The Feasibility of Sparing the Hippocampus and Hypothalamic -Hypophysial Axis During Whole Brain Radiotherapy: A Dosimetric Study

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ABSTRACT

We aimed to investigate the feasibility of simultaneously sparing the hippocampus and hypothalamic-hypophysial axis (HHA) during whole brain radiotherapy (WBRT) using helical tomotherapy. Images of totally 12 patients were analyzed. Hippocampi and HHA were delineated according to available guidelines. First, radiotherapy plans were analyzed according to dose constraints of the Radiation Therapy Oncology Group-0933 for 30 Gy (3 Gy/fr). Second, dose constraints were decreased by 1/6 to simulate the 25 Gy prophylactic cranial irradiation practice. The mean $D_{98\%}$ and $D_{2\%}$ was 25.9±0.85 Gy and 35.0±1.32 Gy, and 21.4±0.40 Gy and 30.5±1.33 Gy for planning target volumes in the original and modified protocol plans, respectively. The $D_{100\%}$ and D_{max} for the hippocampus was 8.1±0.47 Gy and 15.7±0.84 Gy in the original and 7.1±0.68 Gy and 13.2±1.08 Gy in the modified protocol, respectively. The mean doses for the hypothalamus and hypophysis was 12.6±0.76 Gy and 11.4±1.22 Gy in the original and 10.8±1.38 Gy and 9.8±1.50 Gy in the modified plans, respectively. This study demonstrated the feasibility of sparing the hippocampus and HHA simultaneously during WBRT with helical tomotherapy regarding target dose coverage and dose constraints suggested by the literature.

Keywords: Hippocampus, Hypothalamic-hypophysis axis sparing whole brain radiotherapy, Prophylactic cranial radiotherapy

ÖZET

Tüm Beyin Radyoterapisi Esnasında Hipokampüs ve Hipotalamo-Hipofizer Aksın Korunabilirliği: Dozimetrik Çalışma

Tüm beyin radyoterapisi (TBR) esnasında hipokampüs ve hipotalamo-hipofizer aksın (HHA) eşzamanlı olarak helikal tomoterapi yardımıyla korunabilirliğini araştırmayı amaçladık. Toplam 12 hastanın görüntüleri analiz edilmiştir. Hipokampüs ve HHA mevcut rehberlere göre konturlanmıştır. İlk olarak hastalar 30 Gy (3 Gy/fr) için Radiation Therapy Oncology Group-0933 doz sınırlamalarına göre analiz edilmiştir. İkinci olarak ise doz kısıtlamaları 1/6 oranında azaltılarak 25 Gy'lik proflaktik kranial radyoterapi pratiği simüle edilmiştir. Orjinal ve modifiye edilen protokollerde ortalama $D_{\%98}$ ve $D_{\%2}$ sırasıyla 25.9±0.85 Gy ve 35.0±1.32 Gy; 21.4±0.40 Gy ve 30.5±1.33 Gy olarak bulunmuştur. Orjinal planda hipokampüs için $D_{100\%}$ ve D_{max} sırasıyla 8.1±0.47 Gy ve 15.7±0.84 Gy iken modifiye planda 7.1±0.68 Gy ve 13.2±1.08 Gy olarak tespit edilmiştir. Orjinal plandaki ortalama hipotalamus ve hipofiz dozları 12.6±0.76 Gy ve 11.4±1.22 Gy; modifiye planda ise 10.8±1.38 Gy ve 9.8±1.50 Gy olarak bulunmuştur. Bu çalışma literatür tarafından önerilen doz sınırlamaları ve hedef doz sarımı açısından helical tomoterapiyle hipokampüs ve HHA'ın aynı anda korunabilir olduğunu gösterir niteliktedir.

Anahtar Kelimeler: Hipokampüs, Hipotalamo-hipofizer aks koruyucu tüm beyin radyoterapisi, Proflaktik kranial radyoterapi

INTRODUCTION

Prophylactic cranial irradiation (PCI) is an integral part of standard treatment algorithms in some malignancies including small-cell lung carcinoma and acute lymphoblastic leukemia.[1-4] The main rationale underlying the use of PCI in patients is the well-recognized limited permeability of the blood-brain-barrier to many chemotherapeutics, rendering the brain a sanctuary site for malignant cells.[5] In this setting, PCI decreases brain relapses by eradication of occult tumor cells, which cannot be determined by current diagnostic tools. Thus, PCI enhances the overall survival rates with relatively lower radiotherapy doses compared the dose utilized for palliation of brain metastases.[6] Despite these advantages of PCI, there is a significant risk of deterioration of neurocognitive functions (NCF) according to the objective baseline measurements, which is the major limitation against its usage.[7]

Radiation-induced hippocampal injury is the most established cause of neurocognitive dysfunction in patients treated with PCI and/or palliative whole brain radiotherapy (WBRT); this is related to the injury of neural progenitor cells in the subventricular zone and hippocampus in addition to damage of the vascular structure and glial precursors.[8-13] In this regard, hippocampus-sparing WBRT has repeatedly been demonstrated to be safe and useful in sparing NCF with no sacrifice of potentially microscopically involved brain sites.[14-16]

Given the separated parts of the brain with sophisticated interconnections, it seems reasonable to assume that other parts of the brain can contribute to the NCF as well as the master neurocognitive organ, the hippocampus.[17] Recent studies report that a limited post-development neurogenesis can occur in other sides of the brain including striatum, spinal cord, and neurocortex as well as the hypothalamus.[18] The hypothalamus is responsible for the maintenance of homeostatic functions and quality of life (QOL). Therefore the preservation of the hypothalamic-hypophysial axis (HHA), known as the master of the neuroendocrine system, can reduce the risks of both neuroendocrine dysfunction and NCF particularly in groups of patients with longer survival expectations.[19-22]

Radiation-induced HHA dysfunction has been determined to be a dose- and time- dependent adverse event, but the radiation doses causing impaired QoL as a result of HHA-related damage has not yet been determined.[23,24] On the other hand, some suggestions about the dose constraints of hippocampus were offered: <7.3 Gy to 40% of bilateral hippocampi 14 and a maximum dose (D_{max}) of 9 Gy to 100% of the hippocampi.[25] Therefore, it is logical to anticipate that sparing of both the hippocampi and HHA can be a more effective approach for maximum maintenance of the NCF, rather than the hippocampus-sparing-WBRT alone in patients undergoing PCI. Enlightened by the available literature, we evaluated the feasibility of simultaneously sparing hippocampus + hypothalamus + hypophysis (3HS) which can be abbreviated as 3HS-WBRT in patients undergoing WBRT.

PATIENTS AND METHODS

Contouring

Datasets including planning computerized tomography (CT) fused with T1-weighted post-contrast axial MRI images (slices 1.5 mm thick) of 12 patients accessible on the Picture Archiving and Communication System were selected. The CT images were obtained 120 kVp, 400 mA, and 1.25 mm thickness. Hippocampi were delineated according to the Radiation Therapy Oncology Group (RTOG)-0933[26], and hippocampal avoidance zones were uniformly defined by 5 mm expansion in all directions from the hippocampi.

The hypothalamus was delineated by utilizing the method described by Elson et al[27] and additional MRI atlases.[28] In brief, the most cranial contouring section corresponded to the anterior commissure, which is located at the medial sides of the third ventricle (Figure 1). The most inferior section of the contour was 1.5 mm (1 axial slice) superior to the slice where the optic chiasm emerges first. The anterior side of the third ventricle and interpeduncular fossa constituted the anterior and posterior boundaries, respectively. Lastly, either the optic white matter or internal capsule was defined as the lateral border of the hypothalamus. The hypophysis was delineated as the concavity within the sphenoid bone, sella tursica, which is located laterally between the cavernous sinuses, the hypothalamus and optic chiasm cranially. As recommended, the bone window was utilized for this purpose as the

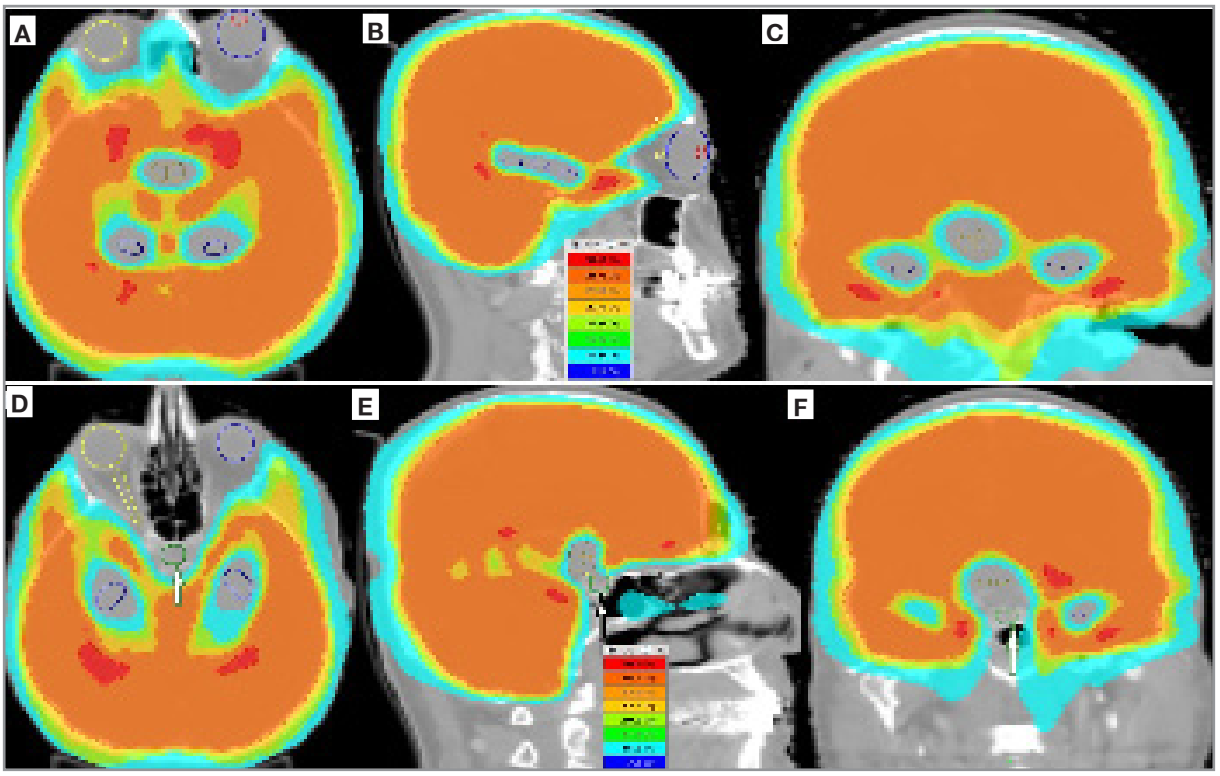

Figure 1. Dose color wash images of a patient receiving 25 Gy of prophylactic cranial irradiation dose utilizing by helical tomotherapy; **A.** axial section of helical tomotherapy plan with the delineations of hippocampus (dark blue) and hypothalamus (brown); **B.** sagittal section demonstrating the hippocampus; **C.** coronal section radiotherapy plan demonstrating the hippocampus (dark blue) and hypothalamus (brown); **D.** axial section plan demonstrating the hippocampus bilaterally and hypophysis (white arrow) in the midline; **E.** sagittal section plan demonstrating the preservation of hypothalamus (brown) and hypophysis (green, white arrow); **F.** coronal section plan demonstrating the hypophysis (white arrow) in the midline

most appropriate CT mode for delineation of the hypophysis. A uniform additional 5 mm was added to both the hypothalamus and hypophysis in all directions to constitute the planning organ at risk volumes. The organs at risk constituted the lenses, globes, optic nerves, and chiasms were delineated according to the accessible contouring guidelines.[29]

The clinical target volume was the whole brain to second cervical vertebra and 2 mm was added to create the planning target volume (PTV). However, the final PTV was defined by subtracting the planning organ at risk volumes of the hippocampus and HHA from the PTV.

Treatment Planning and Procedure

Although our institutional PCI protocol mandates a total dose of 25 Gy in 10 fractions, we also performed alternative plans with 30 Gy in 10 fractions for each patient utilizing helical tomotherapy (HT) Accuray planning system (Tomo HDA, version 2.1.2) to simulate palliative WBRT studies. The dose limitations of the PTV and organs at risk have been identified in accordance with the RTOG 0933 protocol 26 and a modified dose limitation was described by reducing all the recommended doses in the trial by 5/6, in the view of the 25 Gy of PCI. Planning was performed using the 1.048-cm wide field with a pitch of 0.221 and a modulation factor of 5 and dose calculation grid of 0.203 cm x 0.203 cm. All the dose specifications are shown in Table 1. Although the present study was not a comparison study, the mean homogeneity index (HI) defined as the measure of the steepness of the target, was also calculated to compare our results with similar studies. The HI was defined as [($D_{2\%}$ - $D_{98\%}$)/Dmedian], where a value closer to 0 is associated with optimal plan according to the International Commission on Radiation Units and Measurements.[30]

Table 1. Dose specifications

Organ	Per protocol	Acceptable	Modified protocol	Acceptable
PTV	$D_{98\%}$ ≥25.0 Gy	$D_{98\%}$ <25.0 Gy	$D_{98\%}$ ≥20.80Gy	$D_{98\%}$ <20.8.0 Gy
	$D_{2\%}$ ≤37.5 Gy	$D_{2\%}$ >37.5 Gy, ≤40 Gy	$D_{2\%}$ ≤31.25 Gy	$D_{2\%}$ >31.25 Gy, ≤33.3 Gy
Hippocampus	$D_{100\%}$ ≤9 Gy	$D_{100\%}$ ≤10 Gy	$D_{100\%}$ ≤7.5 Gy	$D_{100\%}$ ≤9 Gy
	D_{max} ≤16 Gy	D_{max} ≤17 Gy	D_{max} ≤13.3 Gy	D_{max} ≤17 Gy
Hypothalamus	D_{mean} ≤12 Gy	D_{mean} ≤14 Gy	D_{mean} ≤10 Gy	D_{mean} ≤14 Gy
Pituitary gland	D_{mean} ≤12 Gy	D_{mean} ≤14 Gy	Dmean ≤10 Gy	D_{mean} ≤14 Gy
Optic chiasm and nerves	D_{max} ≤37.5 Gy	D_{max} ≤37.5 Gy	D_{max} ≤37.5 Gy	D_{max} ≤37.5 Gy
Lens	D_{max} ≤5Gy	D_{max} ≤10 Gy	D_{max} ≤5Gy	D_{max} ≤10 Gy

Abbreviations: PTV= planning target volume; $D_{98\%}$= the dose which %98 of the target volume receives; $D_{2\%}$= the dose which 2% of the target volume receives; $D_{100\%}$= minimum dose; D_{max}= maximum dose; D_{mean}= mean dose

Statistical Analysis

All calculations and statistical tests were performed utilizing IBM SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). With respect to dosimetric evaluation, continuous variables were expressed as mean (± SD)

RESULTS

The compliance criteria, limitations of organs at risk which were based on RTOG-0933 and the modified protocol are demonstrated in Table 1. The average dosimetric values in 12 patients are shown in Table 2.

PTV, Homogeneity Index, and Delivery Time

All the plans met the acceptance criteria. The mean $D_{98\%}$ and $D_{2\%}$ was 25.9 ± 0.85 Gy and 35.0 ± 1.32 Gy, and 21.4 ± 0.40 Gy and 30.5 ± 1.33 Gy for PTV in the protocol and modified protocol plans, respectively (Table 2). The HI was 0.30 ± 0.07 in both of the protocols. The mean delivery time was 31.8 minutes ± 1.81.

Volumes and Dosimetry of the Hippocampus, Hypothalamus and Hypophysis

The mean volumes of the hippocampus, hypothalamus, and hypophysis were 5.6 cm^3 ± 1.82, 0.7 cm^3 ± 0.30 and 0.5 cm^3 ± 0.16, respectively. The minimum ($D_{100\%}$) and maximum doses (D_{max}) for the hippocampus were 8.1 ± 0.47 Gy and 15.7 ± 0.84 Gy in the protocol and 7.1 ± 0.68 Gy and 13.2 ± 1.08 Gy in the modified protocol, respectively. The mean doses for the hypothalamus and hypophysis were 12.6 ± 0.76 Gy and 11.4 ± 1.22 Gy in the protocol plan and 10.8 ± 1.38 Gy and 9.8 ± 1.50 Gy, in the modified plan, respectively.

DISCUSSION

To the best of our knowledge, this dosimetric study confirmed the feasibility of simultaneous protection of the hippocampus and HHA without sacrificing PTV coverage by utilizing HT; the only cost was relatively longer treatment times (31.8 minutes ± 1.81) than that for the standard WBRT.

Maintenance of NCF as a major component of QoL has gradually gained increasing consideration in patients with cancer undergoing PCI, because of the significantly increased WBRT-related toxicity rates in long-term survivors of PCI in the presence of more effective systemic and loco-regional treatment options.[31,32] Studies indicate that unilateral or bilateral hippocampal damage is related to neurocognitive disorders, particularly in memory and learning, and hippocampal-sparing techniques have been suggested for either WBRT or partial radiotherapy of the brain in order to spare NCF.[26,33] Although hippocampus-sparing WBRT has been the most utilized approach for this purpose, further complications such as fatigue, sleeping disorders, reduced muscle mass, low energy, and hormonal deficiencies can still alter the NCF, and therefore, the patients' overall QoL in a negative manner.[32]

Table 2. Mean doses in 12 patients

Organ	Parameter	Per protocol	Modified protocol
PTV	D98%	25.9 ± 0.85 Gy	21.4 ± 0.40 Gy
	D2%	35.0 ± 1.32 Gy	30.5 ± 1.33 Gy
Hippocampus	D100%	8.1 ± 0.47 Gy	7.1 ± 0.68 Gy
	Dmax	15.7 ± 0.84 Gy	13.2 ± 1.08 Gy
Hypothalamus	Dmean	12.6 ± 0.76 Gy	10.8 ± 1,38 Gy
Pituitary gland	Dmean	11.4 ± 1.22 Gy	9.8 ± 1.50 Gy
Optic chiasm	Dmax	28.0± 6.80 Gy	25.1± 4.42 Gy
Optic nerves	Dmax	13.3 ± 3.80 Gy	14.6 ± 3.11 Gy
Lens	Dmax	3.5 ± 0.86 Gy	3.2 ± 0.73 Gy

Abbreviations: PTV= planning target volume; $D_{98\%}$= the dose which %98 of the target volume receives; $D_{2\%}$= the dose which 2% of the target volume receives; $D_{100\%}$= minimum dose; D_{max}= maximum dose; D_{mean}= mean dose

In this context, considering the neuroendocrine and homeostatic functions of HHA, as a master organ, 3HS-WBRT can be superior for further sparing of the NCF than the hippocampus-sparing WBRT alone.[34]

Hippocampus sparing-WBRT techniques including the volumetric modulated arc technique and HT are the most frequently used methods to decrease the radiation doses of the hippocampus and HHA.[35-37] In the study of Fan et al, which was the first report of simultaneous hippocampus and HHA sparing during PCI, the authors showed that the mean hippocampus, hypothalamus, and hypophysis doses might be reduced to 9.6 Gy, 11.06 Gy, and 10.66 Gy, respectively, lending support to our respective mean doses in our modified plan: 7.1 Gy, 10.38 Gy and 9.8 Gy.[34] In a phase II randomized trial, a mean hippocampal dose of ≤ 10 Gy was related to a 23% improvement in the Hopkins Verbal Learning Test compared to previous hippocampus sparing-WBRT studies.[26] Accordingly, in another study, emphasizing its radio-sensitivity, a dose-dependent hippocampal atrophy (>40 Gy vs <10 Gy, p= 0.03) was shown to occur on first year MRI scans.[38] Rong et al analyzed the dosimetric differences between HT, step and shot intensity modulated radiotherapy, and rapidarc plans for hippocampus-sparing WBRT. They reported that the mean hippocampal doses of D_{max} 15.1 Gy and $D_{100\%}$ 8.0 with HT were notably lower than their counterparts achieved with other plans which resembled our respective values of 15.7 Gy and 8.1 Gy, achieved in 30 Gy of the WBRT plan.[39] Although the mean Dmax values of the bilateral lens (3.3 Gy vs 3.3 Gy) and optic chiasm (33.9 Gy vs 28 Gy) were similar between the study by Rong and our study, those of the optic nerves were considerably lower in our study (33.9 Gy vs 13.3 Gy). Regarding the mean PTV, $D_{98\%}$, and $D_{2\%}$ in the present investigation (25.9 Gy and 35.0 Gy) were comparable to the study of Rong et al (27.5 Gy and 32.2 Gy) despite relatively higher HI in our study (0.30 ± 0.07 vs 0.15 ± 0.03), which indicated inferior dose homogeneity due to the incorporation of HHA sparing. In a study investigating the effect of inclined and neutral head positions on HS-WBRT, the mean $D_{100\%}$ (10.45 Gy vs 12.07 Gy, p= 0.007) and D_{max} (13.7 Gy vs 15.7 Gy, p= 0.003) of the hippocampus were significantly lower in the inclined position of the head.40 Although the $D_{100\%}$ values of the hippocampus in both of the positions were higher than the value we found (8.1 Gy), the Dmax in the inclined position appeared to be more favorable than ours (13.7 Gy ± 0.25 vs 15.7 Gy ± 0.8).

In addition to the apparent hormonal deficiency risk with > 50 Gy of radiotherapy dose, even 12 Gy of hypothalamic dose can induce neuro-endocrine abnormalities.[41,42] The deficiency of growth hormone, the most radio-sensitive hypophysial hormone, can occur after mean radiotherapy doses of 15 Gy[43-45], and up to 100% of the patients may suffer from endocrine insufficiencies when the ra-

diotherapy doses exceed 30 Gy.[46] While growth hormone insufficiency risk is reported to be about 50% following 16 Gy of radiotherapy[47], 12 Gy for HHA was estimated to be safe.[48] Still, the actual incidence of treatment-related hormone insufficiency can vary as a result of heterogeneities including the presence or extent of surgery, follow-up intervals, cut-off laboratory values, definitions of hormone-insufficiency, and radiotherapy techniques.[49-51] In this respect, the mean doses of the hypothalamus (12.6 Gy) and hypophysis (11.4 Gy) achieved in our study were concordant with the recommended safer range.

The hippocampal dose constraints for 25 Gy of PCI were $D_{100\%} \leq 7.5$ Gy and $D_{max} \leq 13.3$ Gy which appeared to be significantly lower than the values of $D_{100\%} \leq 9$ Gy and $D_{max} \leq 16$ Gy, recommended in the RTOG 0933 guidelines for the protocol of 30 Gy of WBRT.26 The rationale to perform further modifications for hippocampal dose constraints can be the potential intrinsic radiosensitivity variations of the patients which can also enhance the risk of NCF decline even for the cohort receiving a relatively lower dose schedule. Furthermore, because of the lack of the long-term NCF outcomes of RTOG 0933, it can be rational to reduce the threshold radiotherapy doses for hippocampi in accordance with the results of available studies reporting better NCF with lower constraints, such as <7.3 Gy to 40% of bilateral hippocampi[14], a D_{max} of 9 Gy to 100% of the hippocampi[25] and a D_{max} of 5.83 Gy to 100% of the bilateral hippocampi.[52]

In the view of the reasons aforementioned, the use of 3HS-WBRT should not be restricted to only the adult patients with small-cell lung carcinoma patients undergoing PCI but also applied to the pediatric cohort who are relatively more vulnerable to the effects of radiation compared to the adults.53 Additionally, the length of survival in patients with childhood brain tumors at 70% at 10 years renders the further minimization of radiotherapy-related neurotoxicity more meaningful than adults with a relatively shorter expectation of survival.[54] For instance, there is an increased dementia effect after craniospinal irradiation, which was described about a half century ago in patients with medulloblastoma aged < 2 years.[55] This can necessitate further maneuvers besides the efforts of decreasing the radiotherapy doses or delaying the craniospinal irradiation until 3 years of age. Additionally, underlining the importance of sparing of the intracranial endocrine organs the 20-year follow-up series by Institute Curie demonstrated that the endocrine complications were as common as 52% in medulloblastoma survivors after craniospinal irradiation.[56] Accordingly, 3HS-WBRT appears to be rational for conserving NCF.

Radiation-induced HHA damage can also be a source of severe metabolic, social, financial, psychiatric, and educational problems which altogether can negatively influence psychosocial and medical status of the patients.[57] For instance, HHA-associated endocrine abnormalities or obesity can cause diabetes mellitus, hypertension, dyslipidemia, cardiovascular problems, fertility, and pubertal disorders with resultant diminishments in the QoL measures and even shortened life spans.[57] Considering the educational outcomes, compared to those children treated with intravenous/intrathecal methotrexate alone, the combination of chemotherapy with PCI has been shown to cause significantly more severe declines in the achievement, intelligence and attention tasks, and therefore the school success in survivors of acute lymphoblastic leukemia.[58,59] Additionally, recent data indicated that unemployment was reported to be 5 times higher in brain tumor survivors, associated with the primary tumor and related treatments.[57] All these adverse effects of whole- or partial brain radiotherapy mentioned above support our current efforts to achieve 3HS-WBRT or 3HS-partial brain radiotherapy and appear to be an important step in minimizing the social, financial, psychiatric, and educational burden due to impaired HHA.

The present study is the second in the literature to investigate 3HS-WBRT to the best of our knowledge. In addition to available dose constraints for 30 Gy of WBRT, we also recommend an alternative reduced dose schedule of 1 in 6 of the original which can provide a further protection for the cohort who can be more sensitive to radiation. On the other hand, although the delineation of hippocampus and HHA was performed according to the accessible guidelines and atlases, the lack of a neuroradiologist in the study may potentially weaken the accuracy of the 3H contouring process. Despite the

main goal of the study to research the feasibility of HHA as well as the hippocampus, the interconnections between hypothalamus and hypophysis were not included in the sparing volume, which can decrease the reliability of the 3HS-WBRT. Although the mean treatment time was reported to be 15.93 and 20.18 minutes in a dosimetric study evaluating the feasibility of hippocampus sparing-PCI and -WBRT, respectively, the relatively longer treatment time of 31.8 minutes elapsed during 3HS-WBRT can be questionable in cases requiring anesthesia during the treatment process.[60]

In conclusion, as a consequence of improved survival rates of the patients with cancer requiring whole brain or partial brain radiotherapy during the course of disease, the maintenance of neurocognitive and neuroendocrine functions, as the predictors of QoL, has become one of the main goals as well as disease control in the brain. In this context, this study demonstrated the feasibility of 3HS-WBRT with HT taking into account the suggested dose constraints in the literature. Considering the fact that a technique investigation can be more valuable for what it offers in practice, prospective studies evaluating the baseline and follow-up objective measurements for 3H can be required for precise deductions.

REFERENCES

1. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 24: 4539-4544, 2006.
2. Cortes J. Central nervous system involvement in adult acute lymphocytic leukemia. Hematol Oncol Clin North Am 15: 145-162, 2001.
3. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med 354: 166-178, 2006.
4. Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol 29: 532-543, 2011.
5. Larson RA. Managing CNS disease in adults with acute lymphoblastic leukemia. Leuk Lymphoma 59: 3-13, 2018.
6. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341: 476-484, 1999.
7. Gondi V, Paulus R, Bruner DW, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. Int J Radiat Oncol Biol Phys 86: 656-664, 2013.
8. Roman DD, Sperduto PW. Neuropsychological effects of cranial radiation: current knowledge and future directions. Int J Radiat Oncol Biol Phys 31: 983-998, 1995.
9. Rola R, Raber J, Rizk A, et al. Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. Exp Neurol 188: 316-330, 2004.
10. Saxe MD, Battaglia F, Wang JW, et al. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. Proc Natl Acad Sci U S A 103: 17501-17506, 2006.
11. Madsen TM, Kristjansen PE, Bolwig TG, et al. Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat. Neuroscience 119: 635-642, 2003.
12. Winocur G, Wojtowicz JM, Sekeres M, et al. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. Hippocampus 16: 296-304, 2006.
13. Gondi V, Tome WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. Radiother Oncol 97: 370-376, 2010.
14. Gondi V, Hermann BP, Mehta MP, et al. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J Radiat Oncol Biol Phys 85: 348-354, 2013.
15. Redmond KJ, Hales RK, Anderson-Keightly H, et al. Prospective Study of Hippocampal-Sparing Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 98: 603-611, 2017.
16. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys 81: 77-84, 2011.
17. Bressler SL. Large-scale cortical networks and cognition. Brain Res Brain Res Rev 20: 288-304, 1995.
18. Qin Y, Zhang W, Yang P. Current states of endogenous stem cells in adult spinal cord. J Neurosci Res 93: 391-398, 2015.
19. Yoo S, Blackshaw S. Regulation and function of neurogenesis in the adult mammalian hypothalamus. Prog Neurobiol 170: 53-66, 2018.
20. Quik EH, Valk GD, Drent ML, et al. Reduced growth hormone secretion after cranial irradiation contributes to neurocognitive dysfunction. Growth Horm IGF Res 22: 42-47, 2012.
21. Sinha A, Hollingsworth KG, Ball S, et al. Impaired quality of life in growth hormone-deficient adults is independent of the altered skeletal muscle oxidative metabolism found in conditions with peripheral fatigue. Clin Endocrinol (Oxf) 80: 107-114, 2014.

22. Prodam F, Caputo M, Belcastro S, et al. Quality of life, mood disturbances and psychological parameters in adult patients with GH deficiency. Panminerva Med 54: 323-331, 2012.

23. Lam KS, Tse VK, Wang C, et al. Early effects of cranial irradiation on hypothalamic-pituitary function. J Clin Endocrinol Metab 64: 418-424, 1987.

24. Rosen T, Eden S, Larson G, et al. Cardiovascular risk factors in adult patients with growth hormone deficiency. Acta Endocrinol (Copenh) 129: 195-200, 1993.

25. Redmond KJ, Mahone EM, Horska A. Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: a prospective study. Neuro Oncol 15: 1455, 2013.

26. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. J Clin Oncol 32: 3810-3816, 2014.

27. Elson A, Bovi J, Kaur K, et al. Effect of treatment modality on the hypothalamic-pituitary function of patients treated with radiation therapy for pituitary adenomas: hypothalamic dose and endocrine outcomes. Front Oncol 4: 73, 2014.

28. Baroncini M, Jissendi P, Balland E, et al. MRI atlas of the human hypothalamus. Neuroimage 59: 168-180, 2012.

29. Scoccianti S, Detti B, Gadda D, et al. Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. Radiother Oncol 114: 230-238, 2015.

30. Srivastava SP, Cheng CW, Das IJ. The effect of slice thickness on target and organs at risk volumes, dosimetric coverage and radiobiological impact in IMRT planning. Clin Transl Oncol 18: 469-479, 2016.

31. Li J, Bentzen SM, Renschler M, et al. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. J Clin Oncol 25: 1260-1266, 2007.

32. Higham CE, Johannsson G, Shalet SM. Hypopituitarism. Lancet 388: 2403-2415, 2016.

33. Raber J, Rola R, LeFevour A, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. Radiat Res 162: 39-47, 2004.

34. Fan XW, Wang JQ, Wu JL, et al. Simultaneously avoiding the hippocampus and hypothalamic-pituitary axis during whole brain radiotherapy: A planning study. Med Dosim S0958-3947(18)30068-2, 2018. doi: 10.1016/j.meddos.2018.04.004.

35. Gondi V, Tolakanahalli R, Mehta MP, et al. Hippocampal-sparing whole-brain radiotherapy: a "how-to" technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 78: 1244-1252, 2010.

36. Oskan F, Ganswindt U, Schwarz SB, et al. Hippocampus sparing in whole-brain radiotherapy. A review. Strahlenther Onkol 190: 337-341, 2014.

37. Prokic V, Wiedenmann N, Fels F, et al. Whole brain irradiation with hippocampal sparing and dose escalation on multiple brain metastases: a planning study on treatment concepts. Int J Radiat Oncol Biol Phys 85: 264-270, 2013.

38. Seibert TM, Karunamuni R, Bartsch H, et al. Radiation Dose-Dependent Hippocampal Atrophy Detected With Longitudinal Volumetric Magnetic Resonance Imaging. Int J Radiat Oncol Biol Phys 97: 263-269, 2017.

39. Rong Y, Evans J, Xu-Welliver M, et al. Dosimetric evaluation of intensity-modulated radiotherapy, volumetric modulated arc therapy, and helical tomotherapy for hippocampal-avoidance whole brain radiotherapy. PLoS One 10:e0126222, 2015.

40. Moon SY, Yoon M, Chung M, et al. Comparison of the extent of hippocampal sparing according to the tilt of a patient's head during WBRT using linear accelerator-based IMRT and VMAT. Phys Med 32: 657-663, 2016.

41. Merchant TE, Goloubeva O, Pritchard DL, et al. Radiation dose-volume effects on growth hormone secretion. Int J Radiat Oncol Biol Phys 52: 1264-1270, 2002.

42. Azcona C, Preece MA, Rose SJ, et al. Growth response to rhIGF-I 80 microg/kg twice daily in children with growth hormone insensitivity syndrome: relationship to severity of clinical phenotype. Clin Endocrinol (Oxf) 51: 787-792, 1999.

43. Costin G. Effects of low-dose cranial radiation on growth hormone secretory dynamics and hypothalamic-pituitary function. Am J Dis Child 142: 847-852, 1988.

44. Kirk JA, Raghupathy P, Stevens MM, et al. Growth failure and growth-hormone deficiency after treatment for acute lymphoblastic leukaemia. Lancet 1: 190-193, 1987.

45. Vladyka V, Liscak R, Novotny J Jr, et al. Radiation tolerance of functioning pituitary tissue in gamma knife surgery for pituitary adenomas. Neurosurgery 52: 309-316, 2003.

46. Clayton PE, Shalet SM. Dose dependency of time of onset of radiation-induced growth hormone deficiency. J Pediatr 118: 226-228, 1991.

47. Merchant TE, Rose SR, Bosley C, et al. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. J Clin Oncol 29: 4776-4780, 2011.

48. Rappaport R, Brauner R. Growth and endocrine disorders secondary to cranial irradiation. Pediatr Res 25: 561-567, 1989.

49. Feigl GC, Pistracher K, Berghold A, et al. Pituitary insufficiency as a side effect after radiosurgery for pituitary adenomas: the role of the hypothalamus. J Neurosurg 113 Suppl: 153-59, 2010.

50. Agha A, Sherlock M, Brennan S, et al. Hypothalamic-pituitary dysfunction after irradiation of nonpituitary brain tumors in adults. J Clin Endocrinol Metab 90:6355-60, 2005.

51. Rieken S, Habermehl D, Welzel T, et al. Long term toxicity and prognostic factors of radiation therapy for secreting and non-secreting pituitary adenomas. Radiat Oncol 8: 18, 2013.

52. Tsai PF, Yang CC, Chuang CC, et al. Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. Radiat Oncol 10: 253, 2015.

53. Leung RS. Radiation Protection of the Child from Diagnostic Imaging. Curr Pediatr Rev 11: 235-242, 2015.

54. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. N Engl J Med 374: 833-842, 2016.

55. Bloom HJ, Wallace EN, Henk JM. The treatment and prognosis of medulloblastoma in children. A study of 82 verified cases. Am J Roentgenol Radium Ther Nucl Med 105: 43-62, 1969.

56. Frange P, Alapetite C, Gaboriaud G, et al. From childhood to adulthood: long-term outcome of medulloblastoma patients. The Institut Curie experience (1980-2000). J Neurooncol 95: 271-279, 2009.

57. Gupta P, Jalali R. Long-term Survivors of Childhood Brain Tumors: Impact on General Health and Quality of Life. Curr Neurol Neurosci Rep 17: 99, 2017.

58. Hill JM, Kornblith AB, Jones D, et al. A comparative study of the long term psychosocial functioning of childhood acute lymphoblastic leukemia survivors treated by intrathecal methotrexate with or without cranial radiation. Cancer 82: 208-218, 1998.

59. Moore BD, 3rd, Copeland DR, Ried H, et al. Neurophysiological basis of cognitive deficits in long-term survivors of childhood cancer. Arch Neurol 49: 809-817, 1992.

60. Marsh JC, Godbole RH, Herskovic AM, et al. Sparing of the neural stem cell compartment during whole-brain radiation therapy: a dosimetric study using helical tomotherapy. Int J Radiat Oncol Biol Phys 78: 946-954, 2010.

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