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RapidPlan hippocampal sparing whole brain model version 2—how far can we reduce the dose?

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ABSTRACT

Whole-brain radiotherapy has been the standard palliative treatment for patients with brain metastases due to its effectiveness, availability, and ease of administration. Recent clinical trials have shown that limiting radiation dose to the hippocampus is associated with decreased cognitive toxicity. In this study, we updated an existing Knowledge Based Planning model to further reduce dose to the hippocampus and improve other dosimetric plan quality characteristics. Forty-two clinical cases were contoured according to guidelines. A new dosimetric scorecard was created as an objective measure for plan quality. The new Hippocampal Sparing Whole Brain Version 2 (HSWBv2) model adopted a complex recursive training process and was validated with five additional cases. HSWBv2 treatment plans were generated on the Varian Halcyon[™] and TrueBeam[™] systems and compared against plans generated from the existing (HSWBv1) model released in 2016. On the Halcyon[™] platform, 42 cases were re-planned. Hippocampal D_{100%} from HSWBv2 and HSWBv1 models had an average dose of 5.75 Gy and 6.46 Gy, respectively ($p < 0.001$). HSWBv2 model also achieved a hippocampal D_{mean} of 7.49 Gy, vs 8.10 Gy in HSWBv1 model ($p < 0.001$). Hippocampal D_{0.03CC} from HSWBv2 model was 9.86 Gy, in contrast to 10.57 Gy in HSWBv1 ($p < 0.001$). For PTV₃₀₀₀, D_{98%} and D_{2%} from HSWBv2 model were 28.27 Gy and 31.81 Gy, respectively, compared to 28.08 Gy ($p = 0.020$) and 32.66 Gy from HSWBv1 ($p < 0.001$). Among several other dosimetric quality improvements, there was a significant reduction in PTV₃₀₀₀ V_{105%} from 35.35% (HSWBv1) to 6.44% (HSWBv2) ($p < 0.001$). On 5 additional validation cases, dosimetric improvements were also observed on TrueBeam[™]. In comparison to published data, the HSWBv2 model achieved higher quality hippocampal avoidance whole brain radiation therapy treatment plans through further reductions in hippocampal dose while improving target coverage and dose conformity/homogeneity. HSWBv2 model is shared publicly.

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Introduction

Brain metastasis, the most common form of brain cancer, is approximately 10-fold more common than primary brain tumors

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and affects nearly 170,000 Americans annually.^{1,2} Roughly 20% of all patients with solid tumors will develop brain metastases over the course of their disease, with primary lung cancers being the most frequent source.^{1,3–5} For the past 70 years, whole-brain radiotherapy (WBRT) has been the standard palliative treatment for patients with brain metastases due to its effectiveness, availability, and ease of administration.⁵ However, with further improvements

Table 1
Summary of published studies on HA-WBRT

Authors	Publication year	Number of HA-WBRT cases studied	Mean \pm SD WB PTV D _{xx} (Gy)	Hippocampus D _{100%} achieved (Gy)
Nevelsky et al.	2013	10	D _{2%} : 37.28 D _{98%} : 25.37	8.37
Siglin	2014	8	Not reported	7.4
Pokhrel et al.	2015	10	D _{2%} : 33.2 \pm 0.4 D _{98%} : 26.0 \pm 0.4	8.4 \pm 0.3
Shen et al.	2015	20	D _{2%} : 36.1 \pm 0.8 D _{98%} : 26.2 \pm 0.6	8.5 \pm 0.2
Levra et al.	2016	10	D _{90%} : 19.8 \pm 0.2	6.7 \pm 0.3
Vrana	2016	1 (case report)	D _{2%} : 33.91 D _{98%} : 25.20	14.18
Sood et al.	2017	10	Not reported	8.4 \pm 0.3
Kazda et al.	2017	10	D _{2%} : 33.0 D _{98%} : 26.4	9.34
Zieminski	2018	10	D _{99%} : 37.5 \pm 0.3	7.8 \pm 0.5
Yuen	2020	20	D _{2%} : 33.12 \pm 0.34 D _{98%} : 25.84 \pm 0.03	7.86 \pm 0.08
Okada et al.	2021	15	D _{2%} : 32.84–35.50 D _{98%} : 25.49–26.11	8.01–8.13*
NRG CC001†	2020	518	D _{2%} : \leq 37.5 D _{98%} : \geq 25	\leq 9
HSWBv1 model‡	2016	—	D _{2%} : 32.66 \pm 0.20 D _{98%} : 28.08 \pm 0.40	6.46 \pm 0.40
HSWBv2 model‡	2022	42	D _{2%} : 31.81 \pm 0.12 D _{98%} : 28.27 \pm 0.33	5.75 \pm 0.25

* A 3-mm margin was added during contouring of the hippocampus.²⁸

† This phase III clinical trial study only reported HA-WBRT guidelines.

‡ Dosimetric data were obtained on the same 42 training set cases used to create HSWBv2, Halcyon 4 arcs.

in systemic therapy and overall survival, recent efforts have been aimed at reducing cognitive toxicities associated with WBRT.⁵

The hippocampal dentate gyrus, a complex temporal lobe structure that houses an exquisitely radiosensitive compartment of neural stem cells, plays an important role in learning and memory.⁶ Significant WBRT-induced toxicities can be attributed to damage in this region, leading to impairment in cognitive function and quality of life.^{7–9} A prospective multi-institutional randomized phase III trial, NRG-CC001 (ClinicalTrials.gov identifier: NCT02360215), found therapeutic radiation doses to the whole brain while limiting hippocampal radiation doses (D_{100%} \leq 9 Gy and D_{max} \leq 16 Gy) along with twice-daily memantine, significantly reduced cognitive toxicity at 4 and 6 months.⁷

Despite strong clinical evidence that hippocampal avoidance during WBRT enhances clinical outcomes, cognitive function as a result of hippocampal dose gradient remains unknown. However, there has been a steep dose-response relationship between higher maximum dose to the bilateral hippocampus and deterioration in short-term memory.¹⁰ In clinical trials, the lowest point dose goal for hippocampal sparing is generally \leq 9 Gy driven by feasibility of sparing.^{7,11,12} In clinical practice, treatment planning is labor intensive and has high inter-planner variability for parameters, such as organ-at-risk (OAR) sparing, homogeneity index, and conformality index.¹³

RapidPlan™ is a commercial implementation of Knowledge Based Planning (KBP) (Varian Medical Systems, Palo Alto, CA). KBP software utilizes geometric features (i.e., OAR distance to the planning target volume (PTV)) and OAR overlap volume histogram to search for the best prior case(s) from a database or to construct a dose prediction model (i.e., machine learning, statistical model). In 2016, the Hippocampal Sparing Whole Brain Model Version 1.0 (HSWBv1) was made publicly available.¹⁴ HSWBv1 utilized a complex recursive model creation process and leveraged an intricate scorecard to assess plan quality. This scorecard, based on NRG-CC001, contained additional metrics to further reduce dose to the hippocampus and included additional OAR objectives (Table 1).^{15,16}

In this study, we developed a new multi-institutional Hippocampal Sparing Whole Brain RapidPlan™ Model Version 2.0

(HSWBv2) to further improve hippocampal sparing, homogeneity, conformity, and other OAR constraints over HSWBv1. The steep dose relationship between hippocampal dose and cognitive decline suggests tighter constraints may be beneficial.¹⁰

Methods

Target and OAR contouring and treatment planning guidelines

Fifty anonymized whole brain DICOM computed tomography (CT) and structure sets were obtained from Northwestern Medicine Cancer Center Warrenville and Washington University in St. Louis for patients treated per NRG-CC001 protocol. A planning CT protocol that encompassed the entire head was obtained for all patient cases, with maximum axial slice thickness of 2.5 mm or smaller. T1 contrast enhanced magnetic resonance imaging with similar axial slice thickness were registered to CT images. Bilateral hippocampal volumes, OARs, and optimization structures were then generated on the planning CT.

All training and validation cases used head-first supine orientation with the head in a neutral position immobilized with an Aquaplast mask. A 4-arc volumetric modulated arc therapy technique was utilized with 4 full coplanar arcs on Halcyon™ (Varian Medical Systems, Palo Alto, CA). Arcs had alternating clockwise and counterclockwise gantry rotations with collimator positions set at 315, 0, 45, and 90 degrees. The coplanar arcs had 359.8 degrees of arc rotation for each field. Arcs were positioned at a single isocenter located in the center of the target. Each arc utilized 6X Flattening Filter-Free energy at a dose rate of 800 MU per minute. HSWBv2 was also tested with various arc geometries (both coplanar and non-coplanar) on TrueBeam™/C-series (Millennium120 MLC). Full validation with different number of arcs, geometries, energies, and dose calculation methods, including a quantification of the relative dosimetric performance of each method, can be seen in Annex A of the clinical description document included with HSWBv2.

New scorecard tool used

Dosimetric scorecards were used to guide the RapidPlan™ model creation process. The PlanScoreCard Eclipse Scripting Application Programming Interface tool, available free on the Varian Innovation Center GitHub, was used to create scoring metrics, automatically generate additional optimization and evaluation structures, and score candidate plans throughout the process. These dosimetric scorecards use established scoring methodology of multiple piecewise linear score functions which measure specific plan quality metrics.¹³

Dosimetric scorecards as objective measure of plan quality

The original plan quality metrics scorecard Version 1.0 (100 points in total) was developed in 2016 for HSWBv1 and was based on dose constraints from NRG-

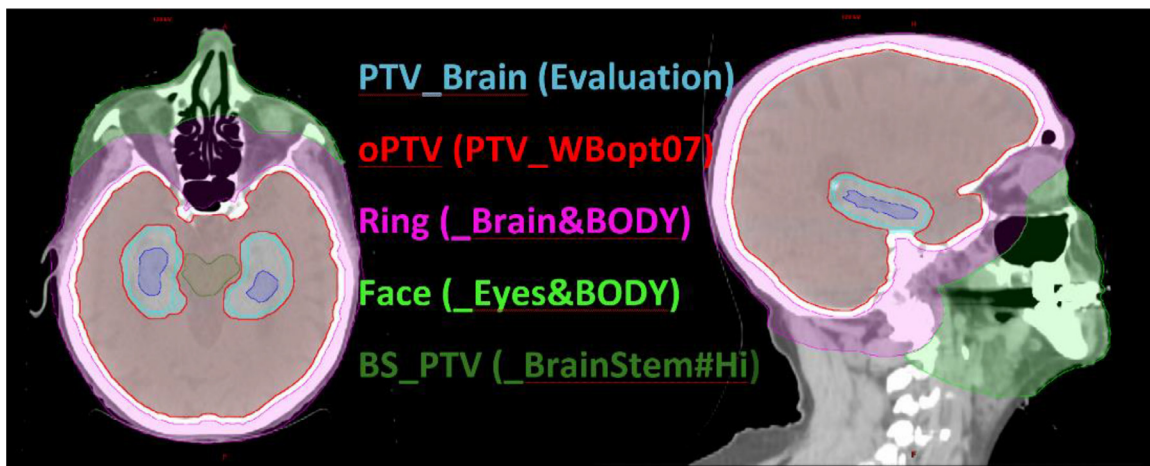


Fig. 1. Derived structures. PTV_Brain (Brain – [Hippocampus +05]) defined in NRG-CC001, used for scorecard evaluation but not used in optimization. oPTV (Brain – [Hippocampus +07]) used as primary target during optimization. Ring ([Brain +20] – [Brain +03]) used to minimize radiation dose outside the brain. Face ([Eyes +100] – [Brain +20]) used to minimize unnecessary lower doses. BS PTV (Brainstem – [Hippocampus +08]) used as secondary target to prevent <Rx dose between Hippocampus structures. (Units: mm). PTV, planning target volume.

CC001. The Version 1.0 scorecard awarded points for OAR doses lower than those cited in NRG-CC001 and added additional metrics for OARs and plan quality indexes not listed in the protocol. The new Version 2.0 dosimetric scorecard used in this study was further revised from the 2016 scorecard to address perceived plan quality issues with HSWBv1 plans (142 points in total). Additional points were awarded to prior metrics and new metrics were added, in-part, via four derived structures (Fig. 1). These new structures and their associated metrics quantify reducing dose to the face, improving conformity, and reducing heterogeneity in the target.

Further hippocampal sparing was also rewarded in the Version 2.0 scorecard. For the maximum dose goal ($D_{0.03CC}$) points are earned from 8 to 17 Gy, minimum dose ($D_{100\%}$) 5 to 10Gy, and D_{mean} 6 to 12 Gy.

This Version 2.0 scorecard, once finalized, guided the model creation process by providing a singular objective measure of plan quality.¹³ Figure 2 shows an example Version 2.0 scorecard scoring a validation case.

HSWBv2 model creation and training

All cases were prescribed 30 Gy in 10 fractions and satisfied the necessary contouring criteria for NRG-CC001 with additional OARs and structures. The original HSWBv1 model and Version 1.0 scorecard were used as a basis for this work. Treatment plans created from HSWBv1 with Varian Halcyon™ System were manually re-optimized to address feedback and improvements quantified using the new version 2.0 scorecard. Those manually improved, reoptimized plans became the training set for the initial HSWBv2 model. More cases were added, and a recursive model creation process was employed to ensure the final HSWBv2 training set consisted, exclusively, of plans generated from the initial HSWBv2 model. Evaluating plan scores at each step in the process informed multiple iterations of re-tuning the optimization objective set. As additional cases were added, geometric outliers became apparent. These outlier cases were omitted from the final HSWBv2 training set, resulting in 42 total cases. See Fig. 3 for process workflow details.

Primary dosimetric planning goals and scorecard comparison

Treatment plan comparisons were made between HSWBv1 and HSWBv2 for the hippocampus and PTV_3000 using student t-tests. Primary dose metrics for the hippocampus include dose at 0.03CC's ($D_{0.03CC}$), mean dose (D_{mean}), and dose at 100% volume ($D_{100\%}$). PTV_3000 primary metrics include dose at 98% volume ($D_{98\%}$), dose at 2% volume ($D_{2\%}$), and volume receiving 105% of prescription dose ($V_{105\%}$). These are included as high scoring individual metrics on the version 2.0 scorecard. The total scorecard points were also compared using student t-tests. Correlation analysis was performed to determine volume associations with hippocampal D_{mean} , $D_{100\%}$, and $D_{0.03CC}$.

Results

Hippocampal sparing comparisons between HSWBv1 and HSWBv2 on Halcyon

HSWBv2 has enhanced hippocampal sparing compared to HSWBv1. On the Halcyon platform, 42 training set cases were re-planned. Hippocampus $D_{100\%}$ from HSWBv2 and HSWBv1 had an average dose of 5.75 ± 0.25 Gy and 6.46 ± 0.40 Gy, respectively ($p < 0.001$). HSWBv2 also achieved hippocampus D_{mean} of 7.49 ± 0.36 Gy, vs 8.10 ± 0.42 Gy from HSWBv1 ($p < 0.001$). The hippocampus $D_{0.03CC}$ from HSWBv2 was 9.86 ± 0.73 Gy, in contrast to 10.57 ± 0.75 Gy from HSWBv1

Table 2

Halcyon™ plan quality comparisons between the HSWBv2 and HSWBv1 models; values were averaged from 42 cases (training set for HSWBv2)

Target/OAR	Mean (SD)		P-value*
	HSWBv2	HSWBv1	
Hippocampus			
$D_{100\%}$ (Gy)	5.75 (0.25)	6.46 (0.40)	<0.001
D_{mean} (Gy)	7.49 (0.36)	8.10 (0.42)	<0.001
$D_{0.03CC}$ (Gy)	9.86 (0.73)	10.57 (0.75)	<0.001
Brain PTV			
$D_{98\%}$ (Gy)	28.27 (0.33)	28.08 (0.40)	0.020
$D_{2\%}$ (Gy)	31.81 (0.12)	32.66 (0.20)	<0.001
$V_{105\%}$ (%)	6.44 (2.56)	35.35 (7.49)	<0.001
Total score (out of 142)	132.97 (1.71)	121.03 (3.48)	<0.001

* p-value were calculated using student t-tests.

($p < 0.001$). In addition to achieving significantly lower doses to the hippocampus, HSWBv2 reduced interplan variability, seen from the smaller standard deviations (Table 2).

PTV comparisons between HSWBv1 and HSWBv2 on Halcyon

For PTV_3000 on the Halcyon platform, $D_{98\%}$ and $D_{2\%}$ from HSWBv2 were 28.27 ± 0.33 Gy and 31.81 ± 0.12 Gy, respectively, compared to 28.08 ± 0.40 Gy ($p = 0.020$) and 32.66 ± 0.20 Gy from HSWBv1 ($p < 0.001$). The smaller difference between $D_{98\%}$ and $D_{2\%}$ represents improved plan homogeneity. This was further exemplified by a large difference in $V_{105\%}$, $6.44 \pm 2.56\%$ and $35.35 \pm 7.49\%$ from HSWBv2 and HSWBv1, respectively, indicating less heterogeneity (“hot” spots) than HSWBv1 (Table 2).

Total score comparisons and correlation analysis between hippocampus volume and hippocampus $D_{0.03CC}$, D_{mean} , and $D_{100\%}$

The average total score achieved by HSWBv2 and HSWBv1 were 132.97 ± 1.71 and 121.03 ± 3.48 , respectively ($p < 0.001$). No correlation was found between hippocampal volume (mean = 4.46CC; SD = 0.94CC) and $D_{0.03CC}$ ($p = 0.066$), D_{mean} ($p = 0.566$), and $D_{100\%}$ ($p = 1.000$).

HSWBv2 validation on Halcyon and TrueBeam

HSWBv2 exhibited superior dosimetry compared to HSWBv1 on the Halcyon platform and similar efficacies were seen on the TrueBeam platform. Using five separate validation cases, both Halcyon and TrueBeam plans created with HSWBv2 generally had improved hippocampal ($D_{0.03CC}$, D_{mean} , and $D_{100\%}$) and PTV_3000 ($D_{98\%}$, $D_{2\%}$, and $V_{105\%}$) metrics, with few exceptions. Nevertheless, HSWBv2 plans always earn higher total scores over HSWBv1. Higher scores result, in part, from increased homogeneity (PTV $V_{105\%}$) across all validated beam geometries (Table 3).

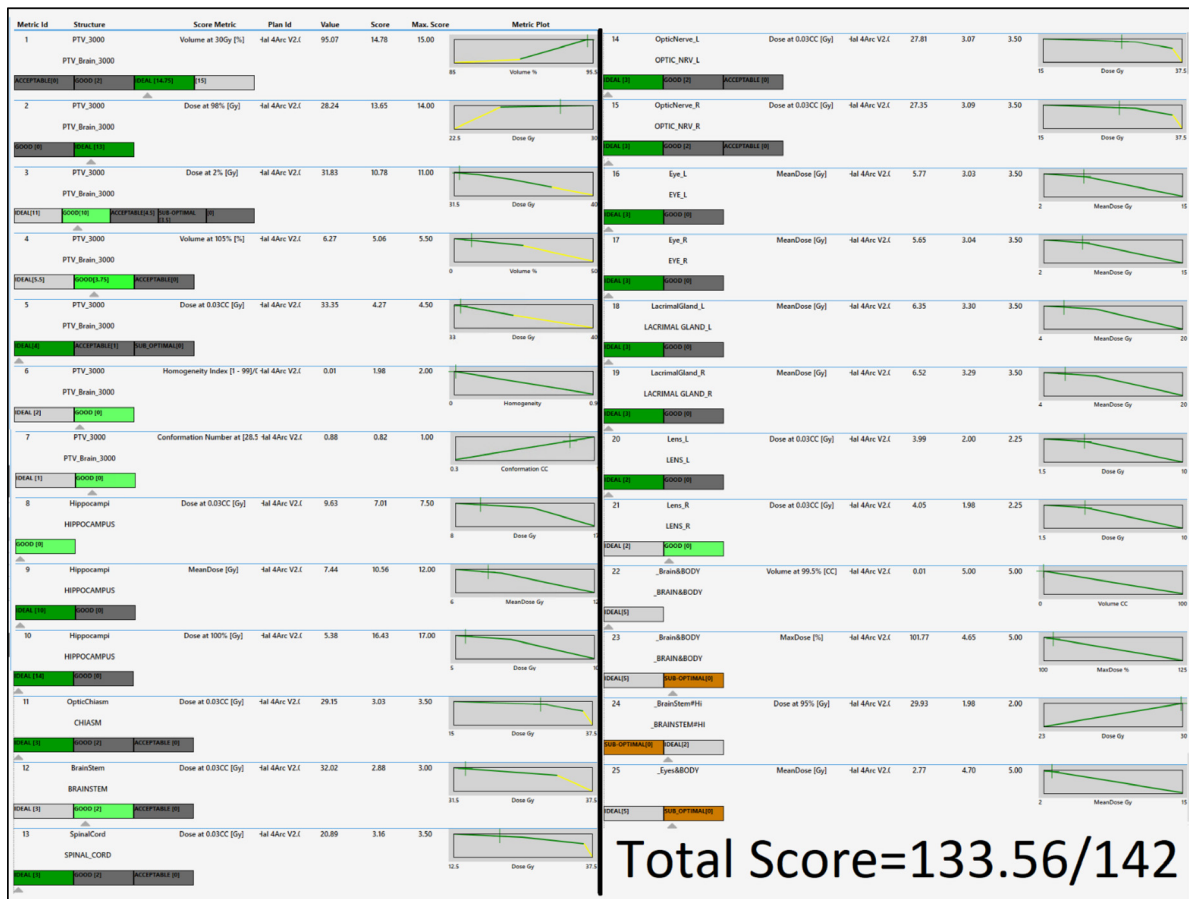


Fig. 2. Example Version 2.0 scorecard; validation case score 133.56/142.

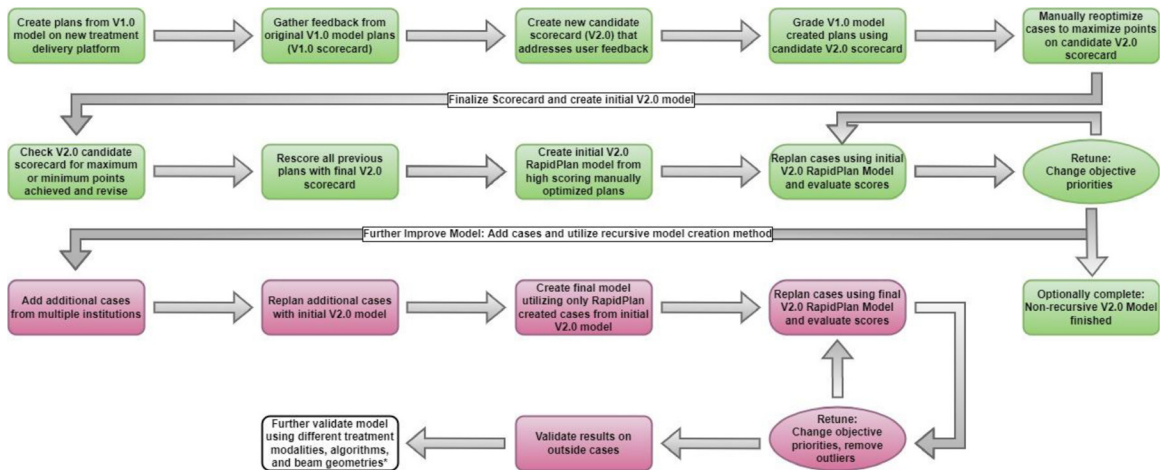


Fig. 3. Flowchart of HSWBv2 Model Creation, Training, and Validation.....

Discussion

KBP studies have been performed for multiple disease sites, such as prostate, lung, and head and neck.¹⁶ KBP methods have several advantages over manually optimized plans in radiotherapy. KBP can streamline the treatment planning process by standardizing plan quality, reducing human input, and decreasing time to perform treatment planning.¹⁶ For example, creating optimization objectives for a glioblastoma disease site took 2 minutes, accompanied by 5 additional minutes for optimization and dose calcula-

tion.¹⁶ Contrarily, it took 4 hours for a planner without KBP assistance to create a plan of similar quality.¹⁷ In a case of malignant pleural mesothelioma, planning time taken when utilizing KBP was 20 minutes vs 4 hours of manual optimization time.¹⁸

We developed a new KBP hippocampal avoidance whole brain radiation therapy treatment model (HSWBv2) with the goal of further reducing dose to the hippocampus, increasing dose homogeneity, and improving other dosimetric parameters. The version 2.0 scorecard added more robust scoring, resulting in a more complete evaluation of dosimetric plan quality. The revised scorecard

Table 3

The HSWBv2 model validation on Halcyon™ and TrueBeam™ using 5 cases (in addition to the 42 training cases)

Target/OAR	Mean (SD)					
	Halcyon™		TrueBeam™			
	4 Arcs (coplanar)	3 Arcs (coplanar)	HyperArc non-coplanar	4 Arcs non-coplanar	4 Arcs coplanar	3 Arcs coplanar
Hippocampus						
D _{100%} (Gy)	5.69 (0.19)	5.67 (0.26)	6.79 (0.11)	6.78 (0.12)	6.77 (0.15)	6.72 (0.07)
D _{mean} (Gy)	7.65 (0.20)	7.67 (0.22)	8.27 (0.13)	8.35 (0.15)	8.45 (0.17)	8.54 (0.19)
D _{0.03CC} (Gy)	10.12 (0.45)	10.13 (0.52)	10.90 (0.22)	11.06 (0.34)	11.04 (0.30)	11.16 (0.36)
Brain PTV						
D _{98%} (Gy)	28.39 (0.15)	28.39 (0.14)	28.23 (0.09)	28.11 (0.15)	27.86 (0.22)	27.88 (0.21)
D _{2%} (Gy)	31.72 (0.09)	31.87 (0.06)	31.73 (0.04)	31.78 (0.07)	31.94 (0.17)	31.99 (0.13)
V _{105%} (%)	4.74 (1.29)	8.73 (1.87)	6.10 (1.06)	6.89 (1.65)	10.24 (4.56)	12.18 (4.38)
HSWBv2 score (out of 142)	133.00 (0.34)	132.21 (0.57)	129.93 (0.48)	129.08 (0.73)	127.19 (1.34)	126.91 (1.06)
HSWBv1 score (out of 142)	120.49 (1.50)	119.56 (0.81)	120.36 (1.69)	120.05 (3.65)	114.11 (1.89)	114.12 (1.68)

Halcyon™ SX2MLC coplanar collimator: 315°, 0°, 45°, 90°. Truebeam™ M120MLC HyperArc: full 4 arc arrangement. Four arcs non-coplanar: 2 full arcs 0° couch, 2 180° arcs 90° couch. Three arcs coplanar collimator: 315°, 45°, 90° 4 arcs coplanar collimator same as 3 arcs except 90° split X jaw superior/inferior to hippocampus. All calculations: 6X-FFF, AcurosXB, convergence mode: extended MR3.

**Fig. 4.** 4 Arc Halcyon™ treatment plans made with single click, RapidPlan™. HSWBv1 (left) and HSWBv2 (right).

integrated feedback from 5 years of clinical use of HSWBv1. The new scorecard tool allows for metrics which automatically generate complex, dynamic structure expansion/contraction and Boolean operations. This automation expedited the creation of the additional derived structures (Fig. 1). These structures were evaluated on the scorecard and used for both optimization and dose volume histogram prediction. Using these derived structures, HSWBv2 enforced enhanced target conformation, homogeneity, and OAR sparing (Fig. 4).

Some previous studies only segmented a limited number of cranial structures which included hippocampus and 2 to 3 other OARs (*i.e.*, optic nerves and chiasm, lens).^{19–23} In comparison to published data, HSWBv2 achieved significantly lower hippocampus D_{mean}, D_{100%}, and D_{0.03CC} without compromising target coverage while also reducing hot spots substantially. Published series with a PTV prescription dose of ≥ 30 Gy generally achieved hippocampus D_{100%} of approximately 8 Gy, in contrast to 5.75 Gy in our study (Table 1). Though Levra *et al.* report a D_{100%} of 6.7 Gy, their study prescribed a PTV whole brain dose of 20Gy while including simultaneous integrated boost to targets greater than 30 Gy.¹⁹

HSWBv2 was tested on two Varian delivery platforms: Halcyon™ and TrueBeam™ of which TrueBeam™ is the most

popular Varian delivery platform. Halcyon utilizes advanced dual-layer MLC which enables high modulation due to faster leaf speed and lower transmission. HSWBv2 created high quality plans on both platforms without user interaction or plan modification (“single click”), allowing for the model to be readily usable in clinics. The advantage of single click optimization is that the planner is not tied to the process. The total time taken for optimization is dependent on the speed of treatment planning system hardware and software configuration (*i.e.*, convergence mode). For reference, HSWBv1 and HSWBv2 total optimization time on our system took 79 and 76 minutes, respectively. This HSWBv2 RapidPlan™ model is free to download to the community for all who can use such models.²⁴

HSWBv2 utilized statistical and machine learning methods available in RapidPlan™ software for selecting the training set cases. The recursive method generated a KBP model that produced narrow and accurate dose volume histogram prediction bands. These well-fit estimation bands allowed for more aggressive and improved OAR sparing.

Our HSWBv2 model contains more metrics/parameters/constraints than prior hippocampal avoidance whole brain radiation therapy treatment models. Preliminary

model validation with five independent cases resulted in similar dosimetric quality and plan scores compared to the testing completed on the training set cases. During development, HSWBv2 included up to 50 cases in its training set. Eight outliers were omitted due to either irregular patient head position or questionable geometric shape and/or volume of hippocampus contours. Although hippocampus volume are approximately 3.00 cc in normal adults,^{25–27} HSWBv2 training set cases averaged 4.46 cc and cases with hippocampus volume >7.50 cc were excluded.

The radiosensitive nature of the hippocampus further emphasizes the need to minimize hippocampus dose while maintaining dosimetric plan quality. In NRG-CC001, maximum doses of 14 Gy and 16 Gy were associated with a 10% and 25% risk of short-term memory deterioration at the 6-month mark.¹⁰ The hippocampus $D_{0.03CC}$ of 9.86 Gy and $D_{100\%}$ of 5.75 Gy achieved in our study are significantly lower than prior studies or current existing clinical guidelines. In conclusion, we demonstrated plan quality improvements by using KBP and dosimetric scorecard to guide the process. Further clinical studies are needed to determine the impact of additional hippocampal dose reduction and its correlation to neurocognitive function.

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Data Sharing Statement

Research data is stored in Varian repository and will be shared upon request to the corresponding author.

Conflict of Interest

Dr Sushil Beriwal has a leadership role as the Vice President of Medical Affairs at Varian Medical Systems, reports grant as an Elsevier consultant, and reports participation in advisory board at Xofig DSMB. Mr Ryan Clark reports employment at Varian Medical Systems. Mr Anthony Magliari reports employment at Varian Medical Systems. Dr Francisco Reynoso reports honoraria for lectures from Varian Medical Systems. Dr Heather Curry reports employment at Varian Medical Systems. Dr Patrick Kupelian reports employment at Varian Medical Systems. Dr Deepak Khuntia has a leadership role as the Senior Vice President and Chief Medical Officer at Varian Medical Systems. Mr Hefei Liu, Mr Robert Foster, Mr Matthew Schmidt, Dr Vinai Gondi, Dr Christopher Abraham have nothing to disclose.

References

- Lamba, N; Wen, PY; Aizer, AA Epidemiology of brain metastases and leptomeningeal disease. *Neuro Oncol* **23**:1447–56; 2021. doi:10.1093/neuonc/noab101.
- Khuntia, D; Brown, P; Li, J; Mehta, MP Whole-brain radiotherapy in the management of brain metastasis. *J Clin Oncol Off J Am Soc Clin Oncol* **24**:1295–304; 2006. doi:10.1200/JCO.2005.04.6185.
- Barnholtz-Sloan, JS; Sloan, AE; Davis, FG; Vignneau, FD; Lai, P; Sawaya, RE Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* **22**:2865–72; 2004. doi:10.1200/JCO.2004.12.149.
- Schouten, LJ; Rutten, J; Huvneers, HAM; Twijnstra, A Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* **94**:2698–705; 2002. doi:10.1002/cncr.10541.
- Brown, PD; Ahluwalia, MS; Khan, OH; Asher, AL; Wefel, JS; Gondi, V Whole-brain radiotherapy for brain metastases: Evolution or revolution? *J Clin Oncol* **36**:483–91; 2018. doi:10.1200/JCO.2017.75.9589.
- Anand, K; Dhikav, V Hippocampus in health and disease: An overview. *Ann Indian Acad Neurol* **15**:239–46; 2012. doi:10.4103/0972-2327.104323.
- Brown, PD; Gondi, V; Pugh, S; et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: Phase III Trial NRG Oncology CC001. *J Clin Oncol* **38**:1019–29; 2020.
- Monje, ML; Mizumatsu, S; Fike, JR; Palmer, TD Irradiation induces neural precursor-cell dysfunction. *Nat Med* **8**:955–62; 2002. doi:10.1038/nm749.
- Gondi, V; Hermann, BP; Mehta, MP; Tomé, WA. 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**:345–54; 2013. doi:10.1016/j.ijrobp.2012.11.031.
- Redmond, KJ; Grimm, J; Robinson, C; et al. steep dose-response relationship between maximum hippocampal dose and memory deficits following hippocampal avoidance whole brain radiation therapy (HA-WBRT) for brain metastases: A secondary analysis of NRG/RTOG 0933. *Int J Radiat Oncol* **108**:S176; 2020. doi:10.1016/j.ijrobp.2020.07.956.
- 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**:3810–16; 2014. doi:10.1200/JCO.2014.57.2909.
- Martinge, G; Hong, AM; Fay, M; et al. Quality assurance analysis of hippocampal avoidance in a melanoma whole brain radiotherapy randomized trial shows good compliance. *Radiat Oncol* **13**:132; 2018. doi:10.1186/s13014-018-1077-z.
- Nelms, BE; Robinson, G; Markham, J; et al. Variation in external beam treatment plan quality: An inter-institutional study of planners and planning systems. *Pract Radiat Oncol* **2**:296–305; 2012. doi:10.1016/j.prro.2011.11.012.
- Magliari, V; Magliari, A; Foster, R hippocampal sparing whole brain: Rapid Plan Model Following the NRG-CC001 Protocol. *AAMD Conf Poster Present 2017*. Published online Available at: <http://conference.medicaldosimetry.org/2017AnnualConference/assets/File/posters/Poster22.pdf>.
- Rusu, I; Roeske, J; Solanki, A; Kang, H Fully automated planning and delivery of hippocampal-sparing whole brain irradiation. *Med Dosim*:1–6 2021. doi:10.1016/j.meddos.2021.06.004.
- Momin, S; Fu, Y; Lei, Y; et al. Knowledge-based radiation treatment planning: A data-driven method survey. *J Appl Clin Med Phys* **22**:16–44; 2021. doi:10.1002/acm2.13337.
- Chatterjee, A; Serban, M; Abdulkarim, B; et al. Performance of knowledge-based radiation therapy planning for the glioblastoma disease site. *Int J Radiat Oncol Biol Phys* **99**:1021–8; 2017. doi:10.1016/j.ijrobp.2017.07.012.
- Dumane, VA; Tam, J; Lo, Y-C; Rosenzweig, KE RapidPlan for knowledge-based planning of malignant pleural mesothelioma. *Pract Radiat Oncol* **11**:e219–28; 2021. doi:10.1016/j.prro.2020.06.003.
- Giaj Levra, N; Sicignano, G; Fiorentino, A; et al. Whole brain radiotherapy with hippocampal avoidance and simultaneous integrated boost for brain metastases: a dosimetric volumetric-modulated arc therapy study. *Radiol Medica* **121**:60–9; 2016. doi:10.1007/s11547-015-0563-8.
- Zieminski, S; Khandekar, M; Wang, Y Assessment of multi-criteria optimization (MCO) for volumetric modulated arc therapy (VMAT) in hippocampal avoidance whole brain radiation therapy (HA-WBRT). *J Appl Clin Med Phys* **19**:184–90; 2018. doi:10.1002/acm2.12277.
- Kazda, T; Vrzal, M; Prochazka, T; et al. Left hippocampus sparing whole brain radiotherapy (WBRT): A planning study. *Biomed Pap* **161**:397–402; 2017. doi:10.5507/bp.2017.031.
- Yuen, AHL; Wu, PM; Li, AKL; Mak, PCY Volumetric modulated arc therapy (VMAT) for hippocampal-avoidance whole brain radiation therapy: planning comparison with Dual-arc and Split-arc partial-field techniques. *Radiat Oncol* **15**:42; 2020. doi:10.1186/s13014-020-01488-5.
- Nevelsky, A; Ieumwananonthachai, N; Kaidar-Person, O; et al. Hippocampal-sparing whole-brain radiotherapy using Elekta equipment. *J Appl Clin Med Phys* **14**:4205; 2013. doi:10.1120/jacmp.v14i3.4205.
- Varian. *Whole brain with hippocampal sparing (NRG-CC001) [RapidPlan]*; 2022. Available at: <http://medicalaffairs.varian.com/wholebrain-hippocampalsparing-vmat2> Accessed March 2, 2022.
- Honeycutt, NA; Smith, CD Hippocampal volume measurements using magnetic resonance imaging in normal young adults. *J Neuroimaging* **5**:95–100; 1995. doi:10.1111/jon.1955295.
- Embong, MF; Yaacob, R; Abdullah, MS; Abdul Karim, AH; Ghazali, AK; Jalaluddin, WMS MR volumetry of hippocampus in normal adult malay of age 50 years old and above. *Malays J Med Sci* **20**:25–31; 2013. Available at: <https://pubmed.ncbi.nlm.nih.gov/24043993>.
- Nobis, L; Manohar, SG; Smith, SM; et al. Hippocampal volume across age: Nomograms derived from over 19,700 people in UK Biobank. *NeuroImage Clin* **23**:101904; 2019. doi:10.1016/j.nicl.2019.101904.
- Okada, H; Ito, M; Minami, Y; et al. Automatic one-click planning for hippocampal-avoidance whole-brain irradiation in RayStation. *Med Dosim Off J Am Assoc Med Dosim* **47**:98–102; 2022. doi:10.1016/j.meddos.2021.09.003.