

# Hippocampal Avoidance Whole Brain Radiation Therapy is Associated with Preservation of Hippocampal Volume at Six Months: A Case Series

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## Abstract

**Background:** WBRTMel is a Phase 3 randomised trial comparing immediate whole brain radiation therapy (WBRT) with or without hippocampal avoidance (HA) with observation after local treatment of 1-3 melanoma brain metastasis. We examined a series of patients from this trial to determine effect of radiation therapy on the whole brain and hippocampal volume.

**Methods:** Patients on the WBRTMel trial without any intracranial failure at 6 months after randomization were included. Whole brain and hippocampal volumes at baseline and 6 months were contoured by investigators blinded to the treatment arm or the timing of scan.

**Results:** Twenty patients (7 observations, 9 non HA-WBRT and 4 HA-WBRT) with the median age of 62 years were included. There was no significant change in the mean whole brain volume from baseline to 6 months (1458.7 cm<sup>3</sup> to 1444.3 cm<sup>3</sup>, -0.78%) in the WBRT group or in the observation group (1569.0 cm<sup>3</sup> to 1572.5 cm<sup>3</sup>, 0.74%). There was evidence that change in the hippocampal volume from baseline to 6 months in the WBRT group (4.65 cm<sup>3</sup> to 4.36 cm<sup>3</sup>, 5.36%) may be larger than in the observation group (4.24 cm<sup>3</sup> to 4.24 cm<sup>3</sup>, 0%). Also, HA-WBRT tended to preserve the hippocampal volume at 6 months (mean change 0.16%) when compared with non HA-WBRT (-7.1%).

**Conclusions:** Preliminary data suggests non HA-WBRT may produce a selective atrophy of the hippocampus volume within 6 months. HA-WBRT can possibly minimise this effect. The full WBRTMel trial will be able to define this effect of RT on the hippocampal volume and correlate any change with neurocognitive function and quality of life data.

**Keywords:** Melanoma; Brain metastasis; Radiotherapy; Hippocampus; Neurocognitive function

**Abbreviations:** ANZMTG: Australia and New Zealand Melanoma Trials Group; TROG: Trans-Tasman Radiation Oncology Group; WBRTMel: Whole brain radiation therapy melanoma trial; WBRT: Whole brain radiation therapy; HA-WBRT: Hippocampal avoidance WBRT; MRI: Magnetic Resonance Imaging; HVL: Hopkins Verbal Learning Test.

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## Background

The Australia and New Zealand Melanoma Trials Group (ANZMTG) and Trans-Tasman Radiation Oncology Group (TROG)

are currently conducting a phase 3 randomised trial (WBRTMel, ANZMTG 01.07) to address the role of whole brain radiation therapy (WBRT) after local treatment of 1 to 3 melanoma metastases [1]. In this study, patients are randomised to WBRT (at least 30 Gy in 10 fractions) or observation. The role of WBRT after surgery or stereotactic radiosurgery of the single or oligo melanoma metastases is controversial. The rationale of WBRT is to treat microscopic disease with the aim to maintain long term cerebral control based on randomised studies including mostly non-melanoma histology. The WBRTMel is a unique as it is the single largest adjuvant whole brain radiation therapy trial including a single histology. However there is a risk of neurocognitive decline associated with WBRT [2]. Modern radiation therapy technologies, such as volumetric modulated arc therapy and helical tomotherapy can deliver a homogenous dose to the whole brain while conformally avoiding the hippocampus (Hippocampal avoidance WBRT, HA-WBRT) [3,4]. This technique has been shown in one phase 2 study to reduce the risk of neurocognitive deficit compared to historical control [5].

Before implementing HA-WBRT, we examined the risk of melanoma metastases in our eligible patients as a previous study by Gondi reported a trend of increased risk of melanoma metastases in the perihippocampal area [6]. We reported only 5.2% incidence of a melanoma metastasis within 5 mm of the hippocampus in 77 WBRTMel eligible patients [7]. As a result, HA-WBRT was introduced in 2013 into the WBRTMel protocol to allow treating clinicians the option of using this technique. Patients who were randomised to WBRT prior to this protocol amendment were treated with non HA-WBRT. This study compared the change in the whole brain volume and the hippocampal volume from baseline to 6 months after randomisation in the observation group, non HA-WBRT group and HA-WBRT group of the WBRTMel trial.

## Methods

### The ANZMTG/TROG WBRTMel

This is an actively accruing, phase 3 randomized trial to determine the role of WBRT after local treatment (surgery, stereotactic radiosurgery or both) in patients with 1 to 3 melanoma brain metastases [1]. After the local treatment of the metastases, patients are randomized to immediate WBRT or observation. The primary endpoint of the trial is distant intracranial control, as assessed by MRI scanning. The secondary objectives are to assess the effect of WBRT on: time to intracranial failure (local, distant) as assessed by MRI, quality of life, performance status, neurocognitive function, overall survival and death from neurological causes or not. Patients on this trial without any intracranial failure at 6 months after randomization were included in this sub-study. This was to minimize the potential impact of cranial failure or subsequent treatment on brain volume.

### Contouring of the hippocampus and whole brain

The hippocampal volumes at baseline and 6 months after randomization were contoured by investigators (HH, MV) without the knowledge of the treatment arm or the timing of scan using

the following technique. T1-weighted or T2-FLAIR structure image were used to contour using Analyze (version 10, Mayo Clinic) on a Windows XP workstation. Images were firstly re-sliced into 1 mm cubes, resulting in one voxel indicating a 1 mm<sup>3</sup> volume. The hippocampus was traced based on our published protocol [8]. Hippocampal tracing began anteriorly, where the head is visible as an enclosed gray matter structure inferior to the amygdala. Tracing continued posteriorly using surrounding white matter or CSF as boundaries. Subiculum was included within the hippocampus. Delineation stopped posteriorly when the wall of the ventricle was visibly contiguous with the fimbria. The whole brain volumes at baseline and 6 months were contoured by investigator (DN) using the automated tool of the Eclipse planning system (Varian Medical Systems).

### Statistical analysis

Summary statistics are provided for baseline measures stratified by group (**Table 1**). For outcomes, average change with respect to baseline along with its 95% confidence interval is calculated in each group [Observation, WBRT (HAWBRT and non HAWBRT)]. The small number of patients precluded inferential statistics and so all results are simply descriptive.

## Results

### Baseline characteristics

Twenty patients (7 observations, 9 non HA-WBRT and 4 HA-WBRT) with the median age of 62 years (range 27-83) were included. There was no significant difference in the baseline characteristics (**Table 1**). The number of metastases per patient was single

**Table 1** Demographic and clinical characteristics of the study population.

	ALL (n=20)	HA-WBRT (n=4)	No HA-WBRT (n=9)	Observation (n=7)
<b>Median Age (range)</b>	62 (27-83)	55 (27-73)	72 (48-83)	50 (39-72)
<b>Gender</b>				
Male	12 (60%)	3	6	3
Female	8 (40%)	1	3	4
<b>No. of metastasis</b>				
1	7 (35%)	1	5	1
2	8 (45%)	2	3	3
3	5 (25%)	1	1	3
<b>Surgery</b>				
Yes	15 (75%)	3	7	5
No	5 (25%)	1	2	2
<b>Stereotactic Radiosurgery</b>				
Yes	9 (45%)	2	2	5
No	11 (55%)	2	7	2
<b>No. of SRS lesion</b>				
0	11 (55%)	2	7	2
1	2 (10%)	1	0	1
2	3 (15%)	0	1	2
3	4 (20%)	1	1	2

(7, 35%), two (8, 40%) or three (5, 25%). Local treatment of the metastasis was craniotomy (15, 75%), stereotactic radiosurgery (9, 45%) or both (4, 20%).

### Change in brain volume

The small number of patients precluded inferential statistics and so these results are descriptive (**Table 2**). There was no significant change in the mean whole brain volume from baseline (1458.7 cm<sup>3</sup>) to 6 months (1444.3 cm<sup>3</sup>, -0.78%) in the WBRT group (non HA-WBRT and HA-WBRT) or in the observation group (1569.0 cm<sup>3</sup> to 1572.5 cm<sup>3</sup>, 0.74%). There was evidence that change in the hippocampal volume from baseline to 6 months in the WBRT group (4.65 cm<sup>3</sup> to 4.36 cm<sup>3</sup>, -5.36%) may be larger than in the observation group (4.24 cm<sup>3</sup> to 4.24 cm<sup>3</sup>, 0%). Also, HA-WBRT preserved the hippocampal volume at 6 months (mean change in hippocampal volume was -0.16%) when compared with non HA-WBRT (-7.81%).

### Discussion

Results from this small descriptive study suggest that non-HAWBRT is associated with atrophy of the hippocampus. there was a 7.3% reduction in the hippocampal volume after 30 Gy of radiation of non-HAWBRT. Whilst the sample size was small, there was no significant change in the hippocampal volume in patients treated with HA-WBRT. A recent study of 19 patients treated with cranial radiation showed a relative decrease in the hippocampal volume of 3% relative to controls [9].

Atrophy of the hippocampus has been related to memory disorders and cognitive impairment. In Alzheimer's disease, the hippocampus is one of the first areas of the brain to be affected by neurodegenerative lesions. The hippocampal volume can be affected by external factors such as heavy alcohol intake and post-traumatic stress disorder [10,11]. Recent studies show that the total dose of radiation to hippocampi plays an important role in the neurocognitive decline of patients after radiation therapy to the brain. In particular, deficits in learning, memory, and spatial processing observed in patients who have received WBRT are thought to be related to the dose to the hippocampus [12]. Radiation dose greater than 7.3 Gy (in 2 Gy equivalent) to 40% volume of the hippocampi was associated with long term impairment in list-learning delayed recall after RT for benign or low-grade adult brain tumors [13]. In the paediatric patients,

**Table 2** Change in the whole brain and hippocampal volumes from baseline to 6 months.

Whole Brain Volume (cm <sup>3</sup> )		
	Baseline	6 months
Observation	1569.0	1572.2
Non HA-WBRT	1446.2	1438.6
HA-WBRT	1486.3	1457.2
Hippocampal Volume (cm <sup>3</sup> )		
Observation	4.24	4.24
Non HA-WBRT	4.78	4.38 (-7.185%)
HA-WBRT	4.37	4.36

there are prospective data demonstrating a significant association between increasing radiation dose to hippocampus and decline in neurocognitive skills following cerebral irradiation [14]. A recent MRI spectroscopy study showed a correlation between memory changes to hippocampal N-acetylaspartate concentration after WBRT [15].

There is only one completed prospective study on HA-WBRT (RTOG 0933) [16]. This phase II clinical trial confirmed the benefit of hippocampal sparing during WBRT in patients with up to 10 brain metastases. At 4 months, the mean relative decline in the Hopkins Verbal Learning Test (HVLT) delayed recall from baseline was 7% (95% CI: -4.7 to 18.7%) and this was significant when compared with historical control with 30% (p=0.0003). Currently NRG Oncology is currently conducting a randomized phase 3 trial of memantine with WBRT with or without hippocampal sparing technique in patients with brain metastases.

The first 100 patients of the WBRTMe1 trial were included in a pre-planned interim analysis. The results were reviewed by an independent Data Safety Monitoring Committee who had recommended continuation of the trial. We are now extending the WBRTMe1 accrual target to increase the number of patients treated with HA-WBRT. This will increase the number of patients treated with HA-WBRT technique to allow for meaningful comparison of the neurocognitive function between the 3 groups of patients (observation, non HA-WBRT and HA-WBRT).

### Declarations

#### Ethics approval

Approval by Sydney Local Health District ethics committee.

#### Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

#### Competing interests

None.

#### Authors' contributions

Study concept and design: Angela Hong, Gerald Fogarty, Michael Valenzuela.

#### Data collection

Angela Hong, Harry Hallock, Michael Valenzuela and Diana Ng.

#### Data analysis

All authors.

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