Original Article

Hippocampus-Avoidance Whole-Brain Radiation Therapy With a Simultaneous Integrated Boost for Multiple Brain Metastases

Ilinca Popp, MD [1]; Stephan Rau[1]; Mandy Hintz, MD[1]; Julius Schneider[1]; Angelika Bilger, MD [1]; Jamina Tara Fennell, MD[1]; Dieter Henrik Heiland, MD[2]; Thomas Rothe, PhD[1]; Karl Egger, MD[3]; Carsten Nieder, MD[4,5]; Horst Urbach, MD[3]; and Anca Ligia Grosu, MD[1,6]

BACKGROUND: The current study was aimed at investigating the feasibility of hippocampus-avoidance whole-brain radiation therapy with a simultaneous integrated boost (HA-WBRT+SIB) for metastases and at assessing tumor control in comparison with conventional whole-brain radiation therapy (WBRT) in patients with multiple brain metastases. **METHODS:** Between August 2012 and December 2016, 66 patients were treated within a monocentric feasibility trial with HA-WBRT+SIB: hippocampus-avoidance WBRT (30 Gy in 12 fractions, dose to 98% of the hippocampal volume ≤ 9 Gy) and a simultaneous integrated boost (51 or 42 Gy in 12 fractions) for metastases/resection cavities. Intracranial tumor control, hippocampal failure, and survival were subsequently compared with a retrospective cohort treated with WBRT via propensity score matching analysis. **RESULTS:** After 1:1 propensity score matching, there were 62 HA-WBRT+SIB patients and 62 WBRT patients. Local tumor control (LTC) of existing metastases was significantly higher after HA-WBRT+SIB (98% vs 82% at 1 year; $P = .007$), whereas distant intracranial tumor control was significantly higher after WBRT (82% vs 69% at 1 year; $P = .016$); this corresponded to higher biologically effective doses. Intracranial progression-free survival (PFS; 13.5 vs 6.4 months; $P = .03$) and overall survival (9.9 vs 6.2 months; $P = .001$) were significantly better in the HA-WBRT+SIB cohort. Four patients (6.5%) developed hippocampal metastases after hippocampus avoidance. The neurologic death rate after HA-WBRT+SIB was 27.4%. **CONCLUSIONS:** HA-WBRT+SIB can be an efficient therapeutic option for patients with multiple brain metastases and is associated with improved LTC of existing metastases, higher intracranial PFS, a reduction of the neurologic death rate, and an acceptable risk of radiation necrosis. The therapy has the potential to prevent neurocognitive adverse effects, which will be further evaluated in the multicenter, phase 2 HIPPORAD trial. ***Cancer* 2020;126: 2694-2703**.

KEYWORDS: brain metastases, hippocampus avoidance, neurocognitive function, whole-brain radiation therapy.

INTRODUCTION

Whole-brain radiation therapy (WBRT) has been for decades one of the main therapeutic options for multiple brain metastases.[1] Although stereotactic radiosurgery (SRS) rather than WBRT is recommended for patients with 1 to 3 brain metastases,[1,2] the optimal treatment for patients with more than 4 metastases has been recently controversially discussed. WBRT has the advantage of better distant intracranial tumor control (DTC) but is associated with relatively low control of existing metastases (local tumor control [LTC]) and a considerable rate of late neurocognitive adverse effects.[1,3,4] Conversely, SRS shows improved LTC but higher rates of distant intracranial tumor progression and neurologic death.[1,2,5]

Neurocognitive decline after WBRT can occur through hippocampal atrophy and irradiation of the neural stem cell niche, which is otherwise responsible for brain plasticity and repair,[6] and through the applied whole-brain radiation dose, which can lead to long-term brain atrophy and leukoencephalopathy.[7,8] Poor LTC and thus progressive brain metastases have also been correlated with significant neurocognitive deterioration,[9-11] and this suggests that LTC plays an essential role in preserving cognitive functions.

An improvement of LTC after WBRT can be attained through the application of additional SRS to the metastases.[12] Furthermore, conformal hippocampus avoidance (HA) in WBRT planning was also shown to preserve memory

Corresponding Author: Ilinca Popp, MD, Department of Radiation Oncology, Medical Center, Faculty of Medicine, University of Freiburg, Robert-Koch Str. 3, 79106 Freiburg, Germany (ilinca.popp@uniklinik-freiburg.de).

[1]Department of Radiation Oncology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [2]Department of Neurosurgery, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [3]Department of Neuroradiology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [4]Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway; [5]Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway; [6]German Cancer Consortium, Partner Site Freiburg, German Cancer Research Center Heidelberg, Freiburg, Germany

We thank the Else Kröner-Fresenius-Stiftung, Germany, for partially funding IP within the EXCEL (Excellent ClinicianScientists in Freiburg – Education for Leadership) Program "Immunological Causes and Therapies of Cancer". The funding source had no involvement in the writing of the manuscript or in the decision to submit the article for publication. We would also like to thank Sam Doerken (Dipl.-Math.) of the Institute of Medical Biometry and Statistics, Division Methods in Clinical Epidemiology, Faculty of Medicine and Medical Center – University of Freiburg, for his valuable input and statistical counseling.

DOI: 10.1002/cncr.32787, **Received:** September 18, 2019; **Revised:** January 12, 2020; **Accepted:** January 27, 2020, **Published online** March 6, 2020 in Wiley Online Library (wileyonlinelibrary.com)

function in a phase 2, multi-institutional trial[13] and in the first results of the randomized, phase 3 NRG Oncology CC001 trial.[14] Combining these 2 modifications of WBRT together with a slightly reduced WBRT dose (with normal brain tissue being considered the clinical target volume [CTV]) could thus improve intracranial LTC, reduce neurologic death rates, and also potentially have a positive impact on cognitive function.

Exploring the combination of hippocampus-avoidance whole-brain radiation therapy (HA-WBRT) and SRS, Prokic et al[15] found in a planning study that the best sparing of the hippocampi can be achieved if the dose escalation to the metastases is planned as a simultaneous integrated boost (SIB) rather than as sequential SRS. Moreover, an SIB has the biological advantage of dose fractionation. The current feasibility study is aimed, therefore, at providing the first systematic clinical information for the compound therapeutic concept of hippocampus-avoidance whole-brain radiation therapy with a simultaneous integrated boost (HA-WBRT+SIB) and assessing whether it can improve intracranial LTC in patients with multiple brain metastases while maintaining acceptable DTC despite dose reduction to the normal brain (CTV) and hippocampus protection (HA). The results are compared with those of a selected, clinically similar group of patients previously treated with conventional WBRT at the same institution.

MATERIALS AND METHODS

HA-WBRT+SIB Patients and Treatment

Sixty-six patients with multiple brain metastases were enrolled between August 2012 and December 2016 at the Department of Radiation Oncology of the Medical Center – University of Freiburg with the intention of undergoing HA-WBRT+SIB parallel and analogously to the experimental arm of the ongoing multicenter, phase 2 HIPPORAD trial ("Whole-Brain Irradiation With Hippocampal Sparing and Dose Escalation on Metastases: Neurocognitive Testing And Biological Imaging," NOA-14, ARO 2015-3, DRKS00004598). The analysis was approved by the local ethics committee. Patients were included if they had at least 4 brain metastases of solid tumors (range, 4-16), no metastases within the hippocampus or within a distance of 7 mm from the hippocampus, and no leptomeningeal disease or acute neurologic symptoms demanding an immediate start of radiation therapy and were not eligible for inclusion in the HIPPORAD trial (eg, because of insufficient language skills for neurocognitive testing, depression, or a refusal to collaborate). Prior radiation treatment to the brain (stereotactic fractionated radiotherapy, 6 × 5 Gy; radiosurgery, 20 Gy) was allowed if the treated areas showed local control and were not located in the hippocampus or within 7 mm of the hippocampus. Patients were treated with HA-WBRT (30 Gy in 12 fractions, dose to 98% of the hippocampal volume [D98%] ≤ 9 Gy, dose to 2% of the hippocampal volume [D2%] ≤ 17Gy, mean dose ≤ 10 Gy) and an SIB with 51 or 42 Gy in 12 fractions (according to the size and location) on multiple brain metastases (2-16) and/or resection cavities (0-2). Pre-irradiated metastases or resection cavities were treated with 30 Gy in 12 fractions without further dose escalation.

TABLE 1. Organ-at-Risk Dose Constraints Analogous to the HIPPORAD Trial Protocol

Organ at Risk	Dose Constraint
Hippocampus	D98% ≤ 9 Gy, D2% ≤ 17 Gy
Optic nerves, chiasm	D98% ≤ 33 Gy
Optic nerve, 1-sided	D2% ≤ 35 Gy
Retina, 1-sided	D2% ≤ 33 Gy
Lenses	D2% ≤ 7 Gy
Inner ear (in case of bilateral involvement)	D2% ≤ 33 Gy
Brain stem	D2% ≤ 33 Gy

Abbreviations: D2%, dose to 2% of the hippocampal volume; D98%, dose to 98% of the hippocampal volume.

HA-WBRT+SIB Radiation Treatment Planning

Patients underwent radiation therapy–planning computed tomography (CT) with a 1-mm slice thickness in thermoplastic mask immobilization (BrainLab, Feldkirchen, Germany) as well as 3-dimensional, contrast-enhanced sagittal T1-weighted magnetic resonance imaging (Gd-T1MRI). Gd-T1MRI and CT scans were rigidly coregistered on the basis of mutual information (iPlan RT Image 4.1.1; BrainLab, Feldkirchen, Germany) and served for the target volume and organ-at-risk delineation.

The planning tumor volume of the brain ($PTV_{whole\ brain}$) was defined as the whole brain plus 3 mm minus the planning tumor volume of metastases ($PTV_{metastases}$) and the hippocampus-avoidance region (HAR). $PTV_{metastases}$ was formed by the addition of 1 mm to the gross tumor volume, whereas for resection cavities, a margin of 2 mm was added to the CTV. The dose was prescribed to cover the 95% isodose. HAR was defined as a 7-mm 3-dimensional margin around the hippocampus, as described previously.[16] Dose constraints to organs at risk are presented in Table 1. Patients were treated with volumetric modulated arc therapy based on 2 to 4 arcs.

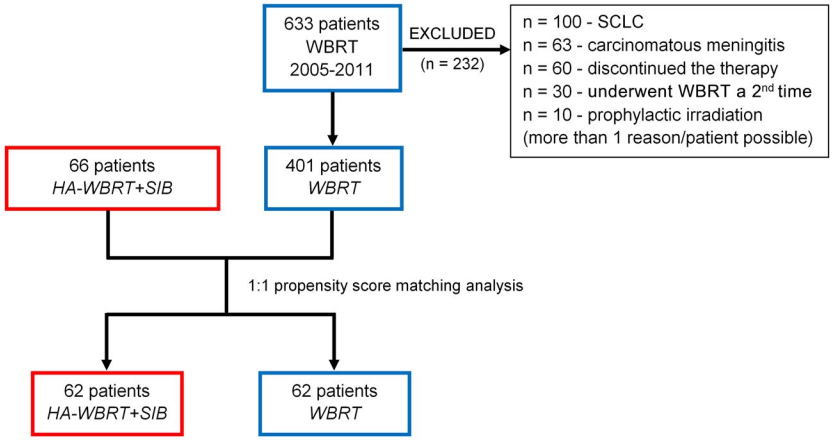

Figure 1. Flow diagram of the study design. HA-WBRT+SIB indicates hippocampus-avoidance whole-brain radiation therapy with a simultaneous integrated boost; SCLC, small cell lung carcinoma; WBRT, whole-brain radiation therapy.

WBRT Patients and Treatment

A total of 633 patients who had received conventional WBRT at our department between January 2005 and December 2011 were identified and retrospectively analyzed (unpublished data; Hintz, M., Freiburg, 2017, https://freidok.uni-freiburg.de/data/12315; accessed February 18, 2020); 232 unsuitable patients were then excluded from further analysis (Fig. 1). WBRT was performed with either conventional 2-dimensional planning (94.8%) or CT-based 3-dimensional planning (5.2%). The applied dose was on average 35 Gy (α/β for the equivalent dose in 2-Gy fractions [EQD2] = 10): 30 Gy in 10 fractions for 49.9%, 35 Gy in 14 fractions for 30.8%, and other for 19.3%. Starting in 2012, all patients who were eligible for CT-based WBRT and did not have (peri)hippocampal metastases underwent HA-WBRT+SIB.

Follow-Up

The HA-WBRT+SIB cohort was scheduled for follow-up examinations, including magnetic resonance imaging (MRI), physical examinations, and toxicity assessments according to version 4.0 of the Common Terminology Criteria for Adverse Events (CTCAE), 6 weeks after therapy and every 3 months thereafter. The retrospective WBRT group was followed up every 3 months according to clinical routine.

Intracerebral LTC and DTC were evaluated from the first day of treatment. Metastases were evaluated along the largest diameters on Gd-T1MRI according to Response Assessment in Neuro-Oncology Brain Metastases criteria.[17]

LTC was defined as complete remission, partial remission, or stable disease with respect to brain metastases that were present at the time of irradiation. Treatment-related changes, including pseudoprogression and radiation necrosis, were not considered local failures for LTC. Existing metastases at the time of irradiation were deemed progressive if they exhibited a relative increase of at least 20% from their nadir or an increase by an absolute value of 5 mm or more. Progressive lesions were treated conservatively for 6 weeks with a therapy consisting of dexamethasone (3×4 mg/d for 4 days followed by a 2-mg dose reduction every 2 days) and parallel pentoxifylline (400 mg twice a day). Pentoxifylline is a well-tolerated hemorrheologic methylxanthine derivative that increases blood flow and facilitates cell passage through microvessels; it improves oxygenation to injured cerebral tissue and limits inflammation by inhibiting tumor necrosis factor α and fibroblast growth factor 2.[18-20] After 6 weeks, a control MRI scan was performed. If no further progression was noted, treatment-related changes were diagnosed, and follow-up was continued. If a further increase in the contrast-enhancing lesions was seen, an intervention was initiated as oncologically indicated and interdisciplinarily decided. Histological evidence of necrosis without vital tumor cells in a biopsy or resection led to the diagnosis of radiation necrosis, whereas histological evidence of a tumor or the initiation of further therapy in the form of re-irradiation or systemic therapy crossing the blood-brain barrier led to the diagnosis of local failure for LTC.

Failure for DTC was defined as the unequivocal appearance (and progression) of a new intracerebral lesion (or lesions) as well as leptomeningeal spread.

Overall survival (OS) was calculated from the first day of irradiation until death of any cause or the day on which the patient was last known to be alive in the case of loss

to follow-up. Progression-free survival (PFS) was calculated from the first day of irradiation until tumor progression or death of any cause or until the day on which the patient was last known to be alive in the case of loss to follow-up.

Assessed toxicity comprised therapy-related adverse events, including alopecia, radiation dermatitis, wound-healing disorders, cerebral edema, headache, vomiting, nausea, vertigo, fatigue, focal neurologic deficits, epilepsy, subjective concentration or cognitive impairments, and radiation necrosis.

Statistics

Data were analyzed with R (release 3.6.1 [2013]; R Foundation for Statistical Computing, Vienna, Austria) and RStudio (2015; RStudio, Inc, Boston, Massachusetts). For OS and PFS, the Kaplan-Meier method was used to provide median point estimates, and groups were compared by means of the log-rank (Mantel-Cox) test. The median follow-up time was calculated with the reverse Kaplan-Meier method.

A propensity score matching analysis was performed with a logistic regression that considered the following: age, sex, Karnofsky performance status, primary tumor, time from the first diagnosis to the diagnosis of brain metastases, number of brain metastases, presence of extracranial metastases, and concurrent systemic therapies (ie, parallel to or following radiation before the diagnosis of further cerebral disease progression). Targeted therapies and immunotherapies were considered relevant systemic therapies. LTC and DTC were estimated with the Aalen-Johansen estimator for cumulative incidences, with death considered as a competing risk.

RESULTS

Along with the 66 patients treated with HA-WBRT+SIB, a total of 401 patients previously treated with WBRT were identified. After 1:1 matching, there were 62 patients in each group. Treatment groups were well balanced across known prognostic covariates (Table 2). There were small, statistically insignificant imbalances in the sex distributions, tumor types, tumor sizes, and the application of immunotherapy. More patients with non–small cell lung carcinoma were found in the WBRT group (59.7% vs 43.5%), whereas more patients with melanoma underwent HA-WBRT+SIB (19.4% vs 8.1%). Also, more patients received immune checkpoint inhibitors in the HA-WBRT+SIB group (8.1% vs 3.2%), and the tumor load was slightly larger in the WBRT cohort (87.2 vs 78.4 mm). The median follow-up time was 8.5 months in the HA-WBRT+SIB group and 6.3 months in the WBRT group.

Intracranial LTC and DTC

The cumulative incidence of local intracerebral progression was significantly lower and thus the LTC of existing metastases was significantly higher in the HA-WBRT+SIB group ($P = .007$; 98% [95% CI, 96%-100%] vs 82% [95% CI, 79%-97%] at 1 year; Fig. 2A) with death as a competing risk. The crude 1-year LTC for boosted metastases was 91.3%. The biologically effective dose (BED) to the metastases was 42.1 ± 4.2 Gy ($\alpha/\beta = 10$) for WBRT and 60.6 Gy ($\alpha/\beta = 10$) for HA-WBRT+SIB ($P < .00001$).

At the last follow-up, there were a total of 380 boosted lesions in the HA-WBRT+SIB cohort: 105 (27.6%) had a complete remission, 153 (40.3%) had a partial remission, 47 (12.4%) were stable, and 11 (2.9%) were progressive. Sixty-four lesions (16.8%) in 12 patients did not receive MRI follow-up because the patients were in bad condition or died within 6 weeks of irradiation (extracranial tumor progression [n = 5], cardiac complications/thromboembolism [n = 3], or unclear [n = 2]) or were lost to follow-up (n = 2).

The probability of DTC was significantly higher in the WBRT group ($P = .016$; 82% [95% CI, 70%-92%] vs 69% [95% CI, 60%-82%] at 1 year; Fig. 2B). Patients treated with HA-WBRT+SIB received a BED to the whole brain (minus HAR and metastases) of 37.5 Gy ($\alpha/\beta = 10$), whereas patients undergoing WBRT received on average 42.1 ± 4.2 Gy ($\alpha/\beta = 10$; $P < .00001$). The EQD2 for $\alpha/\beta = 2$ was also significantly higher in the WBRT group with a mean of 38.9 ± 3.5 Gy versus 33.8 Gy in the HA-WBRT+SIB group ($P < .00001$). Four patients in the HA-WBRT+SIB group and 3 patients in the WBRT group had leptomeningeal disease progression.

The application of targeted therapies and immunotherapies did not influence LTC or DTC significantly ($P = .84$ and $P = .56$, respectively; Fig. 2C,D).

OS and Intracranial PFS

OS was significantly different between the 2 groups, with a median of 9.9 months for the HA-WBRT+SIB group and a median of 6.2 months for the WBRT group ($P = .001$; Fig. 3A). Overall intracranial PFS was also significantly higher in the HA-WBRT+SIB group (13.5 months) than the WBRT group (6.4 months; $P = .03$; Fig. 3B).

Forty-eight patients in the HA-WBRT+SIB group and 42 patients in the WBRT group received concurrent systemic therapies, whereas 24 and 16, respectively, received potentially relevant systemic therapies (for a detailed description, see Table 2). Previous treatment of brain metastases was more frequent in the HA-WBRT+SIB group than

TABLE 2. Patient Characteristics According to the Treatment Group

Patient Characteristic	HA-WBRT+SIB	WBRT	*P* and *d*
Age, mean, y	58.34	58.02	*P* = .8768[a] *d* = 0.026
Sex, No. (%)			
Male	27 (43.5)	33 (53.2)	*P* = .3768[b]
Female	35 (56.5)	29 (46.8)	*d* = –0.195
KPS, No. (%)			
90%-100%	38 (61.3)	40 (64.5)	*P* = .69654[c]
70%-80%	23 (37.1)	19 (30.6)	*d* = –0.066[d]
50%-60%	1 (1.6)	3 (4.9)	
Primary tumor, No. (%)			
NSCLC	27 (43.5)	37 (59.7)	
Malignant melanoma	12 (19.4)	5 (8.1)	*P* = .6464[b]
Breast cancer	15 (24.2)	9 (14.5)	*d* = –0.103[e]
Gastrointestinal cancer	3 (4.8)	4 (6.5)	
Other	5 (8.1)	7 (11.3)	
Occurrence of brain metastases, No. (%)[f]	59 (95.2)/3 (4.8)	60 (96.8)/2 (3.2)	*P* = 1.0000[b] *d* = –0.082
No. of cerebral metastases and resection cavities, mean (range)	5.95 (4-16)	6.39 (4-17)	*P* = .97606[c] *d* = –0.047
Sum of longest diameters of cerebral metastases, mean (range), mm	78.4 (25-172)	87.2 (28-218)	*P* = .67448[c] *d* = –0.188
Extracranial metastases, No. (%)			
Yes	43 (69.4)	44 (71)	*P* = 1.0000[b]
No	19 (30.6)	18 (29)	*d* = –0.035
Targeted therapy: total, No. (%)[g]	19 (30.6)	16 (25.8)	
Gefitinib	4	0	
Lapatinib	3	0	
Trastuzumab	7	1	
Trastuzumab emtansine	3	0	
Pertuzumab	3	0	
Sunitinib	1	3	
Sorafenib	0	1	*P* = .6767[b]
Vemurafenib	1	0	*d* = 0.075
Dabrafenib	2	0	
Trametinib	2	0	
Afatinib	2	1	
Crizotinib	1	0	
Erlotinib	1	7	
Temsirolimus	0	1	
Temozolomide	0	2	
Immunotherapy: total, No. (%)[g]	5 (8.1)	2 (3.2)	
Ipilimumab	3	0	
Pembrolizumab	3	0	*P* = .3711[b]
Nivolumab	1	0	*d* = 0.213
Interferon	0	2	

Abbreviations: *d*, standardized difference; HA-WBRT+SIB, hippocampus-avoidance whole-brain radiation therapy with a simultaneous integrated boost; KPS, Karnofsky performance status; NSCLC, non–small cell lung carcinoma; *P*, statistical significance; WBRT, whole-brain radiation therapy.
[a]Paired *t* test.
[b]McNemar test.
[c]Wilcoxon signed-rank test.
[d]For KPS of 90% to 100% versus KPS of 50% to 80%.
[e]For NSCLC and malignant melanoma versus other.
[f]Synchronous (within 6 months of the first tumor diagnosis)/metachronous (later than 6 months after the first tumor diagnosis).
[g]More than 1 agent per patient was possible.

the WBRT group (resection, 50% vs 14.5%; SRS, 33.9% vs 12.9%). Local salvage therapies (resection and radiotherapy) were similarly used in the 2 groups (24.2% vs 21%).

By the end of the study, 61 patients in the WBRT group and 53 patients in the HA-WBRT+SIB group had died. The most probable cause of death in the HA-WBRT+SIB group was intracranial tumor progression in 17 cases and extracranial progression and other causes (eg, infection and cardiac decompensation) in 26 cases. The cause of death was unclear in 10 cases. No reliable information on the cause of death could be obtained for the retrospective WBRT cohort.

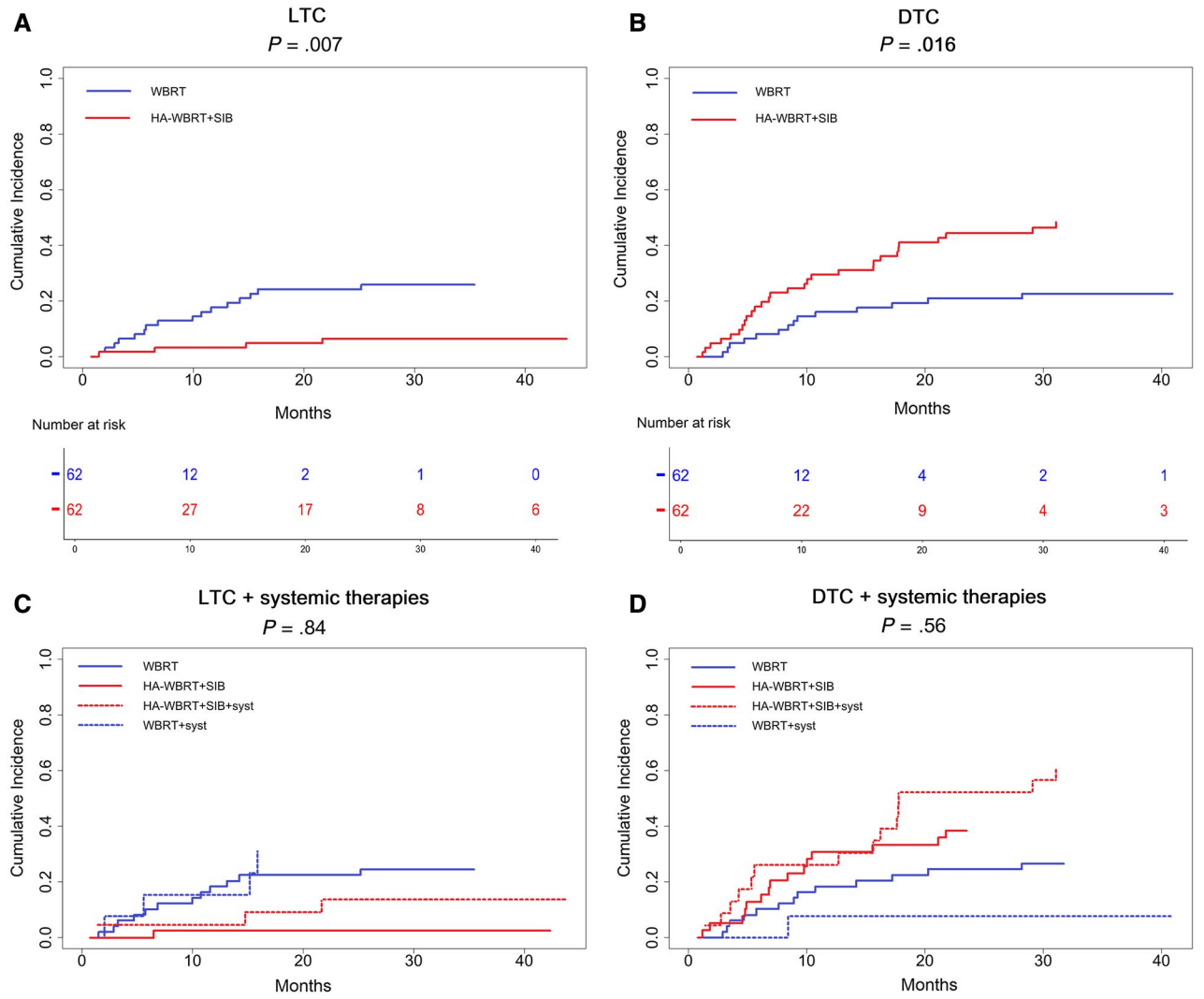

Figure 2. (A) Significantly lower cumulative incidence of local intracerebral progression and thus significantly higher LTC with HA-WBRT+SIB versus WBRT (P = .007). (B) Significantly higher cumulative incidence of distant intracerebral progression and thus significantly lower DTC with HA-WBRT+SIB versus WBRT (P = .016). (C) LTC and (D) DTC were not significantly influenced by the addition of systemic therapies crossing the blood-brain barrier (P = .84 and P = .56, respectively). DTC indicates distant intracranial tumor control; HA-WBRT+SIB, hippocampus-avoidance whole-brain radiation therapy with a simultaneous integrated boost; LTC, local tumor control of existing metastases; syst, systemic therapies; WBRT, whole-brain radiation therapy.

Hippocampal Failure

In the HA-WBRT+SIB group, the mean dose to the bilateral hippocampi was 6.8 ± 0.5 Gy (median, 6.7 Gy; EQD2 $\alpha/\beta = 2$), whereas the dose to 40% of the hippocampal volume (D40%) was on average 6.7 ± 0.5 Gy (median, 6.6 Gy; EQD2 $\alpha/\beta = 2$). The average D2% to the hippocampus was 11.2 ± 1.9 Gy (median, 10.3 Gy; EQD2 $\alpha/\beta = 2$), and D98% was 5.4 ± 0.3 Gy (median, 5.4 Gy; EQD2 $\alpha/\beta = 2$; Fig. 4). Five patients developed a total of 6 metastases in the area of hippocampal avoidance on average 5.8 months after irradiation: 4 (6.5%) were within the hippocampus itself, and 2 were in the 7-mm margin around the hippocampus. The actuarial rate per year was 3.6%. Each new metastasis in the HAR was associated with disseminated progression of brain metastases in the brain regions having received 30 Gy. In the area just around the HAR with doses ranging between 27 and 30 Gy, new metastases appeared in 4 patients. Three of these patients had a simultaneous metastasis in the hippocampus and disseminated progression in the whole brain. In the conventional WBRT group, 3 patients (4.8%) developed a new metastasis in the hippocampus region (actuarial rate per year, 3.3%).

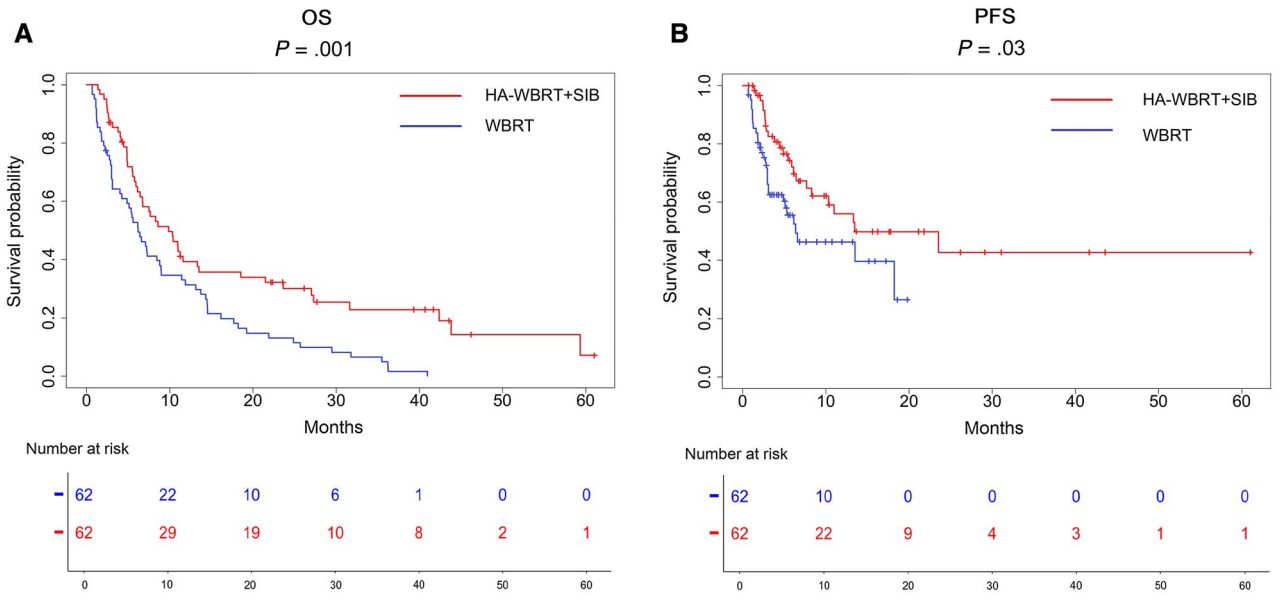

Figure 3. (A) Significantly higher OS and (B) intracranial PFS with HA-WBRT+SIB versus WBRT ($P = .001$ and $P = .03$, respectively). HA-WBRT+SIB indicates hippocampus-avoidance whole-brain radiation therapy with a simultaneous integrated boost; OS, overall survival; PFS, progression-free survival; WBRT, whole-brain radiation therapy.

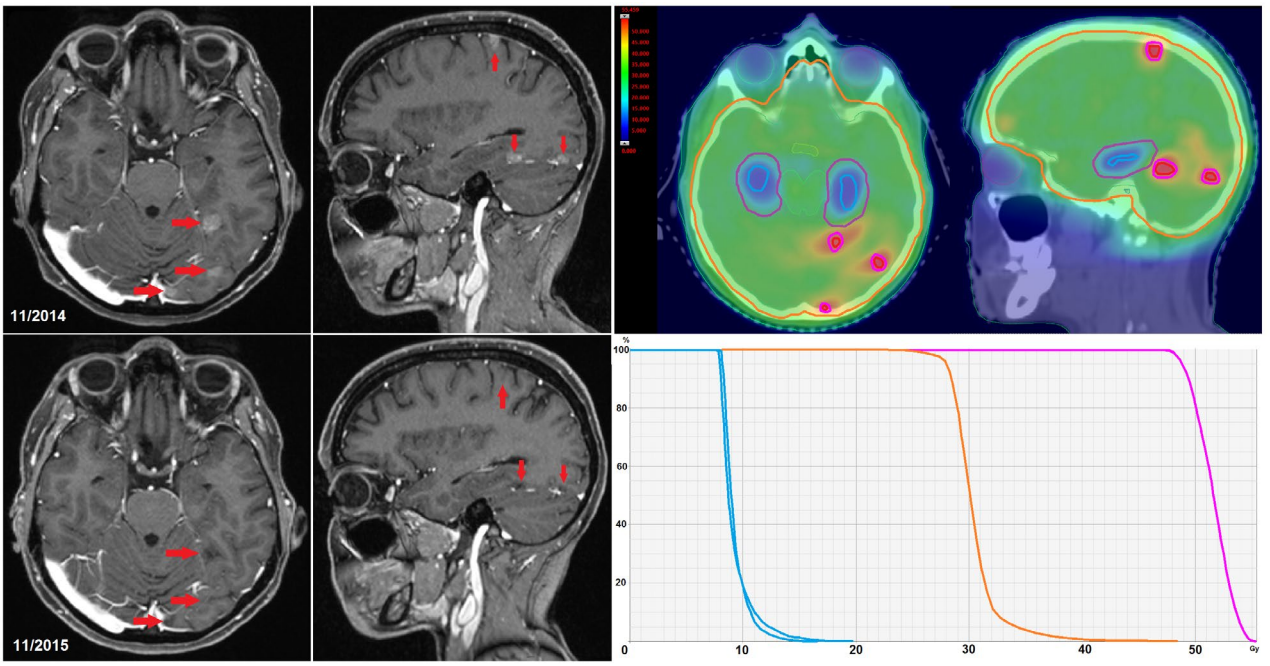

Figure 4. Example of a dose distribution and dose-volume histogram of an HA-WBRT+SIB plan for a patient with 15 brain metastases. Colors indicate the following: blue, hippocampi; purple, HAR; orange, $PTV_{whole\ brain}$ (whole brain + 3 mm – HAR – $PTV_{metastases}$); pink, $PTV_{metastases}$; green, brainstem; and yellow, optic chiasm. The mean dose in both hippocampi remained under 10 Gy, whereas the whole brain and the metastases received means of 30 and 51 Gy, respectively. The 1-year magnetic resonance imaging follow-up showed complete remission of the metastases. Arrows indicate three of the metastases before and after therapy. HAR indicates hippocampus-avoidance region; HA-WBRT+SIB, hippocampus-avoidance whole-brain radiation therapy with a simultaneous integrated boost; $PTV_{metastases}$, planning tumor volume of metastases; $PTV_{whole\ brain}$, planning tumor volume of the whole brain.

Toxicity of HA-WBRT+SIB

In the HA-WBRT+SIB cohort, 2 patients described a subjective memory decline. Adverse events higher than grade 2 (according to the National Cancer Institute's CTCAE, version 4.03) were observed in 4 patients (6.5%): 1 grade 4 epileptic seizure, 1 grade 3 case of radiation necrosis, and 2 grade 3 intrametastatic hemorrhages in 2 patients with malignant melanoma. All patients experienced grade 2 alopecia. One patient had a CTCAE grade 2 case of radiation necrosis treated with bevacizumab.

Therapy-related changes with transient enlargement due to central tumor necrosis, with a gradual return to the initial volume under corticosteroid and pentoxifylline therapy, were observed in 25 of 380 boosted lesions (6.6%). Five further lesions were progressive despite a corticosteroid and pentoxifylline treatment and were either resected (4 of 5) or biopsied (1 of 5) to differentiate progression from radiation necrosis. In 2 of these cases (the biopsy and 1 of the 4 resections), radiation necrosis was confirmed without evidence of vital tumor cells. In the retrospective WBRT cohort, toxicity data could not be reliably collected.

DISCUSSION

The aim of this study was 2-fold: 1) to prospectively assess the clinical efficacy and feasibility of HA-WBRT+SIB in patients with multiple brain metastases and 2) to explore how intracranial LTC compares with LTC for patients treated with conventional WBRT. Data on 20 patients treated similarly were published in 2015, and they suggested favorable intracranial tumor control rates.[16] The current study assessed a total of 62 patients, the largest cohort to date treated with HA-WBRT+SIB, and it is the first study comparing HA-WBRT+SIB with WBRT.

In an era of more efficient local and systemic therapies and improved survival rates, the preservation of neurologic and neurocognitive function becomes all the more important. Several prospective clinical trials have described a correlation between intracranial tumor progression and neurocognitive impairment and subsequently altered quality of life.[9,11,21,22] All in all, intracranial tumor control proved to be very good in the highly selected cohort of patients treated with conventional WBRT. However, in the HA-WBRT+SIB group, the LTC of existing metastases was significantly higher, and this was also reflected in improved intracranial PFS. The 1-year LTC rate of 91.3% for boosted metastases was comparable to that obtained after SRS alone.[5,23,24] A similar improvement in LTC through dose escalation to metastases was shown in a meta-analysis by Patil et al,[25] who explored the combination of WBRT and SRS. In comparison, dose escalation through SIBs has the biological advantage of fractionation for both normal and tumor tissue and ensures better HA.[14] The combination with relevant systemic therapies, including novel immune checkpoint inhibitors, did not alter tumor control significantly, but a definite statement is not possible because of the low number of patients involved.

The occurrence of new intracranial metastases, however, was significantly lower in the WBRT group, and this was related to a significantly higher BED applied to the whole brain. This suggests a dose-dependent potential of WBRT for preventing new metastases. Several randomized trials[26-32] have analyzed various dose-fractionation schedules for WBRT and compared them with the standard 30 Gy in 10 fractions (BED = 39 Gy; $\alpha/\beta = 10$). Although no evidence for improved survival with a higher BED was given, a lower BED proved significantly less efficient.[1] However, lower total doses and doses per fraction, assessed especially in the context of prophylactic cranial irradiation, showed lower incidences of neurocognitive impairment.[33] Other late toxicities, including brain atrophy and leukoencephalopathy, characterized inter alia by neurocognitive dysfunction, also become more prevalent with higher total doses of radiotherapy.[7,8,34,35] Thus, the lower dose prescribed to the whole brain in the HA-WBRT+SIB cohort takes into consideration the multiple SIBs and the smaller prescription volume ($PTV_{\text{whole brain}} - PTV_{\text{metastases}} - HAR$) in order to potentially minimize neurocognitive adverse effects, but it also comes with the trade-off of possibly lower DTC. Assessing the risk-benefit ratio in this case remains an endeavor for the clinician.

The lower DTC could not be attributed to the HA, and this supports the idea that HA-WBRT is a safe treatment concept. Tumor progression in the HAR was observed in only 8.1% of the cases, and each new metastasis in this area was associated with disseminated distant progression in the brain regions receiving 30 Gy. Gondi et al[36] previously explored the risk of developing perihippocampal metastases after HA-WBRT in the phase 2 Radiation Therapy Oncology Group 0933 trial and identified 8.6% to 12.1% of patients as presenting with metastases within 5 to 10 mm of the hippocampus. Oehlke et al[16] similarly reported new hippocampal metastases in 10% of cases.

The dose constraints for the HAR were analogous to those in the ongoing randomized, multicenter, phase 2 HIPPORAD trial. D98% for the bilateral hippocampi was lower than 9 Gy, D2% was lower than 17 Gy, and D40% was lower than 7.3 Gy. These values are also consistent with the constraints of the Radiation Therapy

Oncology Group 0933 trial[12] and the subsequent phase 3 NRG Oncology CC001 trial as well as the dosimetric analysis of Gondi et al.[37] The latter indicated that neurocognitive function impairment was associated with 40% of the bilateral hippocampi having received more than 7.3 Gy. When we take this into consideration, the HA achieved in our study is most likely able to prevent significant hippocampus-related cognitive impairment.

The acute toxicity profile of HA-WBRT+SIB also proved acceptable and was derived primarily from the SIB. Serious adverse events within the first year of follow-up were comparable in type and frequency (6.5%) to those following SRS alone. Yamamoto et al[24] prospectively investigated 1194 patients treated with multiple SRS treatments and reported SRS-induced adverse events in 6% to 8% of their patients.

The OS of patients treated with HA-WBRT+SIB was significantly higher than the OS of the propensity-score-matched cohort of patients treated with conventional WBRT. After we matched accounting for known confounders, the 2 groups differed clearly only in terms of the year of therapy (2005-2011 vs 2012-2017). When we consider recent advances in immune and targeted therapies, the observed improvement in OS was most likely a result of more effective systemic therapies. However, a similar impact on survival of further dose escalation through sequential SRS after WBRT was previously shown by Andrews et al.[12] Hence, an additional benefit of the improved LTC for survival cannot be completely excluded. The neurologic death rate, defined as the rate of intracranial failure as a component of the cause of death, was 27.4%. This rate is similar to the previously reported rate of 28% after WBRT combined with surgery/SRS[2] and shows an improvement in comparison with surgery/SRS alone (44%) and also historical WBRT cohorts (36%).[2,12]

A major limitation of this study is that a structured neurocognitive assessment was not performed. Major depression, anxiety, and fatigue are often diagnosed in patients with advanced cancer and can have a significant influence on neurocognitive function, as shown previously.[38,39] To correctly address these aspects, a thorough neurocognitive evaluation will be performed in the prospective HIPPORAD trial. A further limitation is the 1:1 matched propensity score design, which still retained slight imbalances and might have been stronger if it had been a 2:1 design, had a larger number of patients been available. Because HA-WBRT+SIB is a new irradiation method for a highly selected category of neurologically fit patients with multiple cerebral metastases without meningeal spread, this remains the largest cohort to date treated in this manner. The propensity score matching analysis may also have ignored certain confounders, such as applied molecular therapy or immunotherapy, which have significantly changed in the past years. Although this difference most likely had an impact on survival, it did not seem to influence intracranial tumor control. However, this has to be investigated in a larger number of patients, with special consideration given to the histology of the primary tumor and the systemic therapy. Because the 2 cohorts in our study were chronologically shifted, there is a low probability of further significant differences between the groups.

In conclusion, HA-WBRT+SIB can be an effective therapeutic option for patients with multiple brain metastases and shows improved LTC of existing metastases and improved overall intracranial PFS in comparison with WBRT alone. However, intracranial DTC appears higher after conventional WBRT. These clinical results support the correlation between BED and tumor control in brain metastases. The potential of HA-WBRT+SIB to prevent neurocognitive effects will be further evaluated in the randomized, multicenter, phase 2 HIPPORAD trial (NOA-14, ARO 2015-3, DRKS00004598).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Ilinca Popp: Conceptualization, data curation, formal analysis, investigation, methodology, visualization, and writing–original draft. **Stephan Rau:** Data curation and writing–review and editing. **Mandy Hintz:** Data curation and writing–review and editing. **Julius Schneider:** Data curation and writing–review and editing. **Angelika Bilger:** Data curation, investigation, and writing–review and editing. **Jamina Tara Fennell:** Investigation and writing–review and editing. **Dieter Henrik Heiland:** Investigation and writing–review and editing. **Thomas Rothe:** Investigation and writing–review and editing. **Karl Egger:** Investigation and writing–review and editing. **Carsten Nieder:** Supervision and writing–review and editing. **Horst Urbach:** Investigation and writing–review and editing. **Anca Ligia Grosu:** Conceptualization, investigation, methodology, project administration, resources, supervision, visualization, and writing–original draft.

REFERENCES

1. Tsao MN, Xu W, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev*. 2018;25:CD003869.
2. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*. 2011;29:134-141.
3. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA*. 2016;316:401-409.
4. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10:1037-1044.

5. Nieder C, Grosu AL, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases: a systematic review. *Radiat Oncol*. 2014;9:155.
6. Barani IJ, Benedict SH, Lin PS. Neural stem cells: implications for the conventional radiotherapy of central nervous system malignancies. *Int J Radiat Oncol Biol Phys*. 2007;68:324-333.
7. Shibamoto Y, Baba F, Oda K, et al. Incidence of brain atrophy and decline in Mini-Mental State Examination score after whole-brain radiotherapy in patients with brain metastases: a prospective study. *Int J Radiat Oncol Biol Phys*. 2008;72:1168-1173.
8. Corn BW, Yousem DM, Scott CB, et al. White matter changes are correlated significantly with radiation dose. Observations from a randomized dose-escalation trial for malignant glioma (Radiation Therapy Oncology Group 83-02). *Cancer*. 1994;74:2828-2835.
9. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys*. 2007;68:1388-1395.
10. Regine WF, Scott C, Murray K, Curran W. Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation vs. accelerated-hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group Study 91-04. *Int J Radiat Oncol Biol Phys*. 2001;51:711-717.
11. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol*. 2004;22:157-165.
12. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004;363:1665-1672.
13. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol*. 2014;32:3810-3816.
14. Gondi V, Deshmukh S, Brown PD, et al. Preservation of neurocognitive function with conformal avoidance of the hippocampus during whole-brain radiotherapy for brain metastases: preliminary results of phase III trial NRG Oncology CC001 [abstract LBA9]. Abstract presented at: 2018 ASTRO Annual Meeting; October 21-23, 2018; San Antonio, TX.
15. Prokic V, Wiedenmann N, Fels F, Schmucker M, Nieder C, Grosu AL. Whole brain irradiation with hippocampal sparing and dose escalation on multiple brain metastases: a planning study on treatment concepts. *Int J Radiat Oncol Biol Phys*. 2013;85:264-270.
16. Oehlke O, Wucherpfennig D, Fels F, et al. Whole brain irradiation with hippocampal sparing and dose escalation on multiple brain metastases: local tumour control and survival. *Strahlenther Onkol*. 2015;191:461-469.
17. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16:e270-e278.
18. Okunieff P, Augustine E, Hicks JE, et al. Pentoxifylline in the treatment of radiation-induced fibrosis. *J Clin Oncol*. 2004;22:2207-2213.
19. Williamson R, Kondziolka D, Kanaan H, Lunsford LD, Flickinger JC. Adverse radiation effects after radiosurgery may benefit from oral vitamin E and pentoxifylline therapy: a pilot study. *Stereotact Funct Neurosurg*. 2008;86:359-366.
20. Nieder C, Zimmerman FB, Adam M, Molls M. The role of pentoxifylline as a modifier of radiation therapy. *Cancer Treat Rev*. 2005;31:448-455.
21. Mehta MP, Rodrigus P, Terhaard CHJ, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol*. 2003;21:2529-2536.
22. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol*. 2007;25:1260-1266.
23. Bilger A, Frenzel F, Oehlke O, et al. Local control and overall survival after frameless radiosurgery: a single center experience. *Clin Transl Radiat Oncol*. 2017;7:55-61.
24. Yamamoto M, Serizawa T, Higuchi Y, et al. A multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 study update): irradiation-related complications and long-term maintenance of Mini-Mental State Examination scores. *Int J Radiat Oncol Biol Phys*. 2017;99:31-40.
25. Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. *Cochrane Database Syst Rev*. 2017;25:CD006121.
26. Borgelt B, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 1980;6:1-9.
27. Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 1981;7:1633-1638.
28. Davey P, Hoegler D, Ennis M, Smith J. A phase III study of accelerated versus conventional hypofractionated whole brain irradiation in patients of good performance status with brain metastases not suitable for surgical excision. *Radiother Oncol*. 2008;88:173-176.
29. Graham PH, Bucci J, Browne L. Randomized comparison of whole brain radiotherapy, 20 Gy in four daily fractions versus 40 Gy in 20 twice-daily fractions, for brain metastases. *Int J Radiat Oncol Biol Phys*. 2010;77:648-654.
30. Chatani M, Matayoshi Y, Masaki N, Inoue T. Radiation therapy for brain metastases from lung carcinoma. Prospective randomized trial according to the level of lactate dehydrogenase. *Strahlenther Onkol*. 1994;170:155-161.
31. Harwood AR, Simson WJ. Radiation therapy of cerebral metastases: a randomized prospective clinical trial. *Int J Radiat Oncol Biol Phys*. 1977;2:1091-1094.
32. Priestman TJ, Dunn J, Brada M, Rampling R, Baker PG. Final results of the Royal College of Radiologists' trial comparing two different radiotherapy schedules in the treatment of cerebral metastases. *Clin Oncol (R Coll Radiol)*. 1996;8:308-315.
33. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81:77-84.
34. McTyre E, Scott J, Chinnaiyan P. Whole brain radiotherapy for brain metastasis. *Surg Neurol Int*. 2013;4(suppl 4):S236-S244.
35. Price RA, Jamieson PA. The central nervous system in childhood leukemia. II. Subacute leukoencephalopathy. *Cancer*. 1975;35:306-318.
36. Gondi V, Tome WA, Marsh J, et al. Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: safety profile for RTOG 0933. *Radiother Oncol*. 2010;95:327-331.
37. Gondi V, Hermann BP, Mehta MP, Tome WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int J Radiat Oncol Biol Phys*. 2013;85:348-354.
38. McClintock SM, Husain MM, Greer TL, Cullum CM. Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. *Neuropsychology*. 2010; 24:9-34.
39. Andreotti C, Root JC, Ahles TA, McEwen BS, Compas BE. Cancer, coping, and cognition: a model for the role of stress reactivity in cancer-related cognitive decline. *Psychooncology*. 2015;24:617-623.