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Whole-brain irradiation with hippocampal sparing and intagrated boost for patients with brain metastases: A local control and neurocognitive function analysis

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Abstract
Background: Hippocampal-sparing whole brain irradiation with simultaneous integrated boost (HSIB-WBRT) emerges as a significant advancement in treating brain metastases, aiming to alleviate neurocognitive function (NCF) decline associated with traditional whole-brain radiotherapy (WBRT). This technique combines the advantages of WBRT and simultaneous integrated boost (SIB) through intensity-modulated radiation therapy (IMRT), offering enhanced tumor dosage while safeguarding hippocampal structures.
Methods: This is a prospective, randomized, two-arm single institution study comparing the impact of hippocampal-sparing and integrated boost on NCF and local control after HSIB-VBRT versus WBRT in patients with multiple brain metastases. Radiation therapy consisted of intensity-modulated radiation therapy delivering 30 Gy in 10 fractions over 2 weeks to the whole brain with a simultaneous integrated boost of 40 Gy in 10 fractions to metastatic lesions. Hippocampal regions were limited to 16 Gy. Cognitive performance and cancer outcomes were evaluated.
Results: In the HSIB-WBRT group, the most frequent localization of brain metastases were from the lung tumors, in 60% of patients while in the WBRT group, the most frequent localization were from the breast tumors, for 53.3% of patients. Although there was a trend in local control for patients with HSIB-WBRT, the statistical difference was not reached between the 2 groups at 6 months, progression was 26.4% for HSIB-WBRT group vs. 46.7% in the WBRT group ($p = 0.253$). The neurocognitive function was better in the HSIB-WBRT group, the mean Mini-Mental State Examination (MMSE) score at 6 months was 28.93 with a median of 29, whereas for the WBRT group, the mean was 24.6 with a median of 25, which proved to be statistically significant ($p < 0.001$).
Conclusions: Despite limitations such as sample size constraints and compliance issues with neurocognitive testing, the study supports HSIB-WBRT as a safe and viable treatment option for brain metastases. Further research incorporating larger cohorts is warranted to validate these findings. The HSIB-WBRT group exhibited a favorable outcome in terms of maintenance of neurocognitive function in comparison to the WBRT group after 6 months despite not having superior local control. To amplify the statistical findings, more studies should be undertaken. The study is constrained by the small sample size of each study group, consisting of only 15 patients, which heightens the potential for type II error. In summary, HSIB-WBRT offers promising prospects for preserving neurocognition while potentially being effective regarding intracranial tumor control, emphasizing its potential as a standard therapeutic approach for patients with brain metastases.

Keywords: hippocampal-sparing, brain metastases, integrated boost, whole brain radiation therapy, neurocognitive function

Rezumat
Context: Iradierea întregului creier cu protecție a hipocampului și boost integrat simultan (HSIB-WBRT) apare ca un progres semnificativ în tratarea metastazelor cerebrale, având ca scop atenuarea declinului funcției neurocognitive (NCF) asociat cu radioterapia tradițională a creierului întreg (WBRT). Această tehnică combină avantajele WBRT și ale boost-ului integrat simultan (SIB) prin intermediul radioterapiei cu intensitate modulată (IMRT), oferind o dozare îmbunătățită a tumorii, protejând în același timp structurile hipocampale.
Metode: Acesta este un studiu prospectiv, randomizat, cu două brațe, într-o singură instituție, care compară impactul pe care îl au hipocampal-sparing și boost-ul integrat asupra NCF și controlul local după HSIB-VBRT versus WBRT la pacienții cu metastaze cerebrale multiple. Radioterapia a fost efectuată folosind tehnica cu intensitate modulată, în care s-au administrat 30 Gy în 10 fracții pe parcursul a 2 săptămâni la nivelul întregului creier, cu un boost integrat simultan de 40 Gy în 10 fracții la

nivelul leziunilor metastatice. Regiunile hipocampale au fost limitate la 16 Gy. Au fost evaluate performanța cognitivă și rezultatele cancerului.
Rezultate: În grupul HSIB-WBRT, cea mai frecventă localizare a metastazelor cerebrale a fost cea a tumorilor pulmonare, la 60% dintre pacienți, în timp ce în grupul WBRT, cea mai frecventă localizare a fost cea a tumorilor mamare, la 53,3% dintre pacienți. Deși a existat o tendință de control local pentru pacienții cu HSIB-WBRT, diferența statistică nu a fost atinsă între cele 2 grupuri la 6 luni, progresia a fost de 26,4% pentru grupul HSIB-WBRT față de 46,7% în grupul WBRT (p = 0,253). Funcția neurocognitivă a fost mai bună în grupul HSIB-WBRT, scorul mediu al Mini-Mental State Examination (MMSE) la 6 luni a fost de 28, 93 cu o mediană de 29, în timp ce pentru grupul WBRT, media a fost de 24,6 cu o mediană de 25, ceea ce s-a dovedit a fi semnificativ din punct de vedere statistic (p < 0,001).
Concluzii: În ciuda limitărilor, cum ar fi constrângerile legate de mărimea eșantionului și problemele de conformitate cu testele neurocognitive, studiul susține HSIB-WBRT ca o opțiune de tratament sigură și viabilă pentru metastazele cerebrale. Cercetări suplimentare care să includă cohorte mai mari sunt justificate pentru a valida aceste constatări. Grupul HSIB-WBRT a prezentat un rezultat favorabil în ceea ce privește menținerea funcției neurocognitive în comparație cu grupul WBRT după 6 luni, în ciuda faptului că nu a avut un control local superior. Pentru a amplifica constatările statistice, ar trebui întreprinse mai multe studii. Studiul este constrâns de dimensiunea redusă a eșantionului fiecărui grup de studiu, format din doar 15 pacienți, ceea ce sporește potențialul de eroare de tip II. În concluzie, HSIB-WBRT oferă perspective promițătoare pentru păstrarea neurocogniției, fiind în același timp potențial eficient în ceea ce privește controlul tumorii intracraniene, subliniind potențialul său ca abordare terapeutică standard pentru pacienții cu metastaze cerebrale.

Cuvinte-cheie: hipocampal-sparing, metastaze cerebrale, boost integrat, radioterapie cerebrală integrală, funcție neurocognitivă

Introduction

The research highlights the significance of utilizing hippocampal-sparing whole brain irradiation with simultaneous integrated boost (HA-WBRT + SIB) for the treatment of individuals with brain metastases. While traditional whole-brain radiotherapy (WBRT) has been a common approach for brain metastases, it is associated with a decline in neurocognitive function due to the impact of radiation on neural stem cells in the hippocampal dentate gyrus, a phenomenon extensively supported by various clinical trials. (1-10)

To address this issue, targeted therapies such as stereotactic radiosurgery (SRS) have been employed in specific cases; however, its application in patients with multiple lesions or other medical complexities is limited. (11)

The integration of HA-WBRT + SIB combines the advantages of WBRT and SRS by utilizing advanced conformal radiation techniques like intensity-modulated radiation therapy (IMRT). This approach allows for fractionated cranial radiation that increases tumor dosage while protecting the hippocampal structures, thus reducing the risk of neurocognitive decline. (12-14)

By simultaneously targeting the tumors and vulnerable brain regions, HA-WBRT + SIB aims to provide effective treatment for brain metastases with a potentially superior safety profile compared to conventional. (12)

Methods

A prospective, randomized, two-arm single institution study was conducted to evaluate the feasibility and effectiveness of HA-WBRT + SIB in patients with brain metastasis, assessing changes in cognitive function, local control of intracranial cancer, adverse events, and health-related quality of life. The results of this study are expected to offer valuable insights into the potential benefits of HA-WBRT + SIB in preserving cognitive function while ensuring effective intracranial control in patients with multiple brain metastases.

Eligible participants included adult individuals (aged 18 years or older) diagnosed with a non-hematopoietic malignancy other than small cell lung cancer or germ cell malignancy, with up to 8 untreated brain metastases visible on contrast-enhanced brain MRI beyond a 5 mm margin surrounding the bilateral hippocampi. Additionally, participants were required to have a Karnofsky performance status of 70 or higher, fall into Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis class I or II, and have a treating physician-assessed life expectancy of at least 3 months. Exclusion criteria encompassed individuals with leptomeningeal metastases, those unable to undergo MRI, presented with brain metastases within less than a 1 cm distance from the hippocampus, had undergone previous brain irradiation or those with three or more uncontrolled or untreated extracranial sites of gross disease. Informed written consent was obtained from all participants.

Study design and treatment

Patients were randomized to either Hippocampal avoidance – whole brain radiotherapy with simultaneous integrated boost (HSIB-WBRT) or whole brain radiotherapy (WBRT). The research encompassed individuals who had a maximum of 8 untreated brain metastases that were visible on contrast-enhanced brain magnetic resonance imaging (MRI), excluding those within a 1 cm margin around the bilateral hippocampi. Additional criteria for patient participation in the study included having an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, no prior history of neuropsychiatric illness, having undergone surgery for brain metastases, and a treating physician's assessment of a life expectancy of at least three months. Patients who were ineligible for the study included those with evidence of leptomeningeal metastases, individuals with a contraindication to MRI, patients with brain metastases located less than 1 cm from the hippocampus, individuals with a history of brain irradiation, and patients with an ECOG score of 3. All patients provided written informed consent.

A non-enhanced CT scan for treatment planning covering the entire head area with a slice thickness of 1.25 mm was mandated within a two-week window from treatment commencement. Patients were positioned in a supine posture and secured using a thermoplastic mask. Brain MRI scans incorporating T1 contrast and T2 images with a slice thickness of 1 mm were obtained and integrated with the planning CT images for precise lesion targeting and delineation of the hippocampus. Intensity-modulated radiation therapy (IMRT), either in static or volumetric modulated arc therapy form, was

utilized to administer a total of 30 Gy in 10 fractions over a period of 2 weeks to the entire brain, with a simultaneous integrated boost of 40 Gy in 10 fractions to identified metastatic lesions. Each brain metastasis was assigned a distinct gross tumor volume (GTV) as defined by the physician, followed by a uniform 5 mm expansion to establish the planning target volume. Hippocampal avoidance regions were manually delineated by expanding the hippocampal contours in 3D by 5 mm. As per protocol, the maximum dose to the hippocampus was set not to exceed 16 Gy, with a permissible variation allowing for a maximum dose of up to 17 Gy. Following the initiation of hippocampal-sparing whole brain irradiation with simultaneous integrated boost (HSIB-WBRT), all final treatment plans and contours underwent thorough review, and any deemed unacceptable during the final quality assurance assessment were excluded from the final data analysis.

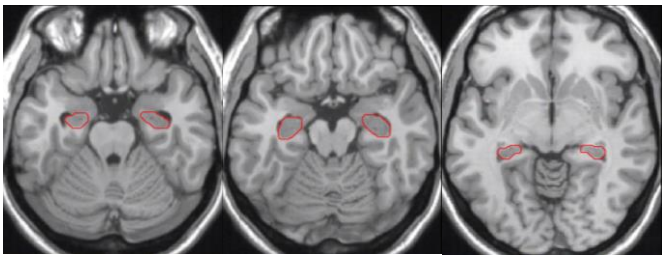


Figure 1 - **Ilustrates the delineation of the hippocampus on various transversal sections of MRI images.** The red line indicates the specific hippocampal regions that should be steered clear of during whole-brain radiotherapy (WBRT).

All VMAT plans underwent optimization utilizing the Philips Pinnacle treatment planning system, and the treatments were administered using 6 MV photon beams on an Elekta Synergy linear accelerator equipped with an Agility 160-leaf collimator. Collapsed cone convolution (CCC) was employed for dose calculation.

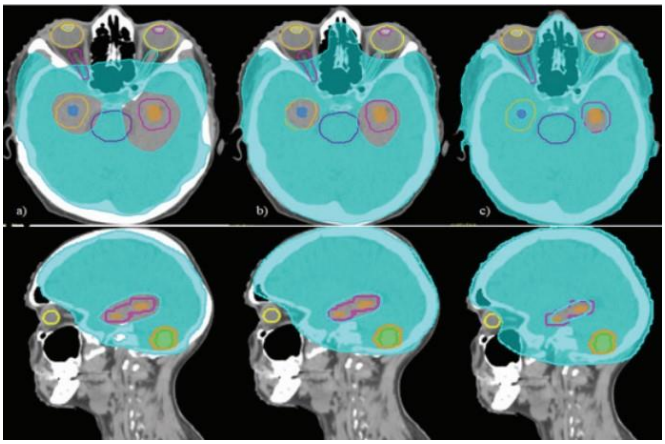


Figure 2 - Axial and sagittal plan dose distribution example. Axial view is illustrating organs at risk including eyes, lenses, optical nerves, brainstem, and hippocampal avoidance region. In sagittal view with green color is highlighted the boost target volume where the dose is escalated: a) blue sky – 30 Gy colorwash isodose; b) blue sky – 25Gy colorwash isodose; c) blue sky – 16 Gy colorwash isodose.

Study Assessments

Prior to being allocated randomly, every patient had a baseline assessment that included a neurologic examination, performance status, thin-slice MRI, history and physical examination, cognitive tests, and measures of patient-reported quality of life and symptom burden. Cognitive parameters were evaluated through validated cognitive tests at the initial assessment and during follow-up at 1 and 6 months. The primary objective of the research was to analyze alterations in neurocognitive function (NCF) from the baseline in areas other than memory using the Mini-Mental State Examination (MMSE). Secondary endpoints encompassed cancer-related outcomes such as physician-assessed radiographic recurrence, overall survival, and adverse events as per the Common Terminology Criteria for Adverse Events (CTCAE).

Statistical Analysis

The statistical analysis was conducted using IBM SPSS (Statistical Package for the Social Sciences) Statistics version 20. Nominal and categorical data were descriptively analyzed using functions such as Frequencies, Explore and Crosstabs. The results of nominal variables were presented in tables and bar charts, while numerical data were depicted using boxplots. In the statistical analysis, Shapiro-Wilk tests were employed to determine normal distribution of the data, and non-parametric tests such as Mann-Whitney U test and Likelihood Ratio were used.

Results

Tabel 1 - Descriptive table of the study groups

			Study group	
			HSIB-WBRT	WBRT
Tumor localization	uterus	Count	1	0
		% within Study group	6.7%	0.0%
	breast	Count	3	8
		% within Study group	20.0%	53.3%
	lung	Count	9	7
		% within Study group	60.0%	46.7%
	colon	Count	1	0
		% within Study group	6.7%	0.0%
	stomach	Count	1	0
		% within Study group	6.7%	0.0%
Total		Count	15	15
		% within Study group	100.0%	100.0%

In the HSIB-WBRT group, the most frequent localization was in the lung, in 60% of patients, the second most frequent localization was in the breast, in 20% of patients, and 6.7% had the primary tumor located in the uterus, 6.7% in the colon, and 6.7% in the stomach.

In the WBRT group, the most frequent localization was in the breast, for 53.3% of patients, and in the lung, for 46.7% of patients. Likelihood Ratio test was used, resulting in the finding that this difference is not statistically significant, with p = 0.149.

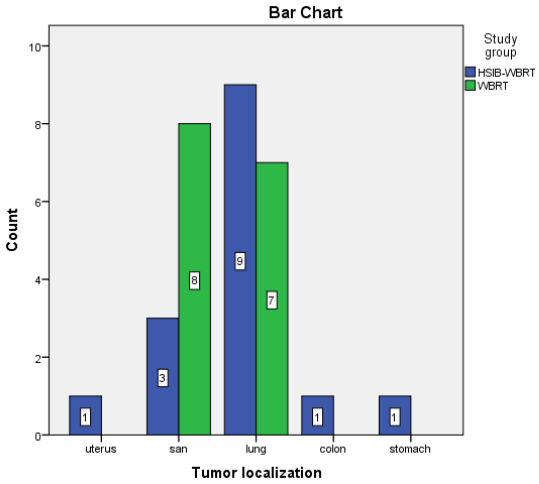


Figure 3 - Tumor localization for the 2 groups

In the HSIB-WBRT group, the mean MMSE score at 1 month was 29.67 with a median of 30, whereas for the WBRT group, the mean was 29.13 with a median of 29.

Tabel 2 - Descriptive table of the MMSE test at 1 month for both groups

Descriptives				
	Study group		Statistic	Std. Error
MMSE test 1 month	HSIB-WBRT	Mean	29.67	.126
		Median	30.00	
		Std. Deviation	.488	
		Minimum	29	
		Maximum	30	
		Interquartile Range	1	
	WBRT	Mean	29.13	.215
		Median	29.00	
		Std. Deviation	.834	
		Minimum	28	
		Maximum	30	
		Interquartile Range	2	

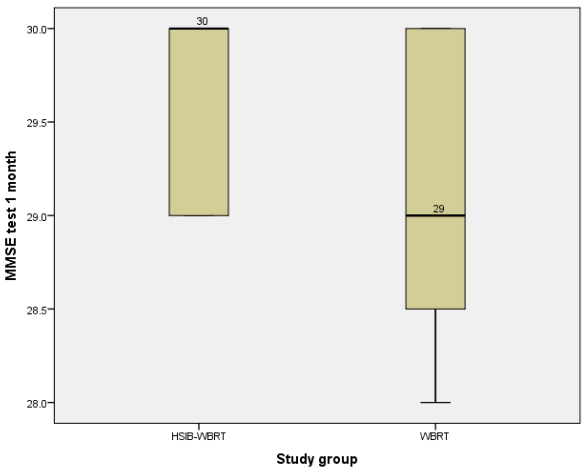


Figure 4 - MMSE test at 1 month

In the HSIB-WBRT group, the mean MMSE score at 6 months was 28.93 with a median of 29, whereas for the WBRT group, the mean was 24.6 with a median of 25.

Tabel 3 - Descriptive table of the MMSE test at 6 months for both groups

Descriptives				
	Study group		Statistic	Std. Error
MMSE test 6 months	HSIB-WBRT	Mean	28.93	.153
		Median	29.00	
		Std. Deviation	.594	
		Minimum	28	
		Maximum	30	
		Interquartile Range	0	
	WBRT	Mean	24.60	.524
		Median	25.00	
		Std. Deviation	2.028	
		Minimum	21	
		Maximum	28	
		Interquartile Range	3	

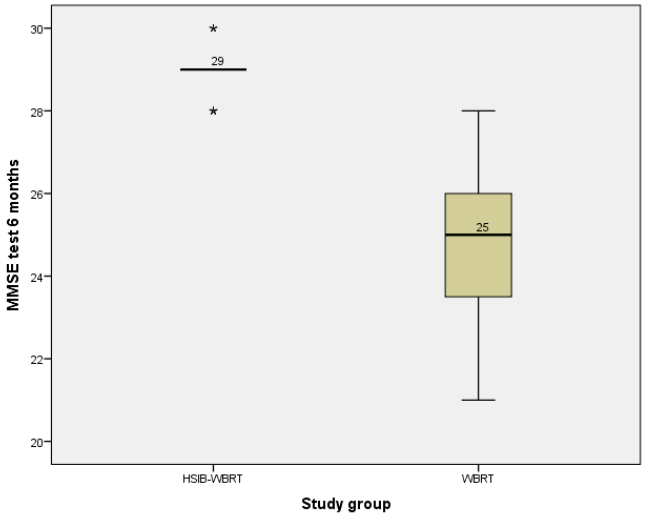
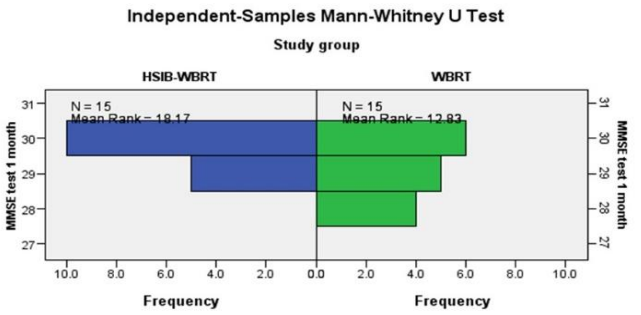


Figure 5 - MMSE test at 6 months

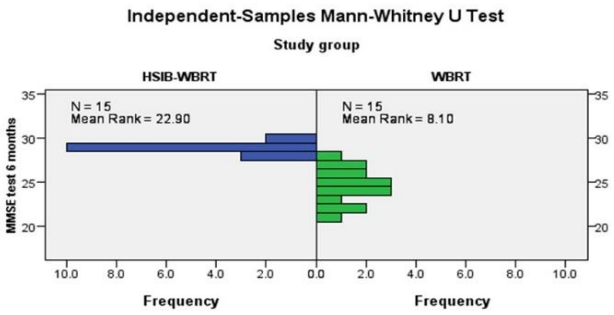
Shapiro-Wilk was conducted to determine if the data were normally distributed. The data were not normally distributed ($p < 0.05$); therefore, the Mann-Whitney U test was used to establish whether there is a statistically significant difference between MMSE scores at 1 month and 6 months and the technique used: HSIB-WBRT and WBRT.

There is no significant difference between the two groups (HSIB-WBRT / WBRT) for the MMSE scores at 1 month, with $p = 0.098$, and $U = 72.500$, $Z = -1.844$.

There is a significant difference between the two groups (HSIB-WBRT / WBRT) for the MMSE scores at 6 months, with $p < 0.001$, and $U = 1.500$, $Z = -4.703$



Total N	30
Mann-Whitney U	72.500
Wilcoxon W	192.500
Test Statistic	72.500
Standard Error	21.695
Standardized Test Statistic	-1.844
Asymptotic Sig. (2-sided test)	.065
Exact Sig. (2-sided test)	.098



Total N	30
Mann-Whitney U	1.500
Wilcoxon W	121.500
Test Statistic	1.500
Standard Error	23.602
Standardized Test Statistic	-4.703
Asymptotic Sig. (2-sided test)	.000
Exact Sig. (2-sided test)	.000

Figure 6 - Mann-Whitney U Test for MMSE at 1 month and Mann-Whitney U test for MMSE at 6 months

One of the most important aspects of our study was the local control at 6 months. The paradigm shift from WBRT to HSIB-WBRT can improve the survival and quality of life of cancer patients.

Tabel 4 - Differences in the local control at 6 months

		Study group	
		HSIB-WBRT	WBRT
6 months	progression	4 cases(26.4%)	7 cases (46.7%)
	control	11 cases (73.7%)	8 cases (52.3%)
Total		15	15

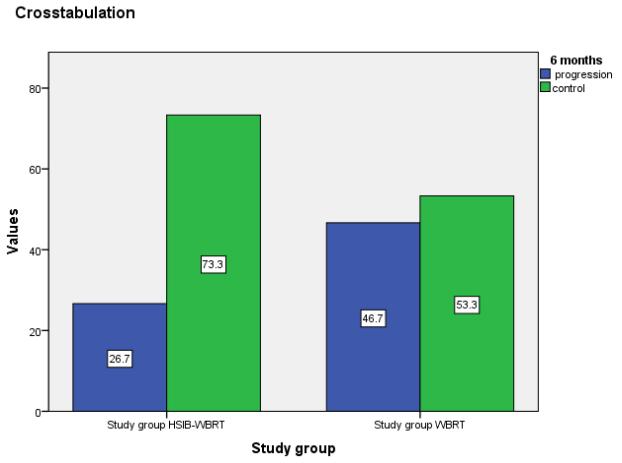


Figure 7- Progression in the two study groups

In the HSIB-WBRT group, progression was observed in 26.4% of the patients included in the study group at 6 months, whereas in the WBRT progression was observed at 6 months for 46.7% of them. There is a descriptive difference between the two groups; therefore, the Likelihood Ratio test was used, resulting in the finding that this difference is not statistically significant, with p = 0.253. We need to specify that the limitation is determined by the small patient sample size, therefore, it was not possible to completely eliminate the risk of type 2 statistical error (false negative).

Discussions

This a prospective, randomized, two-arm single institution study confirms that, in patients with brain metastases, conformal avoidance of the hippocampal neuroregenerative stem-cell niche using VMAT during WBRT better preserves cognitive function and patient-reported symptoms. These results suggest that for patients who plan to receive WBRT with simultaneous integrated boost and no metastases in the HA region, HSIB-WBRT should be the standard of therapy.

Our study delved into the impact of sparing the hippocampal region of the brain, with a focus on reducing toxicity, particularly cognitive decline. Expanding on this investigation, we demonstrated the feasibility and effectiveness of a hippocampal sparing, which integrates a simultaneous integrated boost for visible brain metastases. The selection of the dose was predicated on the hypothesis that MRI sensitivity is adequate for detecting brain metastases necessitating higher doses for control, with 30 Gy potentially sufficient for addressing MRI-undetectable microscopic disease. This approach aligns with previous outcomes observed in patients treated solely with SRS. Similar trends in rates of cognitive decline were noted by Brown and colleagues in patients with 1–3 brain metastases. These findings are consistent with the stereotactic (SRS) boost arm of RTOG 9508, which randomized patients to WBRT ± SRS boost, highlighting the importance of achieving intracranial local control for improved clinical outcomes. (12-16).

Continued advancements in systemic disease control, such as the development of new immunomodulatory and targeted systemic therapies, are expected to underscore the significance of achieving long-term intracranial control while preserving quality of life. HSIB-WBRT was well-tolerated and generally devoid of significant acute or late toxicity. A similar recovery pattern was noted in studies like RTOG 0933 and RTOG 0614. However, this observation was noted only in patients who lived beyond 6 months. In contrast, WBRT without hippocampal avoidance strategies showed minimal neurocognitive recovery. Therefore, HSIB-WBRT may provide additional opportunities for continued neurological recovery as brain metastasis patients survive longer. HSIB-WBRT complements other innovations in the WBRT domain, offering potential benefits through dose reduction to at-risk brain regions and an integrated tumor boost. It may serve as an efficient alternative to the combination of SRS with whole-brain radiation, which often entails additional procedures, expertise, and costs, and is associated with compromised quality of life (12-17). Additionally, SRS does not appear to confer a discernible survival advantage for multiple metastases, aligning with recommendations against combining SRS with whole-brain radiation. HSIB-WBRT presents a promising alternative that addresses these challenges while offering the advantages of intensified local therapy. (18-20)

While our study yields promising results, certain limitations exist. The study is constrained by the small sample size of each study group, consisting of only 15 patients, which heightens the potential for type II error. To enhance the robustness and applicability of the statistical findings, further investigations on this subject matter are warranted. Poor compliance with neurocognitive testing in follow-up was anticipated due to disease prognosis, with many subjects losing motivation in end-of-life care settings. Future studies of this technique may be warranted. The HSIB-WBRT group demonstrated a superior preservation of neurocognitive function, despite failing to illustrate an advantage in terms of local control when compared to the WBRT group after 6 months, most probably because of the small sample size of each study group. In summary, our data support that HSIB-WBRT provides a safe and accessible treatment option that offers excellent intracranial tumor control while preserving neurocognition in patients with brain metastases.

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