Role of Prophylactic Cranial Irradiation in Extensive-Stage Small Cell Lung Cancer

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ABSTRACT

Patients with small cell lung cancer (SCLC) are at significant risk of developing brain metastases during their disease course. Prophylactic cranial irradiation (PCI) has been incorporated into SCLC treatment guidelines to diminish the risk of developing brain metastases. In 2007, a randomized trial suggested that PCI decreases the incidence of brain metastases and prolongs overall survival (OS) in patients with extensive-stage SCLC (ES-SCLC) who have responded to initial therapy. However, this study did not include modern central nervous system imaging with CT or MRI prior to randomization. A more recent Japanese trial with MRI staging and surveillance demonstrated that PCI diminished the incidence of brain metastases but did not improve survival. This review examines the largest clinical studies, controversies, and future directions of PCI in patients with ES-SCLC.

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SCLC has one of the highest propensities to spread to the brain.¹ With as many as three-quarters of patients developing brain metastases during their disease course, reducing the risk of central nervous system (CNS) failure appears important.^{2,3} Additionally, SCLC can present with multiple or diffuse CNS metastases.⁴ PCI has been used since the 1970s to decrease the rate of intracranial failure for patients with SCLC.⁵ This review examines the data and controversy surrounding PCI for ES-SCLC.

Historical Data Supporting PCI

Initial trials of PCI in SCLC demonstrated improved intracranial control but no difference in survival.^{6,7} A meta-analysis of 7 randomized trials from 1965 through 1995 established the value of PCI in SCLC.⁶ Aupérin et al⁶ analyzed 987 patients with limited-stage SCLC (LS-SCLC) and ES-SCLC with a complete response after chemotherapy (with or without thoracic radiotherapy [RT]) and no prior CNS RT or brain metastases. PCI reduced the incidence of brain metastases (relative risk [RR], 0.46; $P < .001$), increased disease-free survival (RR, 0.75; $P < .001$), and decreased the risk of death (RR, 0.84; $P = .01$). This corresponded to a 5.4% increase in 3-year OS rate (20.7% vs 15.3%). ES-SCLC represented 12% of patients receiving PCI and 17% of patients who did not. When the data were analyzed by stage of disease, there were no differences in terms of risk of death or development of brain metastases.

A second meta-analysis by Meert et al⁷ reported similar results analyzing PCI in 12 trials including both LS-SCLC and ES-SCLC. Five of these trials included only patients with a complete response to chemotherapy. Baseline imaging included brain CT for 5 trials and brain scintigraphy for 6 trials. There was a reduced incidence of brain metastases (hazard ratio [HR], 0.48; 95% CI, 0.39–0.6) for all studies. In those with a complete response to initial systemic therapy, PCI was associated with an improved OS (HR, 0.82; 95% CI, 0.71–0.96). Both meta-analyses established PCI as a standard of care for SCLC.

Modern Data on PCI for ES-SCLC

Investigators from the EORTC conducted a phase III trial to clarify the role of PCI for patients with ES-SCLC.⁸

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Adults with ES-SCLC who had a response to 4 to 6 cycles of chemotherapy (n=286) were randomized to PCI (dose fractionation ranged from 20 Gy in 5 once-daily fractions to 30 Gy in 12 once-daily fractions) or no further therapy. Brain imaging before or after chemotherapy was not mandatory unless indicated for neurologic symptoms (completed in 29%). Results showed that PCI reduced the risk of symptomatic brain metastases (HR, 0.27; $P<.001$), which resulted in a 1 year rate of brain metastasis development of 14.6% in those who received PCI versus 40.4% in those who did not. Furthermore, median disease-free survival improved from 12.0 to 14.7 weeks in the PCI group. Extracranial disease-free survival did not differ between the 2 groups. Importantly, median survival was improved with PCI (6.7 vs 5.4 months; $P=.003$). The investigators concluded that PCI diminishes brain metastases development risk and prolongs OS.

A second trial conducted in Japan introduced controversy regarding the benefit of PCI in ES-SCLC.⁹ Takahashi et al⁹ randomized 224 patients with ES-SCLC that responded to chemotherapy to PCI (25 Gy in 10 once-daily fractions) versus no PCI. Importantly, all patients underwent MRI prior to PCI to rule out brain metastases, as well as surveillance MRI at determined intervals. The trial was stopped prematurely at planned analysis of the first 163 patients due to futility. PCI reduced the risk of brain metastasis development at 18 months from 64% to 40%. However, PCI did not prolong progression-free survival or the primary endpoint of OS (HR, 1.27; $P<.094$). As a result, the investigators concluded that PCI does not prolong OS and is not essential for patients with ES-SCLC that responds to chemotherapy.

To reconcile the discrepancies with the EORTC trial, we must highlight the differences in the patient population, CNS imaging, surveillance, and resulting treatment. In the Japanese trial, all patients received brain MRI prior to randomization and at regular surveillance intervals. In the EORTC trial, baseline brain imaging was not mandatory. Thus, a meaningful group of patients in the EORTC trial were included with occult brain metastases. Additionally, the proportion of patients who received salvage radiation for detected brain metastases on the observation arms of each trial was different (83% in the Japanese trial vs 59% in the EORTC trial), likely stemming from the difference in method and resulting promptness of diagnosis (radiographic vs symptomatic, respectively).¹⁰ Patients in the Japanese trial were treated with second-line chemotherapy more often than those in the EORTC trial. Data have suggested that Japanese patients with ES-SCLC respond to chemotherapy differently than European patients.^{11–13} It is uncertain whether these differences affected the results of these trials.

PCI was well tolerated in both trials. In the EORTC trial, patients experienced alopecia and fatigue more

often with PCI ($P<.001$); however, there was no difference in neurocognition ($P=.07$). Both trials provided data indicating that PCI reduces the risk of developing symptomatic brain metastases. However, its impact on OS remains controversial.

Retrospective Studies

A large pooled analysis of 4 trials from the North Central Cancer Treatment Group (NCCTG) examined the role of PCI in a wide spectrum of patients with either stable LS-SCLC (n=318) or ES-SCLC (n=421).¹⁴ Patients who received PCI with either 30 Gy in 15 daily fractions or 25 Gy in 10 daily fractions had a prolonged survival (HR, 0.61; $P<.0001$). This OS benefit remained after adjusting for multiple factors, including patient characteristics and tumor response to initial therapy. Additionally, the survival benefit with PCI remained in both ES-SCLC (HR, 0.77; $P=.0282$) and LS-SCLC (HR, 0.68; $P=.0045$). This benefit did come with an increased rate of grade ≥ 3 adverse events (64%) compared with treatment without PCI (50%) ($P=.0004$). A recent pooled analysis of 5 studies examining PCI in ES-SCLC demonstrated that in 984 patients, PCI did not improve OS (HR, 0.82; $P=.19$) but did improve progression-free survival (HR, 0.83; $P=.03$) and diminished the risk of developing brain metastases (HR, 0.34; $P<.001$).¹⁵

A National Cancer Database analysis of PCI in 4,357 patients with ES-SCLC demonstrated a survival benefit with PCI (median survival, 13.9 vs 11.1 months; $P<.001$).¹⁶ Although only 11% of patients were treated with PCI in this study, the investigators excluded those with a poor prognosis (<6 months). They concluded that in a large modern population of patients, PCI for ES-SCLC may have a survival benefit.

An updated National Cancer Database propensity score-matched analysis of 21,019 patients with ES-SCLC also demonstrated that the addition of PCI and thoracic RT improved survival ($P<.05$).¹⁷ Utilization of MRI for CNS staging varied by cancer facility in the pooled NCCTG analysis and the National Cancer Database analysis.^{14,16} In the context of the Japanese randomized trial, the lack of MRI for CNS is a significant limitation when interpreting these results.

PCI is tolerated in elderly patients. Rule et al¹⁸ investigated the role of PCI in elderly patients (age ≥ 70 years) with LS-SCLC or ES-SCLC enrolled on 4 trials from the NCCTG who had a stable or good response to initial therapy. Patients who had received PCI had prolonged survival (HR, 0.53; $P=.001$). Multivariate analysis of ES-SCLC demonstrated that PCI was the only factor associated with prolonged survival (HR, 0.47; $P=.03$). As seen in other studies of younger patients, PCI did result in a higher rate of grade ≥ 3 adverse events (71.4% vs 47.5%; $P=.0031$).

Optimal Regimen for PCI

Data suggest that 25 Gy in 10 once-daily fractions is a reasonable approach for PCI in SCLC. Le Pécoux et al¹⁹ published results of a randomized trial of 720 patients with LS-SCLC comparing the outcome of standard versus dose-escalated PCI on brain metastasis incidence. Standard dose was 25 Gy in 10 once-daily fractions and the escalated arm received 36 Gy with 18 once-daily fractions or 24 twice-daily fractions. There was no significant difference in the primary endpoint of 2-year brain metastasis incidence in the standard versus dose-escalated arm (HR, 0.80; $P=.18$). The 2-year survival rate was 42% with standard dose versus 37% with dose escalation (HR, 1.20; $P=.05$). The rate of acute fatigue, hair loss, and nausea or vomiting no different. The investigators concluded that dose escalation did not reduce the risk of developing brain metastases and that 25 Gy in 10 daily fractions is the optimal dose.

RTOG 0212 studied the neurotoxic effects of dose fractionation of PCI in LS-SCLC.²⁰ Patients were randomized to 25 Gy in 10 daily fractions versus 36 Gy (second randomization to 18 daily fractions or 24 twice-daily fractions). There was no difference in the risk of brain metastasis development or survival. At 12 months after PCI, there was a higher rate of chronic neurotoxicity in patients who received the higher dose ($P=.02$), with older age being the most significant predictor. In terms of preserving neurocognition, the authors suggested that 25 Gy in 10 fractions should remain the standard of care. For PCI in patients with ES-SCLC who experience a response to initial systemic therapy, 25 Gy in 10 daily fractions is acceptable.

Hippocampal Avoidance PCI

The benefits of PCI come with risks of short- and long-term neurocognitive toxicity.^{21,22} A pooled analysis of RTOG 0212 and RTOG 0214 assessed the impact of PCI on cognitive functioning using the EORTC Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).²³ In this study, PCI was associated with >3 times the risk of self-reported cognitive decline at both 6 (odds ratio, 3.6; $P<.0001$) and 12 months (odds ratio, 3.4; $P<.0001$) as well as decline on the Hopkins Verbal Learning Test-Recall ($P=.002$). Furthermore, a quality-of-life (QoL) analysis of a randomized trial studying dose escalation in PCI demonstrated a deterioration in short-term memory and the ability to communicate.²²

As treatment for SCLC improves, the potential for long-term toxicity including neurocognitive decline will become more evident. Using modern RT techniques, there has been significant interest in avoiding the hippocampus, a structure responsible for memory and learning, to reduce the risk of neurocognitive decline when treating the whole brain.²⁴ Hippocampal avoidance during whole-brain RT (HA-WBRT) preserves memory and

QoL when directly compared with WBRT without HA.²⁵ The neuroprotective benefit of HA remains when combined with memantine.²⁶ The PREMIER phase III randomized trial demonstrated an improved cognitive preservation with HA-PCI versus PCI in 150 patients with SCLC.²⁷ A Dutch phase III randomized trial of PCI with or without HA in 168 patients with SCLC demonstrated no neurocognitive benefit with HA (ClinicalTrials.gov identifier: NCT01780675).²⁸ Both trials used the same dose regimen (25 Gy in 10 daily fractions), which resulted in similar brain metastasis development rate and OS. However, different neurocognitive evaluation and hippocampal dose constraints were used. The PREMIER trial used the Free and Cued Selective Reminding Test and constrained the equivalent dose in 2 Gy fractions delivered to 100% of the hippocampal volume to <9 Gy and maximum dose to 16 Gy. The Dutch trial used the Hopkins Verbal Learning Test and constrained the hippocampal mean dose to ≤ 8.5 Gy and a maximum dose to <28.75 Gy. Whether these discrepancies account for the different outcomes is unknown. We await data from NRG-CC003 (NCT02635009), a randomized trial of PCI with or without HA for LS-SCLC or ES-SCLC. Further study is needed to elucidate a potential benefit of HA-PCI for SCLC.

Future Directions

PCI for ES-SCLC in the MRI era is being questioned, particularly following the results of the Japanese phase III trial that demonstrated no difference in survival with adequate MRI staging and observation.⁹ Physicians in the United States are reporting a reduced utilization of PCI in ES-SCLC.²⁹ Other studies incorporating MRI have confirmed that PCI reduces brain metastases in ES-SCLC without a clear impact on survival and may not be cost-effective compared with MRI surveillance alone.^{30,31} SWOG S1827 (MAVERICK) is an open phase III randomized trial comparing MRI surveillance versus PCI in patients with LS-SCLC and ES-SCLC (ClinicalTrials.gov identifier: NCT04155034). In patients with brain metastasis from SCLC, the FIRE-SCLC multicenter study demonstrated that those treated with first-line stereotactic radiosurgery (SRS) without prior PCI or WBRT have a diminished time to CNS progression but similar survival when compared with those treated with WBRT.³² This is significant, given that SRS is an attractive treatment option with a reduced impact on cognition and QoL. Because most patients who do not receive PCI eventually require treatment with either WBRT or SRS, we await data from NRG-CC009, a phase III trial comparing SRS to HA-WBRT with memantine for patients with brain metastases from SCLC (NCT04804644).

Tumor-treating fields (TTFields) is a therapy that utilizes alternating electrical fields to disrupt tumor cell proliferation that has demonstrated efficacy in glioblastoma.³³

As an alternative to PCI, a multi-institutional prospective study is evaluating the potential for TTFields as a prophylactic option to reduce the rate of brain metastases in both LS and ES-SCLC (NCT03995667). Patients must demonstrate at least a partial response to standard of care treatment of the primary tumor. The investigators hypothesize that TTFields (up to 12 months or until disease progression) without PCI can reduce the incidence of observed brain metastases in SCLC while maintaining QoL and cognitive function.

In the context of novel systemic agents with CNS penetration, the benefit of PCI will be further questioned. Following the results of CASPIAN and IMpower 133, the standard of care for de novo ES-SCLC is chemoimmunotherapy with durvalumab or atezolizumab, respectively.^{34,35} In the CASPIAN study, PCI was only allowed in the chemotherapy control arm. However, a subgroup analysis of the IMpower133 study demonstrated that atezolizumab improved time to intracranial progression (20.2 vs 10.5 months; $P=.046$).³⁶ The benefit of PCI in the setting of chemotherapy and checkpoint blockade is unknown.

Summary

PCI for patients with ES-SCLC that responds to initial systemic therapy reduces the incidence of symptomatic

brain metastases. However, it is uncertain whether PCI improves OS, particularly in the MRI and immunotherapy era. We recommend consideration of PCI with 25 Gy in 10 daily fractions in patients with ES-SCLC that responds to initial systemic therapy. Providers should have a balanced discussion regarding the risks and benefits of PCI versus surveillance. Randomized data of HA-PCI for cognitive preservation are conflicting and results from both NRG-CC003 and NRG-CC009 are awaited. Most patients who do not receive PCI will require RT for brain metastases. Lastly, it is critically important that we enthusiastically support clinical trial enrollment to further understand the role of PCI in ES-SCLC. Until other therapies provide better disease control, brain RT in the form of PCI, SRS, or WBRT will be an important facet of SCLC treatment.

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