

Perihippocampal metastasis following hippocampus-avoiding prophylactic cranial irradiation for small cell lung cancer: a case report

Seung-Gu Yeo

Department of Radiation Oncology,
Soonchunhyang University College of
Medicine, Soonchunhyang University
Hospital, Cheonan, Republic of Korea

Abstract: Prophylactic cranial irradiation (PCI) lowers the risk of brain metastasis (BM) and increases survival in small cell lung cancer (SCLC) patients, but it also entails a risk of neurocognitive dysfunction (NCD). One strategy to mitigate this neurotoxicity is hippocampus-avoiding (HA) whole-brain radiation therapy, as the hippocampus is mainly responsible for radiation-related NCD and hippocampal or perihippocampal metastases are rare. A few prospective clinical trials have demonstrated a reduction in NCD following HA whole-brain radiation therapy. The 59-year-old male patient described in this report had limited-stage SCLC and a complete response to thoracic chemoradiotherapy. Seven months after receiving HA-PCI of 25 Gy in 10 fractions using intensity-modulated radiation therapy, a 36 mm solitary metastasis was detected in the right perihippocampal region. The mass was surgically removed but the patient died 2 months later. The development of a solitary HA region metastasis is uncommon, considering that metastasis in this area usually occurs in patients with high numbers of BMs. Our case demonstrates the need for further validation of HA-PCI for SCLC patients in terms of both neurocognitive protection and the absence of compromise in terms of BM prevention.

Keywords: hippocampus-sparing, lung cancer, neurotoxicity, cognition, brain metastasis, whole brain radiation therapy

Introduction

Prophylactic cranial irradiation (PCI) is the standard of care for patients with small cell lung cancer (SCLC) who have had a good response to chemoradiation for their primary disease.¹ In a meta-analysis, PCI was shown to reduce the incidence of brain metastasis (BM) from 58% to 33% and to improve overall survival by 5.4% at 3 years.² However, a side effect of PCI is neurocognitive dysfunction (NCD). In the clinical trials of the Radiation Therapy Oncology Group (RTOG), PCI increased the risk of NCD in lung cancer patients, who did not develop BM, by almost threefold.³ Common manifestations of NCD include decreased short-term memory, impaired cognition, fatigue, and depression.^{4,5}

Injury to the hippocampus is mainly responsible for NCD following whole-brain radiation therapy (WBRT).⁶ Preclinical and clinical evidence have shown a correlation between hippocampal radiation injury and NCD.^{7,8} Therefore, one strategy to mitigate NCD is to reduce the irradiation dose to the hippocampus during WBRT. Modern, sophisticated radiation therapy (RT) techniques allow the delivery of hippocampus-avoiding (HA) WBRT, in both the treatment of BM and during PCI.^{9,10} However, the risk of subsequent metastasis in this conformal avoidance region must be evaluated to determine the clinical feasibility of HA-WBRT.

Correspondence: Seung-Gu Yeo
Department of Radiation Oncology,
Soonchunhyang University College of
Medicine, Soonchunhyang University
Hospital, 31, Soonchunhyang 6-gil,
Cheonan 31151, Republic of Korea
Tel +82 41 570 3557
Fax +82 41 592 3809
Email md6630@schmc.ac.kr

In this article, we report the outcome of a patient with limited-stage SCLC who received HA-PCI but subsequently developed a solitary BM in the hippocampal avoidance region.

Case report

A 59-year-old male was admitted to the hospital due to blood-tinged sputum. He was a current smoker with a 30-year smoking history. Chest computed tomography (CT) revealed an 18 mm mass in the right upper lobe with enlarged right prevascular, upper paratracheal, hilar, interlobar, and bilateral lower paratracheal lymph nodes. Distant metastasis was not detected on an ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET)/CT, whole-body bone scan or on magnetic resonance imaging (MRI) of the brain. Endobronchial ultrasound-guided biopsy identified metastatic small cell carcinoma bilaterally in the lower paratracheal nodes. Written informed consent was provided by the patient to have the case details and any accompanying images published.

Definitive concurrent chemoradiotherapy was administered for this limited-stage SCLC, with a total of 64 Gy delivered in 32 fractions using static seven-field intensity-modulated radiotherapy (IMRT). Chemotherapy, consisting of cisplatin and etoposide, was commenced simultaneously with IMRT. Four cycles of chemotherapy were administered over a 3-week interval. Chest CT and ^{18}F -FDG-PET/CT performed 2 months after chemoradiation showed a complete response in both the primary lung tumor and the regional lymph nodes.

HA-PCI was performed 3 months after completion of thoracic chemoradiotherapy. The IMRT techniques followed the RTOG 0933 protocol,¹¹ a Phase II trial of HA-WBRT for patients with BM. For CT (Brilliance CT Big Bore; Philips

Medical Systems, Cleveland, OH, USA) simulation, the patient was immobilized in the supine position with an aquaplast mask placed over his head. Planning CT scan images were fused with axial brain MRI. The hippocampus was contoured bilaterally on the fused MRI-CT image set and expanded by 5 mm to generate the HA region. The planning target volume was defined as the whole-brain parenchyma, excluding the HA region. The volumes of the hippocampus, HA region, and whole-brain parenchyma were 5.1 cm³, 30.4 cm³, and 1,343.8 cm³, respectively. The percentage of brain volume occupied by the HA region was 2.3%. An IMRT plan was created using the Eclipse RT planning system (Varian Medical Systems, Inc., Palo Alto, CA, USA). The plan consisted of nine static fields to cover the planning target volume, with a dose of 25 Gy administered in 10 fractions while avoiding the hippocampus (Figure 1). The minimum, maximum, and mean doses to the hippocampus were 7.6 Gy, 13.6 Gy, and 8.7 Gy, respectively. IMRT was performed using a Novalis Tx system (Varian Medical Systems and BrainLab, Feldkirchen, Germany). The patient tolerated the treatments well, with no severe complications.

Brain MRI at 7 months after HA-PCI completion showed a 36×31 mm, well-margined, heterogeneously enhancing mass in the right HA (perihippocampal) region with surrounding edema (Figure 2). The patient's symptoms included lower extremity weakness and dysarthria. The mass was surgically removed and identified by pathology as metastatic small cell carcinoma. The patient subsequently received palliative RT for spinal metastasis, and chemotherapy, but he died 9 months after HA-PCI.

Discussion

The efficacy of HA-WBRT in reducing NCD has been assessed in prospective clinical trials,^{11,12} including

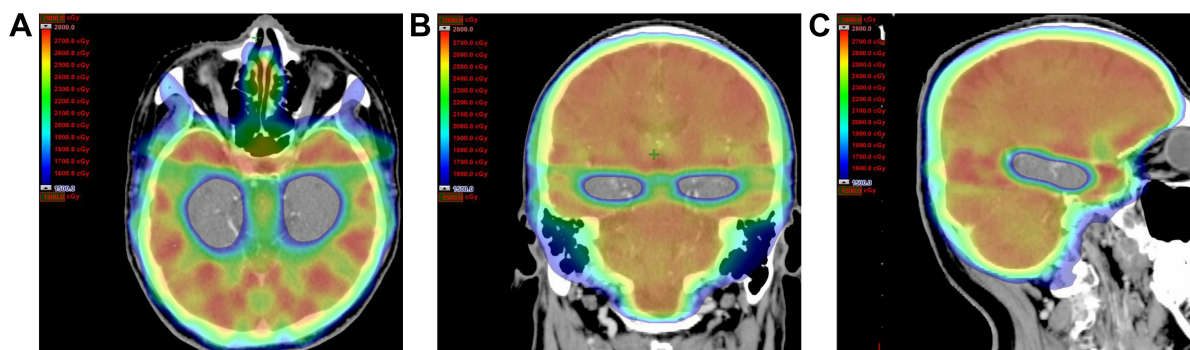


Figure 1 Radiotherapy planning image with the dose distribution illustrated in color.

Notes: (A) Axial, (B) coronal, and (C) sagittal images. The planning target volume was the whole-brain parenchyma excluding HA region.

Abbreviation: HA, hippocampus-avoiding.

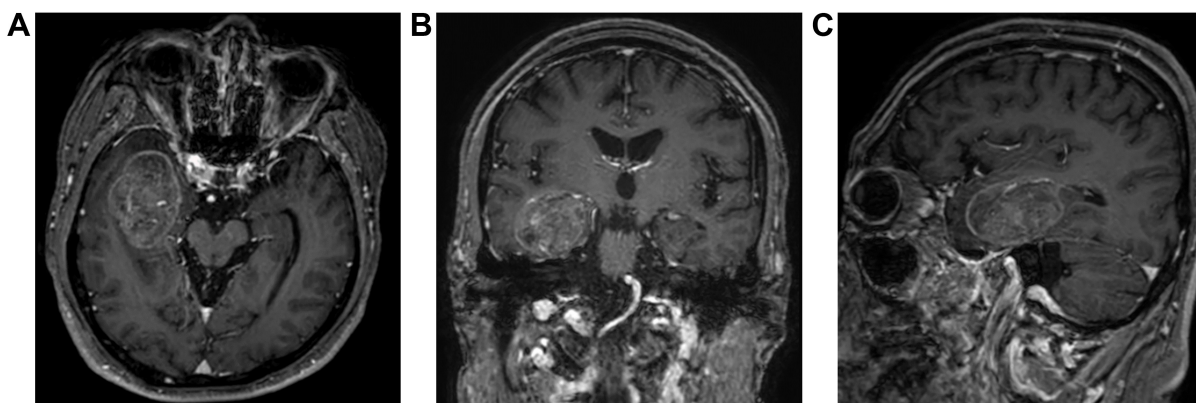


Figure 2 Brain magnetic resonance images showing a 36×31 mm metastatic mass in the right perihippocampal area. **Note:** (A) Axial, (B) coronal, and (C) sagittal images.

RTOG 0933, a Phase II multi-institutional study of HA-WBRT (30 Gy in 10 fractions) for patients with BM.¹¹ The trial included patients with BMs located outside a 5 mm margin around the hippocampus, with a total of 100 patients analyzed. The mean relative decline in delayed recall from baseline to 4 months, as assessed on the Hopkins Verbal Learning Test – Revised, was significantly lower than that in the historical control (7% vs 30%, $P < 0.001$); also, there was no decline in quality-of-life scores. Of the 67 patients who developed intracranial progression, only three (4.5%) experienced progression in the HA area. However, the patients included in the study mostly had non-small cell lung cancer (NSCLC) and breast cancer; those with SCLC were excluded from that clinical trial.

Although sample size was small (20 patients), a recent prospective study demonstrated the potential benefit of HA-PCI for SCLC patients in limiting the neuropsychological sequelae of brain radiation.¹³ Two patients developed a metastasis in a region under-dosed during HA-PCI. Neither involved the hippocampal dentate gyrus, but one involved the HA region. Both patients developed additional concurrent metastases in the fully treated brain regions. In the current case, BM was detected in the HA region 7 months after IMRT-based HA-PCI. A distinctive feature of this case was that the BM was solitary. No concurrent BM outside the HA region was evident, and no other BM was shown prior to death.

One of the rationales for the use of HA-WBRT is that the hippocampus and perihippocampal area are uncommon sites of BM. Two retrospective studies examined the incidence of hippocampal metastasis exclusively in SCLC patients.^{14,15} Guo et al¹⁴ assessed a total of 1,594 BMs (at presentation or follow-up) in 180 SCLC patients. HA region metastasis

was detected in 22 (12.2%) patients: 13 perihippocampal (≤ 5 mm of hippocampus) and nine hippocampal metastases. Kundapur et al¹⁵ evaluated 70 SCLC patients with BM either at presentation (de novo) or after conventional WBRT for BM. Of the 59 patients with de novo BM, three (5%) had HA region metastasis: two hippocampal and one perihippocampal. Collectively, there were 359 (range: 1–33) de novo BMs, with only three (0.8%) within ≤ 5 mm of hippocampal tissue. In 20 patients, metastatic disease in the brain progressed after WBRT, but a perihippocampal metastasis developed in only one patient (5%).

Other retrospective studies have analyzed BM in patients whose primary tumors were mainly NSCLC, breast cancer, and melanoma, but also SCLC. BM in the HA region was detected in $< 10\%$ of the patients.^{16–20} Gondi et al¹⁶ determined a rate of 8.6% ($n=32$) in 371 patients with BM. This rate was not significantly different between patients with SCLC (10.5%; $n=38$) and NSCLC (9.0%; $n=155$). However, a higher rate in SCLC than in other malignancies has also been reported. In a study by Harth et al,¹⁷ BM centered within 5 mm around the hippocampus occurred in 27.3% of SCLC patients. Although there were only 11 SCLC patients, this rate contrasted with that of 8% in overall 100 patients. Wan et al¹⁸ demonstrated that BM in regions of neural stem cells accounted for 2.7% of all BMs in 44 SCLC patients, compared with 0.82% of all BMs in the 283 NSCLC patients.

HA-WBRT will be of greater relevance for prophylactic than for therapeutic purposes. In BM treatment, particularly in brain oligometastases, stereotactic radiosurgery omitting WBRT is gaining acceptance.^{21,22} Stereotactic radiosurgery targets only the metastatic tumor volume, sparing all of the noninvolved brain parenchyma. Most of the ongoing prospective clinical trials of HA-WBRT in lung cancer patients are

evaluating the efficacy of HA-PCI rather than therapeutic WBRT.⁶ In addition, patients with NSCLC may be more suitable HA-PCI candidates versus patients with SCLC, as the former have a lower tendency of BM occurrence within the HA area.^{17,18} However, PCI has not been shown to confer a survival benefit in NSCLC.^{23,24}

A known risk factor for HA region metastasis is a large number of BMs.^{14,18} The current case was therefore unusual as this patient had a single BM in the HA region. Although this solitary BM was removed by surgical resection, stereotactic radiosurgery may be a good alternative.²⁵

While PCI is accepted as the standard of care for patients with lung cancer, it is used suboptimally because of neurotoxicity concerns.²⁶ The rapid development of RT technology has enabled the realization of HA-PCI. This novel approach will find widespread acceptance following its rigorous validation in prospective clinical trials to examine its ability to confer neurocognitive protection and, importantly, to retain the efficacy of BM prevention.

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Disclosure

The author reports no conflicts of interest in this work.

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