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ORIGINAL ARTICLE

# Influence of Prophylactic Cranial Irradiation (PCI) in the First-line Treatment of Limited-stage Small Cell Lung Cancer (LS-SCLC)

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**OBJECTIVE**

The survival benefit of prophylactic cranial irradiation (PCI) in limited-stage small cell lung cancer (LS-SCLC) is generally based on data that do not reflect the modern era in which magnetic resonance imaging (MRI) is actively used. In this study, we aimed to investigate the cumulative incidence of brain metastasis between patient groups treated with and without PCI in a cohort where MRI was routinely used for staging and follow-up.

**METHODS**

A total of 73 patients with LS-SCLC who achieved a response to concurrent chemoradiotherapy (cCRT) at our institution between March 2010 and December 2023 were retrospectively analyzed. Radiotherapy was usually administered with dose escalation using a twice-daily schedule (54 Gy in 30 fractions). Patients were divided into two groups according to PCI administration.

**RESULTS**

Among 73 patients (38 PCI, 35 non-PCI), baseline characteristics were similar between groups. The use of first-line immunotherapy and dose-escalated twice-daily radiotherapy were significantly higher in the non-PCI group. The cumulative incidence of central nervous system (CNS) recurrence in the entire cohort was 26%, and it was similar between PCI and non-PCI groups (26.4% vs. 25.7%, p=0.953). However, the time to CNS recurrence was significantly longer in patients who received PCI (28 vs. 7 months, p=0.013).

**CONCLUSION**

Our study indicates that PCI does not significantly reduce the cumulative incidence of metastasis in patients with LS-SCLC but prolongs the time to metastasis.

**Keywords:** Cranial irradiation; magnetic resonance; small cell lung carcinoma.


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## INTRODUCTION

Small-cell lung cancer (SCLC) is characterized by its aggressive nature and a high tendency for central nervous system metastasis. An estimated 59–67% of patients develop brain metastasis within three years if prophylaxis fails to be administered.[1,2] This high incidence is due to the brain acting as a pharmacologic sanctuary, shielded from systemic chemotherapy. As a result, preventing intracranial metastasis becomes a critical therapeutic objective and a key factor for overall survival (OS) and quality of life of SCLC patients in limited stages, as the median survival rate of patients after brain metastasis was found to be 4–5 months.[3]

Prophylactic cranial irradiation (PCI) has been the standard method in the guidelines for reducing the metastasis risk for many years. The key individual patient data meta-analysis by Aupérin et al.[1] affirmed the historical reasoning for this approach of treatment by showing that PCI considerably reduced the incidence of brain metastasis and, more importantly, improved the 3-year OS rate for patients who achieved complete remission following initial therapy by 5.4%. This finding, which indicated a 16% relative reduction in mortality risk, confirmed PCI's recognition as an internationally accepted standard of care to not delay but rather prevent brain metastasis and improve the patient prognosis and has been backed by international guidelines for more than 20 years.[1,3]

Beyond its survival advantage, the decline in neurocognitive function associated with PCI represents a critical determinant of quality of life.[4] Although hippocampal avoidance techniques and the use of memantine have been implemented to mitigate these toxicities, neurocognitive impairment remains a persistent challenge in this patient population;[5] particularly in the era of immunotherapy, where improved survival has rendered quality-of-life considerations increasingly paramount.

In addition to its detrimental impact on quality of life, the role of PCI has been increasingly questioned in the MRI (Magnetic Resonance Imaging) era. The landmark trial demonstrating a survival benefit was conducted before routine brain MRI, when subclinical metastases frequently remained undetected. In the randomized study by Takahashi et al.[6] in ES-SCLC, all patients underwent baseline MRI; although PCI reduced the incidence of brain metastases, it failed to improve overall survival compared with serial MRI surveillance alone. These and subsequent MRI-based studies suggest that earlier trials may have overestimated the benefit of PCI because of inadequate neuroimaging and the inclusion of patients with occult brain disease.[6,7]

This controversy has now extended to limited-stage SCLC, which is the focus of the present study. Recent MRI-staged cohort studies, such as that of Linde et al.,[7] report no significant difference in overall survival or symptomatic brain metastasis between PCI and observation. Furthermore, a large contemporary multicentre analysis from South Korea indicates that any survival advantage from PCI is largely confined to patients who achieve an complete response to initial therapy, further challenging the rationale for its routine use in all LS-SCLC patients.

As a result, the current discussion has recently shifted from whether PCI should be used to how to select patients that would best benefit from it, weighing the effectiveness of currently available salvage techniques against the potential survival benefits of PCI as well as its neurotoxicity. To further evaluate the effect of PCI on intracranial control and OS in a cohort of patients with limited-stage SCLC, we conducted a retrospective analysis at our centre. Accordingly, patients treated with PCI were compared to those managed without PCI in terms of cumulative brain metastasis incidence and OS, under consistent surveillance with brain MRI.

## MATERIALS AND METHODS

### Patient Population

Patients diagnosed with LS-SCLC between March 2010 and December 2023 who received concurrent definitive thoracic radiotherapy with cisplatin and etoposide chemotherapy at our institution were retrospectively analysed.

Eligible patients were required to meet all the following criteria: 1) Histopathological confirmation of LS-SCLC, 2) Completion of concurrent thoracic radiotherapy with cisplatin-etoposide as first-line treatment, 3) Documented clinical or radiological response to first-line therapy, 4) Absence of brain metastasis on MRI performed prior to PCI.

Patients were excluded if they met any of the following conditions: 1) Presence of brain metastasis at diagnosis, 2) Incomplete chemotherapy or radiotherapy courses, 3) Detection of brain metastasis on MRI prior to PCI, 4) Insufficient clinical data or loss to follow-up.

### Treatment Protocol

In our institution, the standard treatment approach for LS-SCLC consists of concurrent dose-escalated, twice-daily thoracic radiotherapy, initiated during the first or second cycle of cisplatin-etoposide chemotherapy. However, for patients who decline twice-daily treatment schedules due to logistical or personal reasons, once-daily conventional fractionation is applied.

Radiotherapy planning was performed on the basis 4D-CT (4-Dimension Computer Tomography) simulation with integrated gross tumor volume (iGTV) approach, appropriate heterogeneity correction software and intensity modulated radiotherapy planning. The twice-daily radiotherapy protocol utilized a simultaneous integrated boost technique, with a prescribed dose of 54 Gy in 30 fractions to the gross tumor volume (GTV) and 45 Gy in 30 fractions to the clinical target volume (CTV).

Following the completion of first-line treatment, patients demonstrating a clinical or radiological response on systemic imaging and without evidence of brain metastasis on MRI are routinely recommended PCI at a dose of 25 Gy in 10 fractions. PCI was omitted for patients who refuse or had poor performance status, an active MRI surveillance strategy is adopted.

### Statistical Analysis

The primary endpoint of this study was cumulative brain metastasis incidence comparing the PCI group with the non-PCI group. The secondary endpoint was OS, evaluated to determine survival differences between the two groups. Overall survival and time to brain metastasis were calculated from the date of initiation of first-line chemotherapy. Survival outcomes were estimated using the Kaplan-Meier method, and differences between groups were compared with the log-rank test. Cox proportional hazards regression analysis was performed to identify prognostic factors associated with OS. A p-value of $<0.05$ was considered statistically significant.

### Ethics and Helsinki Declaration

The retrospective design of this study was reviewed and approved by the Institutional Review Board (Approval No: 2024.431.IRB2.189), in accordance with the principles of the Declaration of Helsinki and institutional ethical standards.

## RESULTS

A total of 73 patients were analysed, including 38 in the PCI group and 35 in the non-PCI group. The median follow-up duration for the entire cohort was 37 months (5–153 months), 43 months (10–153 months) in the PCI group, and 24 months (5–70 months) in the non-PCI group. The median age was 65 years (range 43–81), with no significant difference between groups (p=0.356). The majority of the patients had a reported ECOG performance score of 0–1 with no significant difference between the two groups.

### Details of Firstline Treatment

Table 1 summarized first-line treatment and recurrence pattern. The distribution number of first-line chemotherapy cycles did not differ significantly between PCI and non-PCI groups (p=0.268). First-line immunotherapy was administered to 24.7% of patients overall and was significantly more frequent in the non-PCI group compared to the PCI group (37.1% vs. 13.2%, p=0.018).

Radiotherapy was delivered predominantly with a dose-escalated BID regimen (79.5%), whereas 20.5% of patients received either twice-daily RT (45 Gy in 30 fractions) or a conventional scheme (60 Gy in 30 fractions). Dose-escalated BID was used more frequently in the non-PCI group compared with the PCI group (94.3% vs. 65.8%, p=0.003). The median time to radiotherapy was 25 days (range 0–100), with no difference between the two groups (p=0.674).

### Details of Recurrence Pattern

Recurrence occurred in 64.4% of patients overall, with no significant difference between PCI and non-PCI groups (p=0.306). Distant recurrence was the most frequent first recurrence pattern, observed in 42.5% of patients, followed by isolated local recurrence (9.6%) and synchronously local and distant recurrence (12.3%). The distribution of recurrence patterns did not differ significantly between PCI vs. non-PCI groups (p=0.209).

Cumulative central nervous system (CNS) recurrence was observed in 19 patients (26%) across the entire cohort, with a median time to brain metastasis of 18 months (range; 4–44 months). The incidence of cumulative CNS recurrence was similar between PCI and non-PCI groups (26.4% vs. 25.7%, p=0.953). However, the median time to CNS recurrence was significantly prolonged in the PCI group compared with the non-PCI group (28 vs. 7 months, p=0.013). Comparing the PCI and non-PCI groups, the cumulative incidence of CNS recurrence at 1, 2, and 5 years was 7.9% vs. 18%, 10.9% vs. 22.1%, and 32.3% vs. 32.6%, respectively (Fig. 1).

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**Table 1** Details of firstline treatment and recurrence pattern

| | All patients (n=73) | | PCI (n=38) | | Non-PCI (n=35) | | p |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Age | | | | | | | |
| Median, range | 65 (43–81) | | 63 (43–80) | | 66 (47–81) | | 0.356 |
| ECOG score | | | | | | | 0.433 |
| 0 | 23 | 31.5 | 15 | 39.5 | 8 | 23 | |
| 1 | 28 | 38.4 | 14 | 36.9 | 14 | 40 | |
| 2 | 17 | 23.3 | 7 | 18.5 | 10 | 28.5 | |
| 3 | 5 | 6.8 | 2 | 5.1 | 3 | 8.5 | |
| Number of first-line CT | | | | | | | 0.268 |
| 3 cycles | 2 | 2.7 | 1 | 2.7 | 1 | 3 | |
| 4 cycles | 45 | 61.6 | 20 | 52.7 | 25 | 71.5 | |
| 5 cycles | 2 | 2.7 | 2 | 5.1 | 0 | 0 | |
| 6 cycles | 24 | 32.9 | 15 | 39.5 | 9 | 25.5 | |
| Time to RT, median, range | 25 days (0–100) | | 25 days (0–92) | | 22 days (0–100) | | 0.674 |
| Firstline immunotherapy | | | | | | | 0.018 |
| No | 55 | 75.3 | 33 | 86.8 | 22 | 62.8 | |
| Yes | 18 | 24.7 | 5 | 13.2 | 13 | 37.2 | |
| Radiation scheme | | | | | | | 0.003 |
| Dose-escaleted BID | 58 | 79.5 | 25 | 65.7 | 33 | 94.2 | |
| Other scheme | 15 | 20.5 | 13 | 46.3 | 2 | 5.8 | |
| Recurrence | | | | | | | 0.306 |
| No | 26 | 35.6 | 12 | 31.5 | 14 | 40 | |
| Yes | 47 | 64.4 | 26 | 68.5 | 21 | 60 | |
| First recurrence pattern | | | | | | | 0.209 |
| No | 26 | 35.6 | 12 | 31.5 | 14 | 40 | |
| Local | 7 | 9.6 | 6 | 15.8 | 1 | 3 | |
| Distant | 31 | 42.5 | 16 | 42.2 | 15 | 42.8 | |
| Local+distant | 9 | 12.3 | 4 | 10.5 | 5 | 14.2 | |
| Infield recurrence | | | | | | | 0.233 |
| No | 56 | 77.6 | 27 | 71 | 29 | 82.8 | |
| Yes | 17 | 23.3 | 11 | 29 | 6 | 17.2 | |
| CNS recurrence | | | | | | | 0.953 |
| No | 54 | 74 | 28 | 73.6 | 26 | 74.5 | |
| Yes | 19 | 26 | 10 | 26.4 | 9 | 25.5 | |
| Time to CNS recurrence Median months, range | 18 (4–44) | | 28 (6–44) | | 7 (4–30) | | 0.013 |

PCI: Prophylactic cranial irradiation; ECOG: Eastern Cooperative Oncology Group; CT: Computed tomography; RT: Radiotheraphy; BID: Bis in die; CNS: Central nervous system

Five (26.3%) of the 19 patients who experienced brain metastasis had isolated central nervous system metastasis. One out of the 38 PCI patients (2.6%) and four of the 35 non-PCI patients (11.4%) showed this isolated CNS metastasis; the statistical difference among the two groups was not statistically significant (p=0.3).

In the univariate analysis of factors that may affect cumulative CNS recurrence, PCI status (p=0.953), first-line IMT (p=0.724), time to RT (p=0.483), number of first-line CT cycles (p=0.307), and radiation scheme (p=0.266), no statistically significant associations were detected.

## Clinical Outcomes

In the overall cohort, the median overall survival (OS) was 53 months, with 2-year and 5-year OS rates of 78.6% and 44.8%, respectively (Fig. 2a) While the median OS was 53 months in the PCI group, it was

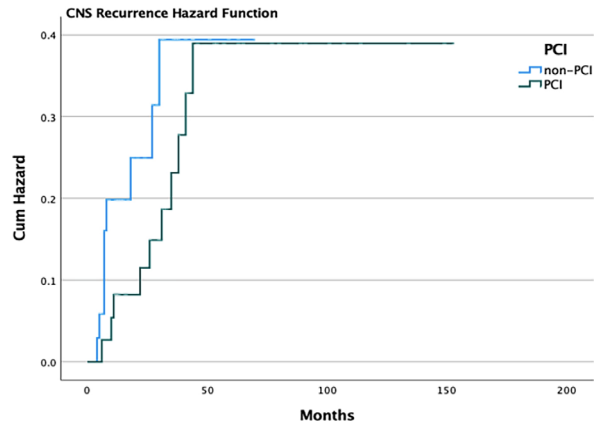


**Fig. 1.** Cumulative incidence of CNS recurrence.
PCI: Prophylactic cranial irradiation; CNS: Central nervous system.

not reached in the non-PCI group, which precludes the identification of a statistically significant difference (Fig. 2b). In the comparison between the PCI and non-PCI groups, no statistically significant difference in median OS was observed (p=0.552). Kaplan-Meier survival curves demonstrated better early survival in patients who underwent PCI; however, this advantage diminished over time, with no apparent long-term difference between the two groups.

## DISCUSSION

According to our retrospective study of 73 LS-SCLC patients, PCI had no significant effect on OS or the cumulative incidence of brain metastasis. The median time to CNS recurrence, however, was significantly prolonged by PCI from 7 to 28 months (p=0.013). These findings should be interpreted with caution, as dose-escalated BID radiotherapy (94.3% vs. 65.8%, p=0.003) and first-line immunotherapy (37.1% vs. 13.2%, p=0.018) were administered significantly more frequently in the non-PCI group, which may have influenced the observed outcomes. The non-PCI group did also have shorter median follow-up intervals planned as compared to the PCI group (24 vs. 43 months).

Our findings add to the increasing amount of recent evidence that raises doubt over the widespread adoption of PCI in LS-SCLC. Findings are in line with the Danish cohort study by Linde et al.,[7] which similarly found no statistically significant difference between the PCI and non-PCI groups in terms of cumulative incidence of brain metastasis (36% overall) and OS (19 vs. 24 months; p=0.40). The authors of the previous research also observed qualitatively that metastasis developed earlier in the group of patients that did not receive PCI; our study confirms this finding with quantitative data. When comparing our analysis to the Danish cohort study, the median survival (53 months) and cumulative incidence of brain metastasis (26%) were better in our study; however, there is a shared consensus regarding the effectiveness of PCI.

In a multicentre study from Korea involving 1,302 patients,[8] PCI was shown to significantly reduce the 2-year cumulative incidence of brain metastasis as well as isolated brain metastasis. However, according to their subgroup analysis, PCI had no beneficial effect for patients who reached a complete response (CR) (HR: 1.03), with those patient modern salvage stereo-

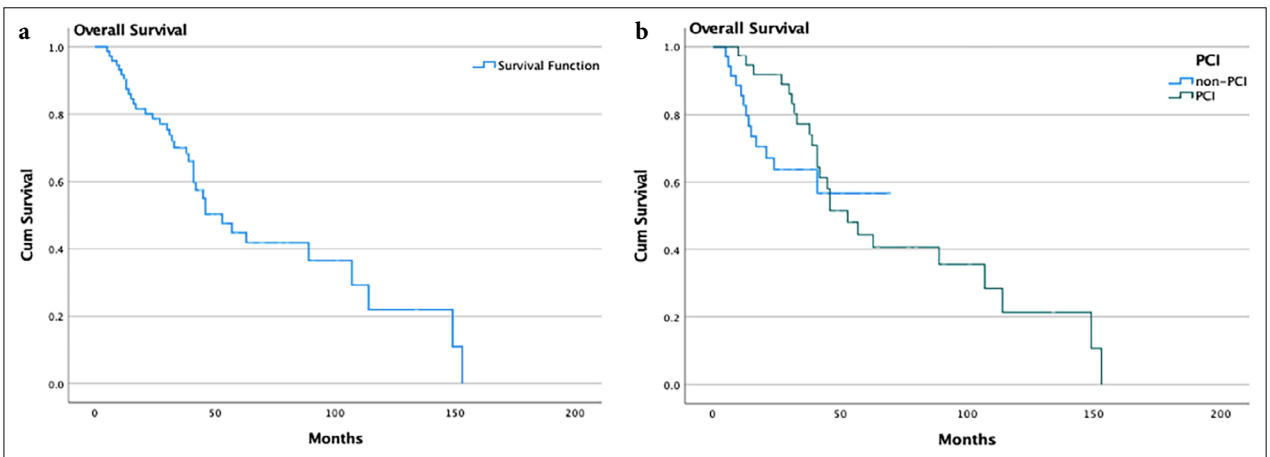


**Fig. 2.** (a) Kaplan–Meier overall survival curve for the entire cohort; (b) Kaplan–Meier overall survival curves according to PCI status.
PCI: Prophylactic cranial irradiation.

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tactic radiosurgery demonstrated excellent results for any developed cranial metastasis. This points to a novel approach for selective PCI use for only a selected group of patients, where MRI surveillance is used instead of PCI in CR patients. Specifically, PCI significantly lowered the cumulative incidence of brain metastasis (PCI:17.4% vs. non-PCI: 27.6% at 2 years; p<0.001), primarily by reducing the rate of isolated brain metastasis (PCI:6.5% vs. non-PCI:16.1% at 2 years; p<0.001), while having no significant impact on non-isolated brain metastasis. In our study, the 2-year incidence of brain metastasis was also lower among patients who received PCI (10.9%) compared with those who did not (22.1%). In line with the Korean study, the incidence of isolated brain metastasis was 2% in the PCI group and 11.4% in the non-PCI group. Nevertheless, due to the limited number of patients and events, this numerical difference did not reach statistical significance.

In a study evaluating with limited-stage small cell lung cancer who did and did not receive PCI using propensity score–matched analysis,[9] the 1-year incidence of brain metastasis tended to be higher in the non-PCI group (26% vs. 17%; p=0.22), although this difference did not reach statistical significance. In our study, while the cumulative incidence of brain metastasis was 26%, the 1-year incidence was 7.9% in the PCI group and 18% in the non-PCI group. We believe that the lower 1-year incidence observed in our cohort may be attributable to the use of first-line immunotherapy and/or dose-escalated radiotherapy.

In contrast to these retrospective data, the results of the prospective ADRIATIC trial—which evaluated the efficacy of immunotherapy as part of first-line treatment for limited-stage small cell lung cancer—have underscored the continuing importance of PCI.[10] This result seems to be at possible conflict with the new evidence. It is necessary to note, though, that ADRIATIC's comparison of the PCI and non-PCI groups was not randomised. Selection bias is unavoidably present because PCI treatment was a classification factor depending on investigator judgement. PCI-eligible patients were likely selected as the subgroup with more favourable response and with higher initial performance status. Therefore, instead of being a direct therapeutic result of PCI, the observed survival advantage is possibly to be the outcome of this bias. The lack of an OS benefit for PCI in our study and other recent studies corresponds with this conclusion.[7,8]

In addition, the median overall survival in our cohort was 53 months, which is comparable to that reported in the ADRIATIC trial (median OS, 55.9 months). We believe that the predominant use of a twice-daily (BID) dose-escalated thoracic radiotherapy regimen, along with the inclusion of patients who received first-line immunotherapy, contributed to achieving a median survival that exceeds the historical standard. It is also conceivable that the observed PCI benefit in the ADRIATIC trial may, in part, be related to the fact that only 26–29% of patients received BID thoracic radiotherapy. Considering that early BID thoracic radiotherapy has been shown to reduce brain relapse even among patients who receive PCI,[11] it can be inferred that early, dose-escalated thoracic radiotherapy may also influence the pattern of brain recurrence. Therefore, although the ADRIATIC trial highlights a benefit of PCI, certain gaps and uncertainties remain.

### Limitations of the Study

The limited sample size, a shorter follow-up time in the non-PCI cohort, considerable baseline imbalances (such as increased immunotherapy and dose-escalated RT in the non-PCI group), and the retrospective study design are some of the key limitations of this study.

## CONCLUSION

PCI failed to reduce cumulative incidence of brain metastasis in this study and just postponed brain metastasis. The efficacy of PCI should be further clarified in patient populations treated with dose-escalated BID regimens, first-line immunotherapy, and MRI-surveillance.

**Ethics Committee Approval:** The study was approved by the Koç University Ethics Committee (no: 2024.431.IRB2.189, date: 12/12/2024).

**Informed Consent:** Informed consent was obtained from all participants.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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