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Editorial

Is prophylactic cranial irradiation indicated for patients with extensive-stage small cell lung cancer with a complete response to first-line treatment?

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ABSTRACT

Prophylactic cranial irradiation (PCI) has been considered standard of care for patients with limited-stage small-cell lung cancer who achieve complete response to definitive treatment after a meta-analysis revealed its favorable effects on survival. In a European trial, PCI was also shown to confer a survival advantage for patients with extensive-stage (ES) SCLC who experienced any positive response after initial chemotherapy, leading to PCI also being considered a standard treatment for these patients as well. However, a recent Japanese trial investigating PCI for patients with ES-SCLC was stopped early when an interim analysis failed to confirm a survival benefit. This finding has motivated the thoracic oncology community to rethink the role of PCI in ES-SCLC.

The brain is considered a pharmacologic sanctuary site owing to the presence of the blood–brain barrier, and thus disease recurrence in the brain after systemic therapy is plausible given the inadequate penetration of drugs across this barrier. The propensity of small-cell lung cancer (SCLC) to seed in the brain is well known. Autopsy studies have shown brain metastases in 50–65% of patients with SCLC [1,2]. Patients with SCLC who live longer bear a higher risk of developing brain metastasis, with a cumulative probability of brain metastases reaching 80% for patients who live 2 or more years [2,3].

The advantage of cranial irradiation is its effectiveness in sanctuary sites and its ability to target not only gross disease but also microscopic disease [4]. In the 1960s, prophylactic cranial irradiation (PCI) was introduced into clinical practice for patients with acute lymphoblastic leukemia, who were at high risk of failure in the central nervous system [5]. The use of PCI for patients with SCLC was first tested in the 1970s.

After publication of a meta-analysis by Auperin and others in 1999 [6], PCI has been regarded as part of standard care for patients with limited-stage (LS) SCLC that responds completely to chemotherapy. A subsequent randomized trial in Europe comparing PCI versus no PCI for patients with extensive-stage (ES) SCLC came to a similar conclusion, leading to the general use of PCI for patients with ES-SCLC that had responded to chemotherapy [7]. Both of these noteworthy studies proclaimed the effectiveness of radiation in the clinically negative brain for improving survival. However, the potential risk of neurocognitive effects has made some reluctant to use PCI. A Japanese phase III study of PCI in ES-SCLC published recently in *Lancet Oncology* is receiving considerable attention from the thoracic oncology community [8]. In that study, which required that all patients undergo brain magnetic resonance imaging (MRI) after completing chemotherapy and during follow-up, PCI reduced the incidence of brain metastasis (48% vs. 69%, $P < 0.001$) but did not extend overall survival (OS) time. The emergence of these results provides an opportunity to reconsider current guidelines and practice. In this commentary, we summarize findings from randomized trials of PCI conducted to date, the potential for neurotoxicity and treatment advances in brain irradiation, and offer a perspective for the future.

Randomized trials of PCI

Early randomized prospective studies of PCI for patients with SCLC published since the late 1970s showed reductions in the rates of brain metastases but no survival benefit [9]. However, one shortcoming of these studies is that complete response (to chemotherapy) had not been confirmed in most patients. During the period from 1977 through 1995, seven randomized trials were conducted that considered PCI for patients with pathologically proven SCLC that had completely responded to definitive therapy [10–15]. In 1999, Auperin and colleagues published a

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meta-analysis of the 987 patients treated in those trials and found a statistically significant absolute survival benefit of 5.4% (20.7% vs. 15.3%; hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.73–0.97, $P = 0.01$) at 3 years among patients given PCI [6]. That meta-analysis also showed a 54% relative reduction in the cumulative incidence of brain metastasis in patients with PCI (33.3% vs. 58.6%; HR 0.46, 95% CI 0.38–0.57, $P < 0.001$). After publication of this study, guidelines were modified to recommend that PCI be given to patients with LS-SCLC who achieved a complete response or a good partial response to initial therapy; PCI was also to be considered for those with ES-SCLC. Because most of the patients in this meta-analysis had LS disease (only 14% had ES-SCLC), the potential efficacy of PCI in ES-SCLC was subsequently addressed in a randomized trial conducted in Europe. In that study, patients who showed any degree of response to chemotherapy received either PCI or no further therapy (control group) [7]. Brain imaging was not mandatory for disease staging or follow-up procedures unless symptoms suggestive of brain metastasis were present. Indeed, only 29% of randomized patients in that trial had brain imaging at diagnosis [16]. The PCI regimens tested were 20 Gy given in 5 fractions (66%), 30 Gy given in 10 fractions (17%), 30 Gy given in 12 fractions (7%), 25 Gy given in 10 fractions (5%), and others (4%). Consequently, the biologically equivalent doses of these regimens varied considerably from 28 to 39 Gy (α/β ratio of 10 Gy). The cumulative risk of brain metastasis within 1 year was significantly lower in the PCI group than in the control group (14.6% vs. 40.4%; HR 0.27, 95% CI 0.16–0.44, $P < 0.001$), and the use of PCI was also associated with a survival benefit (median survival time 6.7 vs. 5.4 months; HR 0.68, 95% CI 0.52–0.88, $P = 0.003$). The 1-year survival rates were 27.1% (95% CI 19.4–35.5) in the PCI group and 13.3% (95% CI 8.1–19.9) in the control group [7]. PCI was found to have a negative effect on some health-related quality of life scores (with the greatest effects noted for fatigue and hair loss), but the impact of PCI on global health status and global functioning scores was limited [17]. However, no comparisons of effectiveness were made among the dose and fractionation regimens.

The finding of reduced symptomatic brain metastases and prolonged survival with PCI in the European trial led to further modifications in guidelines and clinical practice after those results were published in 2007, with the recommendation that PCI should also be considered standard for patients with ES-SCLC who show any favorable response to initial chemotherapy [7]. However, some critics have contended that the absence of brain imaging after chemotherapy in the European trial could have contributed to its positive results, arguing that the PCI was merely treating asymptomatic brain metastases [18,19].

In March 2017, findings from a Japanese randomized phase III trial evaluating the efficacy of PCI for patients with ES-SCLC were reported that addressed this criticism [8]. In that study, all 224 patients underwent brain MRI 4 weeks before study enrollment to establish the lack of brain metastasis at that time; eligible patients also underwent brain MRI during follow-up at 3-month intervals during the first year after treatment, and again at 18 and 24 months after enrollment to detect any asymptomatic brain metastases that appeared during that interval and treated asymptomatic brain metastases when they were found. Moreover, the same PCI regimen was used for all patients in the PCI group, i.e., 25 Gy in 10 fractions, and thus the biologically equivalent dose was uniform at 31.2 Gy (α/β ratio of 10 Gy). Only 47% of the PCI group received etoposide-containing chemotherapy compared with 56% of the no-PCI group in the interim analysis of 163 patients, although this imbalance was slightly improved in the final analysis of 224 patients (53% PCI vs. 59% no-PCI). The Japanese study was closed prematurely for futility when PCI was found to have no superiority over observation in a planned interim analysis; the probability that PCI would be superior to observation by the end of the trial was reported as 0.011%. In the final analysis, the incidence of brain metastases was significantly lower in the PCI group (48% vs. 69%, $P < 0.001$), but no differences were observed in survival, with OS time being marginally shorter in PCI group than in the observation (control) group (1-year OS rates 48% vs. 54%; HR 1.27, 95% CI 0.96–1.68, $P = 0.094$). Severe (grade ≥ 3) adverse events at 3 months were rare in both groups, and no differences in cognitive function (assessed with the Mini-Mental State Examination) were seen between groups. Assessments of quality of life at baseline and during follow-up were lacking in this trial. In light of these findings, the Japanese Lung Cancer Society changed its recommendation regarding PCI for patients with ES-SCLC from "recommended" in the 2014 guidelines to "not recommended" since that time [18]. The results of the Japanese study also gained the attention of physicians in countries outside Japan who treat patients with SCLC.

To summarize, the most important differences between the European and the Japanese randomized trials were the use of brain imaging, in that the Japanese trial mandated brain MRI before chemotherapy or PCI and during follow-up; treatment of asymptomatic metastases during surveillance; and use of a single dose-fractionation schedule for PCI. These and other characteristics of these two trials are shown in Table 1.

Optimal dose and fractionation schedules for PCI

The potential existence of a dose–response relationship in the incidence of PCI and brain metastasis, as had been suggested in an early meta-analysis [6], led to a large randomized Intergroup clinical trial involving 22 countries in which the optimal dose and fractionation of PCI were evaluated for patients with LS-SCLC that responded completely to chemotherapy and thoracic radiation therapy (TRT) [20]. That trial, reported by Le Pechoux and colleagues, compared standard-dose and higher-dose PCI for LS-SCLC after complete response to chemoradiation therapy. The three schedules tested were standard-dose PCI ($n = 360$; 25 Gy in 10 daily fractions) or high-dose PCI ($n = 360$; 36 Gy given in either 18 daily fractions or 24 twice-daily fractions). No significant differences were found between dose groups in the 2-year rates of brain metastasis (29% standard-dose vs. 23% high-dose groups, $P = 0.18$). The 2-year OS rate was significantly higher for the standard-dose group (42% vs. 37% for the high-dose group, $P = 0.05$), although the investigators acknowledged the possibility that this could have been a false-positive finding because this trial was not powered to detect a difference in OS. Rates of acute adverse events were slightly (but not significantly) higher in the high-dose group: fatigue, 30% standard-dose vs. 34% high-dose; headache, 24% standard-dose vs. 28% high-dose; nausea and vomiting, 23% standard-dose vs. 28% high-dose. The conclusion reached by the study investigators was that given the lack of a significant reduction in brain metastases and the increase in mortality after high-dose PCI, PCI at a dose of 25 Gy should continue to be the standard treatment for patients with LS-SCLC [20]. A subsequent evaluation of late neurocognitive function at 3 years after PCI in the Intergroup trial revealed that patients in both the standard-dose and high-dose groups had mild deterioration over time in communication, leg strength, intellect, and memory, measured with the European Organisation of Research and Treatment of Cancer's QLQ-C30 and brain module, but these apparent differences were not statistically significant [21]. However, another analysis of PCI dose and chronic neurotoxicity among patients in one of the component trials of the Intergroup study [22] showed that baseline neuropsychological function (assessed with a different set of tests) was not statistically different among the standard-dose and high-dose groups. However, at 12 months after PCI, the incidence of chronic

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