Letter to the Editor

# Re-thinking about prophylactic cranial irradiation for small cell lung cancer in the MRI era

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Decline of neurocognitive function is a major concern in the treatment with whole brain radiotherapy (WBRT), and it is also the case with prophylactic cranial irradiation (PCI). A previous study suggested the efficacy of memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, in the preservation of neurocognitive function after WBRT (1); however, more effective approach has been required eagerly. Hippocampus avoidance (HA)-WBRT is a newly developed radiation technique which can limit radiation dose to the bilateral hippocampus, and better preservation of neurocognitive function compared with standard WBRT has been reported previously (2). NCT01780675 is a phase III randomized trial of PCI with or without HA technique in small-cell lung cancer (SCLC), and the results of the trial were recently published in the *Journal of Thoracic Oncology* (3). In the study, a total of 168 patients with SCLC who completed chemo (radio) therapy were randomized to receive standard PCI or HA-PCI of 25 Gy in 10 fractions. HA-PCI did not increase the risk of brain metastases including hippocampus and did not show negative impact on survival compared with standard PCI; however, HA-PCI failed to prevent the decline of neurocognitive function compared with standard PCI. As a result, this was a negative study. Nevertheless, the study provided us an opportunity to re-think about PCI for SCLC.

For extensive stage (ES)-SCLC, an European study conducted by European Organization for Research and Treatment of Cancer (EORTC) reported the results supporting PCI. However, screening or follow-up of brain metastases using brain MRI was not mandatory in the study (4). Subsequently, a Japanese phase III study demonstrated that PCI deteriorates survival compared with a periodic follow-up with brain MRI, and the negative impact on quality-of-life due to prolonged anorexia and nausea after PCI was considered to be a primary reason (5). A following retrospective study also support the follow-up strategy instead of PCI (6), and practice pattern has changed in this setting (7). In addition, PCI is not superior to MRI surveillance from the aspect of cost-effectiveness (8). Thus, on the premise of regular follow-up with brain MRI, PCI is no longer a standard treatment for ES-SCLC. If HA-PCI were to be investigated in randomized studies in future, the standard arm should be a regular follow-up with brain MRI.

The decline of cognitive function after PCI is more problematic in limited stage (LS)-SCLC, because patients with LS-SCLC generally live quite longer than patients with ES-SCLC (9). For patients with LS-SCLC who achieved complete response after chemoradiotherapy, PCI has been the standard treatment for a long time (10). However, the significance of PCI for LS-SCLC in the MRI era is still uncertain. In fact, the MD Anderson Cancer Center Group conducted a retrospective analysis including 297 patients with LS-SCLC (205 received PCI and 92 did not) and revealed that PCI was not significantly associated with overall survival (11). The results of ongoing SWOG 1827 (NCT04155034), a randomized phase III trial comparing PCI with MRI surveillance and MRI surveillance alone in patients with SCLC, might redefine the role of PCI for patients with LS-SCLC in the MRI era and increase the importance of avoiding neurocognitive deterioration. In that sense, the development of new radiation techniques, including HA-PCI, should be continued.

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