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Scientific Article

# Advancing Beyond the Hippocampus to Preserve Cognition for Patients With Brain Metastases: Dosimetric Results From a Phase 2 Trial of Memory-Avoidance Whole Brain Radiation Therapy

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**Purpose:** Recent advances to preserve neurocognitive function in patients treated for brain metastases include stereotactic radiosurgery, hippocampal avoidance whole brain radiation therapy (WBRT), and memantine administration. The hippocampus, corpus callosum, fornix, and amygdala are key neurocognitive substructures with a low propensity for brain metastases. Herein, we report our preliminary experience using a "memory-avoidance" WBRT (MA-WBRT) approach that spares these substructures for patients with >15 brain metastases.

**Methods and Materials:** Ten consecutive patients treated with MA-WBRT on a phase 2 clinical trial were reviewed. In each patient, the hippocampi, amygdalae, corpus callosum, and fornix were contoured. Patients were not eligible for MA-WBRT if they had metastases in these substructures. A memory-avoidance region was created using a 5-mm volumetric expansion around these substructures. Hotspots were avoided in the hypothalamus and pituitary gland. Coverage of brain metastases was prioritized over memory avoidance dose constraints. Dose constraints for these avoidance structures included a D100% $\leq$ 9 Gy and D0.03 $cm^3$ $\leq$ 16 Gy (variation acceptable to 20 Gy). LINAC-based volumetric modulated arc therapy plans were generated for a prescription dose of 30 Gy in 10 fractions.

**Results:** On average, the memory avoidance structure volume was 37.1 $cm^3$ (range, 25.2-44.6 $cm^3$), occupying 2.5% of the entire whole brain target volume. All treatment plans met the D100% dose constraint, and 8 of 10 plans met the D0.03 $cm^3$ constraint, with priority

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given to tumor coverage for the remaining 2 cases. Target coverage (D98% > 25 Gy) and homogeneity (D2% ≤ 37.5 Gy) were achieved for all plans.

**Conclusions:** Modern volumetric modulated arc therapy techniques allow for sparing of the hippocampus, amygdala, corpus callosum, and fornix with good target coverage and homogeneity. After enrollment is completed, quality of life and cognitive data will be evaluated to assess the efficacy of MA-WBRT to mitigate declines in quality of life and cognition after whole brain radiation.



## Introduction

Radiation therapy has an important role in the treatment of brain metastases. The initial studies by Patchell et al showed that whole brain radiation therapy (WBRT) after surgical resection reduces rates of local and distant brain recurrence.[1] However, concern over the neurocognitive effects of WBRT has led to increased use of stereotactic radiosurgery (SRS) treatments to spare normal brain tissue. The Alliance N0574 trial showed that the addition of WBRT to SRS resulted in improved local and distant brain control but no change in overall survival and was associated with worsened cognitive deterioration.[2] A trial directly comparing postoperative WBRT with SRS showed no change in median overall survival between arms and better cognitive deterioration−free survival with SRS.[3,4] When considering the neurocognitive outcomes for SRS compared with WBRT, radiation plans that favor focal treatment have become a standard approach for treating brain metastases.[4]

Another approach to reduce neurotoxicity for patients with brain metastases while maintaining the improved intracranial disease control of WBRT involves sparing cognitive substructures. The hippocampus is a curved structure located deep in the temporal lobe and adjacent to the lateral ventricles in the brain. It is involved in a number of cognitive processes including learning, memory, and emotion.[5] Deficits in hippocampal physiology have been implicated in schizophrenia and dementia.[6-8] Higher doses to the hippocampus in patients receiving brain radiation are associated with more significant neurocognitive decline.[9,10] A commonly used radiation technique, hippocampal avoidance, has been shown to reduce cognitive decline and improve patient-reported quality of life and long-term cognitive outcomes in phase 2 (RTOG 0933) and subsequent phase 3 (NRG-CC001) trials treating patients with brain metastases.[11-14] As a result, hippocampal avoidance has been incorporated into the standard of care for eligible patients treated for brain metastases with WBRT.

Despite these advances, a subset of patients who receive radiation therapy with hippocampal avoidance still experience cognitive decline after treatment. Twenty-three percent of patients receiving hippocampal avoidance WBRT (HA-WBRT) and memantine on NRG-CC001 still experienced executive function deterioration at 4 months, with 12% experiencing total recall and delayed recognition deterioration at 6 months.[11] In addition to the hippocampus, other brain structures with important roles in memory and cognition include the amygdala, corpus callosum, and fornix. The amygdala has been proven to have a key role in reward and memory processing, depression, and anxiety.[15,16] The corpus callosum has been previously associated with executive function and complex task performance.[17,18] Injury to the fornix has been associated with impaired memory formation and recall.[19] These substructures collectively comprise a previously published memory circuit where preservation is predictive of memory retention after brain injury.[20] These substructures all have a low propensity for brain metastases and therefore can be safely spared in a WBRT plan without significantly increasing the risk of intracranial relapse.[21]

The aim of this phase 2 clinical trial is to determine whether sparing the amygdala, corpus callosum, fornix, and hippocampus in patients receiving WBRT improves neurocognitive preservation. Herein, we report our preliminary experience and dosimetric feasibility using an advanced "memory-avoidance" WBRT (MA-WBRT) approach that spares these substructures for patients with >15 brain metastases.

## Methods

Inclusion criteria for this study (institutional review board No. 2020C0228) consisted of patients with a stage IV cancer diagnosis planned for treatment in the Department of Radiation Oncology at Ohio State University who were primarily English-speaking and had an estimated survival ≥6 months. Exclusion criteria included patients who received prior WBRT, patients with a pre-existing neurologic disorder often associated with cognitive decline (including but not limited to patients with multiple sclerosis or Alzheimer disease), patients unable to receive magnetic resonance imaging (MRI), and patients who were pregnant or lactating. Prior SRS was allowed. Patients with >15 brain metastases were eligible for MA-WBRT. The MA-WBRT approach avoided the following structures: hippocampus, amygdala, corpus callosum, and fornix. Patients were not eligible for MA-WBRT if they had metastases in these substructures. These structures were contoured by a central nervous system radiation

oncologist, with all contours peer reviewed by the study principal investigator.

The first 10 consecutive patients enrolled onto this study were included in this analysis. All patients underwent a noncontrast thin-slice (1.25 mm) computed tomography simulation scan of the head using a thermoplastic mask for immobilization. Brain MRI scans with contrast were planned for completion within 2 weeks of treatment initiation and included volumetric interpolated breath hold examination with standard axial and coronal fluid attenuation recovery and both contrast-enhanced T1 and axial T2-weighted scans with a 1.25-mm slice thickness. The computed tomography simulation and MRI scans were fused, and avoidance structures were contoured using Eclipse, version 16.1, treatment planning software (Varian Medical Systems, Palo Alto, California).

In each patient, the hippocampus, amygdala, corpus callosum, and fornix were contoured. A memory-avoidance region (PRV) was created using a 5-mm volumetric expansion around the memory substructures and subtracted from the planning target volume (PTV). These contours were reviewed and modified according to previously published consensus contouring guidelines for these structures.[22,23] The amygdala and hippocampus were contoured as separate structures; the hippocampus was defined as the gray matter medial to the temporal horn of the lateral ventricle and lateral to the quadrigeminal cistern, and the amygdala was defined as bound medially and anteriorly by the temporal lobe cortex and posteriorly and inferiorly by the temporal horn of the lateral ventricle and hippocampus. All regions of the fornix were contoured including the septal region. The corpus callosum is the largest of the commissural fibers and links the cerebral cortex of the right and left cerebral hemispheres; these were contoured bilaterally.

All treatment plans were generated in Eclipse, version 16.1 (Varian Medical Systems), and optimized for delivery on TrueBeam (Varian Medical Systems) linear accelerators. Each case was inversely planned with 6 megavoltage volumetric modulated arc therapy (VMAT) arcs; VMAT was chosen owing to more favorable dosimetry with the avoidance of multiple additional structures. The isocenter was placed in the geometric center of the memory avoidance region. To promote midline sparing, the collimation was split to mimic carriage shifting by splitting the X jaw. This was accomplished by offsetting X1 to 14 cm with X2 to 1 cm for the first arc and alternating X1 to 1 cm and X2 to 14 cm for the ensuing paired arc. As a result, each plan comprised 4 total arcs. Two fields were 360° coplanar arcs with a 90° collimator angle using the referenced offset collimation technique. The following 2 fields used 180° vertex half arcs, also using the offset collimation technique and a 90° collimator setting. All plans were optimized to comply with protocol coverage goals for PTVs with a 30 Gray (Gy) prescription dose. Additionally, plans were developed with priority on limiting dose to the brain stem, spinal cord, optic nerves, optic chiasm, eyes, lens, and the PRV to protocol-specific tolerances. Metastases in the PRV (but not within the substructures themselves) were allowed. In these instances, coverage of brain metastases was prioritized over memory avoidance dose constraints. Dose constraints for the memory avoidance structures were modeled after NRG CC-001 and included a D100% $\leq$ 9 Gy and a D0.03 $cm^3$ $\leq$ 16 Gy (variation acceptable to 20 Gy) (Table 1). The hypothalamus and pituitary gland were contoured, and hotspots were avoided in these substructures. When appropriate, gross tumor volumes were simultaneously boosted to 35 Gy during planning at physician discretion. All plans were calculated with an Acuros, version 16.1, algorithm (Varian Medical Systems) and 0.2-mm volumetric grid limit. Memantine was recommended for all patients in the study.

## Results

Ten consecutive clinical trial patients were analyzed for this dosimetric analysis (Table 2). Most patients (60%) had a primary lung tumor. The median patient age was 57 years (range, 48-75 years). All patients had >15 metastases, with a median of 34 (range, 16-137; the patient with 137 metastases had a total tumor volume of 3 $cm^3$). Seventy percent of patients had extracranial metastases at the time of MA-WBRT, with 40% of patients having extracranial disease control. Only 2 patients received prior SRS. All patients were prescribed memantine after radiation oncology consultation.

The hippocampi, amygdalae, corpus callosum, and fornix were successfully contoured in all 10 cases (Figs. 1 and 2). The mean volume of these 4 structures was 37.1 $cm^3$, and the mean brain volume was 1505 $cm^3$. On average, the memory avoidance structures occupied 2.5% (range, 1.6%-3.1%) of the entire brain. All VMAT treatment plans met the D100% $\leq$ 9 Gy dose constraint, and 8 of 10 plans met the constraint of D0.03 $cm^3$ $\leq$ 16 Gy (acceptable to 20 Gy), with priority given to tumor coverage for the 2 cases that did not meet constraints (Table 3 and Table E1). Volumetric modulated arc therapy spared the memory avoidance structures, with a median dose range of 10.8-14.2 Gy and a maximum dose (D0.03 $cm^3$) range of 15.6-22.7 Gy. The mean dose to the memory avoidance structures was 12.7 Gy (range, 11.5-13.8 Gy). Target coverage (D98% > 25 Gy) and homogeneity (D2% $\leq$ 37.5 Gy) were achieved for all plans. An example treatment plan (Fig. 3) shows how these structures were avoided as a part of the clinical trial protocol.

## Discussion

In this clinical trial, we incorporated a novel radiation treatment approach, termed "memory-avoidance"

**Table 1 Dosimetric constraints**

| Structure | Type | Constraint | Goal |
|---|---|---|---|
| PTV | Target | Max ≤ | 3750-4000 cGy |
| Brain | Target | D2% ≤ | 3750 cGy |
| PTV | Target | D98% ≥ | 2250-2500 cGy |
| PTV | Target | V3000 cGy ≥ | 90-95% |
| GTV3000 | Target | Min ≥ | 2400 cGy |
| GTV3000 | Target | D99% ≥ | 2700 cGy |
| GTV3000 | Target | D98% ≥ | 2850 cGy |
| GTV3500 (if applicable) | Target | D99% ≥ | 3500 cGy |
| Memory avoidance region* | OAR | D100% ≤ | 900-1000 cGy |
| Memory avoidance region* | OAR | D0.03 $cm^3$ ≤ | 1600-1700 cGy† |
| Left optic nerve | OAR | D0.03 $cm^3$ ≤ | 3000-3750 cGy |
| Right optic nerve | OAR | D0.03 $cm^3$ ≤ | 3000-3750 cGy |
| Optic chiasm | OAR | D0.03 $cm^3$ ≤ | 3000-3750 cGy |
| Brain stem | OAR | D0.03 $cm^3$ ≤ | 3150-3750 cGy |
| Left lens | OAR | D0.03 $cm^3$ ≤ | 1000 cGy |
| Right lens | OAR | D0.03 $cm^3$ ≤ | 1000 cGy |
| Left eye | OAR | D0.03 $cm^3$ ≤ | 2500 cGy |
| Right eye | OAR | D0.03 $cm^3$ ≤ | 2500 cGy |
| Left lacrimal gland | OAR | Mean ≤ | 2000 cGy |
| Right lacrimal gland | OAR | Mean ≤ | 2000 cGy |
| Left cochlea | OAR | Mean ≤ | 2500 cGy |
| Right cochlea | OAR | Mean ≤ | 2500 cGy |
| Left parotid | OAR | Mean ≤ | 1500 cGy |
| Right parotid | OAR | Mean ≤ | 1500 cGy |
| Left parotid | OAR | V2000 cGy ≤ | 47% |
| Right parotid | OAR | V2000 cGy ≤ | 47% |

*Abbreviations:* cGy = centigray; GTV = gross tumor volume; OAR = organ at risk; PTV = planning target volume.
* Memory avoidance region includes left and right hippocampus, left and right amygdala, fornix, and corpus callosum.
† Variation acceptable to 2000 cGy.

WBRT, designed to minimize the radiation dose to critical neurocognitive substructures including the hippocampus, amygdala, corpus callosum, and fornix, which have previously been shown to have a critical role in learning and memory. We hypothesized that sparing these additional neurocognitive substructures would be feasible and better preserve neurocognition after WBRT. In this study, we showed that modern VMAT techniques allowed for sparing of the hippocampus, amygdala, corpus callosum, and fornix with good target coverage and homogeneity.

These neurocognitive substructures are well studied in literature. The amygdala is a paired structure located anteriorly to the hippocampus. It communicates with many nuclei within the central nervous system, including nuclei associated with the hypothalamus, nucleus accumbens, and cranial nerves. The amygdala mediates emotional responses, including fear and anger, as well as reward and memory processing pathways.[15,16] Abnormalities in signaling through the amygdala are associated with depression and anxiety. The amygdala is also hypothesized to be involved in the pathogenesis and progression of Alzheimer disease, Lewy body dementia, and Huntington disease.[24-26] Atrophy of the amygdala is correlated with radiation dose for patients receiving radiation therapy. In a retrospective cohort of 52 patients, the mean dose to the amygdala was correlated with volume loss, suggesting that atrophy of the amygdala may have a role in postradiation neurocognitive decline.[27]

The corpus callosum is a white matter structure connecting the bilateral hemispheres of the brain. Its role includes motor coordination of the limbs; patients with partial transections of the corpus callosum were found to

**Table 2 Patient characteristics**

| Characteristic | Patients (N = 10)* |
|---|---|
| Sex | |
| Male | 7 (70) |
| Female | 3 (30) |
| Age, median (IQR), y | 57 (51-61) |
| Primary tumor | |
| Lung | 6 (60) |
| Breast | 2 (20) |
| Kidney | 1 (10) |
| Melanoma | 1 (10) |
| Karnofsky performance status score | |
| 100 | 1 (10) |
| 90 | 4 (40) |
| 80 | 3 (30) |
| 70 | 1 (10) |
| 60 | 1 (10) |
| Brain metastases, median (IQR), No. | 34 (29-44) |
| Total brain metastases volume, median (IQR), $cm^3$ | 4.4 (1.9-37.0) |
| Extracranial disease control | |
| Controlled | 4 (40) |
| Uncontrolled | 6 (60) |
| Extracranial metastases | |
| Present | 7 (70) |
| Absent | 3 (30) |
| Previous stereotactic radiosurgery | |
| Yes | 2 (20) |
| No | 8 (80) |
| Memantine prescribed | |
| Yes | 10 (100) |
| No | 0 (0%) |

*Abbreviation*: IQR = interquartile range.
* Data are presented as the number (percentage) of patients unless otherwise indicated.

have deficits in bimanual coordination.[28,29] The exact physiology of the corpus callosum is unclear, yet studies of corpus callosum agenesis in children have revealed variable deficits in executive function and complex task performance.[17,18,30] Lesions on the corpus callosum have been identified as a sequela of brain radiation therapy.[31] Corpus callosum injury has been associated with attention and processing speed decline after radiation.[32] Diffusion imaging studies of children previously receiving brain radiation revealed differences within the corpus callosum

**Table 3 Dosimetric results**

| Patient | MAV, $cm^3$ | Brain volume, $cm^3$ | Percentage of brain | Dose to MAV, median, cGy | Dose to MAV, mean, cGy | Dose to brain, mean, cGy | D0.03 $cm^3$ MAV, cGy | D100 MAV, cGy | D2% brain, cGy | D98% PTV, cGy | D99% GTV3000, cGy |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 25.2 | 1542.7 | 1.6 | 1334.7 | 1323.0 | 3126.4 | 1833.0 | 799.9 | 3472.3 | 2880.9 | 2857.5 |
| 2 | 35.9 | 1419.3 | 2.5 | 1367.0 | 1314.0 | 3001.5 | 1699.7 | 705.1 | 3369.2 | 2579.3 | 3145.3 |
| 3 | 38.3 | 1605.4 | 2.4 | 1343.2 | 1334.0 | 3088.6 | 1698.3 | 865 | 3505.3 | 2780.0 | 3034.3 |
| 4 | 33.4 | 1366.1 | 2.4 | 1297.2 | 1344.3 | 3000.3 | 2266.4 | 723.8 | 3286.5 | 2829.2 | 2942.8 |
| 5 | 44 | 1677.5 | 2.6 | 1246.4 | 1239.6 | 3083.6 | 1693.3 | 851 | 3735.7 | 2767.5 | 3011.1 |
| 6 | 44.6 | 1434.7 | 3.1 | 1078.6 | 1082.5 | 2988.5 | 1559.7 | 671.8 | 3351.5 | 2698.5 | 3043.5 |
| 7 | 40.8 | 1407.0 | 2.9 | 1422.1 | 1378.2 | 2999.7 | 1998.3 | 719.8 | 3323.9 | 2877.6 | 3035.3 |
| 8 | 36.2 | 1366.0 | 2.7 | 1142.5 | 1154.1 | 3041.2 | 1610.9 | 736.7 | 3425.4 | 2655.9 | 3062.6 |
| 9 | 40.2 | 1603.2 | 2.5 | 1229.9 | 1222.6 | 3027.7 | 1629.5 | 790.2 | 3383.7 | 2918.6 | 3211.5 |
| 10 | 32.6 | 1610.9 | 2.0 | 1156.6 | 1218.7 | 3191.0 | 2078.8 | 714.0 | 3714.1 | 2713.2 | 2971.4 |

*Abbreviations*: cGy = centigray; GTV = gross tumor volume; MAV = memory avoidance volume, combined volume of hippocampus, amygdala, fornix, and corpus callosum; PTV = planning target volume.

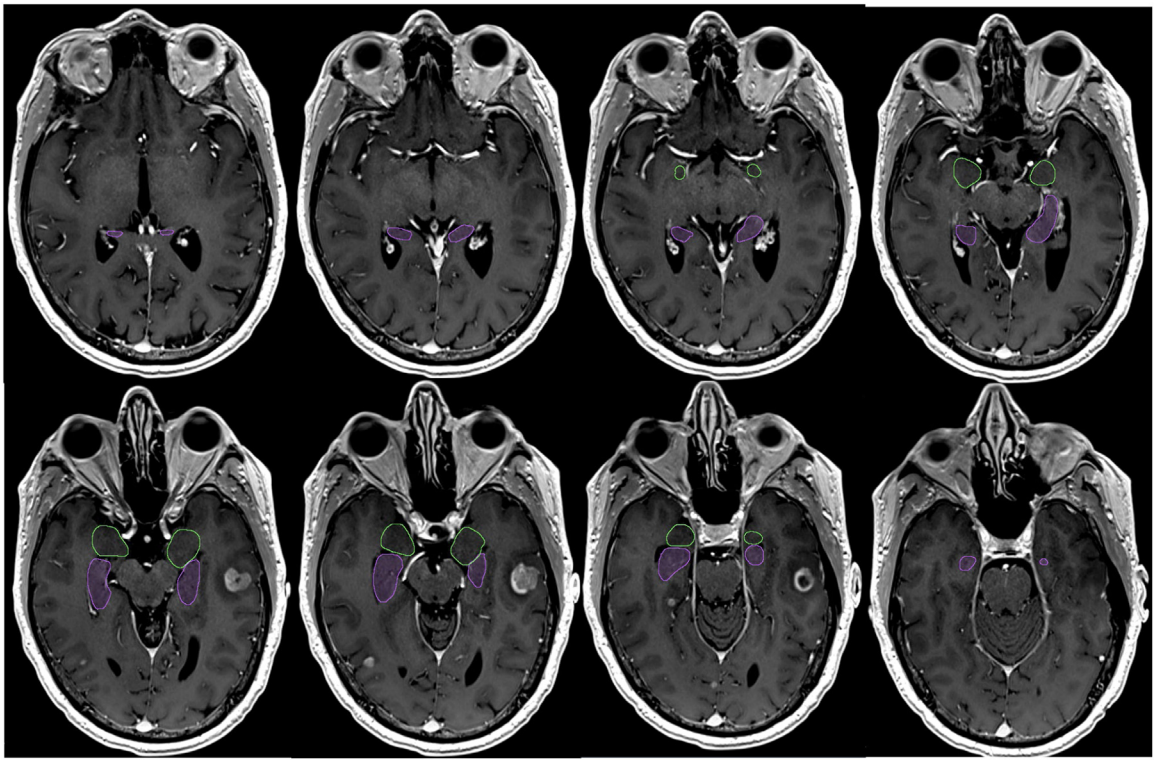

**Figure 1** Contouring example of the hippocampus and amygdala. Purple indicates the hippocampus and green indicates the amygdala.

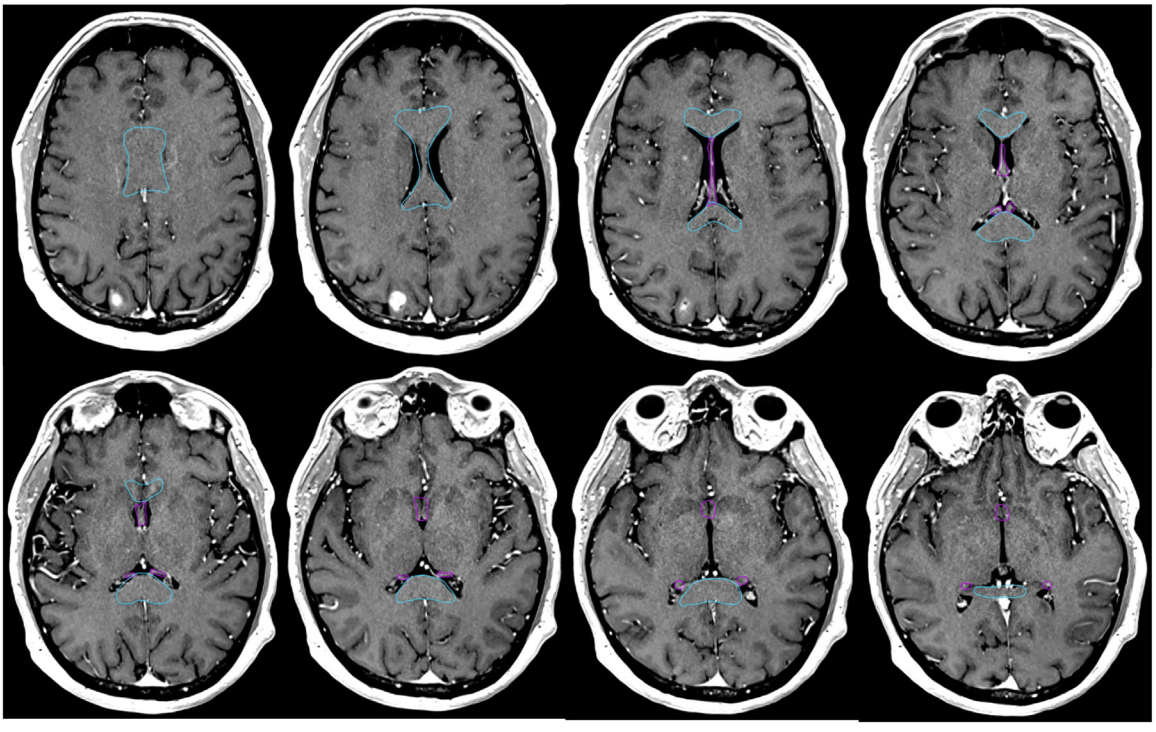

**Figure 2** Contouring example of the corpus callosum and fornix. Blue indicates the corpus callosum and purple indicates the fornix.

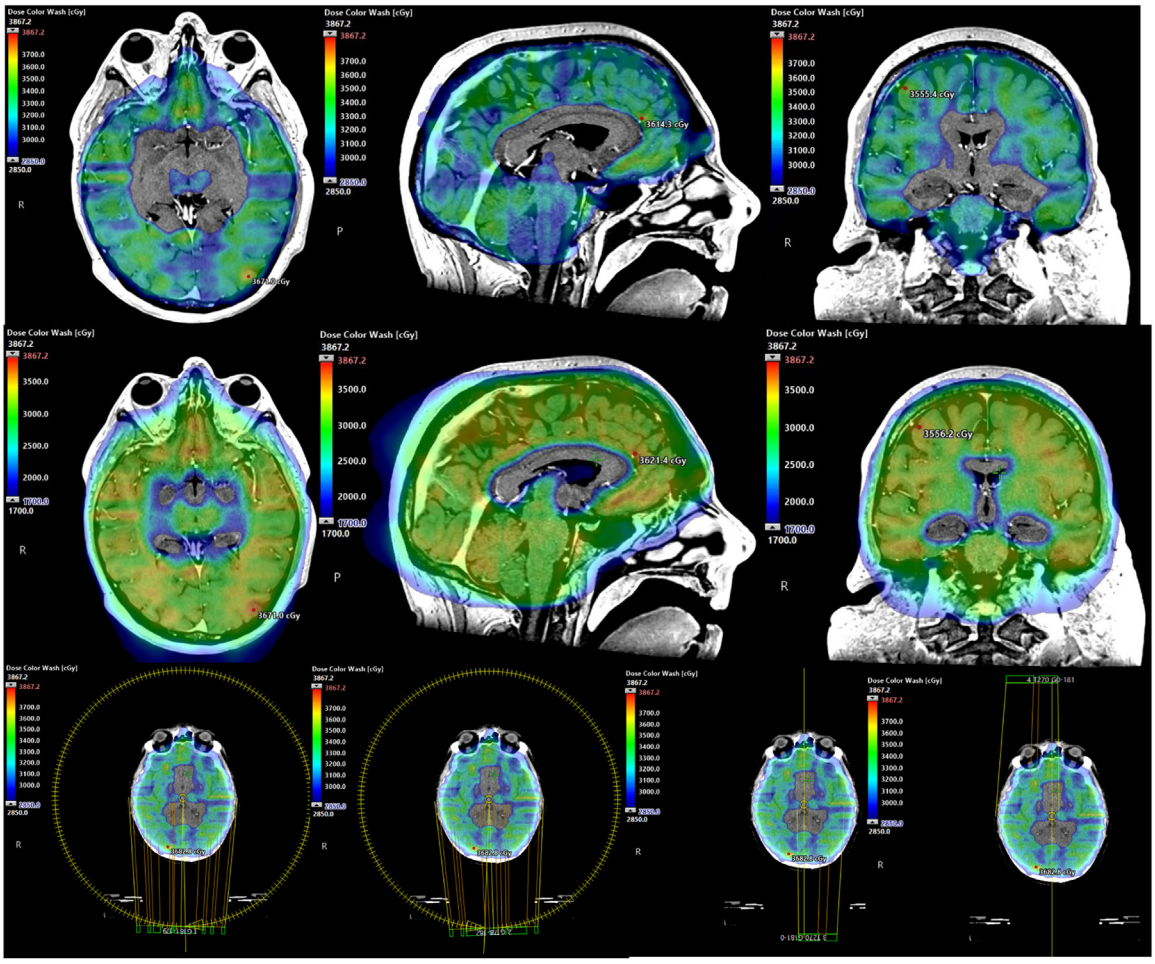

**Figure 3** Example treatment plan for a patient receiving memory avoidance whole brain radiation therapy.

white matter, suggesting that radiation may have long-term effects.[33,34]

The fornix is a brain structure composed of white matter tracts connecting other structures within the limbic system. Lesions in the fornix are known to impair memory formation and recall.[19] It has been reported that the fornix is particularly susceptible to radiation, suggesting that damage to this structure may be similarly involved in neurocognitive decline after radiation therapy.[35] Because of their importance in numerous cognitive pathways, structures within the limbic system should be carefully considered as organs at risk during radiation treatment planning. Guidelines for contouring limbic system structures have been reported[22]; however, further studies should investigate the beneficial effects of sparing these specific structures during radiation treatment.

There are many previous studies documenting the development of HA-WBRT as a method to better preserve cognition for patients receiving WBRT. Gondi et al reviewed the treatment plans of 5 patients with brain metastases treated with HA-WBRT as a part of RTOG 0933.[36] All patients received 30 Gy in 10 fractions. Using a hippocampal sparing approach, the mean dose per fraction to the hippocampus was reduced by 87% (helical tomography) or 81% (LINAC-based intensity modulated radiation therapy). Both approaches achieved adequate target coverage. The mean dose to the hippocampus among the 5 patients was 4.9 Gy (helical tomography) or 7.3 Gy (LINAC-based intensity modulated radiation therapy). Results from this study suggested that HA-WBRT reduced the risk of neurocognitive decline compared with historical controls for patients receiving WBRT.[12] It was concluded that HA-WBRT offered a feasible approach that provided sufficient coverage of the target volume while decreasing dose to the hippocampus. The phase 3 NRG Oncology CC001 trial randomized patients with brain metastases to receive either HA-WBRT or standard WBRT (memantine was given in both treatment groups) and displayed more favorable cognitive results with HA-WBRT, specifically with less decline in memory and executive function.[11] Based on this precedent, our study contributes a successful proof of concept for MA-WBRT. Our dosimetric approach allows for sparing of the hippocampi, amygdalae, corpus callosum, and fornix using similar dose constraints when compared with NRG CC001 (D100% $\leq$ 9 Gy, D0.03 $cm^3$ $\leq$ 16 Gy) for our avoidance

structures while maintaining both target coverage and homogeneity.

One strength of this study is its novelty in examining avoidance of the amygdala, fornix, and corpus callosum for patients receiving WBRT. Our analyses show the success of avoiding these structures using constraints already used for the hippocampus in current practice. This approach avoids areas that comprise 2.5% of normal brain tissue and have a low propensity for brain metastases, providing an avenue to better preserve cognition without significantly increasing risk of intracranial relapse. Both our study and NRG CC001 do not enroll patients with metastases in the specified neurocognitive substructures; one key difference is that our study allows lesions in the PRV, with prioritization of gross tumor volume coverage over memory avoidance constraints. It is unknown whether the dose constraints necessary for preservation of the amygdala, corpus callosum, and fornix function are identical to hippocampus constraints, and further validation is necessary. Further investigation is needed to assess the extent of neurocognitive preservation with MA-WBRT, and these data will be published in our final report.

## Conclusion

Modern VMAT techniques allow for sparing of the hippocampi, amygdalae, corpus callosum, and fornix with good target coverage and homogeneity. Prospective quality-of-life and cognitive data are being collected. After enrollment is completed, these data will be evaluated to assess the efficacy of MA-WBRT to mitigate declines in quality of life and cognition after whole brain radiation.

## Disclosures

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101337.

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