

# Comparison of Volumetric Modulated Arc Therapy and Intensity Modulated Radiation Therapy for Whole Brain Hippocampal Sparing Treatment Plans Based on Radiobiological Modeling

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## Abstract

**Introduction:** In this article, we report the results of our investigation on comparison of radiobiological aspects of treatment plans with linear accelerator-based intensity-modulated radiation therapy and volumetric-modulated arc therapy for patients having hippocampal avoidance whole-brain radiation therapy. **Materials and Methods:** In this retrospective study using the dose-volume histogram, we calculated and compared biophysical indices of equivalent uniform dose, tumor control probability, and normal tissue complication probability (NTCP) for 15 whole-brain radiotherapy patients. **Results and Discussions:** Dose-response models for tumors and critical structures were separated into two groups: mechanistic and empirical. Mechanistic models formulate mathematically with describable relationships while empirical models fit data through empirical observations to appropriately determine parameters giving results agreeable to those given by mechanistic models. **Conclusions:** Techniques applied in this manuscript could be applied to any other organs or types of cancer to evaluate treatment plans based on radiobiological modeling.

**Keywords:** Hippocampal sparing treatment, radiobiological modeling, VMAT versus IMRT

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## INTRODUCTION

Brain metastases are the most common intracranial tumors in adults and occur in 10%–30% of cancer patients.<sup>[1]</sup> One of the treatment options for patients with multiple brain metastases is whole-brain radiation therapy (WBRT) which can be combined with radiosensitizers such as motexafin gadolinium, efaproxiral, and temozolomide.<sup>[1]</sup> Neurological decline may occur in a patient with WBRT treatment causing cerebral edema in the patient within the first few weeks of treatment, symptoms of which include headaches, somnolence, vomiting, nausea, and inability to focus.<sup>[2]</sup> One to six months after WBRT, subacute encephalopathy may occur, which increases patient headaches, somnolence, and fatigue. Six months after WBRT, patients may experience severe dementia and memory loss. Irradiating hippocampi is thought to be a factor in WBRT-associated cognitive decline because the hippocampi are essential in learning, retrieval of information, and the formation of new memories. One of the ways to reduce

cognitive decline is to avoid irradiating the hippocampus when performing WBRT in a process called hippocampal-avoidance WBRT (HA-WBRT).<sup>[2]</sup> It is possible to create WBRT treatment plans that spare hippocampi with equivalent dose distributions to conventional WBRT treatment plans. The most common delivery techniques for HA-WBRT are intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT). VMAT is a subset of IMRT where radiation is delivered in an arc instead of at static angles.

The most common biological metrics used to guide clinical predictions are tumor control probability (TCP) and normal

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tissue complication probability (NTCP). TCP is the probability of localized tumor control for a given dose distribution, while NTCP is the probability of an undesirable effect from an organ due to radiation. A challenge of radiation therapy is to find a balance of these values to give each patient the optimal treatment by raising TCP as high as possible, while lowering NTCPs as low as possible. Dose-response models for tumors and critical structures are separated into two groups: mechanistic and empirical. Mechanistic models formulate mathematically with describable relationships while empirical models fit data through empirical observations. We may not be able to accurately formulate some biological processes because of their complexity to make mechanistic models, but this is not a challenge for empirical models which simply need to fit data.<sup>[3]</sup> Dose-volume histogram (DVH) shows how much dose is being received by a structure. It can be used to view physical parameters such as minimum, mean, and maximum dose to calculate TCP and NTCP. Because of limited information in the setting of HA-WBRT, the purpose of our study was to calculate and compare target doses, normal tissue doses, TCP, and NTCP values for treatment plans utilizing IMRT- or VMAT-based on HA-WBRT.

## MATERIALS AND METHODS

Treatment planning for 15 patients was carried out with Varian Eclipse treatment planning system using 3-arc VMAT (Rapid Arc) and 9-field step-and-shoot (S and S) IMRT, both calculated with Anisotropic Analytical Algorithm. From this point in our manuscript, whenever we refer to IMRT, we are referring to S and S IMRT. The planning target volume (PTV) was defined as the whole-brain excluding a uniform three-dimensional 5-mm expansion around the hippocampus. Prescribed doses in all plans were 30 Gy delivered over 10 fractions normalized to a minimum of 95% of the target volume receiving 100% of the prescribed dose. Simultaneous integrated boost or stereotactic boost was not utilized for any of the treatment plans. The radiation therapy oncology group (RTOG) trial 0933 study criteria<sup>[4]</sup> were followed for contouring and dose-volume constraints. Bilateral hippocampal contours were made on imaging datasets consisting of thin-slice spoiled gradient echo (SPGR) magnetic resonance imaging sequences fused to a treatment planning computed tomography (CT) scan. The PTV was defined as the whole-brain parenchyma excluding the bilateral hippocampal contours plus a 5-mm margin. The variation acceptable criteria for the protocol were used. In brief, these included PTV D2%  $\leq 40$  Gy and D98%  $\geq 25$  Gy. The hippocampal constraints included a D100%  $\leq 10$  Gy and a maximum hippocampal dose of  $\leq 17$  Gy. All treatment plans used identical contour sets and a single radiation oncologist reviewed and evaluated all treatment plans. Calculations of statistical significance were performed using Student's paired *t*-test to compare VMAT and IMRT plans. Treatment plans were evaluated based on tumor dose fall off, amount of dose received by normal brain tissue, and critical structures as well as the radiobiological comparison which was the purpose of

this manuscript. This study was reviewed by our institutional IRB before initiation.

## Equivalent uniform dose

While we strive to give tumors a homogenous dose in radiation therapy, in reality, they are inhomogeneous. To be able to better compare dose distributions, the concept of the equivalent uniform dose (EUD) was conceived. The EUD is the dose, which when homogeneously given to a tumor gives, on average, the same number of surviving clonogens as a real clinical dose distribution gives. This opens a numerical way to be able to compare treatment plans from the DVH. Niemierko<sup>[5]</sup> defined the EUD mechanistically as follows:

$$EUD = \frac{N_f}{D_{ref}} \left( -\frac{\alpha}{\beta} + \sqrt{\left(\frac{\alpha}{\beta}\right)^2 + 4 \frac{D_{ref}}{N_f} \left(\frac{\alpha}{\beta} + D_{ref}\right) \frac{\ln A}{\ln SF_2}} \right) \quad (1)$$

where

$$A = \frac{\sum_{i=1}^n v_i * p_i * SF_2^{\frac{D_i}{D_{ref}} \left(\frac{\alpha}{\beta} + \frac{D_i}{N_f}\right)}}{\sum_{i=1}^n v_i * p_i}$$

In this formulation,  $N_f$  is the number of fractions in the treatment,  $D_{ref}$  is the reference dose of 2 Gy, the  $\alpha/\beta$  is the ratio of two radio-sensitivity parameters found in the linear quadratic model explaining the linear and quadratic parts of cell killing,  $SF_2$  is the clonogenic cell survival fraction at a dose of 2 Gy,  $D_i$  is the dose being received by each partial volume segment, and  $v_i$  and  $p_i$  are, respectively, the local volumes and densities of clonogens.

We calculated EUDs for the IMRT and VMAT treatment plans using the formula shown in equation 1. When calculating the EUDs, we varied the values of  $SF_2$  as 0.4, 0.5, and 0.6 while varying the values of the  $\alpha/\beta$  ratio to 2, 6, and 10 for each value of  $SF_2$  to determine appropriate model parameters for the future studies. Our value for  $N_f$  was 10 and the value for  $D_{ref}$  was 2 Gy. The DVH was divided into 10 partial volume segments each covering 10% of the structure volume.  $D_i$  was taken to be an average of the doses being received by the highest and lowest partial volumes. For example, when calculating the dose for the partial volume segment which spans 80% to 90% of the structure volume, we took  $D_i$  to be the average of the dose covering 80% of the structure volume and the dose covering 90% of the structure volume.

Niemierko<sup>[6,7]</sup> also came up with the concept of a generalized EUD (gEUD) with an empirical formula:

$$gEUD = \left( \sum_{i=1}^n (v_i D_i^a) \right)^{\frac{1}{a}} \quad (2)$$

where  $v_i$  is the fractional volume irradiated to a dose  $D_i$  and "a" is a unitless tissue-specific parameter that describes the dose-volume effect. As the value of "a" becomes a large negative number, the gEUD leans toward the minimum dose

received by the tissue. When “a = 1,” the gEUD is equal to the average dose. As the value of “a” becomes a large positive number, the value of the gEUD leans toward the maximum dose. For tissues which experience serial organ complication, the value of “a” should be a large positive number, for tissues that experience parallel organ complication, the value of “a” should be around 1, and for tumors, the value of “a” should be a large negative number. We also calculated gEUDs using formula shown in equation 2.  $D_i$ 's were reused from our previous EUD calculation. Because the DVH was divided into 10 equal segments,  $v_i$  was kept constant at 0.10. While calculating gEUDs for PTV, we varied our fitting parameter “a” to integers from -1 to -16. For calculating gEUDs for normal tissues, we used fitting parameter “a” equals +7.

### Tumor control probability

The TCP is a quantitative measurement of local tumor control which can be calculated from information obtained from a DVH. While values of TCP calculated from formulas may not be the reflection of reality, the relative values calculated for different DVHs are useful. TCPs are calculated<sup>[8]</sup> with the following mechanistic formula:

$$TCP = e^{-N * SF_2 \frac{\frac{D}{D_{ref}} \frac{\alpha + D}{\beta}}{\frac{\alpha + D_{ref}}{\beta}}} \quad (3)$$

where N is the number of clonogenic tumor cells (assumed in this study to be 4000, 40000, 400000, and 800000), D is EUD,  $N_p$ ,  $D_{ref}$ ,  $SF_2$ , and  $\alpha/\beta$  are terms explained before. Radiation therapy is traditionally given in many fractions. This is because delivering the dose over time allows killing of maximum clonogenic tumor cells while having the least toxic effect on normal tissues. We calculated TCPs for each combination of N,  $SF_2$ , and  $\alpha/\beta$  ratio using the formula shown in equation 3.

Another common way to calculate TCP is with the following empirical formula<sup>[7]</sup> shown in equation 4.

$$TCP = \frac{1}{1 + \left( \frac{TCD_{50}}{gEUD} \right)^{4\gamma_{50}}} \quad (4)$$

where  $TCD_{50}$  is the dose to control the tumor 50% of the time when the tumor is irradiated homogeneously, gEUD is the gEUD calculated with formula shown in equation 2, and is a unitless fitting parameter that determines the slope of the dose-response curve. We also calculated values of TCP using the formula shown in equation 4. We varied the value of parameter “a” in equation 2 from -1 to -16 to get values of gEUD. We used a  $TCD_{50}$  value<sup>[9]</sup> of 22.17 Gy and varied  $\gamma_{50}$  to determine value of TCP that agreed the best with our mechanistic model prediction.

### Normal tissue complication probability

The NTCP is a quantitative measurement of the probability a dose of radiation will have an undesirable effect on an organ. The following mechanistic formula<sup>[10]</sup> is used to calculate the NTCP as shown in equation 5.

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{t^2}{2}} dt \quad (5)$$

where

$$t = \frac{D - TD_{50}(\vartheta)}{m * TD_{50}(\vartheta)} \quad \vartheta = \frac{v}{v_{ref}} \quad TD(\vartheta) = TD(1) \vartheta^{-n}$$

$\vartheta$  is the fraction of the organ irradiated,  $V_{ref}$  is the reference volume for  $TD_{50}$ ,  $TD_{50}$  is the tolerance dose to the reference volume which would lead to a 50% complication probability, n is a parameter which determines the volume dependence of the complication probability, and m is a parameter which determines the slope of the complication probability versus the dose curve. Dose-response models are commonly based on linear-quadratic model of cell killing which has two adjustable parameters:  $\alpha$  (linear component of cell killing) and  $\beta$  (the quadratic component of cell killing). The  $\alpha/\beta$  ratio is the dose at which the linear and quadratic components of cell killing have equal contributions.<sup>[11]</sup> The isoeffective dose is a method to account for the effect of fractionations in radiation therapy treatment that takes into account the behavior of early and late-responding tissues. This is calculated with the following formula<sup>[12]</sup> shown in equation 6 relative to a standard 2 Gy per fractionation scheme usually used in conventional fractionated radiation therapy.

$$EQD_2 = \frac{1 + \frac{D_f}{\alpha / \beta}}{1 + \frac{2}{\alpha / \beta}} \quad (6)$$

where  $D_f$  (=3 Gy) has been the fractionated dose used in the present treatment.

We compared the tissue-sparing capabilities of IMRT and VMAT by calculating the NTCPs for various tissues that included among others hippocampus, optical structures, etc., from each of the corresponding treatment plans. We calculated NTCPs using the formula shown in equation 5. Microsoft Excel's normal distribution function was used to calculate NTCPs once t-values were calculated with the formula shown in equation 5. Conventional fractionated radiation therapy usually uses doses of approximately 2 Gy/fraction and so typical value of the parameters  $TD_{50}$  used to calculate t-values are available in the literature<sup>[13]</sup> for 2 Gy/fraction schemes. However, we used 3 Gy/fraction for treatment in the present study. Using the isoeffective dose value of 1.25 as shown in equation 6,  $TD_{50}$  values<sup>[13]</sup> of brain (since the  $TD_{50}$  value of hippocampus is not known) and optical structures of 60 and 65 are modified and values of the parameters  $TD_{50}$ , m, and n used to calculate t-values are given in Table 1.

Another common method of calculating the NTCP for various tissues is through the following empirical formula<sup>[9]</sup> shown in equation 7.

$$NTCP = \frac{1}{1 + \left( \frac{TD_{50}}{gEUD} \right)^{4\gamma_{50}}} \quad (7)$$

**Table 1:  $TD_{50}$ ,  $m$ , and  $n$  values used to calculate normal tissue complication probability for each critical structure**

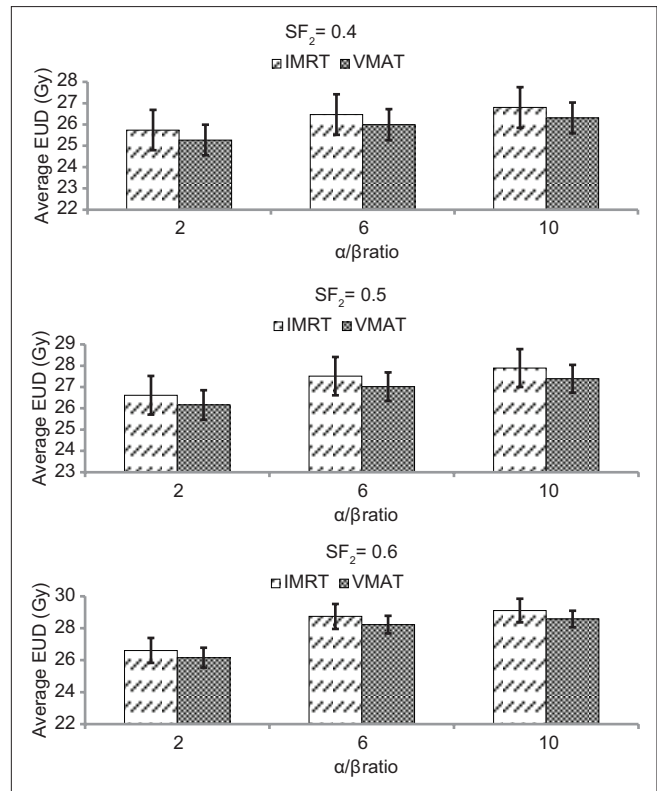
	Hippocampus	Optic chiasm	Right optic nerve	Left optic nerve
$TD_{50}$	48	52	52	52
$m$	0.15	0.14	0.14	0.14
$n$	0.25	0.25	0.25	0.25

where  $TD_{50}$  is the tolerance dose that gives a 50% complication rate, gEUD, and  $\gamma_{50}$  are parameters previously explained. We also calculated NTCPs using the above formula. Modified  $TD_{50}$  values shown in Table 1 were used along with a constant  $\gamma_{50}$  value of 3.<sup>[14]</sup> Secondary to limitations on the availability of hippocampus-specific parameter estimates, the same calculation end point of necrosis that was used for the brain and optic structures were also used for the hippocampus.

## RESULTS

All VMAT and IMRT treatment plans met the RTOG trial 0933 criteria. The average EUDs calculated using equation 1 with  $SF_2$  of 0.4, 0.5, and 0.6 and  $\alpha/\beta$  ratios of 2, 6, and 10 for IMRT and VMAT treatment plans ranged from 25.74–29.11 Gy for IMRT to 25.27–28.58 Gy for VMAT treatment plans. In all cases, the average EUD for IMRT was greater than that of VMAT by about 2% ( $P \leq 0.02$ ) as shown in Figure 1. In general, the average EUD increased with the  $\alpha/\beta$  ratio and the  $SF_2$  for both IMRT and VMAT. Examples of typical EUD (with  $SF_2 = 0.5$  and  $\alpha/\beta = 2$ ) and gEUD (with  $a = -11$ ) for the PTV for each patient are shown in Figure 2. The average EUD and gEUD for IMRT was again greater by 2% compared to that for VMAT. Furthermore, we found that the calculated gEUDs of the PTV using equation 2 decreased when the fitting parameter, “a,” decreased and the average gEUD was 2% higher in IMRT treatment plans than that of VMAT treatment plans when  $-16 \leq a \leq -2$ , and 3% when “a” = -1. In all cases, the difference between average IMRT and VMAT gEUDs were statistically significant ( $P \leq 0.02$ ).

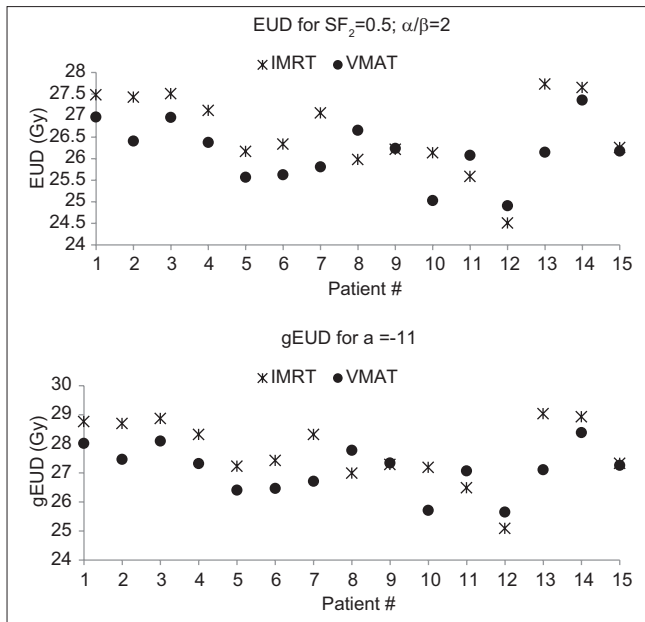
The TCPs for both IMRT and VMAT treatment plans were calculated using equation 3 with various  $SF_2$ ,  $\alpha/\beta$ , and estimated clonogenic cell counts. Figure 3 shows results of a typical TCP calculation with  $SF_2$  of 0.5,  $\alpha/\beta$  ratio of 2, and clonogenic cell counts estimated with CCD of 500 using formula 4. The ratio of average IMRT TCPs to average VMAT TCPs were also found to increase with the increase of  $SF_2$ ,  $\alpha/\beta$  ratio, and CCD values. We varied the value of  $\gamma_{50}$  in equation 4 and found that the TCP values were most agreeable with results obtained using the formula in equation 3 when  $\gamma_{50} = 3.6$ . Using equation 4, it was also found that the ratio of average IMRT TCPs over average VMAT TCPs varied from 1.00 to 1.03, as we varied the parameter “a” from -1 to -16. Figure 3 also shows a typical TCP calculation with “a” equals -11,  $\gamma_{50} = 3.6$  and  $TCD_{50} = 22.17$ . Our results show that on the basis of TCP calculations, IMRT performed 2% better than VMAT using equation 3, and 1% better using



**Figure 1:** Average equivalent uniform dose for various  $SF_2$  and  $\alpha/\beta$  values for intensity-modulated radiation therapy and volumetric-modulated arc therapy treatment plans. Standard deviation is shown by error bars. All  $P \leq 0.02$

equation 4; which again indicated better tumor control in favor of IMRT.

With the mechanistic formula shown in equation 5, NTCPs were calculated for hippocampus, optic chiasm, right optic nerves, and left optic nerves. Specifically, IMRT lowered the NTCP of optic chiasm by a factor of two, right and left optic nerves by a factor of twenty-five but raised the NTCP of hippocampus by a factor of thirty. Figure 4 contains the average gEUDs of critical structures for IMRT and VMAT treatment plans calculated with the formula shown in equation 2. The hippocampus in IMRT treatment plans had a higher gEUD than that of VMAT treatment plans ( $P = 0.19$ ); however, the opposite was true for all the three optical structures ( $P < 0.01$ ) which supports the previous trend obtained using the mechanistic formula. The average NTCPs calculated from gEUDs using equation 7 were greater for IMRT compared to VMAT for the hippocampus by about 27% ( $P = 0.13$ ). The opposite was true for the optical structures, where the NTCPs calculated were lower for IMRT compared to VMAT by about 27% for optic chiasm, 62% for right optic nerve and 56% for left optic nerve ( $P < 0.01$ ). The NTCP values per patient are shown in Figure 5. Figure 6 gives representative examples of dose shown in color-wash superimposed on an axial slice from the treatment planning CT set for both IMRT and VMAT.

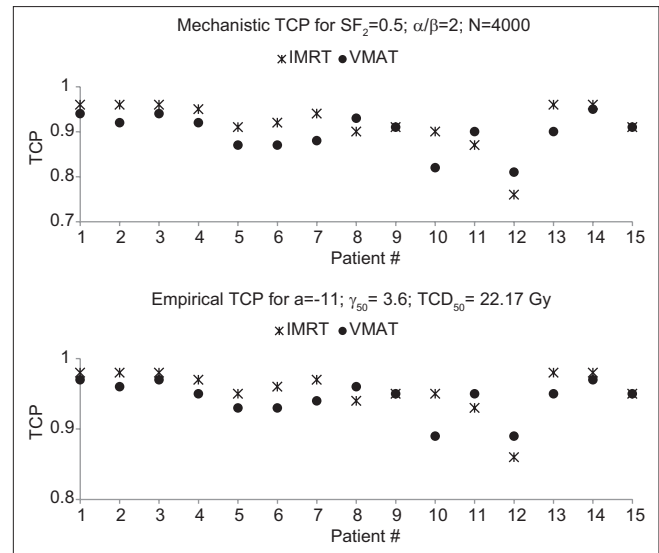


**Figure 2:** Comparison of intensity-modulated radiation therapy and volumetric-modulated arc therapy treatment plans using formulas for equivalent uniform dose and generalized equivalent uniform dose (generalized equivalent uniform dose). The average equivalent uniform dose for intensity-modulated radiation therapy versus volumetric-modulated arc therapy were 26.61 versus 26.16 and the average generalized equivalent uniform dose was 27.73 versus 27.12, respectively, with  $P \leq 0.02$ . For both the equivalent uniform dose and the generalized equivalent uniform dose, the ratio of intensity-modulated radiation therapy/volumetric-modulated arc therapy was 1.02

## DISCUSSION

In this manuscript, we estimate TCP, NTCP, and EUD values for IMRT- and VMAT-based treatment planning for hippocampal sparing WBRT. Our analysis suggests that both of these treatment approaches have their advantages. On the basis of TCP calculations, IMRT performed 2% better than VMAT using equation 3 and 1% better using equation 4. Both of these results indicate improved TCP in favor of IMRT-based treatments. Similarly, IMRT-based treatment plans resulted in lower NTCP values for the optic chiasm and optic nerves while higher NTCP parameters were obtained for the hippocampus. These results are consistent with reports suggesting VMAT may be better at sparing the hippocampus while meeting the treatment goals for the PTV.<sup>[15,16]</sup> Even though the relative difference in NTCP was large, the values for the NTCP's were so small that any rational statement based on this comparison is difficult to make.

In this manuscript, the parameters for empirical TCP and NTCP models were derived by fitting our data to mechanistic models. Values for our mechanistic models were taken from values in literature derived from clinical outcomes and tuned to derive optimal results. While these fitting parameters are not the most optimal, we feel they are appropriate for use. TCP calculations have been utilized for the treatment of brain tumors, both in the setting of stereotactic radiation therapy as well as with

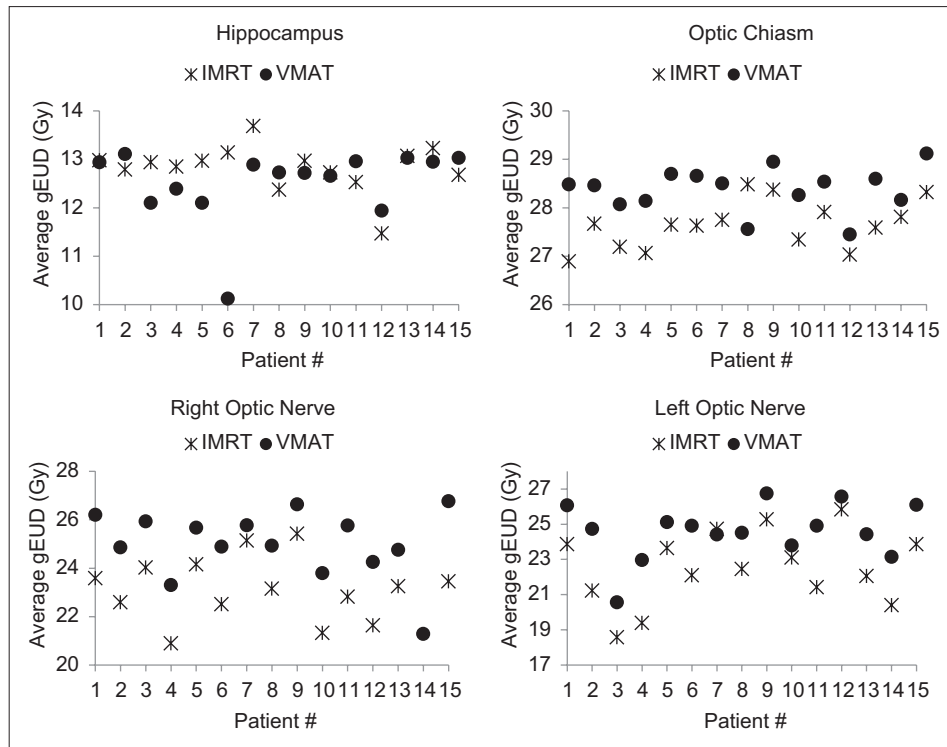


**Figure 3:** Comparison of tumor control probability values of intensity-modulated radiation therapy and volumetric-modulated arc therapy treatment plans. The average mechanistic tumor control probability was 0.92 for intensity-modulated radiation therapy and 0.90 for volumetric-modulated arc therapy, with an average ratio of intensity-modulated radiation therapy/volumetric-modulated arc therapy of 1.02. For the empirical tumor control probability, these values were 0.95 for intensity-modulated radiation therapy and 0.94 for volumetric-modulated arc therapy, respectively, with an average intensity-modulated radiation therapy/volumetric-modulated arc therapy ratio of 1.01

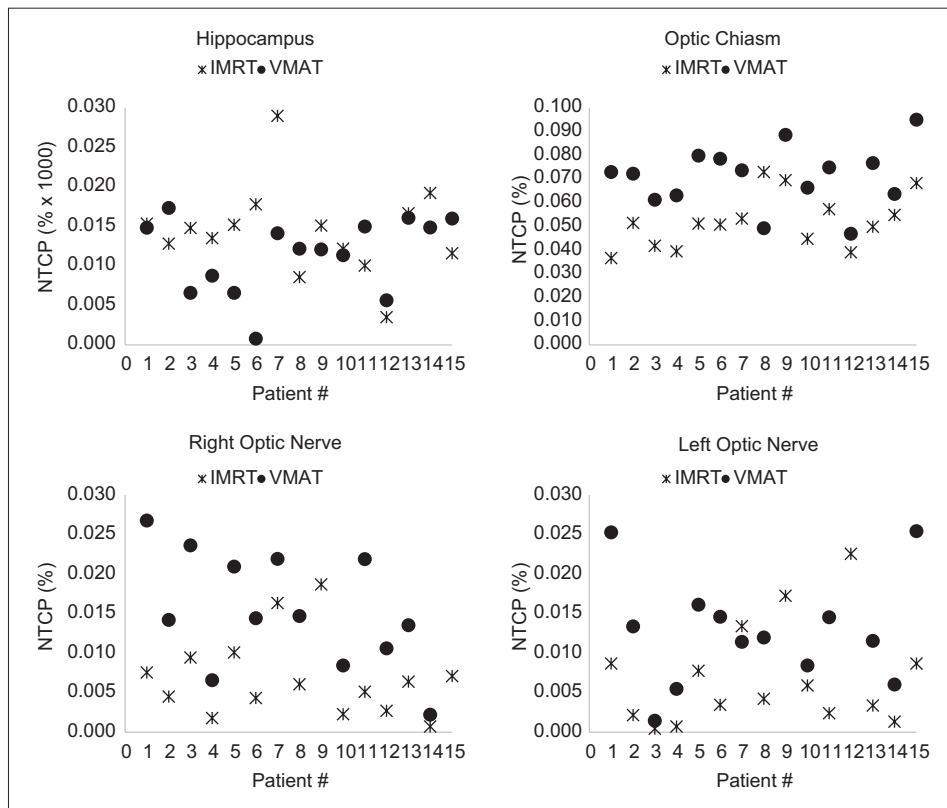
standard fractionation radiation therapy.<sup>[17-19]</sup> The parameters used in our model are consistent with what has been used in these reports. However, there is little information specific to the setting of HA-WBRT with IMRT or VMAT, where the overall dose distribution is more heterogeneous, and our results represent best estimates for this setting. In particular, little information specific to the hippocampus is available. For our NTCP calculations, we used similar parameters for the brain and the hippocampus, while the potential toxicity, as well as the dose at which the toxicity occurs, is very different, both clinically and mechanistically. The toxicity of interest for the hippocampus is the development of neurocognitive function decline which is likely to occur at lower doses than what would be expected for brain necrosis and further studies are necessary to establish TD<sub>5/5</sub> and TD<sub>50/5</sub> estimates that are specific for the hippocampus.

## CONCLUSIONS

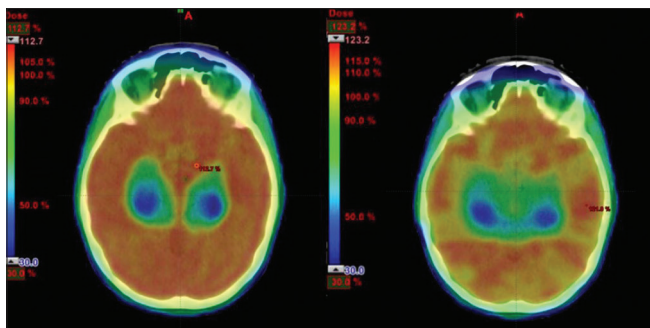
HA-WBRT is an effective treatment to the brain with its goal being to provide adequate coverage of the brain parenchyma while reducing the radiation doses to the hippocampus. The linac-based IMRT or VMAT are potential techniques to reduce doses to the hippocampus while treating the brain parenchyma. We found that IMRT treatment plans had a higher TCP than VMAT treatment plans and also had a lower NTCP for the optical structures. For the hippocampus, when the end point for the calculation was necrosis, IMRT plans had higher NTCP values when compared to VMAT treatment



**Figure 4:** Generalized equivalent uniform doses of critical structures using parameter “a” = +7, for intensity-modulated radiation therapy and volumetric-modulated arc therapy treatment plans. The average generalized equivalent uniform dose in Gy for intensity-modulated radiation therapy versus volumetric-modulated arc therapy for the hippocampus, optic chiasm, right optic nerve, and left optic nerve were, respectively, (12.83 vs. 12.51), (27.64 vs. 28.38), (22.89 vs. 24.98), and (22.52 vs. 24.59)



**Figure 5:** Comparison of normal tissue complication probability values for intensity-modulated radiation therapy and volumetric-modulated arc therapy treatment plans for the hippocampus, optic chiasm, right optic nerve, and left optic nerve



**Figure 6:** Comparison of typical dose distribution for a patient planned with hippocampal avoidance whole-brain radiation therapy-volumetric-modulated arc therapy (left) and intensity-modulated radiation therapy (right) superimposed on axial slice of planning computed tomography. The volumetric-modulated arc therapy plan has a lower maximum dose than that of the intensity-modulated radiation therapy treatment plan

plans. In this study, we have also found appropriate fitting parameters that can be used in empirical models for EUD, TCP, and NTCP. The concept of isoeffective dose to estimate TD50 for hippocampus and optical structures with 3 Gy per fraction used in this study could be applied to any radiation therapy study for other organs and cancers utilizing different fractionation scheme.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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