

Phase 3 International Trial of Adjuvant Whole Brain Radiotherapy (WBRT) or Observation (OBS) Following Local Treatment of 1-3 Melanoma Brain Metastases (MBMs)

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Purpose/Objective(s)

The role of adjuvant WBRT in MBMs is controversial. This phase 3 trial compares WBRT with Obs following local treatment of 1-3 MBMs.

Materials/Methods

The primary endpoint is distant intracranial failure (DIF) within 12 months of randomization. The *a priori* neurocognitive function (NCF) endpoint is Hopkins Verbal Learning Test-Revised (HVLT-R) delayed recall at 4 months. Secondary endpoints include local failure (LF), overall survival (OS) and global quality of life (QoL). Analyses were conducted on intention-to-treat basis with nominal two-sided significance level 5%. Drug therapy was allowed. Effective drugs became available during the trial and their impact was analyzed.

Results

Of 586 eligible patients, 215 consented from 31 sites in 3 countries (Australia, UK and Norway) between 2009 and 2017. Eight (0.04%) who withdrew or had no data collected were excluded. 107 were randomized to Obs and 100 to WBRT. Mean age was 62 years, 67% were males, 61% with single MBM of mean size 2cm, 67% had extracranial disease at randomization. The two arms were well matched. NCF was completed by English speakers; 50 WBRT and 70 Obs pts at baseline, declining to 26 and

35 respectively at 4 months. Within 12 months, 54 (50.5%) Obs patients had DIF compared with 42 (42.0%) WBRT patients (OR 0.71; 95% CI 0.41-1.23; $p=0.222$). There was no difference in LF ($p=0.100$) or OS (log-rank $p=0.861$). 53% (Obs) and 59% (WBRT) patients were alive at 12 months. There was no significant between-group difference in mean intervention effect on global QoL ($p=0.083$). Patients who received T-cell checkpoint inhibitors and/or mitogen-activated protein kinases (MAPK) pathway inhibitors and WBRT before or within 12 months of randomization had DIF rate 29% compared with Obs and no systemic therapy had 44%, but this was not significant ($p=0.228$). Obs patients had greater relative improvement from baseline in HVLt-R at every timepoint. At 4 months, Obs had 20.9% improvement from baseline in HVLt-R-delayed recall compared to 2.7% decline in WBRT; overall adjusted average intervention effect 23.6% (95%CI 9.0, 38.2; $p = 0.0018$). There was no difference in time to cognitive failure or in proportions with global cognitive impairment.

Conclusion

This level one evidence shows WBRT does not improve outcomes in MBMs. This practice-changing trial justifies the recent move away from WBRT that occurred during the course of the trial.