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Stereotactic radiosurgery optimization with hippocampal-sparing in patients treated for brain metastases

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ABSTRACT

Background and purpose: Cranial irradiation is associated with significant neurocognitive sequelae, secondary to radiation-induced damage to hippocampal cells. It has been shown that hippocampal-sparing (HS) leads to modest benefit in neurocognitive function in patients with brain metastases, but further improvement is possible. We hypothesized that improved benefits could be seen using HS in patients treated with stereotactic radiation (HS-SRS). Our study evaluated whether the hippocampal dose could be significantly reduced in the treatment of brain metastases using SRS, while maintaining target coverage.

Materials and methods: Sixty SRS plans were re-planned to minimize dose to the hippocampus while maintaining target coverage. Patients with metastases within 5 mm of the hippocampus were excluded. Minimum, mean, maximum and dose to 40% (mean equivalent dose in 2 Gy per fraction, EQD_2 to the hippocampus) were compared between SRS and HS-SRS plans. Median number of brain metastases was two.

Results: Compared to baseline SRS plans, hippocampal-sparing plans demonstrated D_{min} was reduced by 35%, from 0.4 Gy to 0.3 Gy (p-value 0.02). Similarly, D_{max} was reduced by 55%, from 8.2 Gy to 3.6 Gy, D_{mean} by 52%, from 1.6 Gy to 0.5 Gy, and D_{40} by 50%, from 1.8 Gy to 0.9 Gy (p-values <0.001).

Conclusions: Our study demonstrated that further reduction of hippocampal doses of more than 50% is possible in the treatment of brain metastases with SRS using dose optimization. This could result in significantly improved neurocognitive outcomes for patients treated for brain metastases.

1. Introduction

Radiation is an important treatment modality in the management of brain metastases, which can be treated with either whole brain radiotherapy (WBRT) or with stereotactic radiosurgery (SRS). Unfortunately, cranial irradiation can be associated with significant neurocognitive sequelae including reduced verbal memory, spatial memory, attention and novel problem solving [1]. Some of these neurocognitive effects have been linked to radiation-induced damage of neural progenitor cells within the hippocampus [2–5], thereby generating the hypothesis that reduction of radiation dose to the hippocampus could improve neurocognitive function.

This hypothesis was mainly proposed from a number of preclinical studies [2–6], but more recently has been demonstrated clinically. The phase III NRG-CC001 trial showed less neurocognitive decline in patients treated with hippocampal-sparing in WBRT when compared to WBRT without hippocampal-sparing [7]. The trial proved the utility of hippocampal-sparing; however, a significant proportion of patients continued to experience some neurocognitive decline at 6 months, even with hippocampal-sparing [7]. Therefore, there is significant room for further improvement in preserving patient neurocognitive function.

SRS has been used increasingly over the last several decades as it has been shown to be effective at controlling brain metastases, while minimizing dose to normal brain tissue. Chang et al. compared neurocognitive outcomes in patients receiving WBRT and SRS vs. SRS alone. The study was stopped prematurely because those assigned to WBRT and SRS were significantly more likely to develop neurocognitive decline at 4 months with a 52% probability of decline compared to 24% in those treated with SRS alone [8]. As such, we hypothesized that further neurocognitive benefits could be achieved with hippocampal-

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sparing in stereotactic radiosurgery (HS-SRS). Prior to evaluating this, though, we first needed to establish the feasibility of the technique. The aim of this study was to establish if hippocampal dose could be significantly reduced in the treatment of brain metastases using SRS, while maintaining target coverage and dose constraints to other organs at risk.

2. Materials and methods

2.1. Patient population

The study was approved by our institutional review board. Upon retrospective review, sixty patients who were treated with SRS using CyberKnife for brain metastases at our institution in 2018 were identified. Patients with metastases within 5 mm of the hippocampi were excluded from the study.

The median age of the patients at the time of SRS was 62 years (range 25 years–81 years), seen in supplemental table. Patients had between one and sixteen brain metastases, with the median number being two metastases. Mean volume of the closest metastasis to the hippocampus was 4.0 cm^3 (range 0.0 cm^3–34.5 cm^3). Mean volume of all treated metastases was 6.8 cm^3 (range 0.1 cm^3–67.1 cm^3). Mean distance of closest metastasis to the hippocampus was 23.6 mm (5.6 mm–60 mm). Primary tumor histologies included lung, breast, melanoma and others.

2.2. Hippocampal contours

The hippocampi were contoured as per the RTOG 0933 hippocampal contouring atlas, as illustrated in Fig. 1 [9]. They were contoured without expansion. All hippocampal contours were approved by two radiation oncologists with expertise in central nervous system (CNS) radiosurgery.

2.3. Plan re-optimization

All patients had MRIs with T1 volumetric interpolated breath-hold examination (VIBE) protocol with gadolinium enhancement. They were immobilized with a thermoplastic mask in supine position with a customized neck rest. CT simulation was performed with 1 mm slice separation. SRS with CyberKnife plans were created using the Accuray MultiPlan Treatment Planning System software v5.2.1 and Accuray Precision v2.0.1.1. Prescription doses were determined based on brain metastasis size, regardless of number of brain metastases treated; 21 or 24 Gy in a single fraction if less than or equal to 20 mm, 18 Gy in a single fraction if 21 – 30 mm, 15 Gy in a single fraction or 30 Gy in 5 fractions if 31 – 40 mm (all at the treating physician's discretion). Original plans were modified by implementing a dose constraint on hippocampal contours, thus maintaining the integrity of the original SRS plans and the length of treatment. As per institutional guidelines, at least 98% of the GTV volume received 100% of the prescription dose. When a patient had multiple brain metastases, these constraints were applied to their combined volume, as per institutional guidelines. The plans were re-optimized with this additional objective until a maximum amount of hippocampal sparing could be achieved. This optimization was stopped prior to the point where target coverage and/or organ at risk tolerances were compromised.

Minimum, mean, maximum dose and dose to 40% of the hippocampi were calculated for original SRS and HS-SRS plans. These were calculated as biologically equivalent doses in 2 Gy fractions (EQD_2) assuming an α/β ratio of 2 Gy [10,11]. These dose points were selected to match and compare with published data and dose constraints [10,12,13]. The dose to 40% of hippocampi is the most clinically important, with a well-established dose constraint [10]. Additionally, minimum dose (equivalent to dose to 100% of the hippocampi) is important as any dose above 0 Gy could potentially lead to clinical impact [10].

2.4. Statistical analysis

Dose to the hippocampus was obtained in both the original SRS and HS-SRS plans. The minimum, mean, maximum doses and dose to 40% of the hippocampi in both original and re-optimized plans were compared using paired *t*-test. A significant difference was defined as two-tailed p-value <0.05.

3. Results

All HS-SRS plans met institutional care plan criteria; specifically, that

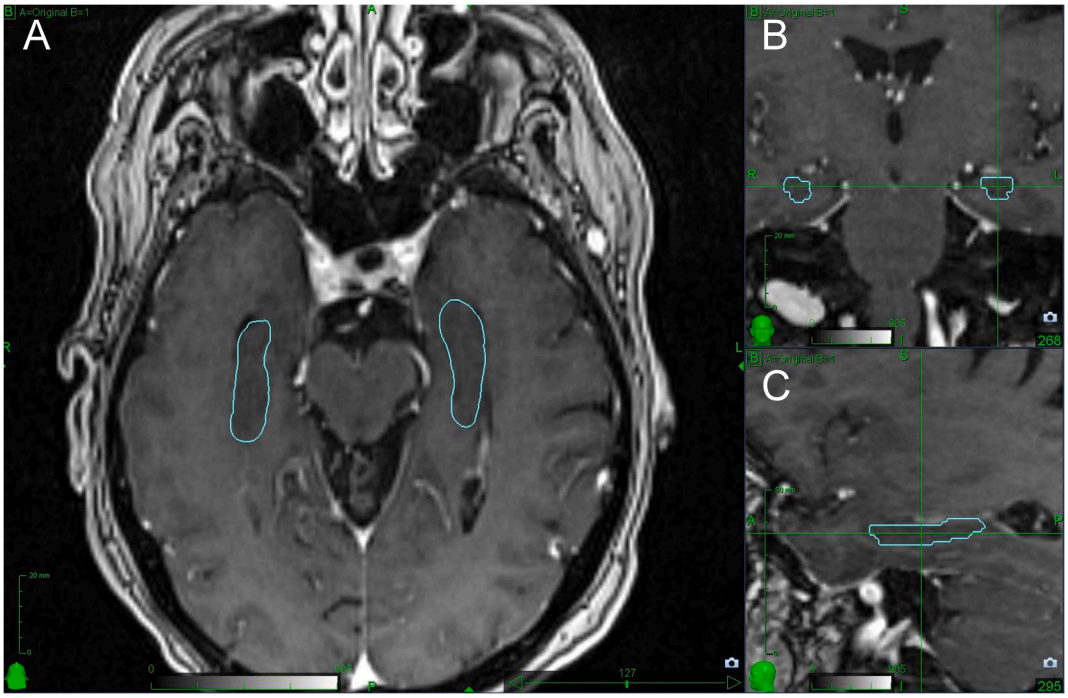

Fig. 1. (A) Axial, (B) Coronal, (C) Sagittal T1 MR images illustrating hippocampal contours in a patient with 11 brain metastases.

GTV D98 was greater than or equal to the 100% prescription dose, and that PTV D100 was greater than or equal to 75% of prescription dose. All plans and hippocampal-sparing re-optimized plans met organ at risk dose constraints.

Average mean dose (EDQ_2) to the whole brain without hippocampal-sparing was 1.8 Gy. Hippocampal-sparing reduced this to 1.7 Gy, an average reduction of 0.04 Gy, seen in Table 1. Similarly, the average mean dose (EDQ_2) to the brainstem without hippocampal-sparing was 2.0 Gy. The addition of hippocampal-sparing reduced this to 1.9 Gy with hippocampal-sparing, an average reduction of 0.2 Gy. Baseline SRS plans had an average mean dose (EDQ_2) to the optic chiasm of 1.9 Gy. There was no significant change to this dose with hippocampal-sparing.

There were not significant changes to mean treatment time, mean number of beams per plan or mean number of monitor units with the incorporation of hippocampal-sparing. Mean treatment time in baseline SRS plans was 52 min and with HS-SRS it was 53 min, seen in Table 1. Mean number of beams per plan in baseline SRS plans was 172 and with HS-SRS it was 176. Mean number of monitor units in baseline SRS plans was 23,686 and with HS-SRS it was 24,261. Fig. 2 illustrates an original SRS plan and that which has been re-optimized for hippocampal-sparing.

In baseline SRS plans, the average mean dose (EQD_2) to the hippocampus was 1.6 Gy (range 0.0–6.7 Gy), seen in Table 2. With hippocampal-sparing, this average mean dose (EQD_2) to hippocampus was reduced to 0.8 Gy (range 0.0–4.0 Gy). This is a mean reduction of 0.8 Gy or 52% dose reduction (p-value <0.001). In baseline SRS plans, the mean maximum dose (EQD_2) to the hippocampus was 8.2 Gy (range 0.1–48.1 Gy). With hippocampal-sparing, this mean maximum dose (EQD_2) to hippocampus was reduced to 3.6 Gy (range 0.1–32.5 Gy), which yields a mean reduction of 4.5 Gy, equivalent to 55% dose reduction (p-value <0.001). Similarly, the mean dose to 40% of the hippocampus volume in baseline SRS plans was 1.8 Gy (range 0.0–7.0 Gy). With hippocampal-sparing, this mean dose to 40% of the hippocampus was reduced to 0.9 Gy (range 0.0–4.9 Gy). This is a mean reduction of 0.9 Gy or 50% dose reduction (p-value <0.001). Lastly, the mean minimum dose to the hippocampus in baseline SRS plans was 0.4 Gy (range 0.02–3.06 Gy). The mean minimum dose to hippocampus was reduced to 0.3 Gy (range 0–2.0 Gy) with hippocampal-sparing, which is a mean reduction of 0.1 Gy, equivalent to 35% dose reduction (p-value <0.02).

4. Discussion

Our study demonstrates that significant dose reduction to the hippocampus is possible using hippocampal-sparing techniques, while maintaining target coverage and organ at risk constraints.

Such dose reduction offers potential neurocognitive benefit to patients treated with radiotherapy for brain metastases. Seibert et al. demonstrated radiation dose-dependent atrophy of the hippocampus by longitudinal MRI [14]. The hippocampal volume loss following radiotherapy was more than could be accounted for by aging. They examined high and lose dose radiotherapy, but nonetheless their findings support the notion that dose reduction may lead to less cognitive impairment for these patients.

Table 1
Doses (EQD_2) to organs at risk and treatment characteristics with and without hippocampal-sparing stereotactic radiosurgery (HS-SRS).

Dose to organs at risk (EQD_2, Gy)	Mean dose without HS-SRS	Mean dose with HS-SRS	P-value
Whole brain	1.8	1.7	<0.05
Brainstem	2.0	1.9	<0.05
Optic Chiasm	1.9	1.8	0.85
Mean Treatment time (min)	52	53	0.36
Mean Beam Number	172	176	0.55
Mean Monitor Units	23,686	24,261	0.06

Studies have observed less neurocognitive sequelae in patients treated with SRS compared to those treated with WBRT. Chang et al., conducted a trial comparing neurocognitive outcomes in patients with brain metastases treated with SRS plus WBRT vs. stereotactic SRS alone. The trial was stopped prematurely as the patients assigned to WBRT and SRS were significantly more likely to show a decline in learning and memory at 4 months than those receiving only stereotactic radiosurgery [8]. Aoyama et al. conducted a phase III trial assessing neurocognitive outcomes in patients assigned to either WBRT or observation following surgery or SRS. This study demonstrated that cognitive function was significantly higher at both 8 weeks and 12 months in the observation arm compared to the WBRT arm [15]. Similarly, Brown et al. randomized patients to SRS alone vs. SRS plus WBRT and assessed cognitive outcomes at 3 months post-treatment. They found that among patients with one to three brain metastases, SRS alone leads to improved cognitive function at 3 months compared to SRS plus WBRT [16].

In RTOG 0933, a study investigating hippocampal-sparing in WBRT, a sub-analysis demonstrated that neurocognitive outcomes were worse in patients with pre-treatment white matter injury. This occurred despite hippocampal-sparing [17], highlighting that hippocampal-sparing in WBRT is in itself not sufficient and further clinical improvements can be made. Nguyen et al. performed a dosimetric analysis comparing single fraction SRS to WBRT with hippocampal-sparing in patients with 10–30 brain metastases. They found that the use of SRS significantly reduced hippocampal doses when compared to WBRT with hippocampal-sparing [11]. This effectively highlights that, more broadly, WBRT with hippocampal-sparing may be insufficient. Additionally, a meta-analysis of randomized controlled trials evaluating SRS with or without WBRT, with a total of 364 patients, showed that for patients 50 years of age or less, SRS alone improved overall survival compared to SRS and WBRT [18]. These studies highlight that WBRT is not appropriate for all patients.

Interestingly, Di Carlo et al., performed a retrospective analysis of hippocampal doses with and without hippocampal-sparing in patient treated with fractionated stereotactic radiotherapy [19]. They found that hippocampal constraints, specifically D_{max} and D_{40}, were exceeded in almost half of the cases without hippocampal-sparing, including all those with multiple brain metastases. With hippocampal-sparing, 50% of cases met hippocampal dose constraints. This highlights the potential benefit of hippocampal-sparing in stereotactic radiotherapy. The finding also highlights that hippocampal doses may be improved with stereotactic radiosurgery, even when compared to fractionated stereotactic radiotherapy with volumetric intensity-modulated arc therapy.

Together, these results indicate that neurocognitive function may be better preserved with hippocampal-sparing and that significant improvement can be made with the use of SRS when compared to WBRT. This may be secondary to even lower doses throughout the brain, but particularly to the hippocampus with SRS, demonstrated herein in this study. Although hippocampal-sparing may reduce neurocognitive sequelae, it cannot altogether prevent it as other regions of the brain are also important in neurocognition. Other causes for this include vascular changes throughout the brain [20], loss of proliferating glial cells [21] and reduction in number of vascular endothelial cells [22]. While the hippocampus does contain progenitor cells, these changes can occur throughout the rest of brain, leading to neurocognitive sequelae. This may be secondary to the fact that semantic memory is widely distributed within the cerebral cortex, such that retrieval of information activates a wide network of neural cells, across the cerebrum [23].

RTOG 0933 provided information about common hippocampal doses with hippocampal-sparing WBRT using helical tomotherapy and LINAC-based IMRT. Hippocampal-sparing WBRT with helical tomotherapy had a median dose of 5.5 Gy and maximum dose of 12.8 Gy, whereas with LINAC-based IMRT, these were 7.8 Gy and 15.3 Gy, respectively [9]. Similar evaluation of hippocampal-sparing WBRT with intensity modulated proton therapy demonstrated mean hippocampal doses of

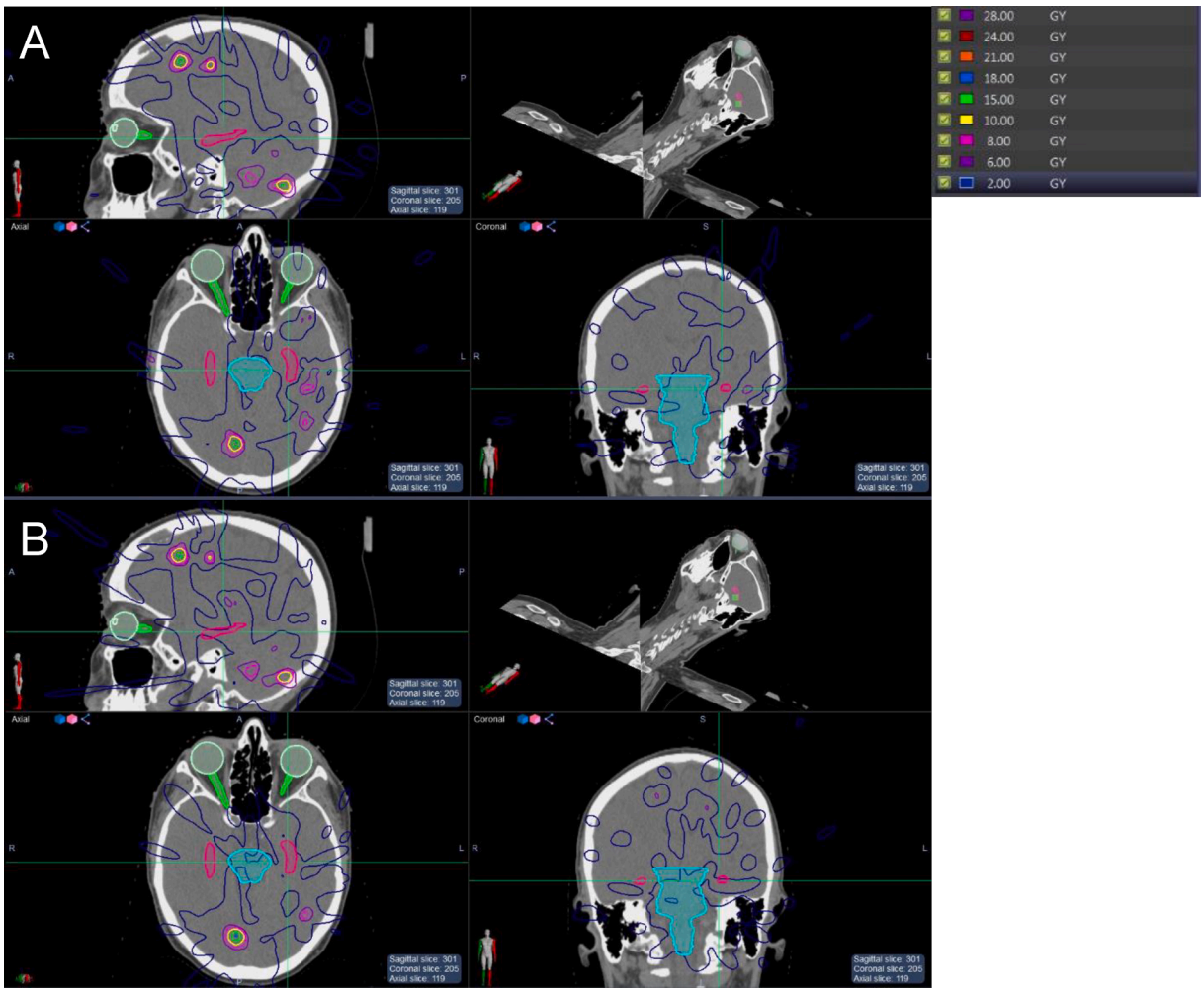

Fig. 2. Example of an SRS plan and dose distribution with hippocampal-sparing (A) and without hippocampal-sparing (B).

Table 2
Doses (EQD_2) with and without hippocampal-sparing stereotactic radiosurgery (HS-SRS).

	Mean dose without HS-SRS (EQD_2, Gy) (range)	Mean dose with HS-SRS (EQD_2, Gy) (range)	Dose reduction with HS-SRS (EQD_2, Gy) (range)	Dose reduction with HS-SRS (%)	P-value
D_{min}	0.4 (0.0–3.1)	0.3 (0–2.0)	0.1 (0–2.53)	35	<0.02
D_{40}	1.8 (0.0–7.0)	0.9 (0.0–4.9)	0.9 (0–5.5)	50	<0.001
D_{mean}	1.6 (0.05–6.71)	0.8 (0.03–4.04)	0.8 (0–5.31)	52	<0.001
D_{max}	8.2 (0.1–48.1)	3.6 (0.1–32.5)	4.5 (0.0–17.0)	55	<0.001

4.4 +/− 0.2 GyE in adults [24]. With all these techniques, the dose to the hippocampi are far greater than what we have demonstrated with SRS. In our study, these doses were reduced further with HS-SRS.

Gondi et al. investigated the specific impact of hippocampal dosimetry on long-term neurocognitive outcomes and found that, assuming an α/β of 2 Gy, a biologically equivalent dose in 2 Gy fractions (EDQ_2) to 40% of the bilateral hippocampi greater than 7.3 Gy was associated with impaired delayed recall long-term [10]. This constraint was found to be most correlated with clinical outcomes. Additionally, his study demonstrated that any dose over 0 Gy to 100% of the bilateral hippocampi (equivalent to minimum dose in our study) leads to a significant decline in delayed recall. Although no cut-off above 0 Gy was established, one could conclude that as much dose reduction as possible would likely yield better neurocognitive outcomes. The study involved patients with benign or low-grade adult brain tumors, but presumably translates to patients treated with radiotherapy for brain metastases.

Other hippocampal dose constraints were established by this same group and others [7,13]. Again, assuming an $\alpha/\beta = 2$ Gy, EQD_2 are as follows; $D_{mean} \leq 5.6$ Gy and $D_{max} \leq 16$ Gy (although $D_{max} \leq 24.7$ Gy was cited in [10]). Our study demonstrates that SRS, even without hippocampal-sparing, lead to an average mean hippocampal dose (EQD_2) of 1.61 Gy, lower than the recommended constraint. With the use of HS-SRS, though, this was reduced further to an average mean hippocampal dose (EQD_2) of 0.78 Gy (p-value <0.001). Without hippocampal-sparing, SRS did meet the newer constraint for D_{max} ($\leq$14.4 Gy), with a mean maximum hippocampal dose (EQD_2) of 8.2 Gy. With HS-SRS, however, this was significantly reduced to a, median dose (EQD_2) of 1.2 Gy and mean dose of 3.6 Gy (p-value <0.001). In addition, D_{40} with SRS without hippocampal-sparing yielded mean dose (EQD_2) of 1.8 Gy, below the 7.3 Gy dose to 40% of bilateral hippocampi volume that leads to impaired delayed recall long-term [10]. Again, remembering that any dose above 0 Gy increases neurocognitive sequelae, this dose was significantly reduced with HS-SRS to a mean dose (EQD_2) of 0.9 Gy (p-value <0.001) to 40% of volume of bilateral hippocampi. It must be noted that, while we know any dose above 0 Gy to the bilateral hippocampi leads to increased neurocognitive sequelae [10], we do not know the true clinical impact of small changes to hippocampal doses. As such, the full extent of the neurocognitive impact of a mean dose reduction of, for example, <1 Gy to the bilateral hippocampi is not

currently known.

Such dose reductions were possible without significant cost to dose to organs at risk, treatment time, number of beams or number of monitor units. There was some reduction in dose to the brainstem and whole brain with hippocampal-sparing. This is intuitive; the hippocampi surround the brainstem and the whole brain encompasses the entire brain and so reduced hippocampal doses will reduce whole brain doses. This suggests that the incorporation of hippocampal-sparing has minimal trade-offs, apart from the time spent by dosimetrists optimizing plans.

Many constraints established for hippocampal-sparing in WBRT were met with SRS, even before hippocampal-sparing techniques are employed. Furthermore, all such dose constraints were easily met with the addition of hippocampal-sparing and, in fact, each one improved by approximately 50%, which is well below dose constraints. This would suggest that even further improvements to neurocognitive outcomes may be achieved using hippocampal-sparing in patients treated with stereotactic radiosurgery. Further investigation could involve identifying which patients benefit most from hippocampal-sparing. While we have demonstrated a benefit across all-comers with brain metastases more than 5 mm away from the hippocampus, clearly some patients see greater dose reduction with HS-SRS than others. In our investigation, patients with greatest dose tended to have more brain metastases, larger prescription doses, larger initial hippocampal doses and larger hippocampal volume. Further study could be done to identify which patients benefit most, however with the minimal trade-offs and benefit in all-comers, we would advise its use in all patients with brain metastases treated with SRS.

Our study demonstrated that not only are most hippocampal dose constraints met with the use of SRS, but dose reduction of approximately 50% to the hippocampus (D_{min}, D_{40}, D_{max} and D_{mean}), can be achieved with HS-SRS, while maintaining target coverage and dose to organs at risk. This suggests that further improvement to neurocognitive outcomes may be achievable with the use of HS-SRS. We propose a prospective evaluation of the potential clinical benefit of hippocampal-sparing in the treatment of brain metastases using stereotactic radiosurgery, with the hopes of further minimizing neurocognitive sequelae.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Malone has the following conflicts of interest: honoraria from Astellas, Janssen, Sanofi, Bayer, Abbvie, AstraZeneca and Amgen; travel expenses from Sanofi and TerSera. There are no other competing financial interests or personal relationships.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2021.02.001.

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