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Comparison of Single and Multiple Treatment Plans for Multiple Brain Metastases in CyberKnife® Radiosurgery System on Phantom

Kevser Sözen [1,a,*], Hasan Uysal [2,b], Nihal Büyükçizmeci [3,c], Kaan Oysul [4,d]

[1] The Graduate School of Selçuk University, Institute of Science, 42130, Konya, Türkiye.
[2] Department of Radiation Oncology, CyberKnife Radiosurgery Center, Medicana International Ankara Hospital, 06510, Ankara, Türkiye.
[3] Department of Physics, Institute of Science , University of Selçuk, 42130, Konya, Türkiye.
[4] Department of Radiation Oncology, CyberKnife Radiosurgery Center, Medicana International Ankara Hospital, 06510, Ankara, Türkiye.

**Corresponding author*

Research Article

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ABSTRACT

While the use of CyberKnife® radiosurgery systems is increasing, the choice of treatment plan is also important. In this study, it was aimed to determine the more advantageous application by comparing the irradiation of all metastases at once and the protocols of irradiation of metastases separately in multiple brain metastases. For this, on an entirely new head phantom; 6 brain metastases and 3 critical organs, including the spinal cord, brain stem, and chiasm, were determined over the spaces where the dosimeters were placed. Computed tomography (CT) images of the head phantom were taken and these 6 tumors and 3 critical organs were drawn (contouring) on the image. In the treatment planning system, the dose we wanted to give was written and irradiation plans were created to be done separately with a single irradiation. Luminescence (OSL) dosimeters with BeO optical excitation were removed from the phantom after each irradiation and the count value obtained from the dosimeter reader device was recorded. Homogeneity index (HI), conformity index (CI), new conformity index (nCI), duration of treatment, and gradient index (GI) values of irradiation at one time and separately were compared. While it was found that irradiation of tumors with a separate treatment plan was more advantageous in terms of conformity index (CI), new conformity index (nCI), homogeneity index (HI), and coverage values, it was seen that a single plan was more suitable in terms of gradient index and duration.

Keywords: Cyberknife System, Radiosurgery, Multiple brain metastases, Conformity, Dose gradient.

[a] *kevser07@gmail.com* *https://orcid.org/0009-0005-9561-4674*
[b] *uysalhasann@gmail.com* *https://orcid.org/0000-0002-4867-304X*
[c] *nihal@selcuk.edu.tr* *https://orcid.org/0000-0002-6030-9574*
[d] *kaan@oysul.com* *https://orcid.org/0000-0002-4359-318X*

Introduction

Brain metastases are the most common malignancies in the central nervous system [1]. Up to forty percent of cancer patients have brain metastases at some point in their disease. The most common cancers that metastasize to the brain are lung, breast, kidney, colorectal, and melanoma. Primary treatment options in patients with brain metastases are surgery, chemotherapy, whole brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS) [2].

Today, various radiotherapy methods are used for cancer treatment. In recent years, developments in engineering and computing have led to great advances in radiotherapy methods. As a result of these developments, technologies such as intensity modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), stereotactic radiotherapy (SRT), and stereotactic radiosurgery (SRS) have been routinely used in clinical practice.

SRS is based on the fact that radiation beams intersect at a precisely placed three-dimensional target. The Gamma Knife device is the first commercially produced intracranial SRS system to prevent patient movement and minimize the risk of damage to tissues adjacent to the tumor. In this system, the stereotactic frame consisting of fixed cobalt sources is fixed to the patient's head by screwing. Thanks to advances in imaging techniques, a robot-mounted CyberKnife® device was developed in the following years that could provide SRS without requiring surgical immobilization of the skull [3]. This radiosurgery system, also called "Space Scalpel", is a robotic radiosurgery system developed for the treatment of not only intracranial cancer but also whole-body cancer [4].

SRS is a treatment method that does not need to open the skull in deep-seated small lesions surgically,and allows to reach the normal brain tissues around the target as much as possible without damaging it. It shows 1mm targeting accuracy on fixed targets, such as cranial or spinal cord tumors, and on moving targets, such as lung tumors [4]. Small and well circumscribed tumors are the most suitable targets for this method [3]. The CT images taken before the treatment of the patient are compared with the snapshots taken during the treatment by the system. According to the obtained tumor coordinates, the radiation dose is adjusted instantly on the computer. Thus, the possible small movements of the patient during the treatment are prevented from affecting the treatment [5].

Whole brain irradiation or SRS can be performed in patients with multiple metastases following the surgical procedure. For patients with multiple metastases following the surgical procedure, it is more preferable to apply SRS alone without whole-brain irradiation due to concerns that whole brain irradiation may cause side effects such as cognitive dysfunction, hair loss, and fatigue that reduce the quality of life. Therefore, SRS has become increasingly important in the treatment of brain metastases [3]. SRS 1-3 is standard in patients with metastases and is increasingly used instead of whole-brain radiation therapy in cases with up to 10 brain metastases, as it provides local tumor control while reducing neurological side effects. [6].

The aim of our study is to determine the more advantageous aspects of treatment plans by comparing the irradiation of all metastases at once and the irradiation of metastases separately in patients with multiple brain metastases based on HI, CI, treatment duration, scope, and gradient index values.

Materials and Methods

Today, irradiation in brain metastases can be done with radiosurgery. In this study, treatment plans for 6 brain metastases were investigated in a homemade phantom to preserve neurocognitive functions and irradiate less normal tissue.

Dose Calibration

In radiation therapy, it is crucial to give the desired dose to the patient in an adequate amount. Because if the adequate dose is not given, it may not be possible to destroy the tumor tissue completely. Radiation dosimetry is a method of checking whether the dose values calculated and displayed in the planning system are actually these values. For this, 11 BeO OSL dosimeters were used in our study. The dimensions of the BeO crystal used are 4.7×4.7×0.5 mm and the sheathed dimensions are 11×11×4 mm. Calibration of these dosimeters was carried out in the PTW brand RW3 solid water phantom. For the calibration, BeO OSL dosimeters were irradiated at 50 MU with 60mm collimator and 6Mv x-ray with SAD=80cm, 30cm x 30cm phantom diameter, dmax=1.5cm. From here, the calibration coefficients obtained by dividing the average OSL number showing the sensitivity of the dosimetry crystals by the dosimetry number were calculated separately for each dosimetry.

İmaging of the Phantom on Computed Tomography

In the study, first of all, the phantom, produced with a three-dimensional printer, was taken on the GE brand Revolution Evo Model CT device with 128 sections in Medicana Ankara hospital, and an image with a 1 mm cross-section range was obtained. Before the CT image of the phantom was taken, a thermoplastic frame was placed on the phantom (figure 1) to match the imaging system coordinate system and the device coordinate system.
All obtained CT data were transferred to the multi-plan treatment planning system.

Figure 1. Fixing the phantom with a thermoplastic mask. Picture is taken during the measurements in the laboratory of Medicana Ankara hospital.

Figure 2.Head phantom produced by using 3D printer. This phantom is produced for this research by H. Uysal

On the tomography images transferred to the Phantom's Multiplan treatment planning system, 6 tumor metastasis volumes as Tumor1, Tumor2, Tumor3, Tumor4, Tumor5, and Tumor6 and is contoured volumes as Critical1 (Spinal cord), Critical2 (Brainstem), Critical3 (Chiasma). In the plans, 3 shells with 2mm, 5mm, and 10mm widths were created at the target volume planned on the phantom. Treatment planning was carried out in such a way that 100 cGy was delivered to the target with the sequential technique, using the ray tracing algorithm for each section. A 10 mm collimator was chosen among 12 different collimators with 5 to 60 mm diameters to be used in planning. Plans have been created to treat all metastases on the phantom, both separately and at once. The locations of the metastatic tumor and critical organs in the phantom were determined as follows. Tumor1 is in the posterior right part of the 4th section, Tumor2 is in the rearmost left part of the 6th section, Tumor3 is in the far right front of the 7th section, Tumor4 is in the anterior left of 7th section, Tumor5 is in the anterior of the 8th section, and Tumor6 is in the right posterior of the 15th section. Critical1 formed in the spinal cord is located in the 15th section; Critical2 formed in the brain stem, and Critical3 formed in the chiasma, are located in the 7th section. The head phantom was irradiated with 6 MV photons with CyberKnife® device and dose measurements were made with BeO dosimeters placed inside the phantom. Count values for a single measurement are given in Table-1.

Table 1. For the 1st measurement, when 1Gy dose was given to each tumor volume, the count values of all tumors and critical organs were read in BeO dosimeters.

1.Measurement	*Tumor1*	*Tumor2*	*Tumor3*	*Tumor4*	*Tumor5*	*Tumor6*	*Single Plan*
T1	429521	6590	6782	4390	5811	4292	455755
T2	4162	432902	6230	5853	2970	3437	439105
T3	10675	15247	401255	6875	33779	4418	500360
T4	4763	23533	4674	397898	14931	3187	465847
T5	3539	4784	51563	8901	516929	4284	422143
T6	3315	3446	2815	2733	3130	389236	429734
K1	3000	2897	2754	3575	3601	37340	27028
K2	5085	8345	30259	11463	13302	3868	109703
K3	3704	4284	32948	12244	108860	3542	165417

Quality Control Indices

The Dose Volume Histogram (DVH) is used to evaluate the tumor volume and the dose delivered to the surrounding healthy tissue and critical structures. From DVH, dose parameters such as maximum dose, minimum dose, and average dose delivered to the volume of interest can be derived [7]. The DVH graph of the third metastasis tumor obtained in our study is given in Figure 3.

Different indices have been defined to evaluate the quality of a treatment plan to obtain an optimal dose distribution. Thanks to these indices, it will be easier for us to choose a plan that provides maximum tumor coverage homogeneously and preserves healthy tissues [8]. Some of these indexes are HI, CI, nCI, GI, and coverage. These indices provide an easy method of quantitatively assessing the dose distribution, which represents the agreement between the predicted dose area and the planned tumor volume

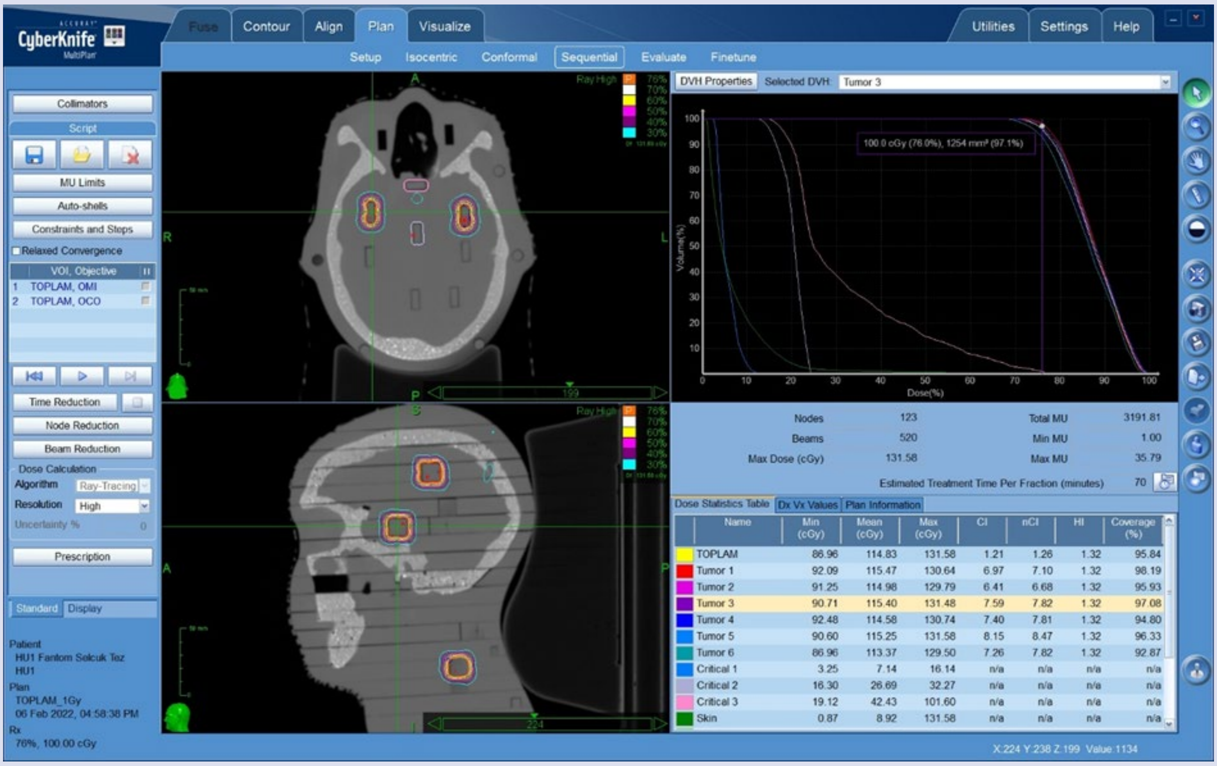

Figure 3. DVH graph of the 3rd metastasis tumor in a single treatment plan (obtained from the Multiplan treatment planning system).

Statistical Calculation

Statistical calculation was done using SPSS version V20. Paired Sample t-test was used in the analysis of all data. 0.01 ≤ p <0.05 status statistical significance, 0.001 ≤ p <0.01 status was accepted as high statistical significance.

Results

6 tumor volumes were determined in the HU phantom study to compare the irradiation of all metastases at once and the irradiation of each metastasis separately in patients with multiple brain metastases. The dose we wanted to give in the treatment planning system and the measurements we read in the BeO dosimeters in the HU phantom were evaluated. In addition, homogeneity index (HI), conformity index (CI), gradient index, duration of treatment, and coverage values, which show the quality of a treatment plan, were tried to determine the more advantageous application in multiple brain metastases by comparing the irradiation of all metastases at once and the irradiation of metastases separately. In our study, the durations for the planning of 6 brain metastases in the head phantom produced by the three-dimensional printer were calculated by the Multiplan treatment planning system. When we create a plan for the irradiation of each tumor separately, the irradiation time varies between 16 and 20 minutes—in total, the average irradiation time lasted 110 minutes. In a single plan, the irradiation time is 70 minutes on average. When the average times were compared, it was seen that the irradiation time in the separate planning took 40 minutes more than in the single planning. Therefore, since irradiation in a single treatment plan takes a shorter time than separate planning, it has been seen that the single plan is advantageous in terms of time.

The steep dose gradient outside the radiosurgery target is one of the factors that enable radiosurgical treatment [9,10]. The GI is an index used to evaluate off-target dose reduction and indicates the optimal off-target dose distribution [7]. The Paddick Gradient index formula, which is defined as the ratio of the volume of half of the defined isodose to the defined isodose volume, was used in our study. While the gradient index value was 4.55 in the single treatment plan, the total GI value of the separate treatment plans was 5.38. A lower GI value means a steeper dose distribution gradient outside the target and better normal tissue preservation. Therefore, the gradient index value was better when a single plan was made compared to the planning made separately.

The homogeneity index is an index that shows how homogeneously the dose given to the tumor volume is distributed in this volume. The HI will be determined as the maximum dose in the treatment volume divided by the prescribed dose. HI values close to 1.0 (the ideal value is expected to be 1) indicate higher dose homogeneity, while values greater than 1 indicate more heterogeneous dose distribution [11,13]. In this study, the homogeneity index ranged from 1.25 to 1.28 in the treatment plan made separately, and the mean value was 1.26. The HI index value was 1.32 in single plan, and a high level of statistical significance ($p = 0.00$) was found between the HI values of the two plans.

The RTOG conformity index formula, given as the ratio of the found isodose volume to the tumor isodose volume, was used. When each of the 6 metastases is planned separately, the conformity index varies between 1.16 and 1.20 and the mean value is 1.17. The CI index value was 1.21 in a single plan. Therefore, a statistically high level of significance ($p = 0.004$) was found in the conformity index between the two plans.

In addition, the nCI value ranged from 1.19 to 1.26 when treatment was planned separately, and the mean value was 1.22. In a single plan, the nCI value is 1.26. ($p = 0.015$), it was found to be statistically significant.

While the dose of 5% of the head volume skin dose is 24.9cGy in single plan, it is 30.7cGy in the separate plan. When we consider the coverage values, when we plan separately, coverage varies between 95.15 and 98.22. The mean value was 95.79. In single treatment planning, it varies between 92.87 and 98.19. The mean value was 95.84.

Discussion and Conclusion

Brain metastases (BM) are the most common malignant brain tumors and are a serious cause of death in cancer cases [14]. Fortunately, there is an increase in cancer survival due to advances in early detection and treatment. After successful cancer treatment, patients have to cope with the physical and psychological effects of the treatment [15]. It is essential to minimize functional and cognitive impairments after treatment.

The aim of radiotherapy is to preserve the healthy tissues and critical organs surrounding the tumor as much as possible and to deliver the entire dose to a defined volume. [16,17]. For this, treatment plans need to be prepared very carefully. While evaluating the prepared plan, it is necessary to consider clinical, biological, geometric, dosimetric, and radiological parameters simultaneously. This is an important but complex and time-consuming process. Often, several plans are prepared for the same patient, and without objective parameters, it becomes difficult to choose. Indexes such as CI, HI, GI and coverage can be used to select the best plan among available treatment options or to compare various devices and techniques [8]. In our study, treatment plans for multiple brain metastases were compared using these indices.

When we compare the irradiation of all metastases at once and the irradiation of each metastasis separately in terms of treatment time, it is seen that the irradiation of a single plan is advantageous in terms of patient comfort as it takes a shorter time. Patients treated in a much shorter time will be able to return to their everyday lives more quickly.

Ideal treatment planning is the one in which the lowest possible dose is given to normal tissues, and the entire prescribed dose is delivered to the target volume. In optimal treatment planning, isodose volume and tumor volume should overlap and be as close to CI=1 as possible [18]. If we consider the CI values in our study, it has been determined that the plans made separately are advantageous compared to a single plan. Yu et al., while finding the CI value similar for both plans, Uzel reported that the plan made separately for each metastasis is more advantageous in terms of CI. In our result, it was found that separately treatment planning was more advantageous in terms of CI, in line with Uzel [19,20]. In our result, it was found that separately treatment planning was more advantageous in terms of CI, in line with Uzel Likewise, it was concluded that it was more appropriate to plan separately according to the nCI values.

In stereotactic radiotherapy treatments, the cases where the dose falling on the surrounding normal tissue decreases sharply while irradiating the target increases the quality of the treatment. While this value expressed by the gradient index value was found to be more appropriate in the separately treatment plan by Uzel, it was found more reasonable in terms of single-plan GI value in our study on the HU phantom.

The homogeneity index gives the ratio between the maximum and minimum dose in the target volume, and a lower value indicates a more homogeneous dose distribution within the tumor volume. It is not the right approach to try to reach the ideal value of HI at all costs. In some clinical situations, inhomogeneity (heterogeneity) may be desired [9]. However, in our study, the homogeneity index (HI) value was within the range of appropriate values in both plans, and a better homogeneity was found for the treatment plan prepared separately for each metastasis. In terms of coverage, both planes cover tumor volume very close to each other.

It has been found that a single plan is more advantageous in terms of treatment duration, gradient index and protecting organs at risk. In addition, planning separately in terms of conformity index, new conformity index and homogeneity index gave more appropriate results. All these results should be evaluated together and the patient's condition should be taken into consideration, and the most appropriate plan should be preferred for the patient.

Conflicts of interest

There are no conflicts of interest in this work.

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