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What is the current role of prophylactic cranial irradiation in the treatment algorithm for small cell lung cancer?

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ABSTRACT

Prophylactic cranial irradiation (PCI) is considered an important technological advance made in oncology in an effort to reduce the incidence of brain metastases (BM) and improve overall survival (OS) of patients with small cell lung cancer (SCLC).

Although it is often reported that PCI improves the therapeutic potential in limited-stage (LS) SCLC, no randomised trial has ever conclusively confirmed this. Nevertheless, PCI has been considered the standard of care for LS-SCLC since the late 1990s. The data supporting the use of PCI in LS-SCLC are based on an analysis of work performed prior to the current approach to staging [brain magnetic resonance imaging (MRI), positron emission tomography (PET)/computed tomography (CT)]. The evidence for the rationale and feasibility of this approach in the modern diagnostic era should be demonstrated.

The situation with extensive stage (ES) SCLC is seemingly easier because, unlike LS-SCLC, we have data from two randomised trials. Unfortunately, their results are in direct conflict with each other.

Although it is generally assumed that good control of brain disease leads to better quality of life, this has never been prospectively demonstrated. In fact, PCI is associated not only with increased treatment costs and some patient discomfort, but also with non-negligible potential toxicity. For this reason, efforts have been made to preserve cognitive function by sparing the hippocampus. This concept is called hippocampal avoidance.

The optimal fractionation regimen is currently less controversial than the optimal integration of PCI into the treatment algorithm. A dose of 25 Gy administered in 10 fractions should remain the standard for the eventual use of PCI in patients with SCLC.

In summary, PCI is not a *conditio sine qua non* in any indication. Neither in patients with LS-SCLC nor in patients with ES-SCLC has a clear improvement in OS been demonstrated at follow-up using current imaging modalities.

Key words: prophylactic cranial irradiation; small cell lung cancer; radiotherapy; neurotoxicity

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Introduction

Small cell lung cancer (SCLC) is a highly aggressive disease with a propensity for brain metastases (BM). Prophylactic cranial irradiation (PCI) is considered an important technological advance made in oncology in an effort to reduce the incidence of BM and improve overall survival (OS) of patients. Patients with BM in SCLC have a median OS of only 4–5 months [1]. Asymptomatic BM are present in approximately 15% of patients with SCLC at the time of diagnosis [2], and at least 18% of patients with SCLC are diagnosed based on the presence of BM. This can further increase to 25% when mag-

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netic resonance imaging (MRI) is used. As the disease progresses, the incidence of BM increases to 80% of patients developing BM within 2 years of diagnosis [3]. The introduction of PCI in 1977 was therefore a major breakthrough [4].

In the 1980s, when chemotherapy (ChT) and radiotherapy (RT) began to be used in treatment regimens for SCLC with the potential for a curative response, it also became apparent that many patients (30–50%) developed central nervous system (CNS) relapse [5]. Based on experience in the treatment of acute leukaemia in children, several research teams began to use PCI in an attempt to eliminate "nests" of tumour cells in the CNS and thus improve OS in patients with limited stage (LS) SCLC [6].

The aim of this review is to provide a comprehensive overview of the current state of scientific knowledge on the role of PCI in the treatment algorithm for SCLC.

PCI in limited-stage SCLC

Although it is often reported that PCI improves the therapeutic potential in LS-SCLC, no randomised trial has ever conclusively confirmed this. Nevertheless, PCI has been considered the standard of care for LS-SCLC since the late 1990s. However, this was not based on a randomised trial, but on the results of a meta-analysis published in 1999 by Aupérin et al. [5]. This meta-analysis, based on individual data from seven randomised trials, showed that OS was improved in patients with PCI compared with those without PCI (relative risk 0.84). A total of 987 patients who were treated between 1977 and 1994 were analysed. The absolute reduction in mortality was found to be 5.4%. However, there was no effect of PCI on the cumulative incidence of metastases at other sites or locoregional recurrence. Thus, the improvement in OS was solely due to better control in the CNS (reduction in the risk of BM from 58.6% to 33.3% at 3 years). The characteristics of the patients evaluated were highly variable (some had extensive stage (ES)-SCLC, different ChT regimens, different fractionation regimens for RT, different ways of assessing treatment response were used, etc.). These results cannot be extrapolated to the current situation with the possibility of using MRI. Most of the trials in this meta-analysis assessed complete response using lung X-rays, not computed tomography (CT).

The rationale for the use of PCI in LS-SCLC was based on the assumption that the brain is either the only site of relapse or, as the initial site of relapse, allows subsequent colonisation of other areas by tumour cells. However, the available data do not support either of these assumptions, at least in the majority of patients. Arriagada et al. [7] analysed data from two randomised trials from the 1980s and found that the 5-year event free rate (relapse in any localisation) was 11% in the PCI group compared with 17% in the non-PCI group. Neither in that study nor in the Aupérin meta-analysis cited above did any patients have brain MRI, and a significant number of patients did not have a CT scan but only pneumoencephalography.

In a Dutch study [8], which included 481 patients, the incidence of BM was 24% in the MRI era compared with 10% in the CT era. While all patients diagnosed with BM in the CT era had corresponding symptoms, about half of the brain recurrences detected by MRI were asymptomatic. Thus, the therapeutic benefit of PCI observed in both meta-analyses [5, 7] may be due to the treatment of pre-existing BM.

A reasonable hypothesis arising from the conclusions of the meta-analyses, using current knowledge, is that the benefit of PCI in the above meta-analyses [5, 7] is due to the treatment of often already metastatic disease, which would be clearly detectable and treated with palliative whole-brain RT (WBRT), whereas patients with no evidence of BM could avoid PCI. However, the interpretation of the results of many older trials and meta-analyses is also complicated by the phenomenon of so-called stage migration, i.e. the fact that the stage of the patients would be different using today's standard staging imaging modalities [whole-body positron emission tomography (PET)/computed tomography (CT), brain magnetic resonance imaging (MRI)]. A significant proportion of patients classified as LS-SCLC in the 1980s would now be classified as ES-SCLC.

Another issue is that the nature of LS-SCLC has also changed in that it is now diagnosed at a lower stage and with a smaller volume (tumour burden) as a result of better availability of CT scans and the expansion of screening options using low-dose CT. Stage I patients can only be treated

surgically as they have been shown to have a low risk of BM. A retrospective study by Xu et al. [9] evaluated a total of 349 patients and found a low risk of BM in patients with localised disease (stage I) and no benefit in terms of brain recurrence and OS in these patients using PCI.

Thus, it is clear that the data supporting the use of PCI in LS-SCLC are based on an analysis of work performed prior to the current approach to staging (brain MRI, PET/CT). It should be noted that the evidence for the rationale and feasibility of this approach should be demonstrated in the same way as for new drugs.

PCI in extensive stage SCLC

The situation with ES-SCLC is seemingly easier because, unlike LS-SCLC, we have data from two randomised trials. Unfortunately, their results are in direct conflict with each other.

The first randomised trial on this topic, which has become a cornerstone in the field of PCI research, was the European Organisation for Research and Treatment of Cancer (EORTC) Slotman trial [10], published in 2017, which looked at PCI only in ES-SCLC patients who responded to initial ChT. The trial was conducted between 2001 and 2006 and enrolled a total of 286 patients. The primary endpoint of the trial was time to the occurrence of symptomatic BM. This was to determine whether PCI could reduce the incidence of symptomatic BM, i.e. the presence of at least one key symptom in combination with radiological confirmation of metastasis. Secondary endpoints were OS, quality of life (QoL), toxicity and treatment costs. PCI was associated with longer median disease-free survival (DFS) (12 weeks *vs.* 14.7 weeks, p = 0.02) and median OS (5.4 months *vs.* 6.7 months, p = 0.003). Symptomatic BM occurred in 24 of 143 patients (16.8%) in the PCI group, and in 59 of 143 patients (41.3%) in the control group. One-year survival was 27.1% *vs.* 13.3% in favour of PCI. There was no significant difference between the groups in terms of cognitive and emotional function. Nor was there any effect of PCI on extracranial disease progression observed. Unfortunately, no standard criteria have been defined to assess treatment response, such as RECIST 1.1 (Response Evaluation Criteria in Solid Tumours) [11]. Any treatment response was acceptable. The presentation of complete remissions is also not reported in this study. CT or MRI scans were not a standard part of staging and follow-up unless symptoms of possible involvement were present. Only 29% of randomised patients had brain imaging performed at the time of diagnosis. Therefore, the presence of asymptomatic BM at the time of diagnosis was not taken into account. Therefore, a significant proportion of patients may have had BM at the time of randomization. Furthermore, it was also not reported how many patients had this imaging prior to randomisation. It is also not reported how many patients were treated with a cisplatin-containing regimen, which has been shown to increase the likelihood of a response and prolong survival [12]. The different fractionation regimens used in this study were 5 × 4 Gy to 20 Gy (89 patients), 10 × 3 Gy to 30 Gy (23 patients), 12 × 2.5 Gy to 30 Gy (9 patients), and 10 × 2.5 Gy to 25 Gy (7 patients).

The second relevant study on a similar topic was a randomised multicentre Japanese phase III trial in 2017 [13] which involved a total of 47 centres. This study also evaluated the efficacy of PCI in the treatment of ES-SCLC. Between 2009 and 2013, 224 patients with any response to initial ChT with a platinum doublet (cisplatin/carboplatin; at least 2 cycles) and no evidence of BM on MRI were evaluated. The groups of patients with PCI (standard 10 fractions of 2.5 Gy to 25 Gy) and without PCI, i.e. the group with observation and brain MRI monitoring group were compared. As part of the follow-up, brain MRI was performed at 3-month intervals until month 12, then at months 18 and 24 after study entry. The primary endpoint was OS. However, the study stopped early at the interim analysis because the hypothesis was clearly not met - the probability that PCI would improve OS was only 0.011% compared to observation. Secondary endpoints were time to detection of BM, progression-free survival (PFS), adverse events, and Mini-Mental State Examination (MMSE) score. Treatment response was assessed by RECIST 1.1 [11] and cognitive function by MMSE score before randomisation and at months 12 and 24. There was no significant difference in median OS, 11.6 months in the PCI group and 13.7 months in the observation group (p = 0.094). One- and two-year survival rates were 48.4% and 15% in the PCI group and 53.6% and 18.8% in the obser-

vation group, respectively. BM were observed in 54 of 113 patients (48%) in the PCI group and 77 of 111 patients (69%) in the observation group. Median PFS was 2.3 months in the PCI group versus 2.4 months in the observation group (p = 0.75). MMSE scores were not significantly different between groups at follow-up. Although the incidence of BM was higher in the observation group, this was not reflected in a shorter OS, but rather in a longer OS. This may be explained by the fact that a larger proportion of observation patients received third or fourth line ChT. This difference may be due to the persistent manifestations of toxicity after PCI in terms of anorexia, nausea, malaise and impaired QoL, and thus the inability to administer systemic therapy. In this study, even 40 (36%) patients in the control group and 29 (26%) patients in the PCI group received a total of 4 lines of ChT, which is not very common in real daily practice. Caution should also be exercised regarding possible ethnic differences between the Asian population studied here and other populations.

A key factor that prevents a relevant comparison between the two studies described above [10, 13] is that they studied two completely different patient populations. In addition to the imaging modalities used (or not used), almost all patients in the Japanese study received second-line ChT, which may prolong survival and reduce symptoms. So, the question is not whether these trials are right or wrong, because they are both right. However, they were designed for different patient populations.

Maeng et al. [14] published a meta-analysis in 2018 in which they set OS as the primary endpoint and included primary and secondary analyses of prospective studies only. The six trials analysed included the EORTC trial [10] and a Japanese trial [13], which provided data from the primary analyses. The authors found no benefit of PCI on OS [hazard ratio (HR) 0.82; p = 0.19]. However, the PCI group showed significantly better 1-year survival (37.1% *vs.* 27.1%; HR 0.83; p = 0.002) and PFS (HR 0.83; p = 0.03) and a reduced risk of BM (HR 0.34; p < 0.001) than the non-PCI group.

To address the current confusion, The Southwest Oncology Group trial (Maverick SWOG 1827), a randomised trial, is currently underway [15]. The trial is enrolling patients with both LS-SCLC and ES-SCLC who are free of evidence of BM at the time of randomisation and is comparing two arms, those with PCI and those without PCI. Both groups will undergo regular brain MRI at 3, 6, 9, 12, 18, and 24 months. PCI can be performed either as hippocampal avoidance (HA)-PCI or as WBRT. The primary endpoint is OS, and the secondary endpoints are cognitive function, BM-free survival, and OS at each stage.

Neurotoxicity of PCI and its prevention

In the absence of a convincing improvement in OS, PCI must at least demonstrate superiority in symptom control and QoL over an observation approach with treatment only when a relapse is detected. Although it is generally assumed that good control of CNS disease leads to better QoL, this has never been prospectively demonstrated. In fact, PCI is associated not only with increased treatment costs and some patient discomfort, but also with non-negligible potential toxicity.

Concerns about neurotoxicity are among the most common reasons for skipping PCI [16]. The latter has been studied in the past mainly in patients with existing BM after WBRT [17]. The pathogenetic mechanism of cognitive deficits is radiation-induced damage to proliferating neuronal precursor cells in the subgranular zone of the hippocampus, a structure of the limbic system that is important for memory formation. This damage is particularly linked to the problems with learning, memory, and spatial orientation problems that can occur after WBRT [18]. There is an early decline in cognitive function within the first 4-6 months. This early component primarily reflects verbal and short-term memory [19–21], and a significant decline in Hopkins Verbal Learning Test (HVLT) scores at 3, 6, and 12 months after PCI [22, 23]. A pooled analysis of the randomised RTOG 0212 [23] and 0214 [22] trials showed that PCI was associated with a higher incidence of self-reported cognitive decline compared with observation in patients who did not experience a cerebral relapse [24].

For this reason, efforts have been made to preserve cognitive function by sparing the hippocampus. This concept is called hippocampal avoidance (HA). The currently dominant use of intensity modulated radiotherapy (IMRT) and volumet-

ric modulated arc therapy (VMAT) techniques allows for easier reduction of radiation doses to the hippocampal region during PCI. One of the earliest studies to support this concept was the phase II RTOG 0933 trial which demonstrated cognitive sparing with HA-WBRT in patients with BM [25]. A major concern with HA-PCI in patients with SCLC is the possibility of BM in the hippocampus and in the "hippocampal avoidance zone (HAZ)" which consists of the hippocampus with a radial extent of 5 mm, particularly for the purpose of developing a safe radiation treatment plan. However, the incidence of metastases in the hippocampus and perihippocampal region is generally low [26]. For example, in the study by Cook et al. [27], which looked at patterns of recurrence after HA-PCI, no patient had an isolated HAZ recurrence and only 3 out of 17 patients had multifocal recurrences that included the HAZ.

Currently, we have two relevant randomised trials investigating the effect of HA-PCI on the rate of cognitive decline which are very similar in design, number of patients and objectives, but have very different results.

In 2021, a study by Rodríguez de Dios et al. [27] was published. This is a phase III study in which a total of 150 patients with SCLC (71.3% LS-SCLC, 28.7% ED-SCLC) were treated with either PCI or HA-PCI. The standard fractionation regimen used was 25 Gy in 10 fractions. HA-PCI resulted in better preservation of cognitive function based on the Free and Cued Selective Reminding Test (FCSRT) performed at month 3 ($p = 0.003$). Thirty (21.8%) patients developed BM (17 in the HA-PCI arm and 13 in the PCI arm). However, there was no significant difference between the two arms. One patient in the HA-PCI arm developed an isolated BM in the hippocampus. No patient had an isolated metastasis in the HAZ. Two of the 12 patients with multiple brain involvement also had metastases in the HAZ. Median OS was 23.4 months in the HA-PCI group and 24.9 months in the PCI group ($p = 0.556$).

In the same year, the study by Belderbos et al. [28] was published, a multicentre randomised phase III study that evaluated 168 patients with SCLC (70% LS-SCLC, 30% ES-SCLC). Like the previous study, it compared PCI and HA-PCI arms using a fractionation regimen of 25 Gy in 10 fractions. The primary endpoint was cognitive decline as assessed by the HVLT-R (revised) test at month 4, but there was no significant difference between the two arms ($p = 1.000$). OS was also not significantly different, with a median OS of 19.9 months in the PCI group and 18.5 months in the HA-PCI group ($p = 0.70$). The cumulative incidence of BM at 2 years was 20% in the PCI group and 16% in the HA-PCI group ($p = 0.60$).

Taken together, these two studies at least confirmed the well-known hypothesis [26] that the incidence of both BM and OS did not differ between the hippocampus-sparing and non-sparing groups. In any case, a larger randomised trial will have to solve this current puzzle. An analysis of the NRG Oncology CC003 trial [29], which has already recruited 418 patients with both LS-SCLC and ES-SCLC, comparing the groups of patients who underwent PCI with 3D CRT (three-dimensional conformal radiotherapy) and HA-PCI with IMRT, is currently underway. The primary endpoints are cognitive decline (as assessed by the HVLT-R) and the incidence of intracranial relapse.

The beneficial effects of memantine, a drug for Alzheimer's disease, on cognitive function were sought to be confirmed in a randomised phase III trial, RTOG 0614 [30] which concluded that neurocognitive function improved after WBRT when combined with the administration of memantine, a drug thought to reduce the release of excitotoxic glutamate in the brain. Memantine may therefore delay the onset of cognitive dysfunction in patients undergoing brain RT. Patients who underwent RT and took memantine had a longer time to cognitive decline (HR 0.78; $p = 0.01$). The study population consisted of patients undergoing WBRT for pre-existing BM from various primary sources. Combination with memantine should be considered in those situations where the HA-WBRT technique is used [31]. However, in many countries, memantine is not approved by drug regulatory authorities for use in this indication.

Fractionation regimen, target volume

The optimal fractionation regimen is currently less controversial than the optimal integration of PCI into the treatment algorithm. For many years, the most commonly used regimen of 10 fractions of 2.5 Gy to 25 Gy has been considered suboptimal by many authors, and some meta-analyses suggest-

ed that the incidence of BM in LS-SCLC might be reduced with higher doses. This assumption was attempted to be confirmed by Le Péchoux et al. [32]. Between 1999 and 2005, a total of 720 LS-SCLC patients who achieved complete remission after ChT and RT were randomised to either a control dose group (25 Gy in 10 fractions of 2.5 Gy) or to a higher dose group (36 Gy in 18 fractions of 2 Gy or in 24 fractions of 1.5 Gy twice daily). Brain imaging (CT scans in 75%, MRI scans in 20% and CT and MRI scans in 5% of cases) had to be performed within one month prior to randomisation and then once a year as part of the follow-up by CT or MRI, if neurological symptoms were present. The primary endpoint was the incidence of BM at 2 years. There was no significant difference between the control and higher dose arms in this regard, with 29% and 23%, respectively (HR 0.80; p = 0.18). Two-year OS was 42% and 37%, respectively (HR 1.20; p = 0.05). Two-year DFS was 33% in the control group and 29% in the higher dose group (HR 1.16; p = 0.10). Therefore, a dose of 25 Gy administered in 10 fractions should remain the standard for the eventual use of PCI in patients with LS-SCLC.

This regimen is also used when PCI is used in patients with ES-SCLC. PCI should not be combined with concurrent ChT because of the risk of neurotoxicity. The target volume is the whole brain up to the inferior border of C2. As mentioned above, there is no consensus on the necessity or appropriateness of the HA-PCI concept.

The future

As the efficacy of systemic therapies for CNS involvement continues to improve, such as the use of PD-L1 checkpoint inhibitors (atezolizumab), the need for CNS prophylaxis with PCI will continue to decrease. This is because checkpoint inhibitors can cross the blood-brain barrier and induce a therapeutic response in patients with known BM. Therefore, their use may be sufficient to improve control of microscopic disease in the CNS and may replace the use of PCI [34]. For example, there are reports on the efficacy of PD-L1 inhibitor durvalumab from the phase III PACIFIC trial which demonstrated a reduction in the risk of brain relapse in patients with non-small cell lung cancer (NSCLC) [35]. Based on data from the CASPIAN study, durvalumab in combination with etoposide and a platinum derivative (followed by maintenance with durvalumab) is also currently recommended in the first-line treatment of ES-SCLC. In this study, an equal proportion of patients with initially present BM (10%) were in both arms, and a significant improvement in OS in the durvalumab group was found. PCI was only allowed in the platinum etoposide group, at the discretion of the investigator, and only 8% of patients in the control group received PCI [36].

Another group of drugs with proven efficacy in the treatment or prevention of BM are anti-angiogenic tyrosine kinase inhibitors. In CALGB 30504 [37], a randomised phase II trial of sunitinib, patients with ES-SCLC who had responded to platinum-based ChT were studied. Although imaging was required prior to enrollment, it was up to the treating physician to decide whether or not to perform PCI. Patients treated with sunitinib in combination with PCI had better PFS and OS. The incidence of BM was significantly higher in the non-PCI group than in the PCI group (27% *vs.* 12%).

With the increasing capabilities of brain imaging and the use of SBRT in the treatment of BM, the status and value of this treatment also needs to be rapidly clarified [38].

Conclusion

So, what can we do with the available information and how should we proceed in routine clinical practice? For PCI to be clearly incorporated into treatment regimens, the concept must meet the following criteria: it must demonstrate an improvement in OS and QoL over observation and MRI controls, followed by salvage therapy for eventual disease progression. This should be demonstrated in the same way as for new drugs.

In general, it can be stated that PCI is not a *conditio sine qua non* in any indication. Neither in patients with LS-SCLC nor in patients with ES-SCLC has a clear improvement in OS been demonstrated at follow-up using current imaging modalities.

However, current internationally widely accepted guidelines — National Comprehensice Cancer Network (NCCN) [39], European Society for Medical Oncology (ESMO) [40] and European Association of Neuro-Oncology (EANO) [41] — still rec-

ommend PCI for patients with LS-SCLC who reach a response after ChT and RT. They all also stated that the benefit of PCI is unclear in patients with very early-stage SCLC (T1–2a, N0M0) who have had definitive therapy (i.e. surgery, SBRT). PCI is not recommended in patients with ES-SCLC with poor PS (3–4) or impaired neurocognitive function, but is justified in the absence of staging or follow-up brain MRI assessments in patients < 75 years of age and a PS of 0-2 who achieved a response after ChT.

Conflict of interest

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