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Evaluation of dose received by organs at risk in radiotherapy of brain tumors

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► ***Original article***

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ABSTRACT

Background: Radiation therapy (RT) is one of the common and successful treatments for brain malignancies and benign disorders. In spite of its irrefutable merits, it is associated with a number of complications caused by radiation damage to the important Organs at Risks (OARs), which is strongly correlated with the radiation dose during RT. This study aimed to determine the range of radiation dose to Hippocampus and certain OARs in the brain. ***Materials and Methods:*** Thirty-two patients with primary brain cancer, undergoing RT, were selected retrospectively. The selected OARs were contoured using the RT Treatment Planning Software through assessing the images from the computed tomography and magnetic resonance imaging (MRI). Dose parameters, namely maximum dose (Dmax) and median dose (Dmedian), to OARs (optic nerves, chiasm, retinas, lenses, orbits, lachrymal glands, brainstem, hippocampi, etc.) were assessed. ***Results:*** The mean age of the patients was 37.8±14.3 years (from 5 to 60 years), and 19 patients (59%) were male. Glioblastoma multiforme and astrocytoma were the most common tumors. The maximum dose received by the brainstem, lenses, and eye ranged between 32-62 Gy, 0.75-40 Gy, 1.5-65 Gy, respectively. The maximum dose received by the hippocampi was 62.7 Gy. ***Conclusion:*** Important OARs can tolerate the received doses which were lower than the threshold level of serious complications. However, the maximum dose received by the hippocampi was higher than the recommended tolerated radiation dose; therefore, it is recommended to conduct more studies in this regard.

Keywords: *Radiotherapy, Brain tumors, Hippocampus*

INTRODUCTION

The main goal of radiotherapy (RT) with ionizing radiation is to deliver the lethal dose to the tumor while saving healthy tissues. Complications in some organs should be prioritized in the treatment plan and receive additional care[1]. In RT of brain tumors, considering the radiation dose constraints to OARs is an important concern [2]. Optic structures and visual pathways are the most important structures since the loss of vision is a deleterious side effect of RT. The brainstem is another important OAR that requires special

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attention during the RT due to its critical role in the central nervous system. The hippocampus is another brain OAR under close investigation [3, 4]. Due to cognitive impairment after the RT, the hippocampus is of great importance [5, 6]. The standard hippocampal dose (radiation) is being examined currently, which has ranged from 10 to 35Gy in various studies [7, 8]. No studies have examined the hippocampal dose during 3D conformal treatment in Iran to the best of our knowledge. Moreover, very few studies have examined the dose reaching brain organs at risk (OARs) [9, 10]. In the study, we have evaluated OARs and the dose range reaching them in treatment of brain tumors using CT/MRI fusion. Additionally, it is the first time that the dose reaching hippocampus, as an OAR, is examined at a radiotherapy center in Iran. It is hoped that the results help, although a little, reduce the delivered dose and thus reduce radiotherapy complications by showing the status quo regarding the radiation dose reaching OARs.

MATERIALS AND METHODS

Thirty-two patients with malignant brain tumors, receiving RT in the Radiotherapy Center of Cancer Institute of Iran between January and August 2014, were included retrospectively. Before the intervention, all patients had undergone MRI (fluid-attenuated inversion recovery [FLAIR], T2-weighted MRI, and/or gadolinium-enhanced T1-weighted MRI) for making a clinical treatment decision.

The patients had received CT simulation before treatment at the treatment position using the immobilization devices. CT scan was done with GE Light Speed 16-Slice CT scanner (USA). The routine protocol of 120kVp, activated GE Smart mA, and standard reconstruction kernel were used. Sagittal and coronal reformatting images were reformatted.

CT scan was used for treatment planning, tumor delineation, and OARs contouring. Radiation therapy was delivered with 3D Conformal Radiation Treatment (3D-CRT) technique up to a dose of 60Gy (2Gy/fraction) to high-risk sites and 54Gy (1.8Gy/fraction) to susceptible sites, with 6MV energy photons. To this end, the linear Elekta compact™ linear accelerator (Sweden) was used. The only exception was a patient with chloroma, whose total treatment dose was 30Gy.

The patients underwent MRI and CT scan in similar positions and the MRI was performed on a 1.5-Tesla Toshiba Aquilion scanner. Both the CT and MR images were imported into the RTDosePlan (Math Resolutions, LLC 5975 Gales Lane, Columbia, MD. 21045). Both images were manually matched in three dimensions according to two anatomical side markers. The matched-images were visually checked in all directions and modified by a radiation oncologist and a medical physicist with at least four years of active clinical experience.

In the RTDosePlan, all components of the visual pathway including lenses, orbits, retinas, optic nerves, and chiasm, as well as the brainstem, lachrymal glands, and hippocampi were contoured (figure 1 a, b and figure 2 a, b).

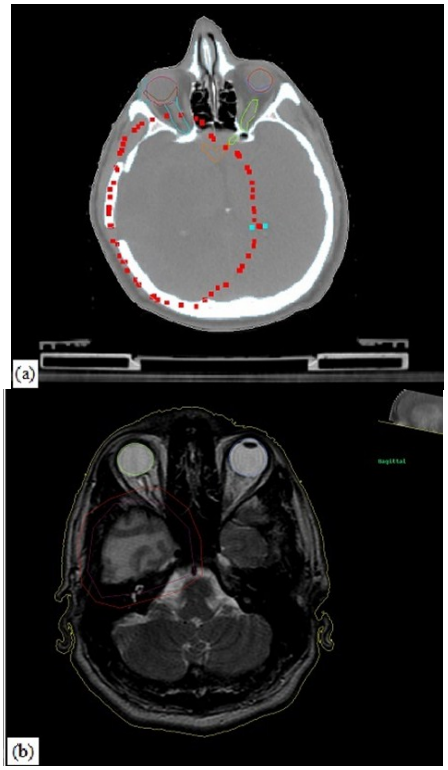

Figure 1. (a) CT image of patient 1 with the contouring of orbits, retinas, chiasm, optic nerves, lachrymal glands and PTV, **(b)** MR image with the contouring of orbits, CTV and PTV.

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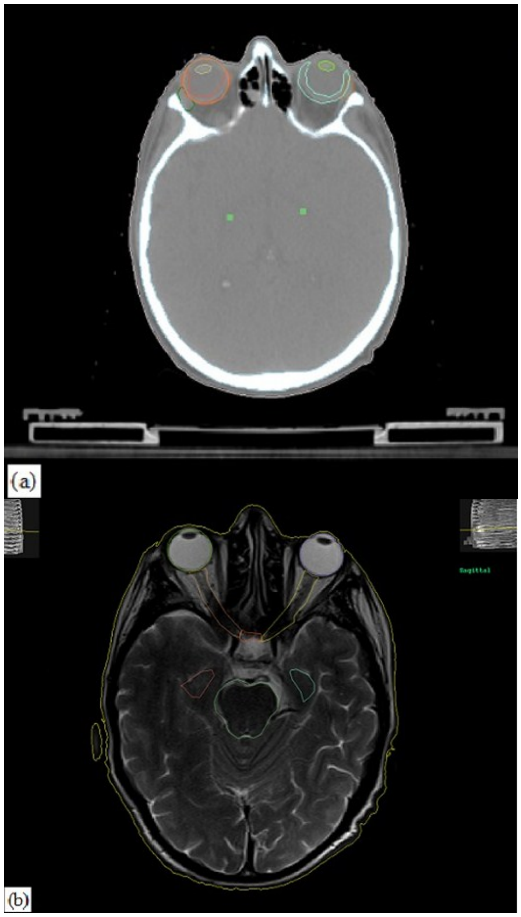

Figure 2. (a) CT image patient 2 with the contouring of orbits, retinas, lens and lachrymal glands **(b)** MR image with the contouring of orbits, optic nerves, chiasm, brainstem and hippocampus.

Dose parameters, namely the maximum dose (D_{max}) and median dose (D_{median}), to OARs including optic nerves, chiasm, retinas, lenses, orbits, lachrymal glands, brainstem, and hippocampi were extracted from the planning system.

Statistical analysis

Data was analyzed in STATA 15.2. The mean, range, and standard deviation (SD) of dose parameters were calculated.

RESULTS

Thirty-two patients were enrolled in this study with the mean age of 37.8±14.3 (5-60 years) and 19 participants were male (59%). Demographic data of patients are presented in table1. The D_{max} and D_{median} to the components of the visual pathway (lenses, chiasm, optic nerves, orbits, retinas) as well as lachrymal glands, brainstem, and hippocampi are presented in table2. Also Table2 shows the dose-related data, namely dose per fraction and the total doses delivered to the OARs.

The maximum dose received by the brainstem, lenses, and eye ranged between 32-62 Gy, 0.75-40 Gy, 1.5-65 Gy, respectively. The peak dose received by the hippocampi was 62.7 Gy.

Table 1. List of the patients and their demographic and radiotherapy data.

Variables	Number	Percent
Age		
< 20	3	10%
20>=	29	90%
Tumor histology		
Astrocytoma-GII, GIII	10	31%
Glioblastoma Multiform	7	21%
Pituitary adenoma	4	12%
Others	11	34%
Prescribed Dose		
30-50	3	10%
50-54	9	28%
54-60	20	62%

Table 2. Delivered doses per fraction and total dose to the visual pathway components.

	Dose range per Fraction (Gy)		Total Dose Range (Gy)	
	D_{max}	D_{median}	D_{max}	D_{median}
Brainstem	1.52-2.13	0.19-2.06	31.95-62.70	51.30-60.90
Right lens	0.04-1.36	1-96	0.75-40.80	0.25-28.80
Left lens	0.03-1.13	0.03-0.61	0.75-33.90	0.75-18.30
Right orbit	0.05-2.19	0.04-1.55	1.35-56.70	1.24-45.00
Left orbit	0.04-2.21	0.03-1.21	1.24-63.30	0.93-36.30
Right lacrimal gland	0.05-2.20	0.04-2.10	1.35-63.00	1.24-45.90
Left lacrimal gland	0.04-2.19	0.02-1.99	1.24-64.50	0.62-44.70
Right retina	0.05-2.19	0.04-2.12	1.35-55.20	1.55-46.80
Left retina	0.05-2.21	0.04-2.04	1.55-60.60	1.24-46.80
RON	0.08-2.20	0.07-2.10	2.48-65.40	1.89-63.00
LON	0.09-2.20	0.06-2.10	2.79-64.50	1.86-62.40
Chiasm	0.11-2.11	0.09-2.10	3.41-63.30	2.79-63.00
Right hippocampus	0.5-2.10	0.23-2.08	15.50-62.70	7.13-61.80
Left hippocampus	1.24-2.13	0.26-2.09	31.95-61.20	8.06-60.00

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DISCUSSION

Radiotherapy is one of the most important treatment modalities in management and control of brain tumors. One of the main goals of RT is delivering the maximum dose to the malignant tumor while saving OARs. There are scant domestic studies on the dose received by OARs in the brain. These studies typically compared the measurement methods and none of them used MRI to determine the range of dose received by OARs [10, 11]. This descriptive study tried to measure the dose received by important OARs in the brain, including the hippocampus with a recently approved role in secondary cognitive disorders.

According to our findings, the maximum dose received by the optic chiasm ranged between 3. 41-63. 3. The maximum doses received by right and left optic nerves (RON and LON) were 65 and 64 Gy, respectively. The threshold of tolerance for the optic nerves and chiasm was 45-60 Gy and up to 1.8-2 Gy/fraction in the literature. The chance of radiation-induced optic neuropathy (RON) significantly increased at higher doses [12, 13]. The maximum dose received by lachrymal glands in the participants was 64-65 Gy; however, the mean dose received by these structures was 44-45 Gy. The predicted radiation dose tolerance for lachrymal glands in the literature was 34-40 Gy [9, 14].

The doses received by the right and left lenses were 40.8 and 33.9 Gy, respectively in our center.In adults, higher doses to lenses are associated with a cataract, in that after 2.5 to 6.5 Gy, the latent period is 8 years with a 33% of progressive cataract; whereas, after 6.51 to 11.5 Gy, the latent period is 4 years, with a 66% risk [15].

The dose received by the brainstem in the patients was up to 62 Gy. Recommended dose-constraints (54-60 Gy) for the brainstem is similar to that of the optic nerves and chiasm. However, recent studies indicate the tolerance threshold of 63 Gy in peripheral regions of the brainstem [16, 17].

The dose received by orbit and retinas varied between about 1 Gy to 60 and 63 Gy. The risk of radiation-induced side effects for the orbit and retina increases at doses >45-55 Gy at 1.8-2 Gy/fraction [18, 19].

The dose received by the hippocampus increased to 65 Gy in the patients under investigation. Currently, there is not any consensus about radiation dose constraints for the hippocampus. This issue was investigated using the RTOG 0933 phase II trial. It is obvious that the chance of neuro-cognitive toxicity in patients is lower at lower radiation doses to the hippocampi. Different studies suggest a wide range of safe doses to the hippocampi from less than 10 Gy to more than 35 Gy based on tumor type and total treatment dose [7, 8, 20]. As a result, there is a significant difference between the dose received by the hippocampus in the patients and the dose tolerance range in the literature. This difference calls for special attention to this organ. Since this is a descriptive study, it cannot determine why a high amount of dose is received by the hippocampus. The lack of access to such methods as the intensity-modulated radiation treatment (IMRT) and stereotactic treatment can be among its major causes. More accurate studies are recommended for assessment of effective factors and reduce the dose received by OARs, such as the hippocampus.

CONCLUSION

A combination of MRI and CT images can be an effective way to achieve more precise contour data and dose calculations. Based on the median and maximum of the delivered dose to OARs and the defined constraint doses, it seems that our treatment plans have generally adopted these recommendations.

Although the treatment dose range for most OARs is slightly higher than the standard tolerance range in the literature, this range for the hippocampi was between 15-62 Gy, which is very higher than the tolerance range in the literature. As a result, special attention and further studies are recommended. Moreover, a wide range of delivered doses to any OAR is due to a) a wide range of tumor locations and proximity to OARs and b) a wide range of total dose prescribed based on the tumor pathology.

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Nevertheless, protecting these OARs requires more advanced RT techniques, including IMRT and stereotactic treatment.

Limitations

In the RT Dose Plan, extracting the mean dose (D_{mean}) is not possible, so the median dose (D_{median}) should be calculated. The sequence of the MRI was another research limitation. In many patients, only T2-weighted or FLAIR sequence of the MRI was fused with CT-Simulation, while the preferred sequence for contouring of OARs is gadolinium-enhanced T1-weighted MRI. In addition, some patients only received the pre-operation MRI, while post-operation MRI generates the optimal imaging data for delineating of OARs and their real position at the beginning of RT.

***Conflicts of interest*:** *Declared none.*

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