Hippocampal Avoidance and Its Impact on Patient Cognition

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Abstract

Treatment effects have become a growing concern in patients treated with whole brain radiation therapy (WBRT). Hippocampal avoidance (HA-WBRT) has become a rather fascinating technique utilized in whole brain therapy, which has led to the emergence of numerous clinical trials assessing its effectiveness against standard WBRT treatment. The following studies have been instrumental in providing evidence of cognitive outcomes during and after fractionation, and the development of treatment plans that spare the hippocampus.

It is becoming more evident that the management of brain metastasis with radiation is an effective technique. However, with the looming side effects in cognitive declines in whole brain radiation therapy (WBRT) patients, there is a growing need to minimize the potential adverse effects. Declines in patient quality of life and neurocognitive function help researchers measure effectiveness and appropriateness in implementation. The purpose of this review is to grasp an understanding behind the rationale of avoiding the hippocampus during whole brain irradiation and to also display treatment outcomes in terms of cognition and symptom severity when HA-WBRT patient populations are directly compared against compared against WBRT populations.

Introduction

Before delving into the effectiveness of hippocampal avoidance, we must first understand how the hippocampus plays a role in cognition. Considering Anatomy and Physiology certainly helps us in doing so. Anatomically, it resides in the medial temporal lobe of the brain. The

hippocampus is comprised of white and gray matter, which coordinates information processing and communication. This organ aids the processes of learning, memory, emotion and motor control. Functionally, it aids in episodic memory retrieval and helps individuals with prospective cognition. Numerous publications have proven that hippocampal tissue is radiosensitive and even low radiation doses may promote damage to this specific region. Now that we understand the location and function of the hippocampus, we can accurately interpret radiation-induced effects of WBRT without sparing the Hippocampus.

The practice of WBRT is widely accepted in Radiation Oncology and has become more of an essential practice after evidence continues to reveal successful control of brain metastases. Unfortunately, irradiating the whole brain produces concerning effects. Specific effects may include demyelination in the white matter and damage to the vascular endothelium, which significantly hinders cognition. Radiation to the hippocampus has also been shown to affect verbal and non-verbal memory, overall function and information processing.

Considering the radiation-induced effects in WBRT, it is apparent that a more appropriate technique should be utilized in order to preserve the Hippocampus in patient populations with brain metastasis, thereby avoiding cognitive declines. This study shows how HA-WBRT may mitigate damage to the Hippocampus by comparing declines to the conventional 2D-WBRT patient populations. It will also answer the question if HA-WBRT promotes improvements in patient prognosis, if it truly prevents hippocampal atrophy and yields better outcomes in patient memory and quality of life.

Methods

In the study titled, “Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001" conducted by Brown et al. patients were chosen according to specific parameters- those who suffered from brain metastases around the hippocampus outside a 5-mm margin, older than 18, Karnofsky performance score greater than 70, and a solid tumor malignancy diagnosis. A randomly assigned stratified sample was treated with WBRT and instructed to ingest the common drug memantine (used to treat dementia). The other patient sample was assigned as the control, which was treated with HA-WBRT and memantine. It is important to note that both patient populations were given the same dose of memantine across groups. MRI computed tomography was the chosen imaging modality that delineated bilateral hippocampal contours. Prior to participating in study, a baseline evaluation using standardized assessments were given to each patient to assess medical history, physical health, neurologic health, cognitive level, and self-reported quality of life (Brown et al., 2020). These evaluations were repeated at month 2, 4, 6, and 12. Both study groups received a dose of 30 Gy in 10 fractions.

According to Brown et al. (2020), the following assessments were utilized to measure cognitive failure in patients: Hopkins Verbal Learning Test-Revised [HVLT-R], Controlled Oral Word Association, Trail Making Test [TMT] Part A, TMT Part B [TMT-B]. Quality of life and symptom burden were assessed by the EQ-5D-5L, and the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT). Secondary assessment points were intracranial progression free survival, overall survival, toxicity, patient reported symptoms, quality of life, and cognitive

function. Brown et al. (2020) employed Gray's statistical analysis to identify significant differences of cognitive failure over time and the Kaplan-Meier method to test for OS and frequency of patient symptoms. Baseline scores of quality of life and symptoms were compared with a t-test using a significance level of .05.

A second study titled, "Hippocampus-Avoidance Whole-Brain Radiation Therapy Is Efficient in the Long-Term Preservation of Hippocampal Volume" was conducted by (Popp et al., 2021). This study utilized a longitudinal design with patients receiving 2D-WBRT or HA-WBRT. Popp et al. (2021) determined inclusion based upon the presence of cerebral metastasis of solid tumors, no spreading of meningeal during treatment, no CNS pathologies, and one imaging study before and another after the treatment course. Images were taken twenty-four months prior and forty-eight months post-fractionation to determine overall effectiveness. Changes in hippocampal volume or atrophy were statistically evaluated using the GAMM model which included dependent variables of volume, fixed effects of interest, fixed effects of nuisance variables, and random effects. The average median prescribed doses for the WBRT group were 39.4 Gy and 34.9 Gy in the Hippocampal avoidant group.

Results

Brown et al. (2020) found that "cognitive failure was significantly lower in the HA-WBRT and memantine patients when compared with the WBRT plus memantine population". After analyzing cognitive scores, there weren't any apparent differences in cognitive deterioration around the two-month mark. At 4 months, the HA-WBRT population was less

likely to have presence of deterioration in TMT-B, and less likely to experience delayed recognition at the 6-month mark. When cognitive test scores were analyzed, more promising rates in cognition were shown in all domains in the "HA-WBRT plus memantine" population (Brown et al. 2020).

After analyzing severity of resulting symptoms, Brown et al. found that significant interactions favored the HA-WBRT plus memantine with longer follow-up. Other treatment outcomes, such as interference of symptoms did not show relevant rates of effect. According to Brown et al. (2020), symptom interference and cognitive factor did in fact show significant differences at 6 months, after including Hochberg's multiplicity adjustment" (p.4), (Figure 1). HA-WBRT/memantine patients showed less symptom interference and fewer overall cognitive symptoms. Brown et al. also found that other measures such as symptom severity and neurologic factor did not display significant rates of effect. Cognitive factor differences at 6 months were influenced by remembrance and aphasia (difficulty speaking). At this milestone, HA-WBRT/memantine patients were not characterized by significant struggle in remembrance (mean, 0.16 *v* 1.29; $P = .01$), and also experienced more success with speaking (Brown et al., 2020). Improvements in fatigue were also achieved in the HA-WBRT/memantine patients when compared with the WBRT patients (Brown et al., 2020). Brown et al. (2020) found no significant in survival rate, intracranial progression-free survival or death rates between both patient groups.

Popp et al. (2021) instituted a GAMM of the changes in hippocampal volume between patient groups, which showed a significant effect of time. Patients who were treated with WBRT encountered significant levels of hippocampal atrophy when compared to the Hippocampal-avoidant group. Popp et al. (2021) found that "In WBRT patients, the estimated average

hippocampal volume loss measured after 6, 12, 24, and 48 months resulted (−0.113 ml, −0.190 ml, −0.320 ml, and −0.519 ml)", (p.6). However, in the HA-WBRT population, the estimated average hippocampal volume loss after 6, 12, 24, and 48 months proved to be only (−0.027 ml, −0.055 ml, −0.116 ml, and −0.196 ml), (Figure 3). Predicted hippocampal atrophy after WBRT was estimated to be three times higher 2 years after treatment than HA-WBRT. This is supported by volume changes at 24, 12, and 6 months before radiation therapy as 2.0% in the WBRT patients and 0.5% in HA-WBRT patients. This displayed that hippocampal volume changes were comparable between groups. Popp et al. also confirmed that the difference of effects between patient groups concerning hippocampal volume and time were apparent post radiation (Figure 3).

Discussion

Popp et al. (2021) successfully confirmed that those treated with WBRT suffered greater levels of hippocampal atrophy compared to patients receiving HA-WBRT. Patients in the WBRT group were also reported to suffer more from symptoms stemming from neurocognitive deterioration, such as difficulty speaking and issues with remembrance. This would suggest that the WBRT group experienced statistically higher rates of radiation-induced damage to the hippocampus. Moreover, (Popp et al. 2021) found that the predicted level of hippocampal atrophy in WBRT patients was three times higher at the 24-month mark after treatment than HA-WBRT patients. Given the tremendous burden patients would experience, it would significantly decrease quality of life. When patient reported symptoms were considered, significant differences were characterized during the latent period in the WBRT group. Not to mention, (Popp et al. 2021) noted fewer cognitive symptoms, which is similar to findings in (Brown et al.,

2020). Cognitive factor differences at latent periods, specifically memory and rates of aphasia were not significant in the HA-WBRT group. This provides strong evidence backing the notion that hippocampal avoidance helps preserve the volume of the Hippocampus. With the findings presented in (Popp et al., 2021), it is apparent that WBRT is not the most appropriate technique for brain metastasis management.

These findings are also strongly supported by (Brown et al., 2020), who presented convincing data that cognitive failure was significantly lower in the HA-WBRT and memantine patients when compared with the WBRT plus memantine population. This helps establish a framework for future clinicians to accept HA-WBRT for those suffering from brain metastasis in patients treated for metastasis management. The second convincing finding in this study was that there were no acute cognitive declines in the HA-WBRT group. There was also evidence that HA-WBRT patients were less likely to experience cognitive deterioration and less likely to experience delayed recognition at different times throughout the latent period. In other words, the HA-WBRT group was not only less susceptible to experience overall cognitive failure, but also less likely to incur acute and latent radiation-induced effects. Both studies provide overwhelming evidence that HA-WBRT prevents hippocampal atrophy, promotes improvements in patient prognosis and yields better outcomes in patient memory and quality of life.

Although HA-WBRT demonstrates superior outcomes in brain metastasis management, other treatment approaches were not considered in this study-particularly brain metastasis management in Stereotactic Radiosurgery. Numerous published trials show promising results, and the feasibility of the technique is well-known. With more concrete evidence in future trials, clinicians will have the ability to prevent cognitive declines in patients treated with WBRT. In

doing so the most appropriate treatment technique in terms of safety and cognition will be discovered.

Conclusion

Conclusive evidence shows that HA-WBRT effectively spares the hippocampus and preserves cognition, which in turn spares patients from experiencing the same levels of symptom severity than those treated with the standard WBRT. Although HA-WBRT trials show convincing results, it is also necessary to gather more data regarding hippocampal atrophy rates in larger populations treated long-term, which can convey preservation of cognition in a more convincing fashion. Unfortunately, hippocampal avoidance is generally thought to be more applicable in clinical trials rather than utilized as an acceptable approach due to limited evidence and potentially dosimetric error. Other emerging alternative techniques used to manage brain metastasis should be investigated in terms of their effectiveness in patient cognition and symptom severity against HA-WBRT groups such as SRS. With more evidence regarding atrophy rates in larger populations and the most appropriate treatment technique, clinicians can confidently manage brain metastasis.

Appendix

A. **(Brown et al., 2020)**

Figure (1)

Kaplan-Meier graph showing time to cognitive failure. (HA-hippocampal avoidance | WBRT-whole-brain radiotherapy)

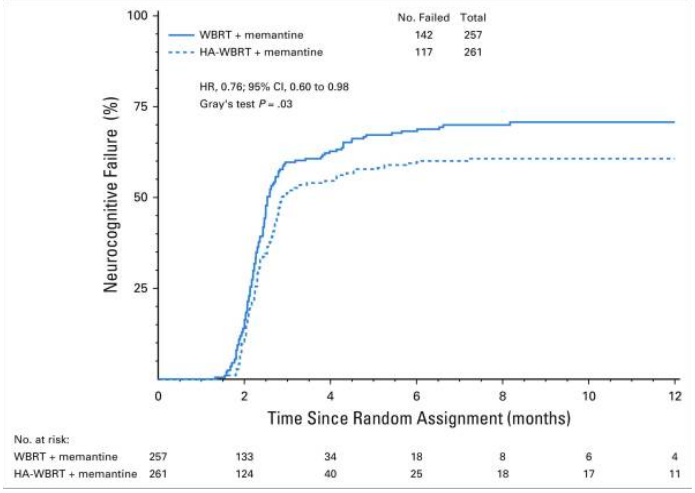
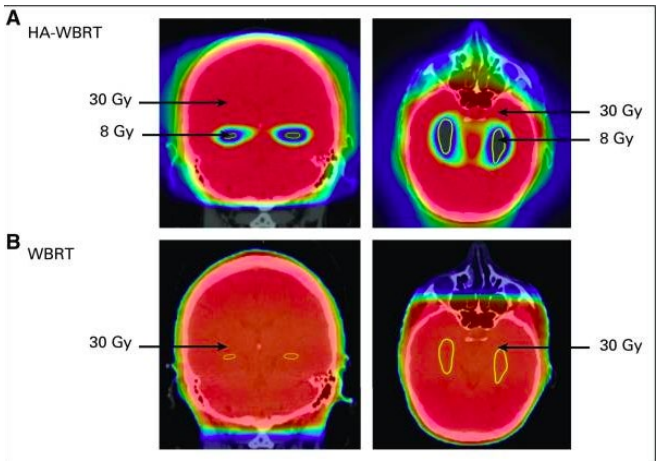


Figure (2)

Dose of radiation to hippocampi contoured in yellow.

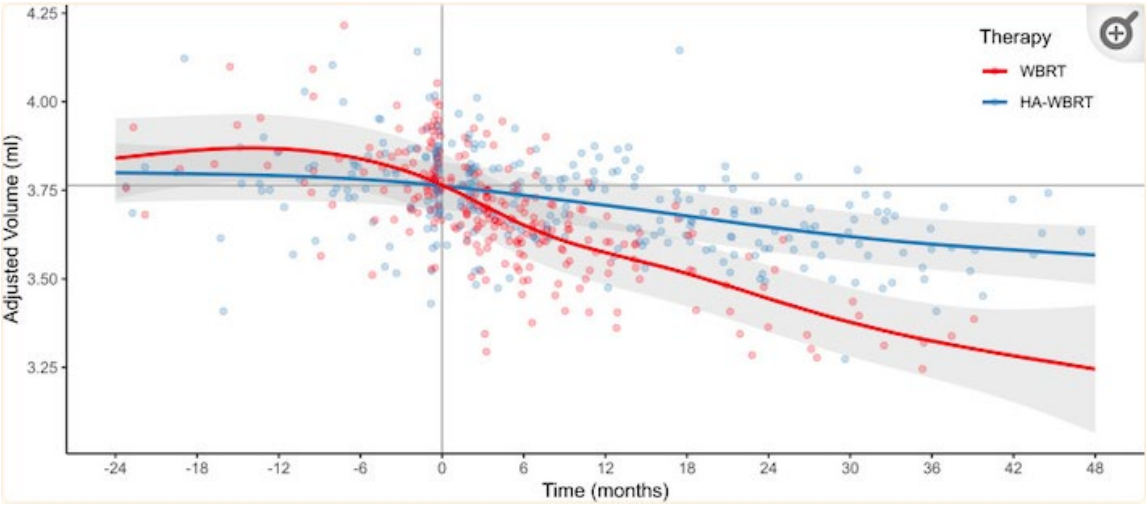
(A) hippocampal avoidant whole-brain radiotherapy (HA-WBRT) | (B) conventional WBRT.



B. **(Popp et al., 2021)**

Figure (3)

Hippocampal decline is 3 times higher in patients treated with WBRT than the Hippocampal Avoidance group.



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Multiple Choice Questions

1. What were the margins utilized to spare the Hippocampus in HA-WBRT group?

a. **2mm**

b. **4mm**

c. **5mm**

d. **1mm**

2. Popp et al. showed that Hippocampal decline is approximately _____ times higher in patients treated with WBRT than those treated with the Hippocampal Avoidance method.

a. **3**

b. **6**

c. **4**

d. **10**

3. Brown et al. found no significant differences in:

a. **Overall survival rate**

b. **Intracranial progression-free survival**

c. **Death rates between the HA-WBRT plus memantine and WBRT population**

d. **All of the above**

4. Which of the following is generally thought to be more applicable in clinical trials due to limited evidence and dosimetric error?

a. **SRS**

b. **Hippocampal avoidance**

c. **WBRT without memantine**

d. **None of the above**

5. What other technique in brain metastasis management is measured against HA-WBRT?

a. **SRS**

b. **SBRT**

c. **Craniospinal**

d. **None of the above**

6. What are the effects of WBRT when compared against HA-WBRT?

a. **Fatigue**

b. **Decreased quality of life**

c. **Cognitive declines**

d. **All of the above**

7. HA-WBRT patients were _____ to experience cognitive deterioration and _____ to experience delayed recognition in at different times throughout the latent period.

a. **Less likely; more likely**

b. **More likely; more likely**

c. **Less likely; less likely**

d. **None of the above**

8. What is the significance of the drug memantine?

a. **Aids in cognitive preservation**
b. **Shows true cognitive decline patterns of radiation to hippocampus when utilized in each group**
c. **Neither a or b**
d. **Both a and b**

9. A significant finding in Brown et al. showed that there was no acute _____ in the HA-WBRT group:

a. **Hippocampal atrophy rate**
b. **Fatigue**
c. **Intracranial pressure increases**
d. **Cognitive decline**

10. Cognitive factor differences at 6 months were driven by what two items?

a. **Remembrance and aphasia**
b. **Atrophy and remembrance**
c. **Radiation-induced damage and aphasia**
d. **None of the above**