Hippocampal avoidance in prophylactic cranial irradiation for small cell lung cancer: benefits and pitfalls

Aswin George Abraham, Wilson Roa

Department of Radiation Oncology, Cross Cancer Institute, Edmonton, Canada

Contributions: (I) Conception and design: Both authors; (II) Administrative support: None ; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Dr. Wilson Roa. Department of Radiation Oncology, Cross Cancer Institute, 11560 University Ave, Edmonton, AB T6G 1Z2, Canada. Email: wilson.roa@ahs.ca.

Abstract: Small cell lung cancers (SCLC) are a group of cancers that are clinically and pathologically different from other lung cancers. They are associated with high recurrence rates and mortality, and many patients present with metastatic disease. Approximately ten percent of SCLC patients have brain metastases at time of diagnosis, and the cumulative incidence of brain metastases increases to more than fifty percent at two years, even with optimal treatment. Hence, in patients without brain metastases at presentation, prophylactic cranial irradiation (PCI) is an important component of treatment along with systemic chemotherapy and radiotherapy. The goal of PCI is to decrease the incidence of subsequent symptomatic brain metastases in patients who show an initial response to the systemic treatment. Various clinical trials have evaluated the utility of PCI and found substantial benefit. Unfortunately, the long-term toxicity associated with PCI, namely the neuro-cognitive impairment that may develop in patients as a result of the radiation toxicity to the hippocampal areas of the brain, has raised concern both for patients and their treating physicians. Various techniques have been tried to ameliorate the neuro-cognitive impairment associated with PCI, including pharmacological agents and highly conformal hippocampal avoidance radiation. All of these have shown promise, but there is a lack of clarity about the optimal way forward. Hippocampal avoidance PCI appears to be an excellent option and a number of groups are currently evaluating this technique. Although there is clear benefit with this specialized radiation treatment, there are also concerns about the risk of disease recurrence in the undertreated hippocampal areas. This review attempts to compile the available data regarding the benefits and pitfalls associated with hippocampal avoidance PCI in the setting of SCLC.

Keywords: Small cell carcinoma; prophylactic cranial irradiation (PCI); hippocampus

Small cell lung cancer and prophylactic cranial irradiation (PCI)

Small cell lung cancers (SCLC) account for about 15 percent of all lung cancers and is associated with high recurrence rates and mortality even in the setting of optimal treatment. These cancers are clinically and pathologically very different from other lung cancers (1). Most of these tumors fall into the category of poorly differentiated neuroendocrine tumors, although a small subset is associated with absence of neural and endocrine properties. SCLC is distinguished from other lung cancers by its rapid doubling time and the early development of distant metastases. Many patients present with disseminated disease or develop metastatic disease soon after presentation, and hence the focus of treatment has been early initiation of systemic treatment.

Patients presenting with SCLC are generally classified into those with limited stage disease (LS-SCLC) and extensive stage disease (ES-SCLC), although the American Joint Committee on Cancer (AJCC) and the International Association for the Study of Lung Cancer (IASLC) currently recommend the Tumor, Node, Metastasis (TNM) staging. LS-SCLC is defined as disease that is limited to the ipsilateral hemi-thorax and regional lymph nodes and which can be encompassed in a safe radiotherapy field. All other patients would be staged as ES-SCLC, and this forms the majority of SCLC patients. The patients with SCLC usually present with distant metastases including to other visceral organs and the brain. The current standard of care especially for LS-SCLC is combination chemotherapy (combination of a platinum agent and a topoisomerase inhibitor) with concurrent radiation treatment to the thoracic disease followed by PCI. ES-SCLC usually presents with extensive disease including distant metastases and extensive intra-thoracic disease. In this setting the primary therapeutic modality is systemic chemotherapy with platinum-based combinations, although radiation may provide additional benefit to patients who show initial response to systemic treatment and those with residual disease after completion of systemic treatment. PCI may bestow some benefit in terms of decreased incidence of symptomatic brain metastases even in this group of patients, especially when they have responded well to initial treatment.

Approximately 10 percent of SCLC patients have brain metastases at time of presentation. Even with optimal treatment, the cumulative incidence of brain metastases increases to more than 50 percent at 2 years. This is of significance especially to the LS-SCLC patients who have responded to treatment and show a median survival of about 17 months and 5-year survival rates of about 20 percent (2,3). In the 1970's, the brain was thought to be a sanctuary for cancer cells, which was inaccessible for existing chemotherapeutic agents and hence these patients started receiving prophylactic radiation to the brain to prevent possible intracranial metastases. Although there was a decrease in the incidence of brain metastases, there was no improvement in survival, and further review of available data suggested that prolongation of survival was restricted to patients who showed complete remission of extracranial disease (4). Furthermore, the addition of cranial radiation to the treatment spectrum was also thought to be associated with toxic neuropsychological effects. To address the benefits of PCI, the Prophylactic Cranial Irradiation Overview Collaborative Group conducted the first large

meta-analysis (5) of seven trials that compared PCI with no PCI in LS-SCLC and found that there was a significant decrease in brain metastases as well as an absolute decrease in the three-year cumulative incidence of brain metastases (26 percent decrease) and a 5.4 percent increase in the 3 year survival rate of patients who received PCI. A separately published review looking at a larger number of trials supported the role of PCI in LS-SCLC, although the lack of toxicity data was also highlighted by the study authors (6). A recent systematic review and meta-analysis also showed that PCI has a significant effect on decreasing brain metastases but had a heterogeneous OS outcome (7).

The use of PCI in ES-SCLC has also been evaluated by different groups. A large retrospective analysis showed that PCI improved median overall survival compared with no PCI (8) and similar findings were reported in another analysis looking at patients with ES-SCLC (9). Due to the lack of prospective data regarding PCI in the setting of ES-SCLC, a Phase III EORTC trial (10) and a further phase III study from Japan (11) were also completed. Interestingly, the concordant finding in the studies was the decrease in the incidence of symptomatic brain metastases in patients who showed an initial response to systemic chemotherapy, with treatment being well tolerated in both trials. Not surprisingly, the benefit in terms of over-all survival was uncertain, with the EORTC trial showing an increase in the overall survival of patients who received PCI and the Japanese study showing no survival benefits, but rather poorer survival outcomes among the patients who received PCI.

The evidence regarding PCI in both LS-SCLC and ES-SCLC gathered over many years thus strongly support the idea that PCI can decrease the incidence of symptomatic brain metastases. This is also associated with increased survival in patients with limited stage disease, but uncertain survival benefits in patients with extensive stage disease. Hence, the current practice is to offer all patients with LS-SCLC, PCI after completion of definitive chemo-radiation to the thoracic disease. ES-SCLC patients who have very good response to initial treatment may also be offered PCI.

PCI generally involves a total dose of 25–30 Gy delivered over a treatment course of 10–15 fractions. Higher doses maybe associated with better disease control, but this benefit has to be weighed against the risk of neuro-toxicity. The original Prophylactic Cranial Irradiation Overview Collaborative Group meta-analysis had looked into the efficacy of increasing the dose of radiation for PCI and they did notice a statistically significant trend for improved control with increasing doses (8 to 40 Gy) of radiation for PCI (5).

But the effect of radiation dose was subsequently studied in randomized trials (12,13) and no advantage was noted for doses above 25 Gy delivered in 2.5 Gy/fraction. The question of the optimal dose was evaluated in the RTOG 0212 trial (13) that compared 25 Gy in 10 fractions or 36 Gy either in 18 fractions of 2 Gy or twice daily in 24 fractions. No significant advantage in terms of disease control was noted in the group that received higher total doses of radiation, and in fact, the patients who received higher doses were also found to have significantly higher long-term toxicity. Hence the current practice is to use the dose of 25 Gy in 10 fractions in all SCLC patients planned for PCI.

In spite of the confirmed benefit of PCI, there has always been concerns about toxicity, especially in the patients having limited stage disease, who are likely to have longer overall survival rates. PCI is usually associated with acute and chronic/long-term toxicity concerns. Most of the acute toxicity is self-limiting and resolves without any significant intervention. These include, fatigue, hair-loss, erythema and occasionally symptoms like nausea and headaches. The primary concern with PCI is the long-term toxicity, namely the neuro-cognitive impairment that may develop in patients who have previously received brain radiation. Previously reported data does seem to show that PCI with concurrent chemotherapy [associated with leukoencephalopathy (14)] or PCI employing large fraction size and higher total doses were associated with severe late neuro-cognitive side effects (14-16). In fact, the RTOG 0212 (13) and the UKCCCR-EORTC (17) trials looked at the neurotoxicity of PCI as an outcome and found that there was no significant increase in the incidence of adverse effects that could be attributed to PCI with the currently used dose of 25 Gy in 10 fractions. Although the current practice of PCI in SCLC is thus considered safe, there is still the concern of late toxicity in the LS-SCLC patients who are now seen to have longer overall survival, especially with improved disease control of the thoracic disease in the current age of systemic therapies. Evidence from a phase III EORTC trial would suggest that PCI is associated with an decline in the quality of life (QoL) characterized by a decrease in neuro-cognition in the patients (18). This has been suggested by other studies as well, both in terms of clinical changes (19,20) as well as changes in the levels of markers of tissue injury (21).

Pathophysiology of brain injury with radiation, with a special focus on the hippocampus

The pathophysiology of brain injury from radiation is multi-factorial, that may be primarily involving two pathways, namely the effect on the vasculature of the brain and the effect on the cells of the central nervous system, especially the neuroglial and the stem cells. Other effects include the changes that can be attributed to inflammatory mediators that are activated or altered by ionizing radiation (22-26). Vascular endothelial damage can be caused by radiation and preclinical studies have shown that radiation can induce the initiation of endothelial cell apoptosis. Vascular damage can lead to various late effects including damage to the blood-brain barrier and development of microvascular abnormalities including telangiectasias. All of these vascular abnormalities' pre-dispose to the development of ischemic or hemorrhagic events and they also result in tissue necrosis in the surrounding brain parenchyma. These events may be exacerbated by the release of various cytokines like interleukins and tumor necrosis factor alpha, which can lead to further tissue injury.

A very important cause of radiation induced toxicity, especially in the context of this article is the effect on the proliferating neuroglial progenitor cells. These cells are very important for neurogenesis and gliogenesis, especially in the areas of the brain that have neurogenic potential. One of the most important of these areas that have a number of progenitor neuroglial cells is the hippocampus. This portion of the brain is essential for memory formation and the neuroglial cells play a pivotal role in this function. Radiation has been shown to decrease the number of neurons in the hippocampus (23), with potentially significant effects on memory. As with the hippocampus, other radio-sensitive areas of the brain include the periventricular area and the white matter tracts, both of which harbor precursor cells that are sensitive to radiation. The injury to the neuroglial precursor cells is implicated in the long-term toxicities associated with brain injury and indeed, the analysis of neuroanatomical targets of radiation-induced neuro-cognitive dysfunction showed that injury to areas of adult neurogenesis including the hippocampus most accurately predicted for the changes in cognitive performance (27). The above-mentioned mechanism may produce a significant effect on memory formation and cognition (28,29), even though there may not be any identifiable imaging findings to suggest the underlying pathology.

The name hippocampus is derived from Greek (hippocampus-hippos, meaning "horse," and "kampos", meaning "sea monster"), due to the structure's shape resembling a sea horse. The hippocampus is located in the medial aspect of the temporal lobe and is a part

of the limbic system, which is important in regulating emotional responses. The hippocampus is also involved in storing memories, principally functioning as an indexing mechanism for memories as well as processing conscious recollection and new memories (30). The hippocampus also supports flexible cognition and relational memory, by forming links between the frontal lobes and structures in the temporal, parietal and limbic circuits (31,32).

Patients with dysfunctions of the hippocampus usually present with history of anterograde amnesia where they are unable to create new memories of facts and events. This is characteristically seen in patients with Alzheimer's disease, where the hippocampus undergoes massive cell loss and subsequent memory deficits that classically present in the early stages of the disease. Hypoxic episodes, especially following strokes, can also adversely affect the hippocampus, with patients presenting with anterograde amnesia.

Most of the adult neurogenesis in the central nervous system happens in the hippocampal dentate gyrus and sub-granular zone (SGZ) and the sub-ventricular zone (SVZ) (33). The hippocampus is commonly exposed to high doses of radiation during therapeutic interventions for various conditions including primary brain tumors, head and neck cancers (34,35) and metastatic intra cranial disease. Radiation suppresses the proliferation of hippocampal SGZ progenitor cells and their differentiation into neurons (36-38). The subsequent hippocampal impairment is derived from damage to differentiated neural cells, altered neurogenesis and impaired cellular plasticity (39,40). Pre-clinical studies have even shown that doses as low as 2 Gy to the hippocampus can cause impaired hippocampal function due to injury to the precursor stem cells (41). In fact, researchers have shown that neural stem cell transplantation attenuated radiation-induced cognitive dysfunction in pre-clinical models (42). Furthermore, the hippocampus, along with the para-hippocampal cortex and the entorhinal and perirhinal cortex are very sensitive to radiation induced vascular injury (40). Activation of the inflammatory pathways by radiation has also been shown to produce gliotic changes as well as inflammation induced inhibition of neurogenesis in the hippocampus (43-45). These inflammatory changes also produce changes in the hippocampal microenvironment, primarily via changes in the microvasculature (43,46,47). At the microanatomical level, radiation induces changes in the neuronal dendritic spine density, and a clear relationship has been identified between the loss of dendritic spine density in the hippocampus and learning and memory dysfunction (48).

The hippocampus has been demonstrated to depend on the differentiation of a large number of neurons every day, to sub-serve its memory and cognition functions (49). These neurons are generated from progenitor cells in the SGZ of the dentate gyrus (50,51) and are believed to be post mitotic cells that migrate to the dentate gyrus and differentiate into mature neurons. These mature neurons in the molecular layer of the hippocampus receive inputs from the entorhinal cortex and this exquisite process of neurogenesis is process of neurogenesis is supported by a niche of cells comprised of glial cells, neurons, astrocytes, oligodendrocytes, extracellular matrix and remodeling microvasculature (40,52). Thus, impairment of any of these components can have a significant cascade effect that affects hippocampal function. The early dysfunction initiated by radiation injury alters inter-cellular signaling producing potent microenvironmental changes that further influence progenitor cell differentiation. In fact, long term dysregulated signaling may cause hippocampal precursor cells to differentiate into glia rather than neurons, resulting in a loss of neurons and the plasticity required for learning, memory, and other aspects of cognition (53,54). Furthermore, work done in the area of Alzheimer's disease has shown that different areas of the hippocampus may show different functions (55) and the different regions may be exposed to different doses of radiation (56) resulting in subjective differences in the neuro-cognitive toxicity phenotype.

The role of hippocampus in processing memory and cognition is thus undisputed, and significant amounts of pre-clinical and clinical data generated over the last few decades strongly support the hypothesis that one of the major toxicities of brain radiation is the result of injury to the hippocampus. The goal thus has been to avoid injury to the hippocampus as far as is reasonably possible, especially in patients where early disease or excellent treatment response would render them excellent candidates for long-term survival.

Therapeutic whole brain radiation and hippocampal-avoidance whole brain radiation

Brain metastases is the most common brain tumor in adults, and the risk of developing brain metastases vary according to the tumor type, although lung cancers account for about half of all these tumors (57,58). The prognosis, once brain metastases has developed, is relatively poor and the patients generally present with significant neurologic, cognitive and

emotional issues. The most widely used treatment for multiple brain metastases has been whole brain radiation treatment (WBRT), which was seen to provide rapid attenuation of symptoms. Various dose schedules for WBRT were studied in multiple randomized studies and currently the most commonly used dose schedules include 30 Gy in 10 fractions or 20 Gy in 5 fractions. While these doses are inadequate for long-term tumor control, these doses do give tumor control in approximately 50% patients at 6 months (58). Unfortunately, multiple reports identified neuro-cognitive dysfunction as a late toxicity of WBRT, although this may have been confounded by multiple other factors including location of the tumor, surgical procedures and the use of neurotoxic drugs like chemotherapy. Early studies identified the pathophysiological changes in the brain that were associated with radiation induced toxicity, and various strategies were suggested to reduce the late neurological toxicity of WBRT. Currently, WBRT is offered for patients who have brain metastases that impinge eloquent areas or have disseminated disease that may be unamenable to surgery or stereotactic radiation. The second indication for WBRT is as an adjuvant treatment after surgery or stereotactic radiosurgery (SRS). Although adjuvant WBRT after surgery or SRS reduces the relative risk of intracranial disease progression, no survival advantages (59,60) were noted and was instead associated with increased risk of side effects including neurocognitive decline (61).

Some of the strategies employed for reducing the late toxicity of WBRT include stereotactic radiation for solitary lesions and tumor bed radiation following surgical metastectomy. In fact the treatment approach for brain metastases have changed significantly in the last couple of decades with the emergence of randomized data supporting the evidence for SRS as initial therapy for up to 4 brain metastases (59,62-64), although some centers practice SRS for even larger number of small tumors. Other targeted strategies to reduce the risk of neurocognitive decline after WBRT include the use of certain pharmacological agents that have been shown to ameliorate the late neuro-cognitive toxicity of WBRT. These agents include memantine, an oral N-methyl-D-aspartate (NMDA) receptor (65,66) and donepezil, a choline esterase inhibitor (66). These medications have been previously used in the management of Alzheimer's disease, and although they do not reverse the radiation induced toxicity, they can delay the time to cognitive decline. In these early studies, donepezil only showed modest improvement in cognitive functions, but memantine did show significantly better benefit with longer

time to cognitive decline and favorable tolerability profile. Hence it has been suggested that memantine may be offered to patients following WBRT for up to 6 months.

Another strategy employed for reducing the risk of late neuro-cognitive toxicity is to avoid the hippocampus during WBRT using newer radiation techniques like intensity modulated radiation therapy (IMRT), where a lower differential dose to the hippocampus is thought to reduce the long-term toxicity associated with conventional WBRT. WBRT with hippocampal avoidance was demonstrated to be feasible with improvements in radiation techniques and planning systems. Evaluation of the feasibility of sparing the hippocampus and the neuronal stem cell compartment showed that it was indeed possible to keep the doses to these structures much lower than the prescription dose using intensity modulated radiation treatment and helical tomotherapy (67). A report from the Gondi group also showed that excellent hippocampal avoidance was possible both with standard linear accelerator based and helical tomotherapy based techniques (68). The group also reported on the RTOG 0933 (69) phase II trial that studied patients with non-hematologic and non-SCLC brain metastases who were planned for WBRT. These patients were treated with hippocampal avoidance WBRT (HA-WBRT) using a dose of 30 Gy in 10 fractions. A decline in the Hopkins Verbal Learning Test (HVLT) was the end-point, and it was noted among the participants that relative decline in HVLT was significantly lesser than in previously reported studies that looked at WBRT as well as WBRT and SRS. This study also set out the possible dosimetric compliance criteria that can indicate the most reasonable outcomes (70). Interestingly, the recent NRG-CC001 trial looked at the combination of memantine with WBRT and memantine with HA-WBRT (71) and an interim analysis showed that hippocampal avoidance better preserves neuro-cognitive Function and other late symptoms without having an impact on disease control and survival.

An area of active research has been to identify hippocampal radiation exposure dose relationships with neuro cognitive function and other effects. Interestingly, it was found in small studies that exposure of even 10% of the hippocampal volume (as seen on imaging) to relatively low doses of radiation (EQD2 <8.81 Gy) was associated with significant neuro cognitive dysfunction (72). An imaging-based study looking at hippocampal atrophy following radiation also identified that there was significant hippocampal atrophy with higher doses of radiation, with a 40 Gy exposure associated with a 6% decrease in volume

at 1 year, whereas there was no obvious volume changes following exposure to <10 Gy of radiation (73). In spite of all these findings, there is a lack of randomized data that supports the routine use of HA-WBRT and there are currently ongoing trials that will hopefully answer this question.

Hippocampal avoidance-PCI in SCLC and its benefits

Unlike in patients with confirmed metastatic disease, prophylactic treatment of the brain especially in patients with LS-SCLC is done with the idea that these patients will have controlled primary disease, and hence will be expected to live longer than a patient with clinically evident brain metastasis. Yet, in many patients, the concern of possible neuro-cognitive impairment following standard PCI, results in their declining treatment (74). This is a justifiable concern, as the decline in QoL following treatment for SCLC and subsequent PCI has been well documented (18). The previously mentioned pathophysiology of brain injury plays an important role even in the setting of PCI, and hence multiple groups have been evaluating various techniques to enhance the safety profile of this treatment. While the previously discussed pharmacological agents have been shown to have a benefit even in the setting of PCI, a number of phase 3 trials are evaluating the benefit of hippocampal avoidance radiation in this setting.

Although many studies have reported on hippocampal avoidance in the context of therapeutic WBRT, prospective studies specifically looking at PCI, especially in the setting of SCLC are few. Much of the data supporting hippocampal avoidance PCI is extrapolated from WBRT studies or is based on studies that had a combination cohort of patients who received whole brain radiation both in the therapeutic and prophylactic setting. A single arm prospective trial with 20 patients looked at adults with LS-SCLC who achieved complete response to chemoradiation and was planned for PCI (75). All patients were treated with a dose of 25 Gy in 10 fractions with a mean dose to the hippocampus limited to <8 Gy and the Hopkins Verbal Learning Test-Revised Delayed Recall test was administered at 6 and 12 months after PCI and the efficacy was compared with the RTOG 0212 study. The study showed that there was no decline in performance on any of the neuro-psychological tests, although 2 of the patients subsequently developed mets in the under-treated areas. But this report did suggest that

hippocampal avoidance PCI should be considered for LS-SCLC patients. The NRG CC-003 trial which is currently accruing is a seamless phase IIR/III trial, with the phase IIR designed to demonstrate non-inferiority and if the margin of the phase IIR component is not exceeded, then the trial would transition to the phase III component. Recently, following an interim analysis of the phase IIR primary endpoint which appeared to show non inferiority, the trial was re-activated to accrue patients to the phase III component (76). Combined with the evidence from hippocampal avoidance WBRT, there is thus emerging support for PCI with hippocampal avoidance in the management protocol of SCLC.

In the last few decades, the proportion of the elderly population being diagnosed with SCLC has shown an upward trend with about 44% of all cases of SCLC being aged >70 years (77). Not surprisingly, these patients also tend to fare worse than younger patients (78-80) and have more risk for developing neuro-cognitive impairment after PCI. Furthermore, PCI was not thought to extend significant survival benefits (80) for this group of patients, as they were likely to have an increased risk of death from other causes, rather than brain metastases. This was also reflected in the ES-SCLC patients (11) where the elderly was not found to have significant benefit from PCI, but were instead seen to develop significant neuro-cognitive toxicity. Hence this is one group of patients who may likely have significant benefit with hippocampal avoidance PCI and efforts should be made to address this sub-set of patients as a separate cohort to avoid biases due to contamination with data from other patient groups.

Concerns about hippocampal avoidance-PCI in SCLC

A primary concern about any conservative treatment option in cancer patients, is about the risk of disease recurrence due to undertreatment. Most of the early cranial radiation studies involving hippocampal avoidance techniques excluded SCLC patients, due to the belief that SCLC can give rise to diffuse brain metastases that can involve the hippocampus, which would in turn negate the neuro-cognitive benefits gained by sparing the Hippocampus. This is also currently the primary concern about universal promotion of hippocampal avoidance PCI for SCLC patients. An early paper (81) looking at the pattern of failure in small cell lung cancer patients who received PCI did not clarify about the incidence of hippocampal failures,

but a recently reported study specifically looked at SCLC patients with brain metastases and noted that the incidence of hippocampal metastases was very low involving <5% patients. Furthermore, even in patients with significant intracranial metastatic load, the actual involvement of the hippocampus by metastatic lesions was very low (0.8%) (82). Another report looked at the distribution of metastases in a larger study set and found that Hippocampal involvement was seen only in about 1% of the study patients and dosimetric studies of these patients showed that even with hippocampal avoidance techniques, about 10% of the patients did receive adequate dosage to the hippocampal areas, making it a reasonable treatment strategy for SCLC patients (83). Intriguingly another group that looking at a similar sized retrospective cohort of SCLC patients, found that a significant number of patients (18.3%) had hippocampal metastases (84), cautioning against the use of hippocampal avoidance radiation. Thus, the lack of clarity about the risks associated with hippocampal avoidance PCI is a significant hurdle that hobbles efforts to reduce the radiation related toxicity associated with PCI in SCLC patients. Only larger prospective trials can bring clarity to the question raised by the contradictory findings. In fact early reports from the OC-0503 phase III trial comparing PCI with or without hippocampus avoidance in SCLC, which was recently published, showed similar OS rates at 18 months and interestingly, none of the patients had developed isolated brain metastases in the hippocampal avoidance area (85). But surprisingly, the study did show a drop in the Hopkins Verbal Learning Test-Revised (HVLT-R) scores across all subjects and no significant difference between the two patient groups. Final study results will be awaited to verify these findings.

Conclusion and discussion

PCI has been very commonly practiced as an adjunct therapy for SCLC patients for the last few decades with a number of reports showing benefits in terms of reducing intra cranial metastases. Along the way there have also been discussions about the ambiguity of this approach especially when taking into consideration the associated neuro-toxicity. A number of studies are currently recruiting to answer this question. Some of the various studies include and are not limited to the NRG-CC003, NCT02906384, NCT02397733, NCT01780675 and NCT02635009 clinical trials that are currently recruiting patients to study the benefit of PCI.

Since long-term neurotoxicity is the primary concern, various groups have investigated techniques to ameliorate the side effects of radiation. Hippocampal avoidance PCI is an excellent technique to overcome the concerns of toxicity associated with PCI and a number of groups are currently looking into this area. Studies like the NRG-CC003 and the PREMER Trial (NCT 02397733) (86) will hopefully answer the question regarding the benefit of PCI as well as the benefit extended by protecting the hippocampal region. Three principle questions that will seek answers from the current studies include (I) the benefits in terms of reduction in toxicity, (II) the risk of local recurrence/metastasis in the spared areas and (III) the benefits in terms of the increased resource utilization and need for reverse radiation treatment planning. Although efficacy and toxicity will be the primary end-points of interest, these studies will also help clarify the question regarding benefits versus the need for increased resource utilization that will be of concern especially for publicly funded healthcare systems. Our own clinical experience suggests that HS-PCI is indeed a good treatment technique, but the overall benefits for individual patients per se have to be carefully weighed against the increased resource requirements for treatment planning and execution.

Although current guidelines including the NCCN recommends PCI for patients with limited stage disease who attain a complete or partial response and suggests "considering" PCI for extensive stage SCLC, there is currently no clarity regarding offering hippocampal avoidance PCI. But whatever maybe the consensus opinion regarding the management options, the final arbitrator will be the patient who decides whether the benefits of PCI are worth the risk of side effects associated with treatment. Hence, any modest improvement in the toxicity profile is also likely to have an impact on the acceptance of these treatments.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Lucyna Kepka) for the series "Radiotherapy for Brain Metastases from Lung Cancer" published in *Journal of Thoracic Disease*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-2019-rbmlc-01). The series "Radiotherapy for Brain Metastases from Lung Cancer" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer 2017;17:725-37.
2. Gaspar LE, Gay EG, Crawford J, et al. Limited-stage small-cell lung cancer (stages I-III): observations from the National Cancer Data Base. Clin Lung Cancer 2005;6:355-60.
3. Janne PA, Freidlin B, Saxman S, et al. Twenty-five years of clinical research for patients with limited-stage small cell lung carcinoma in North America. Cancer 2002;95:1528-38.
4. Rosen ST, Makuch RW, Lichter AS, et al. Role of prophylactic cranial irradiation in prevention of central nervous system metastases in small cell lung cancer. Potential benefit restricted to patients with complete response. Am J Med 1983;74:615-24.
5. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476-84.
6. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic

7. review of the literature with meta-analysis. BMC Cancer 2001;1:5.
8. Yin X, Yan D, Qiu M, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review and meta-analysis. BMC Cancer 2019;19:95.
9. Sharma S, McMillan MT, Doucette A, et al. Effect of Prophylactic Cranial Irradiation on Overall Survival in Metastatic Small-Cell Lung Cancer: A Propensity Score-Matched Analysis. Clin Lung Cancer 2018;19:260-9.e3.
10. Bang A, Kendal WS, Laurie SA, et al. Prophylactic Cranial Irradiation in Extensive Stage Small Cell Lung Cancer: Outcomes at a Comprehensive Cancer Centre. Int J Radiat Oncol Biol Phys 2018;101:1133-40.
11. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664-72.
12. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:663-71.
13. Le Pechoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol 2009;10:467-74.
14. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys 2011;81:77-84.
15. Johnson BE, Patronas N, Hayes W, et al. Neurologic, computed cranial tomographic, and magnetic resonance imaging abnormalities in patients with small-cell lung cancer: further follow-up of 6- to 13-year survivors. J Clin Oncol 1990;8:48-56.
16. Herskovic AM, Orton CG. Elective brain irradiation for small cell anaplastic lung cancer. Int J Radiat Oncol Biol Phys 1986;12:427-9.
17. Ahles TA, Silberfarb PM, Herndon J 2nd, et al. Psychologic and neuropsychologic functioning of patients with limited small-cell lung cancer treated with chemotherapy and radiation therapy with or without warfarin: a study by the Cancer and Leukemia Group B. J

Clin Oncol 1998;16:1954-60.

17. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). Eur J Cancer 1997;33:1752-8.

18. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol 2009;27:78-84.

19. Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. J Clin Oncol 2011;29:279-86.

20. Simo M, Vaquero L, Ripolles P, et al. Longitudinal Brain Changes Associated with Prophylactic Cranial Irradiation in Lung Cancer. J Thorac Oncol 2016;11:475-86.

21. Kalm M, Abel E, Wasling P, et al. Neurochemical evidence of potential neurotoxicity after prophylactic cranial irradiation. Int J Radiat Oncol Biol Phys 2014;89:607-14.

22. Belka C, Budach W, Kortmann RD, et al. Radiation induced CNS toxicity--molecular and cellular mechanisms. Br J Cancer 2001;85:1233-9.

23. Rola R, Raber J, Rizk A, et al. Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. Exp Neurol 2004;188:316-30.

24. Nordal RA, Wong CS. Molecular targets in radiation-induced blood-brain barrier disruption. Int J Radiat Oncol Biol Phys 2005;62:279-87.

25. Sundgren PC, Cao Y. Brain irradiation: effects on normal brain parenchyma and radiation injury. Neuroimaging Clin N Am 2009;19:657-68.

26. Greene-Schloesser D, Robbins ME, Peiffer AM, et al. Radiation-induced brain injury: A review. Front Oncol 2012;2:73.

27. Peiffer AM, Leyrer CM, Greene-Schloesser DM, et al. Neuroanatomical target theory as a predictive model for radiation-induced cognitive decline. Neurology 2013;80:747-53.

28. Monje M, Dietrich J. Cognitive side effects of cancer therapy demonstrate a functional role for adult neurogenesis. Behav Brain Res 2012;227:376-9.

29. Dietrich J, Monje M, Wefel J, et al. Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. Oncologist 2008;13:1285-95.

30. Opitz B. Memory function and the hippocampus. Front Neurol Neurosci 2014;34:51-9.

31. Rubin RD, Watson PD, Duff MC, et al. The role of the hippocampus in flexible cognition and social behavior. Front Hum Neurosci 2014;8:742.

32. Chan RW, Leong ATL, Ho LC, et al. Low-frequency hippocampal-cortical activity drives brain-wide resting-state functional MRI connectivity. Proc Natl Acad Sci U S A 2017;114:E6972-E6981.

33. Hellstrom NA, Bjork-Eriksson T, Blomgren K, et al. Differential recovery of neural stem cells in the subventricular zone and dentate gyrus after ionizing radiation. Stem Cells 2009;27:634-41.

34. Tang Y, Luo D, Rong X, et al. Psychological disorders, cognitive dysfunction and quality of life in nasopharyngeal carcinoma patients with radiation-induced brain injury. PLoS One 2012;7:e36529.

35. Chen SC, Abe Y, Fang PT, et al. Prognosis of Hippocampal Function after Sub-lethal Irradiation Brain Injury in Patients with Nasopharyngeal Carcinoma. Sci Rep 2017;7:14697.

36. Mizumatsu S, Monje ML, Morhardt DR, et al. Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. Cancer Res 2003;63:4021-7.

37. Manda K, Ueno M, Anzai K. Cranial irradiation-induced inhibition of neurogenesis in hippocampal dentate gyrus of adult mice: attenuation by melatonin pretreatment. J Pineal Res 2009;46:71-8.

38. Tada E, Parent JM, Lowenstein DH, et al. X-irradiation causes a prolonged reduction in cell proliferation in the dentate gyrus of adult rats. Neuroscience 2000;99:33-41.

39. Monje ML, Mizumatsu S, Fike JR, et al. Irradiation induces neural precursor-cell dysfunction. Nat Med 2002;8:955-62.

40. Makale MT, McDonald CR, Hattangadi-Gluth JA, et al. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol 2017;13:52-64.

41. Peissner W, Kocher M, Treuer H, et al. Ionizing radiation-induced apoptosis of proliferating stem cells in the dentate gyrus of the adult rat hippocampus. Brain Res Mol Brain Res 1999;71:61-8.

42. Acharya MM, Christie LA, Lan ML, et al. Human neural

stem cell transplantation ameliorates radiation-induced cognitive dysfunction. Cancer Res 2011;71:4834-45.

43. Monje ML, Vogel H, Masek M, et al. Impaired human hippocampal neurogenesis after treatment for central nervous system malignancies. Ann Neurol 2007;62:515-20.

44. Hwang SY, Jung JS, Kim TH, et al. Ionizing radiation induces astrocyte gliosis through microglia activation. Neurobiol Dis 2006;21:457-67.

45. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. Science 2003;302:1760-5.

46. Ekdahl CT, Claasen JH, Bonde S, et al. Inflammation is detrimental for neurogenesis in adult brain. Proc Natl Acad Sci U S A 2003;100:13632-7.

47. Park JA, Choi KS, Kim SY, et al. Coordinated interaction of the vascular and nervous systems: from molecule- to cell-based approaches. Biochem Biophys Res Commun 2003;311:247-53.

48. Frankfurt M, Luine V. The evolving role of dendritic spines and memory: Interaction(s) with estradiol. Horm Behav 2015;74:28-36.

49. Shors TJ, Anderson ML, Curlik DM 2nd, et al. Use it or lose it: how neurogenesis keeps the brain fit for learning. Behav Brain Res 2012;227:450-8.

50. Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. Nat Med 1998;4:1313-7.

51. Seib DR, Martin-Villalba A. Neurogenesis in the Normal Ageing Hippocampus: A Mini-Review. Gerontology 2015;61:327-35.

52. Palmer TD, Willhoite AR, Gage FH. Vascular niche for adult hippocampal neurogenesis. J Comp Neurol 2000;425:479-94.

53. Zhou FW, Roper SN. Impaired hippocampal memory function and synaptic plasticity in experimental cortical dysplasia. Epilepsia 2012;53:850-9.

54. Licht T, Goshen I, Avital A, et al. Reversible modulations of neuronal plasticity by VEGF. Proc Natl Acad Sci U S A 2011;108:5081-6.

55. Greene SJ, Killiany RJ, Alzheimer's Disease Neuroimaging I. Hippocampal subregions are differentially affected in the progression to Alzheimer's disease. Anat Rec (Hoboken) 2012;295:132-40.

56. Zong-Wen S, Lei S, Qinglin L, et al. Results of the radiation dose of head, body and tail of hippocampus in nasopharyngeal carcinoma patients treated with intensity modulated radiotherapy. Sci Rep 2018;8:5595.

57. Yawn BP, Wollan PC, Schroeder C, et al. Temporal and gender-related trends in brain metastases from lung and breast cancer. Minn Med 2003;86:32-7.

58. Khuntia D, Brown P, Li J, et al. Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol 2006;24:1295-304.

59. Soon YY, Tham IW, Lim KH, et al. Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. Cochrane Database Syst Rev 2014;2014:CD009454.

60. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2017;18:1049-60.

61. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009;10:1037-44.

62. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-95.

63. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665-72.

64. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483-91.

65. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 2013;15:1429-37.

66. Day J, Zienius K, Gehring K, et al. Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation. Cochrane Database Syst Rev 2014;2014:CD011335.

67. Marsh JC, Godbole RH, Herskovic AM, et al. Sparing of the neural stem cell compartment during whole-brain radiation therapy: a dosimetric study using helical tomotherapy. Int J Radiat Oncol Biol Phys 2010;78:946-54.

68. Gondi V, Tolakanahalli R, Mehta MP, et al. 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 2010;78:1244-52.

69. Gondi V, Pugh SL, Tome WA, et al. 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 2014;32:3810-6.

70. Pokhrel D, Sood S, Lominska C, et al. Potential for reduced radiation-induced toxicity using intensity-modulated arc therapy for whole-brain radiotherapy with hippocampal sparing. J Appl Clin Med Phys 2015;16:131-41.

71. Gondi V, Deshmukh S, Brown PD, et al. NRG Oncology CC001: A phase III trial of hippocampal avoidance (HA) in addition to whole-brain radiotherapy (WBRT) plus memantine to preserve neurocognitive function (NCF) in patients with brain metastases (BM). J Clin Oncol 2019;37:2009.

72. Tsai PF, Yang CC, Chuang CC, et al. Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. Radiat Oncol 2015;10:253.

73. Seibert TM, Karunamuni R, Bartsch H, et al. Radiation Dose-Dependent Hippocampal Atrophy Detected With Longitudinal Volumetric Magnetic Resonance Imaging. Int J Radiat Oncol Biol Phys 2017;97:263-9.

74. Lok BH, Ma J, Foster A, et al. Factors influencing the utilization of prophylactic cranial irradiation in patients with limited-stage small cell lung cancer. Adv Radiat Oncol 2017;2:548-54.

75. Redmond KJ, Hales RK, Anderson-Keightly H, et al. Prospective Study of Hippocampal-Sparing Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2017;98:603-11.

76. Gondi V, Pugh SL, Mehta MP, et al. NRG Oncology CC003: A randomized phase II/III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer. J Clin Oncol 2019;37:TPS8578.

77. Abdel-Rahman O. Changing epidemiology of elderly small cell lung cancer patients over the last 40 years; a SEER database analysis. Clin Respir J 2018;12:1093-9.

78. Ludbrook JJ, Truong PT, MacNeil MV, et al. Do age and comorbidity impact treatment allocation and outcomes in limited stage small-cell lung cancer? a community-based population analysis. Int J Radiat Oncol Biol Phys 2003;55:1321-30.

79. Rossi A, Maione P, Colantuoni G, et al. Treatment of small cell lung cancer in the elderly. Oncologist 2005;10:399-411.

80. Farooqi AS, Holliday EB, Allen PK, et al. Prophylactic cranial irradiation after definitive chemoradiotherapy for limited-stage small cell lung cancer: Do all patients benefit? Radiother Oncol 2017;122:307-12.

81. Arriagada R, Le Chevalier T, Riviere A, et al. Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients. Ann Oncol 2002;13:748-54.

82. Kundapur V, Ellchuk T, Ahmed S, et al. Risk of hippocampal metastases in small cell lung cancer patients at presentation and after cranial irradiation: a safety profile study for hippocampal sparing during prophylactic or therapeutic cranial irradiation. Int J Radiat Oncol Biol Phys 2015;91:781-6.

83. Zhao L, Shen Y, Guo JD, et al. Analyses of distribution and dosimetry of brain metastases in small cell lung cancer with relation to the neural stem cell regions: feasibility of sparing the hippocampus in prophylactic cranial irradiation. Radiat Oncol 2017;12:118.

84. Effeney R, Nair L, Murphy M, et al. MA22.11 Risk of Hippocampal Metastases in Small Cell Lung Cancer: Implications for Hippocampal Sparing Cranial Irradiation. J Thorac Oncol 2018;13:S437.

85. Belderbos J, Phd M, De Ruysscher D, et al. OC-0503 Phase III trial of Prophylactic Cranial Irradiation with or without Hippocampus Avoidance in SCLC. Radiother Oncol 2019;133:S259.

86. Rodriguez de Dios N, Counago F, Lopez JL, et al. Treatment Design and Rationale for a Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for SCLC: PREMER Trial on Behalf of the Oncologic Group for the Study of Lung Cancer/Spanish Radiation Oncology Group-Radiation Oncology Clinical Research Group. Clin Lung Cancer 2018;19:e693-e697.