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Prophylactic cranial irradiation for extensive-stage small cell lung cancer: Analysis based on active brain MRI surveillance

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ABSTRACT

Background and purpose: The value of prophylactic cranial irradiation (PCI) for extensive-stage small-cell lung cancer (ES-SCLC) has recently been challenged. This study was conducted to evaluate the role of PCI for ES-SCLC under active brain magnetic resonance imaging (MRI) surveillance.
Materials and methods: Patients with ES-SCLC who showed any responses after first-line chemotherapy and no initial brain metastasis (BM) were retrospectively included. Active brain MRI surveillance was performed for all patients. Progression-free survival (PFS) and overall survival (OS) were compared between PCI and non-PCI patients. The time-related hazard of BM was evaluated in non-PCI patients.
Results: One hundred and eighteen consecutive patients were included in the study. The median follow-up time was 26.5 months (3–72 months). The median PFS and OS were better in the PCI cohort than in the non-PCI group. Multivariate analyses revealed first-line chemotherapy cycles (> 4 vs. ≤ 4 cycles, HR: 0.29; 95% CI: 0.15–0.55, $P < 0.01$) and PCI (Yes vs. No, HR: 0.54; 95% CI: 0.29–0.99, $P = 0.04$) were independent prognostic factors for disease progression. In the non-PCI group, 47.4% (46/97) of the patients developed BM and the hazard of BM increased continuously in three-quarters of the first year since diagnosis.
Conclusion: Under active brain MRI surveillance, PCI could be beneficial for patients with ES-SCLC who show good responses after first-line chemotherapy.

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1. Introduction

Small cell lung cancer (SCLC) accounts for approximately 15–20% of all lung cancers. In 2019, approximately 30,000 new cases of SCLC were reported in the United States, representing the fifth leading cause of cancer death [1,2]. According to an epidemiologic analysis, in two-thirds of cases, SCLC was diagnosed as extensive stage [3]. The primary treatment for extensive-stage small cell lung cancer (ES-SCLC) is platinum-based combined chemotherapy. Although SCLC is one of the most chemosensitive types of solid tumor [4], it is highly susceptible to recurrence and metastasis [5].

The brain is a high-risk relapse site for SCLC. Autopsy studies have confirmed that brain metastases occurred in more than 50% of all cases of SCLC [6]. Since the role in improving survival, prophylactic cranial radiotherapy (PCI) has become part of the standard care for patients with limited stage of SCLC [7]. However, the value of PCI in ES-SCLC remains controversial. A European randomized study suggested that PCI could provide survival benefits for patients with ES-SCLC who showed any chemotherapy response in addition to reducing the risk of brain metastases [8]. This result however was challenged by a Japanese study. Of this study, a total of 224 ES-SCLC patients who achieved any responses from the first-line chemotherapy were enrolled. All patients underwent brain MRI scans 4 weeks before enrollment to rule out a possible asymptomatic brain metastases, and then were randomly assigned to the PCI treatment group or an observation group at a scale of 1:1. The final results showed that PCI did not improve

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overall survival (OS) or progression-free survival (PFS), but only reduced the risk of brain metastasis [9].

Recently, a real-world retrospective analysis attempted to analyze the effect of brain MRI screening on the value of PCI. The result showed that adding PCI could provide survival benefits for patients with ES-SCLC who show stable systemic disease, regardless of whether MRI screening was performed [10]. In our institute, active brain MRI follow-up is a routine diagnostic procedure for ES-SCLC during and after completing first-line chemotherapy. Therefore, the aim of this study was to comprehensively analyze the value of PCI for ES-SCLC under active brain MRI surveillance.

2. Materials and methods

2.1. Patients

Between June 2012 and June 2019, 332 patients with SCLC were treated in our institution. Among them, 194 were diagnosed to have extensive-stage disease. Moreover, patients were eligible for inclusion in our retrospective study if 1) they were diagnosed as having extensive-stage SCLC (based on pathological confirmation); 2) they had undergone at least three cycles of first-line chemotherapy; 3) detailed brain MRI follow-up images were available for patients; and 4) they did not have brain metastases at the time of the initial diagnosis (confirmed using brain MRI). Patient selection is shown in Supplement 1.

2.2. Treatments

All patients underwent brain MRI and thoracoabdominal CT within 1 month before any treatment. The primary treatment was platinum-based combination chemotherapy. Thoracic radiotherapy was recommended, but not mandatory, for patients with stable systemic disease after first-line chemotherapy. Consolidative thoracic radiotherapy was performed by intensity-modulated radiotherapy. The gross tumor volume (GTV) was the radiologically evident residual lesion after chemotherapy. The planning target volume was determined based on the GTV by adding a margin of 0.6 cm in the axial plane and 1.0 mm in the craniocaudal plane. The median prescription dose for thoracic radiotherapy was 60 Gy in 30 fractions (range, 30 Gy 10 fractions to 68 Gy/34 fractions). PCI were performed by a three-dimensional radiotherapy under the routing mask fixation technique, and the prescribed dose for all was 25 Gy in 10 fractions.

2.3. Evaluation method and statistical analyses

Prior to treatment, patients required a baseline evaluation, including chest and abdomen enhanced CT and brain MRI scans. During first-line chemotherapy, evaluations, including chest CT and brain MRI, were performed after every two cycles of chemotherapy. Brain MRI scans were the routing items before PCI. When completing the full course of treatment, patients received the same radiographic assessment in every 2 months.

PFS was measured from the date of disease diagnosis to the date of disease progression or death from any cause or the final follow-up. OS was measured from the date of disease diagnosis to the date of death from any cause or date of the final follow-up. Brain progression-specific survival (BSS) was measured from the date of disease diagnosis to the date of death from brain metastases progression. PFS, OS and BSS were evaluated using the Kaplan-Meier method and evaluated by a log-rank test. Multivariate Cox proportional hazards analysis was performed to determine the effect of different covariates on PFS and OS. Monthly hazard rates of BM were calculated as the total number of events per month divided by patients at risk of BM in that month. Hazard rate curves were smoothed by applying an Epanechnikov kernel [11]. All statistical analyses were performed using SPSS, version 20.0 (IBM Inc) and R, version 3.2.1 (R Foundation for Statistical Computing).

3. Results

3.1. Patient characteristics

A total of 118 patients were eligible for inclusion in the study. The median age was 62 years (range, 27 to 80 years). The proportion of elderly patients (>65 years) was relatively low (N = 34, 28.8%). The majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (N = 95, 80.5%). Etoposide combined with platinum was the most common first-line chemotherapy regimen (N = 113, 95.8%). The median cycles of first-line chemotherapy were 5 (range, 3 to 5).

Twenty-one patients underwent PCI. PCI was prescribed at a uniform dose of 25 Gy in 10fractions. Compared to those who did not undergo PCI, the patients who received PCI all completed six cycles of first-line chemotherapy as scheduled. According to the efficacy evaluation after chemotherapy, most of them showed good responses (CR + PR, N = 20, 95.2%). Furthermore, a higher number of patients in the PCI group underwent consolidative thoracic radiotherapy (N = 17, 81.0%). The median prescription dose for thoracic radiotherapy was 60 Gy in 30 fractions (range, 30 Gy/10F-68 Gy/34F). Patients' characteristics are shown in Table 1.

3.2. PCI improves the outcomes of ES-SCLC with good chemotherapy responses

The median follow-up time was 26.5 months (range, 3–72 months). The 0.5- and 1-year PFS rates were 68.3% (95% confidence interval [CI] 57.4–74.7) and 18.5% (95% CI, 7.4–20.3), respectively. Patients receiving PCI showed significantly better PFS at 1 year than those who did not receive PCI; the corresponding 1-year PFS rate was 43.5% and 13.6%, respectively (log-rank test, $P = 0.001$; Fig. 1A). Multivariate analyses showed that PCI was an independent prognostic factor for PFS (HR, 0.54; 95% CI, 0.29–0.99; $P = 0.04$; Fig. 2). At the final evaluation, 48 patients showed BM (PCI group, N = 2 vs. non-PCI group, N = 46). PCI significantly prolonged the time to brain relapse, with the median time to brain relapse being 15.9 months in the PCI group vs. 7.3 months in non-PCI group.

The 0.5- and 1-year OS rates were 89.6% (95% CI, 81.3–93.3) and 52.6% (95% CI, 42.1–61.0), respectively (Supplement 2). Univariate analysis showed that PCI could improve OS: 1-year OS rate was 63.3% in the PCI group and 50.3% in the non-PCI group (log-rank test, $P = 0.037$ (Fig. 1B). However, after adjustment for multiple covariates, PCI was not independently associated with OS (HR, 0.63; 95% CI, 0.30–1.34; $P = 0.23$) (Fig. 2).

3.3. BM risk for ES-SCLC without PCI

In our cohort, a total of 97 patients did not receive PCI, of which 46 patients showed brain metastases during follow-up. The majority of patients (86.9%, 40/46) received whole-brain radiotherapy (WBRT) after diagnosis of brain metastases. Six patients failed to complete WBRT due to severe cranial nerve symptoms caused by BM. A higher proportion of brain progression-specific death

Table 1
Characteristics of patients with extensive-stage small-cell lung cancer with or without PCI.

Variables	Patients no. (%)		*P*
	No PCI (N = 97)	PCI (N =21)	
Age (y)			
≤65	68 (70.1)	16 (76.2)	0.577
>65	29 (29.9)	5 (23.8)	
Sex			
Male	86 (88.7)	20 (95.2)	0.613
Female	11 (11.3)	1 (4.8)	
ECOG performance status			
0–1	78 (80.4)	17 (78.9)	1
>1	19 (19.6)	4 (21.1)	
Smoking status			
Never smoked	22 (22.6)	4 (19.0)	0.963
Previously smoked	75 (77.4)	17 (81.0)	
T stage			
$T_{1/2}$	24 (24.7)	5 (26.3)	0.928
$T_{3/4}$	73 (75.3)	16 (73.7)	
N stage			
N_0	3 (3.1)	3 (14.3)	0.04
N_1	4 (4.1)	3 (14.3)	
N_2	48 (49.5)	5 (23.8)	
N_3	42 (43.3)	10 (47.6)	
Chemotherapy regimen			
EP/EC	93 (95.9)	20 (95.2)	1
IP	4 (4.1)	1 (4.8)	
Chemotherapy cycles			
≤4	23 (23.7)	0 (0)	0.012
>4	74 (76.3)	21 (100)	
Chemotherapy responses			
CR	6 (6.2%)	9 (42.9)	<0.001
PR	76 (78.4%)	11 (52.3)	
SD	15 (15.4%)	1 (4.8)	
Thoracic radiation			
Yes	67 (69.1)	17 (81.0)	0.276
No	30 (30.9)	4 (19.0)	
Thoracic radiation dose			
≥60Gy/30F	30 (30.9)	11 (52.3)	0.061
<60Gy/30F	67 (69.1)	10 (47.7)	

Abbreviations: PCI, prophylactic cranial irradiation; ECOG, Eastern Cooperative Oncology Group; EP, etoposide + cisplatin; EC, etoposide + carboplatin; IP, irinotecan + cisplatin; CR, complete response; PR, partial response, SD, stable disease.

occurred in the non-PCI group (20.2%, 15/74) than that in PCI group (0%, 0/21) (Supplement 3). Patients receiving PCI showed significantly better progression-specific survival at 1 year than those who did not receive PCI, the corresponding 1-year brain progression-specific survival rate was 100.0% and 86.0%, respectively (log-rank test, $P = 0.039$; Fig. 3).

Smoothed hazard plots showed the trend of monthly hazard of brain metastases and yielded information regarding the instantaneous brain metastasis risk for those patients. Within 9 months from diagnosis, the monthly hazard of brain metastases increased gradually and peaked at 10.5% at the time of 9 months. After that time point, the hazard began to decline (Fig. 4A). The cumulative incidence of brain metastases in this cohort at 6, 7, 8 and 9 months after diagnosis was 14.9%, 21.1%, 33.2% and 37.6%, respectively (Fig. 4B).

4. Discussion

PCI is an important component in the treatment of limited-stage SCLC [7]. However, its value in ES-SCLC remains controversial. At our institute, periodic brain MRI screening is a routine examination for all cases of SCLC. We found that even under the active brain MRI surveillance, additional PCI could further improve the PFS and reduce the incidence of BM for ES-SCLC patients who achieved a good response after first-line chemotherapy. Furthermore, we observed that the hazard of BM would increase over time after disease diagnosis.

SCLC is a highly metastatic and relapsing malignancy with a very poor prognosis. The prognosis of ES-SCLC is even worse, with the 5-year OS less than 5% [12]. For many years, platinum combined with etoposide was recommended as the primary standard care for ES-SCLC. To further improve the outcomes, many new drugs such as immune checkpoint inhibitors have been recently employed in cases of ES-SCLC. The randomized trial IMpower 133 reported that the addition of atezolizumab, a PDL-1-targeting checkpoint inhibitor, to carboplatin plus etoposide could significantly improve the median OS from 10.3 months to 12.3 months in comparison with chemotherapy alone [13]. Meanwhile, an ongoing phase III study Caspian preliminarily suggested that the addition of another PDL-1 checkpoint inhibitor durvalumab to cisplatin plus etoposide could also significantly improve the survival for ES-SCLC, with the median OS increasing from 10.3 to 13.0 months [14].

In our cohort, the 1-year OS rate was 52.6% and the median OS was 12.8 months. Our outcomes appear to be comparable to the results from these prospective studies. One possible reason could be that the definition of OS was different. In prospective studies, OS or PFS were often calculated from the time of randomization. However, in our study, the OS and PFS were defined from the time

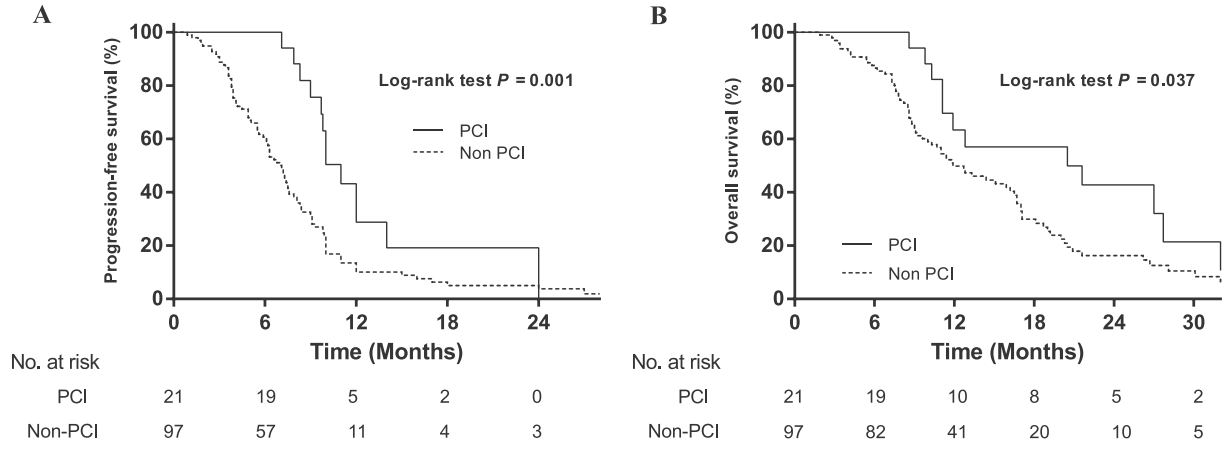
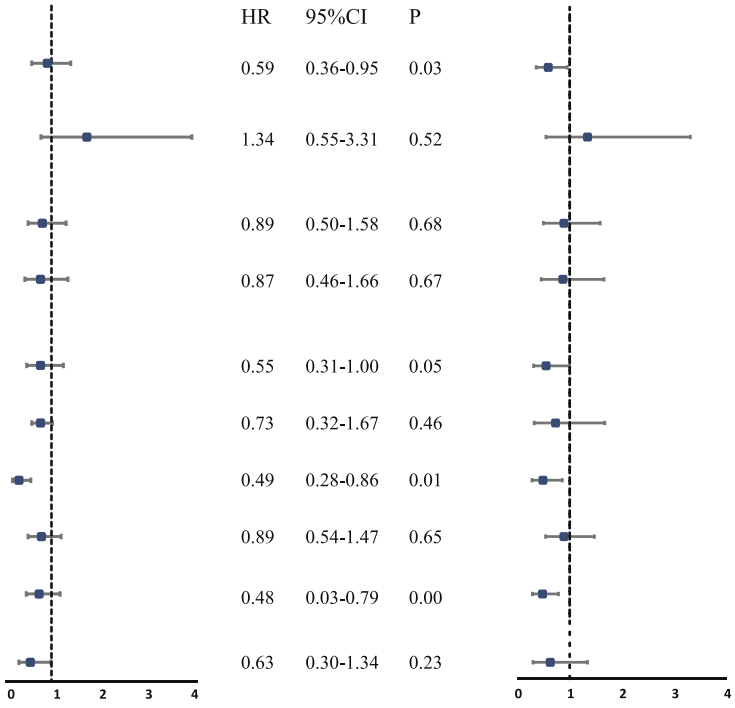


Fig. 1. A, Comparison of PFS between PCI and non-PCI ES-SCLC patients, B, Comparison of OS between PCI and non-PCI ES-SCLC patients. PFS, progression-free survival; OS, overall survival; PCI, prophylactic cranial irradiation; ES-SCLC, extensive-stage small cell lung cancer.

Table 2. Multivariable analysis of the clinical variables for PFS and OS.

	PFS			OS		
Variable	HR	95%CI	P	HR	95%CI	P
Age (y)						
≤ 65 vs.> 65	0.91	0.57-1.42	0.67	0.59	0.36-0.95	0.03
Sex						
Male vs. Female	1.77	0.77-4.06	0.18	1.34	0.55-3.31	0.52
PS						
0-1 vs. >1	0.80	0.49-1.32	0.40	0.89	0.50-1.58	0.68
Smoking						
Never vs. Former	0.76	0.42-1.36	0.36	0.87	0.46-1.66	0.67
T stage						
$T_{1/2}$ vs. $T_{3/4}$	0.76	0.46-1.26	0.30	0.55	0.31-1.00	0.05
N stage						
$N_0/N_1/N_2/N_3$	0.76	0.57-1.02	0.07	0.73	0.32-1.67	0.46
ChT cycles						
> 4 vs. ≤ 4	0.29	0.15-0.55	0.00	0.49	0.28-0.86	0.01
ChT response						
CR/PR/SD	0.78	0.49-1.21	0.26	0.89	0.54-1.47	0.65
Thoracic RT						
Yes vs. No	0.73	0.45-1.19	0.21	0.48	0.03-0.79	0.00
PCI						
Yes vs. No	0.54	0.29-0.99	0.04	0.63	0.30-1.34	0.23



LC: local control; PFS: progression-free survival; OS: overall survival; ChT: chemotherapy; CR: complete response; PR: partial response; SD: stable disease; PCI: prophylactic cranial irradiation; HR: hazard ratio; CI: confidence interval .

Fig. 2. Multivariate analysis and forest plots indicating the independent prognostic factors for PFS and OS in ES-SCLC patients. PFS, progression-free survival, OS, overall survival; ES-SCLC, extensive-stage small cell lung cancer, HR, hazard ratio; CI, confidence interval.

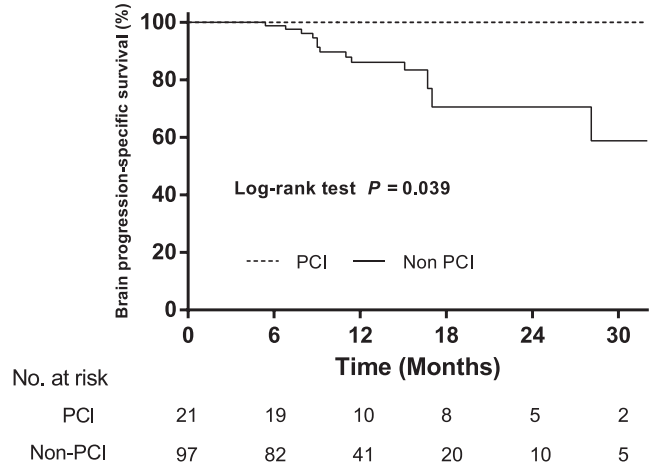


Fig. 3. Comparison of BSS between PCI and non-PCI ES-SCLC patients. BSS, brain progression-specific survival; ES-SCLC, extensive-stage small cell lung cancer; PCI, prophylactic cranial irradiation.

of diagnosis. In general, it took approximately one to three months from diagnosis for a patient to enter randomization. Therefore, we needed to interpret the results of our OS prudently when comparing with those prospective studies.

According to the Japanese prospective study, if the patients were identified as showing no BM in initial diagnosis, PCI after first-line chemotherapy could not provide an additional PFS and OS benefit [9]. In our analysis, all patients underwent active brain MRI surveillance, and we still observed the positive value of PCI for reducing disease progression. Meanwhile, consistent with most studies, PCI significantly reduced the incidence of brain metastases and prolonged the duration of brain recurrence.

Thoracic consolidation radiotherapy plays an important role in ES-SCLC patients who achieved stable control of systemic disease by first-line chemotherapy. The European prospective study confirmed that consolidation radiotherapy to the thoracic region could reduce locoregional recurrence and provide a long-term OS benefit for patients with residual thoracic disease after chemotherapy [15]. Some earlier studies also found that thoracic radiotherapy could prolong the OS for ES-SCLC [16,17]. In our cohort, most patients (71.2%, N = 84) had completed thoracic radiotherapy. In our PCI group, the completion rate of thoracic radiotherapy was higher than that in non-PCI group. The discrepancy in delivering thoracic radiotherapy was another potential reason for the better PFS in the PCI group.

In this cohort, the median dose of thoracic radiotherapy was 60 Gy over 30 fractions, which was higher than the dose applied in Slotman's study. Based on some findings for advanced non-small-cell lung carcinoma (NSCLC), the administration of higher radiotherapy doses to primary sites would lead to better outcomes [18,19]. We speculated that the use of high-dose radiotherapy to the thoracic lesion in our study was another possible explanation for our better prognosis than previous studies.

In the subsequent multivariate analysis, PCI was not confirmed as an independent prognostic factor for OS. One possible reason was that patients would die of the non-intracranial progression, which offset the OS benefit from PCI. In the non-PCI group, the majority of patients developing brain metastases received WBRT.

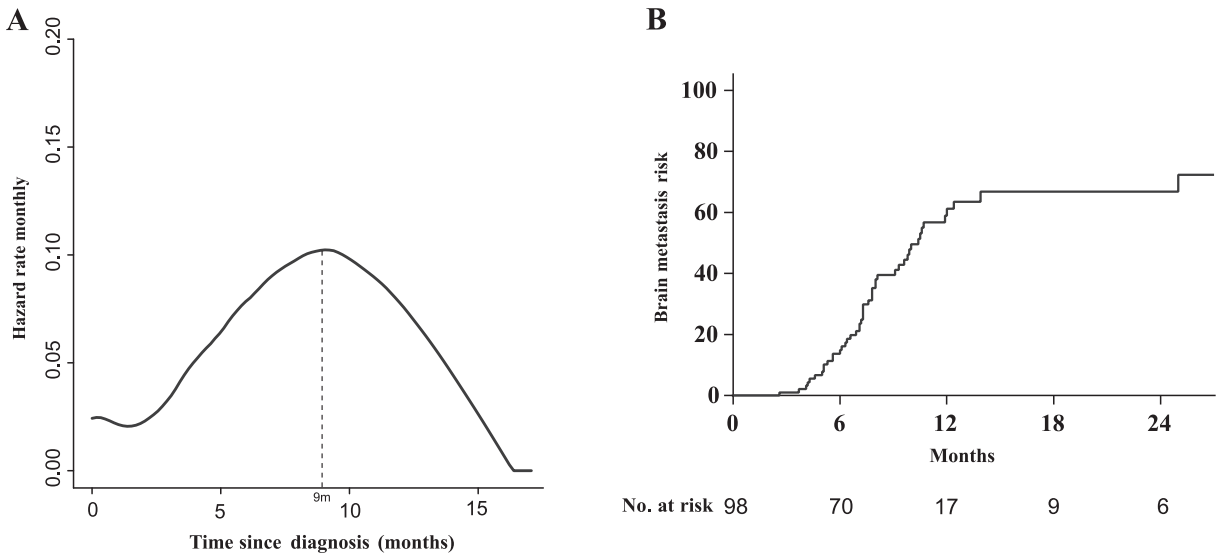


Fig. 4. A, Smoothed hazard plots for the monthly rate of brain metastasis for ES-SCLC without PCI; B, the cumulative incidence of brain metastases of ES-SCLC without PCI. ES-SCLC, extensive-stage small cell lung cancer; PCI, prophylactic cranial irradiation.

However, some patients might occur disease deteriorates rapidly caused by BM, losing the opportunity to complete WBRT. In addition, we observed a higher brain progression-specific death risk in non-PCI group than that in PCI group. Adding PCI significantly improved the 1- year BSS. Therefore, we affirmed the value of PCI based on its effect on improving PFS and BSS and reducing BM.

The timing of PCI has been rarely discussed. Chen et al found that early PCI (started within 6 months from initial chemotherapy) significantly lowered the risk of brain metastases in comparison with late PCI (started more than 6 months from initial chemotherapy) in ES-SCLC [20]. Similarly, as reported by Auperin et al, PCI administered within 6 months was associated with a reduced risk of brain metastases in SCLC (including L-SCLC and ES-SCLC) [7]. In this study, according to the data from patients who did not undergo PCI, the hazard of BM is highly correlated with the time. At 6 months after diagnosis, the cumulative risk of brain relapse was up to 14%. As a result, determining the optimal timing for PCI is an urgent topic.

According to the Impower 133 and Caspian studies, chemotherapy combined with immunotherapy could provide a better objective responses and OS than chemotherapy alone. Based on our results, the optimal population for PCI was those who showed good responses after first-line chemotherapy. Therefore, we speculated that PCI might be more valuable in the coming era of immunotherapy.

The main limitations of our study were the retrospective analysis, and the fact that all patients were from one single institution. In our study, only 21 patients received PCI, and this population might represent a highly selective group. In order to minimize the selection bias, we described their clinical characteristics and treatment courses in a detailed manner. Meanwhile, multivariate analysis was used to determine the prognostic value of PCI after adjustments for several covariates. In addition, due to the retrospective nature, we did not analyze the patients' quality of life and changes in cognitive function.

5. Conclusion

Under active brain MRI surveillance, PCI could still improve the outcomes for ES-SCLC patients who showed good responses after first-line chemotherapy.

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None

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2020.09.005.

References

[1] National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Small cell lung cancer. 2018;v2.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69:7–34.
[3] Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006;24:4539–44.
[4] Lara Jr PN, Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 2009;27:2530–5.
[5] Hanna N, Bunn Jr PA, Langer C, Einhorn L, Guthrie Jr T, Beck T, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006;24:2038–43.
[6] Nugent JL, Bunn Jr PA, Matthews MJ, Ihde DC, Cohen MH, Gazdar A, et al. CNS metastases in small cell bronchogenic carcinoma: increasing frequency and changing pattern with lengthening survival. Cancer 1979;44:1885–93.
[7] Auperin A, Arriagada R, Pignon JP, Le Pechoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. New Engld J Med 1999;341:476–84.
[8] Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. New Engld J Med 2007;357:664–72.
[9] Takahashi T, Yamanaka T, Seto T, Harada H, Nokihara H, Saka H, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:663–71.

[10] Bang A, Kendal WS, Laurie SA, Cook G, MacRae RM. Prophylactic cranial irradiation in extensive stage small cell lung cancer: outcomes at a comprehensive cancer centre. Int J Radiat Oncol*Biol*Phys 2018;101:1133–40.
[11] Epanechnikov VA. Nonparametric estimation of a multivariate probability density. Theory Probab Appl 1969;14:153–8.
[12] Demedts IK, Vermaelen KY, van Meerbeeck JP. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Resp J 2010;35:202–15.
[13] Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. New Engld J Med 2018;379:2220–9.
[14] Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet (London, England) 2019;394:1929–39.
[15] Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, El Sharouni SY, Hatton M, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015;385:36–42.
[16] Zhu H, Zhou Z, Wang Y, Bi N, Feng Q, Li J, et al. Thoracic radiation therapy improves the overall survival of patients with extensive-stage small cell lung cancer with distant metastasis. Cancer 2011;117:5423–31.
[17] Jeremic B, Shibamoto Y, Nikolic N, Milicic B, Milisavljevic S, Dagovic A, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. J Clin Oncol 1999;17:2092–9.
[18] Su S, Li T, Lu B, Wang X, Li J, Chen M, et al. Three-dimensional radiation therapy to the primary tumor with concurrent chemotherapy in patients with stage IV non-small cell lung cancer: results of a multicenter phase 2 study from PPRA-RTOG, China. Int J Radiat Oncol Biol Phys 2015;93:769–77.
[19] Lopez Guerra JL, Gomez D, Zhuang Y, Hong DS, Heymach JV, Swisher SG, et al. Prognostic impact of radiation therapy to the primary tumor in patients with non-small cell lung cancer and oligometastasis at diagnosis. Int J Radiat Oncol Biol Phys 2012;84:e61–7.
[20] Chen Y, Li J, Zhang Y, Hu Y, Zhang G, Yan X, et al. Early versus late prophylactic cranial irradiation in patients with extensive small cell lung cancer. Strahlenther Onkol 2018;194:876–85.