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Original Article

A Randomised Phase II Trial of Hippocampal Sparing Versus Conventional Whole Brain Radiotherapy After Surgical Resection or Radiosurgery in Favourable Prognosis Patients With 1–10 Brain Metastases

G.A. Whitfield [*], H. Bulbeck [†], L. Clifton-Hadley [‡], D. Edwards [‡], S. Jefferies [§], M.D. Jenkinson [¶||], M. Griffin [**], J. Handley [††], D. Megias [‡‡], P. Sanghera [§§], R. Shaffer [¶¶], S. Short [||||], W. Wilson [‡]

[*] *The University of Manchester, Manchester Academic Health Science Centre, The Christie NHS Foundation Trust, Manchester, UK*
[†] *Brainstrust – the Brain Cancer People, Cowes, Isle of Wight, UK*
[‡] *Cancer Research UK and University College London (CR UK and UCL) Cancer Trials Centre, University College London, London, UK*
[§] *Cambridge University Hospitals NHS Foundation Trust, Box 193, Hills Road, Cambridge, UK*
[¶] *The Walton Centre NHS Foundation Trust, Lower Lane, Fazakerley, Liverpool, UK*
[||] *Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Brownlow Hill, Liverpool, UK*
[**] *Department of Oncology, Nottingham University Hospitals NHS Trust, Nottingham, UK*
[††] *The Christie NHS Foundation Trust, Manchester, UK*
[‡‡] *Department of Clinical Oncology, Mount Vernon Cancer Centre, Northwood, UK*
[§§] *Hall-Edwards Radiotherapy Research Group, Cancer Centre, Queen Elizabeth Hospital, Birmingham, UK*
[¶¶] *GenesisCare, Cromwell Hospital, 164-178 Cromwell Rd, Kensington, London SW5 0TU, UK*
[||||] *Leeds Institute of Medical Research at St. James's, St. James's University Hospital, Leeds, UK*

Abstract

Aims: To assess in patients with 1–10 brain metastases, each of which has been treated by neurosurgery or stereotactic radiosurgery, whether hippocampal sparing whole brain radiotherapy (HS-WBRT) better spares neurocognitive function (NCF) than standard WBRT. Further, to assess whether a phase III randomised trial of HS-WBRT would be feasible in the UK.

Materials and methods: A multicentre, randomised, open label phase II trial was undertaken, randomising patients to 30Gy in 10 fractions of WBRT or HS-WBRT. The primary endpoint was decline in Total recall using Hopkins Verbal Learning Test Revised (HVLT-R) at 4 months post treatment. To assess this, we aimed to recruit 84 patients over 3 years. Secondary endpoints included further measures of NCF, quality of life, duration of functional independence, local control of treated metastases, development of new metastases, disease control within the hippocampal regions, overall survival, steroid and antiepileptic medication requirements, and toxicity.

Results: The trial closed prematurely due to slower than anticipated recruitment. From April 2016 to January 2018, 23 patients were randomised. Follow up was a median of 25 months. Fifteen patients (6 WBRT, 9 HS-WBRT) were assessed for the primary endpoint; of these, 1 in each arm experienced significant decline in the 4-month HVLT-R Total recall score ($p = 0.8$). Patients in the HS-WBRT arm experienced less insomnia ($p < 0.01$) and drowsiness ($p < 0.01$). There were no differences in other secondary endpoints.

Conclusion: A phase III randomised trial of HS-WBRT was shown not to be feasible at this time in the UK. As most randomised trials of HS-WBRT reported to date share common endpoints, including NCF, an individual patient data meta-analysis should be undertaken.

Key words: Avoidance; Hippocampal; Neurocognitive; Radiotherapy; Sparing; Whole brain

Author for correspondence: G.A. Whitfield, The Christie NHS Foundation Trust, 550 Wilmslow Road, Manchester M20 4BX, UK.
E-mail address: gwhitfield@nhs.net (G.A. Whitfield).

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Introduction

Brain metastases occur in around 10–40% of people with solid extra-cranial primary tumours [1]. Due to better systemic therapies and increased MRI surveillance, patients are being identified with brain metastases earlier, when aggressive treatment may improve outcomes. Such treatment can include systemic therapy, neurosurgical excision, and radiotherapy. In the past, whole brain radiotherapy (WBRT) was a key treatment, either alone or after surgery. Two randomised trials [2,3] demonstrated that adding stereotactic radiosurgery (SRS) to WBRT improved local control, with the larger trial [3] showing that adding SRS improved Karnofsky Performance Status (KPS), decreased steroid use at 6 months, and with a solitary brain metastasis, improved overall survival (OS). Since then, surgery and/or SRS have more often been used in better prognosis patients [4]. For 1–4 brain metastases, adding WBRT to surgery and/or SRS improves both local and distant intracranial disease control, without affecting OS [5,6]. For 5–10 brain metastases, there is no randomised evidence guiding whether to add WBRT to surgery and/or SRS. It is reasonable to assume a similar effect on local control of individual metastases (as in patients with fewer metastases), while the risk of distant intracranial progression is higher [7], and therefore there might be a stronger case for adding WBRT.

There is a strong rationale for supposing that hippocampal sparing during WBRT might help preserve neurocognitive function (NCF) [8,9]. In patients with brain metastases, the RTOG 0933 trial provided Phase II data for hippocampal sparing WBRT (HS-WBRT), showing better NCF as measured by delayed recall on the Hopkins Verbal Learning Test-Revised (HVLT-DR) at 4 months compared to a historical control group [9].

When initiating our trial, there was no randomised trial data comparing WBRT and HS-WBRT in patients with brain metastases. We identified 4 planned randomised studies of WBRT versus HS-WBRT, each with some differences or limitations such that a UK study had the potential to be complementary.

Materials and Methods

Trial Design and Eligible Patients

The trial was designed as a multicentre, randomised, open label phase II trial to assess whether HS-WBRT was associated with less decline in NCF than conventional WBRT in patients with 1–10 brain metastases after neurosurgery or SRS. It also aimed to determine whether a phase III randomised trial of HS-WBRT would be feasible in the UK.

Eligible patients were $\geq$16 years, with KPS $\geq$70, and $\leq$10 distinct brain metastases (prior to 31/05/2017 $\leq$4 brain metastases) from histologically confirmed systemic malignancy, each brain metastasis to have been treated by surgery or SRS. Ability to complete a NCF assessment in English and provide informed consent was also required.

Prior brain radiotherapy was not permitted, apart from a single course of SRS completed within 1–4 weeks of randomisation and within 4–6 weeks of start of trial treatment. Prior neurosurgery for brain metastases was not permitted, apart from a single operation within 1–4 weeks of randomisation and within 4–6 weeks of start of trial treatment. Exception was made if one or more earlier operations resulted in no residual tumour at the resection site or residual tumour had been treated by SRS immediately prior to trial entry. Exclusion criteria were small cell carcinoma, haematological malignancies or central nervous system malignancies, leptomeningeal metastases, metastases currently or previously within 5mm of either hippocampus, metastases within the brainstem, one or more SRS treated metastases in close proximity to critical normal organs (organs at risk, OARs) preventing safe delivery of the trial protocol doses, contraindication to MRI, disease specific graded prognostic assessment score $\leq$1.0 [10], dementia unrelated to the brain metastases, pregnant women and women of childbearing potential unwilling to use an acceptable method of contraception from informed consent until completion of radiotherapy.

Patients were randomised 1–4 weeks ($\pm$ 3 days if needed for logistical issues) after neurosurgery or last SRS fraction in a 1:1 ratio to HS-WBRT or WBRT using minimisation. Stratification factors were treatment centre, histology (breast/other), and number of brain metastases (single/multiple).

Baseline Assessments

Pre-randomisation assessments included contrast CT chest, abdomen and pelvis within 8 weeks of randomisation, and MRI brain, T1-weighted with gadolinium contrast and maximum 1.5mm slice spacing within 3 weeks of randomisation (after any neurosurgery). On the day of randomisation, or up to 3 days prior to this, KPS, baseline toxicity (NCI CTCAE v4.03) and steroid, anti-epileptic and hormonal drug use were recorded, Quality of Life (QoL) questionnaires (EORTC QLQ C30, BN20 and EuroQol EQ-5D) completed, and NCF assessment undertaken. NCF assessment comprised the Test of Premorbid Function (TOPF), Trail Making Tests A and B (TMT-A, TMT-B), Controlled Oral Word Association Test (COWAT), Hopkins Verbal Learning Test – Revised (HVLT-R), Wechsler digit span, and the Story Recall and Figure Recall parts of the Brain Injury Rehabilitation Trust Memory and Information Processing Battery (BMIPB).

Treatments

The trial treatment (WBRT or HS-WBRT) was required to start between 4 weeks and 6 weeks (+3 days if needed for logistical issues) from neurosurgery or last SRS fraction.

Patients were immobilised supine in a custom thermoplastic mask. A CT planning scan was acquired with $\leq$1.5mm contiguous slices. The SRS mask and CT planning scan could be used if slice thickness was $\leq$1.5mm. The MRI planning scan was the baseline MRI scan obtained in the 3

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weeks before randomisation. For neurosurgical patients this had to be post-operative, while for SRS treated patients optionally the SRS planning scan could be used. A 3D T1w post contrast sequence with ≤1.5mm contiguous slices and in plane voxel size ≤1.0 x 1.0mm, reconstructed in ≤1.5mm slices in all 3 planes was required. A pre-contrast 3D Rapid Gradient Echo sequence with ≤1.5mm thick contiguous slices and in plane voxel size ≤1.0 x 1.0mm with optimisation of inversion recovery for grey-white matter delineation was optional to aid in hippocampal delineation.

Radiotherapy was CT planned in both arms. In the HS-WBRT arm, the MRI planning scan was co-registered to the CT planning scan. In both arms, the whole brain (to upper border of C1, or at least 2cm below any metastasis but not below upper border of C2), eyes and lenses were contoured based on CT. In the HS-WBRT arm, optic nerves, optic chiasm and hippocampi had to be delineated based on CT and MRI. In the WBRT arm, the Planning Target Volume (PTV_3000) was the Brain+ 5mm expansion. In the HS-WBRT arm, the Planning Target Volume (PTV_hs3000) was the Brain+3mm expansion, excluding hippocampal avoidance regions (hippocampi+5mm expansion). Both arms were prescribed 30Gy in 10 fractions (median dose to PTV) over 2 weeks. Prescription to mean dose was permitted if within 1% of median dose.

WBRT was CT planned with parallel opposed 6MV fields, using wedging or forward planned Intensity-modulated radiotherapy (IMRT) if necessary to meet dose constraints. HS-WBRT could be delivered by Tomotherapy™, Intensity Modulated Arc Therapy or fixed field IMRT. PTV dose constraints are shown in Table 1. For OARs, in the WBRT arm, eye and lens doses were to be kept as low as possible consistent with PTV coverage. OAR constraints in the HS-WBRT arm have been previously described [11]. For each hippocampus, D2% (near maximal dose exceeded in only 2% of the volume) was required to be <15Gy, and mean hippocampal dose <11Gy (optimally <10Gy), achievable with linac IMRT and comparable to dosimetry in the RTOG 0933 trial [9] which required minimum hippocampal dose <10Gy and maximum dose <17Gy. As minimum and maximum doses are not reliably reproduced in different planning systems, we preferred to use D2% and mean hippocampal dose.

Treatment verification was per institutional policy. Image guidance in the WBRT arm was per institutional policy. In the HS-WBRT arm, daily image guidance with online positional correction was mandated, preferably using Cone Beam CT, Tomotherapy MV-CT or orthogonal kV imaging where available rather than MV portal imaging. Trial radiotherapy quality assurance (QA) was provided by the NCRI Radiotherapy Trials QA (RTTQA) Group, as outlined previously [11].

Supportive medications including steroids and anti-emetics could be given per standard practice. Anti-epileptics could be started for definite or possible seizures, and patients already on anti-epileptics could continue these. Chemotherapy and targeted agents had to be withheld for at least 7 days prior, during, and for 7 days after radiotherapy.

Follow up Assessments

During treatment at weekly clinical review adverse events (AEs) of all grades and changes in steroid or anti-epileptic medication were to be recorded.

Patients were followed up at 2 and 4 months (± 7 days), then at 6, 9, 12, 18 and 24 months (± 14 days) from the last day of radiotherapy. At each follow up, patients had MR brain imaging (within the same time window or up to 3 days earlier) and completed the same questionnaires as at baseline. The same NCF assessments were completed (at months 2, 4, 6, 12 and 24 months) as at baseline, except that the TPOF was not repeated and different versions of NCF tests were used where available. At each review, KPS (patient and clinician assessed), changes in steroid and anti-epileptic drug usage, systemic anti-cancer therapy and further brain radiotherapy, and AEs were recorded. AEs of all grades were recorded up to the 4 month follow up, after which only AEs of grade ≥3 thought possibly, probably or definitely related to trial treatment and any neurological AEs of grade ≥3 were recorded.

Requirements for the MRI at follow up were 3D T1W pre- and post-contrast and a 3D FLAIR with ≤1.5 mm contiguous slices and in plane voxel size ≤1.0 x 1.0 mm, reconstructed into the other 2 planes in 3 mm slices, and 5–6mm axial T2W and DWI sequences. The follow up MRI should have been reported by the local radiologist in accordance with the RANO-BM criteria for radiographic response [12], without consideration of the steroid dose or clinical response.

Table 1
Summary of dose requirements for the planning target volume in the WBRT arm (PTV_3000) and HS-WBRT arm (PTV_hs3000)

	Dose required		
	WBRT arm (PTV_3000)	HS_WBRT arm (PTV_hs3000)	
	Gy (%)	Optimal (Gy)	Mandatory (Gy)
98%	25.5 (85%)	23.5	22.5
95%	27.0 (90%)	26.0	25.0
90%	-	27.5	26.5
50%*	30 (100%)	30.0	30.0
2%	<33 (110%)	33.0	35.0

* Prescription to mean dose of 30Gy is allowed if within 1% of median dose.

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Endpoints

The primary endpoint was decline in Total recall, using the HVLT-R at 4 months. Secondary endpoints included further measures of NCF, QoL, duration of functional independence (KPS $\geq$70), local control of surgery/SRS treated metastases, development of new metastases (distant intracranial control), disease control within the hippocampal regions, OS, steroid and antiepileptic medication and toxicity (CTCAE v4.03).

Sample Size and Statistical Analysis

Using a single stage design, we required 58 patients to detect a NCF decline rate (defined as a $\geq$5-point decline in HVLT-R Total recall score at 4 months from baseline) [13,14] of 42% in the HS-WBRT arm compared to 64% in the WBRT arm, with 1-sided 20% statistical significance and 80% power. Assuming a 25% mortality rate by the time of the primary endpoint and 5% loss to follow up, we aimed to recruit 84 patients over 3 years.

The proportion of patients with significant NCF decline at 4 months post-treatment was compared between arms using Fisher's exact test. Changes in other measures of NCF between baseline and 4 months were analysed as continuous measures using linear regression with adjustment for baseline scores. Those that contravened the normality assumption were assessed using the Mann-Whitney test. QoL summary measures were assessed across all time points using mixed-effects linear regression models with adjustment for baseline values. Time spent functionally independent was measured from randomisation until the first instance where KPS $<$ 70, with those remaining $\geq$70 censored at the date last seen or death if died during follow up. Control of metastases was split into three time-to-event outcomes, measured from randomisation until local disease progression (of surgery/SRS treated metastases), development of new metastases, or development of new metastases in the hippocampal avoidance regions. In all cases, death was treated as a competing risk and any patients who did not die or experience an event of interest were censored at the date of last MR scan. OS was measured from the date of randomisation until death from any cause, otherwise censored at the date last seen. The number and proportion of patients requiring steroid and/or antiepileptic medication at 4 months post-treatment were tabulated and compared between arms using Fisher's exact tests.

Results

Recruitment

The first study site opened to recruitment on 12/4/2016 and subsequently 6 more sites opened. Twenty-three patients were recruited between August 2016 and January 2018 from 3 sites. The trial closed on 23/01/2018, due to slower than anticipated recruitment. End of trial was declared on 16/02/2021 after all surviving patients had completed final follow up and all data queries had been resolved. Baseline patient characteristics are described in Table 2.

Treatment Compliance

The CONSORT diagram is shown in Figure 1. Two patients had delays which meant they had their fractions over 15 days, both in the HS-WBRT arm: one due to a grade 1 transient ischemic attack and the other due to a grade 3 cushingoid reaction followed by linac breakdown.

Compliance with Follow up Neurocognitive Testing

The 2, 4, 6, 12 and 24 month NCF assessments were completed by 9/11, 6/10, 4/6, 3/4 and 3/3 surviving patients in the WBRT arm and 8/11, 9/11, 7/10, 5/5 and 4/4 in the HS-WBRT arm.

Table 2
Baseline patient characteristics

Characteristic	WBRT N=11	HS WBRT N=11
Age, median years (range)	52 (34–76)	60 (35–71)
Sex, n (%)		
Female	7 (63.6)	6 (54.5)
Male	4 (36.4)	5 (45.5)
Karnofsky performance status, n (%)		
100	1 (9.1)	1 (9.1)
90	6 (54.5)	5 (45.5)
80	4 (36.4)	3 (27.3)
70	0	2 (18.2)
Systemic disease brain metastases originated from, n (%)		
Breast cancer	3 (27.3)	3 (27.3)
Gastrointestinal cancers	1 (9.1)	3 (27.3)
Lung cancer	3 (27.3)	4 (36.4)
Renal cell carcinoma	1 (9.1)	1 (9.1)
Other*	3 (27.3)	0
Number of target and non-target lesions, n (%)		
1	8 (72.7)	8 (72.7)
2	1 (9.1)	1 (9.1)
3	1 (9.1)	0
4	0	2 (18.2)
5	1 (9.1)	0
Does the patient have any extra cranial metastases, n (%)		
No	6 (54.5)	5 (45.5)
Yes	5 (45.5)	6 (54.5)
Did patient have neurosurgery, n (%)		
No	3 (27.3)	3 (27.3)
Yes	8 (72.7)	8 (72.7)
Any steroids taken by the patient, n (%)		
No	6 (54.5)	5 (45.5)
Yes	5 (45.5)	6 (54.5)
Any anti-epileptics taken by the patient, n (%)		
No	6 (54.5)	9 (81.8)
Yes	5 (45.5)	2 (18.2)

* 1 Endometrial carcinoma, 1 'Possibly head and neck or new lung cancer", 1 "Ca cervix adenosquamous'.

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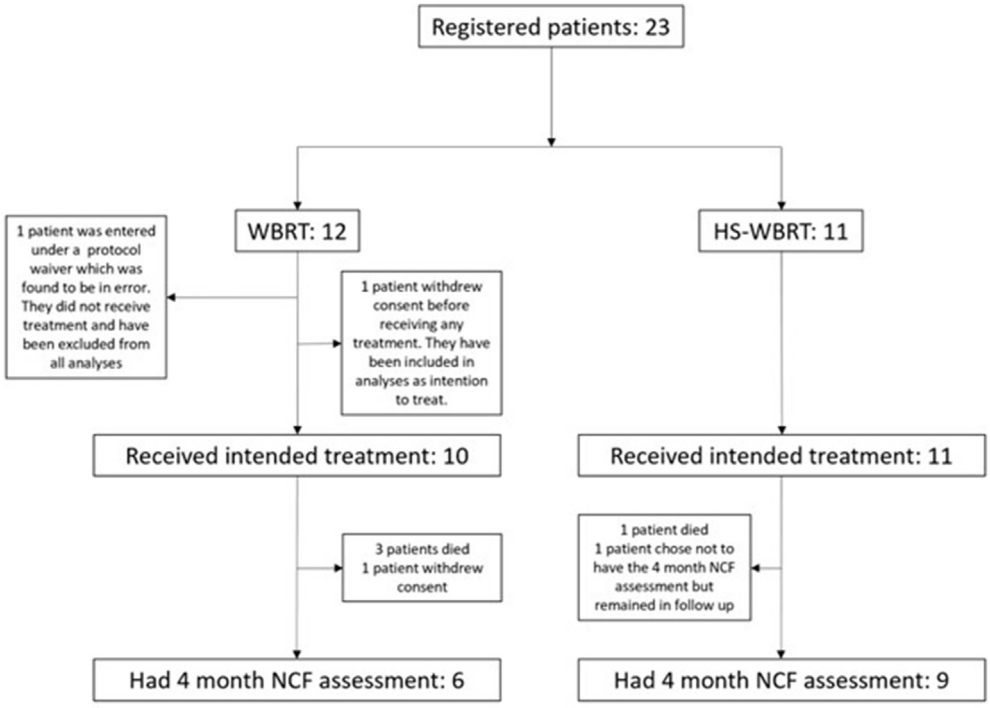

Fig 1. CONSORT diagram for the trial.

Neurocognitive Function and Toxicity

There was no clear difference between arms in proportion of patients experiencing significant decline in NCF (1/6 WBRT vs 1/9 HS-WBRT, $p > 0.99$). The change in HVLT-R scores over time in each arm is shown in supplementary Figure 1. Sensitivity analyses assuming those with missing assessments did or did not have significant NCF decline found no indication of a significant benefit in either arm (supplementary table 1). There was no evidence of a difference in NCF among any of the other measures used (supplementary table 2).

Five patients in each arm experienced at least one grade $\geq$3 AE. There was no apparent difference in toxicity profile between the two arms (supplementary table 3). There was no evidence of a difference between arms in steroid or anti-epileptic medication usage at 4 months post-treatment. Six patients in the WBRT arm and 9 in the HS-WBRT arm received further anti-cancer treatment at some point during their follow up.

Overall Survival and Disease Control

Follow-up was a median of 25 months (range for survivors 4.7 to 26.3 months). There was no clear difference in OS (Figure 2). There was no evidence of a difference between arms in local control of surgery/SRS treated metastases (12-month rate 77.8% WBRT vs 63.6% HS-WBRT, $p = 0.6$) or distant intracranial control (89.9% WBRT vs 72.7% HS-WBRT, $p = 0.2$). Only one patient developed new metastases within the hippocampal avoidance regions and they were in the HS-WBRT arm.

Quality of Life

Patients in the HS-WBRT arm experienced significantly less insomnia on the EORTC QLQ C30 scale ($p < 0.01$) and less drowsiness on the BN20 scale ($p < 0.01$) compared to patients in the WBRT arm (supplementary table 4, supplementary Figures 3 and 4). There was no difference in any other measures of QoL, including in EQ-5D scores or length of time patients remained functionally independent (KPS $\geq$70) (supplementary table 4, supplementary Figure 2).

Discussion

Despite several protocol amendments to improve recruitment, recruitment was slower than planned. The Independent Data Monitoring Committee (IDMC) noted in May 2017 that many sites wishing to set up lacked resources to fulfil QA requirements, while several active sites had not approached or recruited patients despite the protocol amendments and many patients approached had not agreed to participate in the trial. Changes in standard clinical practice with less use of WBRT were likely contributory; a factor in this was the publication [15] of a phase 3 randomised trial of SRS versus SRS plus WBRT showing that cognitive deterioration at 3 months was significantly more likely in the SRS plus WBRT group. The trial was closed to recruitment in January 2018 after the IDMC's target of recruiting 25 patients had not been reached.

The overall aim, to assess whether HS-WBRT is able to reduce decline in NCF compared to conventional WBRT in patients with 1–10 brain metastases after neurosurgery or

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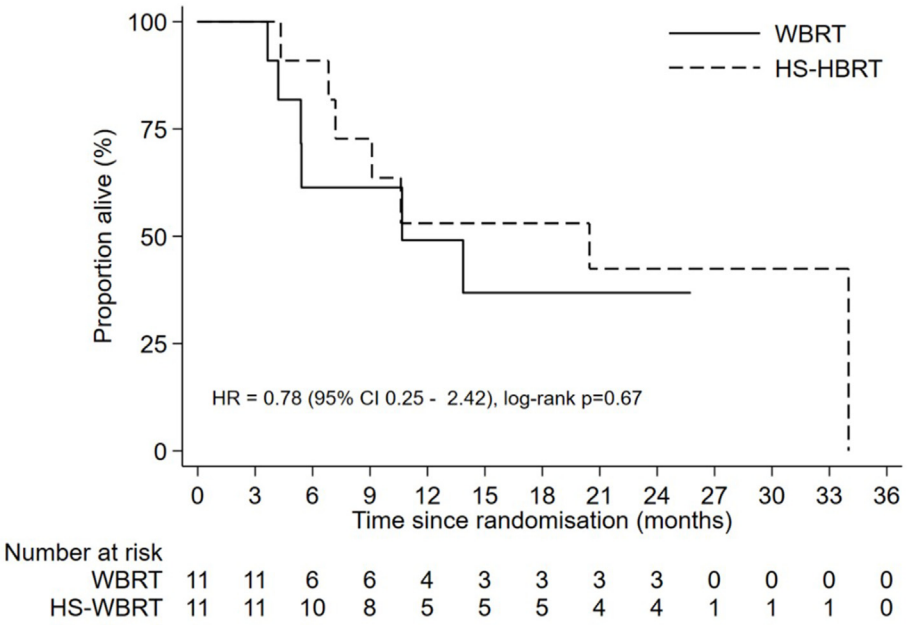

Fig 2. Overall survival curves by treatment arm; 6-month overall survival (OS) WBRT 61.4%, HS-WBRT 90.9%; 12-month OS WBRT 49.1%, HS-WBRT 53.0%; median OS WBRT 10.7 months, HS-WBRT 20.5 months.

SRS, could not be answered, due to the lack of statistical power. Based on the 23 patients recruited there was no evidence of a difference in NCF in the primary endpoint or any other NCF test. Compliance among surviving patients with repeated NCF assessments was high. This is encouraging as the impact of brain treatments on NCF is of importance to patients [16] and a vital area of research in several current studies.

The secondary aim was to determine whether a phase III randomised trial of HS-WBRT would be feasible in the UK. The trial demonstrated that at present this would not be feasible, due to a move away from WBRT. Although some centres had resource issues, several active centres did not recruit, with clinician and/or patient choice accounting for approximately 28% of all screening failures.

The reduction in insomnia and drowsiness in the HS-WBRT arm may be a spurious finding as a result of the small sample and multiple significance testing, but it will be interesting to see whether this is replicated in other studies, and if so, for how long the effect persists.

As well as showing the incidence of expected side effects such as fatigue, nausea and vomiting, headache, taste disturbance, alopecia and radiation dermatitis, patients experienced other side effects which are perhaps under appreciated by clinicians, such as ear and labyrinth disorders and blurred vision or dry eye (Supplementary information).

A search of PubMed on 26 December 2023 (*Search terms:* (((hippocamp*[Title/Abstract]) AND (brain[Title/Abstract] OR cranial[Title/Abstract])) AND (radiotherapy[Title/Abstract] OR radiation[Title/Abstract] OR irradiation[Title/Abstract] OR WBRT[Title/Abstract] OR PCI[Title/Abstract])) AND (trial[Title/Abstract]) showed 4 published trials involving a randomised comparison of WBRT and HS-WBRT, including 2 in patients with brain metastases and 2 of prophylactic cranial irradiation (PCI) in small cell lung cancer (SCLC) (Table 3).

The largest published trial in brain metastases, the Phase III NRG CC001 trial, randomised 518 patients to WBRT plus memantine versus HS-WBRT plus memantine [17], both arms 30Gy in 10 fractions. The primary end point was time to cognitive function failure, defined as decline using the reliable change index [13] on at least one of 6 NCF tests. The risk of cognitive failure was significantly lower in the HS-WBRT arm ($p = 0.03$). OS was not significantly different between arms. The other reported randomised trial in patients with brain metastases, a phase II trial, randomised 70 patients to WBRT or HS-WBRT, both arms 30Gy in 10 fractions [18]. The primary endpoint of decline in HVLT-R delayed recall at 4 months after treatment was not significantly different between arms. OS was also not significantly different between arms.

The largest published study utilising HS-WBRT for PCI in SCLC, a Phase III randomised trial, randomised 168 patients to WBRT versus HS-WBRT [19], both arms using the standard PCI dose of 25Gy in 10 fractions. The primary endpoint, total recall on HVLT-R at 4 months, with $\geq$ 5-point decline deemed clinically significant, did not differ significantly between arms. OS also was not significantly different between arms. In post-hoc analysis, the primary endpoint of the NRG CC001 trial (time to cognitive failure on any of 6 NCF tests) showed a statistically significant difference favouring the WBRT arm. Therefore, this trial could not recommend hippocampal sparing PCI outside a clinical trial [19]. The other published study in PCI for SCLC, also a Phase III trial, randomised 150 patients to WBRT versus HS-WBRT [20], 25Gy in 10 fractions in both arms. The primary endpoint was delayed free recall (DFR) on the Free and Cued

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Table 3
Published randomised trials of WBRT and HS-WBRT

Publication	ClinicalTrials.gov reference	Planned patient number	Patients recruited	Primary endpoint	Primary outcome
Brown *et al.*, 2020 [16]	NCT02360215	510	518	Time to cognitive failure (TTCF)*	Primary endpoint significantly favours HS-WBRT
Yang *et al.*, 2021 [17]	NCT02393131	60	70	Decline in HVLT-R delayed recall at 4 months	No significant difference in primary endpoint
(this trial)	NCT02147028	84	23	Decline in HVLT-R total recall at 4 months	No significant difference in primary endpoint
Trials of prophylactic cranial irradiation (PCI) in small-cell lung cancer					
Belderbos *et al.*, 2021 [18]	NCT01780675	168	168	Decline in HVLT-R total recall at 4 months	No significant difference in primary endpoint
Rodríguez de Dios *et al.*, 2021 [19]	NCT02397733	150	150	Delayed free recall on FCSRT† at 3 months	Primary endpoint significantly favours HS-WBRT

* TTCF - Time to cognitive failure on $\geq$ 1 of HVLT-R total recall, delayed recall, delayed recognition, COWAT, TMT-A, TMT-B.
† FCSRT - Free and cued selective reminding test.

Selective Reminding Test (FCSRT) at 3 months, with a decrease of $\geq$3 points (>1SD) from baseline considered a decline. The decline on DFR at 3 months was lower in the HS-WBRT arm (5.8%) compared to the WBRT arm (23.5%; $p = 0.003$). There was no significant difference in OS between arms. The investigators concluded that hippocampal sparing during PCI for SCLC should be standard of care.

The role of HS-WBRT therefore remains unclear, with the largest two randomised trials [17,19] coming to opposite conclusions on NCF benefit, albeit one is for brain metastases and the other for PCI in SCLC. Of the smaller two trials above, one found no difference in the primary endpoint [18], while the other showed favoured HS-WBRT [20] but did not include any of the same NCF tests as the other studies.

One further important trial has published only in abstract form: the Phase II/III NRG CC003 trial (NCT02635009) of PCI for SCLC which randomised 392 patients to WBRT or HS-WBRT, 25Gy in 10 fractions [21]. While 12-month intracranial relapse rate was non-inferior in the HS-WBRT arm, the phase III primary endpoint of decline in 6-month HVLT-DR did not differ significantly between arms.

The most recent Cochrane meta-analysis of WBRT for multiple brain metastases was unable to pool data from trials related to HS-WBRT [6]. Once NRG CC003 has reported in full, an individual patient data meta-analysis should be performed, as most of the above-mentioned trials used similar NCF tests and other secondary endpoints.

Conclusions

The trial closed without reaching its enrolment target due to slower than anticipated recruitment, a major reason being changes in clinical practice with a reluctance by clinicians and patients to administer WBRT. Compliance of surviving patients with serial NCF assessments was high. There was no evidence of a difference in the primary endpoint of Total recall by HVLT-R at 4 months post treatment, or in any of the other NCF tests, however the study was underpowered at analysis due to the small sample size of recruited patients. Patients in the HS-WBRT arm scored significantly lower (better) on both the EORTC QLQ C30 insomnia symptom scale ($p < 0.01$) and the BN20 drowsiness symptom scale ($p < 0.01$). There was no difference in other secondary endpoints between the arms. The secondary aim was to determine whether a phase III randomised trial of HS-WBRT would be feasible in the UK, and the trial demonstrated this was not feasible at this time. The results of other reported and still ongoing randomised trials should be combined in meta-analysis to help answer whether HS-WBRT should become a new standard of care in any patient group.

Ethics

The trial was approved by the National Research Ethics Service (NRES) Committee North West–Greater Manchester East and managed by the Cancer Research UK and University College London Cancer Trials Centre.

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Author contributions

1 guarantor of integrity of the entire study - GAW.
2 study concepts and design – GAW, PS, LC, JH, DM, HB, MDJ, SJ, SS, RS, MG.
3 literature research – GAW, PS.
4 clinical studies – GAW, PS, RS.
5 experimental studies/data analysis – N/A.
6 statistical analysis – WW, LC, DE.
7 manuscript preparation – GAW, WW.
8 manuscript editing – all.

Conflict of interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Paul Sanghera reports a relationship with Philips Electronics Netherlands that includes: travel reimbursement. Paul Sanghera reports a relationship with Accuray Inc that includes: travel reimbursement. Richard Shaffer reports a relationship with GenesisCare that includes: consulting or advisory. Richard Shaffer reports a relationship with Xstrahl Limited that includes: board membership and employment. Paul Sanghera reports a relationship with AbbVie Ltd that includes: consulting or advisory. Sarah Jefferies reports a relationship with GenesisCare that includes: equity or stocks. Sarah Jefferies reports a relationship with Cambridge Oncology Partnership that includes: employment. Sarah Jefferies reports a relationship with European Society for Therapeutic Radiology and Oncology (ESTRO) that includes: speaking and lecture fees. Sarah Jefferies reports a relationship with Tessa Jowell Brain Cancer Mission that includes: non-financial support. Sarah Jefferies reports a relationship with Various, principle investigator for commercial and non-commercial studies in brain and thyroid tumours that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Appendix A. Supplementary data

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