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The impact of Prophylactic cranial irradiation on the prognosis of patients with limited-stage small cell lung cancer in the MRI era

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Abstract

Purposes To evaluate the impact of prophylactic cranial irradiation (PCI) on the prognosis of patients with limited-stage small cell lung cancer (SCLC) in the era of MRI surveillance.

Methods Limited-stage SCLC patients with complete remission (CR) or partial remission (PR) of tumor after definitive chemo-radiotherapy (CRT) were retrospectively analyzed. Survival data were calculated by Kaplan-Meier methods, Cox proportional hazards model was applied for multivariate prognostic analysis.

Results Between June 2002 and January 2017, 620 patients with limited-stage SCLC were accrued in our study. After CRT, 228 (36.8%) patients achieved CR, of whom, 29 patients did not receive PCI, among the rest 199 patients, 172 (86.4%) received brain MRI to exclude brain metastasis (BM) before PCI. With a median follow-up time of 25.6 months, the cumulative BM rate was 17.1% and 37.9% in patients who received or did not receive PCI ($P=0.011$). The median survival time was 30.2 months and 30.5 months, respectively and the 1 -, 3 -, 5-year survival rates were 93.7%, 42.9%, 35.8% and 83.4%, 46.5%, 41.9%, respectively ($P=0.98$). Multivariate analysis indicated that baseline KPS ≥ 90 was a favorable independent prognostic factor for OS in CR patients (HR: 0.33, 95% CI: 0.23–0.46, $P=0.000$). After CRT, 392 (63.2%) patients achieved PR, 53 cases did not receive PCI and 310 (91.4%) of the remaining 339 patients received brain MRI before PCI. With a median follow-up time of 15.5 months, the cumulative brain metastasis rate was 12.7% and 46.2% respectively ($P=0.000$). The median survival time was 25.7 months and 18.6 months, respectively. The 1 -, 3 -, and 5-year survival rates were 87.6%, 40.2%, 29.2% and 75.7%, 16.7%, 10.3% ($P=0.000$). Baseline KPS ≥ 90 (HR: 0.32, 95% CI: 0.25–0.41, $P=0.000$) and PCI (HR: 0.57, 95% CI: 0.41–0.79, $P=0.001$) were favorable prognostic factors for OS in PR patients.

Conclusions In this study, PCI significantly reduced the incidence of BM in patients with limited-stage SCLC who were evaluated as CR and PR after CRT, but it has no significantly positive impact on overall survival in CR patients. Further prospective randomized studies were warranted.

Keywords Small cell lung cancer, Limited stage, Prophylactic cranial irradiation, Study on the prognosis

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Introduction

Small cell lung cancer (SCLC) accounts for approximately 15–20% of all types of lung cancers currently, it is characterized by rapid doubling time, early dissemination, and a poor prognosis [1]. The standard treatment for patients with limited-stage SCLC involves thoracic radiotherapy combined with EP/EC chemotherapy [2]. SCLC is highly sensitive to chemotherapy and radiation therapy, However, most patients were still suffered from local recurrence or/and distant metastasis within 2 years. Brain metastases (BM) are common in patients with SCLC, occurring in more than 50% of patients, owning to the blood brain barrier restricts the penetration of chemotherapeutic agents into the brain. BM would bring a poor prognosis and the median survival is only 4–6 months [3]. In 1990s, the role of PCI was first demonstrated by a meta-analysis. Among patients with limited-stage SCLC who achieve a complete response(CR), the 3-years overall survival(OS) rates for patients with PCI was 5.4% better than those who did not receive PCI. In addition, the relative disease free survival increased by 25% at 3-years of patients with PCI [4]。.

However, the studies included in this meta-analysis did not perform brain MRI scans before PCI. MRI has a higher soft tissue resolution and more effectively detect brain metastases than CT. Since PCI essentially does not "prevent" the occurrence of brain metastases but rather eradicates microscopic metastases that already exist but are not yet visible to the naked eye, the role of PCI in limited-stage SCLC warrants further investigation in the era where brain MRI scans are routinely performed [5].

Patients and methods

We conducted a retrospective analysis using integrated data from two major cancer centers: Zhejiang Cancer Hospital and Sun Yat-sen University Cancer Center [6–8]. The study included patients with limited-stage SCLC who received radical thoracic radiotherapy and chemotherapy. Chemotherapy regimens included EP (etoposide 100 mg/m² on days 1–3, cisplatin 80 mg/m² on day 1 or 25 mg/m² on days 1–3) or EC (etoposide 100 mg/m² on days 1–3, carboplatin AUC=5 on day 1), repeated every 3 weeks for a total of 4–6 cycles. Thoracic radiotherapy began concurrently with the 3rd cycle of chemotherapy, using a hyper-fractionated regimen of 45 Gy in 30 fractions over 3 weeks. Four weeks after the completion of thoracic radiotherapy and chemotherapy, patients underwent follow-up enhanced CT of the chest and abdomen, as well as enhanced MRI of the brain. Patients achieving CR or PR were recommended to undergo PCI (25 Gy in 10 fractions over 12 days).

The objective of this study was to compare the impact of PCI on overall survival in patients who achieved CR or PR after chemoradiotherapy. Statistical analysis was carried out with SPSS 25.0 software. The chi-square test for categorical data was used to compare the baseline characteristics between the PCI and no-PCI groups. Univariate survival analysis was performed by the Kaplan–Meier method. Multivariate analyses for overall survival was performed using Cox proportional hazards model. Hazard ratios (HRs) and 95% CIs was calculated using Cox's proportional-hazard model. All tests were 2-sided, and statistical significance level was set at 0.05.

Results

Patient characteristics

Between June 2002 and January 2017, 620 patients with limited-stage SCLC were accrued in a our study. All patients underwent baseline brain MRI/CT scans. Among them, 18.1% (112 patients) had brain metastases, and 472 patients reached the follow-up endpoint of death. After chemoradiotherapy(CRT), 228 patients (36.8%) achieved CR. of whom, 29 patients did not receive PCI, among the rest 199 patients, 172 (86.4%) received brain MRI to exclude brain metastasis (BM) before PCI (clinical characteristics shown in Table 1). There were 392 patients (63.2%) achieved PR after CRT, of which 53 did not undergo PCI, while 339 patients who received PCI included 310 patients (91.4%) who had brain MRI to exclude BM (clinical characteristics shown in Table 2).

Thoracic radiotherapy

Among the 228 patients who achieved a CR after CRT, 72 (31.6%) received three-dimensional conformal radiotherapy (3D-CRT), and 156 (68.4%) received intensity-modulated radiotherapy (IMRT). Three patients (1.3%) received a thoracic radiotherapy dose of 43.5 Gy/29 fractions, three patients (1.3%) received 48 Gy/32 fractions, and the remaining 222 patients received 45 Gy/30 fractions in a hyper-fractionated schedule.

Among the 392 patients who achieved a PR after CRT, 68 (17.3%) received 3D-CRT, and 324 (82.7%) received IMRT. One patient (0.3%) received a thoracic radiotherapy dose of 47.1 Gy/30 fractions, one patient (0.3%) received 48 Gy/32 fractions, two patients (0.5%) received 60 Gy/30 fractions, and the remaining 388 patients received 45 Gy/30 fractions in a hyper-fractionated schedule.

Chemotherapy

Among the patients who achieved a CR after CRT, 2 (0.9%) received 2 cycles of chemotherapy, and 1 (0.4%) received 8 cycles. The median total number of chemotherapy cycles was 4 (ranging from 2 to 8 cycles). Among the patients with a partial response (PR), 2 (0.5%) did not receive chemotherapy, and 1 (0.3%) received 8 cycles. The

Table 1 Clinical baseline characteristics of 228 patients with CR after chemoradiotherapy, with or without PCI

Characteristic	PCI (*n* = 199)		Non-PCI(*n* = 29)		*P*
	No.	%	No.	%	
Age(years)					
Mid-Age	58		59		
Range	22–76		34–75		
Gender					0.56
Male	156	78.4	25	86.2	
Female	43	21.6	4	13.8	
KPS					0.04
90	122	61.3	17	58.6	
80	77	38.7	12	41.4	
T					0.56
1	18	9.1	5	17.2	
2	88	44.2	9	31.0	
3	45	22.6	6	20.7	
4	48	24.1	9	31.0	
N					0.53
0	34	17.1	2	6.9	
1	23	11.6	2	6.9	
2	93	46.7	16	55.2	
3	49	24.6	9	31	
TNM					0.51
I	21	10.6	1	3.4	
II	24	12.1	4	13.7	
IIIA	65	32.7	11	37.9	
IIIB	89	44.7	13	44.8	

Table 2 Clinical baseline characteristics of 392 patients with PR after chemoradiotherapy, with or without PCI

Characteristic	PCI(*n* = 339)		Non-PCI(*n* = 53)		*P*
	No.	%	No.	%	
Age(years)					
Mid-Age	57		58		
Range	33–80		47–75		
Gender					1.2
Male	282	83.2	46	86.8	
Female	57	16.8	7	13.2	
KPS					0.86
90	170	50.1	38	71.7	
80	169	49.9	15	28.3	
T					0.57
1	32	9.4	3	5.7	
2	144	42.5	15	28.3	
3	76	22.4	14	26.4	
4	87	25.7	21	39.6	
N					0.54
0	39	11.5	1	1.9	
1	24	7.1	5	9.4	
2	170	50.1	23	43.4	
3	106	31.3	24	45.3	
TNM					0.53
I	19	5.6	0	0.0	
II	25	7.4	2	3.8	
IIIA	113	33.3	18	34.0	
IIIB	182	53.7	33	62.3	

median number of chemotherapy cycles was 4 (ranging from 0 to 8 cycles).

Survival analysis

After CRT, 228 (36.8%) patients achieved CR, With a median follow-up time of 25.6 months . The median brain metastasis-free survival (BMFS) time for patients who received PCI or not was 27.9 months and 29.1 months, the 1-, 3-, 5-year BMFS for patients with PCI and Non-PCI were 88.6%, 40.3%, 34.6% and 69.3%, 41.5%, 38.2% (P=0.85) (Fig. 1A), respectively. The median survival time was 30.2 months and 30.5 months, respectively and the 1-, 3-, 5-year survival rates were 93.7%, 42.9%, 35.8% and 83.4%, 46.5%, 41.9%, respectively (P=0.98) (Fig. 1B).

After CRT, 392 (63.2%) patients achieved PR, 53 cases did not receive PCI. With a median follow-up time of 15.5 months. The median BMFS time for patients who received PCI or not was 23.8 months and 13.6 months, he 1 -, 3 -, and 5-year BMFS were 84.7%, 38.6%, 28.9% and 57.8%, 15.3%, 9.7%(P=0.000) (Fig. 2A). The median survival time was 25.7 months and 18.6 months, respectively. The 1 -, 3 -, and 5-year survival rates were 87.6%, 40.2%, 29.2% and 75.7%, 16.7%, 10.3% (P=0.000) (Fig. 2B).

Patterns of brain failure

Among the patients who achieved a CR after CRT, the cumulative incidence of brain metastasis was 17.1% for those who received PCI and 37.9% for those who did not (P=0.011). For patients with PR, the cumulative incidence of brain metastasis was 12.7% for those who received PCI and 46.2% for those who did not (P=0.000).

Cox regression analysis of clinical characteristics potentially influencing overall survival (OS)

Univariate and multivariate Cox regression analyses were conducted on clinical characteristics potentially affecting OS in both the CR and PR groups (Tables 3 and 4).

Discussion

This study shows that for patients with limited-stage SCLC who achieve CR after CRT, those who receive PCI have a significantly lower incidence of BM compared to those who do not receive PCI, but there is no improvement in overall survival (OS). For patients with PR, PCI not only significantly reduces the incidence of brain metastasis but also improves OS, PCI remains a very important treatment for patients who achieve PR, but for patients with CR, it may be possible to exempt PCI during close MRI Follow-up.

This finding differs from the meta-analysis results of the PCI collaborative group [4], which concluded that PCI improves OS in CR patients. The potential reasons for this discrepancy include the lack of brain MRI scans before PCI in the latter study, which used chest X-rays for imaging evaluation. Chest X-rays are not effective in accurately assessing pulmonary lesions, particularly mediastinal lymph nodes, leading to the possibility that not all CR patients were truly CR, with some potentially being PR patients.

Due to the higher soft tissue resolution of MRI compared to CT, it is more effective in detecting brain metastases. Studies have shown that among patients who achieve a complete response (CR) after chemoradiotherapy, 21.8-32.5% already have brain metastases detected by brain MRI before PCI [9, 10]. Our study also found that among patients with CR or PR after CRT, 30.2% of those have BM before PCI after underwent brain MRI [11].

The EORTC reported a prospective randomized controlled trial in patients with extensive-stage SCLC who responded to chemotherapy, comparing PCI with observation. The results showed that PCI improved the prognosis of these patients. However, this study also did not perform MRI scans to exclude BM, thus presenting similar issues [12]. In contrast, a Japanese Phase III study performed brain MRI scans before randomization to exclude patients with brain metastases and found that PCI did not improve overall survival compared to the observation group [13].

Therefore, among patients who did not undergo brain MRI screening before receiving PCI, a portion might have already had brain metastases. In such cases, the effect of PCI is closer to "treatment" rather than "prevent." Our study included baseline brain MRI/CT screening, and 89.6% (482/538) of patients who received PCI underwent brain MRI to exclude metastases.

Currently, there are no prospective studies comparing PCI based on brain MRI screening versus observation. Most retrospective studies indicate that PCI significantly reduces the incidence of BM compared to observation, but the results are inconsistent regarding OS improvement [14–24]. This may be due to heterogeneity in patient populations, variations in treatment methods, and the impact of subsequent treatments. Although reducing the incidence of BM may improve patients' quality of life, the neurotoxicity associated with PCI remains a significant concern [25, 26]. Additionally, the role of hippocampal-sparing PCI in reducing neurotoxicity requires further investigation [27, 28].

Large-scale retrospective studies and meta-analyses have shown no significant difference in OS between first-line stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT) for patients with brain metastases recently [29, 30]. Furthermore, a retrospective analysis by Ozawa et al. found that administering SRS after detecting brain metastases via MRI follow-up reduced the benefits of PCI [31].

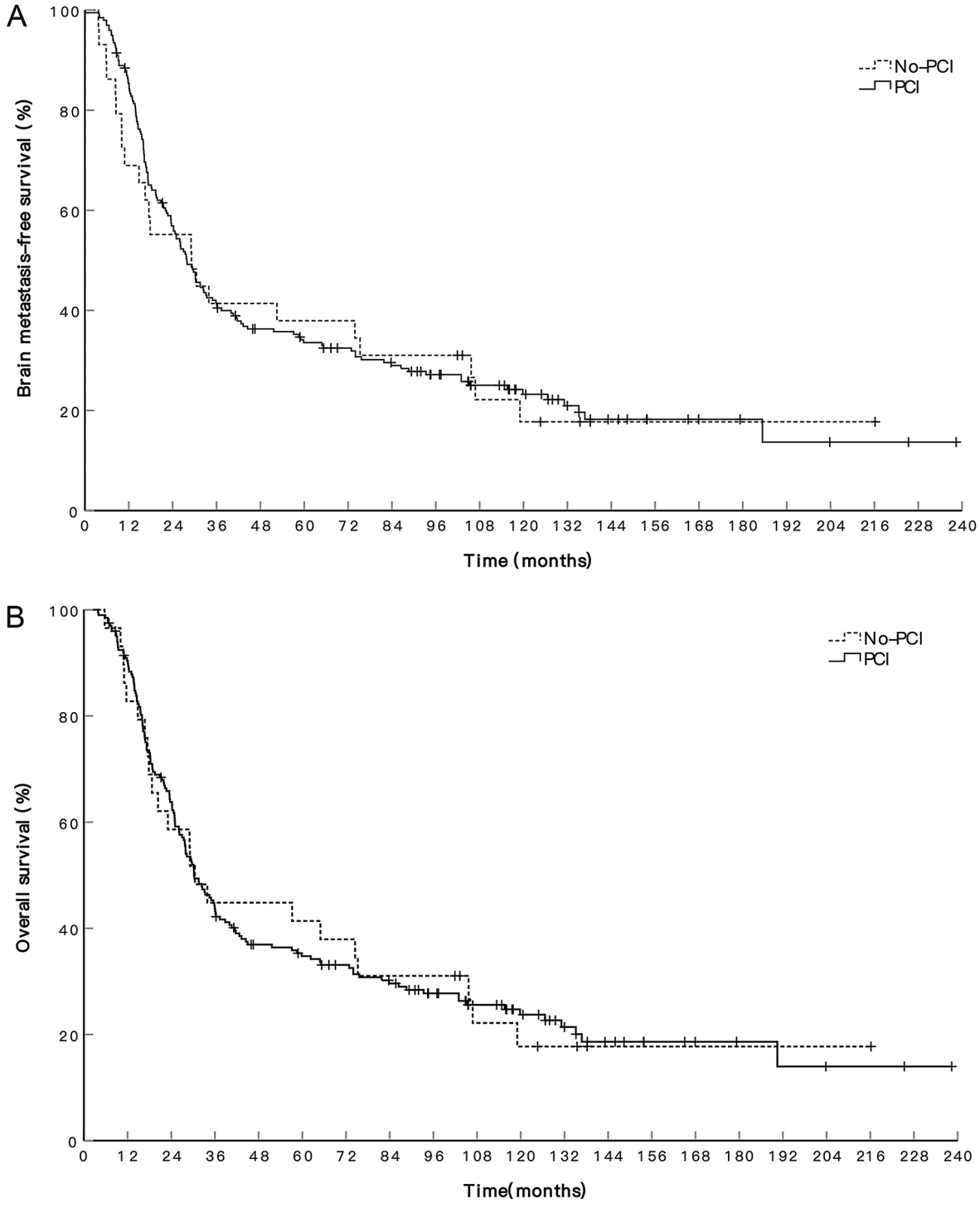

Fig. 1 **A**. Comparison of BMFS of patients achieved CR after CRT between PCI group and non-PCI group. **B**. Comparison of OS of patients achieved CR after CRT between PCI group and non-PCI group

This study has several limitations. Firstly, this study is a retrospective post-hoc subgroup analysis, which may lead to data bias and selection bias. Secondly, among the CR group, the baseline KPS scores of patients who did not receive PCI were significantly lower than those who received PCI, potentially affecting the study's results. Additionally, this study did not analyze the neurotoxic reactions of patients who received PCI or the impact of subsequent treatments on OS after BM occurred. Besides, While multivariate analysis can adjust for some

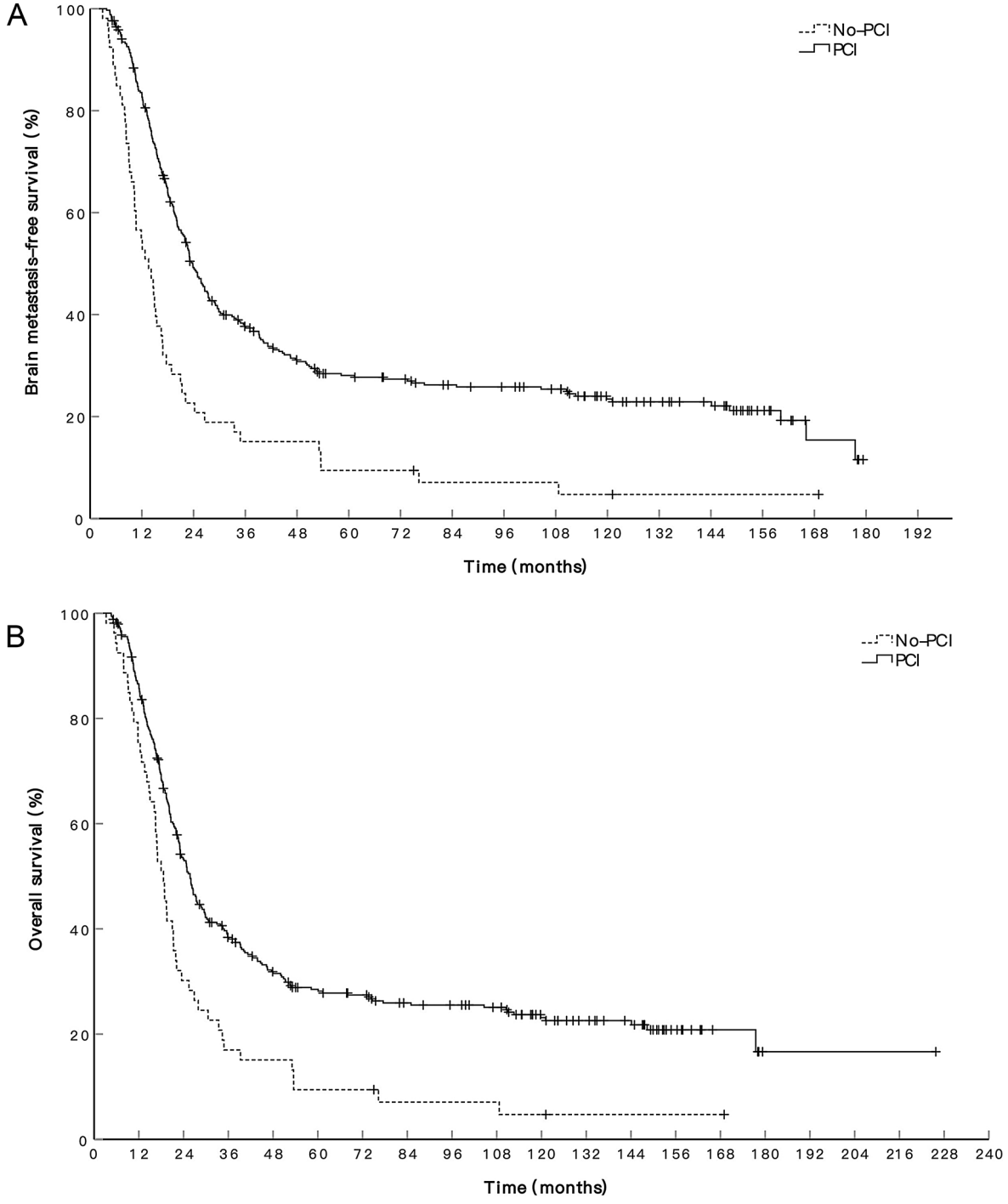

Fig. 2 **A**. Comparison of BMFS of patients achieved PR after CRT between PCI group and non-PCI group. **B**. Comparison of OS of patients achieved PR after CRT between PCI group and non-PCI group

of the differences between the groups, the small sample size of the non-PCI group may still affect the results. Therefore, we recommend that future research should involve larger sample sizes and prospective randomized controlled trials to better evaluate the true impact of PCI on CR patients. This would improve the statistical power and provide more reliable conclusions. In summary, we have made every effort to reduce the effect of the imbalance in patient numbers on the results by employing appropriate statistical methods. However, we recognize the potential limitations of this imbalance, and larger sample studies are necessary to confirm these findings.

Table 3 Univariate analysis and multivariate analysis of the prognostic factors on OS in patients with CR

Characteristic	Feature	Total	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P*	HR(95% CI)	*P*
Gender	Male	182	1	0.178	1	0.142
	Female	47	1.03 (0.89–1.47)		1.24 (0.98–1.74)	
Age(years)	<58	97	1	0.023	1	0.445
	≥ 58	131	1.42 (1.05–1.92)		1.35 (0.82–1.57)	
KPS	80	89	1	0.000	1	0.000
	90	139	0.32 (0.24–0.45)		0.32 (0.22–0.46)	
T	1	23	1	0.667	1	0.731
	2	97	1.02 (0.98–1.16)		1.04 (0.90–1.19)	
	3	51				
	4	57				
N	0	36	1	0.014	1	0.199
	1	25	1.21 (1.04–1.41)		1.24 (0.89–1.72)	
	2	109				
	3	58				
TNM	I	22	1	0.072	1	0.179
	II	28	1.15 (0.99–1.35)		1.04 (0.98–1.65)	
	IIIA	76				
	IIIA	102				
PCI	No	29	1	0.098	1	0.210
	Yes	199	1.01 (0.64–1.56)		1.33 (0.85–2.10)	

Table 4 Univariate analysis and multivariate analysis of the prognostic factors on OS in patients with PR

Characteristic	feature	Total	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P*	HR(95% CI)	*P*
Gender	Male	328	1	0.671	1	0.235
	Female	64	1.07 (0.79–1.45)		1.21 (0.89–1.64)	
Age(years)	<58	199	1	0.065	1	0.719
	≥ 58	193	1.23 (0.61–1.32)		1.04 (0.82–1.32)	
KPS	80	184	1	0.000	1	0.000
	90	208	0.34 (0.27–0.43)		0.32 (0.25–0.41)	
T	1	35	1	0.052	1	0.581
	2	159	1.12 (0.99–1.26)		1.04 (0.90–1.20)	
	3	90				
	4	108				
N	0	40	1	0.015	1	0.074
	1	29	1.18 (1.03–1.34)		1.24 (0.98–1.59)	
	2	193				
	3	130				
TNM	I	19	1	0.013	1	0.082
	II	27	1.12 (1.04–1.41)		1.04 (0.99–1.65)	
	IIIA	131				
	IIIB	215				
PCI	No	53	1	0.000	1	0.001
	Yes	339	0.54 (0.40–0.74)		0.56 (0.41–0.79)	

Conclusions

This study provides valuable data and insights into the efficacy of PCI in patients with limited-stage SCLC. However, due to differences in study methods and patient populations, as well as the influence of subsequent treatments, the precise role of PCI in limited-stage SCLC patients requires validation through prospective studies. Our team will initiate a prospective randomized controlled trial comparing PCI with MRI follow-up versus MRI follow-up alone in patients with limited-stage SCLC who achieve a CR after CRT in feature. We look forward to the results.

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Author contributions
Mengyuan Chen and Xiao Hu was responsible for the study concept and design. Mengyuan Chen, Zehua Sun, Jingcong Pan, Yujin Xu and Yuezhen Wang. acquired and analyzed data. Xiao Hu, Mengyuan Chen and Ming Chen drafted the manuscript. All authors revised the manuscript and approved final submission.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved be ethical committee of Zhejiang Cancer Hospital.

Consent for publication
The authors give their permission for the submission.

Competing interests
The authors declare no competing interests.

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