Feasibility of hippocampal dose-volume parameters associated with memory decline in intensity-modulated radiotherapy for supratentorial tumors

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Abstract. The purpose of the present retrospective study was to evaluate the feasibility of hippocampal dose-volume parameters associated with memory decline for intensity-modulated radiotherapy (IMRT). In total, 18 patients who underwent IMRT for supratentorial tumors were analyzed. Prescribed doses of IMRT in 30 fractions were 60 Gy to planning target volume (PTV) 1 of the local area and 48-51 Gy to PTV2 of the extended local area. Based on previous literature, the present study investigated dose-volume parameters of the bilateral hippocampi: $D_{40\%}$ of 13.1 Gy, $D_{50\%}$ of 29.6 Gy, and V_{55Gy} of 5.0%. It was evaluated which of the parameters was most achievable, and unfavorable factors that interfere with reaching these parameters were identified. As a result, $D_{40\%}$ of 13.1 Gy, $D_{50\%}$ of 29.6 Gy and V_{55Gy} of 5.0% were achieved in 17, 67 and 33% of patients, respectively. For $D_{50\%}$ of 29.6 Gy, PTV2 ≥500 cc (P=0.004) and tumor in temporal/corpus callosum/basal ganglia (P=0.009) were significant unfavorable factors. In conclusion, $D_{50\%}$ of 29.6 Gy was most achievable. In daily clinical practice, it should be primarily attempted to achieve $D_{50\%}$ of 29.6 Gy of the bilateral hippocampi.

Introduction

Gliomas and meningiomas are two representative primary brain tumors (1). Most gliomas are treated using surgery followed by radiotherapy (RT) (2). The treatment of atypical and anaplastic meningiomas are also similar (3). In the long-term survivors with brain tumors after RT, cognitive dysfunction associated with adverse effects of RT is one of the most concerning complication (4). A representative cause of the radiation-induced neurocognitive decline is known to the damage of neural progenitor cells located in subgranular zone of the hippocampus, and RT sparing the hippocampus has been attempted (5). Recently, several prospective cohort studies have reported an association between hippocampal dose-volume parameters and memory decline in patients with primary brain tumors treated by RT (6-8). Gondi *et al* (6) showed that equivalent dose in 2 Gy fractions (EQD2) to 40% of the bilateral hippocampi was associated with long-term memory impairment. Ma *et al* (7) reported that $D_{50\%}$ of the bilateral hippocampi of 22.1 Gy was associated with 20% risk of memory decline: $D_{n\%}$ was irradiated dose to *n*% of the volume of the structure. Okoukoni *et al* (8) mentioned that the hippocampal V_{55Gy} was a significant predictor for memory impairment: V_{nGy} was the percent of the volume of the structure at least irradiated *n* Gy. However, in daily clinical practice, these dosimetric parameters that are easily achieved and the factors that interfere with reaching these parameters remain unclear.

Therefore, we retrospectively evaluated the feasibility of the hippocampal dose-volume parameters that have been associated with memory decline for intensity-modulated radiotherapy (IMRT) in patients with supratentorial tumors in daily clinical practice.

Patients and methods

Type of study. This single-institutional study was retrospectively conducted at our hospital. This study was carried out in accordance with Declaration of Helsinki. Our institutional review board (Ethics committee, Kagawa University Faculty of Medicine, Kagawa, Japan) approved this study (no. 2019-086). After the approval, we investigated the patients who were treated at our hospital between 2016 and 2018.

Patients. The selection criteria of this study were as follows: i) patients over 20 years old; ii) patients had supratentorial primary brain tumors regardless of the tumor size; iii) patients underwent IMRT with a dose of 60 Gy in 30 fractions to the supratentorial tumors; and iv) patients were treated between

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2016 and 2018 at our department. In total, 18 patients met the selection criteria, and we analyzed the 18 patients' data.

Treatment planning. All patients were immobilized with a thermoplastic shell. After the immobilization, planning computed tomography images were obtained. A radiation treatment planning system (Eclipse™ v11.0; Varian Medical Systems) was used for treatment planning. Clinical target volume (CTV) was defined as follows: CTV1, an enhanced lesion plus 0.5-1.5 cm or an edematous lesion as the local area; CTV2, CTV1 plus 0.5 cm or an edematous lesion plus 0.5-1.5 cm as the extended local area. CTV for atypical meningioma was defined as follows: CTV1, an enhanced lesion plus 0.5 cm; CTV2, CTV1 plus 0.5 cm. As a planning target volume (PTV) margin, 0.3-0.5 cm was added to each CTV. Doses of 60 Gy for the PTV1 and 48-51 Gy for the PTV2 were delivered in 30 fractions using simultaneous integrated boost technique. We prescribed the doses to ensure the coverage of 95% of the PTVs. The hippocampi were delineated with the reference to a contouring atlas (9). The hippocampal dose constraint at our institution was as low as reasonably achievable. If there were overlaps between the PTVs and the hippocampi, we gave the priority to irradiate the PTVs rather than to spare the hippocampi. Our goals of the other dose constraints were as follows: mean and maximum doses of the PTV1, <62.4 Gy and <66 Gy, respectively; V_{60Gy}, V_{50Gy}, and V_{45Gy} of the brain, <25%, <33%, and <67%, respectively; maximum dose and V_{55Gy} of the brainstem, <54 Gy and 0%, respectively; maximum dose of the optic nerve and chiasm, <50 Gy; maximum dose of the eye, <40 Gy; maximum dose of the lens, <6 Gy; mean and maximum doses of the at least one ear, <35 Gy and <45 Gy, respectively.

Hippocampal dose-volume parameters. As the hippocampal dose-volume parameters have been associated with memory decline, Ma *et al* (7) reported that $D_{50\%}$ of the bilateral hippocampi of 22.1 Gy was associated with 20% risk of memory decline. Even in the studies of Gondi *et al* (6) and Okoukoni *et al* (8), the threshold dose associated with 20% risk of memory decline were obtained from their graphs for the probability of cognitive impairment. The previous reported parameters for the bilateral hippocampi associated with 20% risk of memory decline were as follows: i) $D_{40\%}$ of 8.0 Gy in EQD_2 with an α/β ratio of 2 Gy (6); ii) $D_{50\%}$ of 22.1 Gy in EQD_2 with an α/β ratio of 2 Gy (7); and iii) V_{55Gy} of 5.0% in 30 fractions (8). We converted the parameters in EQD_2 with an α/β ratio of 2 Gy into those in 30 fractions because we used 30 fractions in daily clinical practice of IMRT for supratentorial tumors. Therefore, we investigated the parameters for the bilateral hippocampi associated with 20% risk of memory decline for 30 fractions as follows: i) $D_{40\%}$ of 13.1 Gy; ii) $D_{50\%}$ of 29.6 Gy; and iii) V_{55Gy} of 5.0%.

Statistical analysis. We retrospectively evaluated which of the parameters was most achievable and used Fisher's exact test to identify unfavorable clinical factors that interfere with reaching these parameters. Statistical significance was defined as P<0.05. The software program JMP 11 (SAS Institute, Inc.) was used for statistical analyses.

Table I. Tumor characteristics.

Characteristics	Value
Histology, n (%)	
High-grade glioma	15 (83)
Atypical meningioma	3 (17)
Tumor location, n (%)	
Frontal	5 (27)
Parietal	3 (17)
Occipital	1 (6)
Temporal	6 (33)
Corpus callosum	2 (11)
Basal ganglia	1 (6)
Tumor spread to the subventricular zone, n (%)	
Yes	12 (67)
No	6 (33)
PTV1, cc	
Median	205
Range	106-403
PTV2, cc	
Median	442
Range	216-915
$D_{40\%}$[a] of the bilateral hippocampi in 30 fractions, Gy	
Median	24.6
Range	3.6-62.5
$D_{50\%}$[a] of the bilateral hippocampi in 30 fractions, Gy	
Median	18.0
Range	3.3-62.0
V_{55Gy}[b] of the bilateral hippocampi in 30 fractions, %	
Median	21.3
Range	0.0-76.6

[a]$D_{n\%}$ was irradiated dose to *n*% of the volume of the structure. [b]V_{nGy} was the percent of the volume of the structure at least irradiated *n* Gy. PTV, planning target volume.

Results

Tumor characteristics are listed in Table I. $D_{40\%}$ of 13.1 Gy, $D_{50\%}$ of 29.6 Gy, and V_{55Gy} of 5.0% were achieved in 17, 67 and 33% of patients, respectively. We accomplished all parameters in 3 patients (100%) with atypical meningioma, while no parameters were achieved in 5 of 6 patients (83%) with PTV2 ≥500 cc. The accomplishment of the parameters is listed in Table II. For $D_{40\%}$ of 13.1 Gy, non-meningioma (P=0.001) and tumor spread to the subventricular zone (P=0.025) were significantly unfavorable. For $D_{50\%}$ of 29.6 Gy, PTV2 ≥500 cc (P=0.004) and tumor located in the temporal, corpus callosum, or basal ganglia (P=0.009) were significant unfavorable factors. Non-meningioma was a significant unfavorable factor for V_{55Gy} of 5.0% (P=0.025).

Table II. Accomplishment of the parameters for the bilateral hippocampi associated with 20% risk of memory decline for 30 fractions.

Clinical factors	$D_{40\%}$[a] of 13.1 Gy, n (%)	P-value	$D_{50\%}$[a] of 29.6 Gy, n (%)	P-value	V_{55Gy}[b] of 5.0%, n (%)	P-value
Non-meningioma						
Yes	0/15 (0)	0.001	9/15 (60)	0.515	3/15 (20)	0.025
No	3/3 (100)		3/3 (100)		3/3 (100)	
Tumor located in the temporal, corpus callosum or basal ganglia						
Yes	0/9 (0)	0.206	3/9 (33)	0.009	1/9 (11)	0.131
No	3/9 (33)		9/9 (100)		5/9 (56)	
Tumor spread to the subventricular zone						
Yes	0/12 (0)	0.025	6/12 (50)	0.054	2/12 (17)	0.107
No	3/6 (50)		6/6 (100)		4/6 (67)	
PTV1 ≥200 cc						
Yes	3/9 (33)	0.206	5/9 (56)	0.620	3/9 (33)	>0.999
No	0/9 (0)		7/9 (78)		3/9 (33)	
PTV2 ≥500 cc						
Yes	0/6 (0)	0.515	1/6 (17)	0.004	0/6 (0)	0.054
No	3/12 (25)		11/12 (92)		6/12 (50)	

[a]$D_{n\%}$ was irradiated dose to *n*% of volume of the structure. [b]V_{nGy} was the percent of volume of the structure at least irradiated *n* Gy. PTV, planning target volume.

Discussion

In this study, we identified that $D_{50\%}$ of 29.6 Gy were easily achieved but large PTV and tumor location interfered with reaching the parameter.

The hippocampus has long been implicated in the acquisition of new memories, with visuo-spatial memory predominantly associated with the right, and verbal or narrative memory with the left hippocampi; the right hippocampi appears to be particularly involved in memory for locations within an environment and the left hippocampi more involved in context-dependent episodic or autobiographical memory (10).

The following mechanisms for radiation-induced neurocognitive dysfunction have been proposed (11). First, pro-inflammatory changes following RT cause an increase in the numbers of microglia, which produce tumor necrosis factor-α and interleukin-1β. And then, this contributes to an ongoing inflammatory state and alteration in the microenvironment, which preferentially drives differentiation of neural precursors to an astrocytic lineage. Moreover, radiation disrupts the vascular niche of the neural precursors and additionally leads to ischemia and toxic neuroexcitation among mature neurons. Finally, radiation exposure reduces the number of dendritic spines on mature neurons, which in turn disrupts synaptic efficiency.

In the clinical course, radiation-induced neurocognitive decline begins with a transient cognitive decline at approximately 4 months posttreatment, followed by an improvement, and then a progressive, irreversible deterioration in cognitive functioning at 12 months or later after irradiation (12).

Recent technical advances have facilitated the evaluation of the hippocampal dose-volume parameters at the time of RT. Several prospective cohort studies have reported an association between hippocampal dose-volume parameters and memory decline in patients with primary brain tumors treated by RT (6-8). Gondi *et al* (6) reported that EQD_2 to 40% of the bilateral hippocampi was associated with long-term impairment in list-learning delayed recall after RT, and concluded that modern IMRT techniques can reduce the dose to the bilateral hippocampi below the dosimetric threshold. Ma *et al* (7) reported that $D_{50\%}$ of the bilateral hippocampi of 22.1 Gy was associated with 20% risk of decline for delayed recall, and concluded that their data support a potential benefit of hippocampal sparing. Okoukoni *et al* (8) reported that the hippocampal V_{55Gy} was a significant predictor for impairment in immediate recall, and concluded that a limiting dose below 55 Gy may minimize radiation-induced cognitive impairment. These findings encouraged us to spare the hippocampus in daily clinical practice, but we have experienced some cases that have been difficult to reduce the dose to the bilateral hippocampi below the threshold. And then, we explored to the dosimetric parameters that are easily achieved and the factors that interfere with reaching these parameters.

As a result, among the previous reported dose-volume parameters of the bilateral hippocampi with 20% risk of memory decline for 30 fractions, we showed that $D_{50\%}$ of 29.6 Gy was most achievable, but even $D_{50\%}$ of 29.6 Gy may be difficult to be reached in patients with PTV2 ≥500 cc or tumors located in the temporal, corpus callosum, or basal ganglia. The large target volumes could become easy to be

close to the bilateral hippocampi. Moreover, tumors in the temporal, corpus callosum, or basal ganglia are also near the bilateral hippocampi anatomically. In the treatment planning, if there were overlaps between the PTVs and the hippocampi, we gave the priority to irradiate the PTVs rather than to spare the hippocampi to aim for cure. Therefore, even the most achievable parameter may be difficult to be reached in patients with the targets near the hippocampi.

Because of its retrospective nature, our study has certain limitations, such as the single institutional design and the small number of samples analyzed.

In conclusion, in IMRT with a dose of 60 Gy in 30 fractions for supratentorial tumors, $D_{50\%}$ of 29.6 Gy was most likely to be achieved in the dose-volume parameters of the bilateral hippocampi associated with 20% risk of memory decline. In daily clinical practice, we may had better primarily try to achieve $D_{50\%}$ of 29.6 Gy of the bilateral hippocampi. However, even the most achievable parameter may be difficult to be reached depending on the target size or tumor location. The further larger study is needed to support our findings.

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Availability of data and materials

The data that support the findings of this study are available from Kagawa University Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of our institutional review board (Ethics Committee, Kagawa University Faculty of Medicine, Kagawa, Japan).

Authors' contributions

The present study was coordinated by ST in terms of conception and design. Data was acquired by ST, MA, TK, TN and SK. The authenticity of data was assessed by ST, MA and TK. Collected data was analyzed by ST. Interpretation of data was performed ST, MA, TK, TN, SK and TS. This article was drafted by ST. Article revisions were critically performed by all authors. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Our institutional review board (Ethics Committee, Kagawa University Faculty of Medicine, Kagawa, Japan) approved this retrospective study (no. 2019-086).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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