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Original Article

Incidence of hippocampal and perihippocampal brain metastases and impact on hippocampal-avoiding radiotherapy: A systematic review and meta-analysis

Shari Wiegreffe [a], Gustavo Renato Sarria [a], Julian Philipp Layer [a,b], Egon Dejonckheere [c,d], Younèss Nour [a], Frederic Carsten Schmeel [e], Frank Anton Giordano [f,g], Leonard Christopher Schmeel [a], Ilinca Popp [h], Anca-Ligia Grosu [h], Eleni Gkika [a], Cas Stefaan Dejonckheere [a,*]

[a] Department of Radiation Oncology, University Hospital Bonn, 53127 Bonn, Germany
[b] Institute of Experimental Oncology, University Hospital Bonn, 53127 Bonn, Germany
[c] Faculty of Psychology and Educational Sciences, KU Leuven, 3000 Leuven, Belgium
[d] Department of Medical and Clinical Psychology, Tilburg School of Social and Behavioural Sciences, 5037 Tilburg, the Netherlands
[e] Department of Neuroradiology, University Hospital Bonn, 53127 Bonn, Germany
[f] Department of Radiation Oncology, University Medical Center Mannheim, 68167 Mannheim, Germany
[g] DKFZ-Hector Cancer Institute, University Medical Center Mannheim, 68167 Mannheim, Germany
[h] Department of Radiation Oncology, Medical Faculty, University Freiburg, 79106 Freiburg, Germany

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ABSTRACT

Background and Purpose: In patients requiring prophylactic cranial irradiation (PCI) or whole-brain radiotherapy (WBRT) for brain metastases (BMs), hippocampal avoidance (HA) has been shown to preserve neurocognitive function and quality of life. Here, we aim to estimate the incidence of hippocampal and perihippocampal BMs and the subsequent risk of local undertreatment in patients undergoing hippocampal sparing radiotherapy.
Materials and Methods: MEDLINE, Embase, and Scopus were searched with the terms "*Hippocampus*", "*Brain Neoplasms*", and related terms. Trials reporting on the incidence of hippocampal and/or perihippocampal BMs or hippocampal failure rate after PCI or WBRT were included.
Results: Forty records were included, encompassing a total of 5,374 patients with over 32,570 BMs. Most trials employed a 5 mm margin to define the HA zone. In trials reporting on BM incidence, 4.4 % (range 0 – 27 %) and 9.2 % (3 – 41 %) of patients had hippocampal and perihippocampal BMs, respectively. The most common risk factor for hippocampal BMs was the total number of BMs. The reported failure rate within the HA zone after HA-PCI or HA-WBRT was 4.5 % (0 – 13 %), salvageable with radiosurgery in most cases. SCLC histology was not associated with a higher risk of hippocampal failure (OR = 2.49; $p = 0.23$). In trials comparing with a conventional (non-HA) PCI or WBRT group, HA did not increase the hippocampal failure rate (OR = 1.90; $p = 0.17$).
Conclusion: The overall incidence of hippocampal and perihippocampal BMs is considerably low, with a subsequent low risk of local undertreatment following HA-PCI or HA-WBRT. In patients without involvement, the hippocampus should be spared to preserve neurocognitive function and quality of life.

Introduction

Recent advancements in systemic therapies have led to improved overall survival in cancer patients [1]. Along with wider availability of improved high-resolution imaging techniques, this has resulted in an increased relative diagnostic incidence of brain metastases (BMs) [2]. Depending on the primary tumour histology (e.g. small-cell lung cancer [SCLC]), BM rates can rise up to 80 % over the course of the disease, even justifying prophylactic cranial irradiation (PCI) in most cases [3–5]. Patients developing BMs often require whole-brain radiotherapy (WBRT) to prevent further neurological morbidity and mortality. Several trials have demonstrated significant neurocognitive impairment

* Corresponding author at: Department of Radiation Oncology, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany.
E-mail address: cas.dejonckheere@ukbonn.de (C. Stefaan Dejonckheere).

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following PCI or WBRT, linked particularly to radiation-induced injury of the hippocampus and damage to the radiosensitive progenitor cells in the dentate gyrus, hampering hippocampal neurogenesis [6–8]. A feasible method to preserve neurocognitive function is employing hippocampal avoidance (HA) PCI or WBRT, achieving > 80 % mean dose reduction to the HA zone (most commonly defined as a 5 mm margin around the hippocampus) using linac-based intensity-modulated radiotherapy, while maintaining adequate target coverage and homogeneity [9–11]. In randomised trials, this conformal avoidance has led to sustained preservation of both memory and quality of life, while maintaining oncological outcomes [12–16]. Even though advances in radiation treatment technique and delivery have allowed for more targeted approaches by means of stereotactic radiotherapy (SRT) or radiosurgery (SRS), yielding superior outcomes in terms of local control, neurocognition, and quality of life, WBRT remains the first-line treatment for the majority of patients, as comparative prospective trials are still largely lacking [17,18].

A question that remains, is the risk of potential local undertreatment (hippocampal failure) in those cases where the hippocampus is spared (HA-PCI or HA-WBRT), i.e. the likelihood of subclinical microscopic disease in the hippocampus or HA zone at the time of radiation treatment. Several trials have investigated the incidence of BMs in these regions. Herein, we aim to comprehensively review the literature on this topic in order to estimate the incidence of hippocampal and perihippocampal BMs and to determine the subsequent risk of hippocampal failure following HA-PCI or HA-WBRT, as well as potential risk factors associated with it.

Materials and methods

Search strategy

Using PubMed as the primary search engine, we performed a comprehensive literature search of the MEDLINE database. All available records up until November 21st, 2023 matching the Medical Subject Headings (MeSH) "*Hippocampus*" and "*Brain Neoplasms*" were screened independently based on title and abstract and without language restriction by two authors (S.W. and C.S.D.). Trials reporting on either (1) the incidence of hippocampal and/or perihippocampal BMs (regardless of radiation) or (2) hippocampal failure rate (i.e. BM development or relapse rate in the HA zone after previous HA-PCI or HA-WBRT, respectively), were included. In the event of a discrepancy, a third party (G.R.S.) was consulted. To further extend the literature search, additional records were identified by cross-searching the already included articles' references and by using related search terms in both Embase and Scopus. Case reports and letters to the editor were screened for additional references, but excluded from the final analysis. Literature research and selection were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Fig. 1) [19].

Data collection and analysis

Following inclusion, all manuscripts, supplements, and trial protocols (where available) were screened. To ensure accuracy, relevant

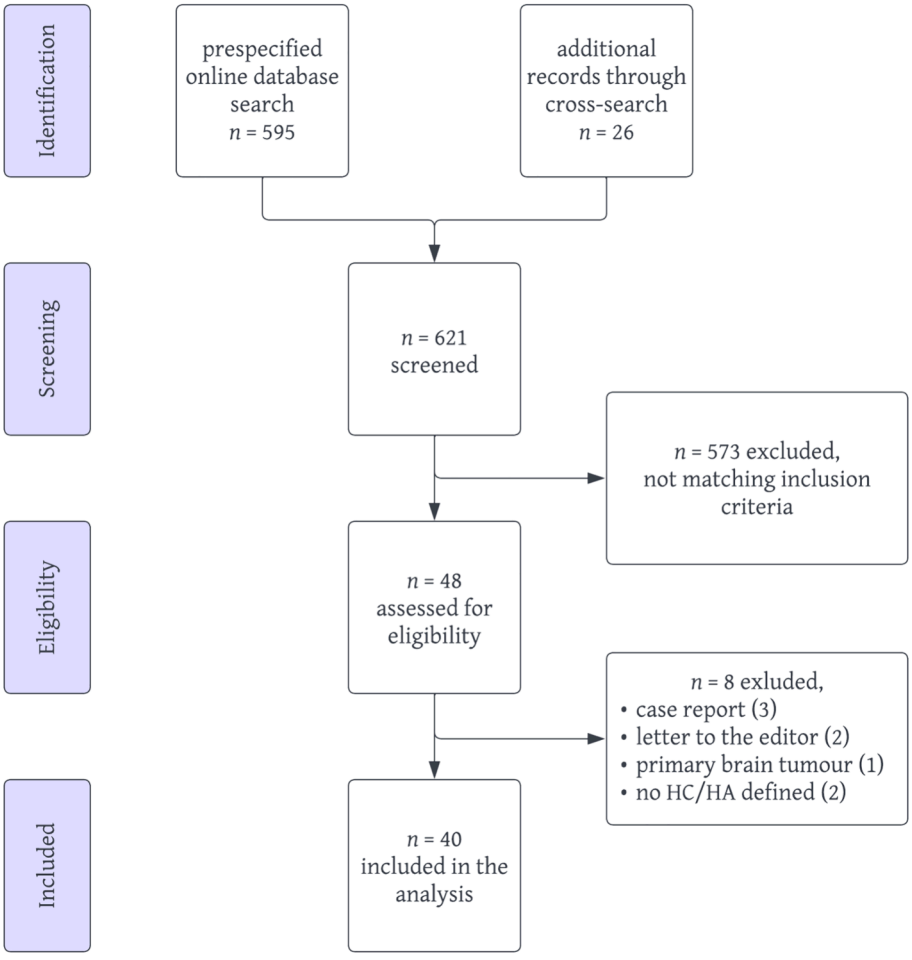

Fig. 1. Flowchart of literature research and selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. HC = hippocampus; HA = hippocampal avoidance zone.

information was extracted by two reviewers separately (S.W. and C.S. D.). The following parameters were collected: authors, year of publication, geographic region, nature of the trial (single or multicenter; retro- or prospective), total number of patients, total number of BMs, histology of the primary tumour and proportion of patients with SCLC, employed margin to define the HA zone, number of patients with hippocampal and/or perihippocampal BMs, number of hippocampal and/or perihippocampal BMs, risk factors for hippocampal and/or perihippocampal involvement, and dosimetric information. In trials investigating the HA failure rate, this was also collected, along with nature of the intervention (i.e. HA-PCI or HA-WBRT), follow-up time, time to HA failure, and subsequent salvage treatment.

Mean, median, standard deviation (SD), and range were calculated for all applicable data. Proportions of HA involvement and failure were pooled after taking the respective sample size into account. In those cases where data on a certain endpoint were not available, said trials were omitted from the respective analyses. Pooled effect sizes were estimated by calculating the odds ratio (OR) with a 95 % confidence interval (CI), using a random effects model. Results were summarised in a forest plot and the heterogeneity between studies was assessed by calculating Cochran's Q test and I^2, with cut-offs as defined by Higgins *et al.* [20]. A p-value < 0.05 was considered as statistically significant. All data were managed using Microsoft Excel version 16 (Microsoft, Redmond, WA, USA) and the analysis was carried out using *R* version 4.1.2 (*R* Foundation for Statistical Computing, Vienna, Austria).

Results

Of 621 records screened, 40 were included in the final analysis (2 prospective and 38 retrospective). Of these, 24 answered the incidence question (Table 1), whereas 16 estimated the failure risk after treatment (Table 2). A 5 mm margin around the hippocampus was the most common way to define the HA zone (85 % of trials). Three trials (8 %) did not provide information on this margin and only reported on the incidence of BMs in the hippocampus itself.

The 24 included trials encompassed a total of 5,374 patients with 32,570 BMs. Overall, 4.4 % (196/4,426) of patients had BMs in the hippocampus (range 0 − 27 % for individual trials; Fig. 2*a*) and 9.2 % (388/4,206) in the HA zone (defined as hippocampus plus a 5 mm margin; range 3 − 41 %; Fig. 2*b*). Of all BMs, 0.8 % (227/27,361) were located within the hippocampus itself (range 0 − 2.6 %; Fig. 2*c*) and 2.0 % (435/22,165; Fig. 2*d*) in the HA zone (range 0.6 − 4.9 %).

In total, 25.5 % (1,198/4,696) of the included patients had been diagnosed with SCLC. Here, the incidence of hippocampal and perihippocampal BMs ranged from 0 − 18 % and 0 − 27 %, respectively.

Several trials (15/24; 63 %) investigated risk factors for hippocampal and/or perihippocampal BMs. The most common risk factor was the total number of BMs (7 trials; 47 %), followed by their total volume and non-oligometastatic disease (3 trials each; 20 %), and younger age, SCLC histology, and presence of extracranial metastases (2 trials each; 13 %).

In total, 16 trials reported on the risk of hippocampal failure after radiation treatment: 5 after HA-PCI, 5 after HA-WBRT, 4 after HA-WBRT with simultaneous integrated boost (SIB), and 2 trials included both HA-PCI and HA-WBRT patients. Overall, the failure rate in the HA zone was 4.5 % (42/937), ranging from 0 − 13 % for individual trials.

In patients experiencing intracranial failure, SCLC histology was not associated with a higher risk of hippocampal failure (8 trials; OR = 2.49; 95 % CI 0.63 − 9.77; $p = 0.23$). Data on laterality (i.e. whether the left or right HA zone was involved in the case of hippocampal failure), were insufficient for statistical analysis. Seven trials reported on the use of salvage SRS upon the development of BMs in the HA zone, with radiation doses ranging from 13 − 18 Gy. Subsequent treatment response was documented in a single trial only [21].

Six trials compared the risk of hippocampal failure with a conventional PCI or WBRT group (i.e. not receiving HA). Overall, HA was not associated with an increased risk of hippocampal failure (OR = 1.90; 95 % CI 0.75 − 4.83; $p = 0.17$; Fig. 3).

Discussion

WBRT remains the first-line treatment in many patients. The recognition of radiation-induced hippocampal injury as a major cause of neurocognitive decline has led to the development of hippocampal sparing radiation techniques, which preserve neurocognition by limiting the radiation dose to the HA zone. On the other hand, however, this approach poses a risk of local undertreatment, as subclinical microscopic disease might be present in this region at the time of radiation treatment, not receiving adequate dose coverage to yield disease control. In this large dataset of > 5,000 patients with > 30,000 BMs, the overall incidence of hippocampal and perihippocampal BMs was considerably low, with a subsequent acceptable risk of undertreatment following HA-PCI or HA-WBRT, not different from non-HA PCI or WBRT. This further consolidates the role of HA in preserving neurocognitive function and quality of life and adding to the evidence that BMs may not be randomly distributed across the brain [22]. In those cases with hippocampal failure, salvage irradiation with SRS is possible in patients with isolated or limited local failure.

This is the first comprehensive review investigating the overall incidence of hippocampal and perihippocampal BMs. Another recently published systematic review and meta-analysis by Leskinen *et al.* summarised the evidence on the impact of HA on neurocognitive function, reporting significant differences in overall cognitive function, memory, and verbal learning if HA was used, at variable follow-up times after radiation [23]. This trial also partly investigated the risk of hippocampal failure after radiotherapy and yielded similar results (overall effect size = 0.04; 95 % CI 0.03 − 0.05). Across five included trials comparing with a non-HA group, there was no significant difference in hippocampal relapse rates (risk difference = 0.01; 95 % CI − 0.02 − 0.03; $p = 0.63$) [13,21,24–26].

NRG CC001, the landmark trial that randomized patients between WBRT + memantine and HA-WBRT + memantine, showed that the latter leads to sustained preservation of cognitive function and continued prevention of patient-reported cognitive symptoms [13,14]. Additionally, treatment arms did not differ significantly in overall survival, intracranial progression-free survival, or toxicity after mature follow-up, justifying its use as the standard of care for patients with good performance status who are scheduled to receive WBRT. In a recently published secondary analysis, the benefit of HA-WBRT + memantine on decreasing neurocognitive function failure was seen only in patients living ≥ 4 months (HR = 0.75; $p = 0.03$), thus implying a differential neuroprotective response [27]. Furthermore, those with lower baseline patient-reported cognitive impairment (HR = 0.64; $p = 0.002$) and those with primary lung histology (HR = 0.58; $p = 0.0007$) derived significantly greater benefit, implying a heterogeneity of the neuroprotective treatment effect of HA-WBRT. This in turn offers useful insights for future clinical trials aimed at a more nuanced understanding of the effects of HA-WBRT among different patient subgroups.

The debate on control versus cognition in the context of radiation treatment for BMs is ongoing, juxtaposing WBRT and SRT/SRS, respectively. Historically, WBRT was the only treatment option for patients developing BMs [17]. Its addition to (radio-)surgery of a limited number of BMs led to reduced intracranial relapses and neurologic deaths, however, failed to improve the duration of functional independence or overall survival and posed a greater risk of a significant decline in learning and memory function, both in the definitive and adjuvant setting [28–31]. Continued research efforts gradually led to the further optimization of targeted approaches such as SRT and SRS, with superior oncological outcomes and improved preservation of neurocognition and quality of life in many cases [18]. These techniques have now become widely adopted as the sole cranial treatment for patients with adequate performance status and a limited number of BMs. In patients with SCLC, who are at high risk of developing BMs, implementation of stereotactic

Table 1
Overview of included trials reporting on the incidence of hippocampal and/or perihippocampal brain metastases, regardless of treatment. All trials are retrospective, apart from those marked with γ. BMs = brain metastases; N/A = not available; SCLC = small-cell lung cancer; HA = hippocampal avoidance; HC = hippocampus.

number	authors [reference]	year of publication	region	total patients (*n*)	total BMs (*n*)	histology	SCLC (%)	HA margin (mm)	patients with BM in HC (*n*)	patients with BM in HA (*n*)	patients with BM in HC (%)	patients with BM in HA (%)	number of BM in HC (*n*)	number of BM in HA (*n*)	BM in HA (%)	BM in HC (%)	SCLC patients with BM in HC (%)	SCLC patients with BM in HA (%)
1	Ghia et al. [43]	2007	US	100	272	mixed	10	5	0	8	0	8	0	9	0	3.3	0	12.5
2	Gondi et al. [44]	2010	US	371	1,133	mixed	10	5	0	32	0	8.6	0	34	0	3	0	10.5
3	Marsh et al. [45]	2010	US	107	697	mixed	N/A	N/A	N/A	N/A	N/A	N/A	16	N/A	2.3	N/A	N/A	N/A
4	Harth et al. [46]	2013	Germany	100	856	mixed	11	5	3	8	3	8.0	3	8	0.4	0.9	18.2	27.3
5	Wan et al. [47]	2013	China	488	2,270	mixed	9	N/A	7	N/A	1.4	N/A	7	N/A	0.3	N/A	N/A	N/A
6	Hong γ et al. [48]	2014	Australia/ NZ/ UK/ Norway	77	116	melanoma	0	5	0	4	0	5.2	0	N/A	0	N/A	N/A	N/A
7	Kundapur et al. [49]	2015	US	59	359	SCLC	100	5	2	3	3.4	5.1	2	3	0.6	0.8	3.4	5.1
8	Wu (1) et al. [50]	2015	China	632	6,064	mixed	8	5	26	35	4.1	5.5	31	37	0.5	0.6	N/A	N/A
9	Sun B. et al. [51]	2016	China	314	1,678	breast	0	5	13	28	4.1	8.9	20	38	1.2	2.3	N/A	N/A
10	Wu (2) et al. [52]	2016	China	192	1,356	breast	0	5	7	14	3.6	7.3	7	N/A	0.5	N/A	N/A	N/A
11	Chen et al. [53]	2017	China	345	1,621	lung	N/A	5	16	16	4.6	4.6	42	45	2.6	2.8	N/A	N/A
12	Guo et al. [54]	2017	China	180	1,594	SCLC	100	5	9	22	5	12.2	23	45	1.4	2.8	5	12.2
13	Han et al. [55]	2017	China	226	1,080	mixed	N/A	5	N/A	7	N/A	3.1	N/A	N/A	N/A	N/A	0	0
14	Kirakli et al. [56]	2017	Turkey	54	446	SCLC	100	5	8	9	14.8	16.7	10	10	2.2	2.2	14.8	16.7
15	Zhao et al. [57]	2017	China	238	1,511	SCLC	100	5	14	N/A	5.9	N/A	15	N/A	1	N/A	5.9	N/A
16	Effeney et al. [58]	2018	Australia	120	754	SCLC	100	5	22	N/A	18.3	N/A	N/A	23	N/A	3.1	18.3	N/A
17	Kazda et al. [59]	2018	Czech Republic	260	2,595	mixed	13	5	20	47	7.7	18.1	35	127	1.3	4.9	N/A	N/A
18	Sun Q. et al. [60]	2019	China	116	565	mixed	16	5	2	11	1.7	9.5	2	11	0.4	1.9	N/A	N/A
19	Yanagihara et al. [61]	2019	US	277	2,757	mixed	8	5	N/A	14	N/A	5.1	1	18	0	0.7	N/A	N/A
20	Lee γ et al. [62]	2020	US	34	438	mixed	0	5	9	14	26.5	41.2	6	17	1.4	3.9	N/A	N/A
21	Ly et al. [63]	2020	Australia	335	N/A	NSCLC	0	5	8	30	2.4	9	N/A	N/A	N/A	N/A	N/A	N/A
22	Wang et al. [25]	2021	China	215	1,033	SCLC	100	N/A	N/A	N/A	N/A	N/A	7	10	0.7	1	N/A	N/A
23	Ahn et al. [64]	2022	South Korea	123	N/A	NSCLC	0	5	N/A	18	N/A	14.6	N/A	N/A	N/A	N/A	N/A	N/A
24	Xie et al. [65]	2022	China	411	3,375	mixed	26	5	30	68	7.3	16.5	N/A	N/A	N/A	N/A	18.1	2.9

Table 2
Overview of included trials reporting on the risk of hippocampal failure after irradiation. All trials are retrospective. HA = hippocampal avoidance; WBRT = whole-brain radiotherapy; PCI = prophylactic cranial irradiation; SIB = simultaneous integrated boost; SCLC = small-cell lung cancer; N/A = not available.

number	authors [reference]	year of publication	region	intervention	total radiation dose (Gy)	mean hippocampal D_{max} (Gy)	total patients (*n*)	histology	SCLC (%)	HA margin (mm)	patients with HA failure (*n*)	patients with HA failure (%)	median follow-up (months)	median time to HA failure (months)
1	Gondi et al. [12]	2014	US	HA-WBRT	30	< 16	100	mixed	0	5	3	3	N/A	N/A
2	Lin et al. [66]	2015	Taiwan	HA-WBRT/ HA-PCI	30	N/A	25	mixed	12	5	0	0	N/A	N/A
3	Redmond et al. [67]	2017	US	HA-PCI	25	N/A	20	SCLC	100	5	1	10	16.7	23.3
4	Kim et al. [68]	2018	South Korea	HA-WBRT + SIB	25 (SIB 35 – 55)	< 17	42	mixed	N/A	5	1	2.4	10	10.6
5	Nielsen et al. [69]	2019	Denmark	HA-WBRT/ HA-PCI	25 – 30	N/A	15	mixed	93.3	5	0	0	10	N/A
6	Brown et al. [13]	2020	US	HA-WBRT	30	< 16	261	mixed	0	5	11	4.2	7.9	N/A
7	Lebow et al. [70]	2020	US	HA-WBRT + SIB	30 (SIB 37.5)	N/A	32	mixed	9.4	0 – 12	4	12.5	11.3	N/A
8	Popp et al. [24]	2020	Germany	HA-WBRT + SIB	30 (SIB 42 – 51)	N/A	66	mixed	0	5	5	7.6	8.5	5.8 **
9	Vees et al. [71]	2020	Switzerland	HA-PCI	25	< 10	42	SCLC	100	2	0	0	12	N/A
10	Westover et al. [72]	2020	US	HA-WBRT + SIB	20 (SIB 40)	< 16 – 17	49	mixed	0	5	1	2	10.5 **	5
11	Belderbos et al. [73]	2021	Netherlands/ Belgium	HA-PCI	30	< 17	84	SCLC	100	5	5	6	26.6	N/A
12	Cho et al. [74]	2021	South Korea	HA-PCI	25	N/A	48	SCLC	100	5	2	4.2	18	10 **
13	Rodríguez de Dios et al. [75]	2021	Spain	HA-PCI	25	< 16 – 17	69	SCLC	100	5	3	4.3	40.4	N/A
14	Wang et al. [76]	2021	China	HA-WBRT	25	16 *	27	NSCLC	0	5	1	3.7	N/A	N/A
15	Yang et al. [26]	2021	Taiwan	HA-WBRT	30	< 20	33	mixed	N/A	5	3	9.1	12.4	N/A
16	Shieh et al. [77]	2022	Taiwan	HA-WBRT	25 – 30	17	24	mixed	17	5	2	8.3	N/A	17.5 **

* Median instead of mean.
** Mean instead of median.

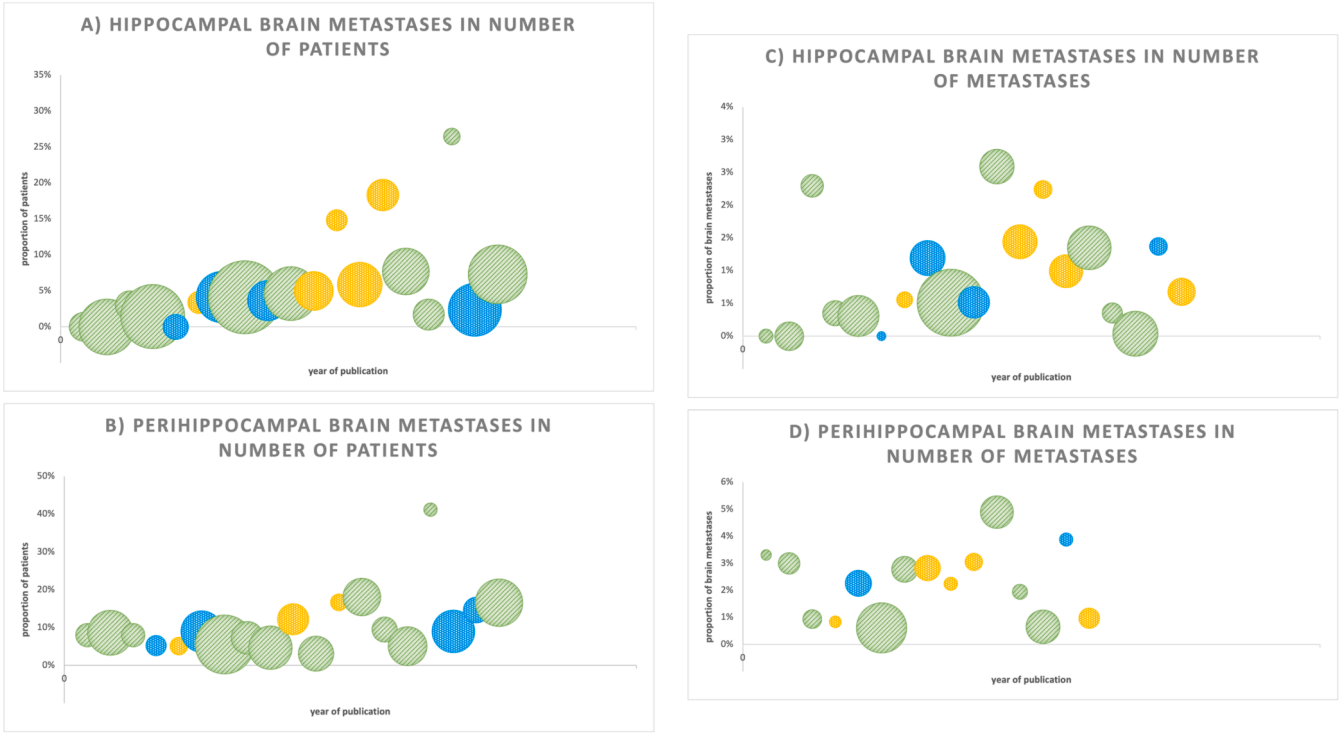

Fig. 2. A – d. Incidence of hippocampal **(a, c)** and perihippocampal **(b, d)** brain metastases as a proportion of total number of patients **(a, b)** and brain metastases **(c, d)**. Bubble size indicates the number of patients or brain metastases, respectively. Bubble colours correspond to the histology (orange = SCLC; blue = no SCLC; green = mixed). Range for **a** and **b** 34 – 632 patients, range for **c** and **d** 116 – 6,064 brain metastases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

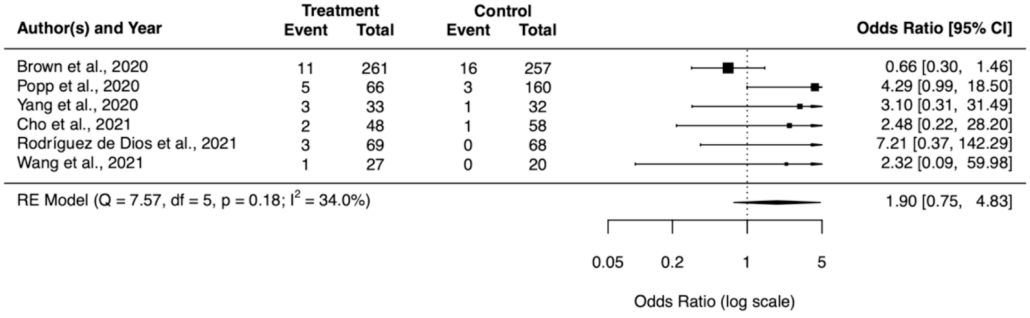

Fig. 3. Forest plot of the individual and pooled effect sizes of hippocampal failure between PCI and/or WBRT with or without hippocampal avoidance. Error bars indicate the 95 % confidence intervals.

approaches has been slower, as robust data are generally lacking. Large retrospective samples indicate that the primary trade-offs in this setting are probably no different to those in which SRS has already been established, i.e. inferior time to central nervous system progression with similar if not superior overall survival [32–34]. Ongoing prospective randomised trials (e.g. ENCEPHALON [NCT03297788] and NRG CC009 [NCT04804644]) will further elucidate the role of SRS in SCLC patients with limited ($\leq$ 10) BMs.

HA approaches to preserve long-term neurocognition have also been investigated in the context of primary brain tumours, which also commonly require radiation treatment. Across different entities, results have been conflicting, however. In primary central nervous system lymphoma, HA is not feasible, whereas (peri-)hippocampal failures are uncommon in paediatric medulloblastoma and glioblastoma, where HA might limit neurocognitive toxicity while maintaining clinical outcomes in selected patients [35–38]. Retrospective dosimetric analyses have demonstrated the feasibility of clinical target volume reduction in glioblastoma, reducing radiation dose to the limbic circuit, with a low likelihood of altering the pattern of local recurrence after primary therapy [39,40]. Prospective trials are needed to validate these results.

The current systematic review is not without limitations. Firstly, not all included trials comprehensively described the hippocampus delineation protocol (e.g. which imaging modality or which sequence was used) or HA margin. Studies have established high interobserver variation in hippocampus delineation, without violating common dose constraints [41]. Furthermore, trials investigating the hippocampal failure rate were heterogeneous in terms of intervention (HA-PCI or HA-WBRT), radiation dose, HA margin, and patients included, which limited further statistical analysis (e.g. differences between left and right HA zone recurrence, as left hippocampal atrophy is thought to be more involved in neuropsychological deficits) [42]. Due to the inherent nature of the underlying diseases, most studies reporting on the hippocampal failure rate were hampered by loss to follow-up.

Conclusion

In this large and comprehensive review, the overall incidence of hippocampal and perihippocampal BMs was low, with a subsequent low and acceptable risk of undertreatment following HA-PCI or HA-WBRT. In patients without hippocampal involvement, regardless of the primary tumour, the hippocampus should be spared in order to preserve neurocognitive function and quality of life.

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CRediT authorship contribution statement

Shari Wiegreffe: Writing – review & editing, Methodology, Investigation, Data curation. **Gustavo Renato Sarria:** Writing – review & editing, Supervision, Methodology, Data curation. **Julian Philipp Layer:** Writing – review & editing, Methodology. **Egon Dejonckheere:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Younèss Nour:** Writing – review & editing. **Frederic Carsten Schmeel:** Writing – review & editing. **Frank Anton Giordano:** Writing – review & editing. **Leonard Christopher Schmeel:** Writing – review & editing. **Ilinca Popp:** Writing – review & editing. **Anca-Ligia Grosu:** Writing – review & editing. **Eleni Gkika:** Writing – review & editing, Supervision. **Cas Stefaan Dejonckheere:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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