 5 Statistical results of OARs for three treatment techniques (The values are the average of 15 patient data)

OARs parameter	IMAT	CK	HT	IMAT vs. CK p*	IMAT vs. HT p*	CK vs. HT p*
R-Optic nerve D_{max} (Gy)	1.72	2.02	0.91	p>0.05 (Kruskal-Wallis)		
L-Optic nerve D_{max} (Gy)	1.4	1.21	1.3	p>0.05 (Kruskal-Wallis)		
Chiasm D_{max} (Gy)	1.98	2.57	0.95	p>0.05 (Kruskal-Wallis)		
Brain stem D_{max} (Gy)	3.18	5.23	2.41	p>0.05 (Kruskal-Wallis)		
Brain stem D_{1} (cc)	2.18	3.54	1.47	p>0.05 (Kruskal-Wallis)		
R-Eye D_{max} (Gy)	1.54	0.26	1.67	p>0.05 (Kruskal-Wallis)		
L-Eye D_{max} (Gy)	1.54	0.37	1.68	0.01	0.548	0.014
R-Lens D_{max} (Gy)	1.01	0.14	0.55	0.001	0.125	0.04
L-Lens D_{max} (Gy)	0.77	0.12	0.72	0.001	0.419	0.001
R-hippocampus D_{max} (Gy)	3.06	5.13	1.63	0.034	0.351	0.036
R-hippocampus D_{mean} (Gy)	1.75	1.84	0.64	p>0.05 (Kruskal-Wallis)		
R-hippocampus $D_{40\%}$ (Gy)	1.84	2.03	0.55	p>0.05 (Kruskal-Wallis)		
L-hippocampus D_{max} (Gy)	2.56	4.13	2.33	p>0.05 (Kruskal-Wallis)		
L-hippocampus D_{mean} (Gy)	1.41	1.27	0.5	p>0.05 (Kruskal-Wallis)		
L-hippocampus $D_{40\%}$ (Gy)	1.42	1.35	0.49	p>0.05 (Kruskal-Wallis)		
R- cochlea D_{max} (Gy)	1.08	2.46	0.2	p>0.05 (Kruskal-Wallis)		
R- cochlea D_{mean} (Gy)	0.88	1.66	0.18	p>0.05 (Kruskal-Wallis)		
L- cochlea D_{max} (Gy)	0.97	2.06	0.2	0.237	0.051	0.025
L- cochlea D_{mean} (Gy)	0.68	0.84	0.18	0.604	0.025	0.031
Pituitary D_{max} (Gy)	1.9	2.66	0.48	0.372	0.05	0.02
Pituitary D_{mean} (Gy)	1.49	0.94	0.34	0.507	0.003	0.135
Spinal Cord D_{max} (Gy)	0.34	0.81	0.1	0.229	0.003	0.001

p*: Significance is found when variables are compared to IMAT-CK, IMAT-HT, and CK-HT, p-value<0.05 determines significance. OARs: Organ at risk; IMAT: Intensity-modulated arc therapy; CK: CyberKnife; HT: Helical radiotherapy; Gy: Gray

between IMAT and HT, but a significant difference was found between CK and other techniques. There was no significant difference in other criteria for hippocampus. Maximum doses were evaluated in the optic nerve, chiasma, and brain stem. Although there was no significant difference between the techniques, the lowest values were obtained with HT. In eye and lens doses, the lowest values were obtained with CK.

When the maximum and mean doses for the pituitary and left cochlea were evaluated, the lowest doses were obtained with HT. There was no significant difference between the techniques in the right cochlea (p>0.05). For the maximum point dose of the spinal cord, while there was no significant difference between IMAT and CK a significant difference was found between CK and other techniques. Better results were obtained by HT.

DISCUSSION

Although WBRT represents the mainstay of treatment for brain metastases, in the modern age of radiotherapy, stereotactic brain radiotherapy and radiosurgery have played a central role in the treatment of patients with brain metastases. These techniques allow better protection of at-risk organs. Therefore, a longer survival can be expected. Especially in stereotactic brain radiotherapy to treat brain metastases, it is important to protect the hippocampus due to the application of high doses. SRS has the potential to provide greater hippocampal protection in the treatment of brain metastases with fall-off gradient.[19]

Chang et al.[20] conducted a study comparing the neurocognitive outcomes of WBRT plus SRS versus SRS alone treatment in patients with brain metastases. The study was stopped early because those who received WBRT combined with SRS were significantly more likely to have decreased learning and memory at 4 months than those who received SRS alone. Similarly, Brown et al.[21] evaluated patients treated SRS alone and patients treated WBRT combined with SRS and observed cognitive outcomes at 3 months post-treatment. They found that in patients with one to three brain metastases, SRS alone resulted in improvement in cognitive function at 3 months compared to WBRT combined with SRS.

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Nguyen et al.[22] performed a dosimetric analysis comparing hippocampal protective WBRT with single fraction SRS in patients with 10–30 brain metastases. They found that the use of SRS significantly reduced hippocampal doses compared to hippocampal-protective WBRT.

The above studies have shown that WBRT is not suitable for all patients. Together with all these data, these results suggest that neurocognitive function can be better preserved by hippocampal protective plans.[20] Therefore, it is reasonable to expect that modalities such as SRS could further reduce the dose on the hippocampus and better preserve neurocognitive function.[23]

According to Gondi et al.,[24] $D_{maximum}$ <16 Gy and $D_{40\%}$ <7.3 Gy were accepted as reference values for hippocampal protection. Kothavade et al.[25] evaluated ten patients with low-grade brain tumors in their study and retrospectively compared IMAT, tomotherapy, and stereotactic conformal radiotherapy. A dose of 54 Gy in 30 fractions was prescribed at the isocenter. The authors concluded that the tomotherapy plans significantly protected the hippocampus compared to stereotactic conformal radiotherapy and intensity-modulated radiotherapy plans. In our study, when the doses of the hippocampus were evaluated, the right hippocampus D_{max} values for IMAT, CK, and HT were found at 3.06 Gy, 5.13 Gy, and 1.63 Gy, respectively. The left hippocampus D_{max} values were also found at 2.56 Gy, 4.13 Gy, and 2.33 Gy, respectively. When evaluated for the $D_{40\%}$ parameter, the right hypocampus $D_{40\%}$ was found for IMAT, CK, and HT at 1.84 Gy, 2.03 Gy, and 0.55 Gy respectively. The left hippocampus $D_{40\%}$ values were obtained as 1.42 Gy, 1.35 Gy, and 0.49 Gy respectively. When evaluated for D_{mean}, the right hippocampus D_{mean} value was 1.75 Gy, 1.84 Gy, and 0.64 Gy for IMAT, CK, and HT, respectively. Left hippocampus D_{mean} values were obtained as 1.41 Gy, 1.27 Gy, and 0.5 Gy, respectively. Lower values were observed in tomotherapy plans for $D_{maximum}$, D_{mean}, and $D_{40\%}$ parameters, and doses below the limit were obtained in other treatment modalities, and no significant difference was found. Gondi et al.[26] discovered that modern radiation therapy techniques such as Linac-based treatment plans or helical tomotherapy, all allow for hippocampus sparing with acceptable target coverage and homogeneity. Yen et al.[27] compared hippocampal-avoidance whole-brain radiotherapy plans for tomotherapy and VMAT in a retrospective study of 21 patients with brain metastases. Hippocampus dose limitation was provided in all tomotherapy plans, but not in 56% of VMAT plans. However, the difference was not significant. In a study by Dogan et al.[28] in which they compared VMAT and HT plans in hippocampal-avoidance prophylactic whole-brain radiotherapy on ten patients with small cell lung cancer, they stated that HT plans provided significantly better hippocampus protection than VMAT when they evaluated the minimum, mean, and maximum doses of the hippocampus. When we compared the results of IMAT and HT in our study, while better protection was provided with HT, values below the dose limits were obtained with IMAT.

Furthermore, the risk of radiation damage must be taken into account when treating multiple brain metastases with SRS. Minniti et al.[17] published a study examining rates of radionecrosis in 206 patients treated with SRS. The authors reported that radionecrosis developed in 24% of treated lesions and V_{10} Gy and V_{12} Gy which are exposed to the brain, were the most determining independent risk factors for radionecrosis.

In a study by the University of Cincinnati and Case Western Reserve, they determined that when the V_{12} Gy exceeds 10 cc, the risk of necrosis increases by 50%. In the USCF study, the risk of necrosis was determined to be 15% when V_{12} Gy was between 7 and 35 cc.[18] Therefore, in our study while evaluating the feasibility of hippocampal protection in the treatment of brain metastases with SRS, we also examined the plan parameters of the brain such as V_8 (%), V_{10} (%), V_{12} (%), V_8 (cc), V_{10} (cc), and V_{12} (cc) to evaluate the risk of necrosis. In our study, as a result of dosimetric analysis, the median V_{10} Gy was obtained as 18.66 cc, 49.75 cc, and 56.04 cc for IMAT, CK, and HT, respectively. V_{12} Gy was obtained as 12.6 cc, 38.23 cc, and 37.46 cc, respectively. As shown in Table 4, based on the V_{12} (%) and V_{12} (cc) values of the brain, the lowest values were obtained from the IMAT plans with 0.97 and 12.6. Thomas et al.[29] compared GK and multiarc VMAT plans, in which plans were designed as 1-arc, 2-arc, and 4-arc with single isocenter. Compared with GK, multiarc VMAT had similar dose falloff.

On the other hand, in a study by Zhang et al.[9] in ten patients with 3–10 metastases, they dosimetrically compared four different techniques (Gammaknife, single-isocenter VMAT, CyberKnife, and tomotherapy). The lowest V_{12} Gy was obtained with Gammaknife, then they determined that the lowest values for brain V_{12} Gy were found in CyberKnife, VMAT, and tomotheraphy technique as 42.42 cc, 90.53 cc, and 106.75 cc, respectively. In the study, 20 Gy dose was defined in a single fraction and ten MV-FFF energy was used.

In our study, mean CI resulted 1.04, 1.38, and 1.34 for IMAT, CK, and HT plans, respectively; the differ-

ences between IMAT, CK, and HT were statistically significant. Differences in CI between IMAT, CK, and HT are attributable to beam collimation systems and the different dose delivering. Because, while dose is delivered by a collimated fan beam along an helical pattern in HT treatments, the irradiation is performed using non-coplanar beams coming from different angles in CK.[12] In IMAT, during delivery, the field shape changes as determined by the required intensity distributions at different beam angles.[30]

Both IMAT and CK reached a high heterogeneity (mean HI 1.21, 1.15 and for IMAT and CK, respectively), while a more homogenous dose distribution (mean HI 1.08) was observed for HT.

In the comparison of CK and HT performed on 19 patients with single brain metastases by Greto et al.,[12] mean HI was found 1.25 and 1.05 for CK and HT, respectively.

In our study, in addition to doses of healthy brain tissue and hippocampus other critical organ doses were also evaluated. As far as we know, there has been no study, in which all critical organs (brainstem, optic nerve, chiasm, eye, lens, hippocampus, cochlea, pituitary, and spinal cord) were evaluated in dosimetric studies for patients with multiple brain metastases and treated with SRS. Table 5 shows that all OAR parameters in the three treatment techniques meet the criteria for a safe treatment. Critical organ doses provided the desired criteria in all treatment techniques, while the lowest doses were generally obtained with HT. Cozzi et al.[31] compared irradiation techniques with photons (stereotactic arc therapy, intensity modulated radiotherapy, helical tomotherapy, CyberKnife and intensity-modulated multiple arc therapy) for benign intracranial tumours in a study. They reported that HT had the best balance between photon techniques in terms of PTV coverage, conformity and OAR protection. In addition, the duration of treatment may also be important in choosing the appropriate treatment method for patients. An important advantage of IMAT is the short treatment time compared to other treatment platforms.

CONCLUSION

The purpose of this study was to determine whether the hypocampal dose could be significantly reduced in the treatment of brain metastases using SRS treatment while providing target coverage and protecting organs at risk. At the same time, we tried to determine the most effective treatment modality for this purpose.

When using SRS for multiple brain metastases, hippocampus doses may vary according to patients and techniques used. If the hippocampus is identified as the risk organ, preservation of this structure can be achieved in most cases without damaging the target coverage area. Performing the hippocampus preservation procedure during brain RT can significantly reduce or even prevent cognitive complications. This should be thought of in all patients who would have multiple brain metastases and be treated with SRS. Given the amount of dose that healty brain tissue receives, the volume of the brain that receives a low or medium dose is significant. When the doses taken by the healty brain tissue were evaluated in this study, the best protection was obtained from the IMAT plans. Tumor location, size, number, and volume should not be ignored because they are important parameters in determining the treatment technique. As a result, in our study, acceptable results were found for target and critical organ doses in the planning made with three different devices.

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