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Review

Impact of Hippocampal Avoidance - Prophylactic Cranial Irradiation in Small Cell Lung Cancer Patients

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Abstract. *Background/Aim: Prophylactic cranial irradiation (PCI) is a well-established treatment of small cell lung cancer (SCLC) patients following response to initial chemoradiotherapy. The benefit of PCI does, however, come at the cost of cognitive decline. This has been attributed to radiation-induced toxicity at the hippocampus, a crucial anatomic area for cognition. Modern radiotherapy techniques allow dose reduction at the hippocampal region. In this review, the safety profile, effect on cognition, and changes on brain imaging modalities of hippocampal avoidance-PCI (HA-PCI) will be presented, aiming to identify a potential clinical rationale for SCLC patients. Materials and Methods: A systematic review of the literature was performed in Pubmed, Cochrane library databases and ClinicalTrials.gov with no past date limitations until 07/01/2022. Principles as outlined in the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement were followed. Results: Eight studies published from 2015 to 2021 were included. Conclusion: HA-PCI is safe, yet its effect on neurocognition and imaging remains unclear, as studies have shown contradictory results.*

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Prophylactic cranial irradiation (PCI) plays a crucial role in the management of patients with small cell lung cancer as it reduces the incidence of brain metastases (BM) and to a lesser improves overall survival (OS) (1-7). PCI is administered in patients with limited disease - small cell lung cancer (LD-SCLC) who show partial or complete response to chemotherapy and thoracic RT. Patients with extensive disease are also candidates for PCI, however, data from randomised trials are conflicting and therefore, PCI is usually reserved for those with good performance status and intact neurological function (3-7).

However, this benefit does not come without a cost. Neurocognitive decline has been attributed to brain radiation and attempts have been made to minimise it in various ways, that is, by administering neuroprotective agents such as memantine or by minimising radiation dose of the hippocampal area (8-10).

In the era of modern radiotherapy techniques, intensity modulated radiotherapy (IMRT), volumetric arc therapy (VMAT), and image guided radiotherapy (IGRT) have offered the opportunity to irradiate the brain parenchyma and at the same time spare the hippocampus, an anatomic area that is considered critical for long-term episodic memory (11, 12). This anatomic avoidance strategy was initially studied in patients with brain metastases and was shown to be beneficial by phase II and III trials (13, 14). Evidence is also evolving and will be presented in this review for small cell lung cancer patients, candidates for PCI. The question whether hippocampal sparing PCI (HA-PCI) lowers the neurocognitive sequelae of radiation therapy without compromising the oncological benefit at the

avoidance area is yet to be addressed. Moreover, should this benefit exist, issues related to feasibility, access to treatment, and cost effectiveness remain to be studied.

Materials and Methods

Search methods: A systematic review of the literature was performed in Pubmed, Cochrane library databases and ClinicalTrials.gov with no past date limitations until 07/01/2022. Our report followed the principles as outlined in the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (Figure 1) (15).

Search terms included: Prophylactic cranial irradiation, hippocampal avoidance, hippocampal sparing, hippocampus, hippocampal avoidance prophylactic cranial irradiation, small cell lung cancer. We considered further references from the articles that were included.

Types of studies: Studies in English language from peer-reviewed journals.

Types of participants: SCLC patients.

Types of intervention: HA-PCI vs. PCI.

Types of outcomes: Safety profile, neurocognitive decline, effects on imaging modalities: magnetic resonance imaging (MRI) and positron emission tomography (PET), survival, and quality of life.

Results

Number and type of studies: Eight studies published from 2015 to 2021 have been included: Two are phase III trials, one phase II trial, one prospective trial, three retrospective trials, and one secondary analysis of a prospective trial.

Clinical studies: Four studies assessed the neurocognitive effect with two of them directly comparing HA-PCI *vs*. standard PCI. Two studies focused on the safety profile and risk of developing metastases at the hippocampal area. Anatomic and functional imaging studies: Three studies focused on the changes observed in imaging modalities (MRI and PET) following HA-PCI. Ongoing studies: a phase II and a phase III trial are still ongoing, results are pending. All studies are included below (Table I).

Safety profile and neurocognition effect of HA-PCI: In theory, reduced radiation dose at the hippocampi increases the risk of recurrence within this area. The safety profile of HA-PCI has been evaluated by two studies, whereas the effect on neurocognition has been assessed by three studies:

Kundapur *et al*. retrospectively reviewed the incidence of brain metastases (BM) at the hippocampal area of SCLC patients, either at presentation or after whole brain radiation therapy (WBRT), both prophylactic and therapeutic (16). The aim was to assess the risk of hippocampal metastases (HM) and to evaluate whether WBRT has any effect on the incidence of HM. They reviewed 70 patients, 59 of them had BM at presentation, with 3 of them (5%) presenting with *de novo* HM, and 20 had BM progression following WBRT, with 1 of them (5%) experiencing HM. The authors did not find any clinical factors correlating with HM incidence.

Redmond *et al*. prospectively evaluated the effect of HA-PCI in LD-SCLC patients on neurocognitive status, brain recurrence patterns, overall survival (OS) and progression free-survival (PFS) (17). Total dose was 25 Gy in 10 fractions. Dosimetry requirements were as below: mean hippocampus dose below 8 Gy and for ≥90% of the brain to receive 90% of the prescribed dose. Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R) at baseline and at 6 months following radiotherapy was used to assess neurocognitive decline. Twenty patients underwent HA-PCI, with two patients (10%) developing a metastasis in the underdosed brain region. Both patients recurred also in fully radiated brain regions. The decline of the HVLT-R score was 0.38 *vs*. 1 of standard PCI as defined by RTOG 0212 (p=0.15, power: 18% for 1-sided 0.05-level test with SD 3.6) suggesting a potential benefit in neurocognition.

Dios *et al*. prospectively assessed the cognitive benefit of HA-PCI through a phase III PREMER trial that randomised 118 patients undergoing PCI. Sixty received PCI and 58 received HA-PCI (18, 19). IMRT/VMAT techniques were applied to a total dose of 25 Gy in 10 fractions. The dose at the HA was minimised to a D100 of 8.4 Gy and a maximum dose of 14.5 Gy. The investigators found a statistically significant difference in the decline of the free delayed recall in PCI *vs*. HA-PCI as assessed by free and cued selective reminding test (FCSRT) at 3 months (21.7 *vs*. 5.1%; p=0.01), at 6 months (32.6 *vs*. 7.3%; p=0.008), at 12 months (18.5 *vs*. 3.8%, p=0.09), and at 24 months (14.2% *vs*. 47.6%).

The most recent study addressing the neurocognitive effect of HA-PCI, published in 2021 by Belderbos *et al*., is a phase III trial that randomised 168 patients with either limited or extensive SCLC and no disease progression following chemoradiotherapy, to receive HA-PCI or non-HA-PCI, 25 Gy in 10 fractions (20). With a median follow up of 24.8 months, the authors did not find a significant difference in failure on HVLT-R Total recall at 4 months between the two groups (29% in the non-HA-PCI *vs*. 28% in the HA-PCI, p=1.000). Similarly, no significant changes were observed on all the other neurocognitive assessment tools. Brain metastasis incidence at 2 years and OS were similar between the two groups.

Finally, Vees *et al*. studied the impact of HA-PCI in patients with LD-SCLC administered concurrently with the second cycle of chemotherapy and thoracic RT as part of SAKK 15/12, a multicenter phase II trial (21). The investigators assessed neurocognitive function (NCF), brain metastases-free survival (BMFS) and OS. Among 38 patients with evaluable NCF tests, 34.2% and 48.5% showed no NCF decline at 6 and 12 months, respectively. BMFS and OS was 84.2% and 87.7% at 12

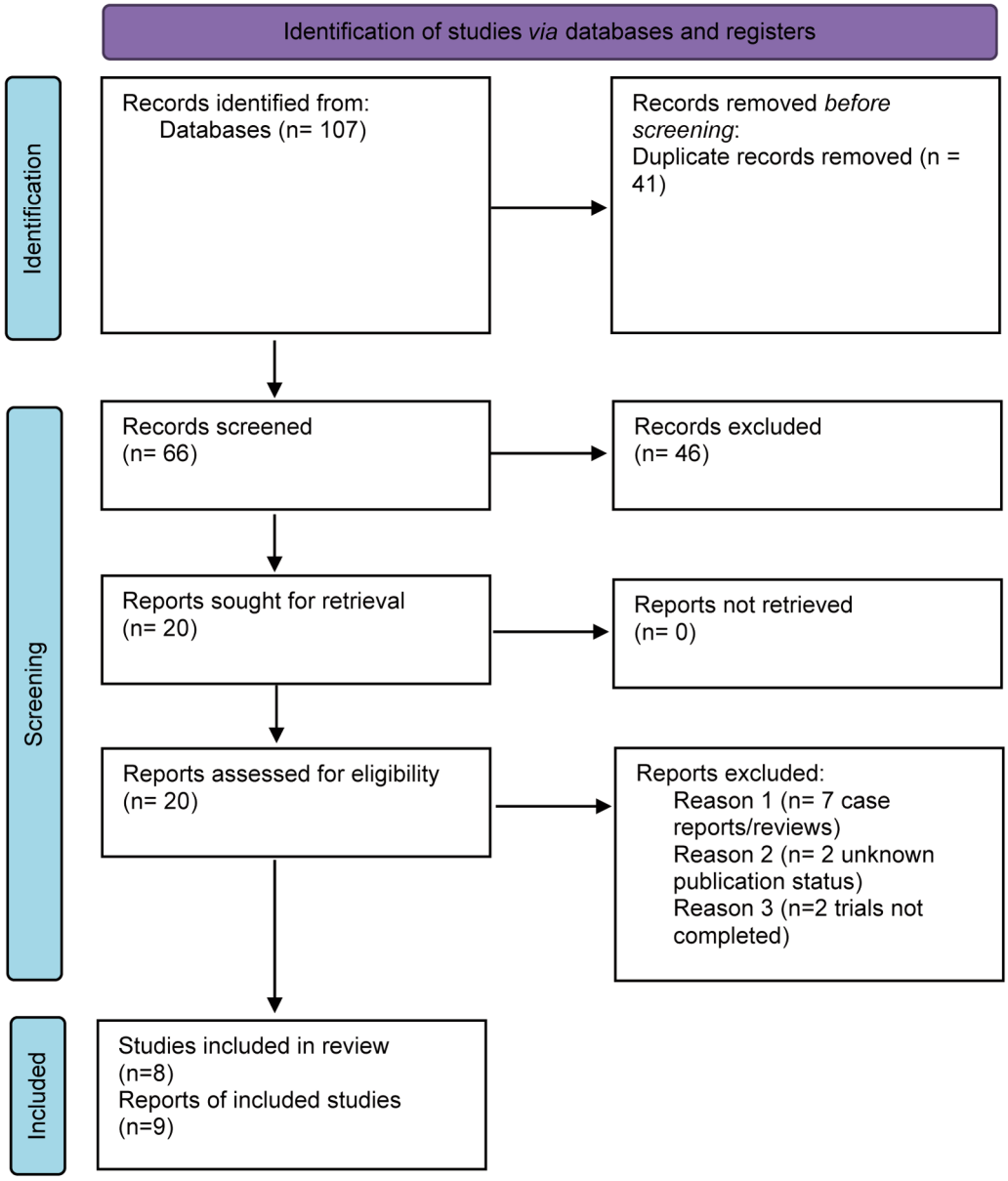

Figure 1. *Methodology according to PRISMA 2020 guidelines: PRISMA 2020 flow diagram (15).*

months, respectively. The commonest grade ≥3 acute events were related to blood cell dyscrasias [anaemia (21.4%), febrile neutropenia (19.1%)] and fatigue (14.3%). The authors concluded that the percentage of patients receiving early HA-PCI with no NCF decline was similar to that reported in patients receiving late PCI without HA suggesting that early HA-PCI in this particular group of patients is a possible option.

Imaging studies: El Chammah *et al*. studied the impact of HA-PCI *vs*. PCI in SCLC patients on ^{18}F-fluoro-deoxy-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT). The authors retrospectively assessed SCLC patients, candidates for PCI (22). Half of them received HA-PCI. Timing of ^{18}F-FDG PET/CT was from up to 144.5 days before and up to 383 days after PCI. Using SUVmean of brainstem as reference for SUV Ratio (SUVR) for various anatomic regions of the brain, including the hippocampi, SUVR was compared before and after PCI. The investigators found a significant decrease in hippocampi metabolism for those who received standard PCI (p=0.033) *vs*. HA-PCI (p=0.783) suggesting that in the area of interest, metabolic activity is maintained with HA-PCI.

Table I. *Studies addressing the impact of HA-PCI.*

Study	Number of patients	Type of study	Objective/Primary endpoint	Objective/Primary endpoint achieved	Neurocognitive test	Follow up assessment (months)
Kundapur *et al*. (16)	70	Retrospective	Safety profile	Yes	N/A	N/A
Redmond *et al*. (17)	20	Prospective	Neurocognitive benefit	Yes	HVLT-R	6
Dios *et al*. (19)	118	Phase III RCT	Neurocognitive benefit	Yes	FCSRT	3, 6, 12, 24
Belderbos *et al*. (20)	168	Phase III RCT	Neurocognitive benefit	No	HVLT – R	4
Chammah *et al*. (22)	22	Retrospective	Effect on metabolic FDG activity (PET)	Yes	N/A	up to 13
Mayinger *et al*. (23)	18	Retrospective	Effect on white matter changes (MRI)	No	N/A	7
Gui *et al*. (24)	22	Secondary analysis of prospective trial	Effect on brain volume (MRI)/neurocognition	No	HVLT-R	6
Vees *et al*. (21)	38	Phase II	Neurocognitive effect of concurrent chemo/HA-PCI	Yes	HVLT – R	1, 6, 12

RCT: Randomised control trial; FDG: Fluorodeoxyglucose; PET: positron emission tomography; MRI: magnetic resonance imaging; HA-PCI: hippocampal avoidance – prophylactic cranial irradiation; HVLT-R: Hopkins verbal learning test-revised; FCSRT: free and cued selective reminding test; N/A: not applicable.

Mayinger *et al*. retrospectively compared brain MRI scans between SCLC patients who received HA-PCI (n=9) and PCI without HA (non-HA-PCI) (n=9) (23). The authors assessed the severity of white matter changes, indicative of worsening leukoencephalopathy according to Fazekas classification scale, before and after radiotherapy to the brain. Pre-treatment and post-treatment scans were compared. A significant increase in Fazekas score was demonstrated in the HA-PCI group, whilst in the non-HA-PCI group no difference was observed. In terms of dosimetry parameters, median Dmax was higher in the HA-PCI group *vs*. non-HA-PCI group, as were V26 Gy values, respectively.

Finally, Gui *et al*. performed a secondary analysis, based on another study, in regard to whole brain volume loss and its possible association with neurocognitive decline following HA-PCI for limited SCLC (24). The investigators found that following HA-PCI, a significant decrease in whole brain volume was observed, reaching a maximum at 18 months. This reduction was associated with verbal memory decline 6 months after HA-PCI, as measured by the Hopkins verbal learning test-revised (HVLT-R). This study was the first to correlate brain volume loss and neurocognitive decline.

Discussion

It appears that HA-PCI is a safe treatment option in terms of BM recurrence risk in the underdosed region. The initial evidence regarding safety was not robust and results from small, non-comparative studies were conflicting. Redmond *et al*. concluded that there is a risk of metastasis in the avoidance area, as 2 out of 20 patients developed secondaries in this area. It should be noted though, that both patients recurred also in fully radiated regions of the brain and no neurologic death was attributed to progression of these hippocampal metastases (HM) (17). On the other hand, Kundapur *et al*. concluded that the risk of SCLC patients developing *de novo* HM is small, with the risk of failure following WBRT at the HA being smaller, suggesting that the risk of relapse probably remains small even after HA-WBRT and therefore, despite the small number of patients, the results are in favour of an initial safety profile for clinical trials to be planned (16). The issue of safety was enlightened further, and more robust evidence came from Belderbos *et al*. phase III trial that showed similar BM incidence and OS compared to standard PCI, indicating that HA-PCI is a safe treatment option (20).

The benefit of HA-PCI on neurocognition is not clear as results from two phase III trials are conflicting (18-20). Although PREMER trial did show a statistically significant difference in decline of FCSRT between the two arms favouring HA-PCI, which was maintained even at 24 months, this was not confirmed by Belberdos *et al*. HA-PCI did not appear to have a negative effect on neurocognition compared to standard PCI as shown by all the comparative studies.

Results from imaging studies are mixed and therefore, no clear conclusion can be reached in favour or against HA-PCI. Although HA-PCI resulted in the preservation of metabolic FDG activity of the hippocampi and this could theoretically explain a positive effect on neurocognition, studies addressing MRI changes, concluded that it led to a reduction in whole brain volume along with worsening neurocognition, as shown from a secondary analysis of another trial for patients who underwent HA-PCI (24). This was not, however, compared to standard PCI. Moreover, a statistically significant increase in Fazekas score was observed from a retrospective analysis following HA-PCI

vs. standard PCI, indicating worsening leukoencephalopathy (23). These results could be partly explained from discrepancies in dosimetric parameters between the two techniques. Traditionally, standard PCI is a 3D lateral opposed field technique, whereas HA-PCI is an IMRT/VMAT inverse planning technique. In HA-PCI, reduction of radiation to the hippocampi comes at the cost of increased maximum radiation dose to other areas of the brain, something that could potentially have a negative effect on neurocognition. Similar dosimetric discrepancies have been reported in previous studies assessing HA-WBRT with therapeutic intent. Possible correlation between these parameters and their effect on white matter changes needs further evaluation (23). NCT02906384 is an ongoing randomised phase II study observing functional MRI changes and memory preservation following HA-PCI that will shed more light and results are yet to be published.

In conclusion, apart from the safety profile of HA-PCI, it is difficult to reach a conclusion on the effect it has on the brain, both on imaging and more importantly on neurocognition. This is due to multiple reasons related to the aforementioned studies. First of all, various cognitive assessment tools were used and therefore, direct comparison of the studies was not possible. Similarly, even in studies with the same cognitive assessment tests (HVLT-R delayed recall), definition of failure, timing of assessment, and follow up differed. In addition, the population of SCLC patients is very inhomogeneous, especially in regard to baseline cognition status, and this poses a challenge when it comes to trial design and interpretation of results. Finally, issues related to contouring of targets and organs at risks as well as treatment planning need to be addressed so as to design future trials with common contouring and planning criteria that could facilitate comparison of larger patient population. Towards this direction, NRG Oncology contouring atlas for hippocampal sparing for the RTOG 0933 trial could be used as a reference. More robust criteria in terms of conformity, dose constraints, and dose distribution would also serve the purpose.

At present, NRG CC003 (NCT02635009, V. Gondi) is the only ongoing phase II/III trial addressing the issue of HA-PCI. After completing accrual of phase IIR part enrolling 182 patients and evaluating the results, the trial is now recruiting patients to its phase III component.

Hippocampal avoidance - prophylactic cranial irradiation appears to be a safe option for the group of SCLC patients, whose management includes prophylactic irradiation of the brain. Hopes regarding preservation of cognition mostly lie on the ongoing randomised trials. Should these trials provide with stronger evidence of its potential benefit, this may lead to significant change of current practice in the future.

Conflicts of Interest

The Authors have no conflicts of interests to declare in relation to this study.

Authors' Contributions

Conceptualisation: Emmanouil Maragkoudakis, Vasileios Kouloulias, methodology: Emmanouil Maragkoudakis, Vasileios Kouloulias, investigation: Emmanouil Maragkoudakis, Maria Grenzelia, writing-original draft preparation: Emmanouil Maragkoudakis, Maria Grenzelia, Andromachi Kougioumtzopoulou, writing-review and editing: Emmanouil Maragkoudakis, Vasileios Kouloulias, Anna Zygogianni, George Ramfidis, Andrianni Charpidou, supervision: Vasileios Kouloulias, Anna Zygogianni, George Ramfidis, Andrianni Charpidou. All Authors have read and agreed to the published version of the manuscript.

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