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RADIOTHERAPY

Impact of whole-brain radiation therapy on neurocognitive functions, alopecia and hearing loss: a systematic review and meta-analysis endorsed by the Palliative Care and Neuro-Oncology Study Groups of the Italian Association of Radiotherapy and Clinical Oncology (AIRO)

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Abstract

Aims We search the literature on data regarding the role of whole-brain radiation therapy on neurocognitive functions, hearing, and alopecia, through the use of hippocampal-, scalp-, and cochlea-sparing radiotherapy (RT).

Methods Prospective and retrospective studies with at least five patients were included in this analysis, following PRISMA recommendations.

Results Eighteen works were selected for hippocampal sparing, published between 2015 and 2025 with 1736 patients. Neurocognitive functions were evaluated with a heterogeneous range of tests (mainly HVLT-R, TMT-A and TMT-B, Cowa test, and MME). For scalp-sparing RT, only three papers were selected, published between 2014 and 2015, for a total of 65 patients. There was an important heterogeneity in terms of scalp definitions, CTV prescriptions, used techniques and doses, and methods and scales adopted to evaluate the clinical efficacy of scalp-sparing RT. Regarding cochlea-sparing RT, no citation was selected. A meta-analysis could only be performed for the papers focusing on hippocampal-sparing procedures. Only nine papers meet the criteria, showing a high heterogeneity (chi-square = 229.96, *df* 8, $p < 0.001$, with the I2 index (96.52%) and the H2M index (27.75)). For this reason, we opted for random effect models DerSimonian Laird, maximum likelihood, and profile likelihood, which provided widely overlapping results. Although the data show an average protective effect of hippocampal avoidance on cognitive performance, the meta-analysis, based on the available studies, is unable to demonstrate its significance.

Conclusions A high heterogeneity in terms of hippocampal-, cochlear-, and scalp-sparing RT was registered as well as different and difficult to compare data. Our findings indicate the need for further studies to explore this issue.

Keywords Hippocampal sparing · Scalp sparing · Cochlea sparing · Whole brain · Radiotherapy

Introduction

Whole-brain radiation therapy (WBRT) is one of the main treatment modalities in the management of brain metastases (BM), including surgery, stereotactic radiosurgery (SRS), chemotherapy, and targeted therapy [1].

Whole-brain radiotherapy (WBRT) has historically played a crucial role in the management of patients with more than 4–10 brain metastases (BMs), as it alleviates symptoms, significantly enhances intracranial disease

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control, and reduces the risk of death from neurological causes [2–4]. It has also been employed prophylactically in patients with small cell lung cancer (SCLC) who have controlled primary disease and no evidence of encephalic lesions. More recently, WBRT has been increasingly utilized as a palliative treatment, particularly in cases with poor prognosis despite targeted therapies or immunotherapy, or when the total volume of intracranial disease—regardless of lesion count—exceeds 15 cc.

In fact, in the presence of a limited number of BM, SRS is generally the preferred approach, while surgery is reserved for larger lesions or when the histology is not known [5].

In recent years, advancements in technology and systemic therapies have contributed to improved survival outcomes for patients with brain metastases (BM) [6]. As a result, increasing attention has been directed toward quality of life in this clinical context, particularly regarding the potential long-term adverse effects associated with whole-brain radiotherapy (WBRT). For instance, several clinical trials have demonstrated a dose-dependent risk of neurocognitive function (NCF) decline, particularly in relation to the radiation dose delivered to the hippocampus [7]. In addition, radiation-induced alopecia—another frequent side effect of WBRT—has been shown to negatively affect patients' quality of life. Comparative studies between conventional and scalp-sparing WBRT suggest that this adverse effect may correlate with the radiation dose received by the scalp [8–10].

Consequently, various strategies have been developed to mitigate the impact of these significant adverse effects, including the implementation of organ-at-risk (OAR) sparing techniques. Modern intensity-modulated radiation therapy (IMRT) techniques can reduce the dose to hippocampal neural stem cells during WBRT to prevent iatrogenic cognitive side effects. This particular technique, called hippocampal-sparing WBRT, has the potential of reducing the mean dose to the neural stem-cell compartment by at least 80%, while providing acceptable coverage and dose homogeneity to the remaining whole-brain parenchyma [11–14].

For RT-induced alopecia, the recent technological improvements in patient positioning and radiation treatment planning allow RT to be performed with reduced margins and scalp-sparing [15]. Additionally, the use of arc techniques may minimize the follicle dose, as the reduction of surface dose is then distributed over the length of the arc [10].

The implementation of these techniques also allowed the irradiation of brain and head and neck tumors, limiting the cochlear dose with the intent to prevent persistent hearing loss [16–19].

Therefore, in light of these new strategies, the Palliative Care and Neuro-oncology Study Groups of the Italian Association of Radiotherapy and Clinical Oncology (AIRO) proposed to review the current literature on data regarding the role of sparing organs at risk in WBRT in order to improve neurocognitive functions and to limit alopecia and hearing loss through the use of hippocampal-, scalp-, and cochlear-sparing RT, respectively.

Materials and methods

This systematic review was performed following recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20]. To avoid the bias induced by post hoc decisions, the eligibility criteria and methods of analysis were specified in advance as described below.

Study selections

The search on MEDLINE and EMBASE published from January 2000 to April 2025 was performed. *Keywords* used were inner-ear OR cochlea AND sparing AND whole brain AND radiotherapy; hippocampal avoidance OR hippocampus avoidance OR hippocampal sparing OR hippocampus sparing AND radiotherapy; scalp OR hair AND sparing AND radiotherapy.

The computer search was enhanced manually by consulting reference lists from all accessible review articles, primary studies, meeting abstracts, and book bibliographies to find studies that were not identified in the computer search.

Retrieved records underwent title-and-abstract review and then full-text review. Independent reviewers screened the studies in duplicate using the eligibility criteria reported above. Seven independent reviewers (RDF, VB, ES, DP, AC, EB, SC, AC, GCM, LB, SL, and AA) performed data extraction: in particular, DP and SL for the cochlea; ES, GCM, and LB for the scalp; EB, SC, and AC for the hippocampal sparing. The reasons for exclusion during the full-text review were documented. Disagreements among reviewers were infrequent (< 20%) and were resolved by discussion.

Inclusion and exclusion criteria

English language full-text articles were selected. Experimental and observational studies, such as case series and prospective and retrospective analyses, focused on at least five patients treated by means of WBRT were included.

The analyzed treatment was WBRT delivered for either prophylaxis or diagnosis of brain metastases with any possible fractionation or techniques, presence of detailed data regarding cochlea-, scalp-, and hippocampal-sparing and available data on alopecia, hearing loss, and neurological functions.

Exclusion criteria were only abstracts, letters, proceedings from scientific meetings, editorials, expert opinions, reviews without original data, meta-analyses, case reports, studies in pediatric patients, studies on proton therapy, studies on stereotactic body radiotherapy and SRS, studies lacking data on the sparing procedures, repetitive data, and animal studies.

Data extraction

Data were extracted from four authors, VB, DP, LDC, and FM, and then independently verified by three additional authors, RDF, VP, and SC.

Data included were author, year, study design, primary tumor, radiation treatment information (techniques, dose, fractionation), scalp-, hippocampal-, and cochlea sparing data (definition, constraints, procedures), neurological evaluations data, alopecia evaluations data, and hearing evaluations data.

Quality assessment

Each selected study was evaluated through a quality assessment score according to the checklist for quality appraisal of case series studies produced by the Institute of Health Economics (IHE) [21].

Statistical analysis

The aforementioned information was gathered and analyzed through descriptive analysis methods.

The papers that performed a cognitive or a scalp evaluation in patients treated with WBRT and Hippocampal Sparing using a control group were included in the meta-analysis.

The analysis was carried out using the MetaEasy software, allowing the estimation of the mean effects, each computed along with the relative confidence interval, to be then placed in a forest plot [22].

The methods, used by MetaEasy, chosen from the literature are the following: fixed-effects model (FE), DerSimonian and Laird random-effects model (DL), maximum likelihood random-effects model (ML), profile likelihood random-effects model (PL), and *t* test (T).

Since some of these methods are based on fixed-effects models and others on variable effects models, a preliminary heterogeneity analysis of the cases reported in the papers was necessary. This analysis was carried out according to different approaches, listed below:

1. Cochran's Q approach that provides a *p* value for the test of homogeneity [23, 24];
2. I2 coefficient, able to assess inconsistency between studies; it can assume values corresponding to low, moderate, and high heterogeneity (25%, 50% and 75% respectively) [25];
3. H2M coefficient that is independent of the number of studies *k*; it can assume values in the $[0, +\infty)$ range with 0 indicating a perfect homogeneity [26].

Results

Hippocampal-sparing RT

A total of 1,091 citations were found; among the excluded works, 337 were duplications, 395 were excluded because of abstracts, reviews, surveys, or case reports, and 341 did not respect the inclusion criteria. Eighteen papers were finally selected. (More details are described in Fig. 1.)

Among the selected works for hippocampal sparing RT, published between 2015 and 2025, 4 were phase 3 prospective studies [27–30], 2 prospective cohort studies [31, 32], 1 prospective observational study [33], 2 retrospective studies[1, 34], and 9 phase II studies [35–43].

A total of 1736 patients were treated with WBRT or for BM; 1251 underwent the sparing procedures. Prophylactic HA-WBRT for SCLC patients was performed for 569 patients. Data related to previous systemic therapies were available only in 3 studies [27, 34, 35] and in one study, the use of memantine was implemented [28]. Median follow-up data, available in all the experiences except one [33], ranged from 0.03 to 56.7 months.

Only in 13 studies did the authors specify contouring guidelines used for the hippocampal sparing technique [1, 27–29, 32, 34–36, 38, 39, 41–43].

In all cases, the authors referred to the Radiation Therapy Oncology Group (RTOG) suggestions based on the RTOG 093321 atlas. In all the experience, a hippocampal avoidance area was generated, giving a 5 mm expansion to the hippocampi. Regarding the used constraints, the mean dose or a punctual maximal dose to the structure was the most used one; more information on the used constraints is detailed in Table 1.

The treatment was delivered through the use of volumetric modulated arc therapy (VMAT), IMRT [1, 28–31, 33, 35–41] or not better specified image-guided RT (IGRT) techniques [27, 30, 32, 34, 42, 43], with doses ranging from 25 to 30 Gy in 10–12 fractions.

Neurocognitive functions (NCFs) were evaluated with a heterogeneous range of tests, and each experience used different combinations, for a total of 27 typologies. The most used tests were the HVLT-R, TMT-A and TMT-B, Cowa test, and MME. Likewise, the timing of test administration was not homogeneous: the applied schedules varied from monthly to biannually (Table 1).

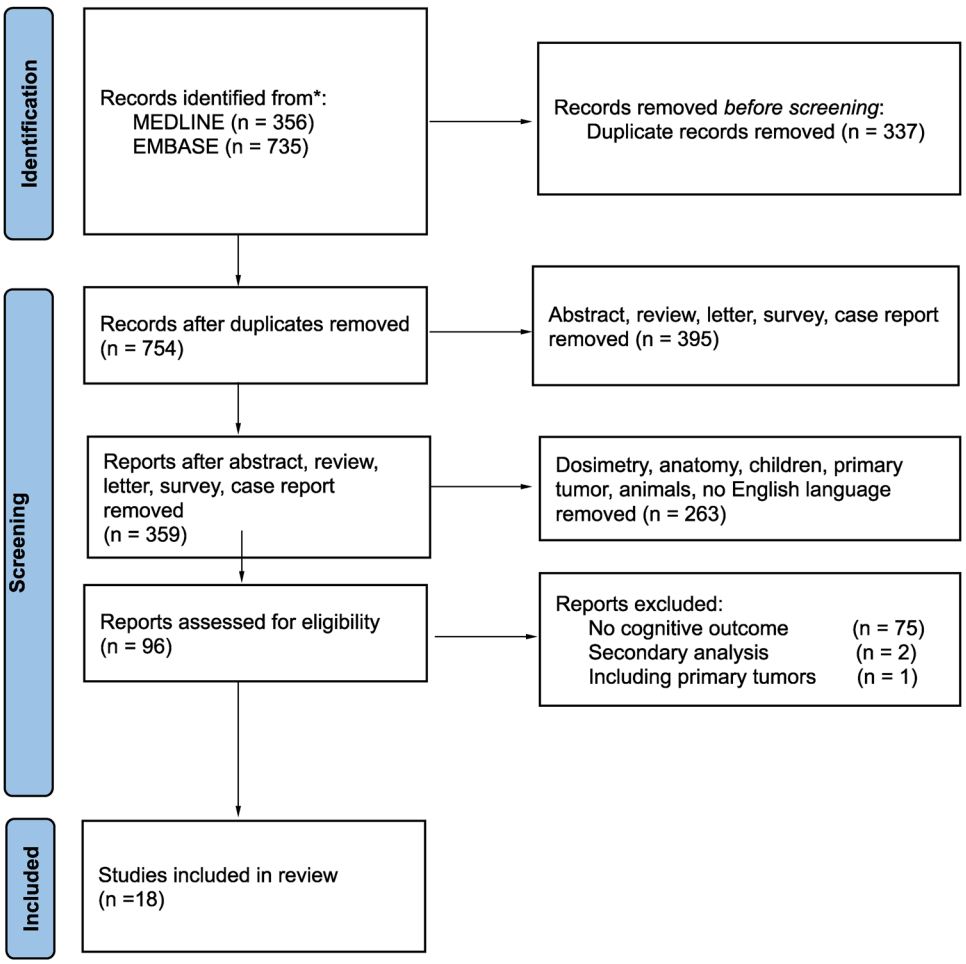

Fig. 1 PRISMA on PubMed Literature Search on hippocampal-sparing RT

Regarding the quality of the considered studies, the score ranged between 11 and 18; more detailed data are reported in Supplementary Table 1.

Scalp-sparing RT

A total of 165 citations were found; among the excluded works, 44 were duplications, 31 were excluded because of abstracts, reviews, surveys, or case reports, and 87 did not respect the inclusion criteria. Three papers were finally selected; more details are described in Fig. 2.

The publication dates of the selected studies spanned from 2014 to 2015. All studies were observational in nature, with two employing a prospective design [11, 12] and one utilizing a retrospective design [44]. The total sample size across these studies was 65 patients.

A wide heterogeneity in terms of scalp and CTV contouring definitions was found, as well as differences in CTVs dose CTV prescriptions, and applied techniques and doses were used. (Table 2 summarizes all characteristics of the selected studies.)

In terms of scalp definition, each experience described it differently: Kao et al. described a volume defined as the skin 3 mm depth from the level of the canthi to the vertex. Puysselyr defined a "hair follicle volume" corresponding to the tissue underlying the skin up to the outer table of the skull, while Mehadevan delimited the volume as a 5 mm hair follicle-bearing scalp. In each study, IMRT [11, 44] or VMAT [12] was used for the sparing procedure.

In terms of RT treatments, 30 Gy/10fx was delivered in the Mahadevan [11] study, 20 Gy/5fx in the De Puysseleyr's experience [12] and 30 Gy/15fx with simultaneous boost up to a total dose of 37.5 Gy in the Kao's paper [44].

Moreover, the methods and scales used to evaluate the clinical efficacy of scalp-sparing RT differ in each experience: the Duke University Severity in Alopecia Tool (SALT) [45] score was used to objectively quantify hair loss from photographs of the scalp taken before and after treatment in the work of Kao; the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Brain Cancer Module (EORTC-QLQ-BN20) was used by De Puysseleyr et al. [12]. On the other hand, Mahadevan et al. choose another strategy [11]: the authors

Table 1 Selected studies on hippocampal-sparing RT

Author/study year	Type of study	N patients/N patients total	Median follow-up time in months/range	Primary Tumor	RT treatment	Total RT dose/n fractions	Hippocampus constraints	Other OARs constraints	Test moment	Primary endpoint neurocognitive function results
Belderbos 2021 [27]	Prospective, multicenter, randomized phase 3 trial (NCT01780675)	168/102	24.8 (23.5–32.8)	SCLC	WBRT PCI (84) vs WBRT HA-PCI (84)	25 Gy/10	DMean hippocampus left ≤ 8.5 Gy (BED ≤ 6.1 Gy for a/b = 2 Gy) DMean hippocampus right ≤ 8.5 Gy (BED ≤ 6.1 Gy or a/b = 2 Gy)) D1% hippocampus left ≤ 10 Gy D1% hippocampus right ≤ 10 Gy	Dmax lenses ≤ 10 Gy	Baseline, 4, 8, 12, 18, 24	Baseline HVLT-R points Median 24 29/102 pts (28%) dropped five points or more on the HVLT-R total recall, not different between the arms
Gondi 2014 [35]	Multi-institution single-arm phase II trial (RTOG0933)	113/100 assessable pts (For the primary end point of HVLT-R DR decline at 4 months, 42 patients were analyzable)	na	Lung, Breast, Other	HA-WBRT	30 Gy/10	Bilateral hippocampi D100% ≤ 9 Gy (Dose to 100% of bilateral hippocampi) Dmax ≤ 16 Gy (Dose to hottest 0.03-cc volume of bilateral hippocampi)	N.A.	Baseline, 2, 4, 6	Mean relative decline and probability of deterioration in HVLT-R from baseline to each time point. Mean relative decline in HVLT-R DR from baseline to 4 months was 7.0% (95% CI, 4.7% to 18.7%), which was significantly lower in comparison with the 30% mean relative HVLT-R DR decline observed in the historical control (P .001) In addition, the probability of HVLT-R TR deterioration, assessed using the reliable change index, was 19.0% at 4 months

Table 1 (continued)

Author/study year	Type of study	N patients/N patients total	Median follow-up time in months/range	Primary Tumor	RT treatment	Total RT dose/n fractions	Hippocampus constraints	Other OARs constraints	Test moment	Primary endpoint neurocognitive function results
Redmond 2017 [36]	Prospective monocentric study (NTC01797159) NRG-CC003	20/17	16.7	SCLC	Standard WBRT hippocampal-sparing PCI (20) confronto con gruppo di controllo di standard PCI arm of RTOG 0212	25 Gy/10	the mean dose to the hippocampus was < 8 Gy Mean dose hippocampus 740,1 cGy (613,6–796,6 cGy) Mean dose hippocampus avoidance structure 1025,0 cGy (787,7–1159,6 cGy)	at least 90% of the whole brain received 90% of the prescription	Baseline, 6, 12	No associations between baseline IQ and change in performance on any of the neuropsychological tests were statistically significant
Lin, 2015 [31]	prospective cohort study	25 pts (3 PCI, 22brain mtx)	At baseline, at 4 months and 12 months after the start of HA-WBRT course	3 SCLC (PCI); 12 NSCLC; 3 breast; 7 others	HA-WBRT	30 Gy/12fz 25 Gy/10fz	N.A.	N.A.	Baseline, 4 months	Long-term memory: significant difference at 4mo
deRodrıguez Dios 2021 [29]	Multicenter phase III randomized trial	137/150	40.4	SCLC	PCI (25 Gy in 10 fractions) or HA-PCI	25 Gy/10fz	Optimum Dmax ≤ 16 Gy; D100% ≤ 9 Gy; acceptable Dmax < 17 Gy; D100% < 10 Gy;	PTV IMRT/VMAT optimum D2%: 26.7 Gy; D98%: 23.7 Gy acceptable D2%: 31,2 Gy; D98%: 20,7 Gy	Baseline, 3, 6, 12, and 24 months	The percentage of patients with decline in the FCSRT-DFR at 3 months was significantly lower in the HA-PCI arm (5.8%) compared with the PCI arm (23.5%; OR, 5.0; 95% CI, 1.57 to 15.86; P 5.003). The analysis imputing patients lost to follow-up as a decline in the FCSRT-DFR at 3 months showed similar results: 13.3% versus 30.7%, respectively, in the HA-PCI arm and PCI arm (OR, 2.9; 95% CI, 1.26 to 6.57; P 5.010)

Table 1 (continued)

Author/study year	Type of study	N patients/N patients total	Median follow-up time in months/range	Primary Tumor	RT treatment	Total RT dose/n fractions	Hippocampus constraints	Other OARs constraints	Test moment	Primary endpoint neurocognitive function results
Tsai 2015 [33]	Prospective observational Trial	24/40	4	primary lung cancer	HS-WBRT VMAT	The prescribed dose was 25 Gy in 10 fractions for prophylactic WBRT or 30 Gy delivered in 10 to 12 fractions for therapeutic or adjuvant WBRT	The hippocampus sparing would be achieved by limiting V40% less than 15% or as low as achievable while maintaining acceptable target coverage	N.A.	4 months	Assessment was available in 24 patients. With regard to neurocognitive outcomes in our study, generally NCF scores were relatively stable before and after HS-WBRT
Vees 2020 [37]	Multicenter prospective phase 2 trial	42/44	13.2(, 12.6–14.1)	SCLC	HA-PCI	25 Gy/10	The dose constraints for the hippocampus were a D98% 10 Gy and a Dmax 10 Gy,	At least 95% of the whole brain was to receive 95% of the prescribed dose	Baseline, at 6 weeks, 6 months, and 12 months after HA-PCI	38 patients evaluable. 13/38 patients showed no decline in any of the NCF tests, as defined in our study, at 6 months (Fig. 2). Most patients who experienced an NCF decline (25 of 38) had a decline in 1 (n Z 12; 48%) or 2 tests (n Z 5; 20%). 11/39 patients at 6 weeks after HA-PCI and 16 of 33 patients 12 months after HA-PCI showed no NCF decline. These patients tend to be at higher risk for a decline in COWAT at 12 months after HA-PCI than those with low psychological distress (odds ratio [OR], 8.37; 95% CI, 1.42–49.51; P Z.02)

Table 1 (continued)

Author/study year	Type of study	N patients/N patients total	Median follow-up time in months/range	Primary Tumor	RT treatment	Total RT dose/n fractions	Hippocampus constraints	Other OARs constraints	Test moment	Primary endpoint neurocognitive function results
Wang 2021 [1]	Retrospective monocentric Trial	47	12 (2–24)	NSCLC	WBRT (20) HA-WBRT (27)	30 Gy/10	The maximum dose of hippocampus cannot exceed 20 Gy	The maximum dose of OAR was defined as 50 Gy for optic nerve, 45 Gy for eye and 10 Gy for lens	Baseline and at 3, 6, 9, 12 and 24 months	The long-term cognitive function of the hippocampal avoidance group was significantly higher than that of the non-hippocampal avoidance group. Statistical differences were found by the MMSE scale, but were not by the MoCA scale at 9 months after radiotherapy. There were significant differences between the 2 groups at 12 and 24 months after radiotherapy. Moreover, single factor linear regression showed that PS score and irradiation methods had significant impacts on cognitive function. It is worth noting that after 12 months of radiotherapy, statistically significant differences were observed between these 2 groups in Attention and Calculation, Language and Praxis, Registration, and Orientation in the MMSE scale. In the MoCA scale, differences were also found in Attention, Language, Memory, Name, and Orientation, of which differences in Attention and Orientation were statistically significant

Table 1 (continued)

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Westover 2020 [38]	Single-arm phase II monocentric trial	49 patients	Mean follow-up of 10.5 months (range, 1–39 months)	Breast 5(10%) lung 39 (80%) other 5 (10%)	HSIB-WBRT	20 Gy in 10 to the whole brain with simultaneous integrated boost of 40 Gy in 10 fractions to identified metastatic lesions	Maximum dose to the hippocampus < 16 Gy maximum dose ≤ 17 Gy was deemed variation acceptable	N.A.	Baseline, 3, 6, 9 months after RT	Mean decline in HVLT-R DR at 3 months after HSIB-WBRT was only 10.6% (95% CI: − 36.5−15.3%). Of the 23 evaluable patients at 3-month follow-up, 18 (78%) Mean decline in HVLT-R DR at 3 months after HSIBWBRT was 10.6% (± 50.43), better than the ~ 60% decline noted in our prespecified historical control

Table 1 (continued)

Author/study year	Type of study	N patients/N patients total	Median follow-up time in months/range	Primary Tumor	RT treatment	Total RT dose/n fractions	Hippocampus constraints	Other OARs constraints	Test moment	Primary endpoint neurocognitive function results
Yang 2020 [39]	Single-blinded randomized phase II trial	70/65 evaluable patients	12,4 months (0,9–54,8)	HA-WBRT: Lung: 97.0% (32) Breast: 0% (0) Others: 3.0% (1) C-WBRT: Lung: 90.6% (29) Breast: 6.2% (2) Others: 3.1% (1)	HA-WBRT (33) WBRT (32)	30 Gy/10	NA.	N.A.	At baseline, 1,2,4,6,9,12,15,18,21,24 months	Significant perpetuation of neurocognitive function in the HVLT-R recognition index and a trend of preservation in HVLT-R total recall at the 6-month follow-up in the HA-WBRT arm. By using the memory score24 (the sum of HVLT-R total recall and recognition index), the preservation of verbal learning and memory was significantly superior in the HA-WBRT arm at 6-month follow-up, and in favor of the HA-WBRT arm thereafter till the completion of follow-up at 24 months. Despite a lack of significant differences in HVLT-R delayed recall, TMT-A, TMT-B, or COWA tests at any time points, patients receiving HA-WBRT outperformed in all aspects of the neurocognitive function tests at 6-month follow-up. No difference in cumulative incidence of neurocognitive failure between the 2 arms after adjusting competing risks. The 4- and 6-month cumulative incidence of neurocognitive failure was 15.2% and 18.2%, respectively, in the HA-WBRT arm and 12.5% and 15.6%, respectively, in the C-WBRT arm

Table 1 (continued)

Author/study year	Type of study	N patients/N patients total	Median follow-up time in months/range	Primary Tumor	RT treatment	Total RT dose/n fractions	Hippocampus constraints	Other OARs constraints	Test moment	Primary endpoint neurocognitive function results
Du 2023 [40]	Randomized Prospective II monocentric Trial	36 evaluable patients	16 months (11.54–20.46) in the HA-WBRT group vs 14 months (12.90–15.21) in the WBRT group	Lung (28), breast (5), ovarian (1), colon (1), Esophageal (1)	15 HA-WBRT; 21 WBRT	30 Gy/10	N.A	Crystalline lens, less than 5 Gy; mean eyeball dose, less than 35 Gy; and optic nerve dose, less than 54 Gy	24 h before WBRT and at 2 months, 6 months, and 12 months after WBRT	The overall mean differences in the Montreal Cognitive Assessment scores between the hippocampal-protection group and the conventional whole-brain radiotherapy group were statistically significant at 6 months ($P = .006$) and 12 months ($P = .04$) after radiotherapy
Albers 2023 [30]	multicenter phase 3 trial	161	N.A	SCLC	82 HA-WBRT; 79 WBRT	25 Gy/10	The mean dose of the hippocampal avoidance zone of the HA-PCI was limited to 8.5 Gy	N.A	At baseline and at 4, 8, 12, 18, and 24 months after WBRT	There was no significant difference in the percentage of patients with deteriorated, stable, or improved SRCF between the treatment arms. Depending on the evaluated time point, 31% to 46% and 29% to 43% of patients in the HA-PCI and PCI arm, respectively, reported a deteriorated SRCF on the basis of the EORTC QLQ-C30 and Medical Outcomes

Table 1 (continued)

Author/study year	Type of study	N patients/N patients total	Median follow-up time in months/range	Primary Tumor	RT treatment	Total RT dose/n fractions	Hippocampus constraints	Other OARs constraints	Test moment	Primary endpoint neurocognitive function results
Gondi 2023 [28]	prospective, multicenter, randomized phase 3 trial NRG Oncology CC001(ClinicalTrials.gov identifier: NCT02360215)	518	12.1 (0.03–15.6)	Bone, Breast, Colon, Esophagus, Gastroesophageal junction, Kidney, Lung, Ovary, Skin, Anal, Pancreas, Other	WBRT (257) HA-WBRT (261)	30 Gy/10	Bilateral hippocampi D100% ≤ 9 Gy (Dose to 100% of bilateral hippocampi) Dmax ≤ 16 Gy (Dose to hottest 0.03-cc volume of bilateral hippocampi)	Optic chiasm Dmax ≤ 30 Gy Dose to hottest 0.03-cc volume of optic chiasm Optic nerve (right side) Dmax ≤ 30 Gy Dose to hottest 0.03-cc volume of optic nerve (right side) Optic nerve (left side) Dmax ≤ 30 Gy Dose to hottest 0.03-cc volume of optic nerve (lefft side)	Baseline, 4, 8, 12	Longitudinal modeling of imputed data showed better preservation of all HVLT-R domains (P < .005). Patients who received HA-WBRT + Memantine reported less symptom burden at 6 (P < .001 using imputed data) and 12 months (P = .026 using complete-case data; P < .001 using imputed data), less symptom interference at 6 (P = .003 using complete-case data; P = .0016 using imputed data) and 12 months (P = .0027 using complete-case data; P = .0014 using imputed data), and fewer cognitive symptoms over time (P = .043 using imputed data). Treatment arms did not differ significantly in overall survival, intracranial progression-free survival, or toxicity
Loga 2024 [43]	prospective, multicenter, randomized, Phase II	113	N.A	SCLC	PCI- HA-WBRT (74) vs PCI-WBRT (39)	25 Gy/10	N.A	N.A	Baseline, two weeks after PCI, and 3 months after the treatment	There were no differences between HA-WBRT and WBRT groups in the MoCA and MMSE tests at any time point. In both groups the values in MoCA and MMSE scales differed between time points I, II and III. The patients in the HA-WBRT group were less likely than patients in WBRT group to experience significant cognitive decline on the MoCA scale (p = 0.003), but not on the MMSE scale (p = 0.103)

Table 1 (continued)

Author/study year	Type of study	N patients/N patients total	Median follow-up time in months/range	Primary Tumor	RT treatment	Total RT dose/n fractions	Hippocampus constraints	Other OARs constraints	Test moment	Primary endpoint neurocognitive function results
Zhan 2024 [34]	Retrospective	112	52 months (95% CI: 47.2–56.7),	Limited-stage SCLC	112	25 Gy/10	The mean dose to the hippocampus and hippocampal avoidance zone should optimally be ≤ 8 and 10 Gy, respectively PORV2 mm	The maximum dose to the lens should be less than 9 Gy PTV D90%: 25 Gy	Baseline, 6, and 12	No differences were observed in the two radiation techniques (tomotherapy [TOMO] vs. volumetric modulated arc therapy [VMAT]). The decline of HVLT-R score remained in a low level and not significant in assessable patients (p = 0.095)
Li 2024 [42]	Prospective phase II	40	14.2 months	SCLC:15 NSCLC:25	40	30–36 Gy delivered in 18–20 fractions to the whole brain, while the dose to the GTV was boosted to 44–52 Gy in 18–20 fractions,	PORV2mm Dmean to the bilateral hippocampus ≤ 8 Gy;Dmax to the hippocampus ≤ 10 Gy, Dmean of bilateral hippocampus PRV ≤ 9 Gy and Dmax ≤ 12 Gy	Dmax to the lens should be < 9 Gy; the Dmax to the spinal cord should be < 40 Gy; the Dmax to the brain stem should be < 50 Gy and the Dmax to the optic nerve pathways should be < 50 Gy	Baseline, 1, 3, 6, and 12	HVLT-R scores at baseline and 1, 3, and 6 months after radiotherapy were 21.94 ± 2.99, 20.88 ± 3.12, 20.03 ± 3.14, and 19.78 ± 2.98, respectively. The HVLT-R scores at 6 months after radiotherapy decreased by approximately 9.8% compared with those at baseline
Whitfield 2024 [41]	multicenter, randomized, open label phase II trial	23	25 months	Breast, gastrointestinal, kidney, Lung, Other	12 WBRT; 11HA-WBRT	30 Gy/10	D2% (near maximal dose exceeded in only 2% of the volume) was required to be < 15 Gy, and mean hippocampal dose < 11 Gy (optimally < 10 Gy)	N.A	baseline and 4 months	The trial closed prematurely due to slower than anticipated recruitment.. Fifteen patients (6 WBRT, 9 HS-WBRT) were assessed for the primary endpoint; of these, 1 in each arm experienced significant decline in the 4-month HVLT-R Total recall score (p 1⁄4 0.8). Patients in the HS-WBRT arm experienced less insomnia (p < 0.01) and drowsiness (p < 0.01). There were no differences in other secondary endpoints

Table 1 (continued)

Author/study year	Type of study	N patients/N patients total	Median follow-up time in months/range	Primary Tumor	RT treatment	Total RT dose/n fractions	Hippocampus constraints	Other OARs constraints	Test moment	Primary endpoint neurocognitive function results
Yang 2024 [32]	single-arm prospective observational study,	125	19.6 months (range 0.43–95.0)	Lung, Breast, Other	125 HA-WBRT	30 Gy/10 or 25 Gy/10 for PCI in SCLC patients	N.A	N.A	Baseline, 4, 12 and 18	The delta values of post-WBRT and baseline NCF scores showed an obvious trend indicating cognitive maintenance rather than deterioration in nearly all assessments. There was an apparent positive tendency toward cognitive changes of left hippocampus-related verbal memory, as represented by the score of Word List Learning-immediate memory ($p = .001$, 4 months after HS-WBRT versus baseline). Moreover, there were better performances in executive functions related to the frontal lobe, as indicated by the score of Modified Card Sorting Test-Completed Categories (MCST-CC, $p < .001$, 4 months after HS-WBRT versus pre-WBRT baseline). The delta values between these two sets still suggested a general tendency toward cognitive maintenance, although not always significant

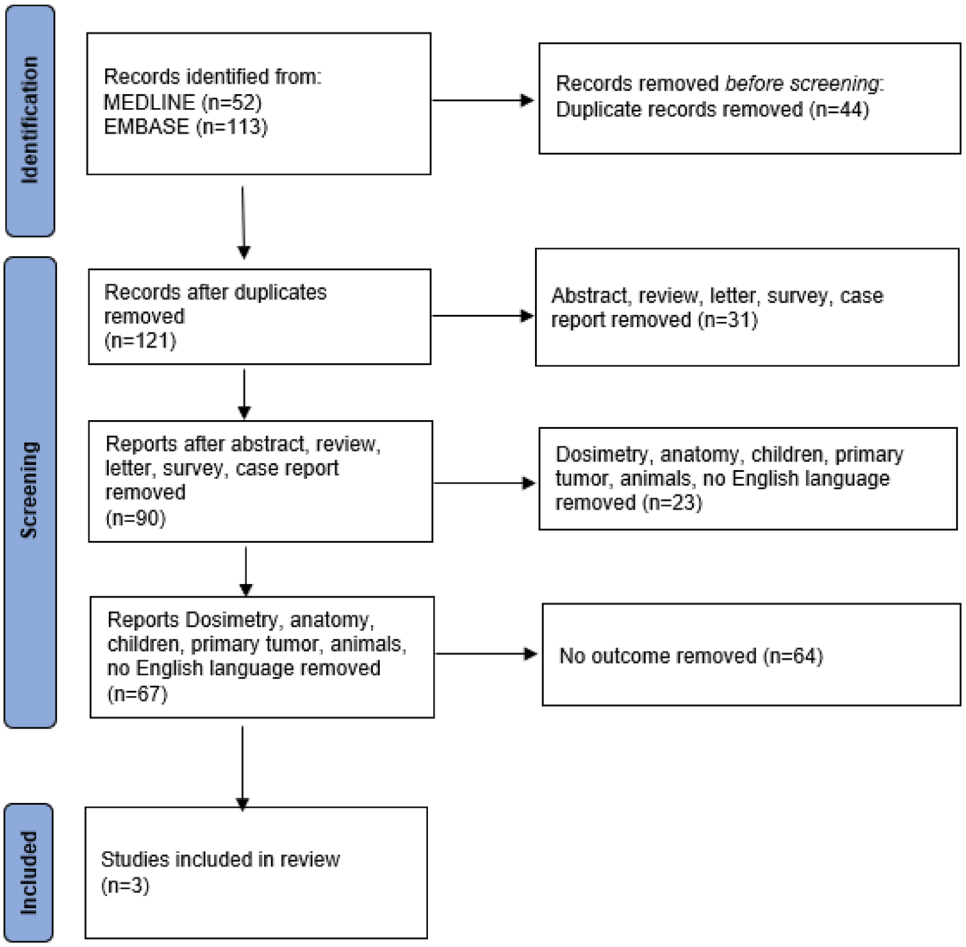

Fig. 2 PRISMA on PubMed Literature Search on scalp-sparing RT

observed that six patients who underwent hippocampal-sparing WBRT at 1-month follow-up had a full scalp hair preservation. So, a 5 mm thickness of follicle-bearing scalp in the radiation field was outlined in the planning CT scans, and then conventional opposed lateral WBRT radiation fields were used on these patient-specific image sets, with the treatment planned to deliver the same nominal dose of 30 Gy in 10 fractions. Then mean and maximum doses to follicle-bearing skin and dose volume histogram (DVH) data were confronted between plans.

The rates of hair preservation reported are also different. Mahadevan et al. analyzed the treatments of the first six consecutive patients who received hippocampal-sparing WBRT and were noted to have full preservation of scalp hair on follow-up, but did not specify how many patients were treated overall in the same way in the same period, and the percentage of this group [11]. In the phase II trial of De Puysseleyr et al., VMAT-WBRT substantially reduced hair follicle dose, especially on the frontal-vertex-occipital medial axis, but these dose reductions were not related to an improved quality of life (QoL) or SALT score, so the study was halted due to futility after interim analysis on the first 10 patients included [12]. In the report of Kao et al., all the 15 assessable patients had complete hair loss. In the subsequent evaluation, at one month to three months following intensity-modulated WBRT, 4 patients (27%) had < 50% hair loss, 6 (40%) had 50 to 74% hair loss, and 5 (33%) had 75 to 99% hair loss; among the 5 patients with 75 to 99% hair loss, 2 had 75 to 99% hair loss prior to WBRT and 1 was receiving chemotherapy at the time of re-evaluation. Five patients surviving more than 6 months had no alopecia at last follow-up. Unfortunately, a clinical comparison of the incidence of alopecia in patients treated without scalp sparing was not done [44].

The quality score ranged between 13 and 15; further details are reported in Supplementary Table 2.

Cochlear-sparing RT

A total of 120 citations were found; among the excluded works, 7 were duplications and the remaining 113 did not respect the inclusion criteria. In conclusion, no citations were selected; more details are described in Fig. 3.

Table 2 Selected studies on scalp-sparing RT

Author/year	N pz	Technique	Dose	Scalp Definition	Endpoint	Results
Kao et al. 2014 [44]	17	IMRT	37.5 Gy in 15 fractions while limiting the uninvolved brain 1 2 mm margin to 30 Gy in 15 fractions and the mean scalp dose to 18 Gy	The scalp contour is defined as the skin 3 mm depth from the level of the canthi to the vertex	The Duke University Severity in Alopecia Tool (SALT) score will be used to objectively quantify hair loss from photographs of the scalp taken before and after treatment Briefly S0 is no hair loss, S1 is 25% hair loss, S2 is 25 to 49% hair loss, S3 is 50 to 74% hair loss, S4 is 75 to 99% hair loss and S5 is 100% hair loss	Using Olsen hair loss score criteria, 4 of 15 assessable patients preserved at least 50% of hair coverage at 1 to 3 months after treatment, while 6 patients preserved between 25 and 50% hair coverage
Puysseleyr et al. 2014 [12]	42 pz (21 for arm)	VMAT	25 Gy in 10fz	Hair follicle volume: tissue underlying the skin up to the outer table of the skull, with the creation of 4 sub-volumes representing the different areas of the scalp: top (vertex), back (posterior aspect of the scalp), left (left profile of the scalp) and right (right profile of the scalp)	The primary endpoint was the mean score of hair loss at 1 month after VMAT-WBRT scored with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Brain Cancer Module (EORTC-QLQ-BN20)	Compared to OF-WBRT, VMAT-WBRT substantially reduces hair follicle dose
Mahadevan et al. 2015 [11]	6 pz (RTOG 0933)	IMRT	30GY	5 mm hair follicle bearing scalp was auto-contoured in all CT simulation image data sets retrospectively	All patients were followed one month after and three monthly thereafter until progression or death, with clinical examination including mini mental state and brain MRI	Compared to HS-WBRT, conventional WBRT delivered significantly higher mean dose to follicle bearing scalp (16.33 cGy vs. 22.42 cGy, $p < 0.0001$)

Pz patients, *IMRT* intensity-modulated RT, *VMAT* volumetric modulated arc therapy, *MRI* magnetic resonance imaging, *WBRT* whole-brain RT, *HS-WBRT* hippocampal-sparing whole-brain RT

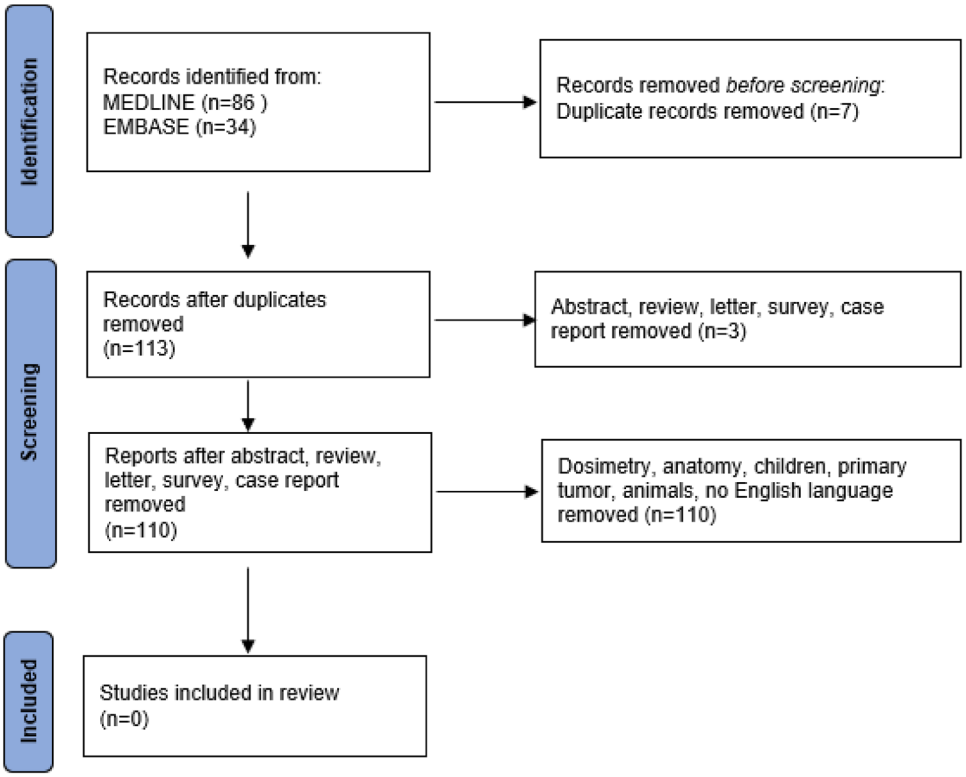

Fig. 3 PRISMA on PubMed Literature Search on cochlea-sparing RT

Meta-analysis

Meta-analysis could only be performed for the papers focusing on the hippocampal-sparing procedures; in fact, from the initial 21 selected papers, only 9 met the inclusion criteria [1, 27–31, 40, 41, 43].

The analysis of the heterogeneity of the studies (carried out for the purpose of choosing the model to apply, fixed effects or random effects) showed a high heterogeneity, both with the Cochran Q test (chi-square = 229.96, $df = 8$, $p < 0.001$), with the I^2 index (96.52%) and the H^2M index (27.75).

For this reason, we opted for random effect models: DerSimonian Laird (DL), maximum likelihood (ML), and profile likelihood (PL) which provided widely overlapping results, as can be seen from the forest plot.

It follows that, although the data show an average protective effect of hippocampal avoidance on cognitive performance, the meta-analysis, based on the available studies, is unable to demonstrate its significance (Fig. 4). However, the findings indicate the need for further studies to explore this issue. The complete forest plot, with all the outcomes considered for each of the seven studies, is described in Supplementary Fig. 1.

Discussion

In contrast to previous practice, the role of WB has become increasingly palliative, reserved for cases where the prognosis is severe despite target therapies or immunotherapy, or when the total treatment volume (regardless of number) exceeds 15 cc. Indeed, thanks to the great advances in cancer treatment with new targeted anticancer drugs, the prognosis of patients with BM has greatly improved, thus leading to a preference for SRS treatment wherever possible. Consequently, there has been a notable shift in emphasis toward the quality of life of patients, with a particular focus on the long-term safeguarding of cognitive, hair, and hearing functions [6].

On the other hand, patients with numerous intraparenchymal BM or leptomeningeal disease are excluded from SRS due to increased risk of intracranial recurrence compared to WBRT [46–51]. Moreover, WBRT remains a possible therapeutic option for prophylactic cranial irradiation (PCI) following thoracic chemo-radiation therapy in patients with limited-stage small cell lung cancer (SCLC) [52].

Unfortunately, WBRT can be associated with a significant decline in NCF linked to radiation exposure of neural stem cells within the hippocampal dentate gyrus [35, 53–58].

Recently, more attention has been paid to symptom-related outcomes of care, especially to NCF and QoL [35, 57–60].

With improvements in RT systems technology, it is now possible to modify treatment plans to selectively spare

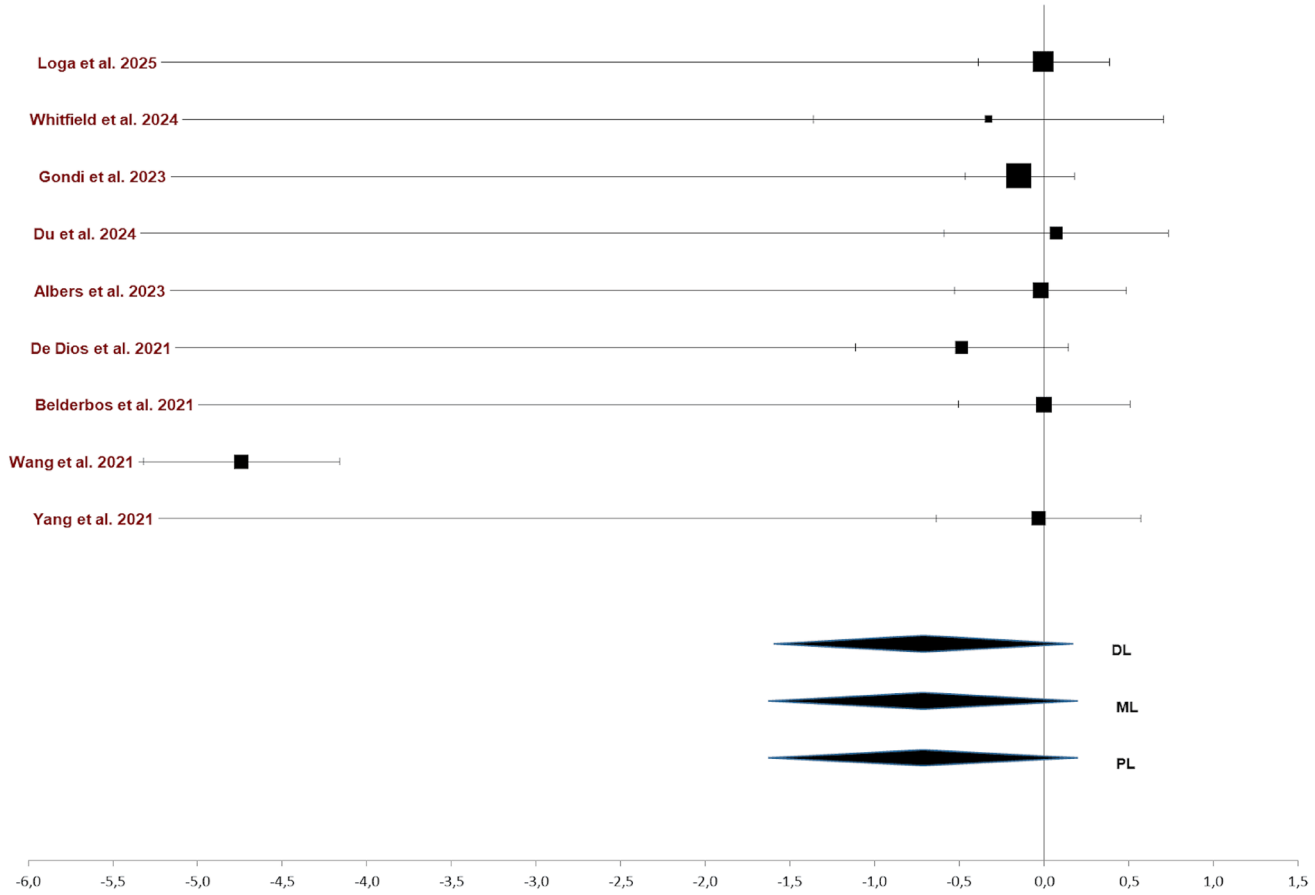

Fig. 4 Forest plot of 7 studies on hippocampal-sparing RT

structures that may contribute to an improvement in patient QoL and NCF.

Neurocognitive functions and hippocampal-sparing RT

The hippocampus and its associated limbic structures have long been recognized as essential for memory formation. Preclinical studies have demonstrated that radiation exposure leads to the depletion of hippocampal stem cells, as well as structural and functional alterations in mature neurons. Numerous feasibility and planning studies have confirmed the potential of modern radiotherapy (RT) technologies to spare the hippocampus during whole-brain irradiation. It is now both technically and dosimetrically feasible to design treatment plans that preserve hippocampal integrity while maintaining adequate coverage of target volumes. Recent advancements have further enabled the delivery of hippocampal-sparing whole-brain radiotherapy (HS-WBRT) in conjunction with a simultaneous integrated boost (SIB) to metastatic brain lesions [14, 61].

In this review, a total of 18 studies have been analyzed for this setting, both prospective and retrospective in nature, describing promising results through the use of the sparing strategy. However, while we observed a certain homogeneity regarding the definition of the hippocampal-sparing WBRT and the used dose constraints, the studies showed a high heterogeneity in terms of sample size and neurocognitive function evaluation. Each experience used different sets of tests for the evaluation, administered to the patients at different time points (sometimes more lax and sometimes more steer), with a follow-up period stated only in ten experiences and ranging from 0.03 to 56 months. Moreover, in one study, memantine was added to the hippocampal-sparing WBRT, probably having a synergic effect [28]. Another possible bias is that we also considered studies in which WBRT was used with a prophylactic intent in SCLC patients among the inclusion criteria for this review, with four studies among the nine considered in the meta-analysis focusing on this setting.

Regarding the meta-analysis, only nine studies could be evaluated [1, 27–31, 41, 43], showing a tendency toward a protective effect of hippocampal-sparing WBRT for the

neurocognitive functions, but not reaching statistical significance. The heterogeneity level described above could also probably explain the meta-analysis results. For the sake of clarity, one of the selected studies [1] showed some inconsistencies regarding the neurocognitive data test, and we tried to reach the authors to have some answers [63], but we did not receive answers. We proceeded with the analysis considering these inconsistencies only an article editing problem.

However, even though of the high heterogeneity among these studies, the tendency to a protection effect in addition to the low rate of hippocampal relapses with this technique, highlighted by the recent systematic review conducted by Leskinen et al. [64], makes the hippocampal-sparing WBRT a very promising therapeutic strategy.

Radiation-induced alopecia and scalp-sparing RT

Hair loss is one of the most frequent side effects in patients receiving WBRT with conventional fractionation [12] with an important impact on patients' quality of life [65, 66].

Different strategies, generally topical ones, have been used to decrease the incidence and severity of alopecia after RT; however, no clinical benefit was found [10, 14, 56–72].

Different papers described a tolerance dose to the scalp for permanent alopecia after definitive RT for brain tumors, and the new technologies, such as IMRT or VMAT, made scalp-sparing WBRT an interesting, useful strategy [10, 65, 66].

In this review, only three studies have been selected for this topic [11, 12, 44], one prospective and two retrospective ones. These three studies, other than a different sample size, show two important differences; the first one is a difference in the definition of the scalp structure (Table 2), while the second one is the use of different scales for the alopecia evaluation. Moreover, in the paper by Mahadevan et al. [11] the alopecia preservation effect was obtained through hippocampal sparing procedures and not a scalp-sparing one. Even though all of them describe positive results with the use of scalp-sparing WBRT, a possible comparison of these results is quite difficult.

Hearing loss and cochlear-sparing RT

This systematic review was not able to find any paper that could fulfill the selection criteria.

Several studies have attempted to relate mean or median cochlear dose to persistent hearing loss in different settings, generally head and neck cancers, without clear results. This could be probably explained by the fact that generally, a dose–volume analysis is impractical for the cochlea due to its small volume and the limitations associated with its delineation. Despite extensive research, no conclusive evidence has been found regarding cochlear toxicity, even in studies focusing on patients diagnosed with cerebral lymphoma, long-term survivors, and the elderly. Moreover, a possible evaluation of the hearing loss could be biased in these patients by other factors, like the type of prescription dose, the platinum-based chemotherapy administered before and/or after cochlear-sparing RT [16–19].

Conclusions

From the data of this review, we observed how the strategy of sparing organs at risk during RT, in particular the hippocampus and scalp during whole-brain irradiation, is still a fascinating issue that still has a certain appeal in the radiation oncology community, but robust data that can verify its actual effectiveness are not yet available. This absence of evidence could be due to the high level of heterogeneity among published studies, especially regarding the modalities of the organs sparing procedures and the lack of adequate tests to evaluate the effectiveness of this approach. Our findings indicate the need for further studies to explore this interesting issue.

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Declarations

Conflict of interest The authors have no conflict of interest to disclosure.

Ethics approval The authors presenting the work are more than 10; this is due to the fact that the work consists primarily of three different systematic reviews, which necessitated the involvement of multiple individuals.

Informed consent Not applicable.

Research involving human participants and/or animals Not applicable.

References

1. Wang B, Fu S, Huang Y, Liu L, Liang Y, An W, Fan Y, Zhao Y (2021) The effect of hippocampal avoidance whole brain radiotherapy on the preservation of long-term neurocognitive function in non-small cell lung cancer patients with brain metastasis. TechnolCancerResTreat 20:15330338211034269. https://doi.org/10.1177/15330338211034269
2. Khuntia D, Brown P, Li J, Mehta MP (2006) Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol 24(8):1295–1304. https://doi.org/10.1200/JCO.2005.04.6185
3. Aoyama H, Tago M, Shirato H, Japanese Radiation Oncology Study Group 99–1 (JROSG 99–1) Investigators (2015) Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases: secondary analysis of the JROSG 99–1 randomized clinical trial. JAMA Oncol 1(4):457–464. https://doi.org/10.1001/jamaoncol.2015.1145
4. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA, Young B (1998) Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 280(4):1485–1489. https://doi.org/10.1001/jama.280.17.1485
5. Thiagarajan A, Yamada Y (2017) Radiobiology and radiotherapy of brain metastases. Clin Exp Metastasis 34(6–7):411–419. https://doi.org/10.1007/s10585-017-9865-7
6. Sperduto PW, Mesko S, Li J, Cagney D, Aizer A, Lin NU, Nesbit E, Kruser TJ, Chan J, Braunstein S, Lee J, Kirkpatrick JP, Breen W, Brown PD, Shi D, Shih HA, Soliman H, Sahgal A, Shanley R, Sperduto WA, Lou E, Everett A, Boggs DH, Masucci L, Roberge D, Remick J, Plichta K, Buatti JM, Jain S, Gaspar LE, Wu CC, Wang TJC, Bryant J, Chuong M, An Y, Chiang V, Nakano T, Aoyama H, Mehta MP (2020) Survival in patients with brain metastases: summary report on the updated diagnosis-specific graded prognostic assessment and definition of the eligibility quotient. J Clin Oncol 38(32):3773–3784. https://doi.org/10.1200/JCO.20.01255
7. Gondi V, Hermann BP, Mehta MP, Tomé WA (2013) Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J Radiat Oncol Biol Phys 85(2):348–354. https://doi.org/10.1016/j.ijrobp.2012.11.031
8. Steinmann D, Paelecke-Habermann Y, Hans G, Aschoff R, Bayerl A, Bölling T, Bosch E, Bruns F, Eichenseder-Seiss U, Gerstein J, Gharbi N, Hagg J, Hipp M, Kleff I, Müller A, Schäfer C, Schleicher U, Sehlen S, Theodorou M, Wypior HJ, Zehentmayr F, van Oorschot B, Vordermark D (2012) Prospective evaluation of quality of life effects in patients undergoing palliative radiotherapy for brain metastases. BMC Cancer 12:283. https://doi.org/10.1186/1471-2407-12-283
9. Gerrard GE, Prestwich RJ, Edwards A, Russon LJ, Richards F, Johnston CF, Kwok-Williams MC (2003) Investigating the palliative efficacy of whole-brain radiotherapy for patients with multiple-brain metastases and poor prognostic features. Clin Oncol (R Coll Radiol) 15(7):422–428. https://doi.org/10.1016/s0936-6555(03)00148-1
10. Lawenda BD, Gagne HM, Gierga DP, Niemierko A, Wong WM, Tarbell NJ, Chen GTY, Hochberg FH, Loeffler JS (2004) Permanent alopecia after cranial irradiation: dose–response relationship. Int J Radiat Oncol Biol Phys 60(3):879–887. https://doi.org/10.1016/j.ijrobp.2004.04.031
11. Mahadevan A, Sampson C, LaRosa S, Floyd SR, Wong ET, Uhlmann EJ, Sengupta S, Kasper EM (2015) Dosimetric analysis of the alopecia preventing effect of hippocampus sparing whole brain radiation therapy. Radiat Oncol 10:245. https://doi.org/10.1186/s13014-015-0555-9
12. De Puysseleyr A, Van De Velde J, Speleers B, Vercauteren T, Goedgebeur A, Hoof TV, Boterberg T, De Neve W, De Wagter C, Ost P (2014) Hair-sparing whole brain radiotherapy with volumetric arc therapy in patients treated for brain metastases: dosimetric and clinical results of a phase II trial. Radiat Oncol 9:170. https://doi.org/10.1186/1748-717X-9-170
13. Gondi V, Tolakanahalli R, Mehta MP, Tewatia D, Rowley H, Kuo JS, Khuntia D, Tomé WA (2010) Hippocampal-sparing whole-brain radiotherapy: a "how-to" technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 78:1244–1252. https://doi.org/10.1016/j.ijrobp.2010.01.039
14. Hsu F, Carolan H, Nichol A, Cao F, Nuraney N, Lee R, Gete E, Wong F, Schmuland M, Heran M, Otto K (2010) Whole brain radiotherapy with hippocampal avoidance and simultaneous integrated boost for 1–3 brain metastases: a feasibility study using volumetric modulated arc therapy. Int J Radiat Oncol Biol Phys 76(5):1480–1485. https://doi.org/10.1016/j.ijrobp.2009.03.032
15. Roberge D, Parker W, Niazi TM, Olivares M (2005) Treating the contents and not the container: dosimetric study of hair-sparing whole brain intensity modulated radiation therapy. Technol Cancer Res Treat 4(5):567–570. https://doi.org/10.1177/153303460500400510
16. Bhandare N, Jackson A, Eisbruch A, Pan CC, Flickinger JC, Antonelli P, Mendenhall WM (2010) Radiation therapy and hearing loss. Int J Radiat Oncol Biol Phys 76(3 Suppl):S50–S57. https://doi.org/10.1016/j.ijrobp.2009.04.096
17. Chen WC, Jackson A, Budnick AS, Pfister DG, Kraus DH, Hunt MA, Stambuk H, Levegrun S, Wolden SL (2006) Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. Cancer 106(15):820–829. https://doi.org/10.1002/cncr.21683
18. Honoré HB, Bentzen SM, Møller K, Grau C (2002) Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. Radiother Oncol 65(1):9–16. https://doi.org/10.1016/s0167-8140(02)00173-1
19. Low WK, Toh ST, Wee J, Fook-Chong SMC, Wang DY (2006) Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. J Clin Oncol 24(12):1904–1909. https://doi.org/10.1200/JCO.2005.05.0096
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. https://doi.org/10.1136/bmj.n71
21. Moga C, Guo B, Schopflocher D, Harstall C (2012) Development of a quality appraisal tool for case seriesstudies using a modified Delphi technique. Institute of Health Economics, Edmonton
22. Kontopantelis E, Reeves D (2009) Metaeasy: a meta-analysis add-in for Microsoft Excel. J Stat Softw 30(7):1–25. https://doi.org/10.18637/jss.v030.i07
23. Brockwell SE, Gordon IR (2001) A comparison of statistical methods for meta-analysis. Stat Med 20(6):825–840. https://doi.org/10.1002/sim.650
24. Hardy RJ, Thompson SG (1998) Detecting and describing heterogeneity in meta-analysis. Stat Med 17(8):841–856. https://doi.org/10.1002/(sici)1097-0258(19980430)17:8%3c841::aid-sim781%3e3.0.co;2-d
25. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557

26. Mittlböck M, Heinzl H (2006) A simulation study comparing properties of heterogeneity measures in meta-analyses. Stat Med 25(24):4321–4333. https://doi.org/10.1002/sim.2692
27. Belderbos JSA, De Ruysscher DKM, De Jaeger K, Koppe F, Lambrecht MLF, Lievens YN, Dieleman EMT, Jaspers JPM, Van Meerbeeck JP, Ubbels F, Kwint MH, Kuenen MA, Deprez S, De Ruiter MB, Boogerd W, Sikorska K, Van Tinteren H, Schagen SB (2021) Phase 3 randomized trial of prophylactic cranial irradiation with or without hippocampus avoidance in SCLC (NCT01780675). J Thorac Oncol 16(5):840–849. https://doi.org/10.1016/j.jtho.2020.12.024
28. Gondi V, Deshmukh S, Brown PD, Wefel JS, Armstrong TS, Tome WA, Gilbert MR, Konski A, Robinson CG, Bovi JA, Benzinger TLS, Roberge D, Kundapur V, Kaufman I, Shah S, Usuki KY, Baschnagel AM, Mehta MP, Kachnic LA (2023) Sustained preservation of cognition and prevention of patient-reported symptoms with hippocampal avoidance during whole-brain radiation therapy for brain metastases: final results of NRG oncology CC001. Int J Radiat Oncol Biol Phys 117(3):571–580. https://doi.org/10.1016/j.ijrobp.2023.04.030
29. de Rodríguez Dios N, Couñago F, Murcia-Mejía M, Rico-Oses M, Calvo-Crespo P, Samper P, Vallejo C, Luna J, Trueba I, Sotoca A, Cigarral C, Farré N, Manero RM, Durán X, Gispert JD, Sánchez-Benavides G, Rognoni T, Torrente M, Capellades J, Jiménez M, Cabada T, Blanco M, Alonso A, Martínez-San Millán J, Escribano J, González B, López-Guerra JL (2021) Randomized phase III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small-cell lung cancer (PREMER): a GICOR-GOECP-SEOR study. J Clin Oncol 39(28):3118–3127. https://doi.org/10.1200/JCO.21.00639
30. Albers EAC, Zeng H, De Ruysscher DKM, Kuenen MA, Kessels R, Hendriks LEL, Belderbos JSA, Schagen SB (2023) Self-reported cognitive function and quality of life in patients with SCLC in the hippocampal avoidance prophylactic cranial irradiation versus prophylactic cranial irradiation randomized phase 3 trial (NCT01780675). JTO Clin Res Rep 4(5):100506. https://doi.org/10.1016/j.jtocrr.2023.100506
31. Lin SY, Yang CC, Wu YM, Tseng CK, Wei KC, Chu YC, Hsieh HY, Wu TH, Pai PC, Hsu PW, Chuang CC (2015) Evaluating the impact of hippocampal sparing during whole brain radiotherapy on neurocognitive functions: a preliminary report of a prospective phase II study. Biomed J 38(5):439–449. https://doi.org/10.4103/2319-4170.157440
32. Yang CC, Chuang CC, Pai PC, Tsan DL, Chou WC, Wang CL, Wu YM, Lin CH, Lu YJ, Lin SY (2025) Trajectory of long-term neuropsychological performances and cognitive-deterioration-free survival after hippocampus-sparing whole-brain radiotherapy in cancer patients mostly with newly diagnosed brain oligometastases. Appl Neuropsychol Adult. https://doi.org/10.1080/23279095.2025.2465850
33. Tsai PF, Yang CC, Chuang CC, Huang TY, Wu YM, Pai PC, Tseng CK, Wu TH, Shen YL, Lin SY (2015) Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. Radiat Oncol 10(1):253. https://doi.org/10.1186/s13014-015-0562-x
34. Zhan TY, Deng L, Wang WQ, Zhang T, Wang JY, Wang X, Liu WY, Zhai YR, Xiao ZF, Feng QF, Bi N, Li YX, Zhou ZM (2024) Implementing the optimized hippo-avoidance prophylactic cranial irradiation for limited-stage small cell lung cancer by tomotherapy and volumetric modulated arc therapy. Thorac Cancer 15(34):2449–2455. https://doi.org/10.1111/1759-7714.15462
35. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, Rowley H, Kundapur V, DeNittis A, Greenspoon JN, Konski AA, Bauman GS, Shah S, Shi W, Wendland M, Kachnic L, Mehta MP (2014) 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 32(34):3810–3816. https://doi.org/10.1200/JCO.2014.57.2909
36. Redmond KJ, Hales RK, Anderson-Keightly H, Zhou XC, Kummerlowe M, Sair HI, Duhon M, Kleinberg L, Rosner GL, Vannorsdall T (2017) Prospective study of hippocampal-sparing prophylactic cranial irradiation in limited-stage small cell lung cancer. Int J Radiat Oncol Biol Phys 98(1):603–611. https://doi.org/10.1016/j.ijrobp.2017.03.009
37. Vees H, Caparrotti F, Eboulet EI, Xyrafas A, Fuhrer A, Meier U, Mark M, Elicin O, Aebersold DM, Zwahlen DR, Finazzi T, Allal AS, Putora PM, Martucci F, Rudolf CB, Ribi K, Swiss Group for Clinical Cancer Research (SAKK) (2020) Impact of early prophylactic cranial irradiation with hippocampal avoidance on neurocognitive function in patients with limited disease small cell lung cancer. A multicenter phase 2 trial (SAKK 15/12). Int J Radiat Oncol Biol Phys 107(2):279–287. https://doi.org/10.1016/j.ijrobp.2020.02.029
38. Westover KD, Mendel JT, Dan T, Kumar K, Gao A, Pulipparacharuv S, Iyengar P, Nedzi L, Hannan R, Anderson J, Choe KS, Jiang W, Abdulrahman R, Rahimi A, Folkert M, Laine A, Presley C, Cullum CM, Choy H, Ahn C, Timmerman R (2020) Phase II trial of hippocampal-sparing whole brain irradiation with simultaneous integrated boost for metastatic cancer. Neuro Oncol 22(18):1831–1839. https://doi.org/10.1093/neuonc/noaa092
39. Yang WC, Chen YF, Yang CC, Wu PF, Chan HM, Chen JLY, Chen GY, Cheng JCH, Kuo SH, Hsu FM (2021) Hippocampal avoidance whole-brain radiotherapy without memantine in preserving neurocognitive function for brain metastases: a phase II blinded randomized trial. Neuro Oncol 23(3):478–486. https://doi.org/10.1093/neuonc/noaa193
40. Du J, Liao Y, Zhang Y, Yang B, Wu Y, Liu C, Liao X (2024) The impact of hippocampal-sparing whole-brain radiotherapy on survival and cognitive function in patients with brain metastases. Altern Ther Health Med 30(1):111–115
41. Whitfield GA, Bulbeck H, Clifton-Hadley L, Edwards D, Jefferies S, Jenkinson MD, Griffin M, Handley J, Megias D, Sanghera P, Shaffer R, Short S, Wilson W (2024) A randomised phase II trial of Hippocampal sparing versus conventional whole brain radiotherapy after surgical resection or radiosurgery in favourable prognosis patients with 1–10 brain metastases. Clin Oncol (R Coll Radiol) 36(11):681–689. https://doi.org/10.1016/j.clon.2024.07.001
42. Li Z, Wang J, Deng L, Zhai Y, Zhang T, Bi N, Wang J, Wang X, Liu W, Xiao Z, Chen D, Lv J, Feng Q, Wang W, Zhou Z (2024) Hippocampal avoidance whole-brain radiotherapy with simultaneous integrated boost in lung cancer brain metastases and utility of the Hopkins verbal learning test for testing cognitive impairment in Chinese patients: a prospective phase II study. BMC Cancer 24(1):899. https://doi.org/10.1186/s12885-024-12559-1
43. Loga K, Wojcik B, Stanislawek A, Papis-Ubych A, Kuncman L, Fijuth J, Gottwald L (2024) Hippocampal protection during preventive cranial irradiation and neurocognitive functions in patients with small cell lung cancer. Rep Pract Oncol Radiother 29(5):558–565. https://doi.org/10.5603/rpor.102617
44. Kao J, Darakchiev B, Conboy L, Ogurek S, Sharma N, Ren X, Pettit J (2015) Tumor directed, scalp sparing intensity modulated whole brain radiotherapy for brain metastases. Technol Cancer Res Treat 14(5):547–555. https://doi.org/10.7785/tcrt.2012.500426
45. Olsen EA, Canfield D (2016) SALT II: a new take on the severity of alopecia tool (SALT) for determining percentage scalp hair

loss. J Am Acad Dermatol 75(6):1268–1270. https://doi.org/10.1016/j.jaad.2016.08.042
46. Gani C, Muller AC, Eckert F, Schroeder C, Bender B, Pantazis G, Bamberg M, Berger B (2012) Outcome after whole brain radiotherapy alone in intracranial leptomeningeal carcinomatosis from solid tumors. Strahlenther Onkol 188:148–153. https://doi.org/10.1007/s00066-011-0025-8
47. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WK, Brada M, Newlands E (1996) The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. Qual Life Res 5(1):139–150. https://doi.org/10.1007/BF00435979
48. Kalkanis SN, Kondziolka D, Gaspar LE, Burri SH, Asher AL, Cobbs CS, Ammirati M, Robinson PD, Andrews DW, Loeffler JS, McDermott M, Mehta MP, Mikkelsen T, Olson JJ, Paleologos NA, Patchell RA, Ryken TC, Linskey ME (2010) The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 96(1):33–43. https://doi.org/10.1007/s11060-009-0061-8
49. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, Sperduto PW, Vogelbaum MA, Radawski JD, Wang JZ, Gillin MT, Mohideen N, Hahn CA, Chang EL (2012) Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2(3):210–225. https://doi.org/10.1016/j.prro.2011.12.004
50. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G (2006) Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 295(7):2483–2491. https://doi.org/10.1001/jama.295.21.2483
51. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Hassel MB, Kouri M, Valeinis E, van den Berge D, Collette S, Collette L, Mueller RP (2011) 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 29(2):134–141. https://doi.org/10.1200/JCO.2010.30.1655
52. Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, Kristjansen PE, Johnson BE, Ueoka H, Wagner H, Aisner J (1999) Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. N Engl J Med 341(7):476–484. https://doi.org/10.1056/NEJM199908123410703
53. Monaco EA, Faraji AH, Berkowitz O, Parry PV, Hadelsberg U, Kano H, Niranjan A, Kondziolka D, Lunsford LD (2013) Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. Cancer 119(1):226–232. https://doi.org/10.1002/cncr.27504
54. Roman DD, Sperduto PW (1995) Neuropsychological effects of cranial radiation: current knowledge and future directions. Int J Radiat Oncol Biol Phys 31(4):983–998. https://doi.org/10.1016/0360-3016(94)00550-8
55. DeAngelis LM, Delattre JY, Posner JB (1989) Radiation-induced dementia in patients cured of brain metastases. Neurology 39(6):789–796. https://doi.org/10.1212/wnl.39.6.789
56. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 10(11):1037–1044. https://doi.org/10.1016/S1470-2045(09)70263-3
57. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Hassel MB, Kouri M, Valeinis E, van den Berge D, Mueller RP, Tridello G, Collette L, Bottomley A (2013) A European Organization for Research and Treatment of Cancer phase III trial of adjuvant wholebrain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. J Clin Oncol 31(1):65–72. https://doi.org/10.1200/JCO.2011.41.0639
58. Gondi V, Tomé WA, Mehta MP (2010) Why avoid the hippocampus? A comprehensive review. Radiother Oncol 97(3):370–376. https://doi.org/10.1016/j.radonc.2010.09.013
59. Meyers CA, Brown PD (2006) Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. J Clin Oncol 24(8):1305–1309. https://doi.org/10.1200/JCO.2005.04.6086
60. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, Choucair A, Fox S, Suh JH, Roberge D, Kavadi V, Bentzen SM, Mehta MP, Watkins-Bruner D, Radiation Therapy Oncology Group (RTOG) (2013) Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 15(10):1429–1437
61. Gutiérrez AN, Westerly DC, Tomé WA, Jaradat HA, Mackie TR, Bentzen SM, Khuntia D, Mehta MP (2007) Whole brain radiotherapy with hippocampal avoidance and simultaneously integrated brain metastases boost: a planning study. Int J Radiat Oncol Biol Phys 69(2):589–597. https://doi.org/10.1016/j.ijrobp.2007.05.038
62. Jiang A, Sun W, Zhao F, Wu Z, Shang D, Yu Q, Wang S, Zhu J, Yang F, Yuan S (2019) Dosimetric evaluation of four whole brain radiation therapy approaches with hippocampus and inner ear avoidance and simultaneous integrated boost for limited brain metastases. Radiat Oncol 14(1):46. https://doi.org/10.1186/s13014-019-1255-7
63. Pezzulla D, Maurizi F, Rocchi E, Peluso S, De Cicco L, Chiesa S, Di Franco R (2023) Letter to the editor regarding "The effect of hippocampal avoidance whole brain radiotherapy on the preservation of long-term neurocognitive function in non-small cell lung cancer patients with brain metastasis." Technol Cancer Res Treat 22:15330338231169600. https://doi.org/10.1177/15330338231169599
64. Leskinen S, Shah HA, Yaffe B, Schneider SJ, Ben-Shalom N, Boockvar JA, D'Amico RS, Wernicke AG (2023) Hippocampal avoidance in whole brain radiotherapy and prophylactic cranial irradiation: a systematic review and meta-analysis. J Neurooncol 163(3):515–527. https://doi.org/10.1007/s11060-023-04384-6
65. Scoccianti S, Simontacchi G, Greto D, Perna M, Terziani F, Talamonti C, Teriaca MA, Caramia G, Lo Russo M, Olmetto E, Delli Paoli C, Grassi R, Carfora V, Saieva C, Bonomo P, Detti B, Mangoni M, Desideri I, Francolini G, Di Cataldo V, Marrazzo L, Pallotta S, Livi L (2020) Dosimetric predictors of acute and chronic alopecia in primary brain cancer patients treated with volumetric modulated arc therapy. Front Oncol 8(10):467. https://doi.org/10.3389/fonc.2020.00467
66. Satragno C, Verrico A, Giannelli F, Ferrero A, Campora S, Turazzi M, Cavagnetto F, Schiavetti I, Garrè ML, Garibotto F, Milanaccio C, Piccolo G, Crocco M, Ramaglia A, Di Profio S, Barra S, Belgioia L (2022) High dose craniospinal irradiation as independent risk factor of permanent alopecia in childhood medulloblastoma survivors: cohort study and literature review. J Neurooncol 160(3):659–668. https://doi.org/10.1007/s11060-022-04186-2
67. Metz JM, Smith D, Mick R, Lustig R, Mitchell J, Cherakuri M, Glatstein E, Hahn SM (2004) A phase I study of topical Tempol for the prevention of alopecia induced by whole brain

radiotherapy. Clin Cancer Res 10(19):6411–6417. https://doi.org/10.1158/1078-0432.CCR-04-0658
68. Hahn SM, Krishna CM, Samuni A, DeGraff W, Cuscela DO, Johnstone P, Mitchell JB (1994) Potential use of nitroxides in radiation oncology. Cancer Res 54(7 Suppl):2006s–2010s
69. Geng L, Hanson WR, Malkinson FD (1992) Topical or systemic 16, 16 dm prostaglandin E2 or WR-2721 (WR-1065) protects mice from alopecia after fractionated irradiation. Int J Radiat Biol 61(4):533–537. https://doi.org/10.1080/09553009214551291
70. Hyun MY, Kim BJ, Lee C, Kim JW (2014) Radiation-induced alopecia treated with Botulinum toxin type a injection. Plast Reconstr Surg Glob Open 2(10):e226. https://doi.org/10.1097/GOX.0000000000000149
71. Soref CM, Fahl WE (2015) A new strategy to prevent chemotherapy and radiotherapy-induced alopecia using topically applied vasoconstrictor. Int J Cancer 136(1):195–203. https://doi.org/10.1002/ijc.28961
72. Haider M, Hamadah I, Almutawa A (2013) Radiation- and chemotherapy-induced permanent alopecia: case series. J Cutan Med Surg 17(1):55–61. https://doi.org/10.2310/7750.2012.12033

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