

Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer: A Meta-Analysis

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ABSTRACT

The role of prophylactic cranial irradiation (PCI) in limited-stage small cell lung cancer (LS-SCLC) has been questioned in the era of magnetic resonance imaging (MRI). The purpose of this study was to re-evaluate the efficacy of PCI in patients with LS-SCLC. Three electronic databases were searched, including PubMed, Embase, and the Cochrane Library from January 2012 to April 2022. All relevant publications were included based on the inclusion criteria, and survival data and brain metastasis (BM) rates were extracted and pooled. Ten studies were selected which involved 532 patients who received PCI and 613 patients who did not receive PCI. In pooled estimates, PCI significantly improved overall survival (OS) and progression-free survival (PFS) [hazard ratio (HR) = 0.71, 95% confidence interval (CI): 0.61-0.82, $p < 0.001$; HR = 0.68, 95% CI: 0.48-0.97, $p = 0.03$, respectively]. Additionally, the use of PCI was associated with a significant reduction in the risk of brain metastasis (BM, risk ratio = 0.64, 95% CI: 0.46-0.90, $p = 0.009$). In subgroup analyses. The authors found that the PCI effects on OS were independent of region and the use of brain imaging after initial treatment. These findings demonstrate that PCI improves OS and PFS while decreasing the risk of BM in patients with LS-SCLC, implying that PCI remains necessary even in the MRI era.

Key Words: Prophylactic cranial irradiation, Small cell lung cancer, Magnetic resonance imaging, Brain metastasis.

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INTRODUCTION

Small cell lung cancer (SCLC) is a deadly neuroendocrine tumour, comprising approximately 13-15% of all lung cancers.¹ It is characterised by rapid progression and early metastasis, resulting in a poor prognosis and a median survival of <1 year.² SCLC frequently metastasizes to the brain, with a 2-year brain metastases (BM) rate of 67% in patients with limited-stage SCLC (LS-SCLC) who achieved a complete response (CR) after treatment. In patients who survive >2 years, the BM rate ranges from 50-80%. The median survival duration for patients with BM is only 4-5 months.³

Most cytotoxic drugs are incapable of penetrating the blood-brain barrier. Since SCLC is extremely responsive to radiotherapy, numerous studies have investigated the use of prophylactic cranial irradiation (PCI) in patients with this cancer. Many studies have indicated that PCI improves survival conditions in patients with LS-SCLC.⁴ According to a meta-analysis by Auperin *et al.*⁵

PCI increased 3-year survival by 5.4% (20.7% vs. 15.3%, $p = 0.01$) and decreased the cumulative incidence of BM. Based on the findings of this meta-analysis, the American Society of Clinical Oncology recommends that patients who achieve a partial response or CR, subsequent to their initial treatment should be administered PCI. In contrast, a Japanese randomised trial in 2017 found no significant improvement in patients with extensive-stage SCLC (ES-SCLC) without BM confirmed by MRI before PCI.⁶ Subsequently, the application of PCI in ES-SCLC caused great controversy. As a result, the evaluation of LS-SCLC was considered. Early clinical trials had limitations in tumour staging and BM detection, and PCI was sometimes considered as a treatment for patients with asymptomatic BM. Given the availability of modern staging techniques, such as computed tomography (CT), positron emission tomography, and high-resolution MRI, it raises the question of whether PCI remains necessary. Some studies examined the link between PCI and LS-SCLC. However, the findings have been inconsistent.

Hence, a systematic review and meta-analysis was performed by the authors, employing nearly a decade of clinical studies, to re-evaluate the significance of PCI in patients with LS-SCLC in the era of MRI.

METHODOLOGY

The study protocol was registered in the International Prospective Register of Systematic Reviews database (CRD42022332723,

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available at http://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022332723, and designed following the Cochrane handbook guidelines.⁷

From January 2012 to April 2022, three electronic databases were searched, namely the Cochrane Library, EMBASE, and PubMed. Various combinations of the following keywords were used without language limitations: small cell lung carcinoma, small cell lung cancer, or SCLC, and prophylactic cranial irradiation or PCI. Additionally, the references of individual studies were manually searched and reviewed articles to guarantee that all pertinent studies were included.

The study's inclusion criteria were patients who were diagnosed with SCLC through pathology or cytology, and LS disease was confirmed through imaging examinations; brain imaging via MRI or CT was conducted at baseline or after the initial treatment to rule out BM; the intervention of interest was PCI; and the outcome of interest was overall survival (OS) or BM. Only full-text studies were eligible for inclusion. The exclusion criteria were patients diagnosed with non-small cell lung cancer, ES-SCLC, or other metastatic tumours; abstracts, case reports, commentaries, and studies that reported outcomes but did not provide raw data.

As per the aforementioned inclusion and exclusion criteria, two authors independently screened the literature. The data were extracted and recorded using a data extraction form. The Newcastle-Ottawa scale (NOS) (Cache-Ottawa scale) was used to assess the risk of bias in retrospective cohort studies, and the quality of each study was assessed.⁸ The quality of randomised trials was evaluated using the Cochrane Handbook 5.1 literature quality assessment method.⁷ Disagreements, if any, were resolved through negotiation.

Stata 15 and Review Manager 5.3 were used for statistical analyses. For a combined estimate, statistical significance was fixed at $p < 0.05$. Two independent reviewers directly extracted and estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for OS, progression-free survival (PFS), and BM risk using

other available statistical data based on Tierney's technique.⁹ To analyse the statistical heterogeneity of the trial outcomes, the Cochrane Q test and the I^2 statistic were employed.¹⁰ Results with $p < 0.1$ or $I^2 > 50\%$ were considered heterogeneous, and a random effects model was employed, whereas $p > 0.1$ or $I^2 < 50\%$ showed no significant heterogeneity, and a fixed effect model was used.¹⁰ To study the origins of heterogeneity, a subgroup analysis was conducted based on the region and used brain imaging following the initial therapy. In analyses with significant heterogeneity in the overall effect estimates, sensitivity analyses were also conducted to investigate the effects of specific studies.¹¹ To visually assess the potential for publication bias, funnel plots were generated.

RESULTS

A total of 1,797 relevant studies were identified, which were reduced to 1,148 after eliminating duplicates. Following a review of their titles and abstracts, 1,130 studies were subsequently excluded. Three reviews, four studies with missing data, and one study that did not report the outcomes of interest after reviewing the full texts of the remaining 18 articles were excluded. Finally, the meta-analysis included 10 retrospective cohort studies.¹²⁻²¹

The retrospective cohort studies included in the meta-analysis were published between 2012 and 2022 and are listed in Table I along with their basic characteristics.¹²⁻²¹ The total number of patients included was 1,138, with 525 receiving PCI and 613 not receiving it. Brain imaging using MRI or CT was performed at baseline or after the initial treatment to rule out BM. If provided in the literature, propensity score-matched data was used; six studies provided such data.^{13,15-18,20} For the remaining four articles,^{12,14,19,20} overall cohort data was used. Multivariate analysis results were preferred over univariate analysis results if provided, as they minimised the influence of confounding factors. In seven studies,¹⁴⁻²⁰ provided HRs and related 95% CIs were obtained, while for the remaining three studies,^{12,13,21} the HRs were obtained using the method provided by Tierney.⁹

Table I: Baseline characteristics of included studies in the systematic review and meta-analysis.

Study	Year	Patients, n		Age, years (Median)		Male, %		Median follow-up, mo		PCI schedule (Gy/fraction)	Chemotherapy regimen	Screening for Baseline Brain Metastases, %	brain imaging after initial treatment, %	Outcomes
		PCI	No PCI	PCI	No PCI	PCI	No PCI	PCI	No PCI					
Mads	2022	28	21	62.2	65.5	43	52	33 (9-64)	26 (3-73)	25Gy/10f	EP/EC	MRI (100)	MRI was used for patients with neurological symptoms	probability of developing symptomatic BM, OS, and PFS
Yu	2022	26	81	60	69	85	85	48		25-35Gy/10-17f	platinum-based chemotherapy or others	MRI (100)	NR	OS
Yuichi	2015	29	95	65	74	93	90	20 (6-82)	20 (6-94)	NR	UK	CT/MRI (total[100])	MRI (69)	OS, the cumulative incidence of BM
Nobuaki	2018	60	20	64	72.5	72	55	41 (7-151)	36 (14-145)	25Gy/10f	platinum-based chemotherapy	NR	MRI (100)	OS, PFS, the cumulative incidence of BM
Ghanta	2021	83	83	65.8	67.7	38.6	37.3	21.3 (11.5-39.4)	16.3 (7.9-27.7)	25-36Gy/10-18f	platinum-based chemotherapy	CT/MRI (total[100])	CT/MRI (total[100])	OS, neurological survival, BMFS, SBMFS
Qi	2022	75	75	NA	NA	70.7	78.7	25 (4-102)		25Gy/10f	EP/EC	MRI (100)	MRI (100)	OS, PFS
Li	2021	69	69	NA	NA	72.5	73.9	17.8 (8.1-56.7)		25Gy/10f	EP	NR	MRI (100)	OS, BMFS
Michael	2019	39	53	NA	NA	51	53	56.7(38-69.4)		25Gy/10f	EP/EC or others	CT	CT/MRI (total:52.2)	OS, PFS, BMFS
Todd	2020	84	84	65	67.5	58.3	56	83.64 (2.5-235)	83.97 (2.5-235)	25-30Gy/10-15f	EP or others	MRI (100)	NR	OS, the cumulative incidence of BM
Yuko	2021	32	32	NA	NA	87.5	78.1	49.9(7.5-107.5)	20.6(7.3-168.4)	25Gy/10f	NR	MRI (100)	CT/MRI (total:65.6)	OS, BMFS

n: Number; y: Year; mo: Month; PCI: Prophylactic cranial irradiation; MRI: Magnetic resonance imaging; CT: Computed tomography; EP: Etoposide and cisplatin; EC: Etoposide and carboplatin; NA: Not available; NR: not reported; UK: Unknown. BM: Brain metastases; OS: Overall survival; PFS: Progression-free survival; BMFS: Brain metastases-free survival.

Table II: Assessment of quality among included studies.

	Selection of exposed and non-exposed cohorts				Comparability of cohorts	Outcome of interest			Overall Quality
	Representativeness of exposed cohort	Comparability of cohorts	Ascertainment of exposure	Outcome present at the start of the study		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Yuichi 2015	*	*	*	*		*	*		Low
Nobuaki 2018	*	*	*	*	**	*	*		High
Michael 2019	*	*	*	*	*	*	*		High
Todd 2020	*	*	*	*	**	*	*		High
Ghanta 2021	*	*	*	*	**	*	*		High
Li 2021	*	*	*	*	**	*	*		High
Yu 2022	*	*	*	*	*	*	*		High
Mads 2022	*	*	*	*		*	*		Low
Qi 2022	*	*	*	*	**	*	*		High
Yuko 2021	*	*	*	*	**	*	*		High

Studies that received seven stars at least were judged to be of "high" quality.

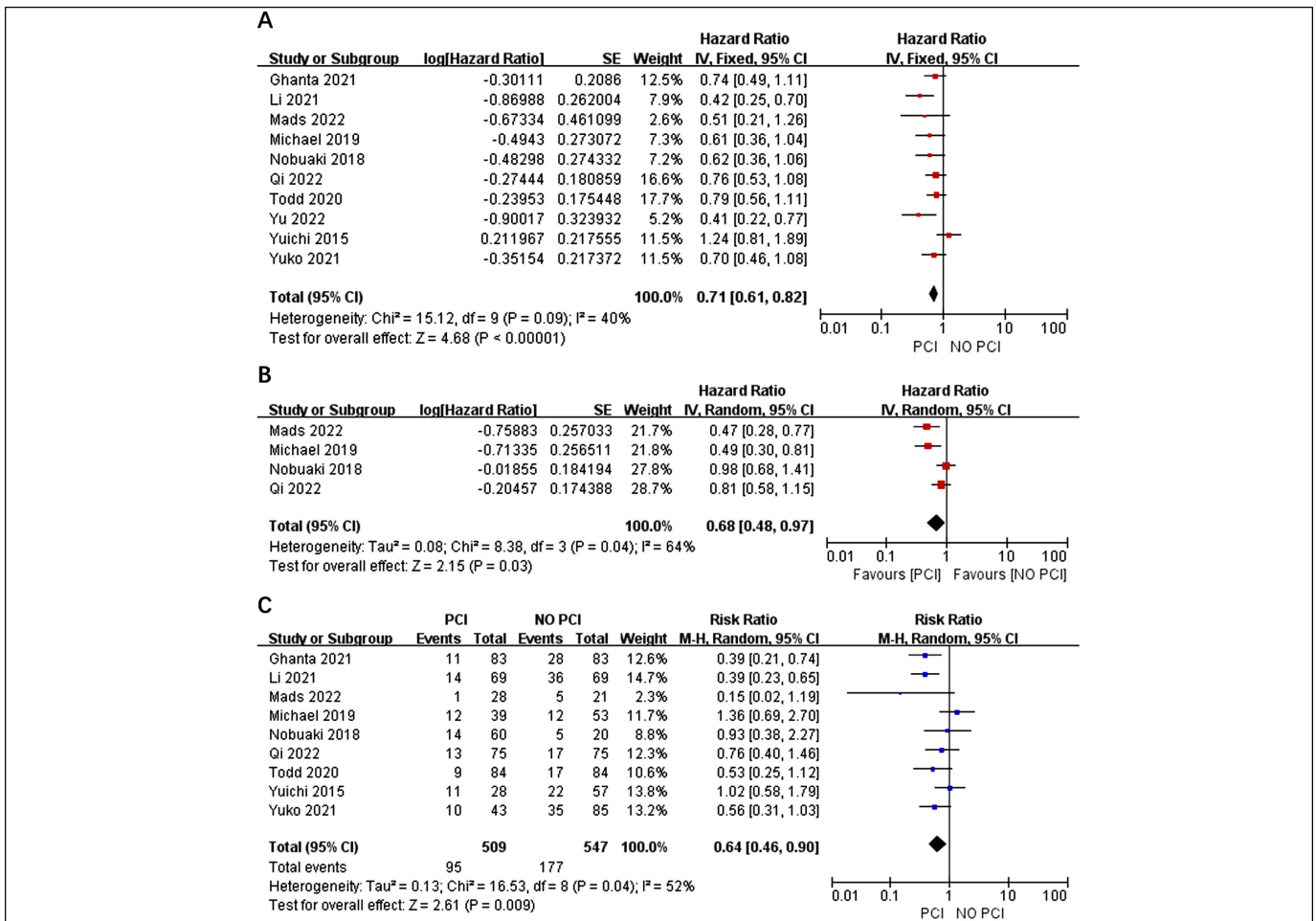


Figure 1: Forest plots for OS (A) PFS (B) and the risk of BM (C) in-patients who received PCI or not.

All trials included in this analysis were retrospective cohort studies, and their quality using the NOS method were evaluated.⁸ Of the 10 articles, two were rated as low quality, mainly due to the lack of matching for important confounding factors such as age and incomplete follow-up. Table II presents the quality assessment results for the retrospective cohort studies.

Based on the I² value of 40%, fixed effect model, findings demonstrated that the use of PCI was related to a significant improvement in OS compared to the control among patients with an HR of 0.71 and a 95% CI of 0.61-0.82 (p<0.001, Figure

2A). Four studies were used to extract HRs,^{12,14,18,20} and significant statistical heterogeneity was observed (I² = 64%, p = 0.04). Therefore, a random effect model was used to combine the results. The pooled estimates revealed that the PFS of patients treated with PCI was substantially better than that of the control group (HR=0.68, 95% CI: 0.48-0.97, p=0.03, Figure 2B). The incidence of BM was less prevalent in the PCI group than in the non-PCI group (RR=0.64, 95% CI: 0.46-0.90, p=0.04, Figure 2C). Given the I² value of 52%, a random effects model was employed.

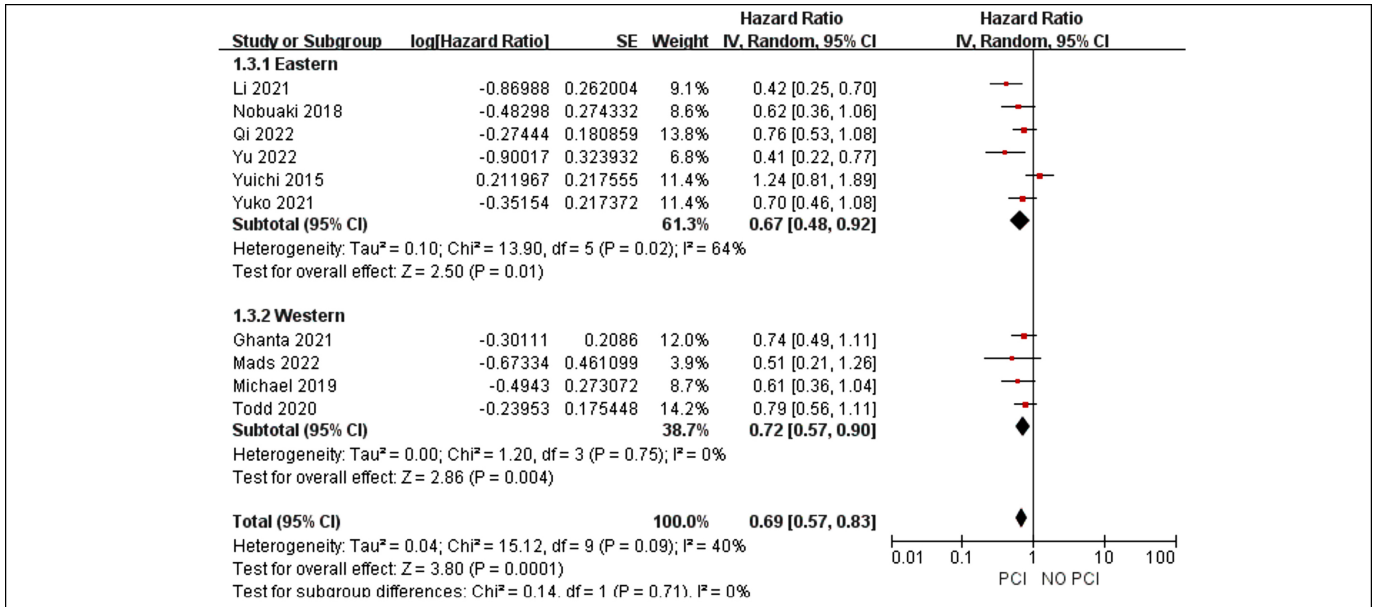


Figure 2: Forest plots for subgroup analysis of region in patients who received PCI or not.

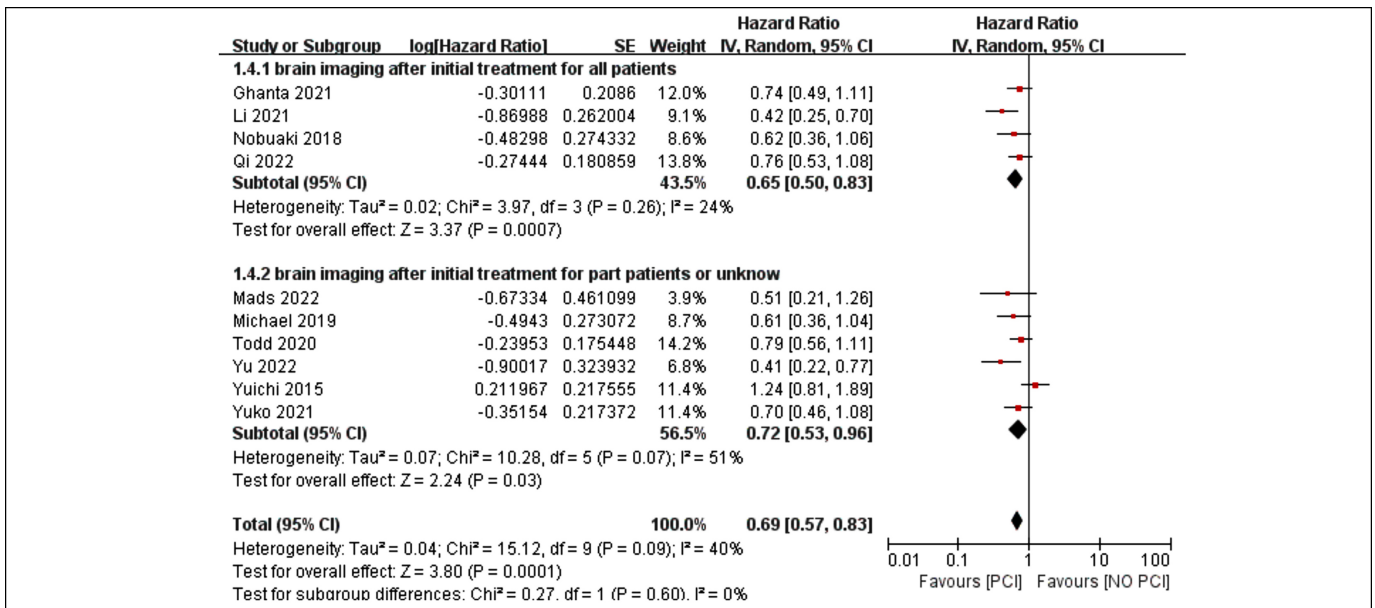


Figure 3: Forest plots for subgroup analysis of the use of brain imaging after initial treatment in patients who received PCI or not.

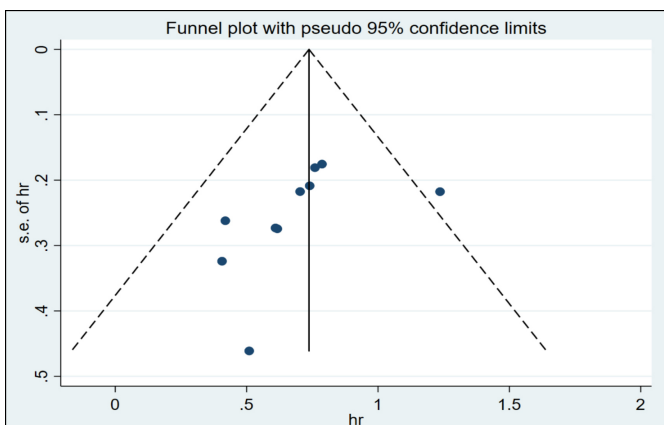


Figure 4: Funnel plot for OS.

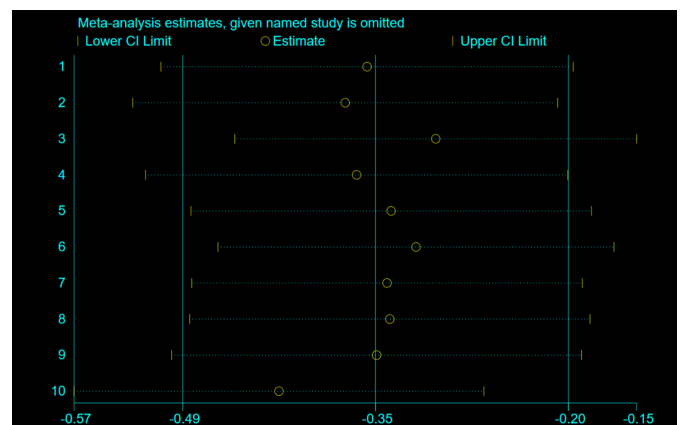


Figure 5: Sensitivity analysis of PCI vs. control for OS in LS-SCLC.

Although the I^2 value of 40% in pooled HRs of PCI vs. the control for OS suggests low heterogeneity, further analysis revealed moderate heterogeneity. The findings of the subgroup analyses showed that the treatment effects were consistent and that there were no statistically significant differences in the treatment effects across these subgroups (region, $p = 0.71$; use of brain imaging following initial treatment, $p = 0.6$, Figures 3 and 4).

Based on the analysis of funnel plots (Figure 5), there was no indication of publication bias. A sensitivity analysis was conducted by computing the pooled HRs and omitting one study at a time to determine the effect of each study on the overall meta-analysis estimate. The results, presented in Figure 5, support the robustness of the findings.

DISCUSSION

PCI has been the conventional treatment scheme for LS-SCLC since the 1900s. However, a recent prospective study by Takahashi *et al.* challenged this assumption by demonstrating that PCI did not increase OS (HR=1.27, 95% CI: 0.96-1.68, $p=0.094$) in patients with ES-SLCL without BM who underwent close brain MRI monitoring and early radiotherapy remediation.⁶ This study raised questions about the function of PCI in the treatment of ES-SCLC, prompting a re-evaluation of that role. In light of these advancements, this study was conducted to ascertain whether the function of PCI in LS-SCLC has changed. This is the first meta-analysis to investigate the significance of PCI in LS-SCLC patients in the era of MRI. Consistent with the findings of another meta-analysis,⁵ the present findings imply that PCI exhibited a positive effect on increasing survival and decreasing the incidence of BM in LS-SCLC. However, the Auperin meta-analysis might no longer be applicable in 2022 due to changes in the staging of LS-SCLC. Most studies in the Auperin meta-analysis used CT imaging rather than MRI to assess the involvement of the central nervous system (CNS). Seute *et al.* compared the occurrence of BM in 481 patients with SCLC across different periods and found that the detection rate of BM was 24% in the MRI era and 10% in the CT era.²² All diagnosed cases of BM in the CT era were symptomatic, whereas 11% of cases in the MRI era were asymptomatic, and multiple BM were detected more frequently. These findings indicate that MRI is superior to CT for detecting CNS disease. In the era of CT, SCLC staging at the initial diagnosis might have been inaccurate, and brain imaging completion to check for BM before PCI treatment was not emphasised. As a result, some patients may have developed asymptomatic BM after enrolling in the PCI trial group, raising the possibility that the effect of PCI in the meta-analysis was obtained from treating a disease that is now more clearly recognised and treated with whole-brain radiotherapy. Only these studies were included where brain imaging was performed at baseline or before PCI, with MRI being the primary method for detecting BM to address this issue. After the first treatment, patients with and without brain imaging underwent subgroup analysis, but no remarkable variations were found between the two groups.

The PCI group showed superiority over the control group, indicating that PCI is still necessary for LS-SCLC even after excluding BM in the MRI era. In the authors' opinion, the aforementioned hypothesis is invalid.

It should be highlighted that administering PCI to patients with LS-SCLC entails higher costs, inconveniences, and a possible risk of toxicity, which has raised concerns among patients and physicians. Neurotoxicity, which has been linked to PCI and described in numerous studies, is of special concern. Numerous studies have noted long-term consequences, including severe memory loss, intellectual disability, dementia, and ataxia.²³⁻³⁰ In a notable pooled analysis of the Radiation Therapy Oncology Group (RTOG) 0212 and RTOG 0214 trials, at 6 and 12 months following treatment, PCI was discovered to be linked to an increase in both tested and self-reported cognitive toxicity.²⁵ It is worth noting that developments in radiation delivery methods may be able to lessen PCI toxicity. According to research, administering 25 Gy in 10 once-daily fractions is a feasible approach for PCI in SCLC, and increasing the dose does not diminish the likelihood of developing BM but increases neurotoxicity.^{4,31} Furthermore, developing approaches like hippocampus sparing and the use of protective medicines like memantine may improve the therapeutic index.³² However, the authors were unable to pool the incidence of toxicity in this meta-analysis due to insufficient data.

The present study has some limitations. First, the sample size was small, and all the studies were retrospective. Retrospective studies are prone to selection bias and selective reporting and are considered less conclusive than randomised controlled trials. However, no prospective studies on the effect of PCI on LS-SCLC have been conducted in the past decade or longer. Second, some studies did not provide direct HRs, which required us to estimate them from the survival curve, potentially leading to inaccuracies. Third, there was statistical heterogeneity in the meta-analysis that could not be explained which might be due to various factors, such as differences in baseline characteristics, including response after initial treatment, the timing of PCI, follow-up time, radiation dose, different tumour and node stages, etc. However, further analysis was not feasible due to the limited data available. Finally, although no obvious publication bias was found, it is possible that some studies were not included, such as unpublished trials or abstracts, due to data unavailability.

With the advent of immunotherapy, a new era has begun. IMPower133 and CASPIAN studies have confirmed that combining immunotherapy with chemotherapy can significantly prolong the OS of patients with ES-SCLC.^{33,34} Based on the findings of these two studies, the Food and Drug Administration has approved the Programmed death-ligand 1 inhibitors Atezolizuma and Durvalumab in combination with chemotherapy as a first-line treatment for ES-SCLC. In LS-SCLC, although the Small Cell Lung Carcinoma Trial With Nivolumab and Ipilimumab in Limited Disease study did demonstrate positive outcomes,³⁵ it did identify a trend of OS

benefit in the hyperfractionated radiotherapy subgroup. Moreover, immune checkpoint inhibitors have been shown to cross the blood-brain barrier and produce objective responses in patients with known BM.³⁶ Two ongoing clinical trials, the Southwest Oncology Group trial and the Prophylactic Cerebral Irradiation or Active Magnetic Resonance Imaging Surveillance in SCLC patients study are currently underway to gain a better understanding of the role of PCI in the modern staging era of immunotherapy. It remains to be seen whether their results will change the role of PCI.

CONCLUSION

This meta-analysis indicates that PCI might enhance survival and lower the probability of BM in patients with LS-SCLC, even after ruling out BM through MRI or CT before PCI. However, given the limited number of studies included in this meta-analysis, all of which were retrospective cohort studies, additional randomised controlled trials are required to validate these results.

COMPETING INTEREST:

The authors declared no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS:

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

AUTHORS' CONTRIBUTION:

LX, XL: Conceived, designed the research, and critically revised the manuscript.

LX, CW: Screened the literature and conducted the quality rating.

LX, CC, LD: Involved in conducting the statistical analyses.

LX, CW, CC: Drafted the manuscript.

All authors read and approved the final manuscript for publication.

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