Radiation Oncology

REVIEW

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Prophylactic cranial irradiation in resected early stage small cell lung cancer: an updated systematic review and meta-analysis

Ze Yuan[1†], Dan Tao[1,2†], Dingyi Yang[1], Yong Jiang[1], Erha Munai[3], Siwei Zeng[3], Zhiying Zhou[3], Wei Zhou[1,2*] and Yongzhong Wu[1,3*]

Abstract

Background The use of prophylactic cranial irradiation (PCI) in early stage small cell lung cancer (SCLC) patients post-surgery remains controversial. This meta-analysis aimed to evaluate the efficacy of PCI in resected early stage SCLC patients.

Methods Relevant literature was reviewed through PubMed, Cochrane, and Embase databases. The pooled hazard ratios (HRs) for overall survival (OS) were analyzed for the overall population, as well as for pathologically node-negative (pN0) and pathologically node-positive (pN+) patients. We also assessed the pooled HRs for brain metastasis-free survival (BMFS) in all patients. Sensitivity analyses were conducted to validate these results.

Results A total of 13 retrospective studies were included, encompassing 3,530 postoperative SCLC patients, of whom 880 received PCI treatment. In the overall patient population, PCI significantly improved OS compared to non-PCI group (HR: 0.66, 95% CI 0.58–0.74, $p < 0.001$). For pN0 patients, there was no significant OS benefit from PCI (HR: 0.85, 95% CI 0.65–1.10, $p = 0.22$). In contrast, pN + patients showed a significant OS improvement with PCI (HR: 0.52, 95% CI 0.41–0.66, $p < 0.001$). Furthermore, PCI significantly improved BMFS in all patients (HR: 0.42, 95% CI 0.29–0.60, $p < 0.001$). Sensitivity analyses confirmed the stability of these results.

Conclusions PCI was associated with a significant improvement in OS and BMFS in resected early stage SCLC patients. The benefits of PCI were particularly pronounced in pN + patients, whereas pN0 patients did not experience a significant OS benefit. These findings supported the selective use of PCI based on nodal status to optimize treatment outcomes in postoperative SCLC patients.

Keywords Small cell lung cancer, Prophylactic cranial irradiation, Postoperative patients, Radiation therapy

†Ze Yuan and Dan Tao contributed equally to this work.

*Correspondence:
Wei Zhou
zhouwei998@cqu.edu.cn
Yongzhong Wu
cqmdwyz@163.com

[1]Department of Radiation Oncology, Chongqing University Cancer Hospital, 181, Hanyu Road, Shapingba District, Chongqing 400030, China
[2]Chongqing Key Laboratory of Translational Research for Cancer Metastasis and Individualized Treatment, Chongqing University Cancer Hospital, Chongqing, China
[3]Medical School of Chongqing University, Chongqing University, Chongqing, China

Introduction

Small cell lung cancer (SCLC) is a highly aggressive form of lung cancer, characterized by rapid growth and early dissemination, which accounts for approximately 15% of

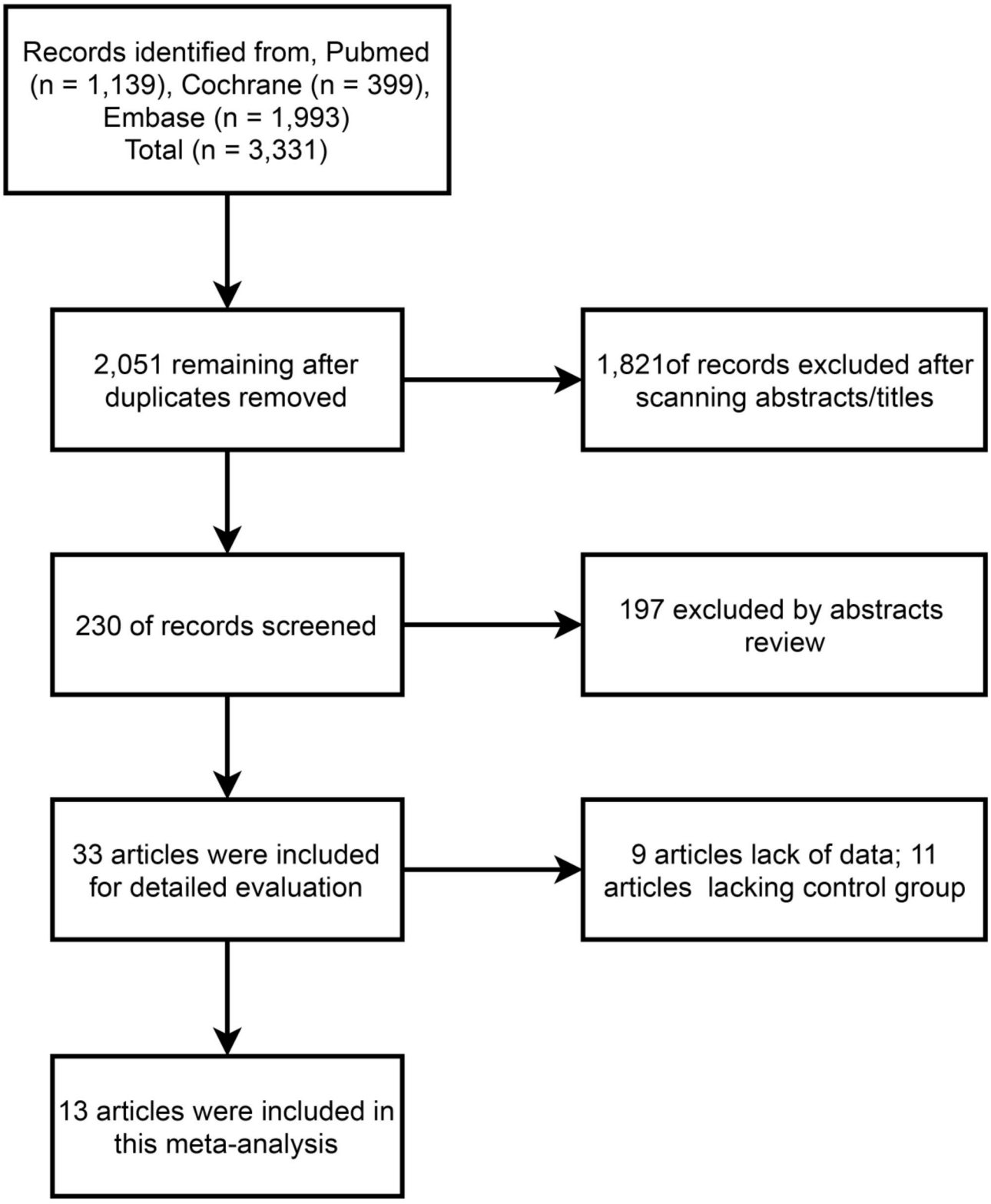

Fig. 1 Flow chart of the article selection process

Table 1 Baseline clinicopathologic characteristics of the study patients

Study	Source	Study type	Fllow-up (months)	Accrual years	No. of patients	Non PCI	PCI	Stage	RTT	PCI dose
Bischof 2007	Germany	Retrospective	29 (2–110)	1995–2006	39	18	21	p-stage IA-IIB	Not reported	30 Gy/15F
Chen 2018	China	Retrospective	Not reported	2003–2015	52	33	19	p-stage I-III	3D-CRT	25 Gy/10F
Guo 2020	China	Retrospective	46.8 (1.0–166.6)	2005–2016	251	192	59	p-stage I-IV	Not reported	Not reported
Luo 2020	China	Retrospective	27.5	2006–2017	146	100	46	p-stage I A-IIA	Not reported	Not reported
Resio 2019	USA	Retrospective	Not reported	2004–2015	859	657	202	p-stage I-III	Not reported	Not reported
Wang 2018	China	Retrospective	35.1 (6.5–113.6)	2005–2014	91	80	11	p-stage I-IV	3D-CRT/IMRT	25 Gy/10F
Xu 2016	China	Retrospective	Not reported	2006–2014	349	234	115	p-stage I-III	Not reported	Not reported
Yang 2016	USA	Retrospective	43 (20–68)	2003–2011	453	354	99	p-stage I A-IIA	Not reported	Not reported
Yang 2021	China	Retrospective/SEER	Not reported	2006–2014 (Retrospective)/1975–2016 (SEER)	664	540	124	p-stage I-IIIA	Not reported	Not reported
Yin 2018	China	Retrospective	30 (3–87)	2010–2015	116	55	61	c-stage II-IIIA	Not reported	30–40Gy/10–20F
Yokouchi 2015	Japan	Retrospective	25.5 (0.4–130.9)	2003–2013	156	140	13	c-stage I-III	Not reported	25 Gy/10F or 30 Gy/15F
Zhou 2021	USA	Retrospective	Not reported	1986–2019	164	121	43	p-stage I-III	Not reported	25 Gy/10F
Zhu 2014	China	Retrospective	39.4 (4.0–96.8)	2003–2009	193	126	67	c-stage I-III	Not reported	25 Gy/10F

(PCI, Prophylactic cranial irradiation; RTT, radiotherapy technology; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; SEER, Surveillance, Epidemiology, and End Results)

all lung cancers [1]. Although SCLC is highly sensitive to chemotherapy and to radiotherapy at initial diagnosis, the majority of patients were still experiencing local recurrence or distant metastases. Brain metastases (BM) are the most prevalent location of distant failure in individuals with SCLC [2]. Nearly 10-24% of patients suffered brain metastasis at the time of diagnosis and above 50% of patients develop BM during the course of disease two years after diagnosis [3]. BM is associated with a dismal outcome with median overall survival of 5 months [4].

Prophylactic cranial irradiation (PCI) is recommended for patients with limited-stage SCLC who achieved complete response to initial curative therapy, including surgery and chemoradiotherapy. Aupérin et al.'s meta-analysis [5] in 1999 revealed that PCI significantly lowered the incidence of brain metastases and improved both disease-free survival and overall survival in patients with SCLC in complete remission. Subsequently, a number of clinical trials also confirmed that patients with both limited-stage small cell lung cancer (LS-SCLC) and extensive-stage small cell lung cancer (ES-SCLC) who had PCI after achieving partial response or better after systemic treatment had a much higher survival rate [6, 7]. However, it is worth noting that the majority of these patients were initially treated with chemoradiotherapy.

Approximately 5% of patients with SCLC present as stage I–IIA (T1–2,N0,M0) tumors. Surgery is recommended for this subgroup of patients with stage I–IIA SCLC. However, the role of PCI in resected early stage SCLC patients remains controversial. Currently, several retrospective studies have evaluated the efficacy of PCI in postoperative SCLC. Regarding the OS benefit in postoperative patients, most studies suggest that PCI after surgery for SCLC is beneficial in extending OS [3, 8–14], while some studies have reached opposite conclusions [15, 16]. Although a recent meta-analysis has shown that PCI was associated with a favorable survival benefit and a lower risk of BM in patients with completely resected SCLC, except for p-stage I patients [17]. However, the results have been insufficiently powered to show which subgroup of patients can be benefit from PCI.

Therefore, in this study, we did an updated systematic review and meta-analysis of all trials of PCI in postoperative SCLC to clarify PCI's therapeutic value and guide clinical decision-making.

Materials and methods

Before commencing this study, we registered our meta-analysis on PROSPERO using the ID CRD42024549509 [18]. In order to improve transparency and reproducibility, our study design followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

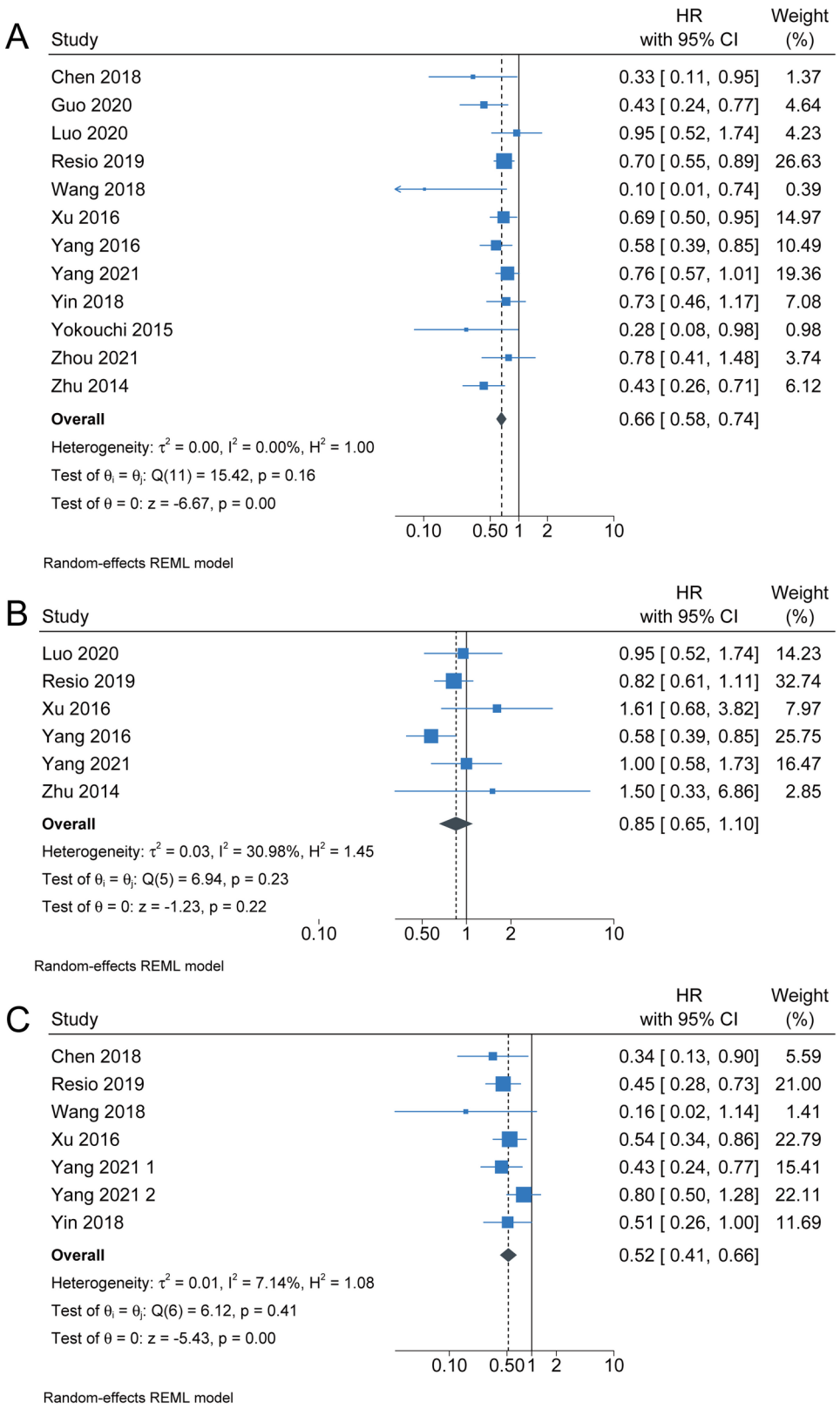

Fig. 2 Forest plot of the effect of PCI on the OS in resected early stage SCLC patients. (**A**) OS for all patients. (**B**) OS for pN0 patients. (**C**) OS for pN + patients

Publication search strategy

A systematic search was conducted in PubMed, Cochrane Library, and Embase databases to identify articles published between January 1990 and May 2024. The search terms were 'small cell lung cancer' or 'SCLC' and 'prophylactic cranial irradiation' or 'PCI'.

Selection criteria

The inclusion criteria for our meta-analysis were as follows: (1) studies involving patients with SCLC who underwent radical excision; (2) direct comparison of patients who received postoperative PCI treatment to those who did not; (3) the primary endpoints were overall survival (OS) and brain metastasis-free survival (BMFS); (4) sufficient data for quantitative meta-analysis.

The exclusion criteria included single-arm studies, studies with insufficient data, meta-analyses, reviews, case reports, discussions, and conference abstracts, as well as studies published in languages other than English.

Data extraction

Data extraction was carried out independently by two researchers, spanning factors such as the main author, the year of release, study source, length of follow-up and the kind of study, patient count, radiotherapy technology, PCI dose, survival, brain recurrence, and additional relevant factors. The HR values for OS and BMFS, along with their 95% confidence intervals (CIs), were primarily obtained from multivariate Cox regression analyses provided in the articles. For articles that did not provide exact HR values, we extracted data from Kaplan-Meier survival curves using GetData Graph Digitizer 2.26 and calculated the HR values according to the method reported by Tierney JF et al. [20].

Statistical analysis

Meta-analysis of HRs and sensitivity analysis were conducted using STATA 18.0 software. The heterogeneity among the studies was assessed using the Cochrane Q test and the I^2 statistic, with a p-value < 0.1 indicating significant heterogeneity [21]. All pooled HRs were obtained using a random-effects model [22]. Publication bias was assessed using Egger test, with a p-value < 0.1 considered statistically significant [23]. To ensure the stability of the results, a sensitivity analysis was performed by excluding each study one at a time to evaluate its impact on the overall results.

Results

Study selection and patient characteristics

Initially, 3,331 articles were identified from PubMed (n = 1,139), Cochrane (n = 399), and Embase (n = 1,993) using the designated search formula. Subsequently, 1,280 duplicate studies were eliminated. Following this, 1,821 studies were excluded after scanning abstracts and titles. An additional 197 studies were excluded after abstract review, which included studies that were not directly relevant or did not meet the inclusion criteria. Furthermore, 9 articles were excluded due to lack of data, 11 articles were excluded due to lack of a control group. Thus, 13 articles were ultimately included in the meta-analysis [3, 8–16, 24–26] (Fig. 1). Overall, all studies were based on retrospective data. Three studies were from the United States [10, 16, 25], eight from China [3, 8, 9, 11–13, 15, 26], one from Japan [14], and one from Germany [24]. The studies collectively included 3,530 patients with surgically treated SCLC, of whom 880 patients received PCI postoperatively, and 2,650 patients did not receive PCI. Eight studies provided median follow-up times ranging from 25.5 to 46.8 months. Two studies reported the radiotherapy techniques used (3D-CRT/IMRT), and seven studies reported the PCI doses used (25–40 Gy). Table 1 displays the baseline characteristics of the included studies. The quality of all included studies was deemed to be medium to high, as indicated by the Newcastle-Ottawa Scale (NOS) scale presented in Supplementary Table 1.

Table 2 Number of patients with pN0 and pN+ stage

Study	N0		Study	*N+*	
	Non-PCI (No.)	PCI		Non-PCI (No.)	PCI
Luo 2020	100	46	Chen 2018	16	9
Resio 2019	459	159	Resio 2019	163	35
Xu 2016	59	19	Wang 2018	52	7
Yang 2016	354	99	Xu 2016	108	57
Yang 2021	252	37	Yang 2021 1	122	39
Zhu 2014	32	17	Yang 2021 2	166	48
			Yin 2018	16	35

Overall survival

Among the 13 studies included in the analysis, 12 provided OS data for postoperative SCLC patients. Overall, the administration of PCI significantly improved OS in these postoperative patients (HR: 0.66, 95% CI 0.58–0.74, p < 0.001, Fig. 2A). Heterogeneity testing revealed minimal heterogeneity among these 12 studies (I^2=0%). To achieve more precise treatment for postoperative patients, we categorized them into pN0 and pN + groups and further explored the impact of postoperative PCI on OS in these two subgroups using meta-analysis (Table 2). A total of 6 studies reported OS data for pN0 patients, with 1,256 patients in the non-PCI group and 377 patients in the PCI group. The results indicated that for pN0 patients, PCI treatment did not significantly improve OS (HR: 0.85, 95% CI 0.65–1.10, Fig. 2B). Heterogeneity testing suggested moderate heterogeneity among these six studies (I^2=30.98%). Six studies reported OS data for pN + patients. Yang et al. [13] reported OS

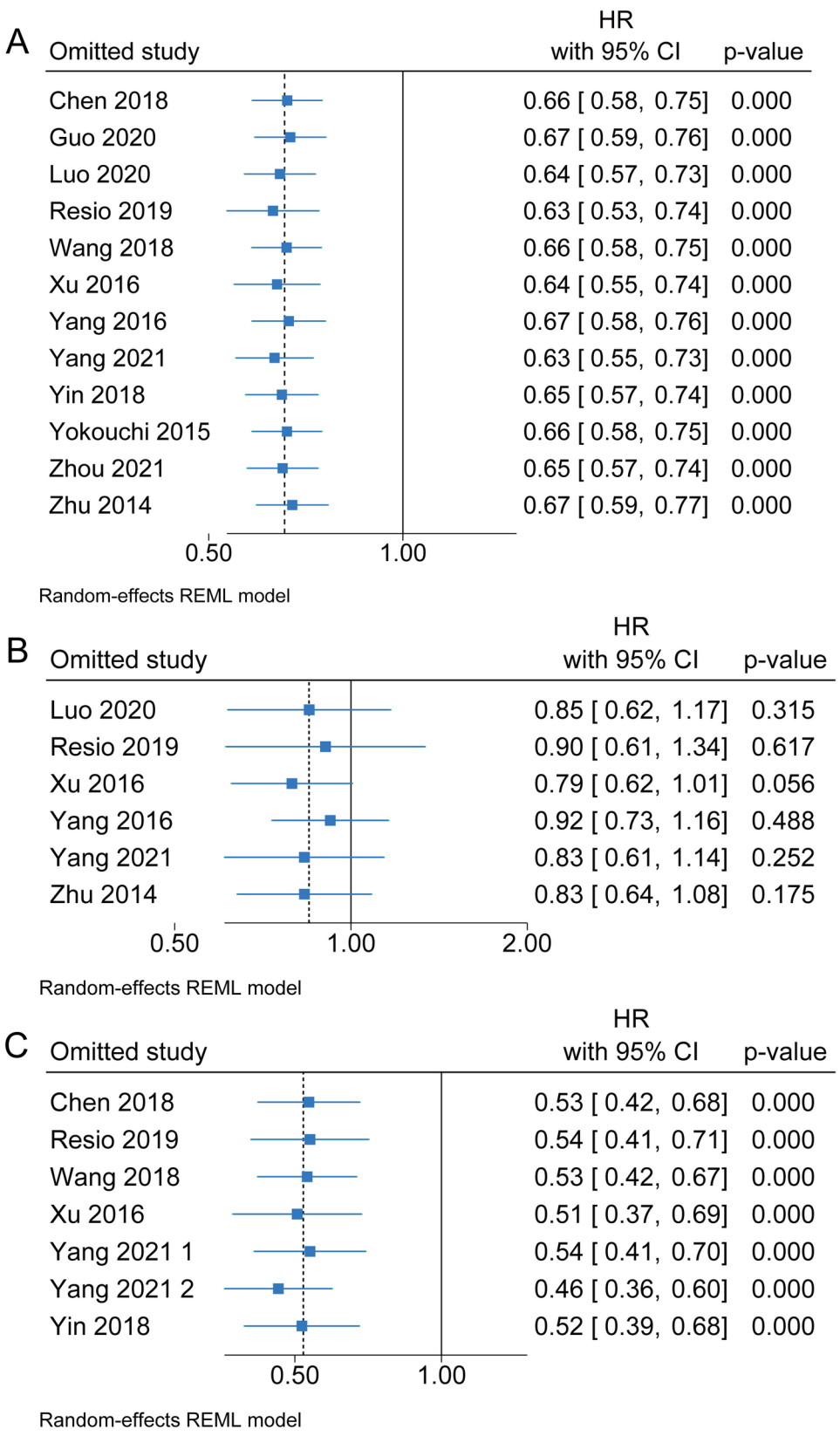

Fig. 3 Sensitivity analysis for OS in resected early stage SCLC patients. (**A**) Sensitivity analysis of all patients. (**B**) Sensitivity analysis of pN0 patients. (**C**) Sensitivity analysis of pN + patients

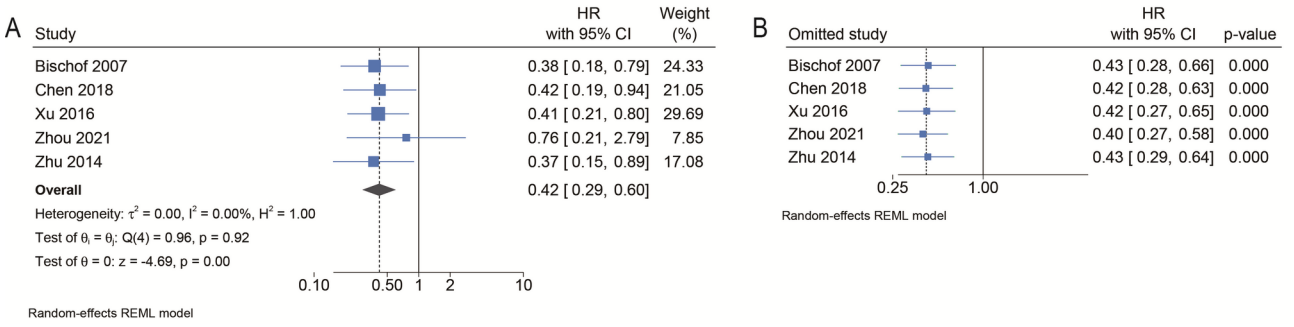

Fig. 4 Forest plot and sensitivity analysis of the BMFS in resected early stage SCLC patients. (**A**) Forest plot of the effect of PCI on the BMFS in resected early stage SCLC patients. (**B**) Sensitivity analysis of the effect of PCI on the BMFS in resected early stage SCLC patients

separately for N1 and N2 patients, and since these two groups did not overlap, we included them as two separate studies in our analysis. This resulted in a total of 617 non-PCI patients and 195 PCI patients. The final results showed that for pN + patients, PCI significantly improved OS (HR: 0.52, 95% CI 0.41–0.66, Fig. 2C). Heterogeneity among these seven studies was very low (I^2=7.14%).

To ensure the accuracy of the results, the sensitivity analysis was performed by using the leave-one-out method on the combined effect of OS in different groups. The results indicated that the combined effect of OS was stable for all patients (Fig. 3A), as well as for both the pN0 and pN + subgroups (Fig. 3B-C).

Brain metastasis-free survival

Regarding BMFS, a total of 5 studies reported the impact of PCI on BMFS in postoperative patients. The combined effect indicated that postoperative PCI was significantly prolonged BMFS (HR: 0.42, 95% CI 0.29–0.60, $p < 0.001$, Fig. 4A). Heterogeneity testing showed no heterogeneity among these studies (I^2=0). Furthermore, sensitivity analysis confirmed the stability of these results (Fig. 4B).

Discussion

PCI holds a significant importance for patients with SCLC due to its ability to reduce the incidence of brain metastases, which are common in this aggressive disease and can severely impact prognosis and quality of life [7]. However, the side effects of PCI, such as neurocognitive decline and other neurological toxicities, cannot be overlooked. These adverse effects can detract from the overall benefit of PCI, especially in patients who may already have compromised health due to their cancer and other treatments [27, 28]. Current guidelines recommend PCI for all postoperative SCLC patients, primarily based on the study by A. Aupérin et al. [5] on PCI in patients who achieved complete remission after chemotherapy. Our meta-analysis indicated that PCI significantly improved OS and BMFS in postoperative SCLC patients, especially those with pN + status, for whom PCI was critical. However, for pN0 patients, PCI did not significantly benefit OS, necessitating a cautious and individualized approach based on each patient's risk profile. To the best of our knowledge, this study represents the largest meta-analysis to date on PCI in postoperative SCLC patients.

The benefit of PCI for postoperative early stage SCLC patients remains a matter of debate. Some retrospective studies indicated that PCI could extend OS and reduce the incidence of brain metastases [3, 8–14], while others did not show a significant benefit in OS [15, 16]. In addition, in patients with pN0, most studies have not shown an OS benefit from postoperative PCI [10–13, 15], which is not consistent with the current guideline recommendations. This controversy underscores the need for precise research that evaluates the benefit of PCI in postoperative SCLC patients across different subgroups.

A previous meta-analysis indicated that PCI improved OS in postoperative SCLC patients (HR: 0.52, 95% CI: 0.33–0.82) [17]. However, no significant OS benefit was observed for stage I patients (HR: 0.87, 95% CI: 0.34–2.24). This previous study included only a small number of studies, with three studies assessing OS in both the overall population and stage I patients, resulting in considerable heterogeneity. In contrast, our meta-analysis included 13 retrospective studies, with data from 12 studies used to assess OS in all postoperative SCLC patients and with significantly reduced heterogeneity. The larger sample size also enabled us to conduct subgroup analyses for pN0 and pN + patients, providing a definitive answer regarding the benefit of PCI for postoperative pN + patients for the first time. Regarding brain metastasis prevention, the previous meta-analysis indicated that PCI significantly reduced the risk of brain metastasis (RR: 0.50; 95% CI: 0.32–0.78). However, each retrospective study had varying follow-up durations, which were not accounted for when using RR as an effect measure. In contrast to this approach, our analysis utilized HR as an effect measure to compare BMFS between groups—providing a more comprehensive understanding considering both time and risk differences.

Our study has several limitations. Most notably, all included studies are based on retrospective data, which limits the reliability of our conclusions. For patients with pN+, more specific staging data (e.g., pN1 vs. pN2) was not available, which prevented a more precise stratification to evaluate the benefits of PCI for different subgroups within the pN + category. When assessing BMFS, existing retrospective studies did not provide separate BMFS benefit data for pN0 and pN + subgroups; thus, we could only evaluate the overall population's BMFS benefit. Additionally, variations in radiotherapy techniques and doses can affect patient outcomes, but some of the studies we included lacked detailed information on the radiotherapy techniques and dosages used. Therefore, further high-quality prospective studies are needed to confirm the reliability of our conclusions.

Conclusion

Our meta-analysis revealed that PCI significantly improved OS and BMFS in the resected early stage SCLC patients, particularly in those with pathologically node-positive. However, no significant OS benefit was found in patients with pathologically node-negative. Our findings highlight the significant value of PCI in improving survival outcomes for resected early stage SCLC patients, particularly for those with pathologically node-positive.

Abbreviations

PCI	Prophylactic cranial irradiation
SCLC	Small cell lung cancer
HRs	Hazard ratios
OS	Overall survival
BMFS	Brain metastasis-free survival
pN0	Pathologically node-negative
pN+	Pathologically node-positive
LS-SCLC	Limited-stage small cell lung cancer
ES-SCLC	Extensive-stage small cell lung cancer

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-025-02644-5 .

Supplementary Material 1

Author contributions

Conceptualization: DT and ZY; design of methodology: DY and YJ; data collection: EM and SZ; Data Curation: ZZ; writing: DT and ZY; visualization: DT and ZY; modifying and polishing: WZ and YW.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Human ethics and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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