Editorial

Prophylactic cranial irradiation for extensive-stage small-cell lung cancer: an evolving view

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Small-cell lung cancer (SCLC) is an aggressive malignancy with high rates of brain metastasis (BM) and poor long-term survival (1,2). It is estimated that nearly 80% of SCLC patients will develop brain metastases at some point during their treatment course, and up to 15% of SCLC patients will have asymptomatic brain metastases at diagnosis (1,3,4). Against this backdrop, there have been multiple efforts to assess the role of prophylactic cranial irradiation (PCI) in the treatment of SCLC, both to decrease the incidence of BM as well as improve other disease-related outcomes, including overall survival (OS). Meta-analyses have demonstrated that patients with complete response (CR) after initial chemotherapy (or chemoradiation) have decreased incidence of BM and improved OS with the addition of PCI (5,6). That said, the majority of SCLC patients will present with extensive-stage disease (ES-SCLC), and of ES-SCLC patients only approximately 15% will have a CR to initial chemotherapy (2,7,8). To assess the role of PCI for ES-SCLC patients with any response to chemotherapy, the European Organization for Research and Treatment of Cancer (EORTC) undertook a phase 3 trial, published in 2007 (7). This trial demonstrated decreased BM incidence and improved OS with the addition of PCI for ES-SCLC patients who had any response [CR or partial response (PR)] to chemotherapy (7). For the decade following its publication, this trial has been the primary piece of evidence supporting the routine use of PCI for ES-SCLC patients with any response to initial systemic therapy. PCI has therefore been incorporated into national and international guidelines, and has been widely recommended by providers (9-11). However, this standard approach is now challenged following the recent publication of results from a phase 3 trial from Japan (8). This trial demonstrates that for patients with ES-SCLC, with any response to chemotherapy and no brain metastases by magnetic resonance imaging (MRI), the addition of PCI did not improve OS or progression-free survival (PFS). Here, we provide a critical analysis of these two landmark studies, and assess our own evolving practice patterns in light of the newly-published Japanese trial.

From the time of its initial publication, many have noted the merits as well as the pitfalls of the EORTC trial (7,12). The EORTC 08993 trial enrolled 286 patients with ES-SCLC with any response to systemic chemotherapy, and randomized patients to PCI versus observation. The primary endpoint for the trial was time to symptomatic BM, which was shown to be improved with the use of PCI (symptomatic BM at 12 months: 15% with PCI *vs.* 40% with observation). Moreover, the addition of PCI improved disease-free survival (at 6 months: 23% *vs.* 15%) as well as OS (at 12 months: 27% *vs.* 13%). Despite these findings, there are a number of caveats to bear in mind. For instance, brain imaging was not mandatory as part of staging, randomization, or follow-up, provided the patient was neurologically asymptomatic (7). Only 29% of patients on the trial underwent any brain imaging prior to randomization, with no details provided regarding whether this imaging was CT-based or MRI-based (12).

Moreover, there was no standardization with regard to initial chemotherapy or dose/fractionation for PCI. Neither the specific chemotherapy regimens nor the number of treatment cycles was defined. Similarly, PCI dosing and fractionation were variable, resulting in biologically equivalent doses ranging between 28 and 39 Gy (at $\alpha/\beta=10$).

There are other concerns regarding the overarching treatment paradigm presented in the EORTC trial. In the study, patients in the PCI arm were much more likely to receive any treatment at time of extracranial progression (68% *vs.* 45%) (7). The authors suggest this may reflect PCI improving the candidacy of patients for second-line therapies. While this may be the case, it is conceivable that it is the greater utilization of second-line therapy (rather than the PCI itself) that contributed to improve OS among patients in the PCI arm. This notion is supported by the unexpectedly impressive effect of PCI on OS compared with prior studies. The addition of PCI in the EORTC study was approximately twice as effective (half the hazard ratio) with regard to OS as in a prior meta-analysis (5,7). Furthermore, since 90% of patients (irrespective of treatment arm) experienced extracranial disease progression, the importance of second-line therapy utilization rates is difficult to understate. Also noteworthy is the fact that only 59% of patients in the observation arm received brain radiotherapy (RT) for symptomatic BM (7). Collectively, the absence of brain imaging, heterogeneity of initial chemotherapy and PCI regimens, and differential second-line treatments between the two arms are among the most significant limitations of the EORTC trial.

Enter the Japanese trial. Like the EORTC trial, the Japanese study included patients with ES-SCLC with any response to initial chemotherapy, who were then randomized to PCI versus observation (8). Initial systemic therapy for all patients was based on a platinum-based doublet regimen, and PCI was standardized to 25 Gy in 10 fractions. All patients were required to have an MRI of the brain at the time of randomization, and enrollment was contingent on the absence of intracranial metastasis by MRI. Patients were also followed with surveillance brain MRI scans after randomization to assess for intracranial disease progression. The primary endpoint for the trial was OS, which was similar between the treatment arms (at 12 months: 48% with PCI *vs.* 54% with observation). Cumulative incidence of BM (including asymptomatic BM detected by MRI) was improved with the addition of PCI (at 12 months: 33% *vs.* 59%). However, PFS was not different between the treatment arms [median PFS 2.3 months (PCI) *vs.* 2.4 months (observation)] (8). Similarly, high proportions of patients in each treatment arm received second-line systemic therapy (88–89% regardless of treatment arm), and the large majority (83%) of patients on the observation arm who later developed BM underwent brain RT. This was in contrast to the EORTC trial, which had significantly lower rates of second-line systemic treatment, disproportionate use of second-line therapy among patients in the PCI arm, and a smaller fraction of patients on the observation arm receiving brain RT for intracranial progression (7,8).

Taken together, the Japanese trial represents a truly 'modern' approach, with techniques and treatment patterns that most closely mirror our own clinical practice. Routine use of MRI has become an integral part of staging patients, and in our institution is commonly incorporated as part of follow-up to assess for intracranial disease (9). There are a number of potential reasons for the observed differences in outcomes between the two trials, but one critical difference may lie in the use of baseline MRI in the Japanese trial to identify and exclude the approximately 15% of ES-SCLC patients who present with asymptomatic BM at diagnosis (3,4). Inclusion of these patients in the EORTC study, which called for brain imaging only for symptomatic patients, may have accounted for some of the improvement in disease-related outcomes in the PCI arm. In response to this concern, the EORTC lead author performed a post-hoc analysis excluding patients in the observation arm who developed symptomatic BM within 2 months of randomization, assuming that asymptomatic BM would become symptomatic within this time (13,14). Even excluding these patients in the EORTC study, the survival advantage in the PCI arm persisted, although one may argue that this post-hoc analysis may still only account for a fraction of all patients with asymptomatic BM at diagnosis (14).

Therefore, we return to the rates of second-line therapy utilization, which may be another source for the observed OS benefit among the EORTC PCI patients, who had markedly higher rates of second-line systemic treatment than the EORTC observation patients. While it has been suggested that the addition of PCI itself facilitates a greater proportion of patients being able to proceed to second-line treatment, this point is weakened by the fact that a markedly higher proportion of patients in the observation arm on the Japanese trial (89%) received second-line therapy compared with PCI patients in the EORTC study (59%). A potentially-unifying explanation for a number of differences between the two trials centers

on MRI usage. With the inclusion of MRI, the Japanese trial was able to identify higher rates of BM in follow-up than the EORTC trial, likely through increased detection of asymptomatic BM. Consequently, a higher proportion of patients with intracranial progression proceeded with brain RT in the Japanese trial, as presumably these patients were generally more likely to be asymptomatic and have better performance status. Similarly, use of MR at time of randomization in the Japanese trial obviously excluded patients with asymptomatic BM, a group of patients whose overall clinical course is exceedingly poor, particularly if randomized to observation. This MRI-based patient selection may therefore account for the higher rates of second-line treatment among patients in the Japanese trial (regardless of randomization) compared with the EORTC PCI arm.

At MD Anderson Cancer Center (MDACC), the Thoracic Radiation Oncology section met recently to review the results of the Japanese trial, and discussed how future cases of PCI for ES-SCLC patients should be managed based on the new evidence. All of the above discussion points were raised, and at the conclusion of the conference it was agreed that the Japanese trial best reflected our current treatment practices, including utilization of MR imaging as well as high rates of second-line therapy for appropriately-selected patients. While the majority of faculty supported changing practice patterns in accordance with the Japanese study, some expressed doubts. Some considered that while the Japanese data did not demonstrate an OS benefit with PCI, there was a benefit with regard to incidence of BM. Is the reduction in the rate of BM sufficient to justify PCI, given the absence of other disease-related outcome benefits? One thing for certain is that the original standard to provide PCI in ES-SCLC is based on an OS improvement with PCI, but that standard will certainly need to change given the evidence from the Japanese trial. Multiple randomized trials of PCI in patients with locally-advanced non-small-cell lung cancer (NSCLC) also demonstrated significantly reduced BM in patients who received PCI, but in the absence of an OS benefit, PCI is not standard of care for NSCLC patients (15-18). PCI carries significant neurocognitive morbidity, and causes fatigue and hair loss that to some patients may be a loss in quality of life that cannot be ignored (19,20). The balance between benefit and toxicity must be evaluated for each individual patient. There may be a subset of patients whose values, experiences, and circumstances mean that they will prefer to proceed with PCI when presented the data. It is in this context where shared decision-making between patient and provider can facilitate tailoring care to the individual effectively (21).

Along the same lines, there could be subsets of patients where PCI may be recommended depending on the context. Given the integral role of routine surveillance MRI in the Japanese trial, patients with poor compliance/poor follow-up, or patients with limited access to MRI facilities, could be considered for PCI. Patients residing in regions or countries with limited MRI accessibility may also favor the use of PCI given that their conditions are more akin to those in the EORTC trial. There are also unanswered questions about whether ES-SCLC patients with CR to initial chemotherapy may benefit from PCI. Older data support the usage of PCI in ES-SCLC who achieve a CR to up-front systemic therapy (5,6,22-24). Both the EORTC and Japanese studies report similar rates of CR after initial chemotherapy (13–15%), but neither present post-hoc analyses examining the effect of PCI on this subgroup of patients. Given that the role of PCI for ES-SCLC patients who achieve CR has not been well-defined in the MRI era, we are hopeful that secondary analyses from the Japanese trial will focus on CR patients in particular to shed light on this question. Lastly, ongoing efforts should similarly focus on PCI for limited-stage SCLC (LS-SCLC) patients. Recent data from our institution suggest that while LS-SCLC patients who achieve CR may benefit from PCI, questions remain about the generalizability of the PCI recommendation for LS-SCLC patients in the modern era (25).

In conclusion, the Japanese trial represents a practice-changing study, providing high-level evidence that PCI does not confer a survival benefit for ES-SCLC patients who have responded to systemic therapy. Certain clinical contexts may still warrant PCI consideration, but collectively we believe that the Japanese data better reflects modern practice, at least at our institution. We therefore advocate against routine PCI use in ES-SCLC patients. Identifying subsets of SCLC patients who may benefit from PCI remains a significant challenge for future research efforts.

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References

1. Nugent JL, Bunn PA Jr, Matthews MJ, et al. CNS metastases in small cell bronchogenic carcinoma: increasing frequency and changing pattern with lengthening survival. Cancer 1979;44:1885-93.
2. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006;24:4539-44.
3. Hochstenbag MM, Twijnstra A, Wilmink JT, et al. Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. J Neurooncol 2000;48:243-8.
4. Seute T, Leffers P, Wilmink JT, et al. Response of asymptomatic brain metastases from small-cell lung cancer to systemic first-line chemotherapy. J Clin Oncol 2006;24:2079-83.
5. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476-84.
6. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 2001;1:5.
7. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664-72.
8. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:663-71.
9. National Comprehensive Cancer Network. Small Cell Lung Cancer (Version 3.2017). Available online: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf, accessed June 13, 2017.
10. Früh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi99-105.
11. Jain A, Luo J, Chen Y, et al. Current Patterns of Care for Patients with Extensive-Stage SCLC: Survey of U.S. Radiation Oncologists on Their Recommendations Regarding Prophylactic Cranial Irradiation. J Thorac Oncol 2016;11:1305-10.
12. Slotman B, Postmus P, Senan S. Author reply: prophylactic cranial irradiation in small-cell lung cancer. N Engl J Med 2007;357:1978.
13. Slotman BJ. Prophylactic cranial irradiation postchemotherapy response. J Thor Oncol 2015;10:S171.
14. Slotman BJ. Time to reconsider prophylactic cranial irradiation in extensive-stage small-cell lung cancer? Lancet Oncol 2017;18:566-7.
15. Cox JD, Stanley K, Petrovich Z, et al. Cranial irradiation in cancer of the lung of all cell types. JAMA 1981;245:469-72.
16. Umsawasdi T, Valdivieso M, Chen TT, et al. Role of elective brain irradiation during combined chemoradiotherapy for limited disease non-small cell lung cancer. J Neurooncol 1984;2:253-9.
17. Russell AH, Pajak TE, Selim HM, et al. Prophylactic cranial irradiation for lung cancer patients at high risk

for development of cerebral metastasis: results of a prospective randomized trial conducted by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 1991;21:637-43.
18. Gore EM, Bae K, Wong SJ, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. J Clin Oncol 2011;29:272-8.
19. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol 2009;27:78-84.
20. Gondi V, Paulus R, Bruner DW, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. Int J Radiat Oncol Biol Phys 2013;86:656-64.
21. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. N Engl J Med 2012;366:780-1.
22. Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. J Natl Cancer Inst 1995;87:183-190.
23. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). Eur J Cancer 1997;33:1752-8.
24. Laplanche A, Monnet I, Santos-Miranda JA, et al. Controlled clinical trial of prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Lung Cancer 1998;21:193-201.
25. Farooqi AS, Holliday EB, Allen PK, et al. Prophylactic cranial irradiation after definitive chemoradiotherapy for limited-stage small cell lung cancer: Do all patients benefit? Radiother Oncol 2017;122:307-12.

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