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Clinical Features of Brain Metastases in Small Cell Lung Cancer: an Implication for Hippocampal Sparing Whole Brain Radiation Therapy[1]

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Abstract

PURPOSE: To assess the clinical features and distribution of brain metastases (BMs) of small cell lung cancer (SCLC) in the hippocampal and perihippocampal region, with the purpose of exploring the viability of hippocampal-sparing whole-brain radiation therapy (HS-WBRT) on reducing neurocognitive deficits. *METHODS:* This was a retrospective analysis of the clinical characteristics and patterns of BMs in patients with SCLC. Associations between the clinical characteristics and hippocampal metastases (HMs)/perihippocampal metastases (PHMs) were evaluated in univariate and multivariate regression analyses. *RESULTS:* A total of 1594 brain metastatic lesions were identified in 180 patients. Thirty-two (17.8%) patients were diagnosed with BMs at the time of primary SCLC diagnosis. The median interval between diagnosis of primary SCLC and BMs was 9.3 months. There were 9 (5.0%) and 22 (12.2%) patients with HMs and PHMs (patients with BMs located in or within 5 mm around the hippocampus), respectively. In the univariate and multivariate analysis, the number of BMs was the risk factor for HMs and PHMs. Patients with BMs ≥ 5 had significantly higher risk of HMs (odds ratio [OR] 7.892, 95% confidence interval [CI] 1.469-42.404, $P = .016$), and patients with BMs ≥ 7 had significantly higher risk of PHMs (OR 5.162, 95% CI 2.017-13.213, $P = .001$). Patients with extracranial metastases are also associated with HMs. *CONCLUSIONS:* Our results indicate that patients with nonoligometastatic disease are significantly associated with HMs and PHMs. The incidence of PHMs may be acceptably low enough to perform HS-WBRT for SCLC. Our findings provide valuable clinical data to assess the benefit of HS-WBRT in SCLC patients with BMs.

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Introduction

Small cell lung cancer (SCLC) is a worldwide public health problem. There are approximately 30,000 new patients annually, accounting for 14% of all lung cancers [1,2]. SCLC has several characteristics which can be distinguished from the other lung cancer types, mainly its high tendency to disseminate and the high risk of developing brain metastases (BMs) [3]. About 10% to 14% of SCLC patients will have BMs at the time of diagnosis [4]. Another 50% of patients will develop central nervous system involvement as their disease progresses [5]. Prophylactic cranial irradiation (PCI) has become a standard of care in decreasing the incidence of brain failure and improving the survival in patients with nonmetastatic and metastatic disease [6,7]. When the central nervous system is clinically involved, therapeutic whole-brain radiation therapy (WBRT) offers temporary control and palliation.

Associated toxicities with WBRT included significantly worse neurocognitive function and quality of life (QOL) [8,9]. The hippocampus is sensitive to radiation and prone to damage by radiation. At present, it is regarded as a potential contributing cause for neurocognitive deficits after WBRT [10,11]. More recent trials have also addressed the issue of the possible neurotoxicity of PCI [12,13]. On the other hand, the Radiation Therapy Oncology Group (RTOG) 0933 trial indicated that hippocampal-sparing (HS) WBRT was associated with preservation of memory test performance and QOL as compared with historical controls [14]. However, patients with SCLC were not included into this trial due to the potential dissemination of the disease [14,15]. In this study, we assessed the clinical features and the distribution of BMs with relation to the hippocampus and perihippocampal region for the purpose of exploring the viability of HS-WBRT on reducing neurocognitive deficits in patients with SCLC.

Materials and Methods

Primary SCLC patients diagnosed by pathology in the Guangdong General Hospital, China, from January 2005 to December 2015 were retrospectively reviewed. BMs were found in all patients at the time of diagnosis or during the follow-up period by magnetic resonance imaging scanning, including T1-weighted, postcontrast, and axial magnetic resonance imaging image data. Patients with a secondary malignant tumor after diagnosis of SCLC were excluded. The study was approved by the ethics committee of the Guangdong General Hospital.

Based on the criteria of the RTOG 0933 study [14], the hippocampus was delineated in the T1-weighted series. Due to the error and shift during radiotherapy, the perihippocampal region was defined as the area of the hippocampus plus a 5-mm margin, which was delineated according to researches of Ghia et al. and Gondi et al. [16,17].

Clinical characteristics included age of diagnosis, sex, BM status (synchronous versus metachronous), and extracranial metastases. The number of BMs was used to predict the risk of hippocampal metastases (HMs) and perihippocampal metastases (PHMs) (patients with BMs located in or within 5 mm around the hippocampus). A synchronous brain metastasis was defined as a BM diagnosed within 60 days of the diagnosis of the primary SCLC; otherwise, the BM was considered metachronous.

All data were analyzed using the SPSS statistical software package (version 16.0; IBM Corporation, Armonk, NY). The optimum cutoff point for the number of BMs was determined by use of the area under the receiver operating characteristic (AUROC) curve. The relationship between patient clinical characteristics and the risk of HMs and PHMs was examined by univariate and multivariable binary logistic regression analysis. A P value $< .05$ was considered significant in all analyses.

Table 1. Clinical Characteristics of 180 Patients Diagnosed with BMs from SCLC

Age (years)	*n*
<60	84
≥60	96
Sex	
Male	166
Female	14
BM status	
Synchronous	32
Metachronous	148
Extracranial metastases	
No	112
Yes	68
Number of brain metastases (*n*)	
Median (range)	4 (1-50)
<5	108
≥5	72
<7	126
≥7	54

Results

A total of 180 patients were identified. The majority (92.2%, 166/180) of patients were male. The median age was 60 years (range, 39-84 years). In total, 17.8% (32/180) of patients had synchronous disease and 37.8% (68/180) had extracranial metastases. The patient characteristics are summarized in Table 1.

The median time for BMs was 9.3 months (range, 3.0-41.7 months). A total of 1594 brain metastatic lesions were identified in 180 patients. The median number of BMs was 4 (range, 1-50), and 29.4% (53/180) of patients presented with a single BM. The most frequently distributed sites of BMs were the frontal lobe (22.5%), parietal lobe (22.1%), temporal lobe (17.1%), occipital lobe (17.0%), cerebellum (15.8%), and brain stem (4.0%) (Table 2). There were 9 (5.0%, 9/180) patients with HMs with a total of 23 (1.4%, 23/1594) BMs. A total of 22 (12.2%, 22/180) patients presented with PHMs. The distribution of metastatic brain lesions among patients is shown in Table 2.

The optimal cutoff points of the correction among the number of BMs, HMs, and PHMs were analyzed using the ROC curve. Five was the optimal cutoff point of the number of BMs for predicting HMs (AUROC = 0.775, $P = .005$), and seven was the optimal cutoff point for predicting PHMs (AUROC = 0.742, $P < .001$).

From the univariate logistic regression analysis, the number of BMs was the risk factor for HMs and PHMs (Table 3). When adjusted for age, sex, BM status, and extracranial metastasis in the multivariable analysis, the number of BMs remains the independent risk factor for HMs and PHMs (Table 4). Patients with BMs ≥ 5 had significantly higher risk of HMs (odds ratio [OR] 7.892, 95% confidence interval [CI] 1.469-42.404, $P = .016$), and patients with BMs ≥ 7 had significantly higher risk of PHMs (OR 5.162, 95% CI 2.017-13.213, $P = .001$). The risk of PHMs increased with an increase in the BM number. In patients with PHMs, 63.6% (14/22) of patients had BMs ≥ 7, while 25.3% (40/158) of patients with BMs < 7 had PHMs (Table 5). Patients with extracranial metastases were also associated with HMs in univariate (OR 6.311, 95% CI

Table 2. The Distribution of BMs by Location

Location	*n* (%)
Frontal lobe	358 (22.5)
Parietal lobe	353 (22.1)
Temporal lobe *	273 (17.1)
Occipital lobe	271 (17.0)
Cerebellum	252 (15.8)
Brain stem	64 (4.0)
Hippocampus	23 (1.4)
Total	1594

* Exclusion of metastases involved in hippocampus.

1.271-31.333, $P = .024$) and multivariable analysis (OR 7.728, 95% CI 1.458-40.964, $P = .016$), but there was no significant correlation with PHMs (Tables 3 and 4).

Discussion

Due to its tendency to disseminate, patients with SCLC were not included in the RTOG 0933 trial [14]. In this study, we assessed the clinical features and the distribution of BMs with relation to HMs and PHMs in SCLC patients with BMs. To date, the highest rate of HMs (18.2%) was reported from a small group of only 11 patients with SCLC [18]. In our study, the rate of HMs was only 5% from the 180 patients with SCLC. This low rate is similar to that observed in other studies (i.e., 0.44%-2.1%) [19,20]. Therefore, our findings with a large cohort of patients could be a true representation of the characteristics of BMs in patients with SCLC.

HS-WBRT has previously been shown to preserve memory outcome in patients with BMs [15]. A perihippocampal region, defined as the area of the hippocampus plus a 5-mm margin, was delineated for the radiation-sparing area to reduce the error and shift during HS-WBRT [16,17]. In a previous study, Harth et al. found that a high percentage (27.3%) of patients had PHMs, and this was attributed to a higher rate of HMs (18.2%) in their patient population [18]. However, Kundapur et al. reported only 3 (5%) patients with PHMs in their study consisting of 59 patients with SCLC with *de novo* BMs before WBRT [21]. Gondi et al. also reported only 4 patients (10.5%) with PHMs in their cohort of 38 patients with SCLC [22]. Similarly in our study, PHMs was observed in only 12.2% of patients with SCLC.

Table 3. Univariate Analysis of Risk Factors for HMs and PHMs

Characteristics	HMs			PHMs		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)						
<60	1			1		
≥60	3.225	0.651-15.970	.151	0.698	0.285-1.709	.431
Sex						
Male	1			1		
Female	0.371	0.152-0.423	.481	0.531	0.066-4.272	.552
BM status						
Synchronous	1			1		
Metachronous	1.771	0.214-14.684	.596	2.344	0.519-10.577	.268
Extracranial metastases						
No	1			1		
Yes	6.311	1.271-31.333	.024	1.162	0.468-2.883	.747
Number of BMs (*n*)						
Continuous variable	1.063	1.022-1.107	.003	1.065	1.034-1.097	<.001
<5	1			–		
≥5	5.708	1.151-28.313	.033	–	–	–
<7	–			1		
≥7	–	–	–	5.162	2.017-13.213	.001

Table 4. Multivariable Analysis of Risk Factors for HMs and PHMs

Characteristics	HMs			PHMs		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)						
<60	1			1		
≥60	4.433	0.815-24.123	.085	0.783	0.304-2.019	.612
Sex						
Male	1			1		
Female	0.451	0.123-0.863	.521	0.584	0.065-5.212	.630
BM status						
Synchronous	1			1		
Metachronous	0.846	0.084-8.553	.887	1.728	0.362-8.256	.493
Extracranial metastases						
No	1			1		
Yes	7.728	1.458-40.964	.016	1.101	0.424-2.856	.843
Number of BMs (*n*)						
<5	1			–		
≥5	7.892	1.469-42.404	.016	–	–	–
<7	–			1		
≥ 7	–	–	–	5.162	2.017-13.213	.001

SCLC is highly sensitive to radiation. As such, even after the occurrence of BMs, WBRT is valuable and effective in tumor control [3]. Indeed, the 1-year overall survival rate of patients with SCLC after WBRT has been reported to reach 40% [23]. The results of the RTOG 0933 trial showed that the decrease of the neurocognitive function from baseline to 4 months in the HS-WBRT group was significantly lower than that in the historical control group (7.0% vs 30.0%, $P < .001$) [15]. Despite the potential to disseminate to the brain, the incidence of HMs and PHMs in patients with SCLC is not significantly higher than other malignant tumors [18–20,24,25]. Therefore, HS-WBRT in patients with SCLC is also feasible.

Currently, clinical data on HMs and PHMs in patients with SCLC after HS-WBRT are lacking. Kundapur et al. found only one (5%, 1/20) patient with SCLC with PHMs following WBRT [21]. There were only three patients with PHMs (4.5%, 3/67) following HS-WBRT in the RTOG 933 trial; however, this trial excluded patients with SCLC [15]. The study on patients with breast cancer also indicated that an estimated 2% of patients were at risk for PHMs if HS-WBRT was used [24]. Although patients with SCLC showed a relatively high rate of HMs in the study by Harth et al., they pointed out that the use of HS-WBRT only mildly increased the absolute risk

Table 5. The Incidences of PHMs in Subgroups

Characteristics	PHMs	
	No (%)	Yes (%)
Age (years)		
<60	72 (45.6)	12 (54.5)
≥60	86 (54.4)	10 (45.5)
Sex		
Male	145 (91.8)	21 (95.5)
Female	13 (8.2)	1 (4.5)
BM status		
Synchronous	30 (19.0)	2 (9.1)
Metachronous	128 (81.0)	20 (90.9)
Extracranial metastases		
No	99 (62.7)	13 (59.1)
Yes	59 (37.3)	9 (40.9)
Number of BMs (*n*)		
<7	118 (74.7)	8 (36.4)
≥7	40 (25.3)	14 (63.6)

of developing hippocampal recurrence (4%) compared with regular WBRT through a dose-response model [18]. Therefore, the type of the primary tumor may not be a major decisive factor for choosing HS-WBRT. There are several ongoing phase II to III clinical trials that are assessing the benefits and risks of HS-WBRT in patients with SCLC treated with PCI. We also suggest that patients with SCLC with BMs should also be explored in an HS-WBRT clinical trial in terms of improving the neurocognitive function and QOL.

The low incidence rate of HMs has made it difficult to identify the risk factors for predicting HMs and PHMs among patients with SCLC. Kundapur et al. reported a potential relationship between the number of BMs and PHMs (OR 1.4, 95% CI 0.9-2.2, $P = .09$); the number of BMs in the three patients with PHMs was 22, 23, and 33, respectively [21]. The number of BMs was also an independent predictor of PHMs in patients with breast cancer; the incidence of PHMs significantly increased if the number of BMs was >4 (OR 3.45 for 4-9 BMs vs 1-3 BMs, OR 10.50 for ≥10 BMs vs 1-3 BMs) [24]. Marsh et al. [19] also found that in patients with HMs, 15% of them occurred in 1 to 3 BMs, while 85% of metastases occurred in nonoligometastatic patients (4 or more metastases). In our study, we also found that BMs ≥ 5 and BMs ≥ 7 were risk factors for HMs and PHMs, respectively. It is quite natural that patients with larger number of BMs have a higher possibility of HMs and PHMs. The results of above studies suggested that there was a potential correlation between the number of BMs and HMs/PHMs. However, the final stage of BMs with radiographic changes could be not obtained from all patients due to the limitations of retrospective studies. Therefore, we were unable to accurately obtain the number of BMs and the time of HMs/PHMs. Furthermore, for SCLC patients with multiple BMs, the potential risk of hippocampal regional recurrence should be considered when performing HS-WBRT. The RTOG 0933 trial excluded all patients with more than 10 BMs [14].

There may be a best hippocampal-sparing approach such as stereotactic radiosurgery. However, Yomo and Hayashi reported 41 SCLC patients with BMs who received stereotactic radiosurgery as initial treatment, follow-up imaging data were available for 34 patients and 59% of them were developed new BMs after stereotactic radiosurgery [26]. It is also possible that most patients with intracranial progression may require subsequent radiotherapy after stereotactic radiosurgery. Therefore, a stereotactic radiosurgery approach might actually induce cognitive impairment rather than protect cognitive function [27]. WBRT remains the standard of care for SCLC patients with BMs, and HS-WBRT might lower the risk of cognitive decline.

Prognosis in SCLC patients with BMs is poor and probably too short to develop neurocognitive deficits. It is highly questionable whether HS-WBRT should be performed, especially in patients with multiple BMs. In addition, the recently concluded Quartz trial places question marks for WBRT benefit over best supportive care for non–small cell lung cancer with BMs unsuitable for resection or stereotactic radiotherapy [28]. Therefore, HS-WBRT should be more important in patients with PCI. In a prospective study with hippocampal-sparing PCI in limited-stage SCLC, the results showed that 20% (4/20) of patients had intracranial progression after PCI, of which 1 patient had PHM [29]. The ongoing randomized controlled trials will give us more results in the future.

In addition, we found that extracranial metastases are also associated with HMs in univariate and multivariable analysis. The mechanism underlying why the extracranial metastases impact HMs is still unclear. However, patients diagnosed with BMs and extracranial diseases were shown to have a higher metastatic disease burden, and the median overall survival was less than 6 months [3]. Thus, for BM patients with extracranial disseminated disease, the choice of palliative treatment should not only consider the effects of the brain disease alone.

There were several limitations in our study. First, this is a retrospective study from a single institution. However, to the best of our knowledge, this study had the largest sample size to date, and our results could be a true representation of the clinical characteristics in this very aggressive malignancy. Second, we lack data on HMs and PHMs in these patients after WBRT.

In conclusion, patients with nonoligometastatic disease are significantly associated with HMs and PHMs. The incidence of PHMs may be acceptably low enough to perform HS-WBRT for SCLC. Our findings provide valuable clinical data for the opportunity to assess the benefit of HS-WBRT in patients with SCLC and BMs.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of Guangdong General Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed Consent

As a retrospective study, individual informed consent was waived given the anonymous analysis of routine data.

Conflict of Interest Statement

No actual or potential conflicts of interest exist.

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