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*Original Article*

# Risk factors associated with brain metastases in patients with limited-stage small-cell lung cancer after prophylactic cranial irradiation

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**Abstract:** Purpose: Prophylactic cranial irradiation (PCI) has been the standard of practice for patients with limited-stage small-cell lung cancer after concurrent chemoradiotherapy (CRT), however, high brain metastasis rate and potential neurotoxicity limit the benefits from PCI. Thus, we conducted a retrospective study to identify the risk factors associated with brain metastases and provide evidence for personalized PCI. Methods: Between 2005 and 2010, 188 patients with limited-stage SCLC were included in the study, chi-square test and Cox proportional hazards analysis were used to assess the risk factors associated with brain metastases. Results: The median follow-up duration was 28 months (from 5 to 99 months), and the median survival time was 28 months. One-year, 2-year overall and 3-year overall survival (OS) rates were 95%, 69%, 55%, respectively. Thirty-one patients were diagnosed with brain metastases. One-year, 2-year and 3-year cumulative incidence of brain metastases were 4%, 15%, 20%, respectively. Univariate analysis showed that stage III before treatment (P=0.044), elevated levels of tumor markers (P=0.037), failure to achieve complete remission after CRT (P=0.005), and local-regional recurrence (P=0.007) were significantly associated with an increased risk of brain metastases. However, multivariate analysis indicated only failure to achieve complete remission after CRT (P=0.003) and local-regional recurrence (P=0.040) were independent factors predicting brain metastases. Conclusions: In conclusion, our study suggests that patients with local-regional recurrence or failed to achieve complete remission after CRT have higher risk of brain metastases. Close follow-up with brain MRI followed by salvage cerebral irradiation may be an alternative to PCI for those patients, which should be verified by random clinical trials.

**Keywords:** Limited-stage small-cell lung cancer, prophylactic cranial irradiation, brain metastases, risk factors

## Introduction

Concurrent chemoradiothery (CRT) is the standard care for limited-stage SCLC (LS-SCLC) [1], however, about 58% patients will develop brain metastases within two years after CRT [2].

In addition to reducing the risk of brain metastases, prophylactic cranial irradiation (PCI) can improve overall survival. Therefore, PCI has been considered as a standard treatment for patients with LS-SCLC in complete remission following systemic therapy [3]. However, even after PCI, one third of patients will experience intracranial recurrence [3-5]. Such high recurrence rate suggests that quite a number of patients cannot really benefit from PCI which might also induce potential neurocognitive impairment and other adverse effects [6]. Moreover, for those patients who develop brain metastases after PCI, further rescuing treatment strategy is challenging and difficult [7].

With the improvement of imaging techniques, the prevalence of detected brain metastases increases [8]. In addition, with more effective rescuing strategies available [9], the validity of PCI is being constantly challenged [10]. One retrospective study from Japan exploring the possibility of magnetic resonance imaging (MRI) followed by stereotactic irradiation (SRI) instead of PCI in patients with LS-SCLC found no difference in median survival time between the two groups [11].

**Table 1.** Univariate analysis of the risk factors associated with brain metastases in patients with LS-SCLC

| Characteristics | No. of cases | No. of patients with BM | Chi-square | P |
|---|---|---|---|---|
| Age | | | | |
| <50 | 66 | 11 | 0.523 | 0.727 |
| 50-65 | 104 | 16 | | |
| >65 | 18 | 4 | | |
| Gender | | | | |
| Men | 147 | 26 | 0.702 | 0.281 |
| Women | 41 | 5 | | |
| Smoking status | | | | |
| Smoking | 133 | 21 | 0.162 | 0.419 |
| Non-smoking | 55 | 10 | | |
| ECOG score | | | | |
| 0 | 48 | 6 | 1.698 | 0.601 |
| 1 | 136 | 25 | | |
| 2 | 4 | 0 | | |
| Weight loss | | | | |
| <5% | 174 | 29 | 0.053 | 0.585 |
| ≥5% | 14 | 2 | | |
| Stage | | | | |
| I+II | 75 | 7 | 4.640 | 0.044 |
| III | 113 | 24 | | |
| Tumor markers† | | | | |
| Elevated | 80 | 19 | 3.945 | 0.037 |
| Normal | 64 | 7 | | |
| TRT | | | 0.199 | |
| Yes | 179 | 30 | | 0.546 |
| No | 9 | 1 | | |
| TRT dose (Gy) | | | | |
| <50 | 12 | 2 | 0.201 | 0.899 |
| ≥50 | 167 | 28 | | |
| Response to first-line CT | | | | |
| CR | 56 | 8 | 0.336 | 0.750 |
| PR | 132 | 23 | | |
| Response to CRT | | | | |
| CR | 152 | 19 | 9.174 | 0.005 |
| PR | 36 | 12 | | |
| PCI dose (Gy) | | | | |
| <25 | 6 | 2 | 1.959 | 0.376 |
| 25-30 | 153 | 23 | | |
| >30 | 28 | 6 | | |
| Time from CT to PCI | | | | |
| <24 w | 93 | 18 | 1.097 | 0.197 |
| ≥24 w | 95 | 13 | | |
| LRR before BM | | | | |
| Yes | 58 | 16 | 7.501 | 0.007 |
| No | 130 | 15 | | |

Abbreviations: CR, complete remission; PR, partial remission; BM, brain metastases; PCI, prophylactic cranial irradiation; CT, chemotherapy; CRT, chemo (radio) therapy. †Tumor makers included CEA, NSE, Ca125 and Ca199, they were considered as be elevated, if one of them was higher at least.

Therefore, personalized PCI is the direction of future studies, especially for those patients with higher rate of brain metastases after PCI, close follow-up with brain MRI followed by salvage cerebral irradiation may be an alternative choice. To explore the risk factors associated with brain metastases after PCI and provide the foundation for personalized PCI, we reviewed the patients with LS-SCLC undergoing PCI in Zhejiang Cancer Hospital from March 2005 to December 2010.

## Patients and methods

### *Study population*

A total of 479 patents with LS-SCLC were treated in Zhejiang Cancer Hospital from March 2005 to December 2010, and 188 cases were included in our analysis. The eligible criteria were: 1) patients with stage I-III SCLC (according to the 7th edition AJCC staging system) confirmed by pathological examinations; 2) patients with a complete remission (CR) or partial response (PR) after chemo (radio) therapy; 3) patients underwent PCI after chemo (radio) therapy. Patients underwent staging evaluation before the initiation of chemotherapy. Staging evaluation included computed tomography (CT) of the chest and upper abdomen, ultrasonography of neck and upper abdomen, MRI or computed tomography of the head, radionuclide bone scan. Elevated levels of tumor markers were considered if one of them (CEA, NSE, Ca125 and Ca199) was higher. The response evaluation of chemo (radio) therapy was completed in one month after treatment. The characteristics of patients were listed in **Table 1**.

Patients were excluded from analysis for the following reasons: 1) second malignancy; 2) contralateral supraclavicular lymph node metastasis; 3) ≤2 cycles of first-line chemotherapy; 4) <40 Gy of thoracic radiotherapy; 5) mixed with squamous cell carcinoma or adenocarcinoma; 6) progressive disease during chemo (radio) therapy.

### *Treatment*

More than 3 cycles of cisplatin-based regimens were administered. Thoracic radiotherapy (TRT) was performed concurrently or sequentially or alternatively with chemotherapy. TRT was administered with 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated

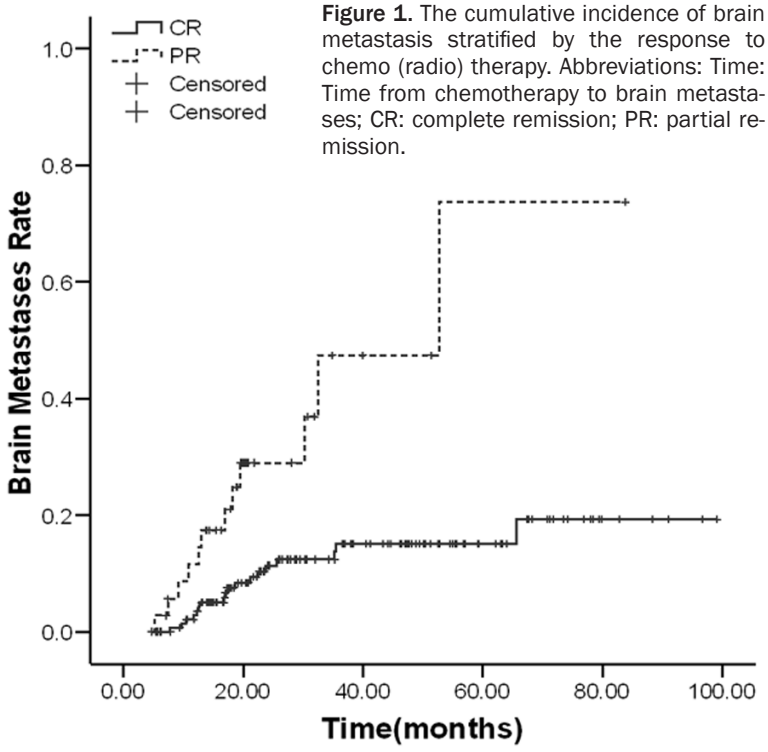


**Figure 1.** The cumulative incidence of brain metastasis stratified by the response to chemo (radio) therapy. Abbreviations: Time: Time from chemotherapy to brain metastases; CR: complete remission; PR: partial remission.

radiotherapy (IMRT) technique. The target volume included all gross disease, the ipsilateral hilum, and the mediastinum. Supraclavicular fossa was not irradiated routinely if there were no enlarged lymph nodes in these sites. A total dose of 40-60 Gy was administered with 1.8-2.0 Gy per fraction. Patients received PCI that involved 4-6-MV photons delivered with opposed lateral portals with at least normal tissue sparing of the lens. Fields had to include at least a 1-cm margin on the calvarium. PCI was performed after primary chemo (radio) therapy.

*Response evaluation and follow-up*

Response assessment at the end of primary chemo (radio) therapy was based on the results of chest CT, brain MRI or CT, CT of the upper abdomen. CR was defined as the disappearance of all target lesions. PR was defined as at least a 50% decrease in the sum of the longest diameter of target lesions. Chest CT, abdomen CT and ultrasonography of neck and upper abdomen were repeated every 3 months for 2 years after the end of treatment, and every 6 months thereafter. Patients had MRI of the head if they had headache or neurologic symptoms suggestive of brain metastases (BM), a bone scan if they had bone pain.

*Statistical analysis*

All the statistical analyses were performed using SPSS 13.0 software. Intracranial progression-free survival was defined as the time from the start of treatment to the diagnosis of brain metastases. The Kaplan-Meier method was used to calculate the incidence rate of brain metastases. Univariate (Pearson chi-square test) and multivariate analysis (Cox proportional hazards regression model) were performed to determine the risk factors associated with brain metastases (BM). Covariates included in the analysis were age (<50 y, 50-65 y, >65 y), sex (male, female), smoking status (smoking, non-smoking), ECOG score (0, 1, 2), weight loss (<5%, ≥5%), clinical stage (I+II, III), tumor markers (elevated, normal), TRT (yes, no), TRT dose (<50 Gy, >50 Gy), response to first-line chemotherapy (CR, PR), response to chemo (radio) therapy (CR, PR), PCI dose (<25 Gy, 25-30 Gy, >30 Gy), time from chemotherapy to PCI (<6 months, ≥6 months) and locoregional recurrence (LRR) before brain metastases (yes, no). P<0.05 was considered as statistically significant.

## Results

The follow-up deadline was March 31, 2015, the median follow-up time was 28 months (5-99 months), and 83 patients were still alive. The median survival time was 28 months, and 1, 2, 3-year survival rates were 95%, 69%, 55%, respectively.

31 of 188 patients (16.5%) developed brain metastases. The median time from the first-line chemotherapy to brain metastases was 26 months, and the median time from the start of PCI to brain metastases was 11 months. The 1, 2, 3-year cumulative incidences of brain metastases were 4%, 15%, 20%, respectively (**Figure 1**).

In univariate analysis, patients with stage III (P=0.044), elevated tumor markers (P=0.037),

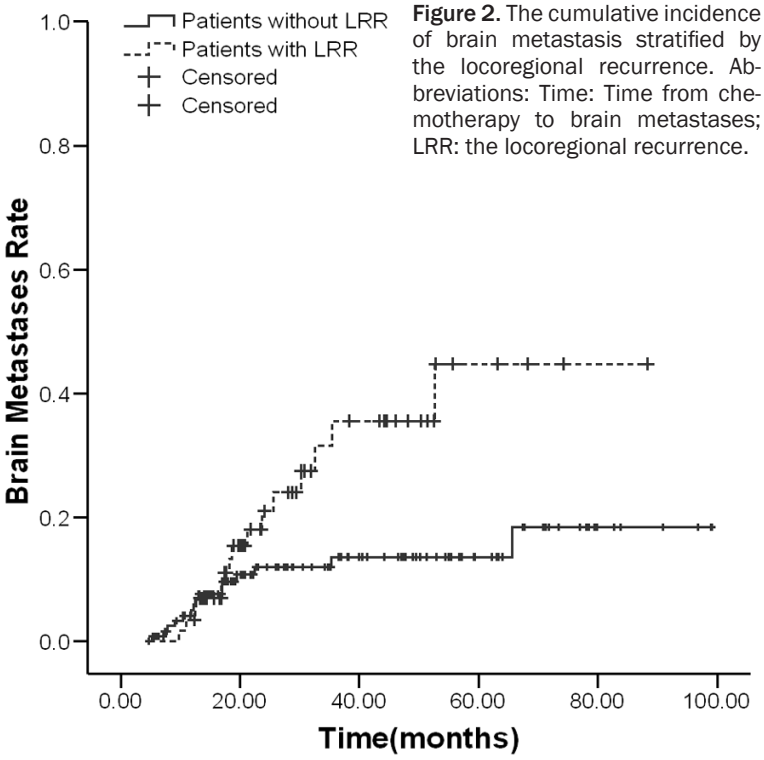


**Figure 2.** The cumulative incidence of brain metastasis stratified by the locoregional recurrence. Abbreviations: Time: Time from chemotherapy to brain metastases; LRR: the locoregional recurrence.

**Table 2.** Multivariate analysis of the risk factors associated with brain metastases in patients with LS-SCLC

| Characteristic | B | SE | Wald | Sig | Exp (B) |
|---|---|---|---|---|---|
| Tumor markers | 0.487 | 0.519 | 0.877 | 0.349 | 1.627 |
| Stage | 0.785 | 0.505 | 2.414 | 0.120 | 2.191 |
| Response to chemo (radio) therapy | 1.438 | 0.481 | 8.935 | 0.003 | 4.211 |
| LRR | 0.961 | 0.467 | 4.231 | 0.040 | 2.614 |

partial response to chem (radio) therapy (P=0.005) or LRR (P=0.007) had a significantly higher incidence rate of brain metastases (**Table 1**). The 1, 2, 3-year cumulative incidence of brain metastases were 3%, 11%, 15% in CR group and 11%, 31%, 48% in PR group, respectively. The 1, 2, 3-year cumulative incidence of brain metastases were 3%, 20%, 34% in LRR group and 5%, 12%, 14% in no LRR group, respectively (**Figure 2**). Cox multivariate regression analysis further revealed only partial response to CRT (P=0.003) and LRR (P=0.040) were significantly associated with increased risk of brain metastases (**Table 2**).

## Discussion

PCI has been widely used in clinical practice, however, few studies reported the relevant risk factors associated with intracranial relapse after PCI. In present study, the 3-year cumulative incidence of brain metastases was 20%, which was consistent with the result reported by Manapov *et al. [12]*, and lower than the results found in previous meta-analysis [3]. The possible explanation was that brain CT or MRI was routinely performed in our study before PCI to exclude the possibility of brain metastases. Our results revealed that failure to achieve CR after chemo (radio) therapy or LRR was significantly associated with intracranial recurrence after PCI. Although univariate analysis showed that elevated tumor markers or advanced stages were significantly correlated with brain metastases after PCI, these two factors were not further confirmed by multivariate analysis.

PCI is widely accepted and justified by the premise that existing intracranial subclinical metastases before PCI are difficult to be eliminated thoroughly by chemotherapy due to the blood-brain barrier and become the resources of intracranial relapse. Accordingly, the dose of 25 Gy for PCI used in clinical practice may be insufficient to eradicate the subclinical metastases, and the rate of intracranial relapse can be reduced dramatically by increasing PCI dose. However, One randomized trial showed that no significant reduction in the total incidence of brain metastases was observed after higher-dose PCI [4]. The present study indicated that failure to achieve complete remission after CRT or local-regional recurrence was significantly associated with brain metastases after PCI. In univariate analysis, advanced diseases, which were more likely to develop local-regional recurrence, were also found to have a higher risk of intracranial recurrence. It's well known that residual or recurrent tumor cells after CRT have a stronger ability of

invasiveness and metastasis, so secondary hematogenous spread of these tumor cells might be the main cause of intracranial relapse after PCI. For those patients, upfront PCI can not reduce the incidence rate of brain metastases and even cause potential damage to cognitive function. Therefore, close follow-up with brain MRI followed by rescuing cerebral irradiation may be preferred choice. In addition, good locoregional disease control is important for reducing the incidence rate of BM after PCI [8-11]. Since our results come from a single-center retrospective study, the findings should be interpreted carefully and verified by randomized clinical trials.

Early studies have shown that the superiority of PCI is limited to those patients who achieved complete remission after induction therapy [3, 13]. In one randomized trial evaluating the early and late timing of thoracic radiotherapy in patients with LS-SCLC, significant improvements in PFS and OS for "early" arm and "late" arm was observed, and the proportion of brain metastases in the "late" arm (28%) was significantly higher than in the "early" arm (18%) (P=.0425, Fishers' exact test) [14, 15]. Another phase III study from Japan evaluating the optimal timing of thoracic radiotherapy also confirmed that concurrent radiotherapy not only yielded better CR, PFS and OS than sequential radiotherapy but also experienced lower occurrence of brain metastases [1]. In addition, the largest international multicenter study published in 2009 failed to find a significant reduction in the total incidence of brain metastases with higher dose (36 Gy), compared to the standard dose for PCI (25 Gy), the potential benefits brought by higher dose might be offset by secondary brain metastases caused by an increased rate of thoracic relapses. These results suggest that good locoregional disease control might be the main contributor for lower incidence of intracranial metastases. The study by Manapov et al. also showed that primary tumor response to chemoradiotherapy in LS-SCLC correlated with duration of brain-metastasis free survival [12]. These results mentioned above are in accordance with the findings in our study, indicating the importance of good localregional control in reducing the recurrence rate of BM after PCI.

There is still no standard methods to evaluate the efficacy of CRT in patients with LS SCLC. None in our study underwent fiberoptic bronchoscopy and few received PET-CT scan, however, all were evaluated by brain CT or MRI, chest and abdomen enhanced CT. CR is defined as complete disappearance of all target lesions, and PR as more than 50% decrease in the sum of the longest diameter of target lesions. Although the evaluation criteria above may not accurately reflect pathologic changes, they are proved to be significantly associated with locoregional recurrence (Fisher's exact test, P=0.088). In some early studies, chest CT scan was not routinely used for response evaluation, therefore, CR rates might be overestimated or underestimated, which in turn could interfere with objective evaluation of the relationship between therapeutic efficacy and brain metastases [3, 16, 17]. Therefore, a more comprehensive therapeutic effect evaluation system should be established and more sensitive methods are needed to detect early LRR [18].

## Conclusions

Our results indicate that those patients with LS-SCLC who fail to achieve complete remission after chemo (radio) therapy or experience locoregional recurrence still have higher risk of developing intracranial relapse after PCI.

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## Disclosure of conflict of interest

None.

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