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 prophyactic cranial irradiation practice. The mean D\textsubscript{98}% and D\textsubscript{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\textsubscript{100}% and D\textsubscript{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 yardımcıla 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 sınırlamaların 1/6 oranı üzerinden 25 Gy’lik profilaktik kranial radyoterapi pratığı simulü edilmiştir. Orjinal ve modifiye edilen protokollerde ortalamalı D\textsubscript{98}% ve D\textsubscript{2}% sırasıyla 25.9±0.85 Gy ve 35.0±1.32 Gy’yi; 21.4±0.40 Gy ve 30.5±1.33 Gy olarak bulunmuştur. Orjinal planda hipokampüs için D\textsubscript{100}% ve D\textsubscript{max} sırasıyla 8.1±0.47 Gy ve 15.7±0.84 Gy’yi; modifiye planda 7.1±0.68 Gy ve 13.2±1.08 Gy olarak tespit edilmiştir. Orjinal planda hipotalamus ve hipofiz dozanı 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 helikal tomoterapiyle hipokampüs ve HHA’nın aynı anda korunabilir olduğunu gösterir niteliktedir.

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

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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. 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. 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. 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.

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. 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.

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. 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. 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.

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. On the other hand, some suggestions about the dose constraints of hippocampus were offered: ≤7.3 Gy to 40% of bilateral hippocampi and a maximum dose (Dmax) of 9 Gy to 100% of the hippocampi. 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 hippocampi + 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, 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 and additional MRI atlases. 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 sphenoidal 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
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. 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 \([(D_{2%} - D_{98%})/D_{median}]\), where a value closer to 0 is associated with optimal plan according to the International Commission on Radiation Units and Measurements. Wasserburg and colleagues. 30

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**Figure 1.** Dose color wash images of a patient receiving 25 Gy of prophylactic cranial irradiation dose utilizing 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.
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 D98% and D2% 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 cm³ ± 1.82, 0.7 cm³ ± 0.30 and 0.5 cm³ ± 0.16, respectively. The minimum (D100%) and maximum doses (Dmax) 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 1. Dose specifications

<table>
<thead>
<tr>
<th>Organ</th>
<th>Per protocol</th>
<th>Acceptable</th>
<th>Modified protocol</th>
<th>Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV</td>
<td>D98% ≥25.0 Gy</td>
<td>D98% &lt;25.0 Gy</td>
<td>D98% ≥20.80 Gy</td>
<td>D98% &lt;20.8.0 Gy</td>
</tr>
<tr>
<td></td>
<td>D2% ≤37.5 Gy</td>
<td>D2% &gt;37.5 Gy, ≤40 Gy</td>
<td>D2% ≤31.25 Gy</td>
<td>D2% &gt;31.25 Gy, ≤33.3 Gy</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>D100% ≤9 Gy</td>
<td>D100% ≤10 Gy</td>
<td>D100% ≤7.5 Gy</td>
<td>D100% ≤9 Gy</td>
</tr>
<tr>
<td></td>
<td>Dmax ≤16 Gy</td>
<td>Dmax ≤17 Gy</td>
<td>Dmax ≤13.3 Gy</td>
<td>Dmax ≤17 Gy</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Dmean ≤12 Gy</td>
<td>Dmean ≤14 Gy</td>
<td>Dmean ≤10 Gy</td>
<td>Dmean ≤14 Gy</td>
</tr>
<tr>
<td>Pituitary gland</td>
<td>Dmean ≤12 Gy</td>
<td>Dmean ≤14 Gy</td>
<td>Dmean ≤10 Gy</td>
<td>Dmean ≤14 Gy</td>
</tr>
<tr>
<td>Optic chiasm and nerves</td>
<td>Dmax ≤37.5 Gy</td>
<td>Dmax ≤37.5 Gy</td>
<td>Dmax ≤37.5 Gy</td>
<td>Dmax ≤37.5 Gy</td>
</tr>
<tr>
<td>Lcis</td>
<td>Dmax ≤5Gy</td>
<td>Dmax ≤10 Gy</td>
<td>Dmax ≤5Gy</td>
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</tr>
</tbody>
</table>

Abbreviations: PTV= planning target volume; D98%= the dose which %98 of the target volume receives; D2%= the dose which 2% of the target volume receives; D100%= minimum dose; Dmax= maximum dose; Dmean= 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.34 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 $D_{\text{max}}$ 15.1 Gy and $D_{100\%}$ 8.0 Gy 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 $D_{\text{max}}$ 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 $D_{\text{max}}$ (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 $D_{\text{max}}$ 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 Gy43-45, and up to 100% of the patients may suffer from endocrine insufficiencies when the ra-
diotherapy doses exceed 30 Gy. While growth hormone insufficiency risk is reported to be about 50% following 16 Gy of radiotherapy, 12 Gy for HHA was estimated to be safe. 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. 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 $D_{\text{max}} \leq 13.3$ Gy which appeared to be significantly lower than the values of $D_{100\%} \leq 9$ Gy and $D_{\text{max}} \leq 16$ Gy, recommended in the RTOG 0933 guidelines for the protocol of 30 Gy of WBRT. 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, a $D_{\text{max}}$ of 9 Gy to 100% of the hippocampi and a $D_{\text{max}}$ of 5.83 Gy to 100% of the bilateral hippocampi.

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. 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. 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. 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. 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. 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. 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. 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. 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 neuro-radiologist 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. 80

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.

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