

Hippocampal Avoidance Prophylactic Cranial Irradiation using Helical Tomotherapy in Small Cell Lung Cancer

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ABSTRACT

OBJECTIVE Prophylactic cranial irradiation (PCI) is a standard treatment for small cell lung cancer (SCLC). Reduced radiation doses at the hippocampal region during PCI might protect against neurocognitive decline after radiotherapy (RT). The purpose of this study is to report the outcome of hippocampal avoidance PCI (HA-PCI) in our center.

METHODS After the initial treatment of SCLC, patients whose radiographic data confirmed the absence of intracranial metastasis and controlled of the primary disease received HA-PCI. Thai Mental State Examination (TMSE) and bilateral hippocampal volumes were recorded and analyzed using the Wilcoxon Singed Rank test to compare baseline and two time points (3 and 6 months). The two-year overall survival (OS) and brain control rates were estimated using the Kaplan Meier method.

RESULTS Between 2018 and 2021, a total of 10 patients were included in the analysis. The median TMSE and bilateral hippocampal volumes showed no statistically significant difference between baseline and 3 and 6 months. Two-year OS and brain control rates were 78.8% and 71.4%, respectively. Three patients developed intracranial relapses after HA-PCI which were located outside the hippocampal region.

CONCLUSIONS HA-PCI did not increase intracranial relapse in this study. HA-PCI should be considered as a treatment option which can potentially protect neurocognitive functions.

KEYWORDS hippocampal avoidance, prophylactic cranial irradiation, small cell lung cancer

INTRODUCTION

Small cell lung cancer (SCLC) is a subtype of pulmonary cancer with a high propensity for spreading to the brain. The incidence of intracranial metastases is approximately 10%-14% at the time of diagnosis and 40%-50% during progression of the disease (1, 2). SCLC is classified as limited disease (LD) and extensive disease (ED) following the Veteran's Administration Lung Cancer Study

Group (3). Systemic chemotherapy and thoracic radiation therapy (RT) constitute the primary treatment for SCLC. In both LD and ED, patients who did not experience disease progression were further treated with prophylactic cranial irradiation (PCI) (4, 5). However, PCI can potentially affect neurocognitive function from radiation painting to the entire brain. Higher radiation exposures to the whole brain have been found to be directly

correlated with more neurological deterioration (6, 7). Therefore, the standard PCI dose is 25 Gy in 10 fractions (Fx). Another strategy to reduce neurocognitive deficits is to minimize the radiation dose along bilateral hippocampal regions. This technique is typically applied to patients who require whole brain irradiation to diminish multiple brain metastasis (8). According to previously published preclinical data, memory-specific neural stem cell components reside in the hippocampal region, the subgranular zone (SGZ) of the dentate gyrus, and the subventricular zone (SVZ) which is located on the lateral aspect of the lateral ventricle (9, 10). These neuro-progenitor stem are extremely radiosensitive and are easily destroyed by radiation (11, 12). The outcome of the Radiation Therapy Oncology Group (RTOG) 0933 study indicated that hippocampal-avoidance whole brain radiotherapy (HA-WBRT) with a prescribed radiation dose of 30 Gy in 10 Fx reduced memory impairment in patients with multiple brain metastases (8). Hippocampal-avoidance zones (HAZ) are defined as 5-mm isotropic expansions from bilateral hippocampi. Radiation dose restrictions in these regions are 16 Gy for the maximum dose (Dmax) and 9 Gy for 100% of the HAZ volume (D100%). The hippocampal metastatic rate following HA-WBRT was 4.5%, which is lower than the estimated rate of 8.6%. However, RTOG 0933 did not include patients with primary SCLC in the study and there were few data regarding the prevalence of hippocampal metastases in SCLC. Some studies have reported finding 5.1% of de novo brain metastases in the hippocampi and that 5% of patients who received WBRT experienced a relapse in the hippocampi (13). Consequently, a lower radiation dosage to the bilateral hippocampi may be safe for SCLC patients requiring PCI as part of the standard treatment. Moreover, a reduced radiation dose to these regions may reduce the neurocognitive deficit induced by radiation.

This study aimed to report the outcome after hippocampal-avoidance PCI (HA-PCI) for SCLC patients who were treated at our center using a Helical Tomotherapy (HT) machine.

METHODS

This study selected patients who fulfilled the following inclusion criteria: Age 18 to 80 years; Thai nationality; Completion of the Thai Mental

State Examination (TMSE); Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (14); Histopathological diagnosis from either lung or lymph nodes confirmed as SCLC; No progression of primary tumor after chemotherapy and thoracic RT for LD-SCLC; No progression of primary tumor and/or extra-cranial metastases after standard systemic treatment for ED-SCLC; No evidence of intracranial dissemination on magnetic resonance imaging (MRI) before HA-PCI. Patients who had a history of cranial irradiation were excluded from this study.

After completing the standard initial treatment and confirmation of the absence of intracranial dissemination from MRI findings, patients began the radiation procedure for HA-PCI. Patients were placed in a supine position and immobilized by a thermoplastic mask. Computed-tomography simulation (CT-SIM) from the vertex to level 5 of the cervical spine without contrast media was applied using a 2-mm slice thickness. The entire brain volume, excluding the HAZ, was defined as the clinical target volume (CTV). The planning treatment volume (PTV) was expanded by 3-mm from the CTV. Cranial MRI was registered in the CT-SIM dataset in order to delineate bilateral hippocampi and other critical structures, including bilateral orbits, lenses, optic apparatus, brainstem, and pituitary gland. The hippocampal organs were contoured in accordance with RTOG 0933 recommendations (8). All patients in this study received radiation planning and delivery by HT.

Radiation dose prescriptions and hippocampal dosage limitations were as follows:

Target: The whole volume of the brain exclusive of HAZ received a radiation dose of 25 Gy in 10 Fx. The prescription dose of 25 Gy covered at least 95% of PTV, Maximal dose to 2% of PTV (D2%) was limited to 31.3 Gy, and Minimum dose to 98% of PTV (D98%) was at least 20.8 Gy.

Hippocampi: Dose limitation to hippocampi was prescribed at HAZ identified by 5-mm isotropic expansion from hippocampal contouring. D100% did not exceed 10 Gy whereas D2% was less than 18 Gy.

HA-PCI was administered within 2-4 weeks after enrolling in this study. In the first year after HA-PCI completion, regular brain MRIs with contrast were evaluated every three months, and in the second year, every four months. TMSE, a

national learning test, was used to assess cognitive functions in the Thai population (15). This test evaluated memory, attention, language, executive, and visuospatial abilities. It has been extensively used in Thailand to screen for cognitive impairment and dementia, with a suggested cut-off point 23 out of 30. Patients who had a TMSE score below 23 were considered to have cognitive impairment. TMSE was tested before starting HA-PCI and during the follow-up period of MRI surveillance.

Sample size

The sample size of this pilot study was 25 patients (16), and to accommodate an estimated drop-out rate of 20%, the desired sample size in this study was set at 30 patients.

Statistical analysis

Baseline characteristics of patients, including sex, age, stage of SCLC, baseline TMSE score, and hippocampal volume, were described individually. The two-year brain control rate and overall survival (OS) rate were estimated using the Kaplan Meier method. The median scores of cognitive functions and bilateral hippocampal volumes with interquartile range (IQR) were calculated and compared between two different time points (at 3 and 6 months after completion of RT) using the Wilcoxon Signed Rank test and a statistically significance level of 5%. All analyses were performed using Stata 16.0 (Stata Corp LP, College Station, TX, USA).

Ethical approval

Ethical approval was granted by the Institutional Research Board (Grant no. 368/2561)

Clinical trial registration number

Thai Clinical Trial Registry (TCTR) ID No. TCTR20200725001.

RESULTS

From 2018 to 2021, eighteen patients with SCLC who underwent chemotherapy were referred to our department. Twelve patients had LD-SCLC, while the remaining six patients had ED-SCLC. However, four patients, two with LD-SCLC and two with ED-SCLC, were excluded from the investigation due to brain metastases detected on MRI screening. Two patients declined to participate in the protocol, and two patients died prior to CT simulation. A total of 10 patients (6 with LD- and 4 with ED-SCLC) were included in the analysis. The median age was 60 years. The median TMSE score at baseline was 23 points. The median hippocampal volumes were 2.3 cc on the right side and 2.1 cc on the left side. Patients' characteristics are presented in Table 1. Memantine was not administered to all patients in conjunction with HA-PCI due to its non-reimbursement under national universal coverage. All patients received HA-PCI in accordance with the protocol. Information regarding the dose-volume histogram (DVH) of bilateral hippocampi for each patient is shown in Table 2. After complete HA-PCI at 3 and 6 months, TMSE and bilateral hippocampal volumes showed no statistically significant difference when compared to baseline values, as shown in Table 3. No patients experienced severe acute toxicity, and none were administered steroids.

The median follow-up time was 27.8 months (IQR = 22.0–35.3 months). The two-year OS and brain control rates were 78.8% and 71.4%, respectively,

Table 1. Patients' characteristics

Patient No.	Sex	Age (year)	SCLC stage (LD or ED)	Baseline TMSE score	Hippocampal volume (cc)	
					Left	Right
1	Female	60	ED	20	2.7	2.6
2	Female	56	LD	16	2.0	2.1
3	Male	60	ED	25	2.4	2.5
4	Male	68	LD	27	2.4	2.4
5	Male	59	LD	24	2.2	2.4
6	Male	60	LD	27	2.1	1.8
7	Male	62	LD	23	1.9	1.9
8	Male	79	ED	20	2.0	2.1
9	Male	59	LD	25	2.3	2.0
10	Male	67	ED	23	2.6	2.4

SCLC, small cell lung cancer; LD, limited disease SCLC; ED, extensive disease SCLC; TMSE, Thai Mental State Examination

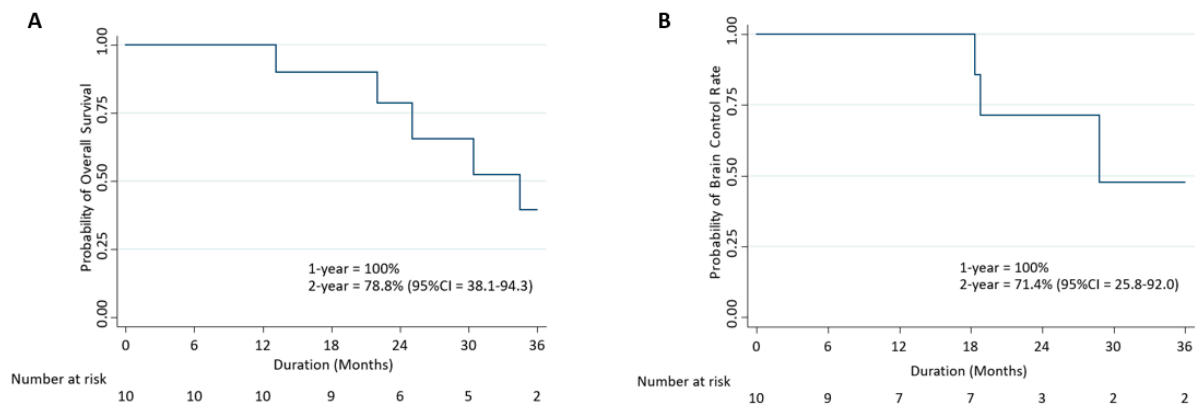
Table 2. Dose-volume histogram (DVH) of bilateral hippocampi for each patient

Patient No.	Dose to right hippocampus (Gy)		Dose to left hippocampus (Gy)	
	D2	D100	D2	D100
1	11.6	8.4	11.6	7.8
2	14.5	7.8	14.7	8.0
3	13.3	8.9	13.6	8.9
4	12.7	9.0	12.8	9.1
5	9.9	7.1	9.8	7.6
6	9.9	6.7	9.4	7.1
7	9.8	7.2	10.0	7.3
8	13.5	9.4	13.8	9.0
9	14.1	8.9	12.6	8.6
10	11.1	8.2	10.7	8.0

Table 3. Comparison of TMSE score and hippocampal volumes between baseline and after complete HA-PCI at 3-month and 6-month

Parameters	Baseline	At 3-month	p-value	At 6-month	p-value
Median TMSE score (IQR)	23 (20-25)	21 (19-26)	0.61	23 (21-27)	0.07
Median Rt hippocampal volume (cc) (IQR)	2.3 (2.0-2.6)	2.3 (1.8-2.7)	0.87	2.2 (2.0-2.7)	0.45
Median Lt hippocampal volume (cc) (IQR)	2.1 (2.0-2.4)	2.2 (1.9-2.6)	0.93	2.2 (2.0-2.5)	0.80

p-value: Wilcoxon Signed Rank test

**Figure 1.** Overall survival (A) and brain control rates (B)

as presented in Figure 1. Brain metastasis was detected from surveillance MRI in patients number 4, 7, and 8 after completing HA-PCI at 20 months, 16 months, and 12 months, respectively. Cerebellum, frontal, and post-central gyrus are the sites of the relapsed brain lesions. All of the patients were asymptomatic and received either whole-brain or salvage stereotactic radiotherapy. All of them also had tumor progression at the lungs and extra-cranial tumor progression, and all died within 6 months after brain lesion recurrence.

DISCUSSION

Small cell lung cancer has a high propensity for intracranial metastasis. In our study, 4 out of 18 patients (22.2%) had brain dissemination detected on MRI screening prior to RT. PCI remains a standard treatment option following chemotherapy, either with or without thoracic RT. A reduced radiation dose to the neural stem cells that reside in the hippocampal region is theorized to protect against neurocognitive impairment from radiation. In this single-center study, there was no statistically significant difference between the

TMSE scores at baseline and after RT completion. Many studies have documented neurocognitive preservation following HA-PCI. In a Spanish national clinical trial, SCLC patients were randomized to undergo either standard PCI or HA-PCI (17). Patients who received HA-PCI experienced less cognitive decline without an increase in the incidence of brain metastases (17). In this study, the incidence of intracranial recurrence was slightly higher than in previous studies. Intracranial recurrence was observed in three out of ten patients in our study. All were located outside the hippocampal region. The landmark NRG Oncology CC003 study conducted in the United States reported an intracranial relapse rate of 14.2% at 12 months (18), while an investigation conducted in South Korea reported a relapse rate of 20.8% (19). However, the rate of intracranial failure in that study did not differ significantly between conventional PCI and HA-PCI groups, and no clinical factor was found to be associated with the intracranial failure (19). In our study, the bilateral hippocampal volumes following HA-PCI did not decrease significantly. A European study found that HA-PCI reduced hippocampal atrophy at 4 and 12 months compared to conventional PCI (20) but no correlation was observed between hippocampal atrophy and memory (20).

The major limitation of this study was the small sample size. We proposed this research in 2018, but participation was inadequate. This may be the result of the coronavirus 2019 (COVID-19) outbreak, which has impeded hospital service by reducing the number of healthcare employees and delaying treatment schedules. In addition, patients and their caregivers were concerned about the spread of these viruses. The small sample size limited the robustness of the data analysis in our study. A previous study with a limited sample size of 20 patients from Johns Hopkins University reported that there was no significant decline in neuropsychological testing results at 6 and 12 months following HA-PCI (21). In that study, the two-year OS was 88%, which is better than our study that found a two-year OS of 78.8%. In addition, an intracranial recurrence was documented in the under-dosed hippocampal avoidance region of 2 patients in this study (21).

CONCLUSIONS

Reduced radiation dose at the hippocampal region during prophylactic cranial irradiation does not increase intracranial relapse in SCLC patients. HA-PCI should be considered as a treatment option which can protect neurocognitive functions without negatively impacting treatment outcome.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author Contribution

B.J.: conceptualization, writing-review and editing this article; W.V.: imaging interpretation; W.N.: radiation dosimetry data collection; P.K.: patient data collection; P.S.: statistical analysis; I.C.: Patient data collection; E.T.: patient data collection; S.C.: patient data collection; W.O.: patient data collection.

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