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The impact of prophylactic cranial irradiation for post-operative patients with limited stage small cell lung cancer

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Abstract

To evaluate the impact of prophylactic cranial irradiation (PCI) on the prognosis of patients who received definitive surgery for surgically resected small cell lung cancer (SCLC).

A retrospective analysis was performed on post-operative SCLC patients treated in Zhejiang Cancer Hospital from January 2003 to December 2015. According to the treatment modality, patients were allocated to PCI group and non-PCI group. Univariate survival analysis was performed by the Kaplan–Meier method. Multivariate survival analysis was performed by a Cox proportional hazards model.

A total of 52 patients were included for analysis, among which, 19 patients were in PCI group and 33 were in non-PCI group. Multivariate analysis revealed that PCI (HR = .330; $P = .041$) was an independently favorable prognostic factor for the overall survival. The median overall survival (OS) time was 32.9 months in PCI group, and 20.4 months in non-PCI group. The 2-year OS rates were 78.0% and 38.0% in PCI and non-PCI group respectively ($P = .023$). The brain metastasis-free survival (BMFS) rate at 2-year in PCI group was significantly higher than those of non-PCI group (89.0% vs 53.0%, respectively, $P = .026$).

In conclusion, PCI might be suggested for limited SCLC patients who received definitive surgery.

Abbreviations: BM = brain metastases, BMFS = brain metastasis free survival, CR = complete response, MST = median survival time, PCI = prophylactic cranial irradiation, SCLC = small cell lung cancer.

Keywords: brain metastases, PCI, prognosis, small cell lung cancer, surgical resection

1. Introduction

Small cell lung cancer (SCLC) accounts for approximately 15% of all types of lung cancers.[1] It is characterized by rapid doubling time, early dissemination, and a poor prognosis.[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 to 6 months.[3–6]

In 1990s, the role of prophylactic cranial irradiation (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.[7] Over the previous10 years, several clinical studies confirmed that PCI could decrease the incidence of BM and improve the survival of the patients with SCLC.[8–10]

Is PCI necessary for all post-operative patients with limited SCLC? According to TNM classification, the role of PCI in patients with surgically resected and pathological stage I SCLC is undefined. Thus, we retrospectively investigated the effect of PCI on the outcome of patients who received definitive surgery for surgically resected SCLC.

2. Methods and materials

2.1. Patients

We retrospectively reviewed the records of post-operative patients who were diagnosed with SCLC and received definitive operation TNM at Zhejiang Cancer Hospital from January 2003 to December 2015. The TNM stage was defined according to the 7th American Joint Committee on Cancer (AJCC) criteria edition. The selection criteria were as follows:

(1) patients had undergone surgery and pathologically proven SCLC;
(2) patients with primary, non-metastatic SCLC;
(3) no history of any other cancer.

All patients underwent conventional evaluation including thoracic and abdominal CT scanning or abdominal ultrasonog-

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raphy, and bone radionuclide imaging, brain magnetic resonance imaging (MRI). According to the treatment model, patients were divided into PCI group and non-PCI group. The ethics institutional review board of Zhejiang Cancer Hospital approved the protocols for data collection and analyses. The study did not involve patient consent; all the methods described here were performed in accordance with the relevant guidelines and regulations.

2.2. Treatment

The surgical procedures consisted of lobectomy or pneumonectomy with ipsilateral hilar and mediastinal lymphadenectomy. Patients received 2 to 3 circle induction chemotherapy (EP; etoposide, 100 mg/m^2 on days 1–3 and cisplatin, 30 mg/m^2 on days 1–3) and 2 to 4 circle adjuvant chemotherapy (EP; etoposide, 100 mg/m^2 on days 1–3 and cisplatin, 30 mg/m^2 on days 1–3, EC; etoposide, 100 mg/m^2 on days 1–3 and carboplatin AUC 5 on day 1). Three-dimensional conformal radiotherapy (3D-CRT) was used in chest radiotherapy. The clinical target volume (CTV) included bronchial stump, ipsilateral hilar, and adjacent mediastinal lymph nodes. The planning target volume (PTV) included the CTV with a 0.5 to 1 cm margin. The total dose of radiotherapy is 50 to 60Gy with 1.8 to 2Gy per fraction for 5 days a week. The dose fractionation of PCI was 25Gy in 10 fractions over 2 weeks.

2.3. Follow-up

Patients were followed up every 3 months for the first year, and every 4 months for the next year, then every 6 months for the following years, and annually over 5 years. Follow-up imaging included chest CT, abdominal CT, and other necessary examination as clinically indicated. During the follow-up period, routine brain imaging was not performed unless BM was suspected. The follow-up schedule started from the time of first treatment. The last follow-up time was October 1, 2017. Overall survival was calculated from the time of first treatment to the date of death or censored at the date of last follow-up (if patient was alive). The brain metastasis-free survival (BMFS) was calculated from the time of first treatment to the date of the patient first diagnosed with BM.

2.4. Statistical analysis

Statistical analysis was carried out with SPSS 22.0 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 were performed using Cox proportional hazards model. Hazard ratios (HRs) and 95% CIs were calculated using Cox's proportional-hazard model. All tests were 2-sided, and statistical significance level was set at 0.05.

3. Results

3.1. Patient characteristics

From January 2003 to December 2015, 52 patients with SCLC underwent surgery were diagnosed and treated at Zhejiang Cancer Hospital. According to the treatment modality, patients were allocated to PCI group and non-PCI group, 19 patients (stage I = 5; stage II = 5; stage III = 9) were allocated to PCI group versus 33 (stage I = 12; stage II = 5; stage III = 16) in non-PCI group. The patients' characteristics are summarized in Table 1. 13(19.2%) patients received induction chemotherapy. 44(84.6%) patients received adjuvant chemotherapy. 20(38.5.6%) patients received at least 4 cycles of adjuvant chemotherapy. 14(26.9%) patients received adjuvant radiation therapy.

Table 1

Clinical features of patients with resectable SCLC in PCI group and ono-PCI group.

Characteristic	Total	PCI group		Non-PCI group		χ^2	*P*
		No.	%	No.	%		
Gender							
Male	42	15	75.0	27	81.8	0.064	.800
Female	10	4	25.0	6	18.1		
Age (years)							
Range	38–74	44–73		38–74			
<60	30	13	68.4	17	51.5	1.412	.235
≥60	22	6	31.6	16	48.5		
POP							
Yes	29	12	36.8	17	51.5	0.663	.416
No	23	7	63.2	16	48.5		
PNT							
Yes	13	7	36.8	6	18.2	2.235	.135
No	39	12	63.2	27	81.8		
PAT							
Yes	42	18	94.7	24	72.7	3.760	.052
No	10	1	5.3	9	27.3		
ChT							
Yes	44	19	100	25	75.8	3.669	.055
No	8	0	0	8	24.2		
PORT							
Yes	14	8	42.1	6	18.2	3.508	.061
No	38	11	57.9	27	81.8		

ChT = chemotherapy, KPS = Karnofsky performance status, PCI = prophylactic cranial irradiation, PORT = postoperative radiotherapy, SCLC = small cell lung cancer, χ^2 = chi-square statistic.

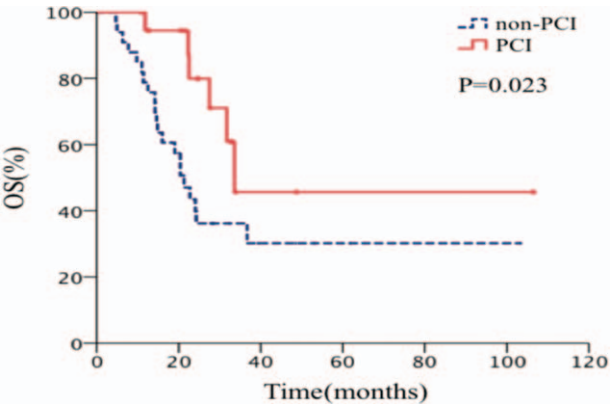

Figure 1. Comparison of overall survival of patients with surgically resected small cell lung cancer between PCI group and non-PCI group. PCI = prophylactic cranial irradiation.

3.2. Survival

The median survival time (MST) for PCI group was 32.9 months, and non-PCI group was 20.4 months. The 2-year and 5-year OS rates were 72.0%, and 38.0% for the PCI group of patients, respectively, and those of non-PCI were 48.1% and 29.8%, respectively ($P = .023$; Fig. 1). The 2-year and 5-year survival rates for patients with pathologic stages I, II, and III were 83.0%, 58.1%, 40.6% and 65.3%, 34.3%, 21.1%, respectively, $P = .011$. PCI could confer survival benefit in the patients with p-stage III, the difference of the 2-year and 5-year OS rates of PCI group and non-PCI group was significant (69.8%, 24.7% and 22.4%, 16.8%, respectively; $P = .031$; Fig. 2), however, the patients with p-stage I ($P = .924$), II ($P = .094$) could not get benefit from PCI.

3.3. BM

For the whole group of patients, the results showed that PCI group had a lower incidence of BM, 3 patients (15.7%) developed brain metastasis in PCI group, and the BM rate of non-PCI group was 33.3%(11 patients), $P = .041$. In addition, The BM rate for patients with pathologic stages I, II, and III were 11.7%, 30%, 36%. Specifically, in PCI group, the incidence of brain metastasis was 0% (0/5) in patients with p-stage I disease, 20.0% (1/5) in p-stage II patients, and it was 22.2% (2/9) in patients with p-stage III. In non-PCI group, the incidence of brain metastasis was 16.6% (2/12) in patients with p-stage I disease, 40.0% (2/5) in p-stage II patients, and it was 43.8% (7/16) in patients with p-stage III.

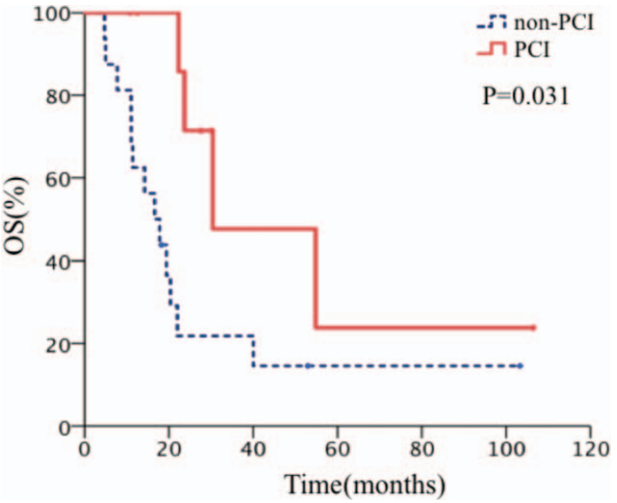

Figure 2. Comparison of overall survival of patients with p-stage III small cell lung cancer between PCI group and non-PCI group. PCI = prophylactic cranial irradiation.

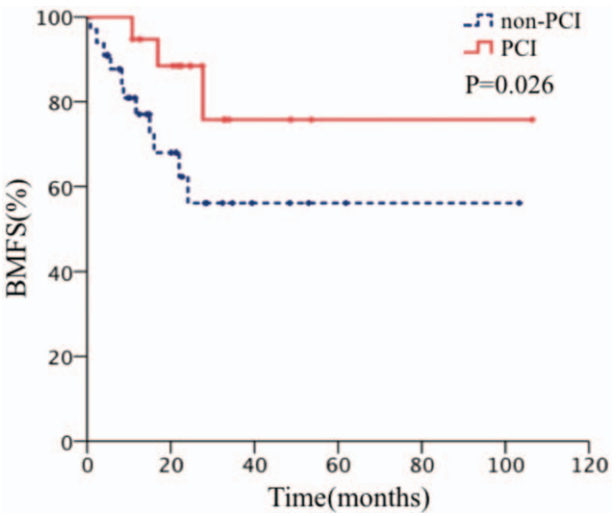

Figure 3. Comparison of BMFS of patients with surgically resected small cell lung cancer between PCI group and non-PCI group. BMFS = brain metastasis free survival, PCI = prophylactic cranial irradiation.

The 2-year BMFS rate in PCI group was significantly better than non-PCI group (89.0% vs 53.0%, $P = .026$); Fig. 3). Further subgroup analysis showed that 2-year BMFS benefits of PCI therapy were significant in patients with stage III disease (83.6% vs 51.3%, $P = .030$); however, the difference of the patients with stage I ($P = .325$) or II ($P = .520$) disease was not statistically significant.

3.4. Prognostic factors

The results of univariate and multivariate analysis were shown in Table 2. Pathologic stage (HR: 2.442, 95%CI: 1.406–4.242, $P = .002$) and PCI (HR: 0.330, 95%CI: 0.114–0.954, $P = .041$) were independently prognostic factor for the OS.

4. Discussion

SCLC is characterized by highly malignant, early recurrence and metastasis. Especially, brain metastasis is 1 of the main reasons for its failure of treatment. As early as the 1970 s, people realized the importance of PCI in controlling brain metastases. In 1999, 987 SCLC patients who achieve a CR were analyzed by a meta-analysis which had shown a significant survival benefit of PCI, a 5.4% increase of 3-year survival rate (20.7% vs 15.3%, $P = .01$) and a 25.3% decrease of 3-year survival cumulative incidence of BM (33.3% vs 58.6%, $P < .001$). Owning to this study, the important role of PCI in the comprehensive treatment of patients with limited SCLC was determined.[7]

In recent years, there are still many controversies in the application of PCI. The efficacy of PCI on patients who received

Table 2

Univariate analysis and multivariate analysis of the prognostic factors on OS in patients with resectable SCLC.

Factors	Univariate analysis					Multivariate analysis		
	MST (m)	2-year-os%	5-year-os%	χ^2	*P*	HR	95% CI	*P*
Gender								
Male	40.2	45.6	32.1	0.023	.881	1.202	0.405–3.569	.741
Female	31.9	69.1	30.3					
Age (years)								
<60	40.1	53.5	32.3	0.083	.773	0.558	0.219–1.424	.222
≥60	32.0	48.1	26.7					
POP								
Yes	–	59.0	37.0	2.541	.111	0.546	0.207–1.442	.222
No	23.0	38.1	20.7					
PNT								
Yes	37. 1	68.2	43.6	0.788	.375	1.176	0.340–4.066	.797
No	21.3	43.1	27.2					
PAT								
Yes	37.0	53.0	31.1	1.006	.316	1.195	0.145–9.874	.869
No	21.3	40.2	27.5					
Stage								
I	—	83.0	65.3					
II	27.1	58.1	34.3	8.985	.011	2.442	1.406–4.242	.002
III	22.0	40.6	21.1					
ChT								
Yes	37.0	52.0	31.3	1.334	.248	0.545	0.056–5.324	.601
No	20.0	38.0	26.2					
PORT								
Yes	37.2	59.0	40.4	0.341	.559	1.105	0.383–3.185	.854
No	32.5	47.0	31.5					
PCI								
Yes	32.9	72.0	48.1	5.202	.023	0.330	0.114–0.954	.041
No	20.4	38.0	29.8					

2-year-OS = overall survival rate at 2 years, ChT = chemotherapy, CI = confidence interval, HR = hazard ratio, MST = median survival time, OS = overall survival, PAT = Postoperative adjuvant therapy, PCI = prophylactic cranial irradiation, PNT = preoperative neoadjuvant, POP = preoperative pathology, PORT = postoperative radiotherapy, SCLC = small cell lung cancer.

definitive surgery for surgically resected SCLC is undefined,[11] According to the article published in recent years, the incidence of BM in patients with stage I, II, and III SCLC were 6.25% to 14%, 13% to 38%, and 11% to 36%.[12–16] Patients with complete resection and incomplete resection had significant differences in the incidence of BM (20.5% vs 42.9%, $P = .028$).[14] In this study, the BM in overall patients with complete resection of stage I, II, and III were 11.7%, 30%, and 36%, respectively.

Gong et al[14] study included 126 patients who underwent surgical resection with SCLC, the results showed that the 5-year OS rate of patients with stage I, II, and III were 54.8%, 35.6%, and 14.1%, respectively, $P = .001$. Another retrospective study analyzed 193 patients with completely surgical resection SCLC. The 2-year and 5-year OS rates in PCI group were significantly better than those of non-PCI group (92.5%, 54.9% and 63.2%, 47.8%, $P = .005$). But the patients with p-stage I couldn't get the survival benefit from PCI, $P = .601$. Therefore, the authors suggested that PCI might confer survival advantage in completely surgically resected patients with p-stage II/III SCLC, but not for p-stage I disease because of its lower incidence of BM.[15]

A large study by Xu et al[16] analyzed 349 patients with completely surgically resected SCLC, 115 patients were allocated to PCI group versus 234 in no-PCI group. The MST in PCI group was significantly better than non-PCI group (36.4 months vs 25.62 months, $P = .023$). PCI could confer OS advantage for stage II (36.40 months vs 24.05 months, $P = .047$) or III (29.34 months vs 21.16 months, $P = .009$) SCLC patients, but not for patients of stage I ($P = .282$). In terms of the cumulative incidence of BM, the patients who received PCI had lower 2-year BM (13% vs 22.6%, $P = .009$). Subgroup analysis shows that the cumulative incidence of BM in PCI group patients with stage III were significantly reduced (14% vs 27.8%, $P = .018$), while stage I (10.5% vs 13.6%, $P = .389$), and stage II (12.8% vs 22.4%, $P = .094$) were not.

PCI could improve the OS and BMFS of patients with completely surgically resected SCLC in our study. Patients who received PCI had a longer 5-year survival rate (46.7% vs 29.8%, $P = .023$) and 2-year BMFS rate (89.0% vs 53.0%, $P = .026$). The 2-year and 5-year survival rates for patients with pathologic stages I, II, and III were 83.0%, 58.1%, 40.6% and 65.3%, 34.3%,21.1% respectively, $P = .011$. However, in a further subgroup analysis, we found that PCI can improve 5-year survival rates in patients with stage III patients (24.7% vs 16.8%, $P = .031$) but not for I ($P = .924$) and II ($P = .094$). Similarly, PCI was associated with 2-year BMFS benefit in stage III patients (83.6% versus 51.3%, $P = .030$) but not I ($P = .325$) and II ($P = .520$). The small overall sample size for stage I/ II patients might affect the statistical analysis.

The incidence of BM of patients with stage I in this study was 11.7%. Patients with stage I have a lower incidence of BM compared with stage II, III patients, PCI is not recommended for patients with stage I in many studies, but there are still some studies hold different views. A small retrospective study analyzed 39 patients who underwent completely surgical resection with stage I and II SCLC. In this study, no-BM occurred in 21 patients of PCI group and 22.2% (4/18) of the patients who did not

receive PCI developed BM at follow-up of 8 to 27 months. Additionally, the BMFS ($P = .01$) and OS ($P = .01$) of PCI group were significantly better than non-PCI group. So the researchers suggested that PCI might be considered for all completely surgically resected patients with stage I and II.[17] Another large sample study which based on the National Cancer Database (NCDB)[18] enrolled 954 patients with stage I disease. The results showed that PCI group could confer better survival than any other group in this study, ($P < .01$). Although patients of stage I have a much lower risk of BM than stage II and III patients, the stage I patients who received PCI could get survival benefit if the sample size big enough.

Our study did not show the value of postoperative adjuvant chemotherapy and radiotherapy clinical. We analyzed the reasons as follow:

1. The 26.9% (14/52) patients received postoperative adjuvant radiotherapy in this study, and the number of receiving radiotherapy patients was insufficient or could affect the statistical analysis.
2. The study showed that radiation was not associated with a significant survival advantage even had lower OS compared with simple surgery when used alone or combined chemotherapy.[18] Patients of stage I and II accounted for 28.5% (4/14) received postoperative adjuvant radiotherapy in our study, which may affect the outcome.
3. In our study, although 84.6% of patients received postoperative adjuvant chemotherapy, only 38.5% (20/52) of patients received ≥4 cycles of chemotherapy after surgical resection. The study showed that the 2-year and 5-year OS of patients undergoing adjuvant chemotherapy and non-adjuvant chemotherapy group were 52.0%, 31.3% and 38.0%, 26.2%. The survival of adjuvant chemotherapy group was better than non-adjuvant chemotherapy group, due to the small sample size which could not show the statistical differences.

There are several limitations in our study as follow:

1. retrospective study of its own characteristics, the bias of treatment options may affect the conclusions.
2. The small sample size of the subgroup analysis might affect the statistical analysis.
3. Failure to assess the acute toxicity of both groups of patients.

5. Conclusions

In conclusions, the OS benefits of PCI were significant in limited SCLC patients treated with definitive surgery, especially for those with stage III diseases. It is difficult to determine whether the patients with stage I, II could benefit from PCI or not due to the small number of sample. Accumulate enough cases to identify high-risk patients for PCI warrants further study.

6. Additional Information

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Xiao Hu.
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Formal analysis: Meng-yuan Chen.
Methodology: Ming Chen.
Resources: Ming Chen.
Software: Ming Chen.
Supervision: Xiao Hu, Yu-jin Xu.
Validation: Xiao Hu, Ming Chen.
Writing – original draft: Meng-yuan Chen.
Writing – review & editing: Meng-yuan Chen, Ming Chen.

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