Hippocampal-sparing radiotherapy and neurocognitive impairment: A systematic literature review

Review Article

Hippocampal-sparing radiotherapy and neurocognitive impairment: A systematic literature review

Zanirato Rambaldi Giuseppe, Cammelli Silvia[1], Farina Eleonora[1], Macchia Gabriella[2], Ferro Marica[2], Chiesa Silvia[3], Balducci Mario[3], Deodato Francesco[2], Cilla Savino[4], Buwenge Milly[1], Frezza Giovanni P[5], Zompatori Maurizio[1], Morganti Alessio G[1]

Radiology Unit, Department of Experimental, Diagnostic and Specialty Medicine - DIMES, University of Bologna, Bologna, [1]Department of Experimental, Radiation Oncology Center, Diagnostic and Specialty Medicine - DIMES, University of Bologna, [5]Radiotherapy Department, Ospedale Bellaria, Bologna, [2]Radiotherapy Unit, Fondazione di Ricerca e Cura "Giovanni Paolo II," Catholic University of Sacred Heart, [4]Medical Physics Unit, Fondazione di Ricerca e Cura "Giovanni Paolo II," Catholic University of Sacred Heart, Campobasso, [3]Department of Radiotherapy, Fondazione Policlinico Universitario "A. Gemelli," Catholic University of Sacred Heart, Rome, Italy

For correspondence: Dr. Zanirato Rambaldi Giuseppe,

ABSTRACT

Introduction: Whole-brain radiation therapy (WBRT) is an effective therapeutic modality in patients with brain metastases. However, nearly 90% of patients undergoing WBRT suffer from a neurocognitive function (NCF) impairment at diagnosis, and up to two-thirds will experience a further decline within 2–6 months after WBRT. Focal-dose reduction on bilateral hippocampus is thought to improve NCF preservation. The aim was to present a systematic review of clinical results on NCF after hippocampal-sparing (HS) WBRT.

Materials and Methods: A systematic review of published literature was performed on PubMed and the Cochrane Library. Only prospective clinical trials reporting NCF outcome in patients treated with HS-WBRT have been analyzed.

Results: A total of 165 patients from three studies were included. These studies are characterized by small sample size and different methods in terms of WBRT technique but with similar planning analysis and NCF assessment tests. No significant changes in NCF (i.e., verbal and nonverbal learning memory, executive functions, and psychomotor speed) between baseline and 4-month follow-up after RT and only a mean relative decline in delayed recall at 4 months (7% compared to 30% of historical control) were observed.

Conclusions: Considering preliminary results on NCF preservation, further studies seem justified in patients undergoing brain irradiation for brain metastases or referred for prophylactic cranial irradiation to evaluate long-term effects on NCF and quality of life.

KEY WORDS: Brain metastases, hippocampal sparing, neurocognitive impairment, review, whole-brain radiotherapy

INTRODUCTION

Cranial irradiation is an effective therapeutic modality in multiple different settings: whole-brain radiotherapy (WBRT) of brain metastases (BMs), prophylactic cranial irradiation (PCI) in small cell lung cancer (and controversially for nonsmall cell lung cancer), and cranial-spinal irradiation in pediatric central nervous system malignancies.[1]

Nearly 90% of patients affected by BM suffer from decline of neurocognitive function (NCF) at diagnosis, and up to two-thirds will experience further neurocognitive impairment (NCI) within 2–6 months after WBRT.[2] Due to improvement in oncological treatments and consequent prolonged survival in patients receiving WBRT, NCI prevention is increasingly considered an emerging need in clinical practice.[3]

Clinical studies suggest that radiation-induced damage of the hippocampus plays a considerable role in NCI, being demonstrated the association between delivered dose to the hippocampus and NCI.[4] In fact, the pathogenesis of radiation-induced NCI may involve injury to proliferating neuronal progenitor cells in the hippocampus subgranular zone.[5] Moreover, a recent study showed the development of a radiation dose-dependent hippocampal atrophy

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Radiology Unit, Department of Experimental, Diagnostic and Specialty Medicine - DIMES, University of Bologna, S.Orsola-Malpighi Hospital, Via Giuseppe Massarenti 9, 40126 Bologna, Italy.
E-mail: giuseppe.zanirato@gmail.com

after brain tumor irradiation: quantitative magnetic resonance imaging (MRI) showed a median 6% hippocampal volume loss 1 year after radiotherapy (RT) with dose >40 Gy.[6] Therefore, hippocampal-sparing WBRT (HS-WBRT) with focal-dose reduction on the hippocampus may be theoretically helpful.

Several planning studies evaluated the feasibility of HS-WBRT using different RT techniques: intensity-modulated radiation therapy (IMRT), intensity-modulated arc therapy, volumetric-modulated arc therapy (VMAT), tomotherapy, and stereotactic RT.[7-20] All these techniques were able to achieve adequate coverage of the planning target volume (PTV) while providing an efficient HS.

However, despite the clear technical feasibility of HS-WBRT, evidence about its impact on NCF is still limited and based on preliminary studies generally performed on small patient populations.[21] Furthermore, no literature reviews addressed this clinical issue.

Therefore, the aim of this analysis is to present a literature review of the clinical effects of HS-WBRT on NCF in patients undergoing cranial irradiation.

MATERIALS AND METHODS

Inclusion criteria

Type of studies

in this review, included were all prospective clinical trials reporting NCF outcome in patients treated with HS-WBRT. Case reports were excluded.

Type of participants

only studies enrolling patients suffering from BM with pathologically proven diagnosis of nonhematopoietic malignancy or undergoing PCI for lung cancer were included in this analysis.

Type of interventions

Radiotherapy

Eligible interventions were RT with any dose and fractionation schedule performed with a HS technique.

Chemotherapy

All systemic treatments regardless of antineoplastic agent type and use of single or combination protocols were allowed.

Supportive care

Studies were included in the analysis regardless of supportive therapy type or other treatments such as blood transfusions, analgesic treatments, or corticosteroids.

Neurocognitive function evaluation

All neurocognitive evaluation scales and tests were eligible to evaluate NCF impairment.

Type of outcome measures

primary endpoint of the analysis was to evaluate the NCF preservation after HS-WBRT and secondary endpoint was intracranial control of the disease using HS-WBRT.

Literature search strategy

A bibliographic search was performed based on the PRISMA methodology[22] using PubMed and the Cochrane Library. The search algorithm was "hippocampal" [MeSH] AND "sparing" [MeSH] AND ("radiotherapy" OR "radiation therapy"). The research in PubMed and the Cochrane Library was complemented by an additional screening of the references of publication identified through the database. The search was not limited to a particular time interval. It was restricted to English-language peer-reviewed journal publications. Papers were independently selected and evaluated by two different authors (GZR and EF). Any discrepancies in the selection of papers and data collection were managed by the senior author (AGM). Potentially eligible studies were retrieved, and a full-text evaluation was performed as to whether it satisfied both inclusion and exclusion criteria.

Only clinical trials reporting NCF outcome of patients treated with HS-WBRT were included in the review process. Studies not reporting a complete NCF evaluation before and after treatment were excluded.

RESULTS

Search results

Through the literature search, performed as previously described, 82 papers were identified. Figure 1 describes the process of paper selection. Nine papers underwent full-text examination. In this phase: one paper was excluded because it was a study protocol;[23] two papers were excluded because they did not report a complete pre- and post-treatment NCF evaluation;[13,24] one paper was excluded because it referred to a pediatric population only estimating the risk of NCI;[21] one paper was excluded because it was a planning study;[17] and one paper was excluded because it reported the NCF outcome in patients undergoing cranial irradiation without HS technique.[25] Therefore, three studies fulfilled the inclusion criteria and were included in this review, with a total of 165 patients enrolled.

Literature review

Gondi *et al.*[26] designed a Phase II multi-institutional trial in patients with BM 5-mm outside the hippocampal borders.

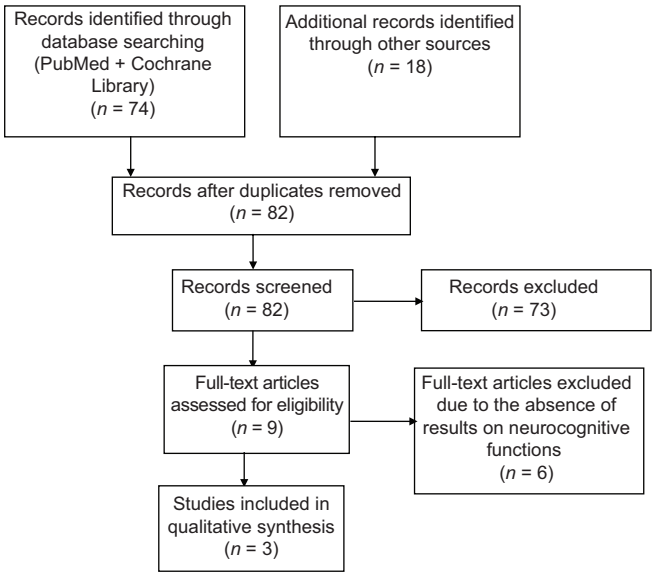

Figure 1: Process of papers selection

They enrolled 100 patients who underwent HS-WBRT (30 Gy in 10 fractions) delivered with IMRT. NCF was evaluated with the Hopkins verbal learning test-revised (HVLT-R) at baseline and at 2-, 4- and 6-month follow-up. Primary endpoint was HVLT-R score decline from baseline to 4 months after the start of HS-WBRT and secondary endpoint was quality of life (QoL) evaluation after HS-WBRT. They observed a mean relative decline in HVLT-R score from baseline to 4 months of about 7%, significantly lower compared to the value (30%; $P < 0.001$) recorded in the PCI-P-120-9801 Phase III trial.[27] Age ≥60 years, presence of at least minor neurologic symptoms at baseline, and higher hippocampal $D_{100\%}$ predicted a stronger decline over time in HVLT-R. Even if only 42 patients were evaluable at 4-month follow-up, the authors concluded that HS-WBRT is associated with memory and QoL preservation compared to historical series.

Lin *et al*.[28] reported the results of a Phase II study on HS-WBRT in patients with oligometastatic BM (≤3 metastatic foci at MRI with the largest diameter <4 cm) or in patients with lung cancer undergoing PCI. Twenty-five patients received HS-WBRT using VMAT with the following doses: 30 Gy in 12 fractions for palliative or adjuvant WBRT and 25 Gy in 10 fractions for PCI. NCF was evaluated with several neurocognitive tests: Wechsler memory scale-III (verbal and non-verbal episodic memory), modified card sorting test (conceptual formation and mental shifting), digit span subtest of the Wechsler adult intelligence scale – 3rd edition (verbal working memory), and psychomotor speed index. Patients were evaluated at baseline and at 4-month follow-up. Endpoints of the study were HS-WBRT feasibility and its impact on NCF. Only eight out of 25 patients were able to receive 4-month follow-up NCF assessment, and no significant differences between pre- and post-HS-WBRT neurocognitive assessment were observed, except for long-term memory on the world list. Based on these results, the authors concluded that HS-WBRT is a feasible technique able to preserve NCF.

The same group published a larger prospective trial[29] on the effects of HS-WBRT on NCF. They enrolled 40 patients with the same indications and receiving the same treatment and NCF assessment as in the previous study. Based on the results of NCF score of 24 patients at 4-month follow-up, they found a significant association between better functional preservation in immediate recall and lower doses delivered to the hippocampus (maximal dose <12.6 Gy, $D_{80\%}$ <6.8 Gy, and minimal dose <5.83 Gy delivered to bilateral hippocampus). However, no significant differences between pre- and post-HS-WBRT neurocognitive assessment were observed. Therefore, they concluded that hippocampal dosimetry correlates with neurocognitive outcomes and that modern VMAT can effectively reduce the hippocampal dose below dosimetric threshold while maintaining intracranial disease control.

Analysis of the selected studies

Table 1 shows the study and treatment characteristics of the analyzed series. Based on selection criteria, all studies had a prospective design. The number of patients enrolled was 25–100 (median: 40). They enrolled patients with BM without lesions <5 mm from the hippocampus and two of them included even patients undergoing PCI. In one study,[26] historical data on NCF from another trial[27] were used as control group, due to ethical concerns about enrolling patients in a non-HS arm. Prescribed radiation dose was similar in the three studies: 25–30 Gy in 10–12 fractions. RTs were similar: IMRT in one case and VMAT in two other cases. For hippocampal contouring and HS-WBRT planning, all patients underwent an MRI scan of the brain with ≤1.5 mm thick axial slice. These images were fused with computed tomography (CT) simulation scans, and the bilateral hippocampal contours were manually generated on the fused MRI-CT images. These volumes were expanded by 5 mm to generate the hippocampal avoidance regions. The clinical target volume (CTV) was defined as the whole-brain parenchyma, and the PTV was defined as the CTV excluding the hippocampal avoidance regions. No setup margin was added to the CTV to define the PTV. NCF was assessed using several tests but similar regarding figural and verbal memory. Evaluations were performed at baseline before RT and with similar follow-up timing (4 months).

Table 2 reports planning and clinical results as well as some notes emphasized by the authors. Hippocampal avoidance was achieved in all studies since radiation dose delivered to the 80%–100% of the hippocampal volume ($D_{80\%–100\%}$) was <9 Gy and maximum dose was <16 Gy. In one study,[26] significant memory preservation was observed in comparison with historical control arm. The other two studies did not report significant differences in NCF assessment performed pre- and post-RT.

Maximal dose <12.60 Gy, $D_{80\%}$ <6.80 Gy, and minimal dose <5.83 Gy delivered to bilateral hippocampus were significantly associated with functional preservation (immediate recall of verbal memory), with the minimal dose irradiating left

Table 1: Study characteristics

Authors (year)	Study design	Setting	Patients	Inclusion criteria	Exclusion criteria	Dose, Gy (dose/fx, Gy)	RT technique	Neurocognitive impairment evaluation scale	Follow up (month)
Gondi *et al*., 2014	Prospective single-arm phase II trial (RTOG 0933)	Brain metastases	100	Lesions 5 mm outside H margin; pathologically proven diagnosis of nonhematopoietic malignancy other than SCLC or germ cell malignancy; RTOG recursive partitioning analysis class I or II; English proficiency	Age <18 years; leptomeningeal metastases; radiographic evidence of hydrocephalus; prior brain RT; planned upfront radiosurgery or surgical resection; contraindication to MRI; serum creatinine >1.4 mg/dl; NSCLC associated brain metastases with ≥2 organ sites of extracranial metastases	30 (10)	IMRT	HVLT-R (cognitive assessment); FACT-BR and ADLs (QOL)	2, 4, 6
Lin *et al*., 2015	Prospective phase II trial	PCI in lung cancer, nonhematopoietic malignancy, brain metastasis (surgically resected or not)	25	KPS ≥70 or ECOG ≤2; ≤3 metastatic foci with greatest diameter<4 cm (MRI); RTOG recursive partitioning analysis class I or II; pathologically proven diagnosis of nonhematopoietic tumor	Clinical suspicion of leptomeningeal spreading; prior RT to the brain/head; contraindication to MRI; distance H margin-lesion <5 mm	30 (12) (in case of oligometastatic brain or postcraniotomy with tumor removal)	VMAT	WMS-III (verbal and nonverbal episodic memory); modified card sorting test (executive functions); DS subtest of the WAIS-III (verbal working memory); PSI (performance in psychomotor speed)	4, 12
Tsai *et al*., 2015	Prospective trial	PCI in lung cancer, nonhematopoietic malignancy, brain metastasis (surgically resected or not)	40	KPS ≥70; ECOG ≤2; ≤3 metastatic foci with greatest diameter<4 cm (MRI); RTOG recursive partitioning analysis class I or II pathologically proven diagnosis of nonhematopoietic tumor	Clinical suspicion of leptomeningeal spreading; prior RT to the brain/head; contraindication to MRI; distance H margin-lesion <5 mm	30 (10-12): therapeutic/ adjuvant aim; 25 (10): prophylactic aim	VMAT	WMS-III (verbal and not-verbal episodic memory); modified card sorting test (executive functions); DS subtest of the WAIS-III (verbal working memory); PSI (performance in psychomotor speed)	4

ADLs=Barthel index of activities of daily living, DS=Digit span; ECOG=Eastern Cooperative Oncology Group performance status scale, c.e.=Contrast-enhanced, FACT=Functional assessment of cancer therapy-brain subscale, fx=Fractions, H=Hippocampus, HVLT-R=Hopkins verbal learning test-revised, IMRT=Intensity-modulated RT, KPS=Karnofsky performance status, MRI=Magnetic resonance imaging, PCI=Prophylactic cranial irradiation, PSI=Psychomotor speed index, QOL=Quality of life, RT=Radiation therapy, SCLC=Small cell lung cancer, VMAT=Volumetric-modulated arc therapy, WMS-III=Wechsler memory scale-3rd ed..ition, NSCLC=Nonsmall cell lung cancer, RTOG=Radiation therapy oncology group

hippocampus resulting an independent predictor of this specific NCI.[29] No independent effects of right hippocampus-specific dosimetric parameters on verbal or nonverbal memory were observed. Moreover, in the same study, as the mean dose delivered to the left hippocampus (converted to EQD2, biologically equivalent dose in 2 Gy fractions) increases by one more Gy, there would be an approximately 4-fold increase in the risk of NCI in immediate recall of verbal memory.

A relevant dropout rate during follow-up was observed in all three studies: only 45% (mean) of enrolled patients received NCF assessment after treatment. The majority of not compliance at follow-up was attributed to deteriorated performance status and high patient death rate.

Overall HS-WBRT seems to preserve NCF since NCF scores were quite stable between baseline and 4-month assessment

Table 2: Study results

Authors (year)	Planning results (hippocampal dosimetry)	Clinical results	Patients at last follow up (%)	Notes
Gondi *et al.*, 2014	$D_{100\%}$ <9 Gy D_{max} <16 Gy	Mean relative decline (HVLT-R DR) (follow up 4th months): 7% versus 30% versus (control group*) (P<0.001); preservation of QOL 67% patients with intracranial failure (3 patients in H area)	50 (50)	Median OS (months): 6.8 versus 4.9 (control group*) median PFS (months): 5.9 versus - no QOL data in control group*; HVLT-R, FACT-BR, ADL data compliance >70% (2nd-4th months), >50% (6th months); long term effects: Not assessed due to limited sample size and high patient death rate (46% by 6 months)
Lin *et al.*, 2015	NR	No significant differences between pre- and post-RT in memory, executive functions and psychomotor speed; Significant difference in delayed recall verbal memory (P=0.048); 16% patients with intracranial progression; No intracranial failure in H area	10 (40)	No presence of a control group (conventional WBRT)
Tsai *et al.*, 2015	$V_{40\%}$: 15.42±17.34% (left H) and 15.3±17.528% (right H); EQD_2 doses: $D_{20\%}$, $D_{40\%}$, $D_{50\%}$, $D_{80\%}$ <8.5 Gy; median EQD2 values of D_{max} and D_{min}: 12.6 Gy and 5.8 Gy (left H) and 12.4 Gy and 5.7 Gy (right H)	NCF score quite stable for H-dependent memory; Significantly associated with neurocognitive preservation (as median EQD_2): D_{max} <12.64 Gy (P=0.004), $D_{10\%}$ <8.81 Gy (P=0.041), $D_{50\%}$ <7.45 Gy (P=0.041), $D_{80\%}$ <6.80 Gy (P=0.041), D_{min} <5.83 Gy (P=0.041); dosimetric left H parameters as predictive factor in neurocognitive decline (immediate recall) (P=0.042); No significant associations between dosimetric right H parameters and verbal functional preservation; 2.5% patients with intracranial failure in H area	24 (60)	Overall compliance with NCF tests 68%; a decline after 4 months cannot be completely excluded

*PCI-P-120-9801. EQD_2=Biologically equivalent dose in 2-Gy fractions, HVLT-R DR=Hopkins verbal learning test-revised delayed recall, NCF=Neurocognitive functions, NR=Not reported, PS=Performance status, OS=Overall survival, WBRT=Whole brain radiation therapy, RT=Radiation therapy, H=Hippocampus, PFS=Progression-free survival, QOL=Quality of life, PCI=Prophylactic cranial irradiation

or only a significantly lower mean decline in HVLT-R DR at 4 months (7%) compared to historical control (30%).

None of the three studies included in this review evaluated the intracranial control of the disease after HS-WBRT, particularly the late onset of new metastases in the hippocampal avoidance regions.

DISCUSSION

Due to improved survival, NCF preservation is considered a relevant issue in patients undergoing WBRT. Although nearly 90% of patients affected by BM suffer from NCI at diagnosis, up to two-thirds will experience a further decline within 2–6 months after WBRT.[2] The purpose of this systematic review of the literature was to evaluate the efficacy of the "HS" WBRT in preserving NCF. Very few data are available about this issue, and only three studies were included in this review.

All patients enrolled in these studies underwent HS-WBRT with different techniques but with similar hippocampal dosimetric results. Two of this studies[28,29] demonstrated no significant changes in NCF (verbal and nonverbal learning memory, executive functions, and psychomotor speed) between baseline and 4-month follow-up after RT. Although these studies are limited by the absence of a control group treated with conventional WBRT, each patient served as his/her own control by evaluating the score differences (baseline and 4-month posttreatment). The authors commented that patients fitting the same eligibility criteria and randomized to receive conventional WBRT without HS should be the ideal control group. However, ethical considerations can represent a limit, assuming that HS-WBRT could achieve similar oncological outcomes and more favorable NCF outcomes compared to conventional WBRT.

In contrast, the Gondi *et al.*'s study[26] showed 7% (confidence $interval_{95\%}$: 4.7%–18.7%) decline in NCF score after HS-WBRT. However, this value was significantly lower compared to 30% mean decline in historical control group ($P < 0.001$). This difference compared to the other two studies might be due to the inclusion criteria since Gondi *et al.* enrolled patients with BM regardless of tumor burden, while Lin *et al.*[28] and Tsai *et al.*[29] included only patients with oligometastatic brain disease (resected or not) and patients referred for PCI. These better baseline conditions might explain the better NCF outcome.

In fact, worse baseline conditions have been correlated with unsatisfactory outcome. Bodensohn *et al.*[25] published their experience in patients with primary brain tumors (anaplastic astrocytoma or glioblastoma multiforme) undergoing definitive or postoperative RT without HS. They reported that the differences in NCF decline due to radiation exposure of the hippocampus were less pronounced than expected, despite the fact that median average dose delivered to bilateral hippocampus was significantly high (37.6 Gy). However, their patient population included patients presenting with

hippocampal unilateral and bilateral tumor involvement with a clear performance deficit at baseline and in worse clinical conditions compared to the other studies. Moreover, the NCF assessment was performed in a variable time follow-up (from 81 to 491 days) and therefore potentially too early to detect a significant impact almost in some patients.

HS-WBRT has the theoretical potential to foster the development of metastases near the hippocampus, but the analyzed studies did not report data on the onset of new metastases after WBRT. However, several studies[30-39] evaluating the pattern of BM distribution reported a very low incidence of metastases (3.3% of all metastases) within the hippocampal region in both unselected and specific tumors (i.e., SCLC, breast cancer, and melanoma) [Table 3]. In fact, only 8.8% of 1881 patients (presenting 9633 metastases) experienced hippocampal and perihippocampal localizations (respectively, 2.1% and 6.7%). We can assume that the risk of a posttreatment recurrence pursues the same patterns as at the time of the first diagnosis. On average, a very low percentage of BM develops in the hippocampus (1.1%), and also, the percentage of metastases developing within 5 mm margin from hippocampus is low (2.2%). Therefore, the pattern of BM confirms the safety of sparing this region while delivering WBRT.

Limitations

First, only three studies were included in this review reporting results based on limited sample size at follow-up evaluation (<50 patients in all studies), and none of them was a randomized clinical trial. Moreover, in two studies,[28,29] from the same group, it was not possible to establish if there was an overlap of patients' populations: They reported different data and different endpoints, with similar results. We decided to include both studies in this review because of the qualitative nature of our analysis.

Furthermore, no evaluation of QoL based on patient-reported outcomes was performed, which should be one of the most important endpoints in palliative treatments. In all three studies, a relevant dropout rate (mean: 55%) was observed. The majority of not compliance at follow-up might be attributed to deteriorated performance status or early patient's death. Being deteriorated performance status, one reason for lack of compliance, it could represent a bias, especially in two studies.[28,29] In fact, reported results were probably based on better-performing patients.

In addition, these studies did not evaluate some other potential patient/disease-related factors affecting patients' NCF changes, such as the extent of brain edema caused by mass effect or surgical intervention, nutritional condition, electrolyte imbalance, and confounding effect of increased intracranial pressure. Moreover, none of the analyzed studies evaluated the onset of new metastases in the hippocampal-avoiding regions.

Finally, given the limited follow-up time of these studies, the efficacy of HS technique in preventing long-term (i.e., beyond 6 months) NCI produced by WBRT could not be assessed.

Perspectives

The overall conclusion is that future studies of HS-WBRT appear justified in patients undergoing brain irradiation for BM or referred for PCI, considering the feasibility and safety profile of HS-RT and preliminary results on NCF preservation. To confirm the safety of this technique, it would be helpful if these studies could analyze the site of new BM following HS-WBRT. In addition, it would be interesting to evaluate the potential combined neuroprotective effects of hippocampal avoidance in addition to prophylactic neuroprotective drugs, such as memantine, during brain irradiation. Moreover, it would be useful to improve the selection of patients who would experience the best benefits in clinical practice: As shown using a mathematical model,[40] HS-WBRT is a cost-effective therapy for long-term survivors (12–24 months). Furthermore, new studies could evaluate whether baseline biomarkers of white matter injury and hippocampal volumetry at MRI are potential predictors of cognitive decline and differential benefit from HS-WBRT.

Table 3: Summary of studies on patterns of brain metastases

Authors (year)	Type of tumor	Patients	Metastases	Hippocampal incidence of metastases (%)	Perihippocampal incidence of metastases (%)	Hippocampal incidence (percentage of patients)	Perihippocampal incidence (percentage of patients)
Ghia *et al*., 2007	Miscellanea	100	272	0 (0.0)	9 (3.3)	0 (0.0)	8 (8.0)
Gondi *et al*., 2010	Miscellanea	371	1133	0 (0.0)	34 (3.0)	0 (0.0)	32 (8.6)
Marsh *et al*., 2010	NSCLC, SCLC, breast, other	107	697	16 (2.3)	NA	NA	NA
Harth *et al*., 2013	NSCLC, SCLC	100	856	3 (0.4)	8 (0.9)	3 (3.0)	8 (8.0)
Wan *et al*., 2013	Miscellanea	488	2270	7 (0.3)	NA	7 (1.4)	NA
Hong *et al*., 2014	Melanoma	77	115	0 (0.0)	4 (3.4)	0 (0.0)	4 (5.2)
Kundapur *et al*., 2015	SCLC	59	359	NA	3 (0.8)	N.A.	3 (5.0)
Sun *et al*., 2016	Breast	314	1678	20 (1.2)	59 (3.5)	13 (4.1)	35 (11.0)
Wu *et al*., 2016	Breast	192	1356	49 (3.6)	99 (7.3)	7 (3.6)	14 (7.3)
Guo *et al*., 2017	SCLC	180	1594	23 (1.4)	NA	9 (5.0)	22 (12.2)
Sum of available data*	Miscellanea	1881	9633	102 (1.1)	216 (2.2)	39 (2.1)	126 (6.7)

*Marsh's study is not included in the summary of number of patients because the number of patients who developed hippocampal metastases was not reported. NSCLC=Nonsmall cell lung cancer, SCLC=Small cell lung cancer, NA=Not available data

One of the most interesting perspectives in the treatment of BM is the possibility to irradiate the whole brain with simultaneous integrated boost on metastases in oligometastatic patients.[41] Therefore, it would be interesting to evaluate the possibility to combine this technique with HS RT, to maximize intracranial tumor control, and to reduce NCI after RT.

Moreover, novel indications could be considered for HS technique, such as the treatment of primary brain tumors, in which a reasonable protection seems to be possible in about half of all cases,[42] or other neoplasms: head and neck cancers,[10] and particularly nasopharynx[8] and maxillary tumors, and pituitary and base of skull neoplasms.

Finally, it is known that WBRT for metastatic tumors has, in many cases, a palliative aim and many patients suffer from neurologic symptoms, memory decline, and pain. For these reasons, future studies should answer the question whether NCF preservation based on HS techniques has a positive impact on patients QoL evaluated by patient reported outcome measures.

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Conflicts of interest
There are no conflicts of interest.

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