

Supplementary Methods

Radiation Therapy Guideline

Dose specification

The whole brain planning target volume (PTV) will receive 30 Gy in 10 fractions.

Treatment will be delivered once daily, 5 fractions per week, over 2 to 2.5 weeks.

Breaks in treatment should be minimized.

Hippocampal Avoidance-WBRT:

The dose is prescribed such as 90% of cranial content PTV is covered by the prescription dose.

Maximum dose to 2% of the PTV (D2%) is 37.5 Gy, and minimum dose to 98% of the PTV (D98%) is 25 Gy. Minimum dose to 100% of the hippocampal avoidance regions is 10 Gy, and dose to any point within the hippocampal avoidance regions cannot exceed 17 Gy.

Conformal WBRT:

The dose is prescribed such as 95% of cranial content PTV is covered by the prescription dose.

Maximum dose to 1% of the PTV (D1%) is 36 Gy, and minimum dose to 99% of the PTV (D99%) is 27 Gy.

Technical factors

Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. A megavoltage beam of 6MV must be used.

Simulation and immobilization

Patients will be immobilized in the supine position using an immobilization device such as an Aquaplast mask over the head. Patients will be treated in the immobilization device. A non-contrast treatment-planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2.5 mm will be required to define clinical and planning target volumes and hippocampal avoidance regions. The treatment-planning CT scan must be acquired with the patient in the same position and immobilization device as for treatment. This should be obtained within 2 weeks prior to initiating treatment. The MRI for radiotherapy planning and treatment-planning CT should be fused semi-automatically for hippocampal contouring.

Target volumes

- The clinical target volume (CTV) is defined as the whole brain parenchyma.
- The planning target volume (PTV) is defined as the CTV for conformal

WBRT.

- The PTV is defined as the CTV excluding the hippocampal avoidance regions for HA-WBRT.

Critical structures

- Bilateral hippocampal contours will be manually generated on the fused planning MRI CT image set by the treating physician according to contouring instructions specified on <http://www.rtog.org/corelab/contouringatlases/hippocampalsparing.aspx>.
- Hippocampal avoidance regions will be generated by three-dimensionally expanding the hippocampal contours by 5 mm. In the treatment arm of hippocampal avoidance, minimum dose to 100% of the hippocampal avoidance regions is 10 Gy, and dose to any point within the hippocampal avoidance regions cannot exceed 17 Gy.
- The lenses, orbits, optic nerves, and optic chiasm will be contoured as per the clinical experience of the treating physician. Care should be taken to minimize the dose to the lens and orbits. Dose to any point within the optic nerves or optic chiasm cannot exceed 37.5 Gy.
- The middle ear will be contoured as per the clinical experience of the treating physician. Dose to any point within the middle ear cannot exceed

37.5 Gy.

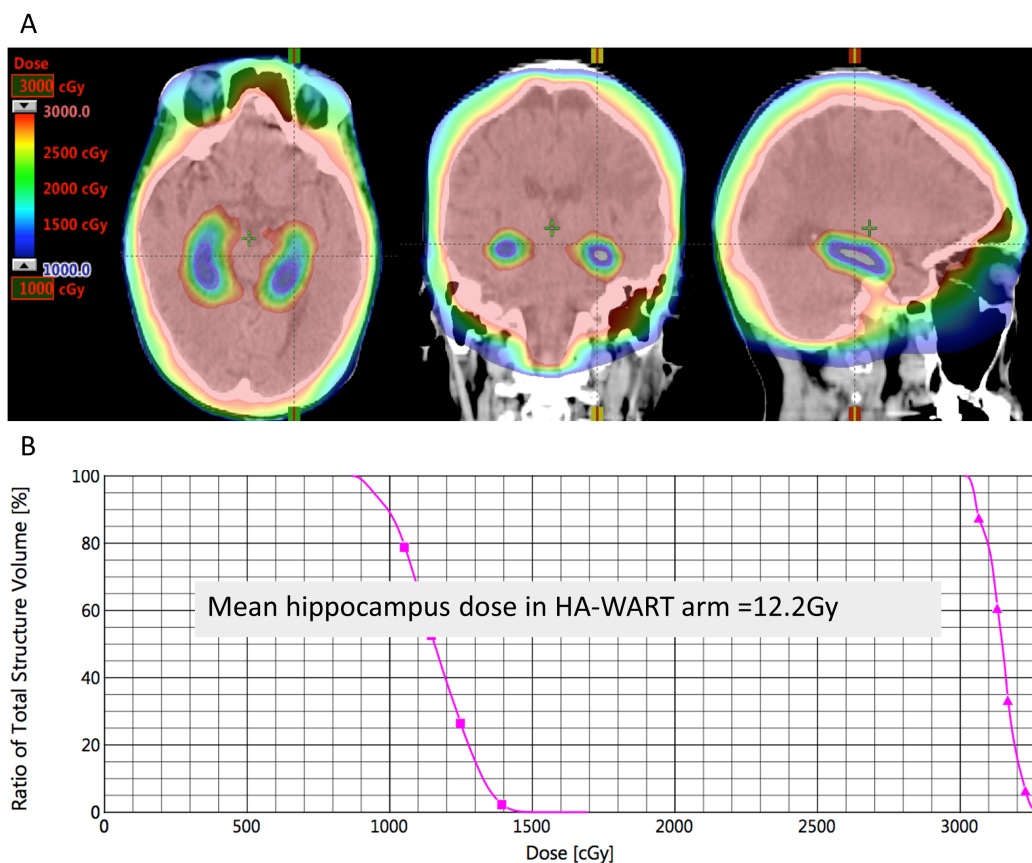
- The lens will be contoured and dose to any point within the lens cannot exceed 10 Gy.
- The parotid glands will be contoured and the mean dose to parotid glands cannot exceed 10 Gy.

Image verification and guidance

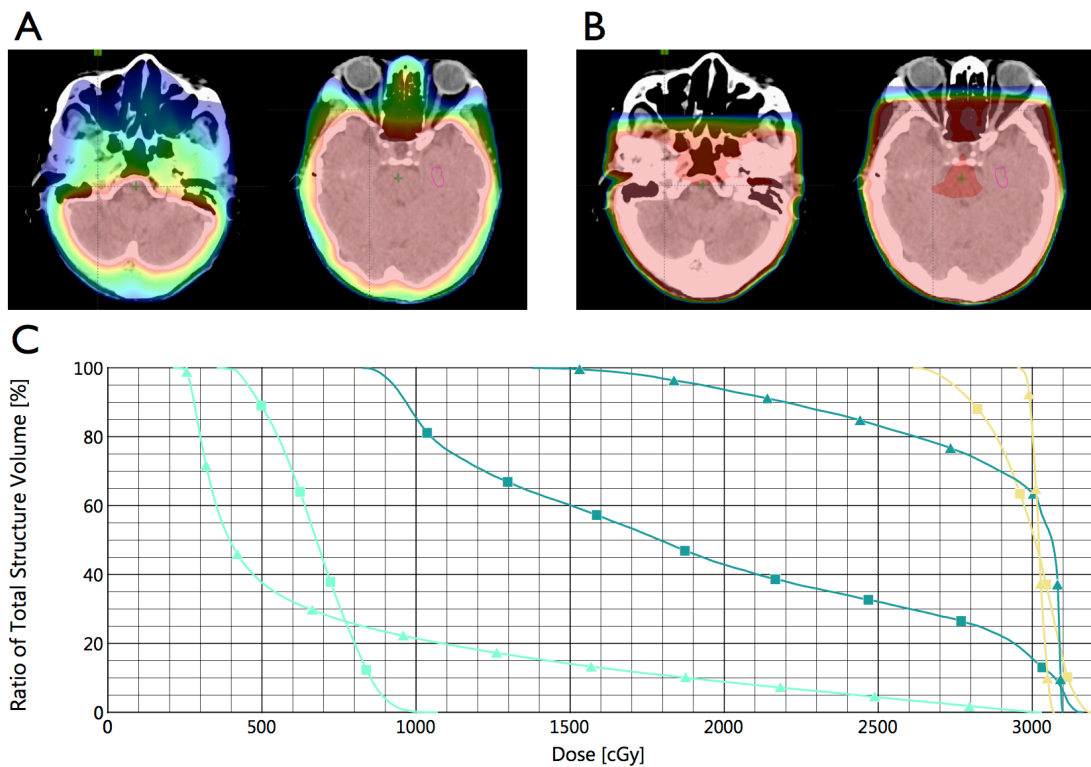
- Verification images are required. For all forms of dose delivery (IMRT, VMAT, RapidArc, or Tomotherapy), images that localized the isocenter placement shall be obtained.
- Before each daily fraction, reconstructed on-board CT images will be obtained to verify treatment position. A computer-assisted, bone-based automated alignment method will be registered with the skull on reference simulation CT images. Any deviation greater than 1 mm will be corrected.

Supplementary Figures

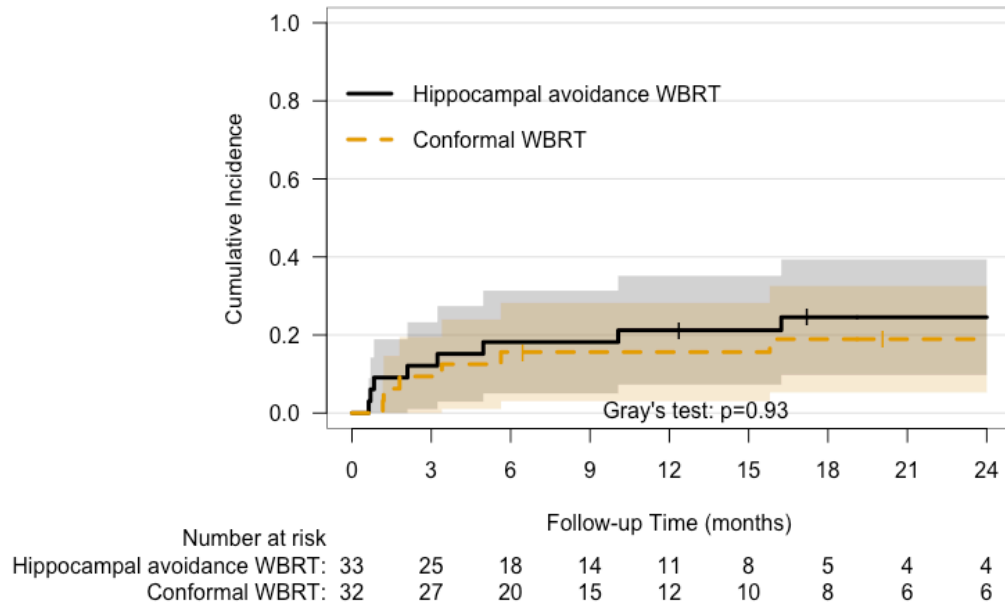
Supplementary Figure S1. (A) Representative iso-dose color-wash in axial, coronal, and sagittal views of the hippocampal avoidance conformal whole brain radiotherapy plan. (B) The cumulative dose volume histogram for hippocampus plotted according to treatment plans. The line with the square symbol denotes the plan from hippocampal avoidance conformal WBRT showing hippocampus D100% < 10 Gy. The line with the triangle symbol denotes the plan from standard WBRT showing hippocampus D100% > 30Gy.



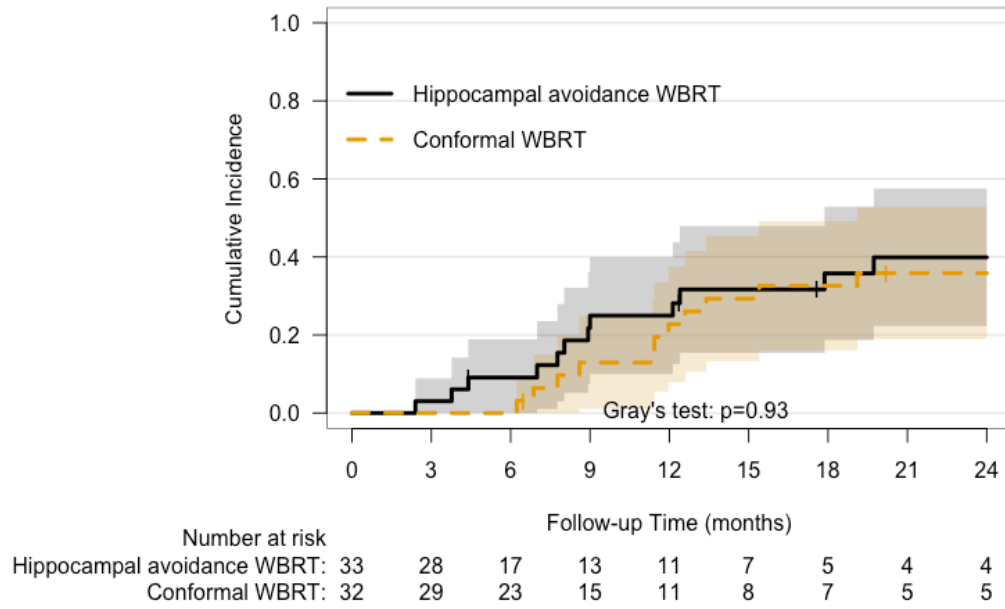
Supplementary Figure S2. (A) Representative iso-dose color-wash in axial views of conformal whole brain radiotherapy plan. (B) Representative iso-dose color-wash in axial views of standard 2-dimensional whole brain radiotherapy plan. (C) The cumulative dose volume histogram for eyes, ears, and optic nerves plotted according to treatment plans. The line with the square symbol denotes the plan from conformal WBRT. The line with the triangle symbol denotes the plan from 2-dimensional standard WBRT. The turquoise line is plotted for the eyes, the teal line is plotted for optic nerves, and the khaki line is plotted for the ears.



Supplementary Figure S3. Cumulative incidence of neurocognitive failure.



Supplementary Figure S4. Cumulative incidence of intracranial progression.



Supplementary Table 1. The summary of dosimetry results (average \pm standard deviation)

Dosimetry parameter	HA-WBRT	Conformal WBRT
PTV mean dose	3125.2 \pm 13.2 cGy	3130.1 \pm 93.1 cGy
Hippocampus mean dose	1219.3 \pm 55.9 cGy	NA
Hippocampus minimal dose	862.8 \pm 39.8 cGy	NA
Hippocampus maximal dose	1540.9 \pm 88.1cGy	NA
Right eye mean dose	1318.0 \pm 186.8 cGy	1175.2 \pm 159.9 cGy
Left eye mean dose	1278.8 \pm 124.0 cGy	1190.6 \pm 145.0 cGy
Right ear mean dose	2809.0 \pm 142.8 cGy	2785.6 \pm 162.9 cGy
Left ear mean dose	2785.7 \pm 149.6 cGy	2778.6 \pm 179.5 cGy

Abbreviations: HA-WBRT, hippocampal avoidance whole brain radiotherapy; WBRT, whole brain radiotherapy; PTV, planning target volume; cGy, centi-Gray, NA, not available