Hippocampal Avoidance in Multi-Target Radiosurgery

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Department of
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ABSTRACT

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Abstract

Purpose

Brain metastases are a common complication for cancer patients. Single isocenter multi-target (SIMT) radiosurgery planned with volumetric modulated arc therapy (VMAT) is a method of treating multiple brain metastases simultaneously. These treatments deliver high doses which emphasizes the need for accuracy and avoidance of critical neurological structures to maintaining a patient's quality of life (QOL). QOL is highly correlated to patient memory, suggesting the hippocampus as a critical structure to avoid in treatment due to its significant role in episodic memory development. Radiosurgery treatments commonly use specialized MLC leaves (HD) that have a narrower width to improve dose conformity around metastases. This work serves to evaluate the feasibility of hippocampal avoidance (HA) in SIMT treatments planned with VMAT. Additionally, this work evaluates the effects of MLC leaf width on both HA and plan quality.

Methods

40 patients, each previously treated with SIMT planned with VMAT for between 4-10 brain metastases using HD-MLCs, enrolled in an IRB approved protocol. The plans were evaluated for meeting RTOG 0933 recommended dose constraints to the hippocampus. If constraints were not met, then treatments were replanned with

optimization objectives added to the hippocampus and/or arc orientation adjustments to meet constraints without compromising target coverage or other organ-at-risk (OAR) dose constraints. Afterwards, the treatments both with and without hippocampal objectives were replanned using standard width MLC leaves (SD-MLCs). All 4 plan types were then evaluated for plan quality using conformity index, V20%[cc], V50%[cc], V75%[cc] and D50%[cGy].

Results

8 total hippocampi across 7 patient plans exceeded constraints. 4 of these hippocampi could be spared through optimization objective adjustment, and 1 more with an arc orientation adjustment. Biological effective dose (BED) to the 8 hippocampi decreased by 29% ± 23% ($p= 0.007$) with no significant changes in dose to normal tissue when planned with the addition of hippocampal objectives. SD-MLCs showed similar results, sparing the same 5 of the 8 hippocampi exceeding constraints, but also increased dose to healthy tissue, most substantially in V20%[cc] which increased 59.56% ± 53% ($p= 0.015$) and 48.22% ± 32.17% ($p= 0.0056$) in plans with and without hippocampal objectives respectively. Also, in plans both with and without hippocampal optimization objectives, there was no significant change in conformity index when switching MLCs from HD to SD leaves.

Conclusion

Meeting recommended hippocampal constraints was possible in 57% of patients that initially exceeded constraints. The ability to spare this structure was independent of MLC width, and correlated to the distance between the hippocampus and the nearest target. From this data set, the smallest distance avoidable was 0.45cm. All un-avoided hippocampi were at least touching a target, if not overlapped. The larger MLC leaves resulted in higher doses to larger volumes of normal tissue, however the planning technique of VMAT was able to meet target coverage without compromising treatment conformity when larger MLC leaves were used.

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1. Introduction

1.1 Brain metastases

Metastatic brain tumors are the most common intracranial neoplasm in adults [1]. These metastases are frequent complications from other primary cancer sites. Considering both primary and secondary cases, around 170,000 patients receive this diagnosis of metastatic brain tumors in the US each year [2]. Patients with brain metastases commonly have a poor prognosis with a median survival time of about 1 month if untreated [3], and about 4-6 months when they are treated [4]. Given these parameters and the palliative nature of these treatments, it is necessary to consider the patients quality of life (QOL) when evaluating treatment options.

1.2 Treatment methods

Historically, the treatment of brain metastases has been performed with whole brain radiotherapy (WBRT) [5]. Early evidence suggested adding a focused ablative aspect to WBRT, known as stereotactic radiosurgery (SRS), for potential improvements of local tumor control [6]. However, further research and improved technology have both brought SRS alone to the forefront of radiation therapy for both limited metastases as well as more extensive metastatic cases. [6].

The RTOG 9508 randomized phase 3 trial investigated the outcomes of patients who were treated with WBRT and those treated with WBRT and an SRS boost for 1-3 metastases. The study showed a survival advantage for patients receiving WBRT with an SRS boost, having a median survival time to be 6.5 months, as opposed to 4.9 months seen in the patients receiving WBRT alone [7]. Additionally, patients who received the SRS boost also showed improved Karnofsky Performance Status (KPS) scores after 6 months [7]. KPS is a metric to classify a patient's impairment after various therapies, where higher scores imply a more positive outcome. Overall, this study suggests value in the use of SRS when treating limited metastases[7]. A separate randomized control study showed similar survival rate improvement as well as improved local disease control when using an SRS boost with WBRT in the treatment of 2-4 metastases [8].

While there is evidence that WBRT with an SRS boost can improve treatment outcomes when compared to WBRT alone, these same benefits are not necessarily recognized when comparing to SRS alone. A randomized controlled trial concerning 132 patients with between 1-4 metastases showed that patients treated with both WBRT and SRS had shown reduced recurrence of disease within 12 months after treatment [9]. However, the patients treated with SRS alone had a slight improvement of overall survival rate in comparison to WBRT plus SRS (8.0 months vs 7.5 months respectively) [9].

The excellent local tumor control and reduced rates of relapse seen in WBRT with SRS do not necessarily correlate to improved neurocognitive function. In fact, the use of WBRT at all often results in reduced neurocognitive function [6, 10, 11]. A study performed by Eric L Chang et al. (2009) sought to evaluate SRS alone compared to

WBRT with SRS with neurocognitive effects being the end point. The study was stopped early by the data monitoring committee according to early stopping rules due to the substantial probability that patients receiving WBRT with SRS had a high risk of decline in learning and memory, as well as an increased mortality rate at 4 months [12]. This work showed that disease recurrence rates were reduced among the patients who received WBRT with SRS. However, the study concludes by recommending against the use of WBRT in these treatments. It states that the lack of recurrence and improved local tumor control does not outweigh the neurocognitive risk associated with this treatment method [12]. Instead, the study recommends SRS alone with close clinical monitoring as the preferred treatment method when treating brain metastases [6, 12].

1.3 SIMT treatments planned with VMAT

One challenge of SRS is the extensive treatment time required for patients with more than four metastases [13]. This is due to traditional techniques of treating multiple metastases with multiple isocenters, where each metastasis was aligned to its own isocenter. This becomes prohibitively time consuming as the number of metastases increases due to the time spent setting up the patient for each individual isocenter. As a result, historically, such treatments might have been planned for WBRT. With current technology, single isocenter multitarget (SIMT) radiation therapy is a solution to this dilemma [13]. This technique allows for an efficient treatment time of multiple metastases while retaining the conformal dose distributions and neurocognitive benefits of SRS. These treatments are characterized by all gantry arcs rotating around one single point in the patient's head. Factors such as gantry speed, dose rate, and MLC trajectories vary as the gantry rotates for the purpose of delivering the prescribed dose to multiple targets simultaneously while avoiding organs at risk (OARs). Studies have shown this technique can produce comparable plan quality with improved efficiency in both time and monitor units (MUs) used [14].

SIMT treatments for a large number of metastases (≥4) can become complicated, requiring dynamic MLC motion to create complex dose distributions. One way to plan these treatments is through volumetric modulated arc therapy (VMAT). VMAT is an inverse optimization method in Eclipse, Varian's (Varian Medical Systems, Palo Alto, CA) treatment planning system (TPS). The user interface allows a planner to set dose objectives that describe maximum, minimum, or dose-volume constraints for specific organs or areas of the brain. Based on this set of objectives that describe an ideal dose distribution, VMAT software begins to solve for MLC trajectories that best meet the idealized case in a process known as inverse optimization. The VMAT software breaks these calculations into 4 levels, where each consecutive level results in finer MLC motions to fit more complex shapes [15]. SIMT treatments for ≥4 metastases planned with VMAT have shown to not only be efficient in treatment time but deliver comparably good plan quality to treatments with multiple isocenters, with potential improvements in metrics such as dose to normal tissue and conformity index [13, 16, 17].

1.4 NCF and QOL

Quality of life (QOL) is sometimes argued to be the most important outcome metric in radiation oncology with the exception of survival [18]. In the case of brain metastases, it is important to note the relationship between neurocognitive function (NCF) and QOL. It has been long understood that NCF plays a major role in QOL, but the more recent development of brain-specific and cancer-specific NCF and QOL evaluation tools has allowed for a more accurate characterization of this relationship [19].

A study by Li et al. (2008) evaluated 208 patients receiving WBRT by administering baseline tests for NCF and QOL before treatments, as well as follow up tests after the treatment. NCF tests included tests for memory, verbal fluency, fine motor coordination, and executive function. QOL tests included Barthel Index for Activities of Daily Living (ADLs), and Functional Assessment of Cancer Therapy - Brain specific (FACT-Br). Test performance was tracked over time and compared to predictive models for NCF and QOL outcomes. Additionally, spearman correlations were determined between NCF and QOL. It was determined that NCF and QOL are highly correlated and become more highly correlated over time. It also showed that memory, as evaluated by NCF tests, had the strongest correlation to QOL as measured by the ADLs. Furthermore, the data in this study showed that NCF directly precedes QOL, meaning that a deterioration of NCF in a patient will likely soon be followed by a deterioration of that patients QOL.

1.5 OARs and the hippocampus

SRS treatments deliver comparatively high doses relative to other radiation therapy techniques, making it imperative to control and quantify dose distributions in the brain. Even though these treatments are highly conformal, planning the delivery to avoid specific organs can help mitigate neurological or neurocognitive damage to the patient [20]. In general, these organs are referred to as organs at risk (OARs) and are either particularly radiosensitive, critical for survival, or influential for QOL. Common OARs during SIMT SRS treatments include but are not limited to the brain stem, optical chiasm, optical nerves, eye lenses.

There is evidence suggesting that the hippocampus should be considered when planning treatments around OARs .The hippocampus is crucial in the development of episodic memory [21]. Numerous studies have shown how radiation-induced damage to the hippocampus has resulted in the decline of learning, memory, and spatial processing [22, 23], which are key components to NCF and QOL. This is the motivation behind using hippocampal avoidance techniques during WBRT.

The Radiation Therapy Oncology Group (RTOG) 0933 proposed a phase 2 trial that consisted of treating brain-metastasis patients with 30Gy in 10 fractions using hippocampal avoidance techniques in WBRT (WBRT-HA). The protocol outlined procedures and treatment objectives to be met, specifically including dose constraints to the hippocampus. The protocol required that the maximum dose (D_{max}) delivered to the hippocampus be ≤ 16Gy, while the maximum dose to cover 100% of the hippocampus (D_{100}) be ≤ 9Gy. After treatment, patients would be evaluated using standardized cognitive function and QOL assessments at 2, 4, and 6 months post-treatment [24]. The data from this study would then be compared to NCF and QOL evaluations when WBRT is delivered with no hippocampal avoidance.

The results of this trial showed that at 4 months the mean relative decline from baseline results of NCF was about 7%. This is significantly lower than the mean decline of 30% that has been recorded historically when WBRT is used without hippocampal avoidance techniques [24]. This data shows a significant correlation between hippocampal avoidance and the preservation of the patients QOL, making a strong argument for hippocampus as a potential OAR in all brain-metastasis radiation therapies, including SRS. This paper explores the feasibility of meeting hippocampal dose constraints for SIMT SRS planned with VMAT.

1.6 HD-MLCs vs SD-MLCs

SRS treatments using VMAT are commonly performed using specialized MLCs with smaller leaf widths. These MLCs have been shown to provide better conformity for single target SRS [25-27]. However, not all of the benefits of smaller MLC leaves realized for single-target SRS have been recognized in SIMT [28, 29]. Herein, the effect of small and large MLCs on hippocampal avoidance in SIMT is investigated.

In this study, we build upon previous work in evaluating hippocampal avoidance in SIMT SRS for multi-met cases[30], as well as previous work in evaluating the effects of SD-MLCs during multi-met SRS treatments [29]. This study serves to both validate the prior findings of these works using an independent population, as well as to combine these analysis techniques to explore SD-MLC leaf effects in the context of hippocampal avoidance during SIMT SRS treatments planned with VMAT.

2. Methods and materials

2.1 Patient data and constraints

The patient cohort in this study comprises 40 patients enrolled in an IRB approved protocol (Duke Health IRB Pro00081642). Each patient was treated for 4-10 brain metastases with an SIMT plan generated with VMAT. According to protocol, each metastasis was treated with 20Gy in 1 fraction, or 25Gy in 5 fractions if the combined PTV volume exceeded 20cc. There was one exception of a single target in a patient that was prescribed 18Gy due to proximity to brainstem. Each patient was treated on a TrueBeamSTx (Varian Medical Systems, Palo Alto CA) with HD-MLC (2.5mm central leaf width) with 6XFFF beam energy.

The hippocampi for each patient were retroactively contoured by a board-certified radiation oncologist and the dose to each hippocampus was evaluated. Hippocampal dose constraints were given by the Radiation Therapy Oncology Group (RTOG) 0933 as a maximum dose at any point (D_{max}) of 16Gy, and a maximum dose to cover 100% of the hippocampus (D_{100}) of 9Gy in a 30Gy total 10 fraction WBRT treatment. Using an alpha/beta ratio of 2Gy, constraints were converted to one and five fractions according to the biological effective dose (BED). The hippocampal dose constraints for D_{100} and D_{Max} were calculated to have a BED of 13.1Gy and 28.8Gy respectively. Constraints for total dose delivered was calculated to be 421cGy and 665cGy respectively for 1-fraction cases, and 748cGy and 1270cGy respectively for the 5-

fraction case. If a treatment exceeded either of these constraints, it was re-planned with the objective of meeting hippocampal constraints without compromising the other OAR and PTV constraints given in the original plans.

2.2 Hippocampal avoidance with HD-MLCs

The first objective was to describe the feasibility of meeting hippocampal dose constraints while maintaining PTV coverage. This was done by retroactively re-planning the originally delivered patient plans. All re-plans were done in Eclipse 15.6 (Varian Medical Systems, Palo Alto CA). Most re-planning consisted only of adding upper objectives to the hippocampal structures, however, in some instances adjustments to arc orientations were made when necessary to meet constraints. When hippocampal constraints were not able to be met, the planning objective shifted to reducing the mean dose to the hippocampus.

Re-plans were normalized such that the minimum coverage for any target was equal to the minimum coverage for any target in the original plan.

2.3 HD-MLC Vs SD-MLC plans

The second objective of this study is to investigate the feasibility of using SD-MLC leaves for meeting hippocampal dose constraints, and the associated dose-volume effects on SIMT treatments generated with VMAT. Using Eclipse 15.6 (Varian Medical Systems, Palo Alto), treatments were re-planned using an accelerator model that was identical to the original treatment machine differing only in MLC leaf width. HD-MLCs are 2.5mm thick, while SD-MLCs are 5mm.

Both the clinically delivered plans (i.e. no hippocampal optimization) and plans optimized for hippocampal avoidance were re-planned with SD-MLCs. Optimization objectives were held constant when changing MLC leaf width in the clinically delivered plans. Adjustments to the optimization objectives were permitted when changing MLC leaf widths in the hippocampal avoidance plans if BED constraints were not met. The optimization process used a multi-resolution (MR) model to define MLC apertures and arc fields of a treatment [15]. It begins at MR level 1 as a coarse approximation of angular dose which becomes a finer approximation as it progresses to MR level 4 [15]. As dose calculations become finer, the model becomes less flexible to changes in dose-volume objectives [15]. Adjustments made to optimization objectives were only defined at MR level 4 to minimize effects on the plan.

All plans were normalized such that the minimum coverage for any target was equal to the minimum coverage for any target in the original clinically delivered plan.

2.4 Treatment plan evaluation

Conformity index, V20%[cc], V50%[cc], V75%[cc] and D50%[cGy] were recorded to quantify the effects of both hippocampal avoidance and the use of SD-MLC leaves on the clinically delivered treatment plans in this data set. Conformity index (CI) is defined as:

$$CI = \frac{V100\%[cc]}{V(PTV)[cc]}$$

Where V100%[cc] is defined as the volume that is receiving 100% of the prescribed dose, and V(PTV)[cc] is the volume of the combined planning target volume (PTV). From this definition, a perfectly conformal treatment will have a conformity index of 1. V20%[cc], V50%[cc], and V75%[cc] are defined as the volume of healthy tissue receiving 20%, 50%, and 75% respectively of the prescribed treatment dose. D50%[cGy] is defined as the minimum dose delivered to 50% of healthy brain tissue. Healthy brain tissue volume is defined as the total brain volume subtracted by the total volume of all PTVs in a treatment. Evaluation metrics were chosen to reflect those used in similar studies.

Plan types were compared with average percent change, standard deviations of that percent change, and the associated P-Values. Percent change is defined as:

$$\%\ Change = \frac{final - initial}{initial} * 100\%$$

An increase in a value would result in a positive value for percent change. The average percent change was calculated by summation of the percent change between two plan types for each patient, and then dividing by the number of patients. The standard deviation was calculated from the percent change values between two plans for each patient. P-values were calculated from a two-tailed T-test based on the difference between two plan types for each patient.

3. Results

3.1 Hippocampal avoidance with HD-MLCs

All 40 clinically delivered patient plans met the RTOG 0933 hippocampal constraint on D_{100} (BED =13.1Gy). 7 of the 40 plans (17.5%) did not meet the D_{Max} constraint (BED = 28.8Gy). 6 plans had one hippocampus that exceeded the D_{Max} constraint, and 1 plan had both hippocampi exceeding the D_{Max} constraint (8 total hippocampi at risk).

3 of the 7 patient plans that initially exceeded the maximum hippocampal BED limit could be re-planned to meet this constraint with only the addition of upper objectives on hippocampal dose. A fourth patient plan met the constraint when re-planning included both additional upper objectives on hippocampal dose, and an adjustment in arc geometry for one arc. In total, 4 cases were able to be re-planned for successful hippocampal avoidance (5 out of 8 hippocampi at risk met BED constraints). The remaining 3 patient plans were unable to meet the hippocampal max BED constraint without sacrificing PTV coverage.

The ability of a plan to meet the hippocampal dose constraints was directly related to the distance between the hippocampus and the nearest planning target volume (PTV). In the 3 plans that did not meet the hippocampal constraints, the nearest PTV was either touching or overlapping the hippocampus. In the 4 successfully optimized patient plans, there was at least 0.45 cm between the hippocampus and nearest PTV. The minimum distance required for successful avoidance cannot be concluded from this data set, however the trend of increasing maximum BED with decreasing distance can be seen in **Figure 1**. This graph shows the hippocampal maximum BED of all 8 hippocampi at risk as a function of distance to the nearest target. It includes the plan types of those with and those without hippocampal dose objectives (clinically delivered and re-planned, respectively), each with both HD and SD-MLC leaves, making 4 total data points for each hippocampus at risk.

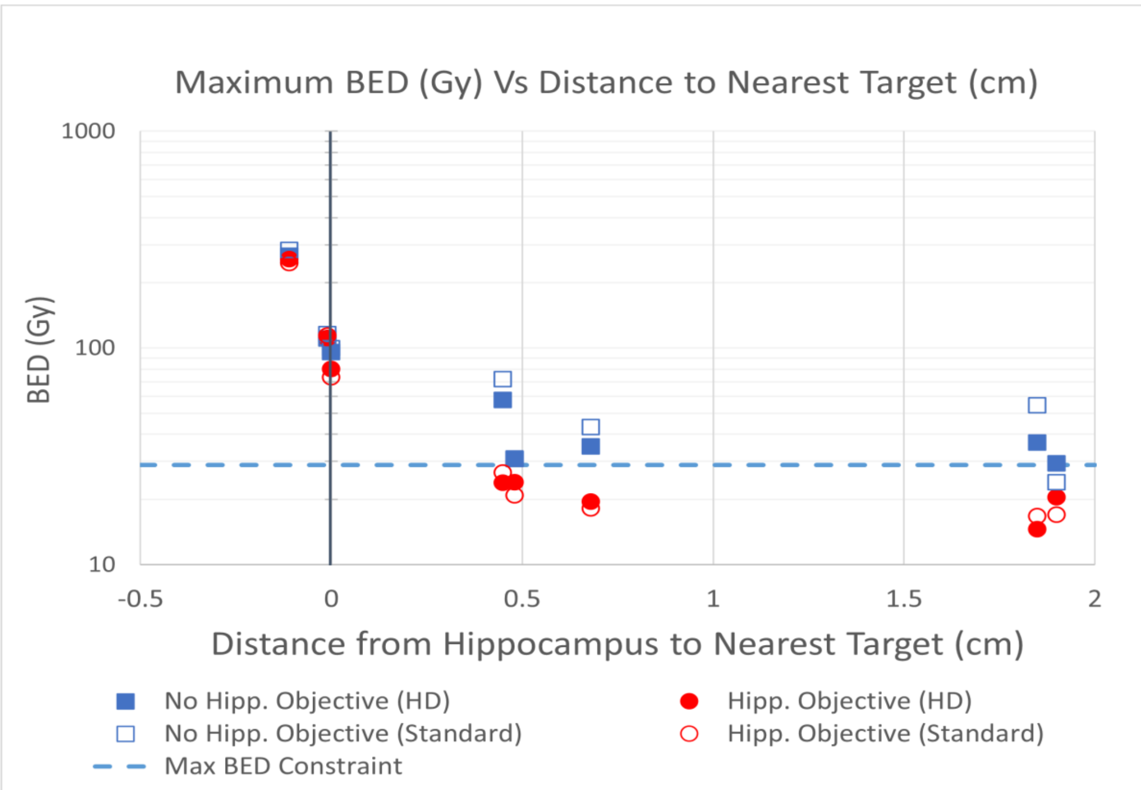

Figure 1: Shows the maximum BED delivered to each of the 8 hippocampi at risk as a function of the distance between that hippocampus and the nearest PTV. Negative values of distance represent the amount of overlap between the hippocampus and PTV. All 4 plan types are displayed. The dotted line represents the RTOG 0933 maximum BED constraint.

Re-planning treatments for hippocampal avoidance with HD-MLC leaves resulted in an average decrease of 29% ± 23% in maximum BED delivered to the 8 hippocampi at risk (p= 0.007). This data includes the 3 hippocampi which were unable to meet the maximum BED constraint. If only considering the 5 hippocampi that were successfully re-planned, then maximum BED decreased an average of 46% ± 17% (p= 0.01).

There was no statistically significant change in V20%[cc], V50%[cc], V75%[cc], D50%[cGy], or conformity index between the clinically delivered plans without hippocampal dose objectives, and the treatments re-planned for meeting hippocampal dose constraints.

3.2 HD-MLC vs SD-MLC plans

3.2.1 HD-MLCs vs SD-MLCs on hippocampal BED

Comparing the effects of SD-MLC leaves versus the Varian HD-MLC leaves is best done by comparing the two leaf sizes on plans without hippocampal optimization objectives, and separately compare them on plans with hippocampal optimization objectives. Positive values of percent change signify an increase in a given metric.

In the plans without hippocampal optimization objectives the maximum BED exhibited an average increase of 11.65% ± 20.09% (p= 0.037) to the hippocampi at risk when SD-MLC leaves were employed versus HD-MLC leaves (**Figure 2**).

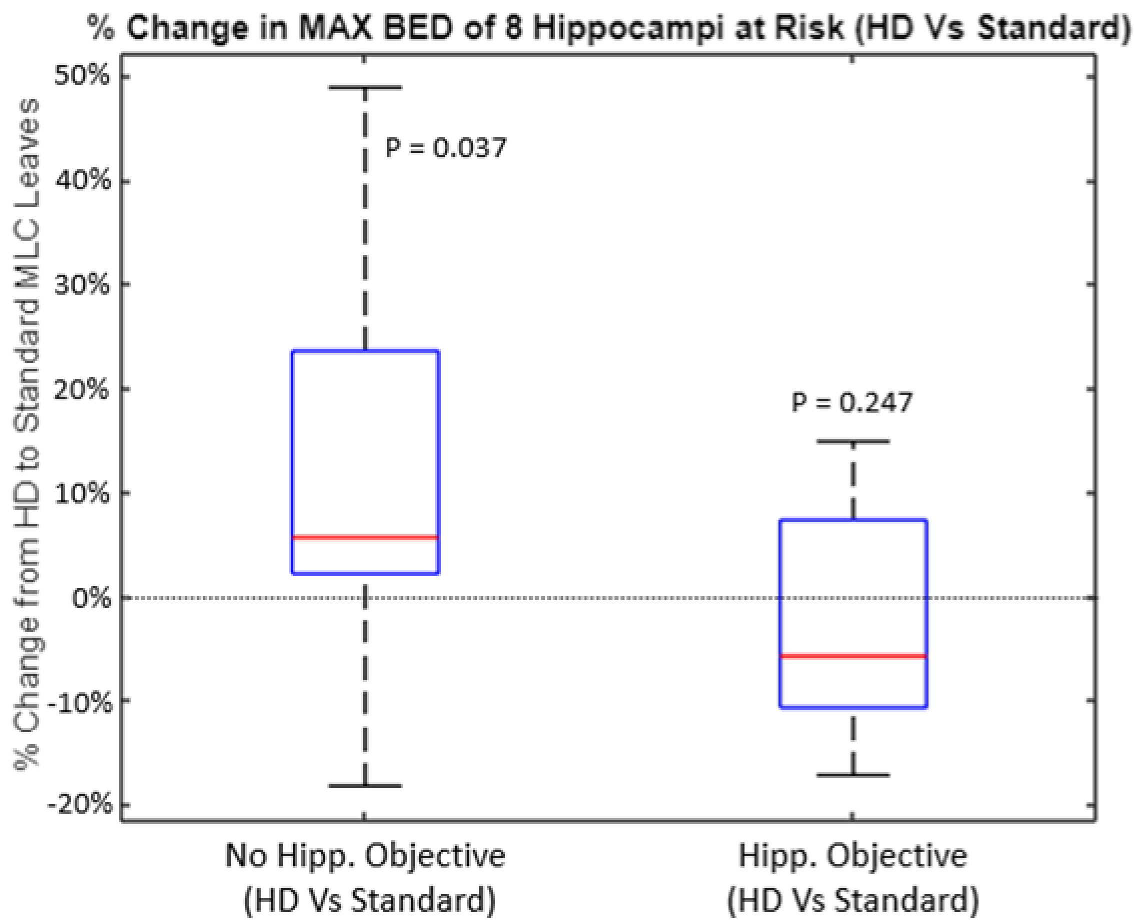

Figure 2: Shows the average Maximum BED values delivered across all 8 hippocampi at risk across the 7 patient plans being evaluated. The left shows the effects of SD-MLCs on plans optimized without hippocampal objectives. The right shows the effect of SD-MLCs on plans optimized with hippocampal objectives. Only maximum BED is displayed because this was the only constraint that was exceeded in any of the initial 40 patient plans.

When plans were optimized for hippocampal avoidance, SD-MLC leaves had no statistically significant effect on the maximum BED to the hippocampus at risk (**Figure 2**). SD-MLC and HD-MLC leaves had the same success rate of meeting the hippocampal maximum BED constraint in the same 5 of 8 hippocampi at risk. This can be seen in **Figure 1.**

SD-MLC leaves resulted in increased BED across all 14 hippocampi in the 7 patient plans being investigated, as stated in the **Tables 1 and 2.** The exception was in the plans that were optimized for hippocampal avoidance, the hippocampal maximum BED had no statistically significant change when using SD-MLC leaves (*p*= 0.75). This is likely due to the optimization objectives in these plans.

Table 1: Displays the BED values of all 14 hippocampi across all 7 plans being investigated. These values show the effects of SD leaves instead of HD leaves on plans without hippocampal optimization objectives.

Hippocampal BED: No Hippocampal Objective		**HD** (Gy)	**SD** (Gy)	Average % Change	P Value
Mean BED	AVG	11.5	14.76	37.99%	0.01427
	STD	9.08	10.65	37.53%	
Min BED	AVG	3.22	4.95	51.10%	0.0002
	STD	1.38	2.43	32.23%	
Max BED	AVG	50.65	56.95	33.76%	0.00457
	STD	67.82	71.12	58.38%	

Table 2: Displays the BED values of all 14 hippocampi across all 7 plans being investigated. These values show the effects of SD leaves instead of HD leaves in the plans that were optimized for hippocampal avoidance.

Hippocampal BED: With Hippocampal Objective		**HD** (Gy)	**SD** (Gy)	Average % Change	P Value
Mean BED	AVG	8.89	10.5	27.88%	0.00004
	STD	7.97	8.17	23.70%	
Min BED	AVG	2.96	3.86	36.91%	0.00401
	STD	1.25	1.28	34.61%	
Max BED	AVG	42.65	42.26	10.62%	0.74742
	STD	66.4	63.5	31.02%	

3.2.2: HD-MLC vs SD-MLC leaves on Brain Dose-Volume Data

In the plans without hippocampal optimization objectives, using SD-MLC leaves results in statistically significant increase of the volume of healthy brain tissue receiving a given percentage of prescribed dose (**Figure 3**). The most substantial change being in the V20%[CC] (volume receiving 20% of the prescribed dose) where the volume has an average percent increase of 48.22% ± 32.17% (p= 0.0056). As for the treatments re-planned for reducing maximum hippocampal BED (**Figure 4**), the SD-MLC leaves also adversely impacted the volume of healthy brain tissue receiving a given dose, but this increase seemed to become less statistically significant for higher dose values (i.e. for V75%[cc] p=0.642). For both the plans without hippocampal optimization objectives and the hippocampal avoidance plans, SD-MLC leaves had no statistically significant effect on conformity index.

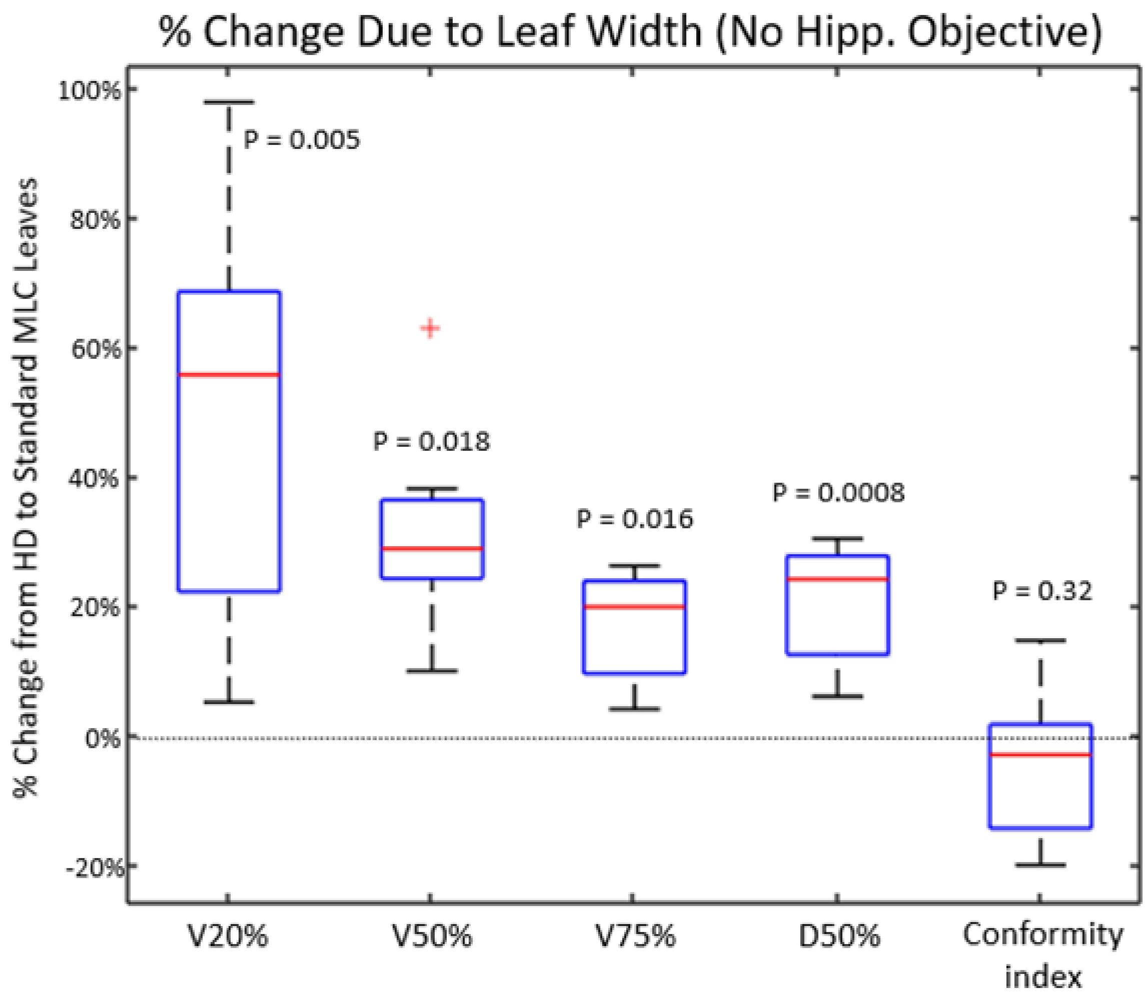

Figure 3: Change in dose-volume metrics when the SD-MLCs (5mm) are used instead of HD MLCs (2.5mm) between plans without hippocampal objectives.

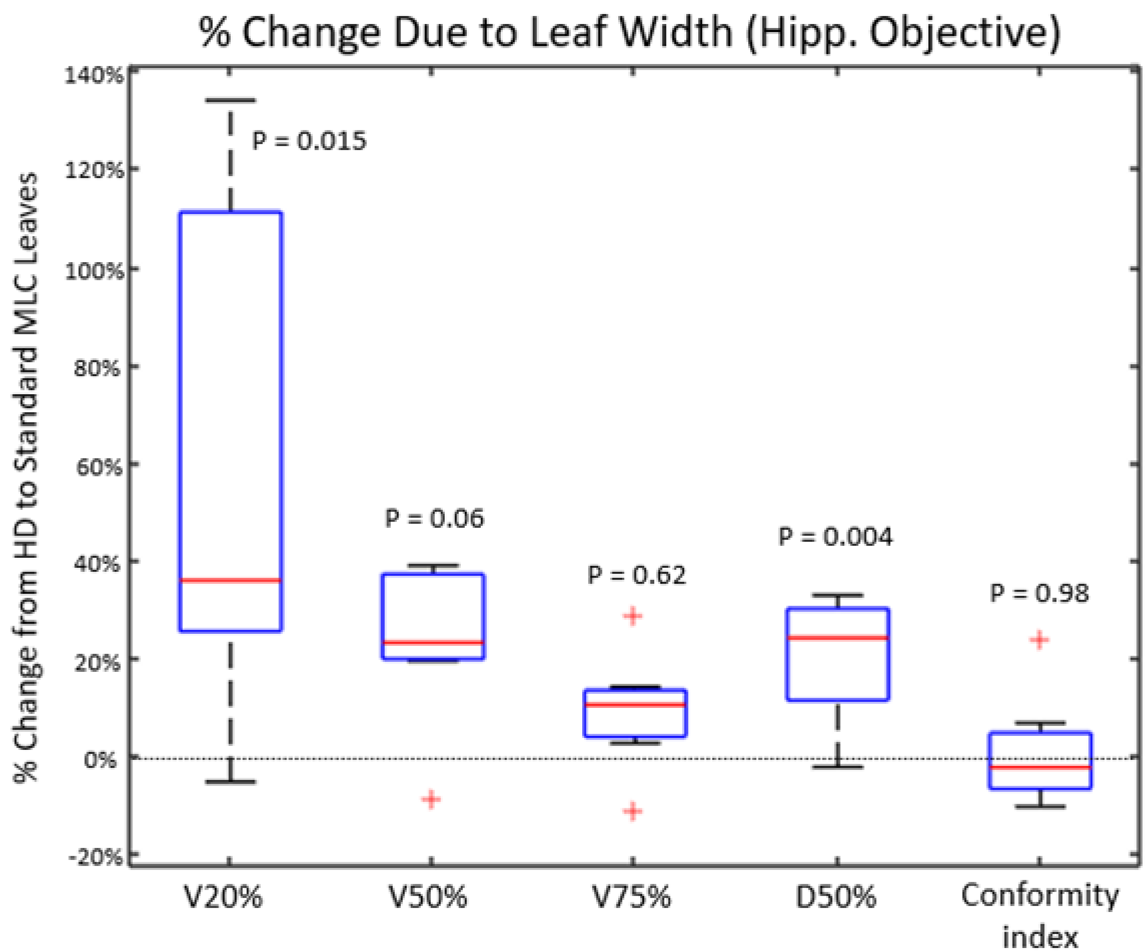

Figure 4: Change in dose-volume metrics when the SD-MLCs (5mm) are used instead of HD-MLCs (2.5mm) between plans with hippocampal objectives.

4. Discussion

Out of the 40 patients considered in this study, 7 had treatment plans that exceeded the RTOG 0933 hippocampal constraint for maximum BED, resulting in 8 total hippocampi at risk. 5 of the 8 hippocampi at risk met BED constraints through small adjustments in the optimization process, while 3 did not. The ability to successfully meet dose constraints correlated with distance between the nearest PTV and the hippocampus at risk. Successful hippocampal avoidance required at least 0.45cm between the hippocampus and the nearest PTV, while the unsuccessfully avoided hippocampi either touched or overlapped with the nearest PTV (as shown in **Figure 1**). These findings were consistent with previous work evaluating the feasibility and risk factors in hippocampal avoidance for single fraction SIMT treatments [30]. In this study, 10 out of 12 patient plans that risked exceeding hippocampal BED constraints had met these constraints through additional optimization [30]. This study also acknowledged the relationship between hippocampal BED and distance between the hippocampus and the nearest target[30]. Neither study noticed significant tradeoffs between hippocampal optimization and changes in dose-volume measurements in healthy tissue[30].

Using the SD-MLC leaves for plans without hippocampal optimization objectives increased the volume of normal brain tissue receiving a given dose and increased the mean dose across all the hippocampi in all treatments. However, SD-MLC leaves did not result in an increase in the number of hippocampi that exceeded the maximum BED constraint.

The 5 of 8 at-risk hippocampi that met BED constraints through optimization adjustments with HD-MLC leaves, also met BED constraints with SD-MLC leaves post optimization. This reinforces that meeting hippocampal BED constraints is more dependent upon the distance between the hippocampus and the nearest target than it is on MLC leaf width. Additionally, SD-MLC leaves had no statistically significant change to the conformity of the treatments. This was true for both plans with and without hippocampal optimization objectives. However, in both cases there were increases in the volumes of healthy tissue receiving a given dose due to leaf width. Use of SD-MLC leaves resulted in V50%[cc] increasing by 24% ± 17% in plans optimized for hippocampal constraints (p= 0.076) and 31% ± 16% in the plans without hippocampal constraints (p= 0.024). These findings are consistent with the findings from Abisheva et al. that also evaluated the effects of SD-MLC leaves on SIMT treatments, which found a 20.04% ± 0.13% increase in V50%[cc][29].

5. Conclusion

The work in this study shows that for patients receiving SIMT using VMAT with between 4-10 metastases, the hippocampus may be at risk of exceeding dose limits from RTOG 0933. For many of these patients, reducing hippocampal dose may be possible granted sufficient distance between the hippocampus and the nearest PTV. Similar results in hippocampal avoidance can be obtained using SD-MLC leaves, however there is a resulting increase in dose to healthy brain tissue elsewhere.

Further research should include evaluating hippocampal dose across all 40 patients as a function of distance to the nearest PTV, and considerations of the effects of varying PTV volume. Additionally, a multi-institutional study should be conducted with a larger number of patients to determine if hippocampal avoidance significantly improves patient outcomes, not only in median survival, but also the preservation of neurocognition and quality of life.

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