Letter to the Editor

What is the role of prophylactic cranial irradiation for extensive-stage small-cell lung cancer in an evolving field?

Andrew Bang[1], Robert M. MacRae[2]

[1]Department of Radiation Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA, USA; [2]Division of Radiation Oncology, The Ottawa Hospital Cancer Centre/University of Ottawa, Ottawa, ON, Canada

Correspondence to: Robert M. MacRae, MD. Assistant Professor, Division of Radiation Oncology, The Ottawa Hospital/University of Ottawa, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada. Email: rmacrae@toh.ca.

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The role of prophylactic cranial irradiation (PCI) for extensive-stage small-cell lung cancer (ES-SCLC) has evolved since the publication of two phase III randomized control trials in the past decade. Despite significant evidence demonstrating improvements in survival and rates of developing brain metastasis in the limited-stage setting, there was no clear evidence supporting its use for ES-SCLC until 2007, with the publication of the European Organization for Research and Treatment of Cancer (EORTC) study. In this publication, patients randomized to receive PCI were found to have a lower incidence of brain metastasis (40% *vs.* 15%), improved median disease-free survival (14.7 *vs.* 12.0 weeks) and improved overall survival (6.7 *vs.* 5.4 months) (1). The study was not without its criticisms, the most conspicuous being the lack of post-chemotherapy and surveillance brain imaging.

In 2017, Japanese investigators published the results of their study in a similar patient population, with a distinction that all patients underwent post-chemotherapy and surveillance brain magnetic resonance imaging (MRI). Though the study showed similarly decreased rates of brain metastasis in patients randomized to receive PCI, they did not show any improvements in progression-free survival, and more importantly, overall survival (2). In fact, they had found a trend towards a survival detriment prior to early termination due to futility.

The findings from the Japanese study were eye-opening, suggesting that despite high rates of developing brain metastases with ES-SCLC, rigorous brain imaging follow-up in conjunction with a rapid and high uptake (83%) of whole brain radiation treatment (WBRT) could negate the survival advantage seen with PCI (2). However, this raises the question of whether such a rigorous schedule is practical in a real world setting outside of clinical trials, and if not, would eliminating the use of PCI as a strategy be detrimental?

To clarify the concern of sustainability, it should be noted that imaging follow-up practices vary across the world, and even within individual health systems themselves. Certainly, a large constraint on a surveillance strategy would be the limitation of resources, specifically, the availability of MRI units. We understand that in Japan, where all the patients in Takahashi *et al.* were accrued, the availability of access to MRIs is significantly higher than the average Organization for Economic Cooperation and Development (OECD) country with 51.7 units per million compared to 15.9 unit per million (3). This represents an MRI availability of greater than three times compared to the average of the 36 member countries. In contrast, Canada, where our study was conducted, has 9.5 MRI units per million. This is not to say that striving to optimize treatment options should not be prioritized, and the authors of Takahashi *et al.* should be commended for further investigating treatment alternatives for this controversial topic, but MRI availability may be a limiting resource with priority given to other indications. Indeed, along the lines of the Choosing Wisely campaign, PCI could reduce the need for such frequent brain imaging, particularly when 46.2% of patients who did not receive PCI developed brain metastases within 6 months (2).

Considering the contrasting outcomes of the two phase III studies, we sought to review our centre's experience. There were limitations to our study, primarily stemming

from the retrospective nature of the analysis. Selection bias likely played a role in determining which patients received PCI, with a preference for choosing patients with better disease responses or performance status. As part of our analysis, we wanted to determine the impact of such potential imbalances between the two groups and found that although performance status was balanced between the groups, patients who received PCI had on average a lower disease burden and higher rates of complete response (4). Both factors could impact survival based on previous data (5). To better tease out the impact of these confounding factors, we performed a multivariate analysis and found that in our cohort, having a complete response was not a significant factor in survival, likely due to the very small rates of such events (9%). The higher rate of extrathoracic metastasis was however found to be associated with worse survival and time to brain metastasis failure (4). Despite this confounding factor, it should be noted that receiving PCI was still found to be associated with improved survival on multivariate analysis (HR 0.55; 95% CI: 0.39–0.77; P<0.001) (4).

Another limitation of our study was the lack of description of second-line systemic therapies, more specifically with regards to second-line chemotherapies. In the study by Takahashi *et al.*, 88% of patients received second-line chemotherapy (4). This represents a very high proportion of patients who were candidates, and who were willing to undergo a second course of chemotherapy. In contrast, a previous report from our centre showed that only 28% of patients received second-line chemotherapy (6). Although irinotecan-based chemotherapy in the second-line setting has been demonstrated to improve survival in the Japanese population (7), it is uncertain whether these findings can be translated to a different geographic population, as the addition of irinotecan was not shown to improve survival in first or second-line chemotherapy in the North American population (8). Therefore, it is difficult to know if the high utilization of second-line chemotherapy and its positive outcomes can be extrapolated outside of Japan.

Everything considered, the use of PCI or surveillance MRI in ES-SCLC is not clear cut with the outcomes of the EORTC and Japanese studies. Certainly, in the clinic, both strategies can be considered on a case-by-case scenario, with Takahashi *et al.* paving the way for surveillance strategies in regions where MRI use is readily available in combination with high patient compliance. The landscape of ES-SCLC, and therefore the role of PCI, likely will change with the introduction of immunotherapy, following the promising outcomes of the IMpower133 study, which demonstrated improvements in overall survival with the addition of atezolizumab in the first-line setting (9). Along with these advances in systemic therapies, hippocampal-avoidance WBRT is continuing to be investigated with the ongoing NRG-CC003 study, which could provide the benefits of PCI while diminishing its deleterious effects (10).

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Footnote

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