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Table S1. Full electronic search strategy in EMBASE (Nov 12, 2023).

ID	Search term	Results
1	("small cell lung cancer" or "small-cell lung cancer" or "small-cell lung carcinoma" or "small cell lung carcinoma" or "SCLC").tw,kf.	154842
2	Small Cell Lung Carcinoma/	12126
3	Carcinoma, Small Cell/	10486
4	Lung Neoplasms/	33012
5	3 and 4	1070
6	1 or 2 or 5	159259
7	(("prophyla*" and ("crani*" or "intracrani*" or "brain" or "CNS") and ("radiation" or "irradiation" or "radiotherapy")) or "PCI").tw,kf.	78643
8	Brain Neoplasms/	45489
9	Central Nervous System Neoplasms/	8220
10	exp Brain/	1762478
11	8 or 9 or 10	1805470
12	exp Neoplasm Metastasis/	847214
13	11 and 12	20870
14	exp Lung Diseases/ or exp Lung/	2400069
15	exp Neoplasms/	6045083
16	14 and 15	754089
17	3 and 16	6362
18	6 or 17	163007
19	exp Radiotherapy/	735269
20	13 and 19	6335
21	7 or 20	84680
22	18 and 21	2760

List of included studies

Ago et al., 2002[1]
Ahn et al., 2018[2]
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Alexopoulos et al., 1997[6]
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Primary outcome: overall survival

Subgroup and heterogeneity analysis

Pre-specified subgroup analyses were performed on all included studies as well as separated by studies consisting exclusively of patients with limited and extensive stage small cell lung cancer (Table 1). Meta-regression was performed on publication year, total study sample size, and median age of participants. Neither predictor led to a significant reduction in study heterogeneity when considering all included studies (p=0·09, p=0·8180, and p=0·1516, respectively), or when investigated separately for limited (p=0·6455, p=0·3814, and p=0·08, respectively) or extensive stage patients (p=0·06, p=0·86, and p=0·6451, respectively).

Of all studies included in the primary analysis, 39 studies reported unadjusted hazard ratios from univariable analysis only, 17 studies reported adjusted hazard ratios from multivariable analysis only, and 56 reported findings in unadjusted and adjusted hazard ratios. Post-hoc sensitivity analyses of unadjusted and adjusted hazard ratios only found prophylactic cranial irradiation (PCI) associated with longer survival (unadjusted HR 0·60; 95% CI, 0·55-0·65; p<0·001; n=52,928 patients; adjusted HR 0·59; 95% CI, 0·55-0·64; p<0·001; n=32,879 patients; Figure S1, S2). Further sensitivity analysis where adjusted HRs were substituted for unadjusted HRs also confirmed these findings (HR 0·62; 95% CI, 0·58-0·67; p<0·001; n=105 studies; n=56,770 patients; Figure S3).

Between-study heterogeneity was significant when pooled amongst all studies (I^2=73·6%; 95% CI 68·4%-77·9%). Subgroup analysis did not reveal sources of heterogeneity. Effect size analysis did not identify any individual studies that contributed disproportionally to overall between-study heterogeneity in the overall study cohort (Figure S4) or when focusing exclusively on studies that used brain MRI to exclude presence of brain metastases among all patients (results not shown).

Egger's test did not suggest any evidence of publication bias (intercept -0.342, 95% CI, -1- -0·16, t=-1·414, p=0·160, Figure S5). Results from evaluation of risk of bias are reported (Figure S6, S7).

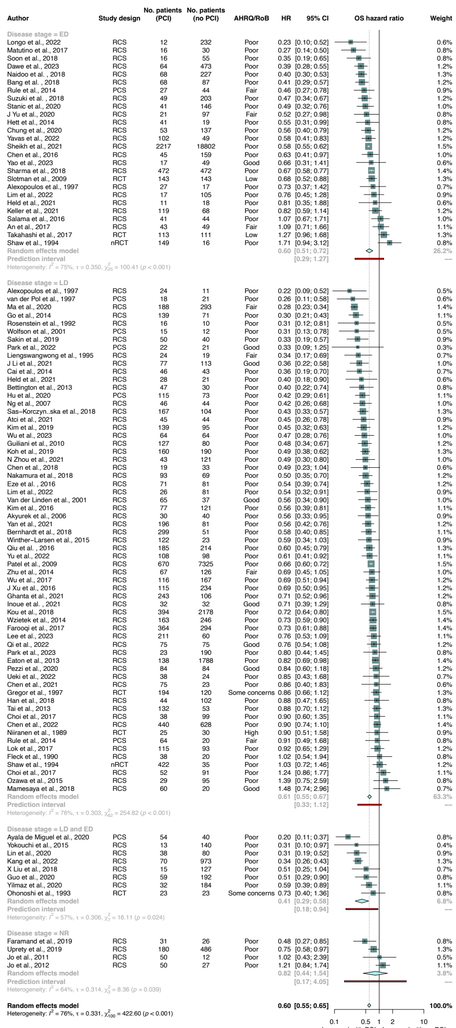


Figure S1. Random-effects meta-analysis of PCI versus no PCI for the primary outcome of overall survival using only unadjusted hazard ratios.

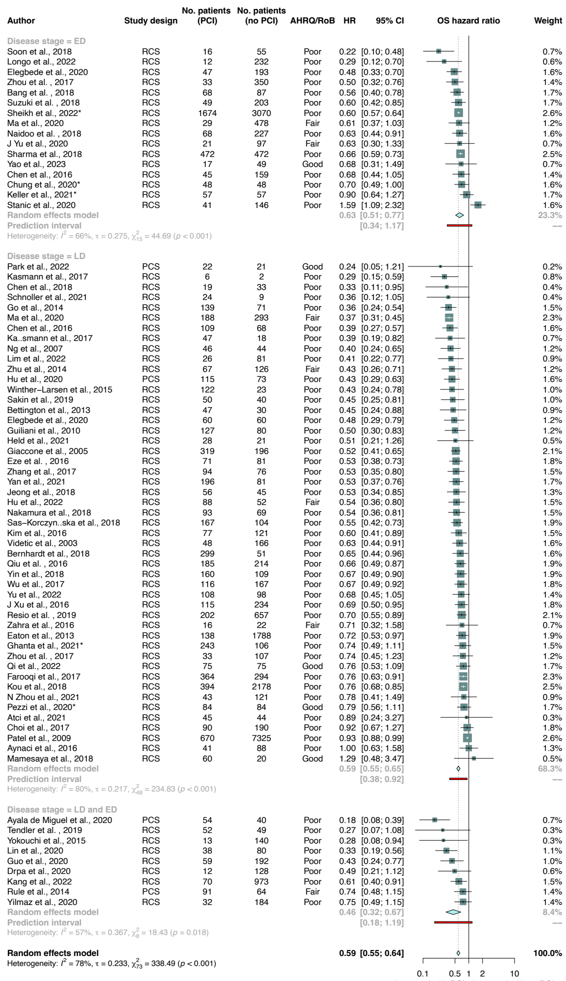


Figure S2. Random-effects meta-analysis of PCI versus no PCI for the primary outcome of overall survival using only adjusted hazard ratios.

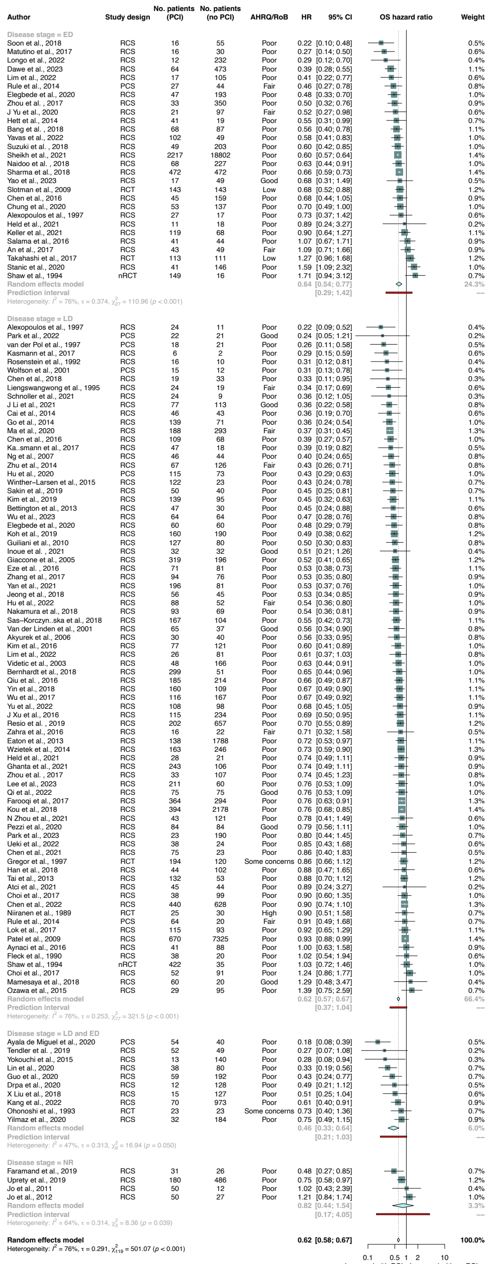


Figure S3. Random-effects meta-analysis of PCI versus no PCI for the primary outcome of overall survival using adjusted instead of unadjusted hazard ratios where available.

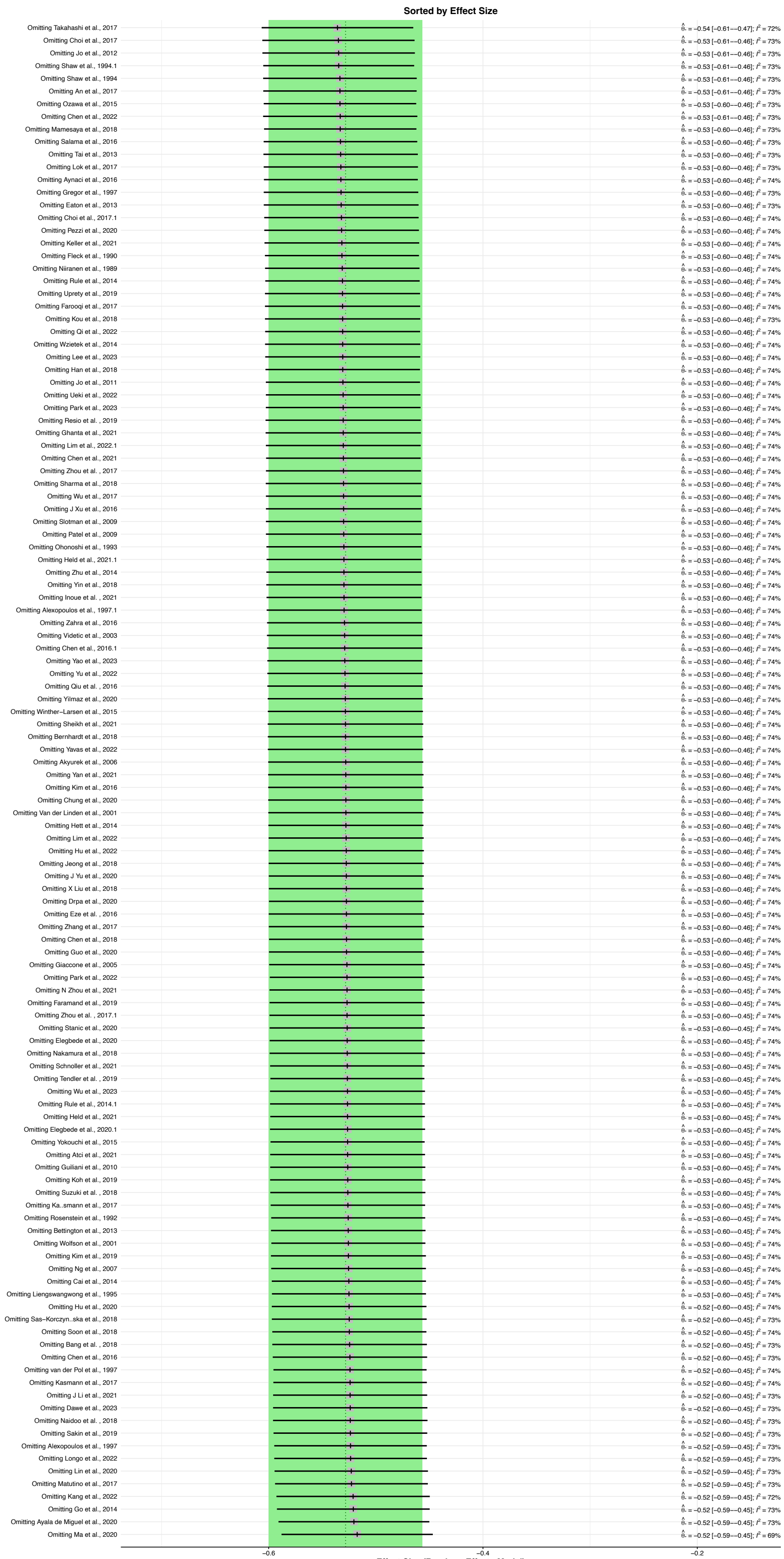

Sorted by Effect Size
−0.6
−0.4
−0.2
Effect Size (Random−Effects Model)

Figure S4. Forest plots for leave-out-one analysis sorted from low to high effect size for the primary outcome of overall survival. The plot shows the recalculated pooled effects, with one study omitted each time. The dashed line and shaded area represent the estimated pooled effect size and the 95% confidence interval of the original meta-analysis, respectively. No substantial changes in heterogeneity or effect size were observed.

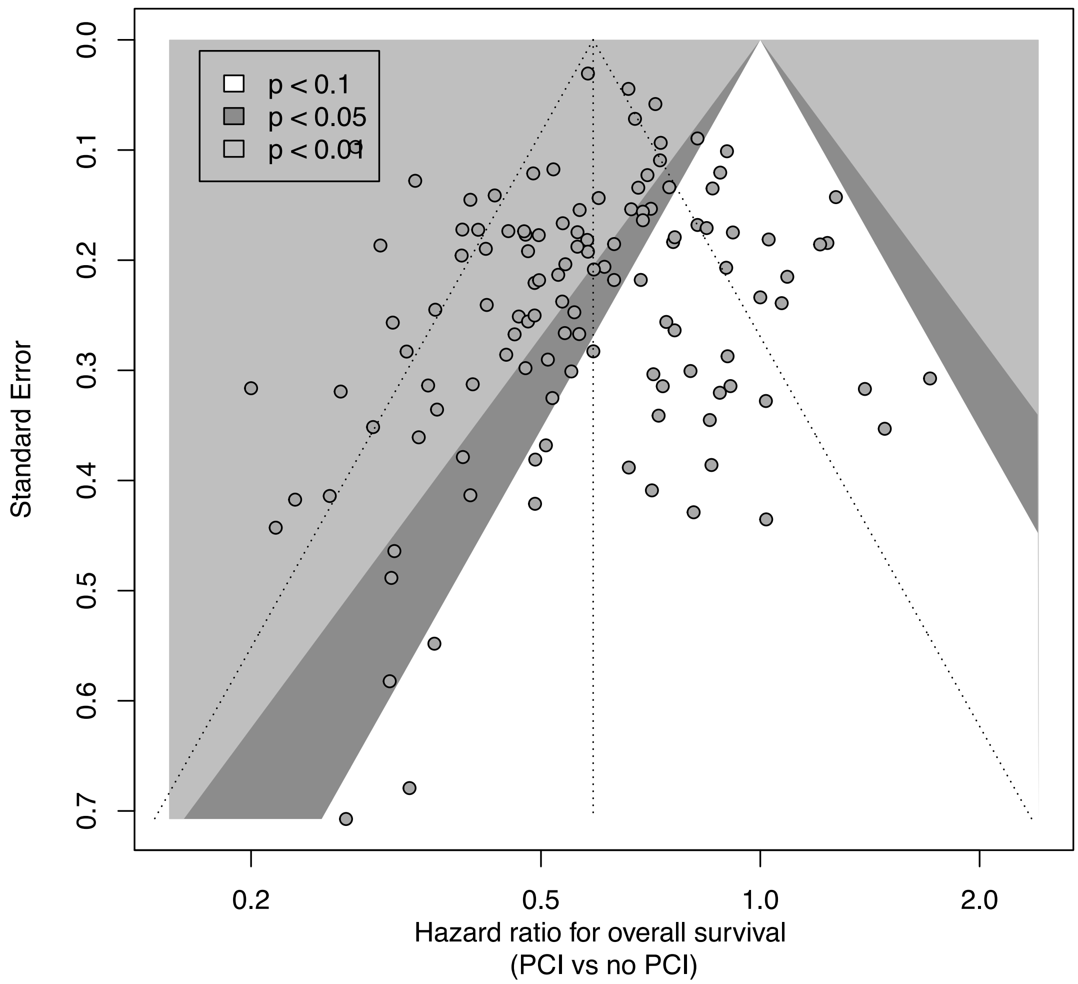
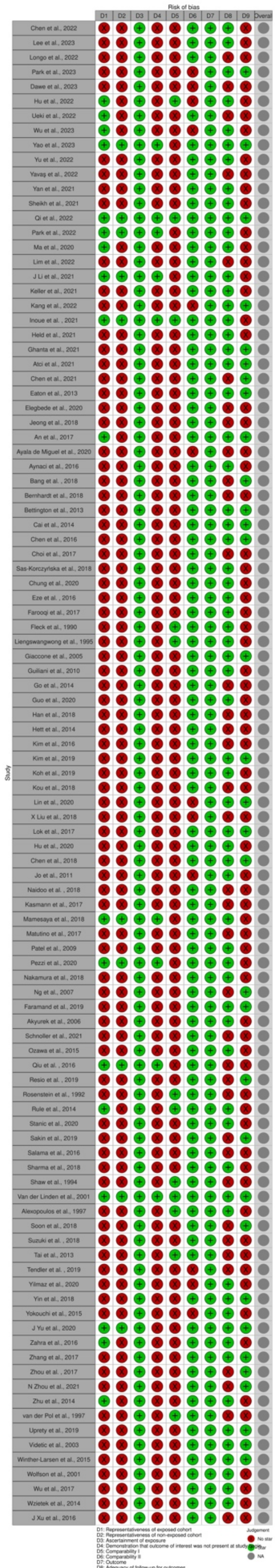


Figure S5. Funnel plot for publication bias among studies comparing PCI with no PCI and reporting on overall survival.
PCI = prophylactic cranial irradiation; vs = versus



Risk of bias
D1
D2
D3
D4
D5
D6
D7
D8
D9
Overall
Study
Chen et al., 2022
Lee et al., 2023
Longo et al., 2022
Park et al., 2023
Dawe et al., 2023
Hu et al., 2022
Ueki et al., 2022
Wu et al., 2023
Yao et al., 2023
Yu et al., 2022
Yavaş et al., 2022
Yan et al., 2021
Sheikh et al., 2021
Qi et al., 2022
Park et al., 2022
Ma et al., 2020
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Keller et al., 2021
Kang et al., 2022
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Held et al., 2021
Ghanta et al., 2021
Atci et al., 2021
Chen et al., 2021
Eaton et al., 2013
Elegbede et al., 2020
Jeong et al., 2018
An et al., 2017
Ayala de Miguel et al., 2020
Aynaci et al., 2016
Bang et al. , 2018
Bernhardt et al., 2018
Bettington et al., 2013
Cai et al., 2014
Chen et al., 2016
Choi et al., 2017
Sas-Korczyńska et al., 2018
Chung et al., 2020
Eze et al. , 2016
Farooqi et al., 2017
Fleck et al., 1990
Liengswangwong et al., 1995
Giaccone et al., 2005
Guiliani et al., 2010
Go et al., 2014
Guo et al., 2020
Han et al., 2018
Hett et al., 2014
Kim et al., 2016
Kim et al., 2019
Koh et al., 2019
Kou et al., 2018
Lin et al., 2020
X Liu et al., 2018
Lok et al., 2017
Hu et al., 2020
Chen et al., 2018
Jo et al., 2011
Naidoo et al. , 2018
Kasmann et al., 2017
Mamesaya et al., 2018
Matutino et al., 2017
Patel et al., 2009
Pezzi et al., 2020
Nakamura et al., 2018
Ng et al., 2007
Faramand et al., 2019
Akyurek et al., 2006
Schnoller et al., 2021
Ozawa et al., 2015
Qiu et al. , 2016
Reslo et al. , 2019
Rosenstein et al., 1992
Rule et al., 2014
Stanic et al., 2020
Sakin et al., 2019
Salama et al., 2016
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Alexopoulos et al., 1997
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Yin et al., 2018
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Zahra et al., 2016
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Zhou et al. , 2017
N Zhou et al., 2021
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van der Pol et al., 1997
Uprety et al., 2019
Videtic et al., 2003
Winther-Larsen et al., 2015
Wolfson et al., 2001
Wu et al., 2017
Wzietek et al., 2014
J Xu et al., 2016
D1: Representativeness of exposed cohort
D2: Representativeness of non-exposed cohort
D3: Ascertainment of exposure
D4: Demonstration that outcome of interest was not present at study begin
D5: Comparability I
D6: Comparability II
D7: Outcome
D8: Adequacy of follow-up for outcomes
D9: Adequacy of follow-up of cohorts
Judgement
No star
Star
NA

Figure S6. Newcastle Ottawa Scale plot of overall study quality assessment for non-randomised studies for the primary outcome of overall survival.

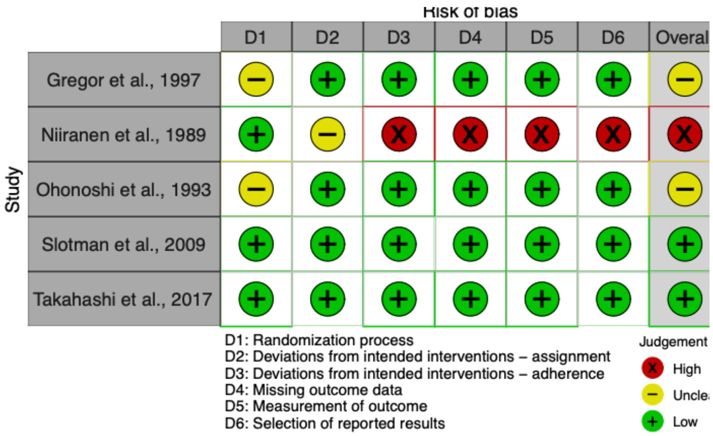

Figure S7. Risk of bias summary plot of randomised studies comparing PCI with no PCI for the primary outcome of overall survival.

Narrative synthesis

Ninety-five studies further reported on survival outcomes in univariable analysis using formats not amenable to meta-analysis (e.g., median survival, annual survival rates; Appendix 2, Table S3). The majority of studies found PCI associated with prolonged survival (Table S4). Out of the studies that radiographically confirmed absence of brain metastases in patients in the whole study cohort (n=5), four found no difference in survival and one did not report statistical significance. Thirty-six of the 105 studies reporting on PCI in multivariable analysis did not report adjusted hazard ratios and were, therefore, not eligible to for meta-analysis (Table S4). None of these studies explicitly reported that absence of brain metastases was confirmed after first-line therapy in patients who did and did not receive PCI therapy.

Table S4. Summary of significant findings of overall survival in studies reporting in formats not amenable to meta-analysis.

Association of PCI with survival	All studies	Studies reporting on limited stage disease patients only	Studies reporting on extensive stage disease patients only
Univariable analysis			
Significant improvement with PCI, n	48	30	7
No significant difference between cohorts, n	32	21	2
Varying results for different subgroups*, n	4	NA	NA
Multivariable analysis			
PCI identified as prognostic factor, n	19	9	3
PCI not significant, n	14	11	2

*Chen et al., 2014: limited stage disease patients only: not significant, extensive stage disease patients only: significant improvement with PCI; Harden et al., 2011: limited stage disease patients only: not significant, extensive stage disease patients only: significant improvement with PCI; Prelaj et al., 2017, overall cohort: significant improvement with PCI, extensive stage disease patients only: not significant; Rosenstein et al., 1992, patients with complete response only: p=0·05, complete response with disease control in the thorax: p<0·05)

Secondary outcome: incidence of intracranial metastatic disease

Subgroup and heterogeneity analysis

Results from pre-specified subgroup analyses are displayed in Table S5. Between-study heterogeneity was moderate (I^2=58·6, 95% CI, 45·4%-68·6%). Subgroup analysis did not reveal sources of heterogeneity. Meta regression showed that total publication year (p=0.02) and median age of study participants (p=0·04) but not sample size (p=0·16) contributed to between-study heterogeneity, although residual between-study heterogeneity remained moderate (I^2=53·4% and I^2=57·9% for publication year and median age, respectively). No individual studies were identified that disproportionately contributed to overall between-study heterogeneity (Figure S8). Egger's test suggests funnel plot asymmetry (intercept -1·352; 95% CI, -2·06- -9·64; t=-3·717; p<0·001, Figure S9).

Table S5. Subgroup analysis of incidence of intracranial metastatic disease.

Study characteristic	All included studies	Limited stage disease patients only	Extensive stage disease patients only
Study design			
RCT	0·44 (95% CI 0·26-0·72), n=7 studies	0·21 (95% CI 0·04-0·97), n=3 studies	0·54 (95% CI 0·22-1·29), n=2 studies
RCS	0·46 (95% CI 0·39-0·54), n=54 studies	0·47 (9% CI 0·39-0·57), n=35 studies	0·50 (95% CI 0·30-0·84), n= 9 studies
PCS	0·35 (95% CI 0·19-0·67), n=3 studies	0·35 (95% CI 0·19-0·67), n=3 studies	NA
Treatment response to first-line therapy			
CR	0·39 (95% CI 0·29-0·52), n=9 studies	0·36 (9% CI 0·21-0·60), n=3 studies	NA
CR/PR	0·46 (95% CI 0·33-0·64), n=14 studies	0·42 (95% CI 0·25-0·71), n=9 studies	0·53 (95% CI 0·32-0·87), n=5 studies
Any response (CR + CR/PR)	0·44 (95% CI 0·35-0·55), n=23 studies	0·39 (95% CI 0·28-0·56), n=15 studies	0·53 (95% CI 0·32-0·87), n=5 studies
CR/PR/SD	0·40 (95% CI 0·27-0·60), n=8 studies	0·43 (95% CU 0·22-0·83), n=5 studies	0·33 (95% CI 0·14-0·89), n=3 studies
CR/PR/SD/PD	0·31 (95% CI 0·11-0·87), n=1 study	0·31 (95% CI 0·11-0·86), n=1 study	NA
NR	0·49 (95% CI 0·38-0·61), n=32 studies	0·51 (95% CI 0·39-0·67), n=20 studies	0·89 (9% CI 0·32-2·45), n=3 studies
Use of brain baseline brain CT/MRI			
Yes	0·42 (95% CI 0·34-0·51), n=30 studies	0·38 (9% CI 0·32-0·47), n=21 studies	0·61 (95% CI 0·29-1·29), n=5 studies
No	0·44 (95% CI 0·21-0·92) n=4 studies	0·34 (9% CI 0·12-0·93), n=1 study	0·41 (95% CI 0·10-1·74), n=1 study
Not in all patients	0·39 (95% CI 0·19-0·77), n=6 studies	0·41 (9% CI 0·09-1·80), n=4 studies	0·37 (95% CI 0·13-1·06), n=2 studies
NR	0·53 (95% CI 0·40-0·70), n=24 studies	0·59 (9% CI 0·41-0·83), n=15 studies	0·54 (95% CI 0·20-1·52), n=3 studies
MRI confirmation of no IMD at restaging			
Yes	0·51 (95% CI 0·26-0·99), n=4 studies	0·44 (95% CI 0·15-1·29), n=3 studies	0·69 (5% CI 0·34-1·39), n=1 study
No	0·39 (95% CI 0·29-0·52), n=18 studies	0·35 (95% CI 0·23-0·55), n=12 studies	0·36 (95% CI 0·14-0·92), n=2 studies
NR	0·48 (95% CI 0·40-0·58), n=42 studies)	0·51 (9% CI 0·41-0·63), n=26 studies	0·54 (95% CI 0·31-0·96), n=8 studies
Use of platinum-based therapy			
Yes	0·40 (9% CI 0·33-0·49), n=24 studies	0·37 (9% CI 0·30-0·45), n=15 studies	0·50 (95% CI 0·30-0·83), n=8 studies
No	0·32 (95% CI 0·22-0·48), n=9 studies	0·32 (9% CI 0·20-0·53), n=6 studies	NA
Not administered to all patients	0·49 (95% CI 0·28-0·84), n=10 studies	0·51 (9% CI 0·28-0·91), n=9 studies	NA
NR	0·58 (95% CI 0·45-0·76), n=21 studies	0·63 (95% CI 0·41-0·90), n=11 studies	0·55 (95% CI 0·22-1·36), n=3 studies
AHRQ*			
Good	0·45 (95% CI 0·24-0·85), n=4 studies	0·44 (9% CI 0·14-1·42), n=3 studies	NA
Fair	0·27 (95% CI 0·09-0·88), n=3 studies	0·31 (9% CI 0·00-43·08), n=2 studies	0·20 (95% CI 0·03-1·20), n=1 study
Poor	0·47 (9% CI 0·40-0·56), n=51	0·47 99% CI 0·39-0·58), n=33 studies	0·55 (95% CI 0·32-0·93), n=8 studies
RoB**			
Low	0·54 (95% CI 0·02-15·12), n=2 studies	NA	0·54 (95% CI 0·22-1·28), n=2 studies
Some concerns	0·34 (95% CI 0·03-3·80), n=2 studies	0·29 (9% CI 0·09-0·89), n=1 study	NA
High	0·10 (95% CI 0·00-2·80), n=2 studies	0·10 (9% CI 0·0=2·80), n=2 studies	NA

AHRQ = Agency for Health Research and Quality; CR = complete response; CT = computed tomography; MRI = magnetic resonance imaging; NA=not applicable; NR = not reported; nRCT = non-randomised controlled trial; PCS = prospective cohort study; PR = partial response; SD = stable disease; RCS = retrospective cohort study; RCT = randomised controlled trial; RoB = risk of bias
*AHRQ only reported for non-randomised trials

**RoB only reported for randomised controlled trials

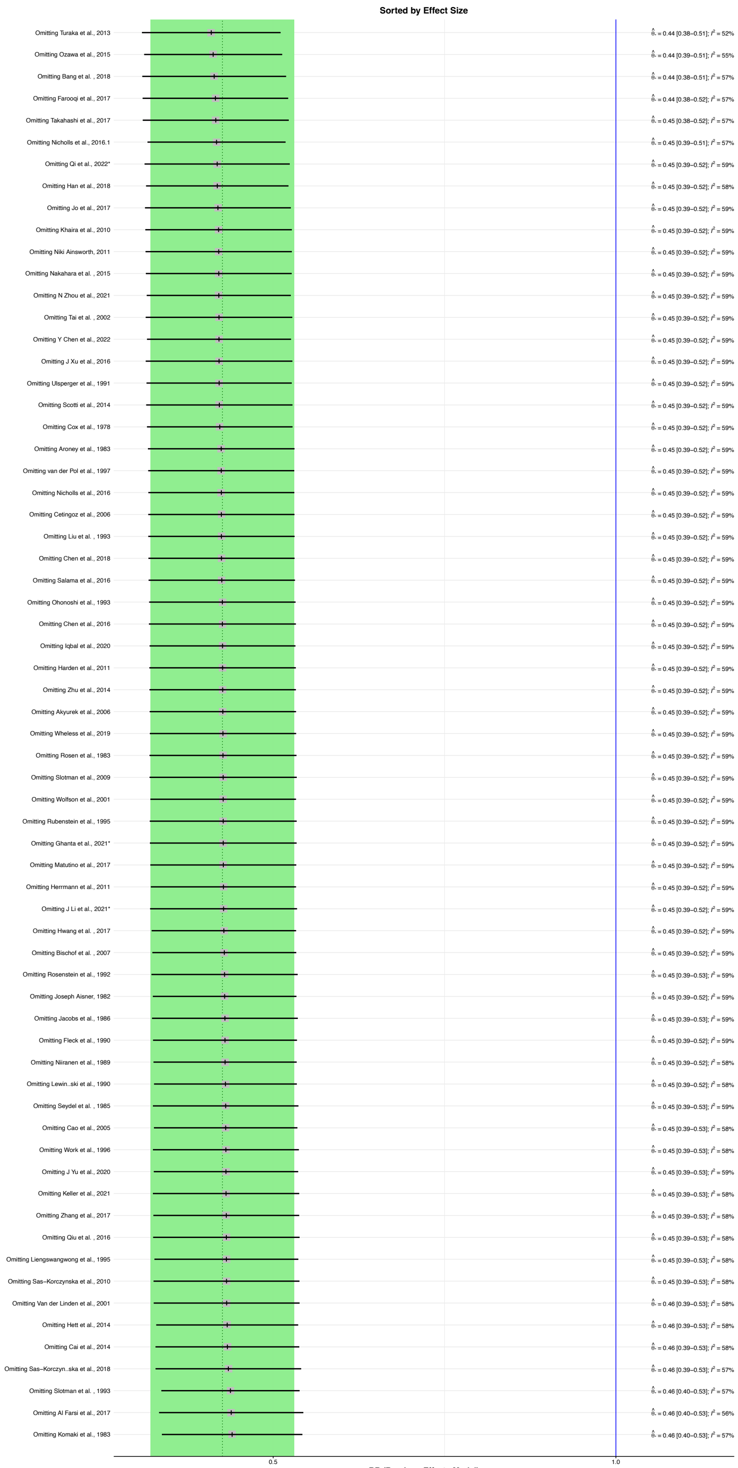

Figure S8. Forest plots for leave-out-one analysis sorted from low to high effect size for the secondary outcome of incidence of brain metastases. The plot shows the recalculated pooled effects, with one study omitted each time. The dashed line and shaded area represent the estimated pooled effect size and the 95% confidence interval of the original meta-analysis, respectively. No substantial changes in heterogeneity or effect size were observed.

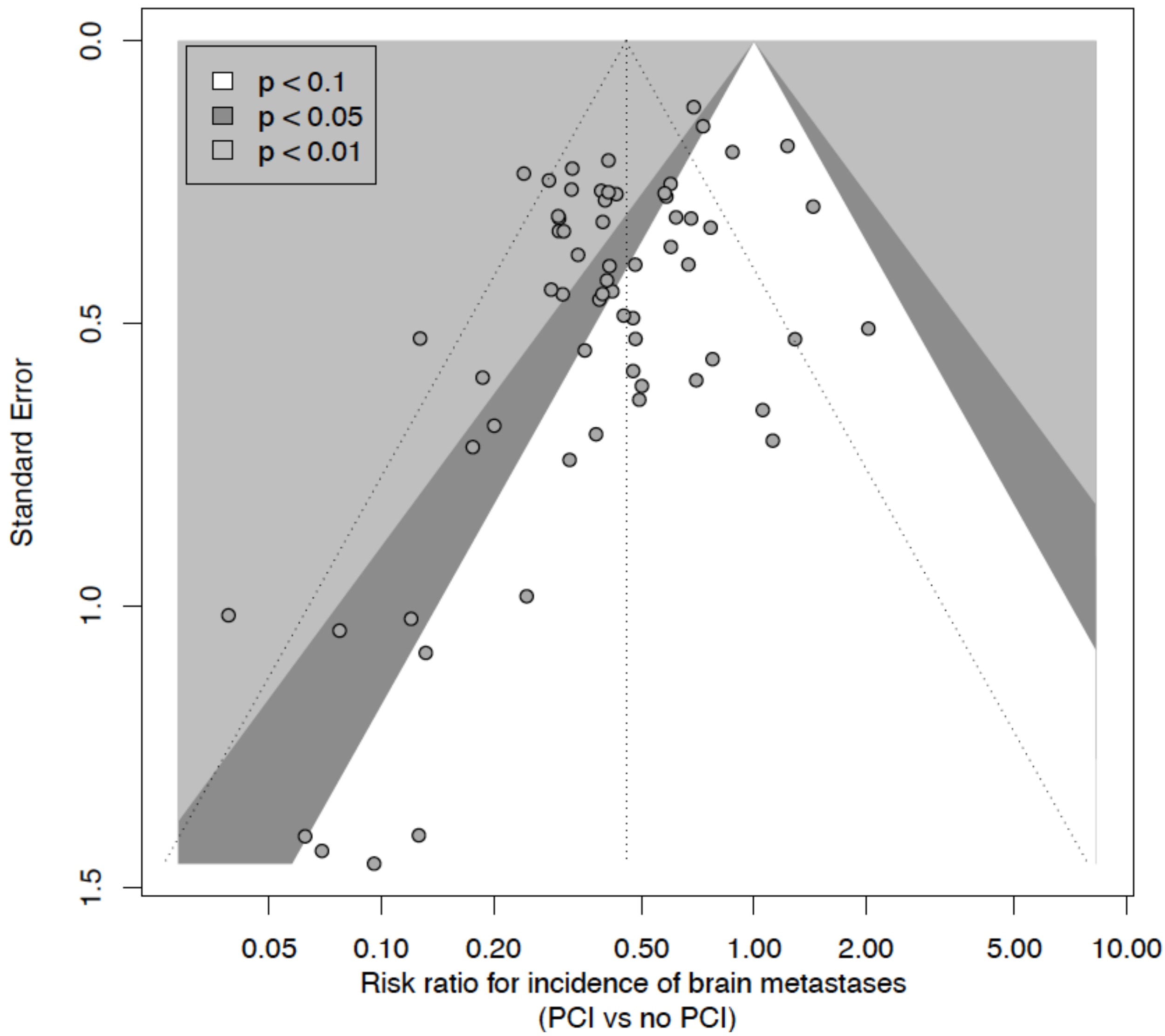

Figure S9. Funnel plot for publication bias among studies comparing PCI with no PCI and reporting on incidence of brain metastases.

PCI = prophylactic cranial irradiation; vs = versus

Narrative synthesis

All studies included in the primary analysis of incidence of brain metastases reported unadjusted risk ratios. Fifteen studies also reported on brain metastases incidence and/or time to brain metastases with or without censoring, but due to inconsistent reporting formats and limited number of studies, these were not included in the formal meta-analysis (Appendix 2, Table S6).

Further, 36 studies reported on brain metastases incidence in formats not amenable to meta-analysis, of which 21 found statistically significant reduction in the incidence of brain metastases in patients who received PCI compared to patients who did not, while 11 reported no difference between treatment cohort. Six out of the 36 studies radiographically ensured absence of brain metastases at restaging, of which 3 found improvement in terms of brain metastases incidence while the other 3 did not (Appendix 2, Table S6).

Secondary outcome: intracranial progression-free survival

Twenty studies reported on intracranial progression-free survival and found superior intracranial progression-free survival in patients who received PCI compared to those who did not (HR 0·37; 95%CI, 0·29-0·48; p<0·001; n=3347 patients; Figure S10).

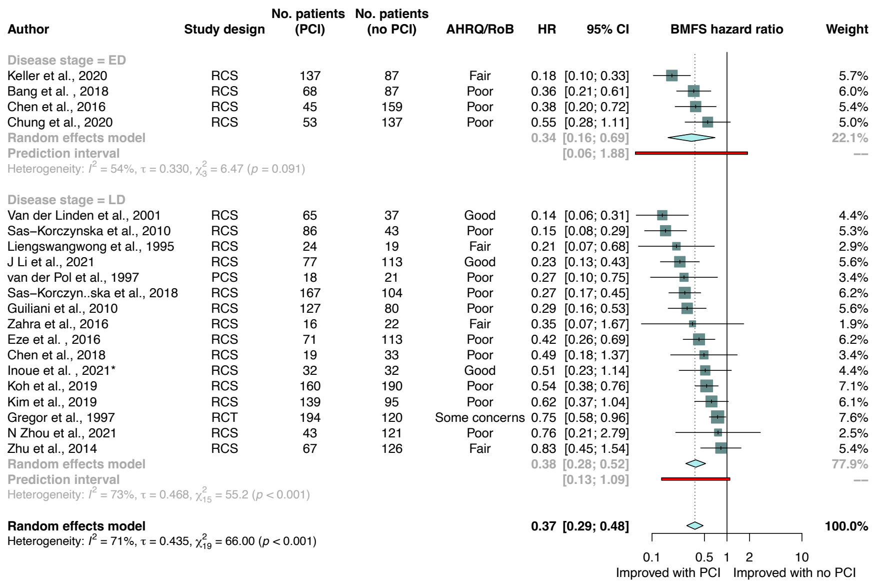

Figure S10. Random-effects meta-analysis of PCI versus no PCI for secondary outcome of intracranial progression-free survival.

Subgroup and heterogeneity analysis

Pre-specified subgroup analyses were performed only for the overall study cohort due to limited sample size when considering studies according to participant disease stage (Table S7).

Between-study heterogeneity for analysis of intracranial progression-free survival was moderate (I^2=71·2%; 95% CI, 54·8-81·7%). This was reduced when considering cohorts exclusively consisting of studies with poor Agency for Health Research and Quality rating (I^2=45·6%) but was not affected by other subgroup analyses. Residual between-study heterogeneity was not reduced in meta regression analysis by publication year, median age of study participants, or study sample size. No individual study was identified that contributed significantly to between-study heterogeneity (Figure S11). Egger's test suggests funnel plot asymmetry (intercept 1·983; 95% CI, 0·66-3·3, t=2·944; p=0·008; Figure S12).

Table S7. Subgroup analysis of intracranial progression-free survival

Study characteristic	All included studies
Study design	
RCT	0·75 (95% CI 0·33-1·71), n=1 study
RCS	0·36 (95% CI 0·27-0·46), n=18 studies
PCS	0·27 (95% CI 0·07-0·97), n= 1 study
Treatment response to first-line therapy	
CR	0·35 (95% CI 0·09-1·28), n=4 studies
CR/PR	0·33 (95% CI 0·22-0·49), n=7 studies
Any response (CR + CR/PR)	0·33 (95% CI 0·23-0·47), n=11 studies
CR/PR/SD	0·23 (95% CI 0·01-4·57), n=2 studies
CR/PR/SD/PD	0·48 (95% CI 0·09-2·55), n=2 studies
NR	0·63 (95% CI 0·44-0·91), n=5 studies
Use of brain baseline brain CT/MRI	
Yes	0·40 (95% CI 0·29-0·57), n=11 studies
NR, only in a subset of patients	0·33 (95% CI 0·21-0·53), n=9 studies
MRI confirmation of no brain metastases at restaging	
Yes	0·33 (95% CI 0·00-45·38), n=2 studies
No	0·36 (95% CI 0·16-0·81), n=5 studies
NR	0·38 (9% CI 0·28-0·53), n=13 studies
Use of platinum-based therapy	
Yes	0·38 (95% CI 0·29-0·51), n=13 studies
No	0·18 (95% CI 0·00-11·97), n=2 studies
Not administered to all patients	0·54 (95% CI 0·28-1·06), n=4 studies
NR	0·18 (95% CI 0·08-0·45), n=1 study
AHRQ*	
Good	0·25 (95% CI 0·05-1·22), n=3 studies
Fair	0·34 (95% CI 0·10-1·17), n=4 studies
Poor	0·38 (95% CI 0·29-0·50), n=12 studies
RoB**	
Some concerns	0·75 (95% CI 0·33-1·70), n=1 study

AHRQ = Agency for Health Research and Quality; CR = complete response; CT = computed tomography; MRI = magnetic resonance imaging; NA=not applicable; NR = not reported; nRCT = non-randomised controlled trial; PCS = prospective cohort study; PR = partial response; SD = stable disease; RCS = retrospective cohort study; RCT = randomised controlled trial; RoB = risk of bias
*AHRQ only reported for non-randomised trials
**RoB only reported for randomised controlled trials

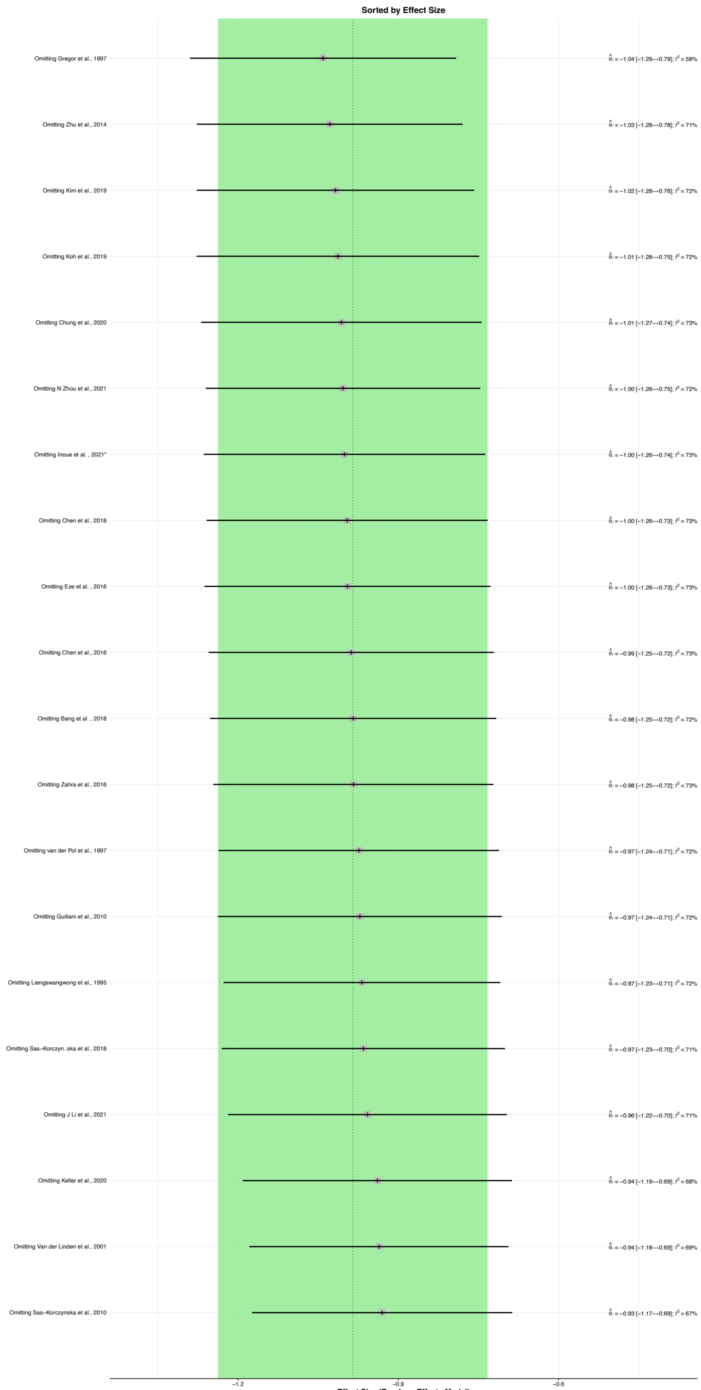

Figure S11. Forest plots for leave-out-one analysis sorted from low to high effect size for the secondary outcome of intracranial progression-free survival. The plot shows the recalculated pooled effects, with one study omitted each time. The dashed line and shaded area represent the estimated pooled effect size and the 95% confidence interval of the original meta-analysis, respectively. No substantial changes in heterogeneity or effect size were observed.

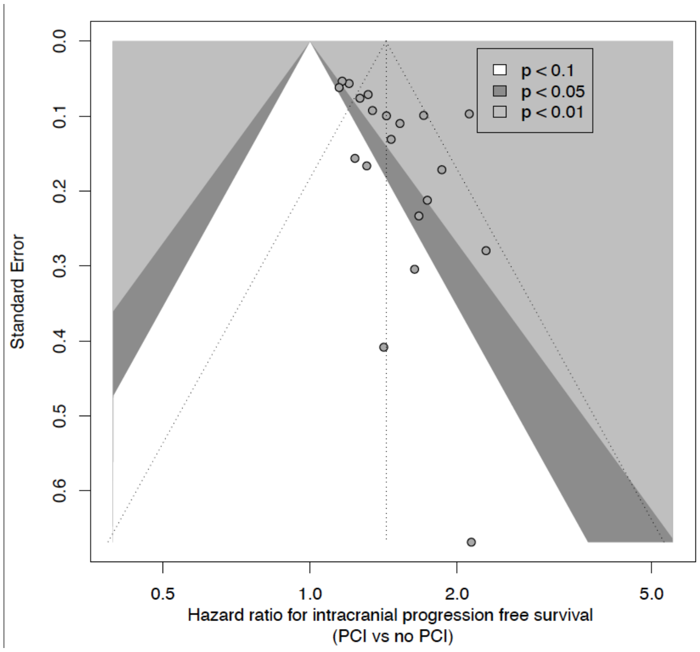

Figure S12. Funnel plot for publication bias among studies comparing PCI with no PCI and reporting on intracranial progression free survival.
PCI = prophylactic cranial irradiation; vs = versus

Narrative synthesis

Forty-two studies reported on time to brain metastases in univariable analysis in formats not amenable to statistical pooling, with 22 studies reporting improvement in patients who received PCI and eight finding no difference. Six out of these 42 studies confirmed absence of brain metastases after first-line therapy: four found superior intracranial progression survival in cohorts who received PCI and one found no difference (Appendix 2, Table S6).

Secondary outcome: progression-free survival

Progression-free survival was in favour of receipt of PCI when considering all available studies in meta-analysis (HR 0·58; 95% CI, 0·50-0·767; p=<0·001; n=19 studies; n=2,224 patients; Figure S13).

Subgroup and heterogeneity analysis

The overall between-study heterogeneity was 49·8% (95% CI, 15·8-73·9), which was reduced in studies reporting on cohorts of patients who received brain imaging at baseline using either computed tomography or magnetic resonance imaging (I^2=31·2%), retrospective cohort studies (I^2=16·6%), and those with poor quality according to the Agency for Health Research and Quality rating (I^2=1·1%, Table S9). Meta regression according to publication year, median age of study participants, or sample size did not significantly reduce residual heterogeneity. Leave-out-one analysis identified that the study by Takayashi et al. contributed significantly to between-study heterogeneity (I^2=17·0%, Figure S14). Overall effect size when omitting this trial from the meta-analysis remained in favour of PCI therapy (HR 0·58; 95% CI, 0·45-0·71; n=18 studies; n=2,000 patients; p<0·001). Egger's test did not indicate presence of funnel plot asymmetry (intercept -1·519; 95% CI, -3·07- -0·030, t=-1·92 p=0·0708; Figure S15).

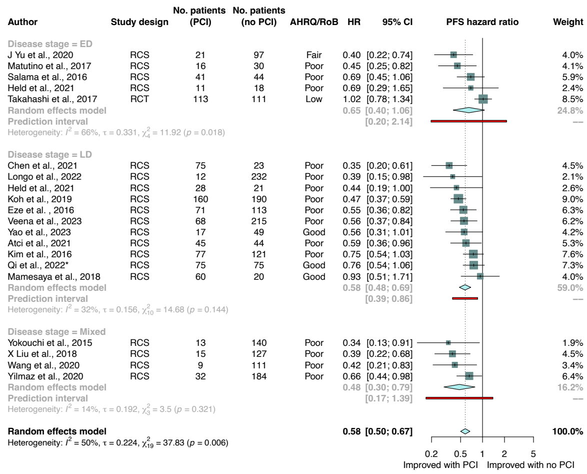

Figure S13. Random-effects meta-analysis of PCI versus no PCI for secondary outcome of progression-free survival.

Table S9. Subgroup analysis of progression-free survival.

Study characteristic	All included studies
Study design	
RCT	1·02 (95% CI 0·68-1·54), n=1 study
RCS	0·56 (95% CI 0·48-0·65), n=19 studies
Treatment response to first-line therapy	
CR/PR	0·62 (95% CI 0·37-1·06), n=6 studies
CR/PR/SD	0·53 (95% CI 0·35-0·82), n=5 studies
CR/PR/SD/PD	0·68 (95% CI 0·16-2·94), n=2 studies
NR	0·52 (95% CI 0·36-0·75), n=7 studies
Use of brain baseline brain CT/MRI	
Yes	0·57 (95% CI 0·45-0·75), n=10 studies
NR	0·58 (95% CI 0·44-0·78), n=10 studies
MRI confirmation of no brain metastases at restaging	
Yes	0·85 (95% CI 0·69-1·24), n=4 studies
No	0·49 (95% CI 0·24-1·04), n=3 studies
NR	0·53 (95% CI 0·45-0·62), n=13 studies
Use of platinum-based therapy	
Yes	0·63 (95% CI 0·51-0·77), n=14 studies
Not administered to all patients	0·47 (95% CI 0·27-0·79), n=1 study
NR	0·50 (95% CI 0·23-1·06), n=5 studies
AHRQ*	
Good	0·74 (95% CI 0·44-1·24), n=3 studies
Fair	0·40 (95% CI 0·21-0·77), n=1 study
Poor	0·54 (95% CI 0·46-0·62), n=15 studies
RoB**	
Low	1·02 (95% CI 0·72-1·46), n=1 study

AHRQ = Agency for Health Research and Quality; CR = complete response; CT = computed tomography; MRI = magnetic resonance imaging; NR = not reported; PR = partial response; SD = stable disease; RCS = retrospective cohort study; RCT = randomised controlled trial; RoB = risk of bias

*AHRQ only reported for non-randomised trials

**RoB only reported for randomised controlled trials

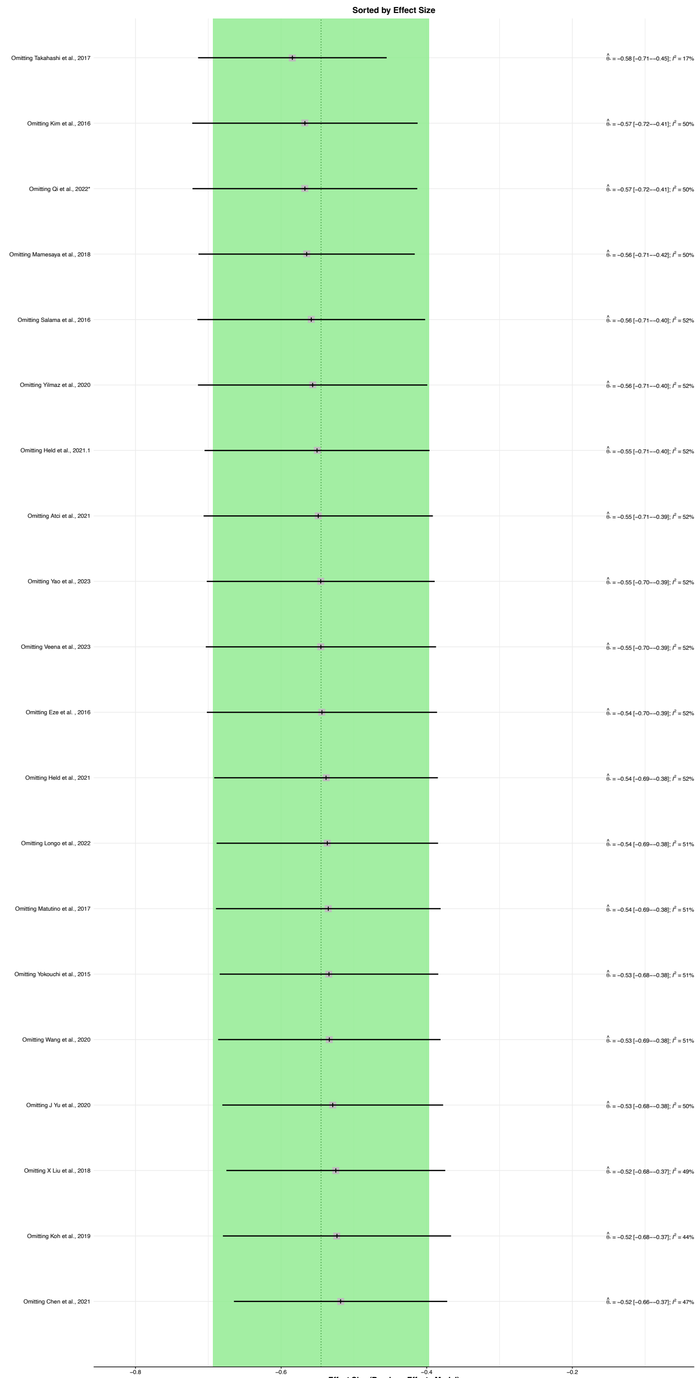

Figure S14. Forest plots for leave-out-one analysis sorted from low to high effect size for the secondary outcome of progression-free survival. The plot shows the recalculated pooled effects, with one study omitted each time. The dashed line and shaded area represent the estimated pooled effect size and the 95% confidence interval of the original meta-analysis, respectively. No substantial changes in heterogeneity or effect size were observed.

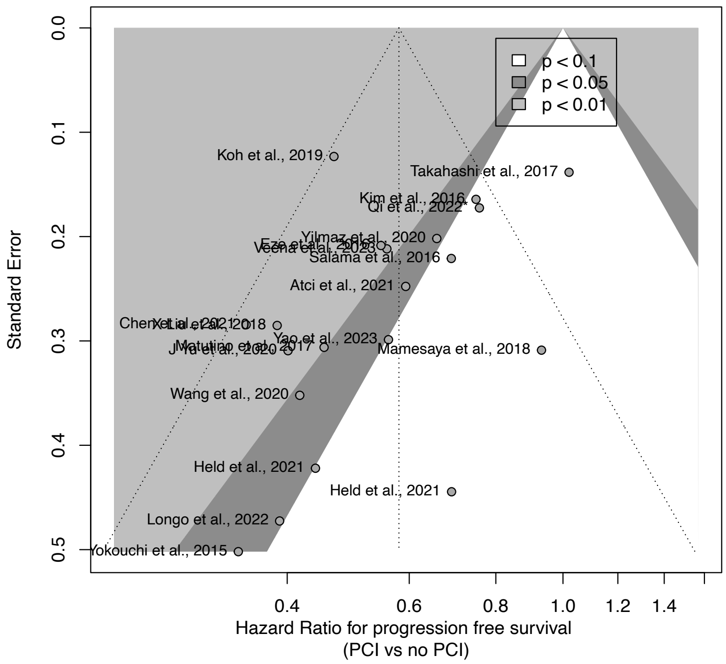

Figure S15. Funnel plot for publication bias among studies comparing PCI with no PCI and reporting on progression free survival.

PCI = prophylactic cranial irradiation; vs = versus

Narrative synthesis

Forty-one studies reported on progression-free survival in univariable and/or multivariable analysis but were not eligible for meta-analysis. Seventeen studies found statistically significant improvement in progression-free survival in cohorts of patients who received PCI compared with those who did not, and 10 found no difference. Three of these radiographically confirmed absence of brain metastases in patients who did and did not receive PCI therapy and all found no difference in progression free survival with the addition with PCI therapy. Information on studies reporting on multivariable analysis can be found in the supplementary materials (Appendix 2, Table S8).

Secondary outcome: disease-free survival

Seven studies[14,16,56,66,156,178,206] reported on disease-free survival in formats amenable to multivariable analysis (HR 0·57; 95% CI, 0·36-0·89; p=0·023; n=866 patients; Figure S16).

Subgroup and heterogeneity analysis

Subgroup analysis according to pre-specified subgroups was performed, but no reduction in the overall between-study heterogeneity (I^2=65·3%; 95% CI, 22·0-84·5) was found (Table S11). Publication year, sample size, and median age of study participants did not contribute significantly to between-study heterogeneity in meta regression (p>0·05). Between study heterogeneity was not significantly influenced by any one study (Figure S17). Egger's test did not suggest presence of funnel plot asymmetry (intercept 0·676, 95% CI -2·62- -3·97, t=0·402, p=0·704; Figure S18).

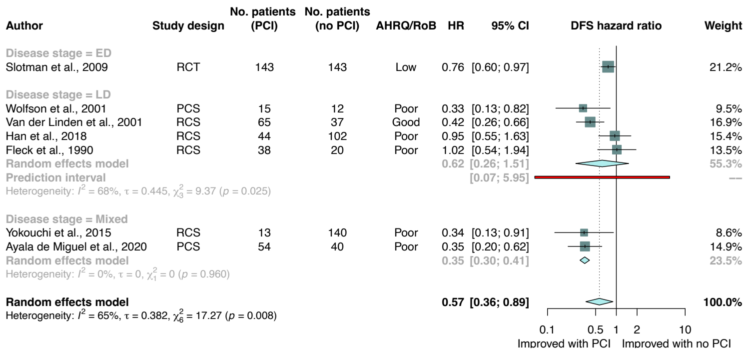

Figure S16. Random-effects meta-analysis of PCI versus no PCI for secondary outcome of intracranial progression-free survival.

Table S11. Subgroup analysis of disease-free survival.

Study characteristic	All included studies
Study design	
RCT	0·76 (95% CI 0·37-1·58), n=1 study
RCS	0·64 (95% CI 0·27-1·50), n=4 studies
PCS	0·34 (95% CI 0·23-0·51), n=1 study
Treatment response to first-line therapy	
CR	0·53 (95% CI 0·12-0·27), n=3 studies
CR/PR	0·76 (95% CI 0·28-2·07), n=1 study
CR + CR/PR	0·60 (95% CI 0·28-1·30), n=4 studies
NR	0·51 (95% CI 0·11-2·26), n=3 studies
Use of brain baseline brain CT/MRI	
Yes	1·02 (95% CI 0·39-2·64), n=1 study
No	0·76 (95% CI 0·36-1·60), n=1 study
NR	0·46 (95% CI 0·26-0·82), n=5 studies
MRI confirmation of no brain metastases at restaging	
Yes	0·42 (95% CI 0·15-1·19), n=1 study
No	0·76 (95% CI 0·28-2·01), n=1 study
NR	0·55 (95% CI 0·26-1·15), n=5 studies
Use of platinum-based therapy	
Yes	0·34 (95% CI 0·09-1·30), n=1 study
No	0·63 (95% CI 0·00-1·78·81), n=2 studies
NR	0·57 (95% CI 0·25-1·32), n=4 studies
AHRQ*	
Good	0·42 (95% CI 0·15-1·19), n=1 study
Poor	0·55 (95% CI 0·26-1·15), n=5 studies
RoB**	
Low	0·76 (95% CI 0·29-2·01), n=1 study

AHRQ = Agency for Health Research and Quality; CR = complete response; CT = computed tomography; MRI = magnetic resonance imaging; NR = not reported; PR = partial response; PCS = prospective cohort study; SD = stable disease; RCS = retrospective cohort study; RCT = randomised controlled trial; RoB = risk of bias
*AHRQ only reported for non-randomised trials
**RoB only reported for randomised controlled trials

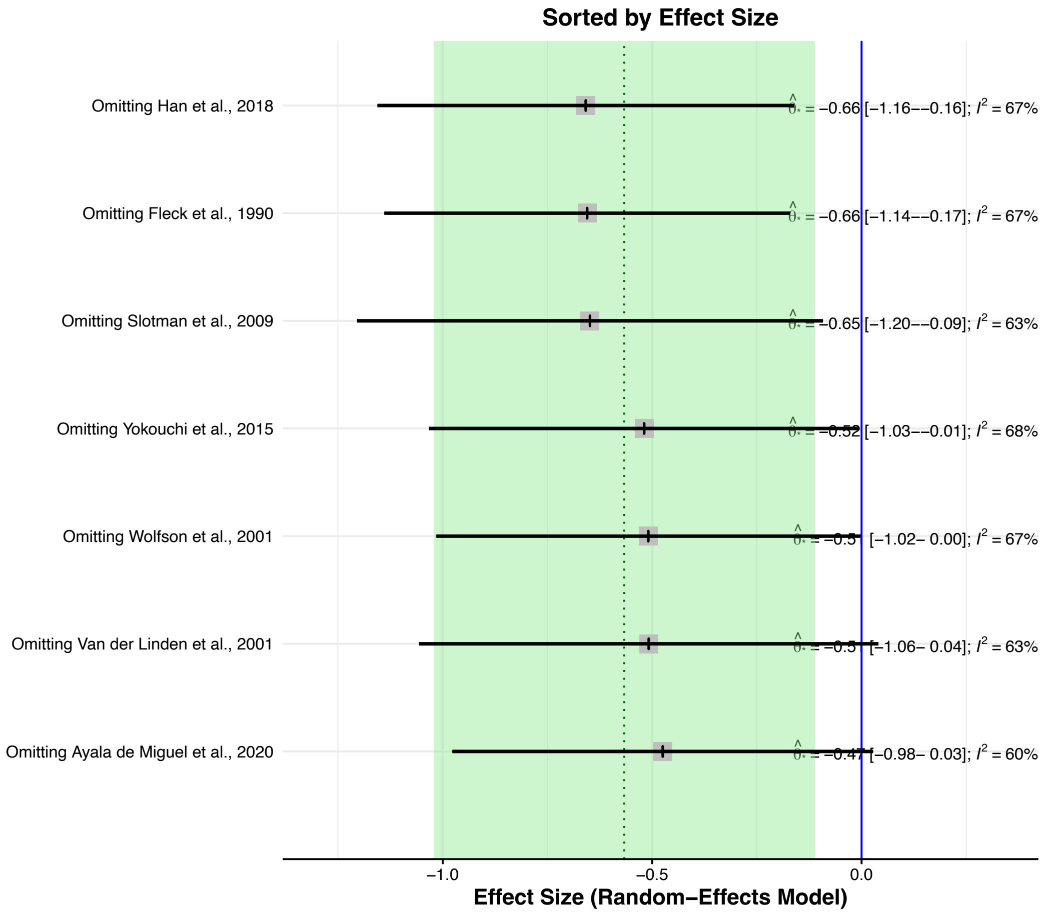

Figure S17. Forest plots for leave-out-one analysis sorted from low to high effect size for the secondary outcome of disease-free survival. The plot shows the recalculated pooled effects, with one study omitted each time. The dashed line and shaded area represent the estimated pooled effect size and the 95% confidence interval of the original meta-analysis, respectively. No substantial changes in heterogeneity or effect size were observed.

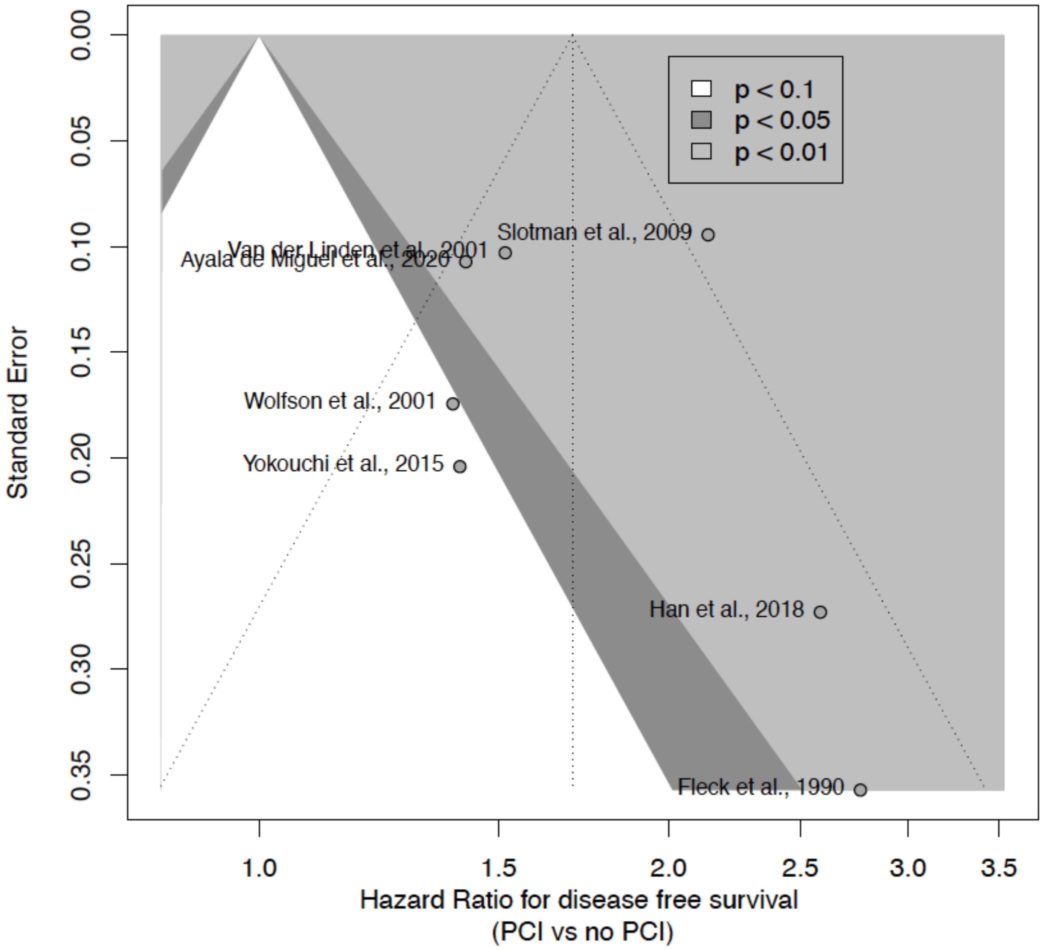

Figure S18. Funnel plot for publication bias among studies comparing PCI with no PCI and reporting on disease free survival.

PCI = prophylactic cranial irradiation; vs = versus

Narrative synthesis

Out of the thirteen studies[14-16,18,51,54,65,88,92,131,156,165,176,183,199,203,206,212,227] that reported on disease-free survival in formats not amenable to meta-analysis, 9 found improvement with administration of PCI therapy[16,51,54,88,92,131,156,165,203] and 2 did not[176,183] while 2 did not report outcomes of statistical analysis[199,227]. None of these studies radiographically confirmed absence of brain metastases at restaging. Ten studies reported on disease-free survival in multivariable analysis with differing endpoint definitions (Appendix 2, Table S10)[14,15,18,51,65,88,92,199,206,212].

Secondary outcome: incidence of brain metastases as first site of recurrence

PCI reduced the indicine of brain metastases as first site of recurrence (RR 0·44; 95% CI, 0·34-0·59; p<0·001; n=18 studies; n=2827 patients; Figure S19).

Subgroup analysis and between-study heterogeneity

Moderate between-study heterogeneity among all studies (I^2=54·1%, 95% CI, 23·9-72·3) was reduced when considering studies reporting on patients who received either computed tomography or magnetic resonance imaging at baseline (I^2=46·5%) or those in which ≥90% of patients received platinum-based chemotherapy (I^2=40·8%) and was unaltered in other pre-specified subgroup analysis (Table S13). Sample size significantly contributed to between-study heterogeneity in meta regression (residual heterogeneity I^2=31.8%). Removing the report by Komaki et al. 2016 from the model also reduced between-study heterogeneity (I^2=46), although the overall effect size remained unchanged (RR 0·42, 95% CI 0·32-0·55, Figure S20). Egger's test indicates presence of funnel plot asymmetry (intercept -1·853, 95% CI -2·72- -1·01, t=-4·271, p<0·0001; Figure S21).

Author	Study design	IMD incidence (PCI)	No. patients (PCI)	IMD incidence (no PCI)	No. patients (no PCI)	AHRQ/RoB	RR	95% CI	Weight
Disease stage = LD									
Ng et al., 2007	RCS	3.00	39	11.00	25	Poor	0.17	[0.05; 0.57]	3.5%
Liengswangwong et al., 1995	RCS	2.00	24	9.00	19	Fair	0.18	[0.04; 0.72]	2.7%
Fleck et al., 1990	RCS	0.00	38	1.00	20	Poor	0.18	[0.01; 4.16]	0.6%
J Li et al., 2021*	RCS	6.00	69	30.00	69	Good	0.20	[0.09; 0.45]	5.7%
Tai et al., 2013	RCS	2.00	40	8.00	48	Poor	0.30	[0.07; 1.33]	2.4%
Rosenstein et al., 1992	RCS	5.00	36	12.00	26	Poor	0.30	[0.12; 0.75]	5.0%
Park et al., 2022	PCS	3.00	22	9.00	21	Good	0.32	[0.10; 1.02]	3.6%
Eagan et al., 1981	RCT	2.00	15	6.00	15	Some concerns	0.33	[0.08; 1.39]	2.6%
Choi et al., 2017	RCS	5.05	38	36.63	99	Poor	0.36	[0.15; 0.84]	5.4%
Nakamura et al., 2018	RCS	17.00	93	28.00	69	Poor	0.45	[0.27; 0.75]	8.5%
Tai et al., 2013	RCS	6.00	128	5.00	49	Poor	0.46	[0.15; 1.44]	3.7%
Videtic et al., 2003	RCS	10.00	48	54.00	166	Poor	0.64	[0.35; 1.16]	7.7%
Komaki et al., 2016	RCS	66.00	307	71.00	271	Poor	0.82	[0.61; 1.10]	11.0%
Choi et al., 2017	RCS	17.84	52	37.40	91	Poor	0.83	[0.53; 1.31]	9.3%
van der Pol et al., 1997	PCS	3.00	18	2.00	21	Poor	1.75	[0.33; 9.34]	2.0%
Random effects model							0.45	[0.33; 0.63]	73.7%
Prediction interval								[0.19; 1.07]	--
Heterogeneity: I^2 = 54%, τ = 0.363, χ^2_{14} = 30.25 (p = 0.007)									
Disease stage = Mixed									
Sculier et al., 1987	RCS	18.00	146	20.00	60	Poor	0.37	[0.21; 0.65]	8.0%
Ohonoshi et al., 1993	RCT	2.00	23	5.00	23	Some concerns	0.40	[0.09; 1.86]	2.3%
Arriagada et al., 2002	RCT	49.00	245	68.00	250	Some concerns	0.74	[0.53; 1.01]	10.7%
Random effects model							0.55	[0.20; 1.51]	21.1%
Prediction interval								[0.01; 52.71]	--
Heterogeneity: I^2 = 57%, τ = 0.271, χ^2_2 = 4.63 (p = 0.099)									
Disease stage = NR									
Lishner et al., 1990	RCS	2.00	48	4.00	10	Poor	0.10	[0.02; 0.49]	2.3%
Disease stage = ED									
Matutino et al., 2017	RCS	2.00	16	16.00	30	Poor	0.23	[0.06; 0.89]	2.9%
Random effects model							**0.44**	**[0.34; 0.59]**	**100.0%**
Heterogeneity: I^2 = 54%, τ = 0.369, χ^2_{19} = 41.43 (p = 0.002)									

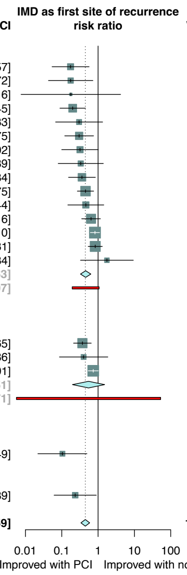

Figure S19. Random-effects meta-analysis of PCI versus no PCI for secondary outcome of incidence of brain metastases as first site of recurrence.

Table S13. Subgroup analysis of incidence of brain metastases as first site of recurrence.

Study characteristic	All included studies
Study design	
RCT	0·58 (95% CI 0·21-1·62), n=3 studies
RCS	0·41 (95% CI 0·29-0·57), n=15 studies
PCS	0·59 (95% CI 0·00-1910·06), n=2 studies
Treatment response to first-line therapy	
CR	0·44 (95% CI 0·25-0·77), n=8 studies
CR/PR	0·44 (95% CI 0·17-1·13), n=4 studies
Any response	0·44 (95% CI 0·30-0·65), n=12 studies
CR/PR/SD	0·28 (95% CI 0·04-1·92), n=2 studies
Incomplete response	0·30 (95% CI 0·05-1·69), n=1 study
NR	0·48 (95% CI 0·20-1·14), n=5 studies
Use of brain baseline brain CT/MRI	
Yes	0·51 (95% CI 0·34-0·75), n=12 studies
No	0·33 (95% CI 0·11-1·02)· n=2 studies
NR	0·38 (95% CI 0·20-0·75), n=6 studies
MRI confirmation of no brain metastases at restaging	
Yes	0·28 (95% CI 0·01-3·71), n=2 studies
No	0·40 (95% CI 0·29-0·55), n=4 studies
NR	0·51 (95% CI 0·35-0·73), n=14 studies
Use of platinum-based therapy	
Yes	0·39 (95% CI 0·28-0·55), n=12 studies
No	0·65 (95% CI 0·05-8·71), n=3 studies
Only in some patients	0·44 (95% CI 0·14-1·38), n=4 studies
NR	0·74 (95% CI 33-1·66), n=1 study
AHRQ*	
Good	0·24 (95% CI 0·01-4·17), n=2 studies
Fair	0·18 (95% CI 0·03-0·83), n= 1 study
Poor	0·48 (95% CI 0·34-0·67), n=14 studies
RoB**	
Some concerns	0·60 (95% CI 0·22-1·60), n=3 studies

AHRQ = Agency for Health Research and Quality; CR = complete response; CT = computed tomography; MRI = magnetic resonance imaging; NR = not reported; PR = partial response; PCS = prospective cohort study; SD = stable disease; RCS = retrospective cohort study; RCT = randomided controlled trial; RoB = risk of bias
*AHRQ only reported for non-randomised trials
**RoB only reported for randomised controlled trials

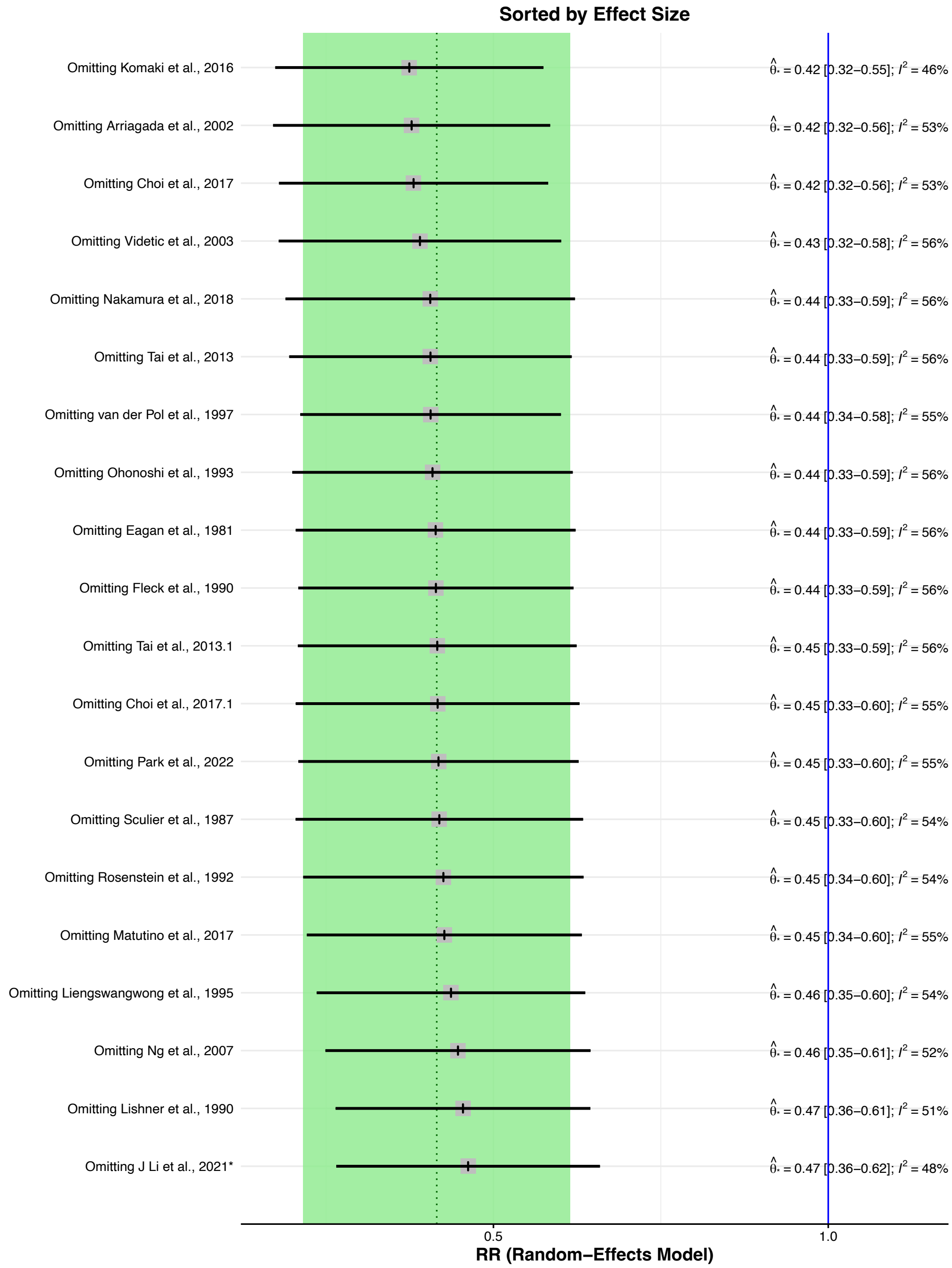

Figure S20. Forest plots for leave-out-one analysis sorted from low to high effect size for the secondary outcome of incidence of brain metastases as first site of recurrence. The plot shows the recalculated pooled effects, with one study omitted each time. The dashed line and shaded area represent the estimated pooled effect size and the 95% confidence interval of the original meta-analysis, respectively. No substantial changes in heterogeneity or effect size were observed.

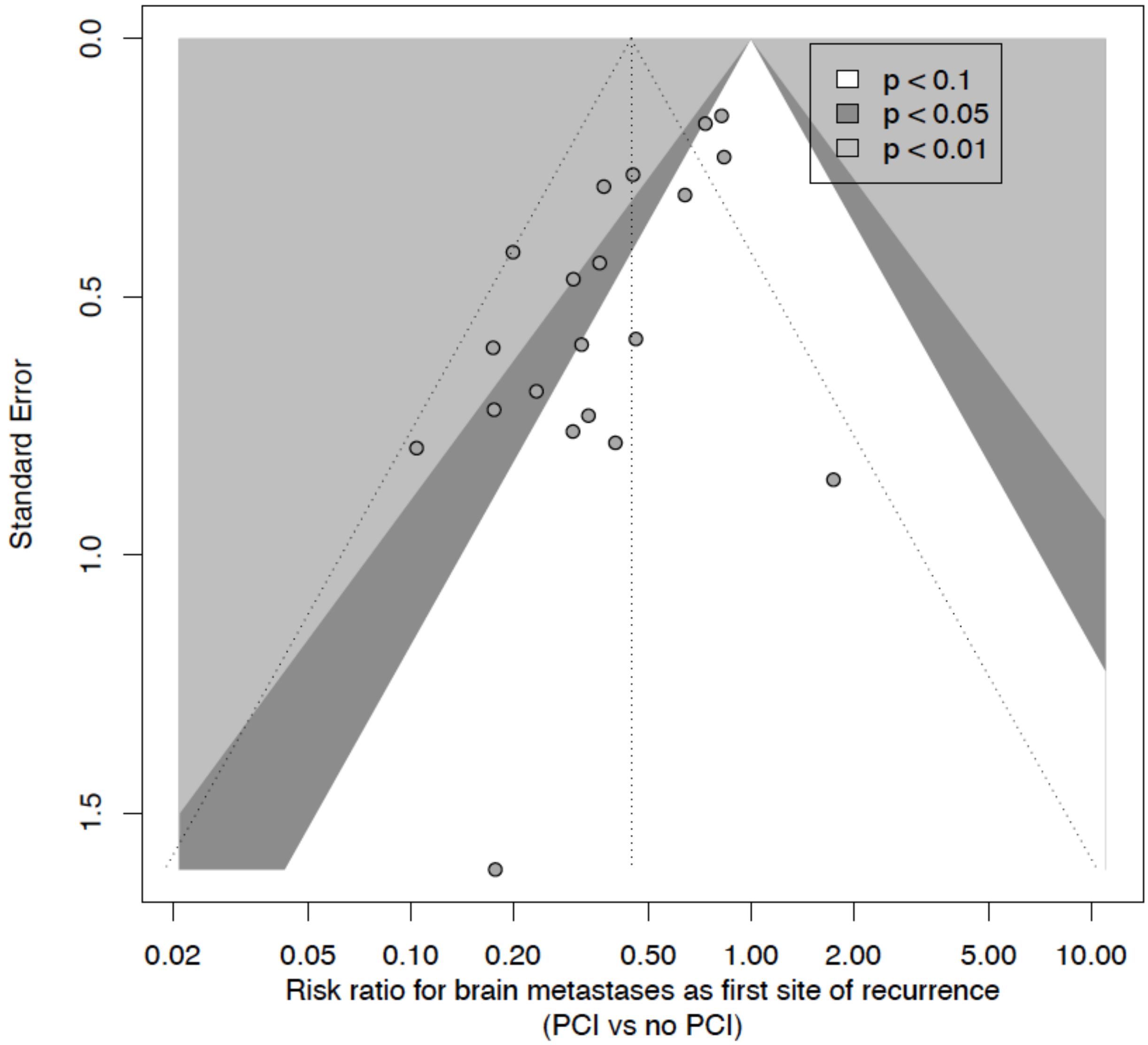

Figure S21. Funnel plot for publication bias among studies comparing PCI with no PCI and reporting on incidence of brain metastases as first site of recurrence.
PCI = prophylactic cranial irradiation; vs = versus

Narrative synthesis

Three studies reported on the brain as the first site of metastatic recurrence with two finding reduced incidence [9,124] and one not reporting on statistical significance[165]. One study radiographically confirmed absence of brain metastases using computed tomography imaging after first line therapy.[9]

Secondary outcomes: neurocognitive decline and adverse events

We identified 15[9,44,63,74,76,110,120,121,139,147,153,155,156,163,206] studies that assessed neurocognitive decline between in relation to receipt of PCI (supplementary excel, "Neurocognitive decline and AEs"). None were amenable to meta-analysis. Two studies found significant reduction in neurocognitive function in patients who received PCI[121,153], 4 found no significant difference[44,63,156,163], and 9 did not report on statistical significance[9,74,76,110,120,139,147,155,206]. Twenty[20,25,29,56-58,63,69,74,78,120,127,129,138-140,142,156,163,189] studies reported on adverse events associated with administration of PCI. Five of these found no grade 3+ adverse events following administration of PCI[20,25,69,74,129] (Appendix 2, Table S12).

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