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Review Article

Hippocampal Avoidance Prophylactic Cranial Irradiation in Small Cell Lung Cancer – A Review of Trials

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Abstract

Small Cell Lung Cancer (SCLC) is a highly aggressive malignancy with a propensity for brain metastases, posing significant challenges in its management. Prophylactic cranial irradiation (PCI) has demonstrated efficacy in reducing brain metastases incidence and improving survival, particularly in limited-stage SCLC (LS-SCLC). However, its role in extensive-stage SCLC (ES-SCLC) remains uncertain, raising concerns about neurocognitive decline. Strategies to mitigate cognitive toxicity, including memantine administration, offer hope for cognitive preservation. Modern radiotherapy techniques aim to minimize radiation exposure to critical brain structures, such as the hippocampus, while maintaining treatment effectiveness. Hippocampal Avoidance PCI (HA-PCI) has emerged as a method to reduce hippocampal radiation exposure. While initial studies indicate its safety and potential benefits, further investigation is required to assess its impact on cognitive function and long-term outcomes. Varying guidelines emphasize the necessity of personalized treatment approaches tailored to patient characteristics and disease stage, particularly in LS-SCLC. This review aims to comprehensively examine the role of Prophylactic Cranial Irradiation in managing SCLC, emphasizing its efficacy, dosing considerations, and the emerging technique of Hippocampal Avoidance PCI. It emphasizes the need for further research to refine treatment strategies and improve outcomes for SCLC patients.

Introduction

Small Cell Lung Cancer is a high-grade neuroendocrine carcinoma that predominantly arises in current or former smokers, as well as in individuals with pulmonary and cardiovascular comorbidities (1). It stands as one of the most aggressive forms of thoracic malignancies, constituting approximately 15 percent of all lung cancer cases. Its defining characteristic lies in its notable propensity for recurrence and elevated mortality rates, even when optimal treatment strategies are employed (2). Small Cell Lung Cancer is the leading cause of cancer death among men and the second leading cause of cancer death among women worldwide (3). Median survival for patients with limited stage disease is 18–24 months, while for those with extensive stage disease, median survival is approximately 12 months (4).

A substantial proportion of SCLC patients manifest metastatic disease upon initial diagnosis, with an approximate incidence of brain metastases standing at ten percent. Furthermore, over the course of two years, the cumulative occurrence of brain metastases escalates to over 50%, even with optimal treatment (5). Those with brain metastases (BM) have an unpromising prognosis, leading to an impaired quality of life. Prophylactic cranial irradiation (PCI) has a well-established place in therapy for patients with limited stage SCLC —who exhibit a partial or complete response to chemotherapy and thoracic radiation therapy (RT). While patients with extensive stage SCLC may also be considered for PCI, its use remains uncertain due to conflicting data from randomized trials. Therefore, PCI is usually reserved for those with good performance status and intact neurological function (6). The data from randomized trials document that PCI reduces brain metastases rate from approximately 60% to 30% and increases 3-year overall survival (OS) by approximately 5%. However, it comes with the drawback of potential side effects, with long-term neurocognitive decline being the most concerning among them (7).

Radiation-induced effects are categorized into early, late-early, and late stages. In the early phase, symptoms appear shortly after irradiation, resulting from changes in the blood-brain barrier, leading to vasogenic edema and white matter damage. Inflammation contributes to the loss of radiosensitive stem cells during this phase. Common early symptoms include sleepiness, confusion, short-term memory issues, attention deficits and fatigue. These symptoms are reversible, and though official guidelines are lacking, steroids are often used to prevent and treat brain edema.

Delayed-early effects, occurring weeks to six months after exposure, are initially dose- dependent and later become dose-independent. Neurapraxia, lethargic syndrome, mental confusion, impaired cognitive function, and fatigue are the most prevalent symptoms during this stage. These effects peak at the end of radiotherapy, with subsequent improvement within 6–8 weeks and resolution in an additional 4-6 weeks due to transient demyelination. Late effects, observed 6–12 months after exposure, result from chronic neuroinflammation, persistent demyelination, reduced neurogenesis due to glial differentiation shift, microvascular damage causing ischemia, and a hyperglutamatergic toxic state. Late symptoms primarily affect cognitive functions, particularly attention, memory, and executive functions. Less common but disabling issues include ataxic gait, urinary incontinence, apathy, and pyramidal and extrapyramidal syndromes (8).

PCI

The current standard of care for LS-SCLC typically involves combination chemotherapy (using both a platinum agent and a topoisomerase inhibitor) along with concurrent thoracic radiation, followed by PCI. The recommendation for PCI is based on the results of a meta-analysis in patients with limited-stage disease, which demonstrated a 5.4% increase in overall survival with the addition of PCI to chemo-radiation therapy for the primary lung tumor (9). For ES-SCLC, which often presents as an extensive disease with distant metastases and significant intrathoracic involvement, the primary treatment approach is systemic chemotherapy with platinum-based combinations. Radiation may provide added benefits for patients showing an initial response to systemic treatment or those with residual disease after the completion of systemic treatment. PCI may also offer advantages by reducing the incidence of symptomatic brain metastases, particularly in patients who respond well to initial treatment (10). Notable differences can be observed among recent guidelines from ESTRO, ASTRO, and NCCN concerning the use of PCI in early LS SCLC.

ESTRO advises PCI and thoracic radiotherapy for resected SCLC with positive lymph nodes. However, for elderly patients with resected node-negative SCLC, most ESTRO experts do not recommend thoracic radiotherapy or PCI.

ASTRO guidelines conditionally do not recommend PCI for patients with stage I SCLC. Instead, they suggest using brain MRI with contrast for surveillance as an alternative. NCCN Guidelines state that the benefit of PCI is uncertain in patients who have undergone complete resection for pathologic stage I-IIA (T1-2N0M0) SCLC, recommending PCI or brain surveillance for N0 patients with a lower metastases risk compared to advanced LS SCLC patients (11). The recommendation summary of the guidelines is shown in table 1.

ASTRO	For patients with stage I SCLC, PCI is conditionally not recommended. Instead, an alternative approach involves opting for brain MRI with contrast as part of surveillance.
	In patients aged under 70 with good performance status (ECOG 0-2) and a positive response to thoracic chemoradiation in stage II-III LS-SCLC, PCI is recommended.
	LS-SCLC patients with limited performance status, advanced age, or notable comorbidities are encouraged to engage in shared decision-making for PCI, taking

	into account individual patient and disease characteristics.
ESTRO	Prophylactic cranial irradiation and thoracic radiotherapy is recommended for patients with resected SCLC and positive lymph nodes. In contrast, for elderly patients with resected node-negative SCLC thoracic radiotherapy or PCI is not the optimal choice.
NCCN	The benefit of PCI is uncertain in patients who have undergone complete resection for pathologic stage I-IIA (T1-2N0M0) SCLC. PCI or brain surveillance should be considered for N0.

Table 1 describes the recommendation guidelines for PCI from various international organizations

The Prophylactic Cranial Irradiation Overview Collaborative Group conducted a meta- analysis involving seven trials comparing PCI with no PCI in LS-SCLC. Their findings demonstrated a significant reduction in brain metastases incidence, a 26% decrease in the three-year cumulative brain metastases incidence and a 5.4% increase in the three-year survival rate for patients who received PCI. Another comprehensive review that examined a larger number of trials supported the role of PCI in LS-SCLC, though it underscored the lack of toxicity data. A recent systematic review and meta-analysis reinforced PCI's efficacy in reducing brain metastases but showed heterogeneous outcomes in overall survival. In ES-SCLC, various studies assessed PCI, including a large retrospective analysis indicating improved median overall survival compared to no PCI. Similar findings were reported in another analysis of ES-SCLC patients. To address the lack of prospective data in ES-SCLC, both a Phase III EORTC trial and a Japanese Phase III study were conducted. Interestingly, both studies found a decrease in the incidence of symptomatic brain metastases in patients initially responding to systemic chemotherapy with well-tolerated treatment. However, overall survival benefits remained uncertain, with the EORTC trial showing increased survival for PCI recipients and the Japanese study indicating no survival advantage and possibly poorer outcomes among PCI-treated patients. The accumulated evidence for both LS- SCLC and ES-SCLC strongly supports PCI's role in reducing symptomatic brain metastases. This benefit is associated with increased survival in limited-stage disease but remains uncertain for extensive-stage disease. Consequently, current practice involves offering PCI to all LS-SCLC patients after completing definitive chemo-radiation for thoracic disease, with the consideration of PCI for ES-SCLC patients who respond well to initial treatment (12).

In the Japanese Phase III trial, patients with extensive-disease Small Cell Lung Cancer, who showed positive responses to platinum-based doublet chemotherapy and had no brain metastases evident on MRI were subjected to random assignment (1:1). They were either assigned to receive PCI with a regimen of 25 Gy delivered in ten daily fractions of 2.5 Gy, or they were placed in the observation group. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) at three time points: before randomization and at 12 and 24 months post-randomization. The MMSE comprises 11 questions assessing five cognitive domains, including orientation, registration, attention and calculation, recall, and language. Physicians conducted the questionnaire in person. Notable grade 3 or worse adverse events at this juncture included anorexia (6% of 106 in the PCI group vs. 2% of 111 in the observation group), malaise (3% vs. <1%), and muscle weakness in a lower limb (<1% vs. 5%). No treatment-related deaths occurred in either group.

In this analysis, MMSE compliance was observed in 212 patients (95%) at baseline (107 in the PCI group vs. 105 in the observation group), 83 patients (37%) at 12 months (37 vs. 46), and 13 patients (6%) at 24 months (5 vs. 8). MMSE scores showed no significant differences between the two groups at baseline, 12 months, or 24 months based on the Wilcoxon test (13).

The potential benefits of high radiation doses, as implied by dose-response characteristics, must be balanced against treatment toxicity. While higher doses may improve disease control, they also pose an increased risk of neurotoxicity. In the RTOG 0212 trial, a total of 720 patients who had LS-SCLC and were in complete remission following chemotherapy and thoracic radiotherapy were enrolled. These patients were randomly assigned to two groups: one receiving a total dose of 25 Gy delivered in 10 daily fractions and the other receiving 36 Gy, which was administered using either conventional fractionation (18 daily fractions of 2 Gy) or accelerated fractionation (24 fractions over 16 days with two daily sessions of 1.5 Gy). No significant difference in the 2-year brain metastasis rates was observed between the standard and higher dose PCI groups, with rates of 29% and 23%, respectively (P = 0.18). The 2-year overall survival was 42% in the standard-dose group and 37% in the higher dose group (P= 0.05). The most common acute toxic events were fatigue (30% in the standard-dose group and 34% in the higher dose group), headache (24% and 28%), and nausea or vomiting (23% and 28%). Although there was a non-significant decrease in the overall incidence of brain metastases after the use of a higher PCI dose, this was counteracted by a significant increase in mortality. In an update, the authors noted a significant rise in chronic neurotoxicity in the 36-Gy cohort (P = 0.02). As a result, a fractionation pattern of 25 Gy in 10 fractions has been widely recommended and adopted as the standard dose for SCLC (14).

Radiation-induced Cognitive Decline

Radiation causes glutamate-induced excitatory stress. Nevertheless, an excess of glutamate disrupts the balance between N-methyl-D-aspartate (NMDA) and Gamma- aminobutyric acid (GABA) receptor activation, resulting in abnormal intracellular calcium levels and triggering apoptotic cell death.

The mechanisms of neurocognitive decline include vasculopathy, oligodendrocyte depletion, central nervous system inflammation and progenitor cell niche degradation in the hippocampus, a crucial structure for memory and learning. PCI has its most significant impact on the functioning of the hippocampus. In particular, radiation damages hippocampal synaptic structures and prefrontal-hippocampal cortex connections, critical for the construction of memory contents and providers of neural progenitors. Even though neurons are conventionally perceived as being resistant to radiation owing to their post-mitotic state, scientific studies have revealed that radiation-induced synaptic injury manifests as an early event. The primary targets of radiation are neurons, which are classified as late-responding cells with a low α/β ratio, as well as stromal and vascular cells.

Cognition requires the integration of sensory input, memory, visuospatial processing, concentration, attention, thought processes, behavioral patterns, personality traits, and emotional well-being. A disruption in any of these domains can have a profound impact on an individual's quality of life and survival. Cognitive Decline (CD) typically manifests with primary symptoms like memory impairment, difficulties in planning daily activities, and behavioral changes. Radiation-induced CD is diagnosed in approximately 90% of irradiated patients and has intermediate severity in most subjects. However, CD may progress to dementia in approximately 2–5% of cases, usually 4–6 months after radiation, with the most common fractionation protocols (15,16).

Reducing neurocognitive toxicity

The use of drugs to reduce neurocognitive toxicity in PCI and whole brain radiation therapy (WBRT) is an area of interest. One of these drugs is memantine, which is an antiglutamatergic drug.

In the RTOG 0614 trial, 554 patients were involved with BM from solid tumors. They were randomized to receive WBRT + memantine or WBRT + placebo. In summary, memantine improved cognitive function over time, delaying time to cognitive decline and reducing the rate of decline in memory, executive function, and processing speed in patients receiving WBRT (10). The National Cancer Care Network has recognized

memantine's potential use for patients receiving WBRT and PCI, but it's not currently recommended in European guidelines (17).

While the dosage of PCI is marginally lower than that of WBRT (25 Gy compared to 30 Gy over 10 fractions), it is reasonable to assume that memantine can provide brain protection against neurotoxic effects in the context of PCI, as it does in WBRT (18). A variety of approaches have been investigated in efforts to ameliorate the neuro-cognitive dysfunction linked to PCI. Alongside the administration of pharmaceutical agents, like memantine mentioned earlier, modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) have been employed to deliver standard radiation doses to the entire brain while minimizing radiation exposure to the hippocampi (19).

HA-PCI

The implementation of intensity-modulated radiation therapy and volumetric modulated arc therapy has made it possible to reduce the radiation dose to the hippocampus during PCI. In a randomized study done by Rodriguez et al, 150 patients were enrolled. Those patients with hippocampal avoidance PCI experienced less decline in delayed free recall from baseline to three months compared with those receiving standard PCI. The incidence of brain metastases, overall survival and quality of life were similar in both the groups. However, avoiding the hippocampus carries the potential risk of diminishing the effectiveness of PCI due to an increased risk of metastatic disease within the hippocampal conformal avoidance region (20).

In a multicenter, randomized phase 3 trial (NCT01780675), SCLC patients received either standard PCI or HA-PCI with a total dose of 25 Gy in 10 fractions. Eligible patients had histologic- or cytologic-proven SCLC, stages I to III (LS-SCLC) or stage IV (ES-SCLC), without clinical or radiologic brain metastases on MRI, and no disease progression post-chemo-radiotherapy in the early stages (I to III) or following chemotherapy as a monotherapy in stage IV. From April 2013 to March 2018, 168 patients participated, with a median follow-up of 26.6 months. In this trial, high-resolution 3D T1-weighted MRIs (1.2-mm slice thickness) were performed at baseline, 4 months, and 12 months to examine hippocampi and track hippocampal atrophy. Pre- and post-gadolinium T1 scans detected brain metastases.

In the HA-PCI group, the objective was to limit the mean dose in the left and right hippocampi to ≤8.5 Gy (biological dose 6.1 Gy for a/b = 2 Gy), with additional constraints on hippocampus doses, PTV doses, and

volume criteria. Neuropsychological assessments, including Hopkins Verbal Learning Test – Revised (HVLT-R), Trail Making Test (TMT), the Controlled Oral Word Association Test (COWA), Wechsler tests, and Lafayette's Grooved Pegboard, were conducted at baseline and 4, 8, 12, 18, and 24 months post-PCI. A total of 168 patients were randomized to ensure 100 assessable patients, with an interim analysis and stopping rules based on O'Brien-Fleming spending function. The primary endpoint, a decline in HVLT-R total recall at 4 months post-radiotherapy, was analyzed based on assigned treatment arms. In addition to primary endpoint analyses, cognitive test profiles over time were evaluated using linear mixed models.

At 4 months, no significant difference in total recall decline was found between PCI and HA- PCI arms (29% PCI vs. 28% HA-PCI, p = 1.000). Performance on other cognitive tests and overall survival did not significantly differ (p = 0.43). There was a decline observed in all the subtests of the HVLT-R. By the 24-month mark, the HVLT-R total score had nearly returned to the baseline level. Scores on the TMT A demonstrated slight improvement over time in the PCI arm, while they decreased in the HA-PCI arm. The interaction at the 4-month point approached statistical significance (p = 0.05). TMT B scores declined in both groups, with the HA-PCI arm showing a somewhat stronger decline at 4 months compared to the PCI arm (p = 0.07). COWA scores initially dropped in both groups but later showed improvement. Digit span forward scores improved over time in the PCI arm, while they fluctuated during follow-up in the HA-PCI arm. Digit span backward scores also showed slight improvement over time in both groups. However, digit symbol scores declined over time in both arms, and Pegboard test scores (both dominant and nondominant) exhibited declines over time in both groups.

While BM in the hippocampus are typically rare, a trial identified five patients with multiple BM in the HA-PCI group, including BM within the underdosed region. This aligns with the initial safety analysis, which estimated an 8.6% risk. BM were detected within the first 24 months in 20% of those assigned to PCI and 16% of those in the HA-PCI group. The trial showed no significant difference in cognitive decline, disparities in BM or overall survival, regardless of disease stage. However, the trial did confirm the safety of HA. Factors explaining these findings include the high biological dose of 6 Gy to the hippocampus without neuroprotective agents and potential neuroprogenitor cell damage. Additionally, other cognitive-supporting brain regions like the amygdala were not spared. Although the quality of radiotherapy preparation and HA-PCI execution was rigorously ensured, there was no central quality control for hippocampus delineation. While there were interobserver variations in specific hippocampal regions, the mean dose constraint for the hippocampi would still have been met in all cases due to the generous 5 mm

margin used in the trial. Given that the hippocampus is more parallel than a serial organ, achieving the mean hippocampal dose constraint may be more crucial than addressing small volumes (<1% of the PTV) with overdosing (21).

In a 2017 cohort of 20 limited-stage SCLC patients who received HA-PCI in a study by Redmond et al., participants underwent a comprehensive array of standardized cognitive assessments, just like in the RTOG 0212 study. These included the HVLT-R, which evaluated immediate and delayed auditory verbal memory; COWAT for measuring processing speed; and TMT parts A and B to assess executive functioning. These involved estimating pre-morbid IQ using the Hopkins Adult Reading Test (HART), evaluating overall cognitive functioning through the MMSE, examining visuospatial learning and memory with the Brief Visuospatial Memory Test- Revised (BVMT-R), assessing auditory divided attention using the Brief Test of Attention (BTA), measuring processing speed via the Perceptual Comparison Test (PCT), and evaluating letter- and category-cued verbal fluency with the Calibrated Ideational Fluency Assessment (CIFA). Furthermore, the participants' quality of life (QOL) was assessed through the EORTC QOL C30 and Brain Cancer Module 20. To assess intracranial outcomes, a series of brain MRIs were conducted at various time points: at the beginning (baseline) and then at 6, 12, 18, and 24 months after the completion of radiotherapy. During these scans, the development of brain metastases and peri- hippocampal metastases was documented. For individuals who experienced the occurrence of brain metastases, a T1 post-gadolinium MRI scan was obtained at the time of the intracranial failure and was manually integrated into the treatment planning system to gather dosimetric data.

The determination of brain failures was based on specific criteria, which included instances where metastases were found within: 1) the hippocampal dentate gyrus; 2) the delineated hippocampal avoidance region; 3) areas of the brain that received insufficient radiation dosage; or 4) regions of the brain that received full radiation treatment. Performance on tests showed no significant decline between baseline and 6 or 12 months for any patients. MRI revealed asymptomatic brain metastases at a cumulative rate of 20% with no concurrent extra-cranial progression. Two patients developed metastases in the underdosed region, one of which involved the avoidance region. Both patients also had additional metastases in fully treated brain regions. Regarding neurotoxicity, one treatment-related grade 3 event was noted (fatigue), and there were no treatment-associated adverse events classified as grade 4 or 5. Grade 1 and 2 toxicities were reported in 20 patients, with 18 experiencing fatigue and 14 reporting alopecia. (22).

In a study conducted in Australia in 2021, a total of 17 consecutive patients with a mean age of 70 years

received HA-PCI between May 2016 and June 2020 after completing their initial chemotherapy. As a result, no patient experienced an isolated Hippocampal Avoidance Zone (HAZ) relapse alone; three out of the 17 patients had multifocal relapses that included the hippocampal avoidance zone. Baseline and periodic assessments of cognitive disruption and concentration issues were conducted for all patients in accordance with the Common Toxicity Criteria Adverse Events (CTCAE) v4.0. Qualitative insights were extracted from electronic medical records to complement this dataset.

Among the 17 patients, 14 (82%) had recorded evaluations for cognitive disruptions based on CTCAE, averaging two assessments per patient. These assessments yielded scores of 1 (indicating mild cognitive impairment without requiring specialized services) for four patients and 0 (indicating no cognitive disruptions) for ten patients at various time points. Supplementary qualitative data from the oncology electronic medical records was also retrieved in addition to the CTCAE's cognitive and concentration domains: One patient encountered temporary word- finding difficulties during HA-PCI treatment, attributed to lethargy, which resolved without subsequent cognitive disruptions.

Another patient, who experienced intracranial and HAZ relapse along with four rounds of salvage therapy, displayed confusion within one month of death due to intracranial progression. A patient without intracranial progression encountered multifactorial delirium on two occasions starting six months after the initial extracranial progression, attributed to hypercalcemia, constipation, and urinary retention. A patient with hippocampal and HAZ relapse experienced increasing word-finding difficulties and forgetfulness 17 months post-HA-PCI. One patient, without intracranial relapse, reported increased forgetfulness at the three-month follow-up but displayed no further cognitive disruptions during subsequent assessments. Another patient without intracranial relapse was noted to have increased forgetfulness during the most recent follow-up, eight months after completing HA-PCI. It's essential to mention that the remaining 11 patients did not exhibit documented cognitive disruptions at any point during their treatment or follow-up. (23).

Another retrospective study evaluated the rate and pattern of intracranial failure after HA- PCI in limited-stage SCLC patients. As a result, two patients experienced peri-hippocampal recurrence after HA-PCI, but HA-PCI did not significantly increase the intracranial failure rate. Disease-free survival (DFS) and OS did not significantly differ between HA-PCI and conventional PCI (C-PCI). However, in two patients from the HA-PCI group who experienced recurrence around the peri-hippocampal region, the lesions were located at the edges. In one of these cases, the patient received an adequate radiation dose (mean dose, 23.6 Gy;

minimum dose, 21.6 Gy). Therefore, the recurrence could not have been attributed to HA. Several Japanese studies have suggested that close observation may be preferable over Prophylactic Cranial Irradiation (PCI) for Small Cell Lung Cancer (SCLC) patients. For instance, Ozawa et al. found that limited-stage SCLC patients who underwent PCI did not experience improved Overall Survival or a reduction in brain metastases incidence. They also proposed that PCI may be less beneficial when Magnetic Resonance Imaging (MRI) and Stereotactic Radiosurgery (SRS) are available for patient management, and not employing PCI could lead to better outcomes. It's worth mentioning that the National Comprehensive Cancer Network guidelines recommend PCI as the standard treatment for both extensive and limited-stage SCLC. Furthermore, we should explore approaches to reduce cognitive issues associated with PCI. Prior dosimetric investigations have shown that neurocognitive dysfunction can occur when the mean dose to the hippocampus exceeds approximately 19–20 Gy. Beyond HA-PCI, reducing the WBRT dose could serve as an alternative approach. In cases where patients have a poor performance status, are elderly, or have extensive-stage disease, low-dose PCI may be a valuable consideration (24).

Summary and Conclusion

The management of Small Cell Lung Cancer (SCLC) remains a formidable challenge due to its aggressive nature and propensity for brain metastases. Prophylactic cranial irradiation (PCI) has established its efficacy in reducing the incidence of brain metastases and improving overall survival, particularly in limited-stage SCLC (LS-SCLC). However, its use in extensive-stage SCLC (ES- SCLC) remains uncertain, and concerns about neurocognitive decline persist. Efforts to mitigate neurocognitive toxicity in PCI and Whole Brain Radiotherapy (WBRT) have included the use of drugs like memantine, which has shown promise in preserving cognitive function. Modern radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) aim to minimize radiation exposure to critical brain structures like the hippocampus while maintaining treatment efficacy. Hippocampal Avoidance PCI (HA-PCI) has emerged as a technique to reduce hippocampal radiation exposure. While initial studies suggest its safety and potential benefit, further investigation is needed to determine its impact on cognitive function and long-term outcomes. Guidelines from different organizations vary in their recommendations for PCI, particularly in LS-SCLC, highlighting the need for individualized treatment decisions based on patient characteristics and disease stage. Ongoing research, including randomized trials, continues to shape our understanding of the role of PCI in SCLC management. In the quest to optimize outcomes for SCLC

patients, balancing the benefits of reducing brain metastases with the risks of neurocognitive decline remains a crucial consideration, and future studies will contribute to refining treatment strategies for addressing this challenge. This article continues to suggest standard PCI but does consider hippocampal avoidance to be an acceptable alternative once more data comes to light.

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