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REVIEW

Survival benefit of prophylactic cranial irradiation in limited-stage small-cell lung cancer in modern magnetic resonance imaging staging: a systematic review and meta-analysis

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ABSTRACT

Background: The use of prophylactic cranial irradiation (PCI) in patients suffering from limited-stage small-cell lung cancer (LS-SCLC) remains controversial in modern brain magnetic resonance imaging (MRI) staging. To this end, a systematic review with meta-analysis was hereby performed to investigate the overall survival (OS) in these patients.

Methods: Relevant studies from the PubMed and EMBASE databases were reviewed, and pooled hazard risks were obtained using fixed-effects models. The PRISMA 2020 checklist was used.

Results: Fifteen retrospective studies were identified, with a total of 2,797 patients with LS-SCLC included in the analysis, 1,391 of which had received PCI. For all included patients, PCI was associated with improved OS [hazard ratio (HR): 0.64, 95% confidence interval (CI): 0.58–0.70]. The combination of subgroup analysis and sensitivity analysis suggested that the effect of PCI on OS was independent of primary tumor treatment, proportion of complete response (CR), median age, PCI dose, publication years, etc. Additionally, the OS curve of 1,588 patients having undergone thoracic radiotherapy (TRT) as the primary tumor treatment from 8 studies were reconstructed, and the pooled 2-, 3- and 5-year OS rates of limited stage patients were 59% vs. 42%, 42% vs. 29% and 26% vs. 19% (HR: 0.69, 95% CI: 0.61–0.77) in the PCI group and the no PCI group, respectively. Another reconstructed OS curve of 339 patients having undergone radical surgery as the primary tumor treatment from 2 studies presented better results, and the pooled 2-, 3- and 5-year OS rates of in the PCI group and the no PCI group were 85% vs. 71%, 70% vs. 56% and 52% vs. 39% (HR: 0.59, 95% CI: 0.40–0.87), respectively.

Conclusions: This meta-analysis demonstrates a significant beneficial effect of PCI on the OS in patients with LS-SCLC in modern pretreatment MRI staging. However, considering the absence of a strict follow-up of brain MRI recommended by the guideline for the control group from most of the included studies, the superiority of PCI to the treatment strategy of no PCI plus brain MRI surveillance remains unclear.

Abbreviations: PCI: prophylactic cranial irradiation; LS-SCLC: limited-stage small-cell lung cancer; MRI: magnetic resonance imaging; OS: overall survival; HR: hazard ratio; CI: confidence interval; OS: overall survival; CR: complete response; TRT: thoracic radiotherapy; Chemo-RT: chemo-radiotherapy; EP: etoposide and cisplatin; TRT: thoracic radiation therapy; 18F-FDG PET-CT: 18F-fluorodeoxyglucose positron emission computed tomography; NCCN: National Comprehensive Cancer Network; K-M: Kaplan-Meier; EQD2: Equivalent Dose in 2 Gy/f; SWOG: South West Oncology Group; EORTC: European Organization for Research and Treatment of Cancer

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Introduction

Small cell lung cancer (SCLC) is a neuroendocrine tumor highly-associated with smoking, accounting for about one-seventh of all lung cancers [1]. Besides, about one-third of the patients are initially diagnosed with limited-stage disease and receive comprehensive treatment with the potential to cure. However, few significant change has been made to the treatment regimen for chemo-radiotherapy (Chemo-RT) sensitive limited-stage small cell lung cancer (LS-SCLC) over the past 20 years. A recent open-label, randomized, phase II study [2] by Grønberg et al. presented a 2-year OS in the 60 Gy group of 74.2%, better than 48.1% in the 45 Gy group [odds ratio 3.09 (95%CI 1.62–5.89); $p = 0{\cdot}0005$]. Generally speaking, in addition to concurrent thoracic radiation therapy (TRT), the combination of 4–6 cycles of etoposide and

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cisplatin (EP) chemotherapy is considered the standard treatment for the disease, followed by prophylactic cranial irradiation (PCI). Nonetheless, long-term outcomes for this patient group have been improved with the median survival period approaching 25–30 months, and currently, approximately one-third of patients can survive another 5 years [3–4], which is partly attributed to the use of brain magnetic resonance imaging (MRI) and positron emission tomography with 18 F-fluorodeoxyglucose positron emission computed tomography (18 F-FDG PET-CT), advances in radiation therapy planning, and better supportive care.

Patients with LS-SCLC are still subject to a high tendency of recurrence and metastasis after initial treatment, while brain metastases are a common pattern of recurrence and metastasis in SCLC patients. About 50%-60% of the patients will develop brain metastases within 2 years after diagnosis [5], and approximately 45% achieving complete response (CR) to initial therapy will develop BMs as the only relapse [6]. A meta-analysis in 1999 confirmed that PCI significantly reduced intracranial metastases and improved the 3-year survival by 5.4% in SCLC patients, especially those with limited-stage diseases [7], which was thus recommended by the National Comprehensive Cancer Network (NCCN) guidelines for LS-SCLC patients after comprehensive treatment. In previous meta-analyses, however, advanced imaging examinations such as pretreatment brain MRI and PET-CT were not extensively used; etoposide or irinotecan combined with platinum was not admitted to the first-line regimen; and precise radiotherapy was not rather pervasive. The initial stage and final curative effects of these patients were greatly affected, making the aforementioned findings slightly controversial, among which, the efficient applicability of PCI in the modern era of MRI is a heated contention point [8–16]. The results of the above five studies [8,10,12,13,15] suggest that PCI fails to significantly prolong the OS of patients with LS-SCLC in modern pretreatment MRI staging.

In the absence of a meta-analysis specifically examining whether PCI improves the OS of LS-SCLC patients in the MRI era, this meta-analysis was hereby conducted to investigate the pooled OS data in LS-SCLC patients having undergone pretreatment brain MRI and to reconstruct the survival curves.

Methods

Literature review

Relevant studies from PubMed and EMBASE databases from 1978 to August 2022 were carefully reviewed using the search terms, including "whole brain irradiation or wbrt or whole brain radiotherapy or cranial irradiation or prophylactic cranial or pci or prophylactic brain or prophylactic cerebral or whole brain radiation", "small cell lung cancer or sclc or oat cell lung or small cell lung carcinoma", and "overall survival or mortality" (Supplementary Table 1). The present literature review was limited to studies in English, and references in the identified publications were also reviewed for more relevant studies. The screening protocol is shown as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Figure 1). Disagreements between researchers were resolved through discussion amongst them and consultation with another author (Bin, Shen).

Inclusion criteria

Studies included for meta-analysis should meet the following criteria: 1) All patients included were diagnosed with LS-SCLC; 2) There were pretreatment brain MRI data of all patients available to ensure no brain metastases; 3) OS was included in the endpoints; 4) Quantitative data on the effect of PCI on the endpoints could be obtained.

Studies included for survival reconstruction should meet the following criteria: 1) The above inclusion criteria were satisfied; 2) The K-M overall survival curve should contain censored values or numbers at risk; 3) Each study included in the study had a high homogeneity, and there should be no obvious bias between different studies that seriously affects the overall survival rate; Actually, patients received thoracic radiotherapy (TRT) or radical surgery rather than both as the primary treatment in survival reconstruction. 4) There should be no other reasons for the inclusion of the study that leads to the inability of researchers to reconstruct the survival curve, such as technical reasons.

Data extraction

Information including author's name, publication year, primary tumor treatment, proportion of CR, proportion of male, proportion of smoking history, proportion of stage III, patient number, median age, median follow-up time, restaging brain scan and PCI dose was extracted from each included article. For survival analysis, hazard ratio (HR) was taken as the most proper statistic for the analysis of the time-event outcomes, with both the number and timing of events taken into consideration. Thus, the multivariable adjusted HR with its 95% confidence interval (CI) was extracted from each original study. Data extraction was done independently by two authors, and disagreements were resolved by cross-checking of each researcher.

Statistical methods

The heterogeneity across studies was evaluated using the Cochran's Q and I^2 statistics, and $p < 0.10$ was considered statistically significant [17]. In the case, the random effects model was used to pool the individual HR estimates. Otherwise, the fixed-effects model would be employed [18]. Publication was investigated using the Egger test, with $p < 0.1$ considered statistically significant [19], and meta-analysis of HRs and sensitivity analysis were performed using STATA16.0 software (Stata Corporation, College Station, TX, USA). To reconstruct the survival curves, the survival rates corresponding to each year in the survival curves of each study were extracted using the GetData Graph Digitizer software, and the obtained data were saved to an excel sheet. The reconstruction of the

survival curve was accomplished in the excel, and the weight of each study was determined by the annual number of patients in that study, with the number of censored patients taken into account. Based on the total number of patients, the survival rates each year (extracted by the curve data extraction software or found in the original text), and the censored value each year (extracted by the manual counting of the investigator), the patient number at risk under the K-M survival curve of some studies can be roughly calculated.

Results

Study selection and patient characteristics

A total of 15 retrospective studies [8,10–16,20–26] on the effect of PCI on the OS of LS-SCLC in the pretreatment brain MRI era were hereby included. Figure 1 and Table 1 present the study selection and the main characteristics of the included studies, respectively.

The patient number of different studies ranged from 49 to 658. All patients were diagnosed with LS-SCLC and had

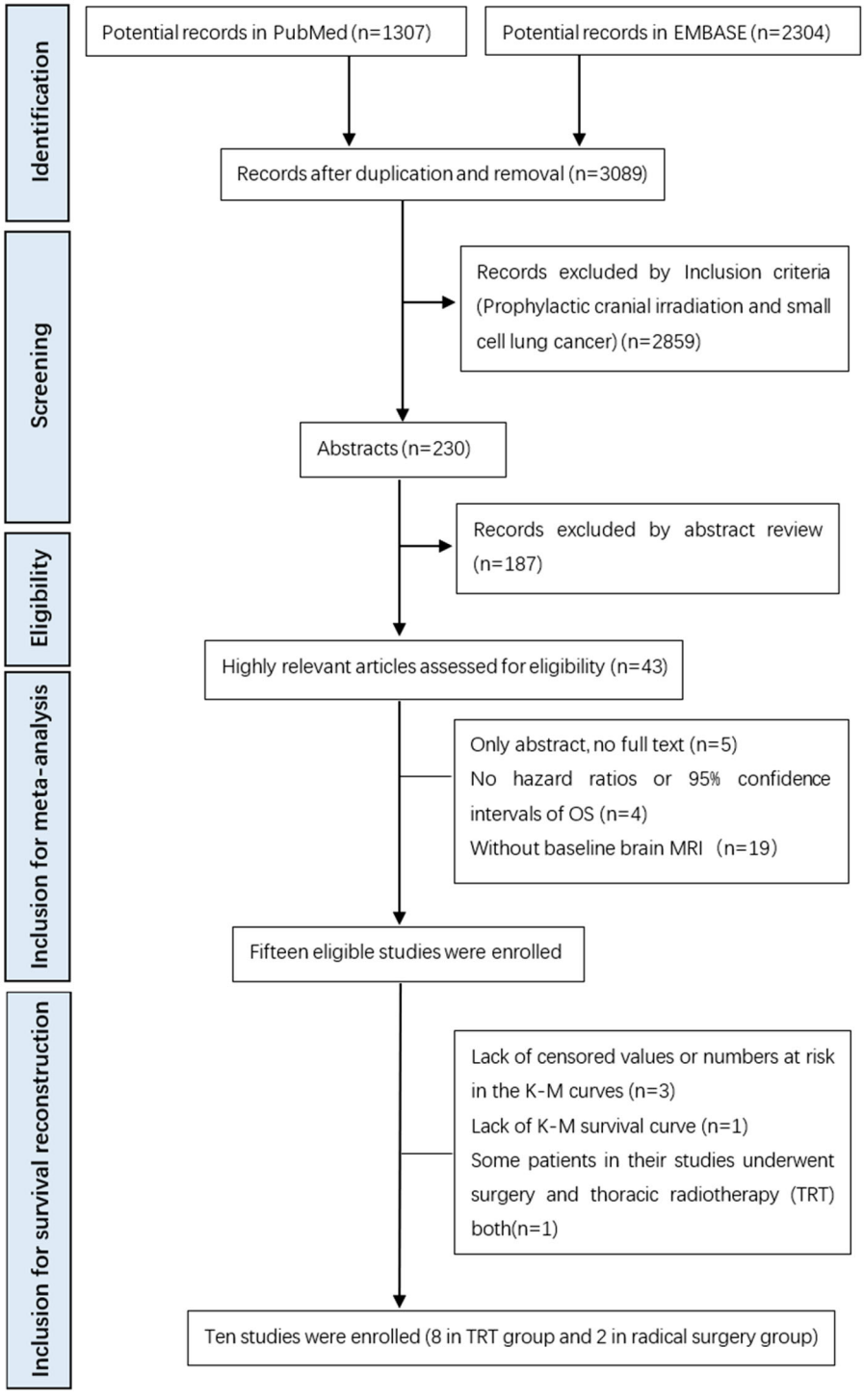

Figure 1. Flow chart of literature search in the meta-analysis.

Table 1. Characteristics of the included trials in the meta-analysis.

Study, y	Median age, y	Patients, *n*		Male, %		Complete response (%)		Proportion of stage III (%)	Primary therapy	PCI schedule (Gy/fraction)	Restaging brain scan	Median FU (months)
		PCI	No PCI	PCI	No PCI	PCI	No PCI					
Farris, 2019 [8]	NR	39	53	10 (26.0)	28 (53.0)	12 (30.8)	17 (32.1)	67.0	TRT	25Gy/10F	no routine	NR
Lim, 2022 [16]	68	26	81	22 (84.6)	69 (85.2)	NR	NR	NR	Both	25–37.5 Gy in 1.5–3Gy	NR	NR
Pezzi, 2020 [10]	66	84	84	49 (58.3)	47 (56.0)	27 (71.1)	35 (53.8)	NR	TRT	25–30Gy/10–15F	yes	84
Qi, 2022 [15]	<65	75	75	11 (14.7)	59 (78.7)	16 (21.3)	8 (10.7)	68.0	TRT	25Gy/10F	yes	25
Li, 2021 [11]	<70	69	69	50 (75.3)	51(65.5)	29 (42.0)	21(30.4)	76.1	TRT	25Gy/10F	yes	17.8
Ghanta, 2021 [13]	66	83	83	32 (38.6)	31 (37.3)	23 (27.7)	22 (26.5)	75.1	TRT	25–36Gy/10–18F	yes	21.3
Eze, 2017 [14]	63	71	113	36 (50.7)	75 (66.4)	NR	NR	NR	TRT	30Gy/15F	yes	NR
Zhu, 2014 [23]	55	67	126	49(73.1)	101 (80.2)	NR	NR	52.3	Surgery	25Gy/10F	no routine	39.4
Farooqi, 2017 [25]	62	364	294	187(51.4)	155 (52.7)	NR	NR	NR	TRT	25Gy/10F	NR	21
Korczynska, 2018 [21]	60	167	104	103(61.7)	71 (68.3)	Total, 172 (63.5)		NR	TRT	30Gy/15F	yes	33.2
Yin, 2018 [24]	<60	88	52	Total, 81(57.9)		NR	NR	72.9	Both	30–40Gy in 2–3Gy	NR	30
Kim, 2019 [26]	61	139	95	123(88.5)	81 (85.3)	Total, 126 (53.8)		77.2	TRT	25Gy/10F	NR	22
Jeong, 2020 [20]	64	45	56	Total, 88(87.1)		Total, 62 (61.4)		84.2	TRT	25Gy/10F	NR	27
Lou, 2020 [22]	63	46	100	40 (87.0)	88 (88.0)	NR	NR	NR	Surgery	NR	NR	28
Held, 2021 [12]	63 ~ 65	28	21	12 (43)	11 (52)	NR	NR	NR	TRT	25Gy/10F	no routine	26–33

PCI: prophylactic cranial irradiation; FU: follow-up; TRT: thoracic radiotherapy; NR: not reported.

undergone pretreatment brain MRI. The median age of the patients in the included studies ranged from 55 to 68 years old, but was not reported in 3 studies. The stage III proportions ranged from 52.3% to 84.2%, not reported in 7 studies. The primary tumor treating approach was surgery alone in 2 studies, surgery and thoracic chemoradiotherapy in 2 studies, and thoracic chemoradiotherapy alone in the remaining 11 studies. The PCI dose [Equivalent Dose in 2 Gy/f (EQD2),α/β10] was 26 Gy in 8 studies, over 26 Gy in 3 studies, not reported in the remaining 4 studies. Post-treatment restaging brain scans were performed in all patients in 6 studies, but were not mentioned or routinely performed in the remaining 9 studies. The median follow-up time $\geq$ 24 months was reported in 8 studies,<24 months in 4 studies, and not reported in 3 studies.

Effects of PCI on OS in the pretreatment brain MRI

Data on 2-year and median OS estimates are presented in Table 2. The weighted mean 2-year OS was 59.8% vs. 42.0% after PCI vs. no-PCI. The mean estimate across studies for the median OS, weighted for the study sample size, was 55.0 vs. 24.0 months for the PCI group vs. the no-PCI group. Combined analysis of the total patients by fixed-effects model revealed that the pooled HR for OS based on 15 studies was 0.64 (95% CI: 0.58–0.70), featuring a low heterogeneity (I^2=24.9%, P-heterogeneity = 0.179), which indicated the efficiency of PCI in significantly improving the OS in patients with LS-SCLC in the pretreatment brain MRI (Figure 2).

Subgroup analyses

Subgroup analyses were carried out to explore the heterogeneity in the OS analysis (Table 3), and those for OS were performed by taking into account factors including primary tumor treatment, proportion of CR ($\geq$50% vs. <50%), median age ($\geq$65 years vs. <65), publication years (>2018 vs. $\leq$2018), restaging brain scan (yes vs. no routine or not reported), PCI dose (26 Gy vs. >26Gy), proportion of males ($\geq$60% vs. <60%), proportion of smoking history (<80% vs. $\geq$80%) and proportion of stage III (<75.0% vs. $\geq$75.0%). Statistically significant difference in pooled HR estimates was observed in 7 studies, with male patients accounting for over 60% vs. 5 studies with male patients taking up less than 60% (i.e. pooled HR 0.53 vs. 0.74, respectively, $p = 0.002$, as shown in Figure 3). This subgroup stratification occupied 33.0% of the overall heterogeneity. No statistically significant differences were identified in pooled HRs between other subgroups of studies, i.e. those based on primary tumor treatment, proportion of CR, median age, etc.

Pooled OS curve of 10 studies (8 in TRT group and 2 in radical surgery group)

After carefully reviewing 15 studies, 3 [11,20–21] were excluded due to the lack of censored values or numbers at risk in the K-M curve; Considering the existence of only the K-M survival curve for the surgical subgroup other than the

Table 2. Overall survival (OS) outcomes and adjusted hazard ratios (HR) of included studies.

Study, year	2-year OS PCI (%)	2-year OS No-PCI (%)	Median OS PCI (M)	Median OS No-PCI (M)	Adjusted HR (95% CI)
Farris, 2019 [08]	74.0*	52.7*	37.9	30.5	0.61 (0.36–1.05)
Lim, 2022 [16]	50.0	29.0	23.4	13.9	0.41 (0.22–0.77)
Pezzi, 2020 [10]	56.7*	52.8*	30.5*	25.0*	0.79 (0.56–1.11)
Qi, 2022 [15]	66.7*	57.4*	35.0	28.0	0.76 (0.53–1.08)
Li, 2021 [11]	69.1*	44.2*	35.3*	20.1*	0.42 (0.25–0.70)
Ghanta, 2021 [13]	62.3	50.0	35.0	25.0	0.74 (0.49–1.11)
Eze, 2017 [14]	53.0*	18.7*	26.0	14.0	0.53 (0.38–0.73)
Zhu, 2014 [23]	92.5	63.2	NR	NR	0.43 (0.26–0.71)
Farooqi, 2017 [25]	56.9	43.8	27.0*	20.3*	0.76 (0.63–0.91)
Korczynska, 2018 [21]	49.2*	23.3*	26.0	14.0	0.56 (0.42–0.74)
Yin, 2018 [24]	NR	NR	NR	NR	0.64 (0.43–0.95)
Kim, 2019 [26]	59.1	35.9	29.8*	14.7*	0.54 (0.38–0.77)
Jeong, 2020 [20]	NR	NR	NR	NR	0.53 (0.33–0.84)
Lou, 2020 [22]	71.4*	71.2*	49.7*	43.9	0.95 (0.52–1.75)
Held, 2021 [12]	74.6*	47.6*	55.0	24.0	0.51 (0.21–1.28)
Weighted mean	59.8	42.0	30.1	20.7	–

CI: confidence interval; M: months. *Extract data from Kaplan-Meier survival curves by data extraction software.

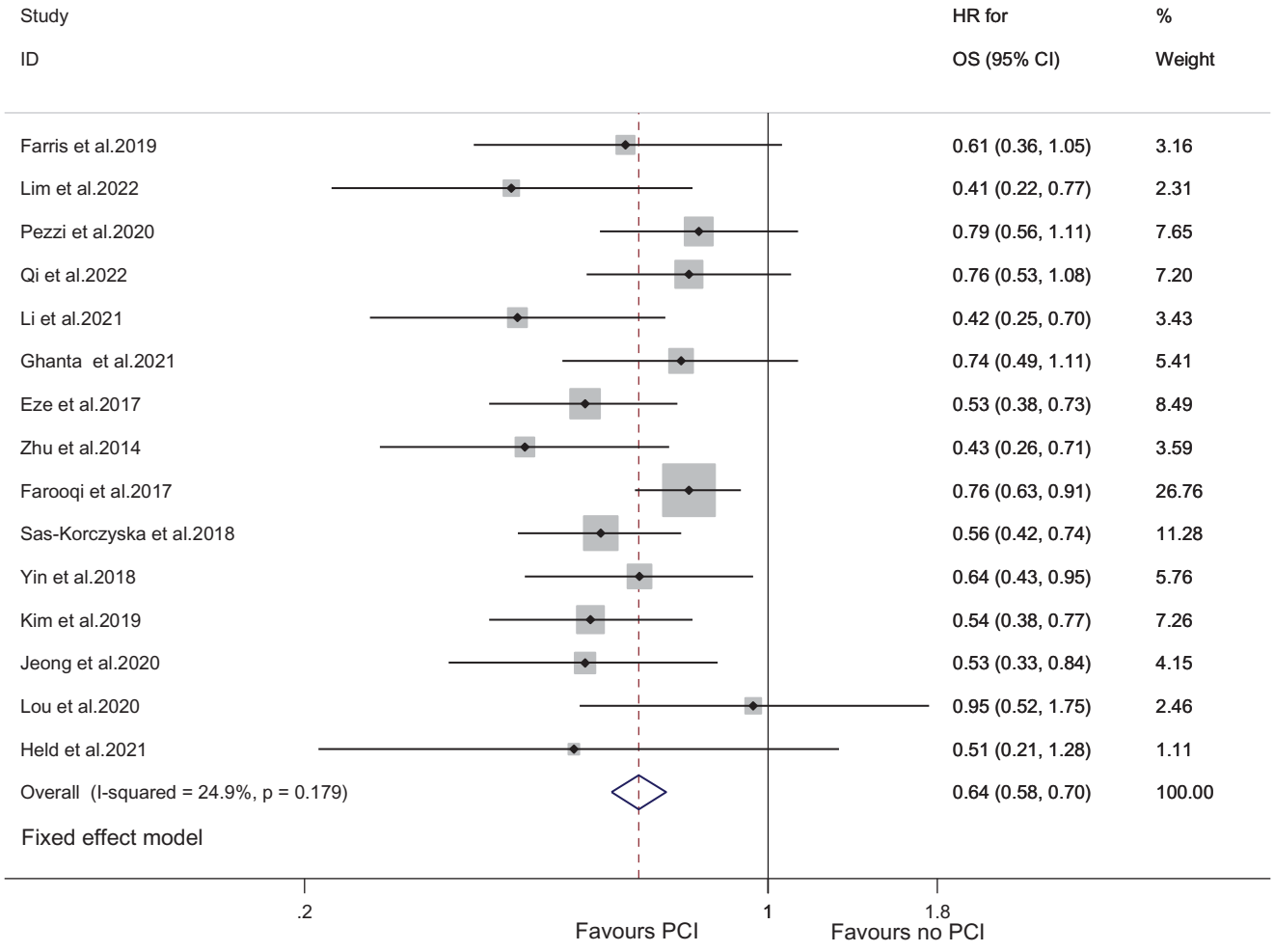

Figure 2. Forest plot of HR for OS in the era of pretreatment Magnetic Resonance Imaging (MRI) staging for patients with limited-stage small-cell lung cancer (LS-SCLC) with and without PCI.

whole group, the study by Yin et al. [24] was excluded. The study by Lim et al. [16] where some patients underwent both surgery and TRT was also excluded. Besides, it is noteworthy that the 1-year OS data from the study by Farooqi et al. [25] was not included for technical reasons.

Finally, 10 studies (8 in TRT group and 2 in radical surgery group) were included in the reconstructed survival curves, where all patients underwent TRT and radical surgery as the primary tumor treatment, retrospectively. The pooled HR for OS of the TRT group was 0.69 (95% CI: 0.61–0.77), presenting a low heterogeneity (I^2=0.2%, P-heterogeneity = 0.427, Figure 4(A)), and the pooled 2-, 3-, 5-year OS and the median OS time of LS-SCLC patients in the PCI group and the no-PCI group were 59% vs. 42%, 42% vs. 29%, 26% vs. 19% and 2.47 vs. 1.63 years, respectively (Figure 4(B)), while the pooled 2-, 3-, 4-, 5-year OS and the median OS time for the total

Table 3. Subgroup analyses of the overall survival.

Subgroups	*N* studies	Pooled HR (95% CI)	P value (Heterogeneity between subgroups)	I^2
Primary tumor treatment			0.680	24.9%
Surgery	2	0.59 (0.40–0.87)		
TRT	11	0.62 (0.59–0.72)		
Both	2	0.56 (0.40–0.79)		
Proportion of CR			0.545	7.8%
≥50%	5	0.60 (0.51–0.71)		
<50%	4	0.65 (0.53–0.81)		
Median age (years)			0.520	24.6%
≥65	3	0.70 (0.55–0.89)		
<65	10	0.64 (0.57–0.71)		
Publication years			0.931	24.9%
>2018	10	0.64 (0.55–0.73)		
≤2018	5	0.64 (0.56–0.73)		
Restaging brain scan			0.726	24.9%
Yes	6	0.63 (0.54–0.72)		
No routine or NR	9	0.65 (0.57–0.74)		
PCI dose ($EQD2_{\alpha/\beta}10$)			0.257	22.3%
26Gy	8	0.65 (0.57–0.73)		
>26Gy	3	0.57 (0.47–0.68)		
Proportion of male			0.002	33.0%
≥60%	7	0.53 (0.45–0.62)		
<60%	5	0.74 (0.64–0.85)		
Proportion of smoking history			0.113	28.6%
<80%	4	0.53 (0.42–0.67)		
≥80%	4	0.70 (0.54–0.91)		
Proportion of stage III			0.453	0%
<75.0%	4	0.63 (0.51–0.78)		
≥75.0%	4	0.56 (0.45–0.69)		

N: number; HR: hazard radio; CI: confidence interval; TRT: thoracic radiation therapy; CR: complete response; NR: not reported; EQD2: Equivalent Dose in 2 Gy/f.

group were 53%, 37%, 28%, 24% and 2.17 years, respectively. The pooled HR for the OS of the radical surgery group was 0.59 (95%CI: 0.40–0.87), presenting a high heterogeneity (I^2=74.3%, P-heterogeneity = 0.049, Figure 4(A)), and the pooled 2-, 3-, 5-year OS and the median OS time of LS-SCLC patients in the PCI group and the no-PCI group were 85% vs. 71%, 70% vs. 56%, 52% vs. 39% and 3.45 vs. >5 years, respectively (Figure 4(C)), while the pooled 2-, 3-, 4-, 5-year OS and the median OS time for the total group were 77%, 62%, 50%, 44% and 4.11 years, respectively. Data required for the reconstructed survival curve are presented in Supplementary Table 2.

Sensitivity analysis and publication bias

With one study excluded and the rest analyzed, sensitivity analysis showed that the pooled HR for OS did not change significantly, which justifies the reliability of the present results (Supplementary Figure A). Besides, no evidence of publication bias was observed in this meta-analysis using Egger's ($p = 0.076$) tests (Supplementary Figure B).

Discussion

The findings of earlier meta-analyses [7,27,28] revealed the efficiency of PCI in improving the survival rate in LS-SCLC, in accordance with which, PCI is still considered a standard care approach for patients with LS-SCLC who are responsive to thoracic chemoradiotherapy, or stage II-III patients with radical resection [29]. However, patients in some studies included in the previous analysis did not undergo either pretreatment brain MRI examinations or appropriate frequency of subsequent brain MRI monitoring [30]. The detection rate of brain metastases from small cell lung cancer was different in the CT and the MRI era, i.e. 10–18% and 24%, respectively [31]. Brain metastases were detected in 13/40 patients in a single-center study involving 40 consecutive patients with limited-stage small-cell lung cancer who had a complete response to chemoradiotherapy and underwent pre-PCI brain MRI [32]. This indicated that some patients who did not undergo brain MRI might have developed occult brain metastases before or during treatment, thereby possibly exaggerating the benefits of PCI. Lacking mature prospective studies as the confirmation, the advances in diagnostic techniques and the increased sensitivity of MRI in detecting brain metastases make it unclear whether PCI improves the overall survival in patients with LS-SCLC compared with MRI surveillance. However, data from a previous study conducted from the Japanese prospective showed that PCI did not significantly improve the overall survival in extensive stage small-cell lung cancer compared with regular brain MRI monitoring (median overall survival 11.6 months vs. 13.7 months in the PCI group and the no PCI group, HR 1.27, 95% CI 0.96–1·68; $p = 0.094$) [33], which also aroused extensive academic reflection in the field of radiation oncology upon the possibility of replicating this finding in LS-SCLC. However, it is difficult to conduct brain MRI surveillance in the clinical practice of small cell lung cancer, which is mainly attributed to the following possible reasons: First, intensive brain MRI is expensive, especially for the developing world; Second, for most countries, each intensive brain MRI and appointment is rather time-consuming; Moreover, according to the NCCN guidelines, brain MRI should be

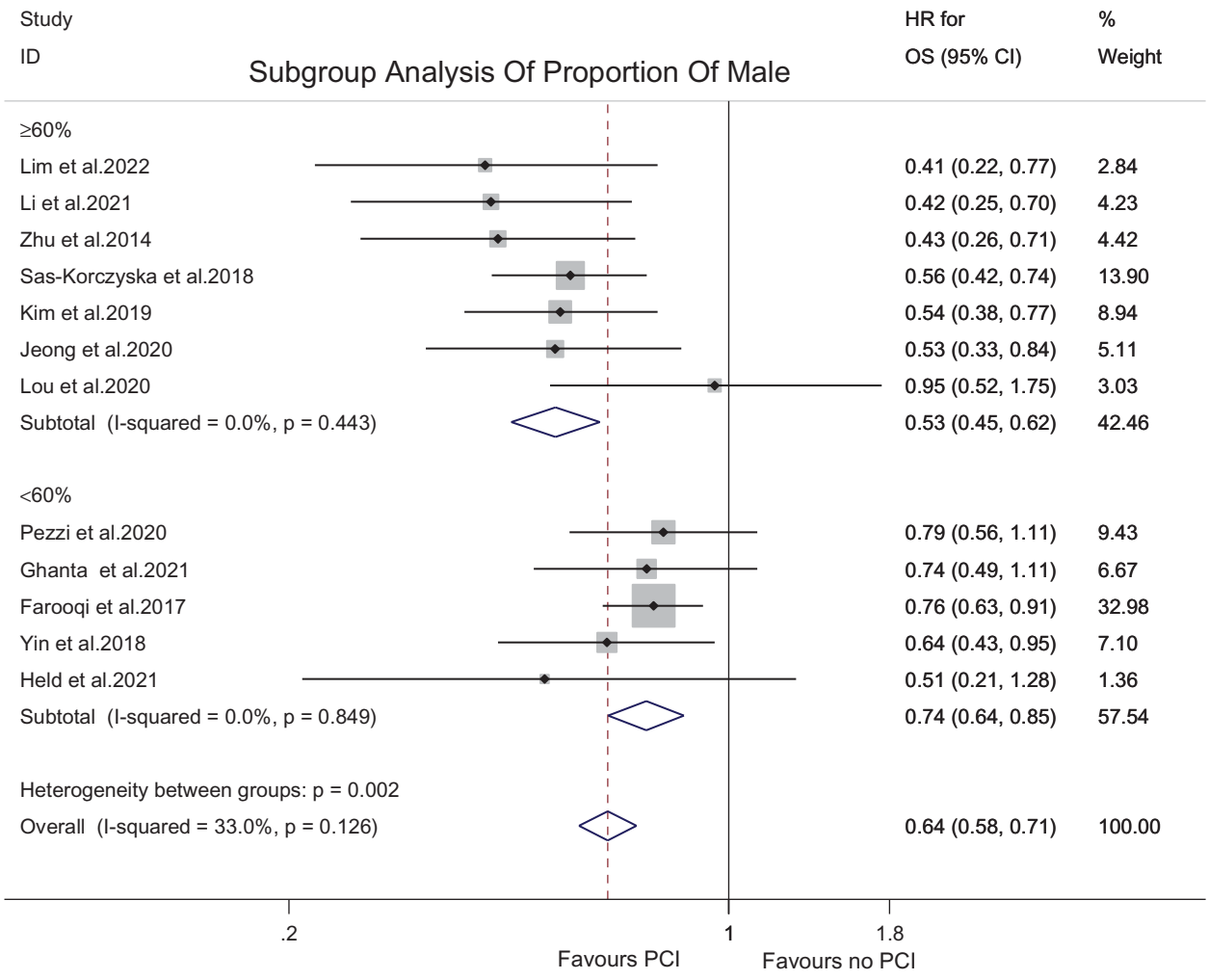

Figure 3. Subgroup analysis for OS according to the male proportion.

conducted every 3–4 months in the first year after the treatment of LS-SCLC, which is a high frequency for most patients.

In a recent retrospective study involving 168 LS-SCLC patients having undergone pretreatment brain MRI, the use of PCI was found not associated with the difference in the overall survival between the patient groups (2-year OS 46 months vs. 42 months in the PCI group and the no PCI group, HR 0.79; 95% CI, 0.56–1.11; $p = 0.17$) [10]. Two other recent retrospective studies included in the present meta-analysis, which covered a similar number of samples and similar designs, also failed to demonstrate the utility of PCI in improving OS in patients with LS-SCLC in the modern MRI era [13,15]. However, the present meta-analysis based on 15 retrospective studies [8,10–16,20–26] demonstrated a pooled HR of PCI vs. no PCI for OS of 0.64 (95% CI: 0.58–0.70), suggesting the efficiency of PCI in significantly improving OS in patients with LS-SCLC in the pretreatment brain MRI. In this case, it is highly recommended to consider PCI an important standard care choice for the LS-SCLC patients responsive to treatment until the emergence of relevant prospective results.

Subgroup analysis showed that studies with a high proportion (≥60%) of male patients had lower estimates of pooled HR for PCI than those with a low proportion (<60%) of male patients (i.e. pooled HRs of 0.53 and 0.74, respectively, $p = 0.002$), indicating that PCI may be more beneficial for OS in male patients.

The hereby reconstructed OS curve (Figure 4(B)) revealed that the median OS time and 3-year OS of LS-SCLC patients in the PCI group were 29.64 months and 42%, rather similar to the data of 29.0 months (95% CI: 25.8–35.7 months) and 45% in the CONVERT Trial [4,34]. However, the median OS in the no PCI group was 19.56 months, higher than 13.9 months (95% CI: 9.5–24.8 months) in the CONVERT Trial [4,34]. Furthermore, the survival rate of the entire large group in the CONVERT study was better than that in this study, with a 5-year survival rate of nearly one-third compared with a rate of 24% in the present study [34].

Meanwhile, this meta-analysis is still exposed to several limitations inherent to the shortcomings of the included studies. Firstly, all included studies had a retrospective design rather than a randomized controlled one, which might lead to confounding and selection bias. Although considerable attempts was made to minimize confounding and selection bias while calculating the HRs in multivariate survival models, only a limited number of studies were adjusted for a few confounders. Secondly, in the selection of patients,

PCI might be merely implemented in patients with effective chemoradiotherapy, instead of those with poor chemoradiotherapy effect, thereby leading to selection bias (that is, the proportion of patients with poor chemoradiotherapy effect in the no PCI group increased, and led to the illusion of poor prognosis in the no PCI group). Finally, the design of the thereby included studies was pretreatment brain MRI with or without PCI rather than entire brain MRI surveillance with or without PCI, so whether the efficacy of entire brain MRI surveillance without PCI on overall survival is non-inferior to that of PCI on LS-SCLC remains to be further explored. Nonetheless, the bias introduced by therapeutic PCI was ruled out in the present study, endowing this very study with critical significance.

Although there is no strong evidence clarifying whether no PCI + MRI surveillance is non-inferior to PCI in terms of the overall survival in limited-stage small cell lung cancer, a number of relevant large randomized controlled trials are still underway. A recently activated phase III noninferiority study (South West Oncology Group, SWOG 1827 aka MAVERICK) was designed to enroll 668 participants, with OS as the primary endpoint, and brain metastasis-free survival, cognitive failure-free survival and toxicity as the secondary endpoints, and compared PCI with MRI surveillance in both LS-SCLC and ES-SCLC (NCT04155034). Another similar ongoing Phase 3 study from China was designed to enroll 534 participants of LS-SCLC, with OS as the primary endpoint, and progression-free survival, brain metastasis rate and cumulative incidence of neurocognitive impairment as the secondary endpoints (NCT04829708). Additionally, European Organization for Research and Treatment of Cancer (EORTC) has recently initiated a similar phase III trial (PRIMALung study), involving 600 ES-SCLC and LS-SCLC patients randomized to MRI surveillance vs. MRI surveillance + PCI (NCT04790253).

Conclusion

In conclusion, the present findings confirm the efficiency of PCI in improving the OS in patients with LS-SCLC in modern pretreatment MRI staging. However, considering the absence of brain MRI surveillance in the control group of most included studies, it remains unclear whether PCI outperforms no PCI + MRI surveillance in dealing with LS-SCLC.

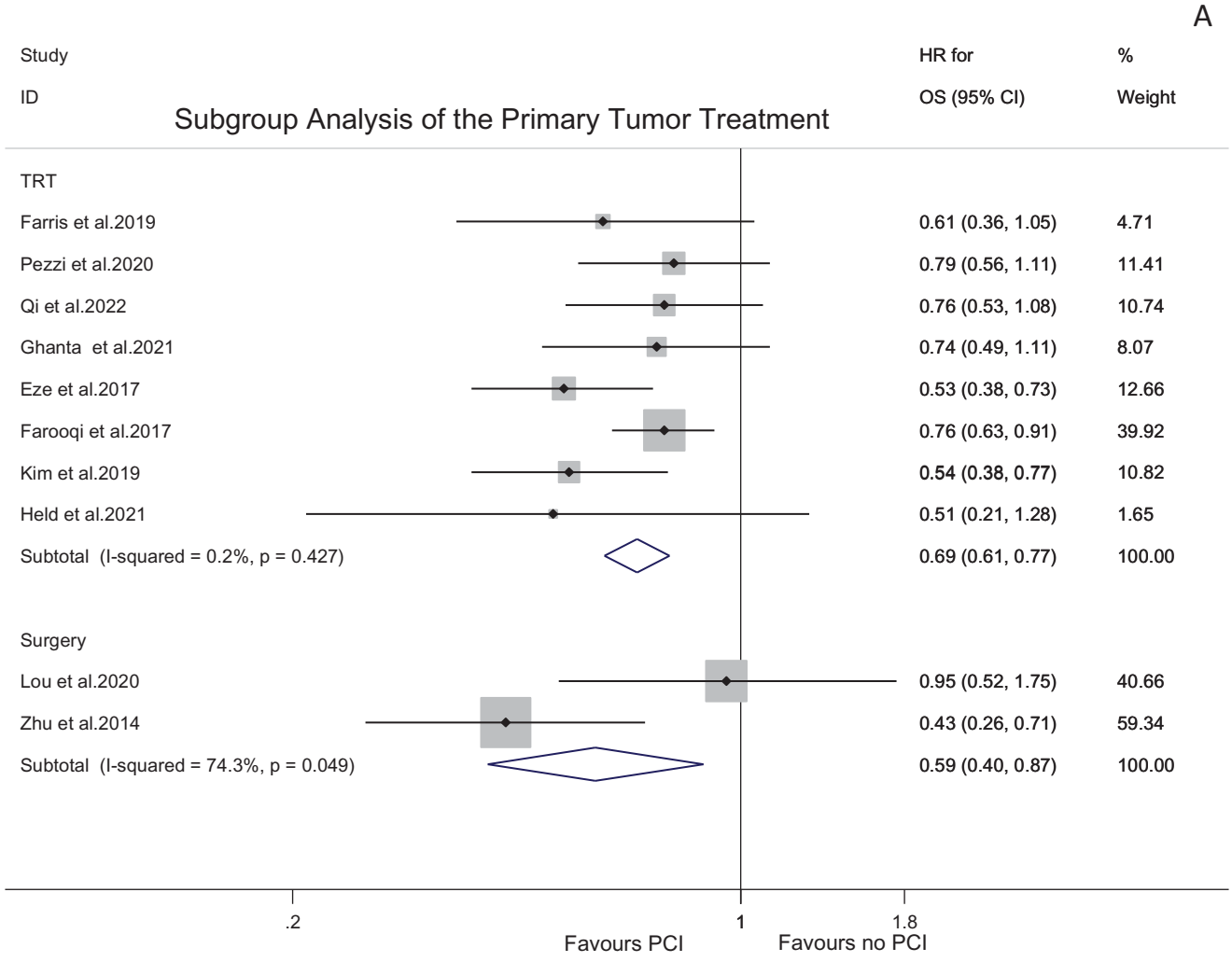

Figure 4. Forest plot of HR for OS (A) and pooled OS curve where all patients underwent thoracic radiotherapy (B) or radical surgery (C) as the primary tumor treatment.

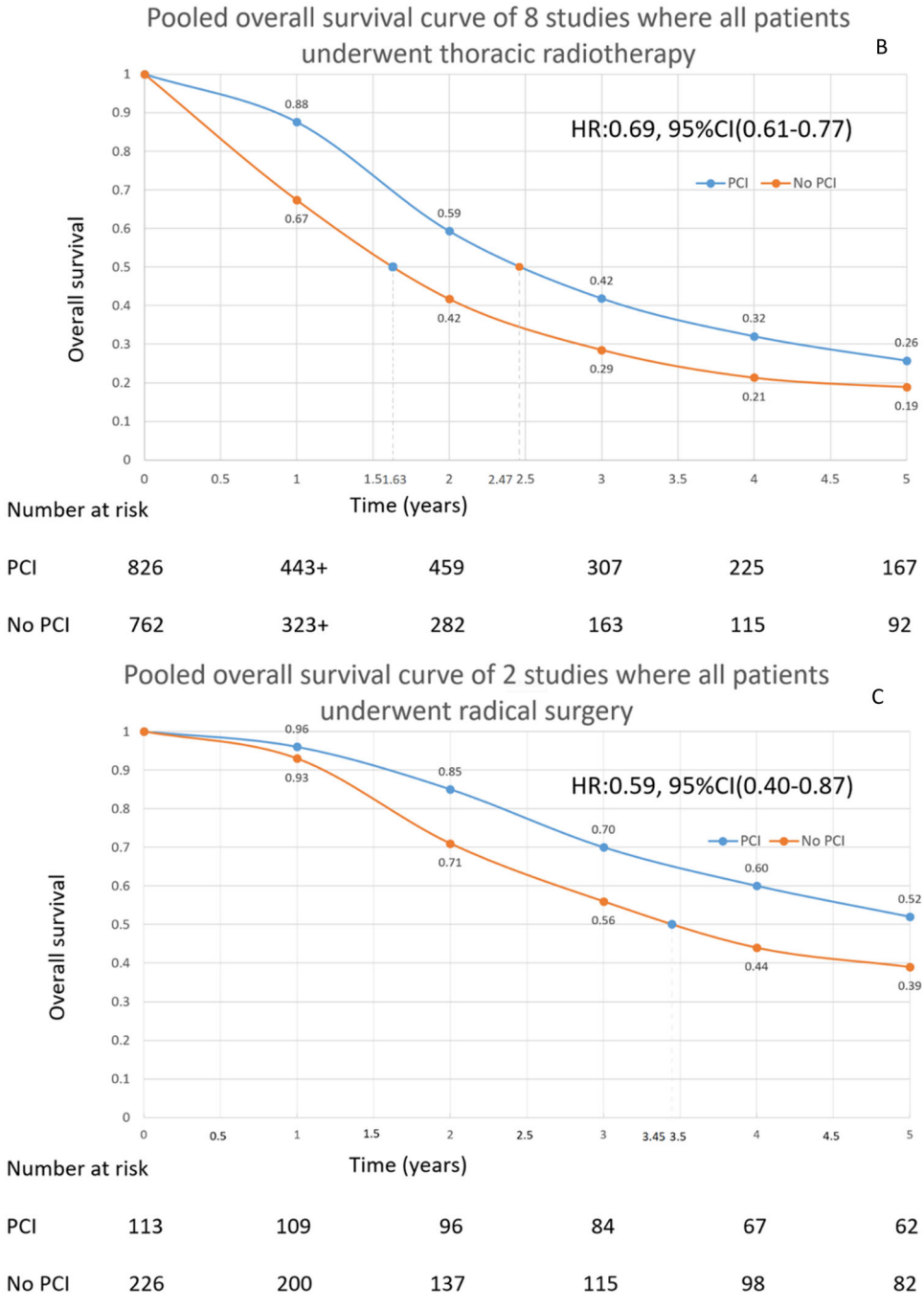

Figure 4. Continued.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Consent for publication

All the authors agreed to publish the article.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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