Prophylactic cranial irradiation (PCI), hippocampal avoidance (HA) whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) in small cell lung cancer (SCLC)

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Prophylactic Cranial Irradiation (PCI), Hippocampal avoidance (HA) Whole Brain Radiotherapy (WBRT) and Stereotactic Radiosurgery (SRS) in Small Cell Lung Cancer (SCLC): where do we stand?

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Abstract

Small cell lung cancer (SCLC) is an aggressive form of lung cancer associated with an increased risk of developing brain metastases (BM), which are a significant cause of morbidity and mortality. Prophylactic cranial irradiation (PCI) was first introduced in the 1970s with the aim of reducing BM incidence and improving survival and quality of life (QoL). Prospective clinical trials and meta-analyses have demonstrated its effectiveness in reducing BM incidence and improving survival, across all stages of the disease following response to induction chemotherapy. Despite its long history, “unknowns” surrounding PCI use still exist and there are particular subgroups of patients for which its use remains controversial. PCI is known to cause neurocognitive toxicity which can have a significant impact on a patient’s QoL. Strategies to minimise this, including
the use of hippocampal avoidance radiotherapy techniques, neuroprotective drugs and stereotactic radiosurgery in place of whole brain radiotherapy for the treatment of BM, are under evaluation.

This review offers a summary of the key PCI trials published to date and the current treatment recommendations based on available evidence. It also discusses the key questions being addressed in ongoing clinical trials and highlights others where there is currently a knowledge gap and therefore where further data are urgently required.

**Keywords:** SCLC; PCI; brain metastases; hippocampal avoidance; SRS; neurotoxicity.

**Introduction**

SCLC is an aggressive form of lung cancer with a natural history that often involves rapid tumour growth, early dissemination, early treatment resistance and ultimately poor outcomes (5-year overall survival [OS] <10%).(1,2) The diagnosis is associated with an increased risk of brain metastases (BM), which can be a cause of significant morbidity and mortality.(1,2) Prospective randomised controlled trials (RCTs) and meta-analyses have demonstrated the effectiveness of PCI, for patients with both limited stage (LS) and extensive stage (ES) disease who have responded to induction therapy, in reducing the rate of BM and improving OS and disease-free survival (DFS).(3–5) There are however a number of “unknowns” and controversies associated with its use which need to be explored further.

Over 50% of patients with SCLC may develop BM over the course of their disease and their presence carries a poor prognosis.(6) The management of BM for patients with SCLC differs to that of other solid tumours owing to its diffuse and aggressive nature.(7) Their management also differs depending on the timing of the BM presentation in relation to their initial diagnosis (synchronous versus [vs.] metachronous), and the patient’s symptoms. Furthermore, treatment in the metachronous setting will depend upon the patient’s extracranial disease status at the time and whether radiotherapy has been delivered previously. At present, whole brain radiotherapy (WBRT) continues to play a significant role but the role of stereotactic radiosurgery (SRS) is emerging.(7)

The toxicity of PCI and WBRT is an ongoing area of concern. The potential risk of resultant neurocognitive decline and other side effects which may detrimentally impact quality of life (QoL) have been the focus of several trials.(8–10) In the PCI setting, the neurocognitive concern has led to reduced acceptance of PCI by clinicians and patients.(11) Consequently, there has been a decline in
PCI use particularly in certain populations, such as the elderly, where data are more limited.\(^{11–13}\)

The role of hippocampal avoidance (HA) radiotherapy and neuroprotective drugs have been the subject of clinical trials. The potential benefit of SRS, instead of WBRT, to limit neurotoxicity in patients diagnosed with BM is under investigation.

This review offers a summary of the current status and future directions of both PCI and WBRT for patients with SCLC and highlights areas where further research is urgently needed.

**PCI in limited-stage SCLC**

The landmark PCI Overview Collaborative Group meta-analysis was published in 1999.\(^3\) This included individual data on 987 patients with SCLC who took part in seven phase III RCTs comparing PCI with no PCI, in patients with complete response (CR) to initial treatment. They reported a significant reduction in relative risk of death with the addition of PCI which corresponded to a 5.4% increase in OS at three years (20.7% in the PCI group vs. 15.3% in the control group). In addition, PCI was associated with a significant decrease in cumulative BM incidence from 58.6% in the control group to 33.3% in the PCI group at three years.

There is little detail on disease staging information for the included patients, with 86% of patients classed as having LS and 14% as ES disease. Notably staging investigations did not include fluorodeoxyglucose (FDG)-positron emission tomography (PET). The vast majority of included patients were of ECOG performance status (PS) 0 or 1 and only 25% were aged >65. Initial treatment details were not available for 25% of patients and of the remainder, 24% received chemotherapy without thoracic radiotherapy. Patients included in the meta-analysis needed to have evidence of CR to initial treatment for trial entry, which for most was only assessed by normalisation of a chest x-ray (CXR). In addition, there are details of cranial imaging ahead of enrolment for only two thirds of patients and a variety of PCI dose and fractionation schedules were used.

A subsequent meta-analysis two years later included 1547 patients from 12 phase II-III RCTs including patients with and without CR to initial treatment and also those receiving PCI alongside the initiation of induction chemotherapy.\(^4\) Five of the studies included only patients with LS disease and five studies included brain CT as part of initial disease staging. There is limited detail on age ranges of patients included. A significant reduction in BM incidence was again noted (HR 0.48 [95% CI 0.39-0.60]), however there was no significant OS benefit demonstrated. On subgroup analysis, a significant OS benefit was noted for those with CR on CXR to initial treatment (HR 0.82 [95% CI 0.71-0.96]). Both of these meta-analyses comment on the lack of toxicity reporting in the included trials.
Two RCTs randomising between PCI or no PCI have focused upon the question of PCI dose specifically. (55,56) Gregor et al studied 314 patients with LS SCLC and a CR following induction treatment. They reported a significant reduction in BM incidence for patients receiving 36 Gy/18 fractions compared to no PCI (HR 0.16 [95% CI 0.07-0.36], p=0.0007) but no significant difference for those who received 24 Gy/12 fractions compared to no PCI (HR 0.71 [95% CI 0.36-1.43]). (55) This suggested a dose-response relationship and has been further supported by the results of the meta-analysis by Aupérin et al, which found that BM incidence reduced with increasing dose. (3) Neither of these studies however found that increased dose was associated with a survival benefit. Le Péchoux et al subsequently randomised 720 patients with LS SCLC and a CR to induction treatment to standard dose PCI (25 Gy/10 fractions) or high dose PCI (36 Gy/18 fractions once daily or 24 Gy/32 bidaily fractions). (56) Patients who received high dose PCI had a non-significant reduction in 2-year BM incidence (23% vs. 29%; HR 0.8, 95% CI 0.57-1.11, p=0.18). However, they were also noted to have a lower OS (37% vs. 42%; HR for death 1.2, 95% CI 1.00-1.44, p=0.05). This finding was similarly supported by a pooled analysis by the North Central Cancer Treatment Group which reported that patients who received PCI at 25 Gy/10 fractions had higher median OS than those who received 30 Gy/15 fractions (21.6 vs. 16.7 months, HR 0.67, p=0.018). (57) Therefore, the current recommendation for PCI dose fractionation in the LS setting is 25 Gy/10 fractions.

The two meta-analyses established PCI as standard of care (SOC) in LS disease following response to initial treatment. Since then, PCI has been explored further in patients with ES disease but there has been little additional data in the LS patient population. Despite the chemotherapy backbone of platinum-doublet changing little over the years, many other aspects of patient management have changed, highlighting a need for further evidence in the modern era. Staging imaging has vastly improved with the introduction of FDG-PET, and brain magnetic resonance imaging (MRI), is now considered the gold standard to identify BM. Modern radiotherapy techniques and higher thoracic doses are now employed, and studies are currently investigating the role of immunotherapy. The current clinical practice guidelines are outlined in Table 1. Ongoing PCI clinical trials are summarised in Table 2 (PCI vs. no PCI) and Table 3 (PCI vs. HA-PCI).

**PCI in extensive-stage SCLC**

The clinical burden associated with BM is high in ES SCLC, affecting almost 70% of patients. (14) The European Organisation for Research and Treatment of Cancer (EORTC) trial published in 2007, addressed the role of PCI exclusively in ES patients. PCI reduced the incidence of symptomatic brain failure and resulted in longer OS in patients who had had any response to initial chemotherapy. (5)
As a result the use of PCI in SCLC patients with good response to initial treatment was recommended in international guidelines. However a Japanese study comparing PCI plus MRI surveillance to MRI surveillance alone challenged the role of PCI in these patients and is an ongoing subject of controversy. All patients had a brain MRI at baseline followed by scans at 3-monthly intervals up to 12 months and 18 and 24 months after enrolment. It should also be noted that almost half of the patients were aged ≥70 years.

In the EORTC study (n=286), the cumulative risk of symptomatic BM at one year reduced from 40.4% in the control group to 14.6% in the PCI group (p<0.001), and OS improved (1-year survival: 27.1% [PCI group] vs. 13.3% [control group]; p=0.003). In the Japanese study (n=224), the cumulative risk of developing BM at one year was 32.2% in the PCI plus MRI surveillance group compared with 58.0% with the MRI surveillance alone (p<0.001). Considering both the meta-analysis and the two randomised studies, PCI reduces the risk of developing symptomatic or asymptomatic BM by two- to threefold. Interestingly, the 63.8% brain failure rate at 18 months in the MRI surveillance and 40.1% in the PCI plus MRI surveillance groups are quite similar to the brain failure rates observed in the PC185 trial at two years. One could therefore assume that MRI enables the discovery of BM six months earlier.

In terms of survival, both the EORTC study and the meta-analysis showed an improved survival among patients treated with PCI, but there was no benefit in the Japanese study. It should be highlighted, that the Japanese study was closed earlier than planned because the results of an interim analysis highlighted futility. In the final analysis, with a median follow-up of almost 12 months, the gap in median survival (MS) was reduced from five to two months: 11.6 months (95% CI 9.5–13.3) in the PCI plus MRI surveillance group and 13.7 months (10.2–16.4) in the MRI surveillance alone group (HR 1.27, 95% CI 0.96–1.68; p=0.094). The Japanese study thus showed no positive impact of PCI on survival, with one-year survival rate, 13.3% and 27% in the EORTC study and 53.6% and 48.4% in the Japanese study among patients who had no PCI and patients who had PCI, respectively. Table 4 highlights potential factors contributing to the observed differences in outcomes between these two trials. Another reason for this discrepancy may result from host-related genetic differences such as molecular differences in SCLC between Asian and non-Asian populations, as suggested by studies in metastatic disease. In the EORTC study, more patients in the PCI group were suitable for second line treatment (68% vs. 45.1%), compared to 88% (PCI) vs. 89% (no PCI) in the Japanese study. These results are different from previous studies where <50% patients, with ES disease, were candidates for second-line chemotherapy with poor response
rates (10 to 25%). However, the impact of regular brain MRI surveillance on QoL in a population of patients with poor life expectancy should be taken into account.

Cost-effectiveness is another important consideration. Takahashi et al suggested that PCI plus MRI surveillance is not a cost-effective treatment because of the absence of impact on survival, despite a lower brain failure rate and low toxicity. Cost-effectiveness analysis of PCI plus MRI surveillance vs. MRI surveillance alone for patients with ES SCLC was performed in a recent study from the USA which concluded that PCI did not seem to be cost-effective due to the neurocognitive decline effect based on available evidence. Ongoing PCI trials will be evaluating cost-effectiveness further.

Finally, the use of PCI in patients with ES disease has recently become even more controversial with the increasing use of chemo-immunotherapy. In the two RCTs published in this setting, most patients did not have PCI. Thus, a new study comparing brain MRI surveillance to PCI with or without HA is warranted at this stage. The current practice guidelines for PCI use in ES SCLC are shown in Table 5 and ongoing PCI trials are again shown in Tables 2 and 3.

**Toxicity of PCI**

Although there is a strong evidence-base supporting the clinical benefits of PCI, the risk of short and long-term toxicity should be considered when discussing this treatment with patients. Over the years, concerns regarding toxicity of PCI have led to reluctance from both patients and clinicians.

Short-term side effects of PCI include fatigue, alopecia and delayed hair growth, scalp erythema and symptoms of raised intracranial pressure, some of which can be prevented with the use of low dose steroids. Patients should be warned that fatigue of variable severity may last for several months after completion of PCI, likely due to the cumulative effect of the various treatments delivered. In the longer-term, patients can develop changes identified on brain imaging such as ventricular dilatation, cerebral atrophy, periventricular and subcortical white matter changes as well as subcortical, insular cortex and superior temporal gyrus grey matter changes. In some cases, there may be associated symptoms including intellectual impairment, cognitive impairment and ataxia. Some rarer cases of dementia have also been reported, particularly in older series using radiotherapy techniques that are now considered obsolete.

The best evidence of the impact of PCI on neuropsychological functioning comes from RCTs comparing PCI to no PCI in both LS and ES SCLC. In the majority of these studies, QoL, neurological
and psychological functions were assessed using validated questionnaires and neuropsychological assessments. Major findings include the lack of significant differences in terms of neurotoxicity and QoL between the PCI and no PCI arms and the presence of neuropsychological symptoms prior to starting PCI in as many as 60% of patients. However, the EORTC study in the ES setting showed a significant effect on fatigue in the PCI group at three months. Longer-term data were limited, as life expectancy of patients was short. Such detailed QoL analysis was not performed in the Japanese trial using the Mini Mental State Examination (MMSE) only for the assessment of cognitive function. Early decline, followed by neurocognitive recovery after three months, are of importance when discussing PCI with patients who have a short life expectancy.

A recent systematic review investigated risk factors associated with neurocognitive decline in lung cancer patients treated with PCI. Sixteen studies, including eight RCTs, were identified (3553 patients in total, including 2695 SCLC patients). The baseline rate of cognitive impairment was 23–95%. After PCI, the incidence of mild to moderate cognitive decline was 8-89% compared to 3-42% in those who did not receive PCI. Age, PCI dose, fractionation and timing were factors associated with a higher risk of impairment, with the caveat that risk factors were not reported in a large proportion of studies.

When evaluating the toxicity of PCI reported in studies, it is important to consider other systemic treatments delivered as well as the PCI dose/fractionation used. It has indeed been reported that the use of concurrent chemotherapy with PCI and larger fraction sizes/doses of radiotherapy increase the risk of neurotoxicity. Furthermore, the assessment of PCI-related toxicity can be challenging as the neurocognitive and psychological symptoms reported by patients can be related to a number of other causes including the disease itself, paraneoplastic syndromes, occult BM, associated smoking-related comorbidities, the psychological burden of cancer and aging.

The role of hippocampal avoidance

The hippocampus is a structure located in the ventromedial part of the temporal lobes which has an important role in regulating learning, memory encoding and memory consolidation. Irradiation of the hippocampal region has been linked with altered learning and memory formation and there is therefore a rationale for HA to reduce the toxicity of PCI.

A multicentre phase II study showed encouraging results of HA during WBRT on cognitive function in 42 evaluable patients with BM at four months. Conformal avoidance of the hippocampus during WBRT was associated with preservation of memory and QoL as compared with historical series.
A phase III trial from the Netherlands included 168 SCLC patients and compared PCI and HA-PCI. A phase III trial from the Netherlands included 168 SCLC patients and compared PCI and HA-PCI. (39) The primary endpoint of this trial was a decline on total recall of the Hopkins Verbal Learning Test-Revised (HVLT-R) at four months following completion of PCI. (40) A decline was defined as a drop of ≥5 points from baseline. (41) 

Decline on the HVLT-R total recall score at four months was not significantly different between the arms: 29% of patients in the PCI arm and 28% in the HA-PCI arm had a drop ≥5 points (p=1.000). In addition no significant difference in the percentage of patients who declined on a word-list learning test was seen between those who received HA-PCI compared to those who received standard PCI. This trial therefore failed to demonstrate the efficacy of HA-PCI in preserving memory function. Subsequently a Spanish phase III trial (PREMER-trial) reported on 150 SCLC patients who were randomised to receive PCI or HA-PCI. (42) The primary objective was the delayed free recall (DFR) on the Free and Cued Selective Reminding Test (FCSRT) at 3 months. A decrease in the recall scores ≥3 points from baseline was considered a decline. The decline on DFR from baseline to 3 months was lower in the HA-PCI arm (5.8%) compared to the PCI arm (23.5%; p=0.003). In both studies, the incidence of BM was not significantly different between the arms; however neurocognitive evaluation was done with different tests which may explain these contrasting results. Table 6 compares the two studies. Hopefully, the ongoing larger NRG CC003 trial (NCT02635009) of nearly 400 patients will finally settle whether HA-PCI should be part of the SOC treatment.

Further studies have evaluated HA-WBRT and HA-PCI with larger sample sizes to detect smaller differences. In the NRG CC001 trial, 518 patients with BM from solid tumours were randomised to receive 30Gy/10 fractions WBRT or HA-WBRT, and in both arms memantine was added as part of the treatment strategy. (43) This study observed an approximate 10% difference in cognitive failure rates favouring those with HA-WBRT plus memantine. This trial however also did not find a significant difference in the percentage of patients with cognitive failure at four months using the primary (memory specific) endpoint of HVLT-R total recall. We will have to await the results of the NCT02635009 trial which is still recruiting.

PCI related “unknowns” and controversies

Despite its introduction decades ago, there are still a number of unknowns surrounding PCI use. There are also particular subgroups of patients for whom its use remains particularly controversial, or its benefits remain uncertain.

Contraindications
There are a number of relative contraindications to PCI which relate to the potential exacerbation of underlying neuro-pathology. Due to concerns regarding its potentially deleterious effects on neuro-vasculature, it is not recommended for patients with a history of cerebrovascular disease including cerebrovascular accidents, transient ischaemic attacks, vascular malformations or aneurysms. Patients with active epilepsy may also be at risk of increased seizure activity and PCI should therefore be avoided. In addition, due to its potential effect on cognition, the use of PCI should be more cautious in older patients particularly those with pre-existing cognitive conditions. Informed discussion with patients around these issues to ensure shared decision-making is encouraged.

**Timing of PCI**

A significant trend favouring early PCI delivery (within four to six weeks) after induction therapy has previously been reported. Earlier delivery was associated with a reduction in the incidence of BM (p=0.01) but did not significantly affect OS (p=0.39). A secondary analysis of the CONVERT study (phase III superiority RCT comparing once-daily with twice-daily chemoradiotherapy in LS SCLC) showed that the timing of PCI was not associated with BM incidence. In addition, although PCI timing from the end of chemotherapy was associated with OS on univariate analysis (p=0.007), it did not remain so on multivariate analysis (p=0.2). Therefore, suggesting that a delay between the end of chemotherapy and PCI is not prognostic. At present, earlier delivery of PCI after completion of induction therapy is still preferred provided patients have recovered from the side effects of prior therapies.

**Resected early-stage disease**

Surgery has a limited role in the management of patients with SCLC. However, it can be considered for those with early-stage disease (T1/2N0M0 or stages I-IIA). To date there is no published RCT evidence assessing the use of adjuvant PCI in this cohort but one such trial (NCT03514849) is currently recruiting patients.

A retrospective study of 349 patients reported a significant OS benefit with PCI following surgical resection of stage II/III but not stage I disease. Furthermore, although a review of patients from the National Cancer Database found that there was an OS benefit for patients with early-stage SCLC, who received adjuvant chemotherapy and PCI compared to no adjuvant treatment (HR = 0.52, 95% CI: 0.36–0.75), a subsequent subgroup analysis revealed no OS difference between those who received PCI and those who did not (HR = 1.46; 95% CI: 0.46–4.64). Xu et al also reported no significant difference between the cumulative incidence of BM for patients within the PCI and non-
PCI groups with either stage I or stage II SCLC. Furthermore, a secondary analysis of multi-institutional cohort study (n=74) which investigated the addition of PCI following stereotactic body radiotherapy, instead of surgery, for patients with stage I/II SCLC reported that PCI use did not lead to a statistically significant difference in OS or DFS.(52)

It has been proposed that the reduction in efficacy of PCI for patients with early-stage disease post-surgery may be due to their having a lower incidence of BM generally. Most studies have reported incidence rates of 10–15% for stage I and 15–25% for stage II disease.(48,53) One retrospective surgical series (n=126) has even reported a rate of as low as 6.3% in stage I SCLC following complete resection.(54)

At present, without any clear evidence of PCI benefit, particularly in stage I disease, and the potential risk of associated toxicity, an individualised and share decision-making approach is recommended.(1,2,55) The use of MR surveillance may be a suitable alternative.

**Elderly patients**

Elderly patients account for a significant proportion of patients diagnosed with SCLC but despite this they are often underrepresented in clinical trials.(48,56) Age needs to be considered in the decision to deliver PCI. Concerns relating to potential poor performance status (PS), other co-morbidities and an increased risk of neurotoxicity have led to an increased reluctance to consider PCI for this patient group.(47,57) A Dutch population-based study published in 2018 reported a reduction of PCI use with increasing age (78% in those aged 18-59 vs. 66% for those aged ≥80).(13)

A SEER study investigated the use of PCI in 1926 patients ≥70 years with LS SCLC.(57) PCI use was associated with improved 2- (33.3% vs 23.1%) and 5-year survival (11.6% vs 8.6%) compared with no PCI (combined p=0.028) and age was found to be an independent risk factor for survival on multivariate analysis. Its benefit was maintained in those aged ≥75 years but not for those ≥80 years. Rule et al carried out a pooled analysis of four studies evaluating the efficacy of PCI in 155 patients ≥70 years with either LS and ES SCLC.(58) On univariate analysis PCI led to an improved MS compared to no PCI (12 vs. 7.6 months, p=0.001) for the entire elderly population. For patients with LS disease, age was not associated with a significant survival benefit (12.2 vs. 16.0 months, p=0.7630) but those with ES disease were found to have a survival benefit which remained significant on multivariate analysis (10.8 vs. 7.1 months, p=0.003). In addition, Kim et al evaluated 234 patients with LS SCLC treated with curative-intent and performed age subgroup analyses. Interestingly they reported a trend towards improved OS in patients ≥65 years with PCI (p=0.058) but female patients and those with T3/4 disease were not found to benefit.
All of these studies are retrospective and none of them included QoL or neurocognitive data, therefore their results should be interpreted with caution. Current guidelines advocate a personalised approach and shared decision-making when considering PCI in elderly patients. (1,2)

**Patients with poor performance status**

PS has been reported as an independent prognostic factor for patient with both LS and ES SCLC, with poorer PS associated with a reduced MS. (59) The inferior survival seen within this subgroup may result in a lower incidence of BM and therefore detract from any potential benefit from PCI. Only very small numbers of patients with PS ≥2 have been included in clinical trials however so clear conclusions cannot be drawn. (3,5) PCI should not be delivered to such patients but can be considered on a case-by-case basis. (1,2)

**Immunotherapy/PCI combination**

The use of chemo-immunotherapy combinations has become increasingly prevalent for patients with ES SCLC. Data on the use of PCI alongside immunotherapy are currently lacking. The CASPIAN trial did not allow patients in the experimental arm to receive PCI at all. (22) Patients within both the IMPower133 and Keynote 604 studies were able to receive PCI, but only small numbers did, 22 (10.9%) and 27 (11.8%) patients respectively. (23,60) Unfortunately, toxicity information relating to these patients treated with PCI was not reported but no specific safety concerns were raised. Another unanswered question is whether the addition of PCI to immunotherapy improves patient outcomes. A cohort study (NCT04947774) directly investigating the use of PCI alongside immunotherapy for patients with ES SCLC is currently recruiting. In the interim, shared decision-making between the clinician and patient is recommended as well as enrolment of patients in clinical trials. (1,2)

**Drug neuroprotection**

The use of drugs to help reduce the neurocognitive toxicity of PCI and WBRT is another area of interest, and a few phase III trials have taken place. (61) The RTOG 0614 trial randomised 554 patients with BM from solid tumours to receive WBRT + memantine vs. WBRT + placebo. (62) It did not meet its primary endpoint as a non-significant reduction of recall decline at 24 weeks in the memantine arm was reported. However, significant reductions in the rates of decline in memory, executive function, and processing speed were noted and cognitive failure was also significantly delayed. The National Cancer Care Network have acknowledged its potential use for patients receiving WBRT and PCI. (63) Its use is not currently recommended in European guidelines however.
Rapp et al assessed the use of donepezil in 198 patients ≥6 months following partial or WBRT for brain tumours (8% had PCI).(64) They again reported a non-significant difference in composite cognitive score but significant improvements in several individual cognitive scores with donepezil. The effects of donepezil plus vitamin E have also been studied specifically in patients with SCLC.(65) Unfortunately, poor accrual meant that only nine patients were enrolled and therefore no meaningful conclusions could be drawn. Finally, two further studies (NCT01486459 and NCT01553916) were set up to assess the neuroprotective properties of lithium in SCLC but both again suffered from poor accrual. To date the benefit of neuroprotectant drugs remains unclear and further trials are needed.

**Management of SCLC with brain metastases: a role for SRS?**

Given their poor prognosis, SCLC patients with BM have generally been excluded from prospective, RCTs, including those evaluating the efficacy of brain irradiation. As a result, level one evidence is scarce in this population. The Radiation Therapy Oncology Group used recursive partitioning analysis (RPA) to develop three prognostic classes for patients with BM (Table 7) and their use has been validated in SCLC patients.(66) Interestingly, RPA class I SCLC patients have a MS of 8.6 months.

Given that metastatic spread within the brain is generally diffuse and the radiosensitivity of SCLC, WBRT (30 Gy/10 fractions) has been the recommended local therapy for SCLC patients with BM for decades. In the largest recent trial on WBRT vs. best supportive care (BSC) in stage IV NSCLC (n=538), no difference was reported in terms of OS or QoL between the two groups. In the multivariable analysis, patients with good prognosis (RPA class I) benefited more from WBRT vs. BSC, although the difference was not significant.(67). However, no such study has been done in the SCLC setting.

More recently, the widespread use of brain MRI has facilitated the earlier detection of limited number, asymptomatic BM, that could possibly be eligible for brain SRS. Given increased access to SRS and prospective, non-randomised clinical trial data suggesting that several BM may be treated with similar efficacy as more limited disease, in recent years SRS has been increasingly delivered in the SCLC setting as an alternative to WBRT.(68) A recent large, international, retrospective study evaluated SRS in 710 SCLC patients with BM. In patients with a single BM, median OS, and time-to-CNS progression (TTCP) following SRS were encouraging at 11 and 11.7 months, respectively. After propensity score-matched (PSM) analyses, a comparison was performed with 219 patients treated with WBRT. WBRT was
associated with improved TTCP (HR 0.38, p<0.001), without an improvement in OS (PSM-median 6.5 [SRS] vs. 5.2 months [WBRT], p=0.003). (69) Even if such retrospective analyses should be interpreted with caution, this supports further prospective trials in this setting. (70)

Studies evaluating SRS in patients with SCLC are ongoing (Table 8). Two multicentre phase III trials compare SRS vs. HA-WBRT + memantine in SCLC patients. The Canadian CCTG CE.7 (NCT03550391) aims to include 206 patients with 5-15 BM and the two co-primary endpoints are OS and neurocognitive progression free survival (PFS). The American NRG-CC009 phase III trial (NCT04804644) aims to include 200 patients with 1-10 BM and the main outcome measure is neurocognitive failure. The German ENCEPHALON phase II trial (NCT03297788) includes patients with 1-10 BM and compares WBRT to SRS. The primary objective of this single-centre randomised study of 56 patients is 3-month neurocognitive function. Two American single arm phase II trials are testing the safety and effectiveness of SRS in SCLC patients with BM (NCT04516070 and NCT03391362) with 1-5 and 1-10 BM, respectively.

Finally, BM in the setting of SCLC often respond to systemic treatments. For example a 30% intracranial response rate has been reported after immunotherapy. (71) In the two trials assessing anti PD-L1 agents in stage IV SCLC, 8.5-10% of patients had BM. The addition of immunotherapy was limited in terms of OS but no conclusion can be drawn given the limited number of patients in this subgroup. (22, 23)

Conclusion

Prospective RCTs set in the modern treatment era are urgently needed to offer clarity on the use of PCI, particularly for patients with ES disease and within other controversial subgroups. Such studies are in progress and their results are awaited with eager anticipation. Specifically, both the MAVERICK (NCT04155034) and PRIMALung (NCT04790253) trials may offer evidence for many of the so far unanswered questions. They will be studying PCI plus brain MRI surveillance vs. MRI surveillance alone in patients with SCLC across all disease stages. No age limits will be applied and the trials will also include early-stage patients post-surgical resection and those with ES receiving immunotherapy. Until then, guidelines based on current literature suggest that PCI should be considered for all patients with SCLC who have a response to induction treatment, unless otherwise contraindicated, and discussed on a case-by-case basis. However, additional caution is advised in elderly patients and those with poor PS. The benefit of HA and neuroprotective drugs remain
unclear, as does the use of SRS for the treatment of BM. We strongly encourage the thoracic oncology community to enrol patients in prospective clinical trials and collect high-quality real-world data.

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Table 1: Summary of current ASTRO and ESMO clinical practice guidelines on PCI in LS SCLC (stage I-III disease eligible for treatment with curative intent).[1,2]

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<tr>
<td>Response to induction treatment</td>
<td>PCI is recommended in stage II-III SCLC following a response to CRT</td>
<td>PCI should be offered to patients with stage I-III SCLC, provided there is no evidence of PD following CRT</td>
</tr>
<tr>
<td>Early-stage disease</td>
<td>PCI is <em>not</em> conditionally recommended in patients with stage I SCLC. MRI surveillance may be used as an alternative.</td>
<td>The role of PCI in stage I-II disease is not well defined, including for patients who have undergone surgical resection. Shared-decision making is recommended.</td>
</tr>
<tr>
<td>Restaging cranial imaging</td>
<td>Restaging MRI recommended to guide decision-making</td>
<td>N/a</td>
</tr>
<tr>
<td>Age and performance status</td>
<td>PCI is recommended in patients &lt;70 years old and ECOG PS 0-2. Shared decision-making advised in older patients with limited PS and/or significant comorbidities.</td>
<td>PCI is recommended in patients ≤70 years old and ECOG PS 0-2. Shared decision-making advised in older and/or frail patients.</td>
</tr>
<tr>
<td>Dose/fractionation</td>
<td>25 Gy/10 fractions</td>
<td>25 Gy/10 fractions</td>
</tr>
<tr>
<td>Hippocampal avoidance</td>
<td>N/a</td>
<td>No benefit of hippocampal sparing PCI in terms of neurocognitive decline demonstrated as of yet</td>
</tr>
</tbody>
</table>

Abbreviations: ASTRO; American Society for Radiation Oncology; ESMO; European Society for Medical Oncology; PCI, prophylactic cranial irradiation; SCLC, small cell lung cancer; PD, progressive disease; CRT, chemoradiotherapy; MRI, magnetic resonance imaging; N/a, not applicable; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
Table 2. Summary of SCLC trials, currently listed on [https://clinicaltrials.gov](https://clinicaltrials.gov) (accessed September 2021), investigating the use of PCI vs. no PCI.

<table>
<thead>
<tr>
<th>Trial Name / Number</th>
<th>Trial Location</th>
<th>Patient Population</th>
<th>Trial Design</th>
<th>Target</th>
<th>Primary Endpoint</th>
<th>Trial Status</th>
</tr>
</thead>
</table>
| NCT03514849         | China          | pT1-2 N0 M0 SCLC   | Ph III RCT   | Arm 1: Surgical resection, adjuvant CT & PCI  
Arm 2: Surgical resection & adjuvant CT | 360  | OS  | Recruiting      |
| NCT04829708         | China          | LS SCLC with remission after CRT | Ph III RCT   | Arm 1: PCI & MRI surveillance  
Arm 2: MRI surveillance | 534  | OS  | Recruiting      |
| NCT04168281         | Poland         | LS SCLC with absence of progression after initial treatment | Ph II       | Single arm: MRI surveillance (omitting PCI) | 80   | OS  | Recruiting      |
| NCT02605811         | China          | LS SCLC with absence of progression after initial treatment | Ph II RCT   | Arm 1: PCI  
Arm 2: Temozolomide | 426  | Incidence of BM at 2 years | Recruiting     |
| PRIMALung NCT04790253 | Europe        | LS & ES SCLC with absence of progression after initial treatment | Ph III RCT   | Arm 1: PCI & MRI surveillance  
Arm 2: MRI surveillance | 600  | OS  | Not yet recruiting  |
| SWOG S1827 MAVERICK NCT04155034 | USA  | LS & ES SCLC with absence of progression after initial treatment | Ph III RCT   | Arm 1: PCI & MRI surveillance  
Arm 2: MR surveillance | 668  | OS  | Recruiting      |
| NCT04535739         | China          | ES SCLC with CR/PR after CT | Ph III RCT   | Arm 1: Thoracic RT & PCI  
Arm 2: Thoracic RT | 414  | OS  | Recruiting      |
| NCT04947774         | China          | ES SCLC            | Prospective cohort study | Cohort 1: PCI post CT-IO  
Cohort 2: MRI surveillance post CT-IO | 100  | PFS in Brain | Recruiting      |
Abbreviations: USA; United States of America; LS, limited stage; ES, extensive stage; SCLC, small cell lung cancer; Ph, phase; PCI, prophylactic cranial irradiation; OS, overall survival; LS, limited stage; CRT, chemoradiotherapy; MRI, magnetic resonance imaging; BM, brain metastases; ES, extensive stage; CR, complete response; PR, partial response; RT, radiotherapy; CT-IO, chemo-immunotherapy; PFS, progression-free survival.

Table 3. Summary of ongoing SCLC trials, currently listed on [https://clinicaltrials.gov](https://clinicaltrials.gov) (accessed September 2021), investigating the use of HA-PCI.

<table>
<thead>
<tr>
<th>Trial Name / Number</th>
<th>Trial Location</th>
<th>Patient Population</th>
<th>Trial Design</th>
<th>Target</th>
<th>Primary Endpoint</th>
<th>Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02635009</td>
<td>USA</td>
<td>LS &amp; ES SCLC with absence of progression after initial treatment</td>
<td>Ph II/III Arm 1: PCI using 3D CRT Arm 2: HA-PCI using IMRT</td>
<td>392</td>
<td>HVLT-R delayed recall deterioration status at 6 months (Ph III) Intracranial relapse rate at 12 months (Ph II)</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT02058056</td>
<td>Switzerland</td>
<td>LS SCLC</td>
<td>Ph II</td>
<td>Single arm: HA-PCI concurrent with 2nd cycle of CT &amp; concurrent with thoracic RT</td>
<td>44</td>
<td>NCF at 6 months post PCI, measured using HVLT-R, COWA and TMT A/B.</td>
</tr>
<tr>
<td>NCT01797159</td>
<td>USA</td>
<td>LS SCLC with CR to CRT (on CXR)</td>
<td>Ph II</td>
<td>Single arm: HA-PCI</td>
<td>20</td>
<td>HVLT-R delayed recall deterioration status at 6 months</td>
</tr>
</tbody>
</table>

Abbreviations: USA; United States of America; LS, limited stage; ES, extensive stage; SCLC, small cell lung cancer; Ph, phase; PCI, prophylactic cranial irradiation; 3D, three-dimensional; CRT, chemoradiotherapy; HA, hippocampal-avoidance; IMRT, intensity modulated radiotherapy; HVLT-R, Hopkins Verbal Learning Test-Revised; CT, chemotherapy; RT, radiotherapy; NCF, neurocognitive functioning; COWA, Controlled Oral Word Association; TMT A/B, Trail Making Test Part A and B; CXR, chest X-ray.
Table 3. Differences between the EORTC and Japanese studies of PCI in the ES SCLC setting.\(^{(5,14)}\)

<table>
<thead>
<tr>
<th>EORTC study</th>
<th>Japanese study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response to chemotherapy</strong></td>
<td>Any response following 4-6 cycles of CT (type not specified)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Maximum age ≤75 years</td>
</tr>
<tr>
<td></td>
<td>Median age 62 [PCI arm] and 63 [control arm]</td>
</tr>
<tr>
<td><strong>Baseline brain MRI</strong></td>
<td>No baseline MRI required but performed if symptomatic (29%)</td>
</tr>
<tr>
<td><strong>PCI schedule</strong></td>
<td>20Gy/ 5-8 fractions, 24Gy/ 12 fractions, 25Gy/ 10 fractions or 30Gy/ 10-12 fractions</td>
</tr>
<tr>
<td><strong>Salvage brain radiotherapy</strong></td>
<td>8.3% in PCI arm vs. 59.3% in control arm</td>
</tr>
<tr>
<td><strong>Salvage chemotherapy</strong></td>
<td>68% in PCI arm vs. 45.1% in control arm</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Time to symptomatic BM</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td>Survival</td>
</tr>
<tr>
<td></td>
<td>QoL</td>
</tr>
<tr>
<td></td>
<td>Toxic effects</td>
</tr>
<tr>
<td></td>
<td>Treatment costs</td>
</tr>
<tr>
<td><strong>Overall outcome</strong></td>
<td>Significant reduction in cumulative incidence of BM following PCI (HR 0.27; 95% CI 0.16-0.44; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>PCI led to improved 1-year survival (27.1% vs 13.3%)</td>
</tr>
<tr>
<td></td>
<td>HR for death 0.68 (95% CI 0.52-0.88; p=0.003)</td>
</tr>
<tr>
<td></td>
<td>Early termination of study due to futility</td>
</tr>
<tr>
<td></td>
<td>PCI did not lead to longer survival (HR 1.27, 95% CI 0.96-1.68; p=0.094)</td>
</tr>
<tr>
<td></td>
<td>Final analysis showed MS 11.6 months in PCI arm vs. 13.7 months in control arm</td>
</tr>
<tr>
<td></td>
<td>Significant reduction in cumulative incidence of BM following PCI (32.9% vs 59%; p&lt;0.0001)</td>
</tr>
</tbody>
</table>

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; CT, chemotherapy; PCI, prophylactic cranial irradiation; MRI, magnetic resonance imaging; BM, brain metastases; OS, overall survival; QoL, quality of life; PFS, progression-free survival; MMSE, mini mental state examination; HR, hazard ratio; MS, median survival.
Table 4. Summary of ASTRO and ESMO clinical practice guidelines on the use of PCI in ES SCLC (stage IV or stage III disease not eligible for treatment with curative intent). (1,2)

<table>
<thead>
<tr>
<th>Response to induction treatment</th>
<th>ASTRO Clinical Practice Guideline</th>
<th>ESMO Clinical Practice Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with ES SCLC who respond to chemotherapy, a consultation with a radiation oncologist to enhance decision-making on PCI versus MRI surveillance (considering patient- and disease-specific characteristics) is recommended.</td>
<td>PCI is recommended in patients with ES SCLC with no PD following first line chemotherapy. There is a paucity of data on the integration of PCI and immunotherapy. Additional research is therefore required regarding both the safety and efficacy of this approach.</td>
<td></td>
</tr>
</tbody>
</table>

Cranial imaging

| N/a | Staging or follow-up brain MRIs are not required prior to PCI |

Age and performance status

| N/a | PCI is recommended in patients ≤75 years old and ECOG PS 0-2 |

Dose/fractionation

| 25 Gy/10 fractions or 20 Gy/5 fractions | 25 Gy/10 fractions or 20 Gy/5 fractions |

Abbreviations: ASTRO; American Society for Radiation Oncology; ESMO, European Society for Medical Oncology; ES, extensive stage; SCLC, small cell lung cancer; PCI, prophylactic cranial irradiation; MRI, magnetic resonance imaging; PD, progressive disease; N/a, not applicable; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
Table 6. Comparison between the Dutch (NCT01780675) and Spanish (PREMER) PCI vs. HA-PCI trials. (39,42)

<table>
<thead>
<tr>
<th></th>
<th><strong>Dutch study (NCT01780675)</strong></th>
<th><strong>Spanish study (PREMER)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease stage</strong></td>
<td>70% stages LS</td>
<td>71.3% LS</td>
</tr>
<tr>
<td></td>
<td>30% stage ES (no BM)</td>
<td>28.7% ES (no BM)</td>
</tr>
<tr>
<td><strong>Response to</strong></td>
<td>No PD after CRT (stages I-III)</td>
<td>No PD after CRT (stages I-III)</td>
</tr>
<tr>
<td><strong>chemotherapy</strong></td>
<td>or CT (stage IV)</td>
<td>or CT (stage IV)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>43-87 years (Median 64)</td>
<td>43-82 years (Median 64.5)</td>
</tr>
<tr>
<td><strong>PCI schedule and</strong></td>
<td>25 Gy/10 fractions standard PCI</td>
<td>25 Gy/10 fractions standard PCI</td>
</tr>
<tr>
<td><strong>dose constraints</strong></td>
<td>PCI or HA-PCI delivered using IMRT or VMAT</td>
<td>or HA-PCI delivered using IMRT or VMAT</td>
</tr>
<tr>
<td></td>
<td>Mean dose both hippocampi ≤8.5 Gy</td>
<td>Hippocampus: D100% ≤9 Gy (Optimum) or ≤10 Gy (Acceptable). Dmax ≤16 Gy (Optimum) or ≤17 Gy (Acceptable).</td>
</tr>
<tr>
<td></td>
<td>D1% ≤10 Gy</td>
<td>PTV: D2% - 26.7 Gy (Optimum) or 31.2 Gy (Acceptable). D98% 23.7 Gy (Optimum) or 20.7 Gy (Acceptable).</td>
</tr>
<tr>
<td></td>
<td>PTV Dmax &lt;28.75 Gy (115%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V115% PTV ≤1%</td>
<td></td>
</tr>
<tr>
<td><strong>Neurocognitive test</strong></td>
<td>Carried out at baseline, 4, 8, 12, 18 and 24 months:</td>
<td>Carried out at baseline, 3, 6, 12 and 24 months:</td>
</tr>
<tr>
<td><strong>battery</strong></td>
<td>HVLTR-R</td>
<td>FCSRT-A</td>
</tr>
<tr>
<td></td>
<td>TMT A/B</td>
<td>QLQ C30, BN20</td>
</tr>
<tr>
<td></td>
<td>COWA test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wechsler Adult Intelligence Scale III digit span and digit symbol Lafayette’s Grooved Pegboard test</td>
<td></td>
</tr>
<tr>
<td><strong>Imaging schedule</strong></td>
<td>MRI brain at baseline, 4 and 12 months</td>
<td>MRI brain at baseline, 3,12 and 24 months</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Decline on total recall of the HVLTR-R at 4 months following PCI</td>
<td>Decline of DFR score 3 months following PCI</td>
</tr>
<tr>
<td></td>
<td>Decline defined as a drop of ≥5 points from baseline</td>
<td>Decline defined as a drop of ≥3 points from baseline</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td>Other cognitive outcomes</td>
<td>Immediate total free recall</td>
</tr>
<tr>
<td></td>
<td>Incidence and location of BM</td>
<td>Total recall</td>
</tr>
<tr>
<td></td>
<td>PFS</td>
<td>Delayed total recall</td>
</tr>
<tr>
<td></td>
<td>QoL</td>
<td>QoL</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>Incidence and location of BM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td><strong>Overall outcome</strong></td>
<td>Decline on the HVLTR-R total recall score at 4 months was not significantly different (29% [PCI] vs. 28% HA-PCI; p=1.000)</td>
<td>Decline of DFR score at 3 months significantly different (23.5% [PCI] vs. 5.8% [HA-PCI]; p=0.003)</td>
</tr>
<tr>
<td></td>
<td>No significant difference in other cognitive outcomes, incidence of BM or OS between the arms.</td>
<td>No significant difference in QoL, incidence of BM, toxicity or OS between the arms.</td>
</tr>
</tbody>
</table>

**Abbreviations:** LS, limited stage; ES, extensive stage; BM, brain metastases; PD, progressive disease; CRT, chemoradiotherapy; CT, chemotherapy; PCI, prophylactic cranial irradiation; HA, hippocampus avoidance; IMRT, intensity modulated radiation therapy; VMAT, volumetric modulated arc therapy; PTV, planning treatment volume; HVLTR-R, Hopkins Verbal Learning Test-Revised; TMT A/B, Trail Making Test parts A and B; COWA, Controlled Oral Word Association; FCSRT-A, Free and Cued Selective Reminding Test - A; QLQ C30, BN20, Cancer QLQ-C30 questionnaire and brain cancer module; MRI, magnetic resonance imaging, DFR, delayed free recall; PFS, progression-free survival; QoL, quality of life; OS, overall survival.
Table 7. The Radiation Therapy Oncology Group (RTOG) RPA classes for patients with BM in the setting of SCLC.(63)

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient characteristics</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>KPS ≥70 Age &lt;65 years Controlled primary tumour No extracranial metastases</td>
<td>8.6</td>
</tr>
<tr>
<td>II</td>
<td>All others</td>
<td>5.3</td>
</tr>
<tr>
<td>III</td>
<td>KPS &lt;70</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Abbreviations: KPS, Karnofsky performance status.

Table 8. Ongoing SCLC trials, listed on [https://clinicaltrials.gov](https://clinicaltrials.gov) (accessed September 2021), evaluating the role of SRS for the management of BM.

<table>
<thead>
<tr>
<th>Trial Name / Number</th>
<th>Trial Location</th>
<th>Patient Population</th>
<th>Trial Design</th>
<th>Target</th>
<th>Primary Endpoint</th>
<th>Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03550391</td>
<td>Canada</td>
<td>Any solid malignancy and 5-15 BM</td>
<td>Ph III</td>
<td>Arm 1: HA-WBRT + memantine Arm 2: SRS</td>
<td>206</td>
<td>OS and neurocognitive PFS</td>
</tr>
<tr>
<td>NCT04804644</td>
<td>USA</td>
<td>ES SCLC 1-10 BM</td>
<td>Ph III</td>
<td>Arm 1: SRS Arm 2: HA-WBRT</td>
<td>200</td>
<td>Time to neurocognitive failure</td>
</tr>
<tr>
<td>NCT03297788</td>
<td>Germany</td>
<td>ES SCLC 1-10 BM</td>
<td>Ph II</td>
<td>Arm 1: SRS Arm 2: WBRT</td>
<td>56</td>
<td>Rate of neurocognitive decline at 3 months</td>
</tr>
<tr>
<td>NCT04516070</td>
<td>USA</td>
<td>ES SCLC 1-5 BM</td>
<td>Ph II</td>
<td>SRS</td>
<td>50</td>
<td>Rate of cognitive decline at 3 months</td>
</tr>
<tr>
<td>NCT03391362</td>
<td>USA</td>
<td>ES SCLC 1-10 BM</td>
<td>Ph II</td>
<td>SRS</td>
<td>100</td>
<td>Death due to progressive neurological disease</td>
</tr>
</tbody>
</table>

Abbreviations: BM, brain metastases; Ph, phase; HA, hippocampus avoidance; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; OS, overall survival; PFS, progression-free survival; USA, United States of America; ES, extensive stage; SCLC, small cell lung cancer.
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