Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2010 November 15; 78(4): 1244–1252. doi:10.1016/j.ijrobp.2010.01.039.

Hippocampal-Sparing Whole Brain Radiotherapy: A “How-To” Technique, Utilizing Helical Tomotherapy and LINAC-based Intensity Modulated Radiotherapy

Vinai Gondi, M.D.^{*,1}, Ranjini Tolakanahalli, M.S.^{*,1}, Minesh P. Mehta, M.D.^{*}, Dinesh Tewatia, M.S.^{*,&}, Howard Rowley, M.D.[^], John S. Kuo, M.D., Ph.D.^{*,§}, Deepak Khuntia, M.D.^{*}, and Wolfgang A. Tomé, Ph.D.^{*,&}

^{*}Department of Human Oncology, University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin, USA

[&]Department of Medical Physics, University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin, USA

[^]Department of Neuroradiology, University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin, USA

[§]Department of Neurological Surgery, University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin, USA

Abstract

Purpose—Sparing the hippocampus during cranial irradiation poses important technical challenges with respect to contouring and treatment planning. Herein, we report our preliminary experience with whole-brain radiotherapy using hippocampal sparing for patients with brain metastases.

Materials/Methods—5 anonymous patients previously treated with whole-brain radiotherapy with hippocampal sparing were reviewed. The hippocampus was contoured, and hippocampal avoidance regions were created using a 5mm volumetric expansion around the hippocampus. Helical tomotherapy and LINAC-based IMRT treatment plans were generated for a prescription dose of 30 Gy in 10 fractions.

Results—On average, the hippocampal avoidance volume was 3.3 cm³, occupying 2.1% of the whole brain planned target volume. Helical tomotherapy spared the hippocampus, with a median dose of 5.5 Gy and maximum dose of 12.8 Gy. LINAC-based IMRT spared the hippocampus, with a median dose of 7.8 Gy and maximum dose of 15.3 Gy. On a per-fraction basis, mean dose to the hippocampus (normalized to 2-Gy fractions) was reduced by 87% to 0.49 Gy₂ using helical tomotherapy and by 81% to 0.73 Gy₂ using LINAC-based IMRT. Target coverage and

© 2010 Elsevier Inc. All rights reserved.

Corresponding Author: Vinai Gondi, M.D., Department of Human Oncology, University of Wisconsin Comprehensive Cancer Center, 600 Highland Avenue, Madison, WI 53792 USA, Telephone: 608-263-8500, Fax: 608-262-6256, gondi@humonc.wisc.edu.

¹These authors contributed equally to this work.

Requests for Reprints should be direct to: Wolfgang Tomé, PhD, Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, CSC K4/314, 600 Highland Avenue, Madison, WI 53792 USA, tome@humonc.wisc.edu

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest Notification: Minesh Mehta and Deepak Khuntia serve as consultants to Tomotherapy, Inc.

homogeneity was acceptable with both IMRT modalities, with differences largely attributed to more rapid dose fall-off with helical tomotherapy.

Conclusion—Modern IMRT techniques allow for sparing of the hippocampus with acceptable target coverage and homogeneity. Based on compelling preclinical evidence, a phase II cooperative group trial has been developed to test the postulated neurocognitive benefit.

Keywords

Helical tomotherapy; Whole-brain radiotherapy; Neurocognitive function; Hippocampal avoidance; RTOG 0933

Introduction

RTOG 0933 is a phase II clinical trial that aims to explore the hypothesis that sparing the hippocampus during cranial irradiation may mitigate radiation-induced neurocognitive toxicity. Emerging clinical and preclinical evidence suggests that a neural stem cell compartment in the hippocampus is central to the pathogenesis of neurocognitive deficits observed after cranial irradiation. This “stem cell niche” of the hippocampus has been observed to be exquisitely sensitive to therapeutic doses of cranial radiation, with these neural progenitor cells becoming less proliferative, more apoptotic, and more likely to adopt a gliogenic, rather than neurogenic, fate (1–6). Monje and colleagues found that a major contributing factor to these radiation effects is inflammation in the area surrounding the neural stem cells, with a similar effect observed from non-radiation causes such as bacterial lipopolysaccharide (7).

Notably, these neural progenitor cells seem to be anatomically clustered within the dentate gyrus of the hippocampus (8), availing the opportunity to conformally avoid them during cranial irradiation using modern intensity-modulated radiotherapy (IMRT) technologies, such as helical tomotherapy and linear accelerator (LINAC)-based IMRT. Reducing the dose to the hippocampi may putatively limit the radiation-induced inflammation of the hippocampal region and subsequent alteration of the microenvironment of the anatomically clustered neural stem cells. We propose that hippocampal sparing may delay or reduce the onset, frequency, and/or severity of neurocognitive decline in multiple different clinical settings of cranial irradiation, including WBRT for brain metastases, prophylactic cranial irradiation for small cell lung cancer, and cranial irradiation for pediatric malignancies.

However, sparing the hippocampus during cranial irradiation poses important technical challenges with respect to contouring and treatment planning. At the University of Wisconsin, we have initiated pilot testing of hippocampal sparing during whole-brain radiotherapy (WBRT) in patients with brain metastases (9). Herein, we review five such patients consecutively treated with hippocampal sparing during WBRT. We review our rationale and approach to generating hippocampal avoidance zones and discuss treatment planning and delivery with helical tomotherapy and LINAC-based IMRT. The strategies and techniques herein presented form the basis for credentialing and central quality assurance review for RTOG 0933.

Methods and Materials

MRI-CT Fusion

5 anonymous consecutive patients with brain metastases treated with whole-brain radiotherapy with hippocampal sparing were reviewed. Patients underwent a non-contrast CT simulation scan of the entire head region with 1.25mm slice thickness using an aquaplast

mask for immobilization. Within two weeks prior to treatment, the patients underwent three-dimensional spoiled gradient axial MRI scans (3D-SPGR) with standard axial and coronal fluid attenuation recovery (FLAIR), axial T2-weighted and gadolinium contrast-enhanced T1-weighted sequence acquisitions with a 1.25mm slice thickness (Stealth MRI). The CT simulation and Stealth MRI scans were fused semi-automatically and target and avoidance structures were contoured using the Phillips Pinnacle³ version 8.0m treatment planning software (Fitchburg, WI).

Hippocampal Contouring

The hippocampus was contoured on T1-weighted MRI axial sequences (Figure 1). Given the preponderance of gray matter in the hippocampus, contouring focused on the T1-hypointense signal medial to the temporal horn and distinct from the T1-hyperintense parahippocampal gyrus and fimbriae, located inferomedial and superomedial to the hippocampus, respectively. Contouring began at the most caudal extent of the crescentic-shaped floor of the temporal horn and continued postero-cranially along the medial edge of the temporal horn. The medial border of the hippocampus was delineated by the edge of the T1-hypointensity up to the ambient cistern. The uncus recess of the temporal horn served to distinguish the hippocampus from the gray matter of the amygdala, lying anterior and superior to the hippocampus. The postero-cranial extent of the hippocampus was defined by the curvilinear T1-hypointense hippocampal tail located just antero-medially to the atrium of the lateral ventricle. Contours terminated at the lateral edges of the quadrigeminal cisterns, prior to the emergence of the crus of the fornix. The hippocampal avoidance region was generated by expanding the hippocampal contour by 5mm volumetrically to account for necessary dose fall-off between the hippocampus and the whole brain PTV. Appropriate anatomical contouring was confirmed using T1-weighted MRI sagittal and coronal sequences (Figure 2). The whole brain planned tumor volume (PTV), defined as the whole brain parenchyma excluding the hippocampal avoidance region, and lenses were contoured.

Helical Tomotherapy

The planning CT and accompanying contours were transferred to the Hi-ArtTM helical tomotherapy (version 3.1.4, Tomotherapy, Inc., Madison, WI) planning station using DICOM RT. Details of the inverse planning algorithm used in Hi-ArtTM helical tomotherapy have been previously described (10). During the planning process, the Hi-ArtTM helical tomotherapy treatment planning software down-sampled the CT image resolution to 256×256 pixels per slice, and the slice width was maintained at 2.5 mm for the entire CT image volume set. Plans were optimized such that 96% of the whole brain PTV received the prescription dose of 30 Gy in 10 fractions. Helical tomotherapy plan parameters consisted of a 1.05 cm field width, 0.215 pitch, and 3.0 modulation factor, based on dosimetric results from a prior helical tomotherapy planning study (9). Directional blocking was used for the eyes and lenses. The constraints used for the whole brain PTV, hippocampus, eyes and lenses during inverse planning on helical tomotherapy are listed in Table 1.

LINAC-based IMRT Planning

3D search space on Plan Geometry Optimizer (PGO) (Varian Medical Systems, Palo Alto, CA) was utilized to generate the starting beam angle arrangement that optimized target coverage, homogeneity and sparing of the eyes and lenses. The beam's eye views for each of these beams were then inspected and modified to check for deliverability without any collision of the gantry with the couch. The optimized beam arrangement used in this study is listed in Table 2.

Using one sample patient, multiple different sets of constraints for the whole brain PTV, hippocampus, eyes and lenses were tested for inverse planning for LINAC-based IMRT. 12

sets of constraints were identified to provide optimal hippocampal sparing, target coverage and homogeneity. These 12 sets of constraints were then applied to the other four patients, and only one set of constraints emerged as reproducible in all five patients. This set of constraints is listed in Table 1. 30 Gy in 10 fractions was prescribed to 92% of the whole brain PTV. For inverse planning optimization, the Direct Machine Parameter Optimization (DMPO) algorithm and dose engine on Pinnacle³ version 8.0m treatment planning software (Philips, Fitchburg, WI) was utilized to allow for simultaneous optimization of the shapes and weights of the apertures. The first few iterations were used to find an initial set of control points that meets the user and machine-specific requirements. During the remainder of the iterations, the MLC leaf positions and segment weights were optimized. Throughout this process, the plan remained feasible for delivery.

Treatment Plan Evaluation

The following treatment planning parameters were used to evaluate the treatment plans:

Target Coverage (TC):

TC describes the fraction of the target volume (V_T) receiving at least the prescription dose ($V_{T, \text{presc}}$) and is defined as

$$TC = \frac{V_{T, \text{presc}}}{V_T}$$

For perfect coverage, TC equals 1.0.

Homogeneity Index (HI):

HI quantifies dose homogeneity in the target volumes, as recommended by the International Commission on Radiation Units and Measurements (11). The HI is defined as the greatest dose delivered to 2% of the target volume ($D_{2\%}$) minus the dose delivered to 98% of the target volume ($D_{98\%}$) divided by the

median dose (D_{median}) of the target volume:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{\text{median}}}$$

Smaller values of HI correspond to more homogenous irradiation of the target volume. A value of 0 corresponds to absolute homogeneity of dose within the target.

V90:

V90 quantifies volume of the whole brain PTV receiving 90% of the prescription dose.

V95:

V95 quantifies volume of the whole brain PTV receiving 95% of the prescription dose.

Mean Normalized Tissue Dose (NTDmean):

NTDmean is defined as the total dose that would have the same biological effect as the actual treatment schedule, if it were given in 2 Gy fractions. This parameter allows us to compare the effects on normal tissue for two dose-volume histograms. An α/β ratio of 2 Gy was assumed for the hippocampus.

Statistical Analysis

Statistical analysis was performed using SPSS 14.0 software. Treatment plan metrics were compared using one-way analysis of variance (ANOVA) and multiple comparison tests using critical values from the t distribution with the Bonferroni adjustment and an upper bound of $p < 0.05$.

Results

Hippocampal Contouring

Mean volumes for the hippocampus, hippocampal avoidance region, and whole brain (including the hippocampal avoidance region) are 3.3 cm³ (range 2.8–4.0 cm³), 27.5 cm³ (25.9–30.3 cm³), and 1307.0 cm³ (1204.7–1432.1 cm³), respectively. On average, the hippocampal avoidance volume occupied 2.1% (1.9–2.5%) of the whole brain (Table 3).

Whole Brain Planned Target Volume Coverage and Homogeneity

A cumulative normalized dose–volume histogram for hippocampal avoidance during whole-brain radiotherapy is presented for all five patients using helical tomotherapy and LINAC-based IMRT in Figure 3 and Figure 4, respectively. The spatial isodose distribution at the level of the hippocampi for one sample patient is shown in Figure 5 (A, helical tomotherapy; B, LINAC-based IMRT). Table 4 lists the target coverage, homogeneity index, V90, and V95 for the whole brain PTV for each patient using helical tomotherapy and LINAC-based IMRT. On average, helical tomotherapy offers a 2% improvement in mean target coverage ($p = 0.008$) and greater homogeneity ($p = 0.015$), but similar V90 and V95, as compared to LINAC-based IMRT. These analyses were conducted for the whole brain PTV, defined as the whole brain parenchyma excluding the hippocampal avoidance region (the hippocampus plus a 5mm setup margin). To better understand the difference in target coverage and homogeneity between helical tomotherapy and LINAC-based IMRT, the hippocampal avoidance region was volumetrically enlarged in 1mm increments and the whole brain PTV was re-defined as exclusive of this region. In this analysis, treatment plans were not re-optimized. Statistical differences in target coverage and homogeneity between helical tomotherapy and LINAC-based IMRT were no longer apparent when the whole brain PTV was defined as exclusive of the hippocampal avoidance region plus 2mm (i.e., the hippocampus plus 7mm), at which point the target coverage and homogeneity index for LINAC-based IMRT improved to 0.95 and 0.25, respectively.

Dose to Hippocampus, Eyes, and Lenses

Table 5 describes the dose received by the hippocampus, eyes and lenses for each patient using helical tomotherapy and LINAC-based IMRT. On average, helical tomotherapy offered greater hippocampal sparing compared to LINAC-based IMRT, in terms of NTDmean ($p < 0.001$), median dose ($p < 0.001$), and maximum dose ($p = 0.001$). Using helical tomotherapy, NTDmean, median dose, and maximum dose received by the hippocampus were 4.9 Gy₂, 5.5 Gy and 12.8 Gy, respectively. Using LINAC-based IMRT, NTDmean, median dose, and maximum dose received by the hippocampus were 7.3 Gy₂, 7.8 Gy, and 15.3 Gy, respectively. The mean NTD to the eyes and maximum dose to lenses did not differ significantly.

Discussion

Preclinical evidence suggests that the neural stem cell compartment within the dentate gyrus plays a critical role in hippocampal neurogenesis (8,12–18), and damage to it during cranial irradiation contributes significantly to the development of neurocognitive decline, most notably in memory-related domains (1–7). Conformal avoidance of the hippocampus using intensity-modulated radiotherapy (IMRT) may spare patients some of the neurocognitive sequelae of cranial irradiation without significantly altering the therapeutic benefit. Clinical implementation of hippocampal sparing, however, poses a number of important challenges: 1) accurate delineation of the hippocampus is critical to deriving the postulated neurocognitive benefit and to avoiding excess risk of intracranial disease progression; and, 2) the central location of the hippocampus within the brain necessitates the use of IMRT technology to spare the hippocampus of a clinically significant radiation dose, without compromising target coverage and homogeneity.

The hippocampus consists of two U-shaped interlocking laminae: the cornu ammonis and the dentate gyrus. It is a component of the entire limbic circuit, which includes white matter tracts such as the fimbriae and fornices (the primary efferent system of the hippocampus) and gray matter structures such as the amygdala and parahippocampal gyrus. Memory function has been associated with the pyramidal and granule cells located in the dentate

gyrus of the hippocampus (12). In all adult mammals, including humans, new granule cells are generated from mitotically active neural stem cells, which are located in the subgranular zone of the dentate gyrus and which migrate into the granular cell layer (8,13–18). Preclinical evidence has associated neurogenesis within the dentate gyrus with normal cognitive function (19–21). Cranial irradiation in rat models has been observed to induce apoptosis of these precursor cells and alter their differentiation towards a gliogenic fate, resulting in a significant reduction in hippocampal neurogenesis (1,5) and associated cognitive impairment (3). In contrast, neural progenitor cells within the subventricular zone of the lateral ventricles differentiate into olfactory bulb neurons and play a role in olfactory discrimination (22).

Since the primary avoidance region is postulated to be the subgranular stem cell compartment, we have adopted a targeted approach to contouring the hippocampus, focusing on the dentate gyrus and cornu ammonis, rather than comprehensively contouring the entire limbic circuit or the subventricular zones. Minimizing the avoidance volume is critical to avoiding a clinically unacceptable risk of intracranial disease progression. In this study, the mean hippocampal avoidance volume was 27.5 cm^3 , representing, on average, 2.1% of the whole brain. We used the contouring technique described in this paper to review 371 patients who presented with 1133 metastases (23). In this comprehensive multi-institution analysis, we observed a metastasis within the hippocampal avoidance region (hippocampus plus 5mm margin) in 8.6% of patients, with 11.5% as the upper limit of the 95% confidence interval, and 3.0% of brain metastases. None of the metastases lay within the hippocampus. Assuming that the risk of developing subsequent brain metastasis within the hippocampal avoidance region scales in the same proportion as that at presentation, we estimated that a patient treated with hippocampal sparing during whole-brain radiotherapy (WBRT) will derive 91.4% of the relative benefit of WBRT in terms of preventing the emergence of radiographically visible intracranial lesions, with a lower 95% confidence limit of 88.5%.

Using helical tomotherapy and LINAC-based intensity-modulated radiotherapy (IMRT), we have been successfully able to spare the hippocampus. For a prescription dose of 30 Gy in 10 fractions, the median and maximum dose received by the hippocampus is 5.5 Gy and 12.8 Gy, respectively, for helical tomotherapy and 7.8 and 15.3, respectively, for LINAC-based IMRT. In addition, mean dose to the hippocampus, normalized to 2-Gy fractions (NTDmean), is reduced by 87% from 37.5 Gy_2 (30 Gy in 10 fractions) to 4.9 Gy_2 using helical tomotherapy, and by 81% to 7.3 Gy_2 using LINAC-based IMRT. That helical tomotherapy offered better hippocampal sparing as compared to LINAC-based IMRT, is not surprising. In similar clinical applications of IMRT for sparing of deep anatomic structures, such as parotid sparing in head and neck irradiation, helical tomotherapy has demonstrated improved sparing capability compared to step-and-shoot IMRT (24). However, we postulate that using either helical tomotherapy or LINAC-based IMRT will sufficiently spare the hippocampus to yield a clinically significant neurocognitive benefit. Using a rat model, Michelle Monje and colleagues have observed a radiation dose-dependent effect on neurogenesis, with a single fraction of 10 Gy inducing a 62% reduction in neural stem cell proliferation and a 97% reduction in hippocampal neurogenesis (1,2). On a per-fraction basis, sparing of the hippocampus in this study reduced NTDmean to the hippocampus from 3.75 Gy_2 to 0.49 Gy_2 and 0.73 Gy_2 using helical tomotherapy and LINAC-based IMRT, respectively.

In this study, hippocampal sparing was achieved with acceptable target coverage and homogeneity. Helical tomotherapy achieved improved whole brain target coverage and homogeneity. However, a large component of this difference can be attributed to the more rapid dose fall-off offered by helical tomotherapy. When the whole brain planned target volume was re-defined (but not re-planned) to exclude the hippocampal avoidance region

plus 2mm (that is, the hippocampus plus 7mm), the differences in target coverage and homogeneity between helical tomotherapy and LINAC-based IMRT were no longer apparent. This difference in dose fall-off can be visualized spatially in Figure 5. Given the ability of helical tomotherapy and LINAC-based IMRT to spare the hippocampus with acceptable whole brain target coverage and homogeneity, we conclude that hippocampal avoidance during whole-brain radiotherapy is feasible and safe for clinical testing using both IMRT modalities.

The postulated neurocognitive benefit of hippocampal sparing during cranial irradiation remains to be tested clinically. Through the RTOG (RTOG 0933), we have developed a multi-institutional phase II clinical trial of HA-WBRT in patients with brain metastases (Table 6). This trial has been approved by the Division of Cancer Prevention at the National Cancer Institute and is scheduled to open in 2010. The trial consists of a pilot training component followed by a phase II feasibility component. For the pilot component, attending physicians and institutions planning on treating patients on the phase II component will receive fused Stealth MRI and head CT simulation images in DICOM format for one sample patient. Using the technique described in this paper, they will be asked to 1) manually generate hippocampal contours, 2) expand these three-dimensionally into hippocampal avoidance zones, and 3) develop a treatment plan with hippocampal avoidance. Hippocampal contours and treatment plans will be reviewed centrally by our research group, and instructive feedback will be provided electronically to each site and attending physician. Once an institution's attending physician demonstrates sufficient competence in hippocampal contouring and treatment planning, that institution will be certified to accrue patients to the phase II component. At this point, hippocampal sparing during cranial irradiation should not be used outside this clinical trial.

Conclusion

Hippocampal sparing during cranial irradiation poses important challenges with respect to the accurate delineation of the hippocampus and its central location requiring IMRT to achieve conformal avoidance. Using modern IMRT techniques, we have been able to reduce the mean dose per fraction to the hippocampus (normalized to 2-Gy fractions) by 87% to 0.49 Gy₂ using helical tomotherapy, and by 81% to 0.73 Gy₂ using LINAC-based IMRT. Preclinical evidence suggests that sparing the hippocampus of therapeutic doses of radiation may mitigate neurocognitive decline. To test this hypothesis clinically, we have developed a multi-institutional phase II clinical trial (RTOG 0933) of hippocampal sparing during whole-brain radiotherapy in patients with brain metastases.

Acknowledgments

This work was in part supported by a grant from the National Institute of Health R01-CA109656.

References

1. Monje ML, Mizumatsu S, Fike JR, et al. Irradiation induces neural precursor-cell dysfunction. *Nat Med.* 2002; 8:955–962. [PubMed: 12161748]
2. Mizumatsu S, Monje ML, Morhardt DR, et al. Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res.* 2003; 63:4021–4027. [PubMed: 12874001]
3. Raber J, Rola R, LeFevour A, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res.* 2004; 162:39–47. [PubMed: 15222778]
4. Nagai R, Tsunoda S, Hori Y, et al. Selective vulnerability to radiation in the hippocampal dentate granule cells. *Surg Neurol.* 2000; 53:503–506. discussion 506–507. [PubMed: 10874152]

5. Tada E, Parent JM, Lowenstein DH, et al. X-irradiation causes a prolonged reduction in cell proliferation in the dentate gyrus of adult rats. *Neuroscience*. 2000; 99:33–41. [PubMed: 10924950]
6. Peissner W, Kocher M, Treuer H, et al. Ionizing radiation-induced apoptosis of proliferating stem cells in the dentate gyrus of the adult rat hippocampus. *Brain Res Mol Brain Res*. 1999; 71:61–68. [PubMed: 10407187]
7. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science*. 2003; 302:1760–1765. [PubMed: 14615545]
8. Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med*. 1998; 4:1313–1317. [PubMed: 9809557]
9. Gutierrez AN, Westerly DC, Tome WA, et al. Whole brain radiotherapy with hippocampal avoidance and simultaneously integrated brain metastases boost: a planning study. *Int J Radiat Oncol Biol Phys*. 2007; 69:589–597. [PubMed: 17869672]
10. Shepard DM, Olivera GH, Reckwerdt PJ, et al. Iterative approaches to dose optimization in tomotherapy. *Phys Med Biol*. 2000; 45:69–90. [PubMed: 10661584]
11. International Commission on Radiation Units and Measurements. Bethesda: ICRU; 1999. ICRU Report 62: Prescribing, recording, and reporting photon beam therapy (Supplement to ICRU Report 50).
12. Collier TJ, Quirk GJ, Routtenberg A. Separable roles of hippocampal granule cells in forgetting and pyramidal cells in remembering spatial information. *Brain Res*. 1987; 409:316–328. [PubMed: 3580879]
13. Bayer SA. Changes in the total number of dentate granule cells in juvenile and adult rats: a correlated volumetric and 3H-thymidine autoradiographic study. *Exp Brain Res*. 1982; 46:315–323. [PubMed: 7095040]
14. Cameron HA, Woolley CS, McEwen BS, et al. Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. *Neuroscience*. 1993; 56:337–344. [PubMed: 8247264]
15. Gould E, McEwen BS, Tanapat P, et al. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *J Neurosci*. 1997; 17:2492–2498. [PubMed: 9065509]
16. Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. *Nature*. 1997; 386:493–495. [PubMed: 9087407]
17. Gould E, Beylin A, Tanapat P, et al. Learning enhances adult neurogenesis in the hippocampal formation. *Nat Neurosci*. 1999; 2:260–265. [PubMed: 10195219]
18. Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J Neurosci*. 1996; 16:2027–2033. [PubMed: 8604047]
19. Shors TJ, Miesegaes G, Beylin A, et al. Neurogenesis in the adult is involved in the formation of trace memories. *Nature*. 2001; 410:372–376. [PubMed: 11268214]
20. Cameron HA, Gould E. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience*. 1994; 61:203–209. [PubMed: 7969902]
21. Lemaire V, Koehl M, Le Moal M, et al. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc Natl Acad Sci U S A*. 2000; 97:11032–11037. [PubMed: 11005874]
22. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell*. 2008; 132:645–660. [PubMed: 18295581]
23. Gondi, V.; Tome, WA.; Marsh, J., et al. Estimated risk for perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy; *Radiother Oncol*; 2010. In Press
24. van Vulpen M, Field C, Raaijmakers CP, et al. Comparing step-and-shoot IMRT with dynamic helical tomotherapy IMRT plans for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2005; 62:1535–1539. [PubMed: 15925457]
25. Gutierrez AN, Westerly DC, Tome WA, et al. Whole brain radiotherapy with hippocampal avoidance and simultaneously integrated brain metastases boost: A planning study. *Int J Radiat Oncol Biol Phys*. 2007; 69:589–597. [PubMed: 17869672]

Figure 1. Hippocampal contouring

The hippocampus (orange) was contoured on T1-weighted MRI axial sequences. Given the preponderance of gray matter in the hippocampus, contouring focused on the T1-hypointense signal medial to the temporal horn and distinct from the T1-hyperintense parahippocampal gyrus (A) and fimbriae (D), located inferomedial and superomedial to the hippocampus, respectively. Contouring began at the most caudal extent of the crescent-shaped floor of the temporal horn (B) and continued postero-cranially along the medial edge of the temporal horn. The medial border of the hippocampus was delineated by the edge of the T1-hypointensity up to the ambient cistern (C). The uncus recess (E) of the temporal horn served to distinguish the hippocampus from the gray matter of the amygdala (F), lying anterior and superior to the hippocampus. The postero-cranial extent of the hippocampus was defined by the curvilinear T1-hypointense hippocampal tail located just antero-medially to the atrium of the lateral ventricle (G). Contours terminated at the lateral edges of the quadrigeminal cisterns (H), prior to the emergence of the crus of the fornix.

Figure 2. Hippocampal avoidance region

The hippocampal avoidance region (green) was generated by expanding the hippocampal contour (orange) by 5mm volumetrically to account for set-up error. Appropriate anatomical contouring was confirmed using T1-weighted MRI sagittal and coronal sequences.

Figure 3. Dose-volume histogram for hippocampal avoidance during whole-brain radiotherapy using helical tomotherapy

5 anonymous consecutive patients with brain metastases treated with whole-brain radiotherapy with hippocampal avoidance were reviewed. Treatment plans were optimized such that 96% of the whole brain PTV received the prescription dose of 30 Gy in 10 fractions. Helical tomotherapy plan parameters consisted of a 1.05 cm field width, 0.215 pitch, and 3.0 modulation factor (25). Directional blocking was used for the eyes and lenses. The constraints for the whole brain PTV, hippocampus, eyes and lenses used for inverse planning on helical tomotherapy are described in Table 2.

Abbreviations: PTV, whole brain planned target volume.

Figure 4. Dose-volume histogram for hippocampal avoidance during whole-brain radiotherapy using LINAC-based IMRT

5 anonymous consecutive patients with brain metastases treated with whole-brain radiotherapy with hippocampal avoidance were reviewed. 30 Gy in 10 fractions was prescribed to 92% of the whole brain PTV. The constraints for the whole brain PTV, hippocampus, eyes and lenses used for inverse planning for LINAC-based IMRT are described in Table 2.

Abbreviations: PTV, whole brain planned target volume.

Gray shade: Hippocampus

Orange contour: Hippocampal avoidance region

Figure 5. Spatial isodose distribution for one sample patient at the level of the hippocampi for hippocampal avoidance during whole-brain radiotherapy using (A) helical tomotherapy and (B) LINAC-based IMRT

The gray shaded region represents the hippocampus. The orange contour represents the hippocampal avoidance region. Green isodose represents 12 Gy; light blue, 27 Gy; pink, 29 Gy; yellow, 30 Gy; red, 38 Gy, in 10 fractions. Representative axial, sagittal and coronal images are provided.

Table 1

Clinical criteria and inverse planning algorithm constraints for helical tomotherapy and LINAC-based IMRT Planning.

Structure	Helical Tomotherapy Plan Criteria	Penalty	Importance	LINAC-Based IMRT Plan Criteria	Penalty
Whole Brain PTV	Max Dose: 30 Gy	100	200	Max Dose: 34 Gy	100
	30 Gy to $\geq 96\%$			Min Dose: 32 Gy	100
Hippocampus	Max Dose: 6 Gy	100	500	Max Dose: 11 Gy	5
	3 Gy to $\leq 20\%$	20		9 Gy to $\leq 40\%$	10
Hippocampal Avoidance Volume	Max Dose: 30 Gy	1	5	N/A	N/A
	20 Gy to $\leq 20\%$	10			
Eyes *	Max Dose: 8 Gy	10	20	Max Dose: 7 Gy	5
	5 Gy to $\leq 20\%$	10			
Lenses *	Max Dose: 3 Gy	20	20	Max Dose: 5 Gy	5
	2 Gy to $\leq 20\%$	10			

Abbreviations: PTV, Planned target volume; N/A, not applicable.

* Eyes and lenses were directionally blocked during helical tomotherapy planning.

Table 2

The starting plan configuration in Varian Standard co-ordinate system for non-coplanar treatment planning which follows a basic template provided by the Plan Geometry Optimizer (Varian Systems, Palo Alto, CA) with subsequent modifications of couch and gantry angle combinations for deliverability.

Beam	Couch Angle (°)	Gantry Angle (°)
1	140	150
2	150	230
3	225	360
4	190	76
5	196	131
6	96	171
7	150	275
8	196	223
9	90	221

Table 3

Volumes of hippocampus and hippocampal avoidance regions relative to the whole brain.

Patient	Hippocampal Volume (cm ³)	Hippocampal Avoidance (HA) Volume (cm ³)	Whole Brain* (cm ³)	Percentage of Whole Brain occupied by HA
1	4.0	30.3	1204.7	2.5%
2	3.0	25.9	1341.4	1.9%
3	2.8	26.3	1222.0	2.2%
4	3.1	27.3	1432.1	1.9%
5	3.5	27.5	1334.6	2.1%
Mean	3.3	27.5	1307.0	2.1%

* The whole brain included the whole brain planned target volume plus the hippocampal avoidance region.

Table 4

Whole brain target coverage and homogeneity during whole-brain radiotherapy with hippocampal avoidance using helical tomotherapy and LINAC-based IMRT.

Patient	Target Coverage		Homogeneity Index		V90		V95	
	HT	LINAC	HT	LINAC	HT	LINAC	HT	LINAC
1	0.95	0.95	0.29	0.32	96.9	97.7	96.2	96.5
2	0.95	0.92	0.17	0.31	98.1	98.1	97.3	97.3
3	0.95	0.92	0.18	0.34	98.1	97.6	97.5	96.1
4	0.95	0.93	0.09	0.26	99.2	98.7	98.6	97.5
5	0.95	0.94	0.08	0.29	99.1	98.3	98.5	97.1
Mean	0.95	0.93	0.16	0.30	98.3	98.1	97.6	96.9
p value	0.015		0.008		NS		NS	

Abbreviations: HT, helical tomotherapy; LINAC, LINAC-based IMRT; V90, volume of whole brain receiving ≥90% of prescription dose; V95, volume of whole brain receiving ≥95% of prescription dose; NS, non-significant.

Whole brain planned target volume was defined as the whole brain excluding the hippocampal avoidance region.

Table 5

Dose to hippocampus, lenses and eyes during whole-brain radiotherapy with hippocampal avoidance using helical tomotherapy and LINAC-based IMRT.

Patient	Hippocampus				Eyes		Lenses	
	NTD Mean (Gy ₂)		Median Dose (Gy)		NTD Mean (Gy ₃)		Max Dose (Gy)	
	HT	LINAC	HT	LINAC	HT	LINAC	HT	LINAC
1	5.2	7.2	5.6	7.7	11.8	14.3	5.6	5.5
2	4.8	7.3	5.2	7.8	14.2	14.9	5.0	5.2
3	4.6	7.6	5.8	8.2	12.8	15.5	5.0	4.8
4	4.8	7.3	5.3	7.8	12.3	15.7	5.6	5.2
5	5.3	7.2	5.8	7.6	12.8	15.9	4.8	5.5
Mean	4.9	7.3	5.5	7.8	12.8	15.3	5.2	5.2
p value	< 0.001		< 0.001		0.001		NS	

Abbreviations: HT, helical tomotherapy; LINAC, LINAC-based IMRT; NTD, normalized tissue dose assuming an $\alpha/\beta = 2.0$; NS, non-significant.

Table 6

Study schema for RTOG 0933, a multi-institution phase II trial of hippocampal sparing during WBRT for brain metastases.

For Patients with MRI Evidence of Brain Metastasis Within 1 Month of WBRT		
REGISTER ¹	Within 2 Weeks Prior to Treatment	Radiation Therapy
	1 Stealth MRI with Fused CT Simulation	WBRT with Hippocampal Avoidance using IMRT (30 Gy in 10 Fractions) ³
	2 NCF Testing	
	3 Quality of Life Assessment	
	4 Central Review of Hippocampal Contours and HA-WBRT Treatment Plan ²	

Institutions must be credentialed by the RTOG prior to enrolling patients.

Prior to treatment, all hippocampal contours and HA-WBRT treatment plans will undergo central rapid review for quality assurance. Refinements will be made as needed.

Chemotherapy during WBRT or the subsequent 7 days and stereotactic radiosurgery or surgical resection of brain metastases are not allowed.

Abbreviations: NCF, neurocognitive function; WBRT, whole-brain radiotherapy; HA-WBRT, hippocampal avoidance during WBRT.