# Thirty years of prophylactic cranial irradiation in patients with small cell lung cancer: a meta-analysis of randomized clinical trials*

## Trinta anos de irradiação craniana profilática em pacientes com câncer de pulmão de pequenas células: uma meta-análise de ensaios clínicos randomizados

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## Abstract

**Objective:** To determine the role of prophylactic cranial irradiation (PCI) in patients with small cell lung cancer (SCLC). **Methods:** We searched various databases, selecting randomized clinical trials published in journals or conference proceedings within the last 30 years and investigating the role of PCI in the mortality of patients with SCLC, submitted to PCI or not. **Results:** Sixteen randomized clinical trials, collectively involving 1,983 patients, were considered eligible for inclusion. Of those 1,983 patients, 1,021 were submitted to PCI and 962 were not. Overall mortality was 4.4% lower in the patients submitted to PCI than in those who were not (OR = 0.73; 95% CI: 0.57-0.97; p = 0.01), especially among the patients showing a complete response after induction chemotherapy (OR = 0.68; 95% CI: 0.50-0.93; p = 0.02) and in those submitted to PCI after that treatment (OR = 0.68; 95% CI: 0.49-0.94; p = 0.03). That decrease did not correlate with the stage of the disease: limited disease (OR = 0.73; 95% CI: 0.55-0.97; p = 0.03); and extensive disease (OR = 0.48; 95% CI: 0.26-0.87; p = 0.02). **Conclusions:** Our findings suggest that PCI decreases mortality in patients with SCLC, especially in those showing a complete response after induction chemotherapy and in those submitted to PCI after that treatment, regardless of the stage of the disease.

**Keywords:** Small cell lung carcinoma; Radiotherapy; Survival analysis.

## Resumo

**Objetivo:** Determinar o papel da irradiação craniana profilática (ICP) em pacientes com câncer de pulmão de pequenas células (CPPC). **Métodos:** Foi realizada uma pesquisa para selecionar estudos em várias bases de dados, com os seguintes critérios de inclusão: ensaios clínicos randomizados, publicados em periódicos ou em anais de congressos nos últimos 30 anos, avaliando o papel da ICP sobre a mortalidade em pacientes com CPPC que receberam ICP ou não. **Resultados:** Foram considerados elegíveis 16 estudos clínicos randomizados, os quais envolveram 1.983 pacientes. Entre esses, 1.021 foram submetidos a ICP e 962 não foram submetidos a ICP. Houve uma redução absoluta na mortalidade de 4,4% nos pacientes submetidos a ICP quando comparados com o grupo controle (OR = 0,73; IC95%: 0,57-0,97; p = 0,01), principalmente naqueles com resposta completa à quimioterapia de indução (OR = 0,68; IC95%: 0,50-0,93; p = 0.02) e que foram submetidos a ICP ao término desse tratamento (OR = 0,68; IC95%: 0,49-0,94; p = 0.03). A diminuição da mortalidade não se correlacionou com o estádio da doença: doença limitada (OR = 0,73; IC95%: 0,55-0,97; p = 0,03) e doença extensa (OR = 0,48; IC95%: 0,26-0,87; p = 0,02). **Conclusões:** Nossos achados sugerem que a ICP reduz a mortalidade em pacientes com CPPC, principalmente naqueles com resposta a quimioterapia de indução e que sejam submetidos a ICP ao término desse tratamento, independentemente do estadiamento da doença.

**Descritores:** Carcinoma de pequenas células do pulmão; Radioterapia; Análise de sobrevida.

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## Introduction

Lung cancer is the leading cause of cancer death in the USA, accounting for approximately 31% and 26% of all cancer deaths in men and women, respectively.[1] In Brazil, the estimate for the year 2010 was that 27,630 people (17,800 men and 9,830 women) would be affected.[2] In clinical practice, lung carcinomas are classified as small cell lung cancer (SCLC) and non-small cell lung cancer, the former accounting for 13-20% of all lung cancers and being strongly related to smoking.[3] Regarding the treatment of SCLC, the results are poor. Cisplatin-based chemotherapy regimens remain the best treatment for extensive SCLC, increasing survival without a significant increase in toxicity.[3] However, despite the high rate of initial response to chemotherapy (60-70% of patients with extensive disease responding to chemotherapy), mean survival is approximately 10 months.[3] This is due to the fact that, despite high response rates, recurrences and metastases are common. In 50-60% of the patients who achieve complete remission, brain metastases occur two years later. In 20-30% of those patients, the brain is the only apparent site of relapse. On the basis of the abovementioned data, several randomized clinical trials (RCTs) have investigated the role of prophylactic cranial irradiation (PCI) in patients with extensive or limited SCLC.[4-19] A meta-analysis published in 1999 and including 7 RCTs involving 987 patients with SCLC and complete response to chemotherapy showed a 5.4% increase in the three-year survival of those undergoing PCI.[20] However, ever since that meta-analysis was published, several RCTs have been published, and uncertainties still remain regarding the indications for PCI use in patients with extensive disease and in those with limited disease and an incomplete response to chemotherapy. In addition, there are uncertainties regarding the best PCI dose and treatment-related toxicity. Therefore, the primary objective of our meta-analysis was to evaluate the role of PCI in the mortality of patients with SCLC, our secondary objective being to analyze the impact of chemotherapy response, disease extent, and PCI dose on mortality in those patients.

## Methods

The criteria for inclusion in the present meta-analysis are described below. We included RCTs or systematic reviews of RCTs that were published in full in journals or conference proceedings and that involved patients with SCLC submitted to induction treatment (chemotherapy/radiation therapy), comparing those submitted to PCI with those who were not, regardless of the disease stage (limited or extensive) and the response to chemotherapy. The interventions studied were the use of PCI or the observation of the study population.

Our primary outcome measure was the role of PCI in reducing overall mortality. Our secondary outcome measures were the impact of the PCI dose (< 20 Gy; 20-25 Gy; 25-30 Gy; and > 30 Gy) on overall mortality, the impact that a complete or incomplete response to induction chemotherapy had on overall mortality, and the impact of the disease stage (extensive or limited) on overall mortality.

Our search strategy for the selection of articles is described below. We searched the Medline (Ovid) and CancerLit (Ovid) databases for articles published between January of 1996 and December of 2010, as well as searching the Cochrane Library (Issue 2, 2010). We used the following descriptors: "prophylactic"[All Fields] AND ("skull"[MeSH Terms] OR "skull"[All Fields] OR "cranial"[All Fields]) AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields]) AND ("Small"[Journal] OR "small"[All Fields]) AND "cell"[All Fields] OR "cells"[MeSH Terms] OR "cells"[All Fields]). Those terms were then combined with the following types of articles: guidelines; systematic reviews; meta-analyses; reviews; RCTs; and controlled RCTs. In addition, we searched The Physician Data Query database (http://www.cancer.gov/clinicaltrials/search) for clinical trials and the proceedings of the American Society of Clinical Oncology, the American Society for Therapeutic Radiology and Oncology (1992-2010), the European Society of Therapeutic Radiology and Oncology (2000-2010), and the European Society for Medical Oncology (1998-2010) for relevant abstracts. Relevant articles and abstracts were selected and reviewed by two researchers, and the corresponding lists of references were scanned for additional studies. The RCTs retrieved by our search strategy were

analyzed to determine whether they met the inclusion criteria.

The analysis of the data collected was performed with the Review Manager software, version 5.0 (RevMan 5; Cochrane Collaboration, Oxford, UK). All analyses were based on the intent-to-treat principle, meaning that we employed a method whereby all of the patients assigned to a treatment group were included in the statistical analysis according to the randomization, regardless of whether they actually received treatment or were excluded from the analysis by the investigators. For categorical variables, we calculated the relative risk estimates and respective 95% CIs using the RevMan 5 software, in accordance with the Peto method,[21] which is a fixed effect model. The results were tested for heterogeneity and were considered significant for a p value < 0.05, in accordance with the random effects model developed by DerSimonian & Laird.[22] We used the fixed effect model when there was no evidence of heterogeneity among the studies; otherwise, we used the random effects model. For each RCT, we calculated the OR and 95% CI, which are presented as forest plots. When possible, the analyses were performed separately for each group, namely the PCI group and the control group in each of the two arms. The subgroup analyses for each outcome were performed by recalculating the ORs and 95% CIs for each of the following comparisons: between response to chemotherapy and no response to chemotherapy; between limited and extensive disease; and among the various intervals between chemotherapy and initiation of PCI. We assessed the heterogeneity across studies using the $I^2$ statistic. The $I^2$ statistic describes the proportion of total variation across studies due to heterogeneity rather than chance. The interpretation of $I^2$ depends on the magnitude and direction of the effects, as well as on the strength of evidence for heterogeneity (i.e., the p value for the chi-square test or the 95% CI for $I^2$). In order to detect publication bias, we used funnel plots, thereby an asymmetry in the graph represents the presence of bias, mainly due to the presence of studies with small samples (which are biased in that they show high ORs) but also due to the fact that such studies do not show significant results and are therefore less likely to be published.

## Results

A total of 16 RCTs,[4-19] published between 1977 and 2007, were considered eligible for inclusion in the present study. The principal characteristics of those RCTs are summarized in Table 1. The total number of eligible patients included was 1,983. Of those, 1,021 were randomized to the PCI group and 962 were randomized to the control group. A total of 7 studies (894 patients)[4,5,7,11,15] evaluated the role of PCI in patients who had a complete response after induction chemotherapy. A total of 5 studies[6,9,12-14] evaluated the role of PCI administered at the start of induction chemotherapy in patients considered free of brain metastases. A total of 7 studies (894 patients) [4,5,7,11,15] evaluated the role of PCI in patients who received it during induction chemotherapy. In 2 studies,[6,8] PCI was given as consolidation therapy at the end of chemotherapy, before the response had been evaluated. A total of 10 studies[4-6,11,12,14,15] included patients regardless of their disease stage (limited or extensive).[6-9,13] In contrast, 6 studies included only patients with limited disease, whereas 1 study included only those with extensive disease.[16]

### *Overall mortality*

All 16 studies reported the impact of PCI on one-year mortality, totaling 1,983 patients (1,021 submitted to PCI and 962 who were not). Combining the data from the 16 studies, PCI was associated with a significant reduction in the overall mortality of patients with SCLC in comparison with that of those who did not undergo PCI (OR = 0.73; 95% CI: 0.57-0.97; p = 0.01), with a 4.4% reduction in overall mortality, i.e., for every 25 patients treated, one death is avoided (Figure 1). There was no heterogeneity across studies (p = 0.3), which demonstrates that the results are valid.

### *Mortality and response to chemotherapy*

A subgroup analysis was performed to evaluate the impact of chemotherapy response on mortality. Therefore, the results were stratified by response to chemotherapy, and two groups were formed: one comprising patients with complete response to chemotherapy and the other comprising those

**Table 1 -** Characteristics of the studies included in the present meta-analysis.

| Studies | Patients, n | PCI dose, Gy/fractions, n | Stage | PCI |
|---|---|---|---|---|
| Aisner et al.[15] | 29 | 30/10 | Limited/extensive | EC |
| Arriagada et al.[4] | 300 | 24/8 | Limited/extensive | EC |
| Beiler et al.[12] | 54 | 24/8 | Limited/extensive | SC |
| Cao et al.[18] | 51 | 25.2-30.6/14-16 | Limited | EC |
| Eagan et al.[8] | 30 | 36/20 | Limited | NR |
| Gregor et al.[7] | 314 | 8-36/1-18 | Limited/extensive | EC |
| Hansen et al.[10] | 109 | 40/20 | Limited | NR |
| Jackson et al.[6] | 29 | 30/10 | Limited/extensive | SC |
| Kristjansen et al.[19] | 55 | 24/8 | Limited/extensive | NR |
| Laplanche et al.[5] | 211 | 24/8 | Limited/extensive | EC |
| Maurer et al.[14] | 153 | 30/10 | Limited/extensive | SC |
| Niiranen et al.[13] | 51 | 40/20 | Limited | SC |
| Ohonoshi et al.[11] | 46 | 40/20 | Limited/extensive | EC |
| Seydel et al.[9] | 217 | 30/10 | Limited | SC |
| Slotman et al.[16] | 286 | 20-30/5-12 | Extensive | EC |
| Wagner et al.[17] | 32 | 24/8 | Limited/extensive | EC |

PCI: prophylactic cranial irradiation; EC: at the end of chemotherapy; SC: at the start of chemotherapy; and NR: not reported.

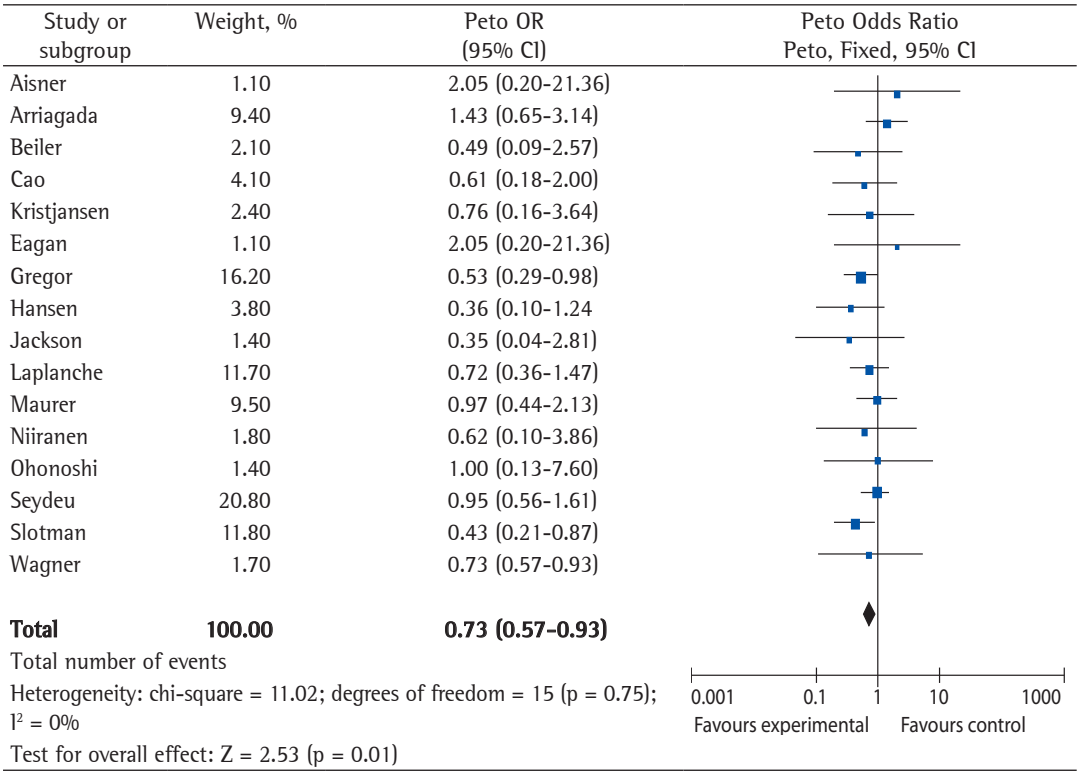


**Figure 1 -** Overall mortality.

without response to chemotherapy. The subgroup analysis showed that the patients who responded to chemotherapy (1,320 patients in 9 studies) benefited from PCI (OR = 0.68; 95% CI: 0.50-0.93; p = 0.02), with a 5% reduction in overall mortality, i.e., for every 20 patients treated, one death is avoided (Figure 2). However, those who did not respond to chemotherapy did not benefit from PCI (663 patients in 7 studies; OR = 0.81; 95% CI: 0.56-1.19; p = 0.29). There was no heterogeneity across studies (p = 0.57), which demonstrates that the results are valid.

### *Mortality and disease stage*

A subgroup analysis was performed to evaluate the impact of the extent of disease on mortality. To that end, the results were stratified by SCLC stage, and two groups were formed: one comprising patients with limited disease and the other comprising those with extensive disease. The subgroup analysis showed that the patients with limited disease (1,305 patients in 12 studies) benefited from PCI (OR = 0.73; 95% CI: 0.55-0.97; p = 0.03), with a 4% reduction in overall mortality, i.e., for every 25 patients treated, one death is avoided (Figure 3). Patients with extensive disease also benefited from PCI (423 patients in 8 studies; OR = 0.48; 95% CI: 0.26-0.87; p = 0.02), with an 8% reduction in overall mortality, i.e., for every 12 patients treated, one death is avoided (Figure 3). There was no heterogeneity across studies (p = 0.83), which demonstrates that the results are valid.

### *Mortality and time to PCI*

A subgroup analysis was performed to assess the time elapsed between induction chemotherapy and PCI, and two groups were formed: one comprising patients who underwent PCI at the start of induction treatment (chemotherapy/radiation therapy) and the other comprising those who underwent PCI after induction therapy. The subgroup analysis showed that the patients who underwent PCI after induction therapy (1,320 patients in 9 studies) benefited from PCI (OR = 0.68; 95% CI: 0.49-0.94; p = 0.03), with a

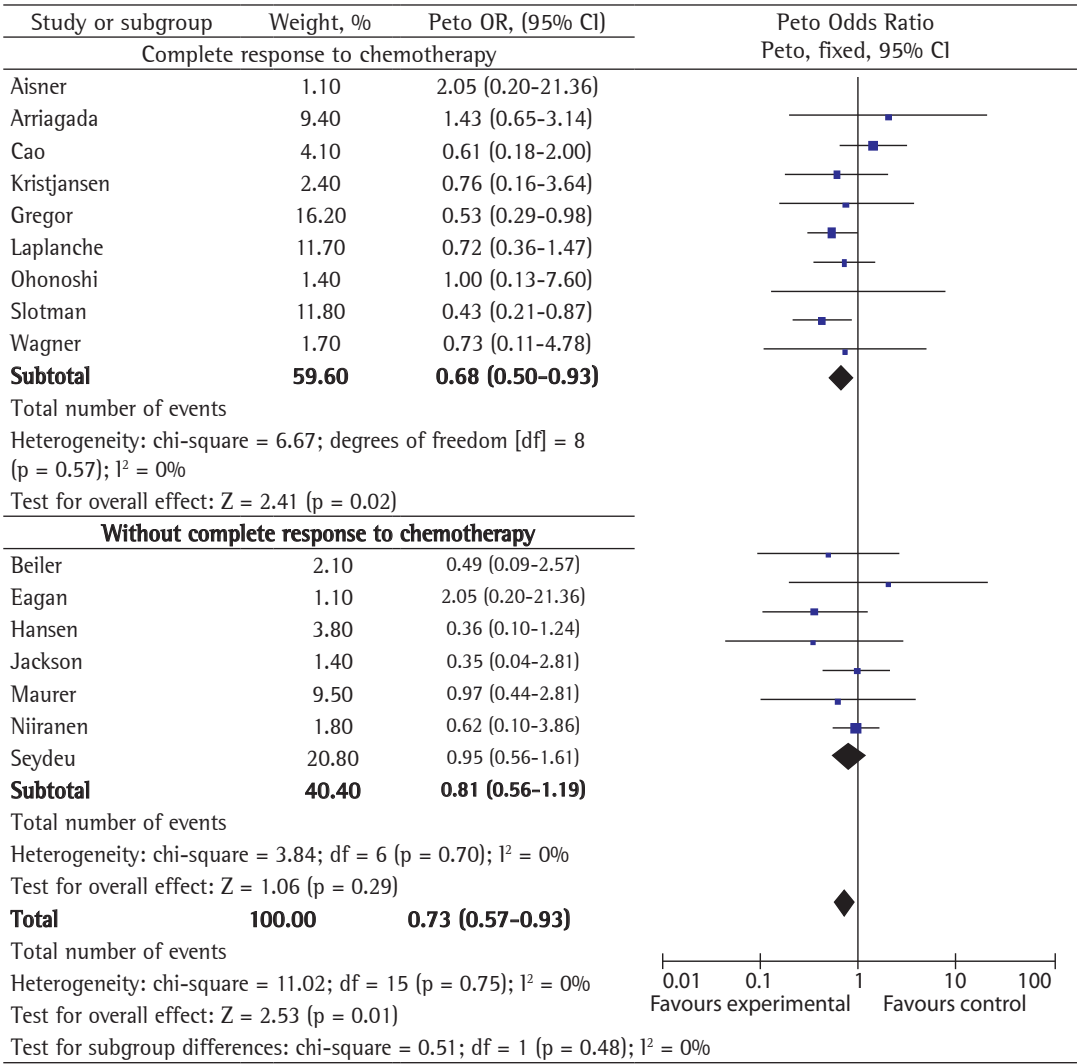


**Figure 2 -** Mortality and chemotherapy response.

| Study or subgroup | PCI Events | PCI Total | No PCI Events | No PCI Total | Weight, % | Peto OR (95% CI) |
|---|---|---|---|---|---|---|
| **Limited disease** | | | | | | |
| Aisner | 11 | 12 | 5 | 6 | 0.70 | 2.22 (0.11-45.94) |
| Arriagada | 108 | 124 | 105 | 120 | 11.50 | 0.96 (0.45-2.05) |
| Cao | 17 | 26 | 19 | 25 | 4.60 | 0.61 (0.18-2.00) |
| Kristjansen | 19 | 23 | 17 | 18 | 1.90 | 0.34 (0.05-2.19) |
| Eagan | 14 | 15 | 13 | 15 | 1.20 | 2.05 (0.20-21.36) |
| Gregor | 152 | 192 | 105 | 1129 | 17.90 | 0.53 (0.29-0.97) |
| Hansen | 46 | 54 | 52 | 55 | 4.20 | 0.36 (0.10-1.24) |
| Laplanche | 64 | 83 | 78 | 95 | 12.20 | 0.73 (0.35-1.53) |
| Niiranen | 22 | 25 | 24 | 26 | 1.90 | 0.62 (0.10-3.86) |
| Ohonoshi | 14 | 16 | 12 | 14 | 1.50 | 1.16 (0.15-9.24) |
| Seydeu | 55 | 107 | 58 | 110 | 23.10 | 0.95 (0.56-1.61) |
| Wagner | 11 | 14 | 10 | 11 | 1.50 | 0.41 (0.05-3.42) |
| **Subtotal** | | **691** | | **614** | **82.20** | **0.73 (0.55-0.97)** |
| Total number of events | 533 | | 498 | | | |
| Heterogeneity: chi-square = 6.26; degrees of freedom [df] = 11 (p = 0.86); $I^2$ = 0% | | | | | | |
| Test for overall effect: Z = 2.19 (p = 0.03) | | | | | | |
| **Extensive disease** | | | | | | |
| Aisner | 2 | 3 | 7 | 8 | 0.60 | 0.28 (0.01-7.44) |
| Arriagada | 25 | 25 | 30 | 31 | 0.40 | 6.09 (0.12-313.90) |
| Kristjansen | 5 | 5 | 7 | 9 | 0.70 | 5.39 (0.27-109.47) |
| Gregor | 1 | 2 | 1 | 1 | 0.40 | 0.22 (0.00-14.26) |
| Laplanche | 15 | 17 | 16 | 16 | 0.80 | 0.13 (0.01-2.26) |
| Ohonoshi | 6 | 7 | 8 | 9 | 0.80 | 0.76 (0.04-13.73) |
| Slotman | 117 | 143 | 132 | 143 | 13.70 | 0.40 (0.20-0.79) |
| Wagner | 3 | 3 | 3 | 4 | 0.40 | 5.75 (0.11-302.04) |
| **Subtotal** | | **205** | | **221** | **17.80** | **0.48 (0.26-0.87)** |
| Total number of events | 174 | | 204 | | | |
| Heterogeneity: chi-square = 7.00; df = 7 (p = 0.43); $I^2$ = 0% | | | | | | |
| Test for overall effect: Z = 2.40 (p = 0.02) | | | | | | |
| **Total** | | **896** | | **835** | **100.00** | **0.68 (0.52-0.87)** |
| Total number of events | 707 | | 702 | | | |
| Heterogeneity: chi-square = 14.83; df = 19 (p = 0.73); $I^2$ = 0% | | | | | | |
| Test for overall effect: Z = 3 (p = 0.003) | | | | | | |
| Test for subgroup differences: chi-square = 1.57; df = 1 (p = 0.21); $I^2$ = 36.1% | | | | | | |

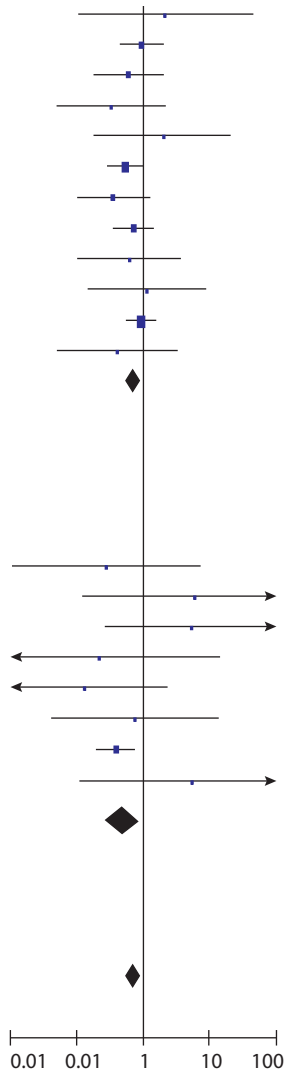


**Figure 3 -** Mortality and disease stage. PCI: prophylactic cranial irradiation.

5% reduction in overall mortality, i.e., for every 20 patients treated, one death is avoided (Figure 4). However, the patients who underwent PCI at the start of induction therapy did not benefit from PCI (663 patients in 7 studies; OR = 0.81; 95% CI: 0.56-1.19; p = 0.29). There was no heterogeneity across studies (p = 0.57), which demonstrates that the results are valid.

### *Mortality and PCI dose*

A subgroup analysis was performed to evaluate the impact of different PCI doses on overall mortality, and four groups were created on the basis of dose levels: < 20 Gy; 20-25 Gy; 25-30 Gy; and > 30 Gy. None of the dose levels contributed to reducing overall mortality in any of the subgroups, and a higher dose did not translate to a lower mortality rate (OR = 0.81; 95% CI: 0.56-1.19; p = 0.29).

## Discussion

In the late 1970s, RCTs comparing patients with SCLC in complete remission treated with PCI and those treated without PCI consistently

| Study or subgroup | PCI Events | PCI Total | No PCI Events | No PCI Total | Weight, % | Peto OR (95% CI) |
|---|---|---|---|---|---|---|
| **At the start of chemotherapy** | | | | | | |
| Beiler | 33 | 37 | 35 | 37 | 2.30 | 0.49 (0.09-2.57) |
| Jackson | 12 | 15 | 13 | 14 | 1.50 | 0.35 (0.04-2.81) |
| Maurer | 62 | 78 | 60 | 75 | 10.40 | 0.97 (0.44-2.13) |
| Niiranen | 22 | 25 | 24 | 26 | 1.90 | 0.62 (0.10-3.86) |
| Seydeu | 55 | 107 | 58 | 110 | 22.80 | 0.95 (0.56-1.61) |
| **Subtotal** | | **262** | | **262** | **39.00** | **0.86 (0.58; 1.30)** |
| Total number of events | 184 | | 190 | | | |
| Heterogeneity: chi-square = 1.50; degrees of freedom [df] = 4 (p = 0.83); $I^2$ = 0% | | | | | | |
| Test for overall effect: Z = 0.70 (p = 0.48) | | | | | | |
| **At the end of chemotherapy** | | | | | | |
| Aisner | 14 | 15 | 13 | 15 | 1.20 | 2.05 (0.20-21.36) |
| Arriagada | 133 | 144 | 135 | 151 | 10.30 | 1.43 (0.65-3.14) |
| Cao | 17 | 26 | 19 | 25 | 4.50 | 0.61 (0.18-2.00) |
| Gregor | 154 | 194 | 106 | 120 | 17.70 | 0.53 (0.29-0.98) |
| Laplanche | 80 | 100 | 94 | 11 | 12.80 | 0.72 (0.36-1.47) |
| Ohonoshi | 21 | 23 | 21 | 23 | 1.60 | 1.00 (0.13-7.60) |
| Slotman | 119 | 143 | 132 | 143 | 12.90 | 0.43 (0.21-0.87) |
| **Subtotal** | | **645** | | **588** | **61.00** | **0.68 (0.49-0.94)** |
| Total number of events | 538 | | 520 | | | |
| Heterogeneity: chi-square = 6.65; df = 6 (p = 0.35); $I^2$ = 1.0% | | | | | | |
| Test for overall effect: Z = 2.37 (p = 0.02) | | | | | | |
| **Total** | | **907** | | **850** | **100.00** | **0.74 (0.58-0.96)** |
| Total number of events | 722 | | 710 | | | |
| Heterogeneity: chi-square = 9.01; df = 11 (p = 0.62); $I^2$ = 0% | | | | | | |
| Test for overall effect: Z = 2.29 (p = 0.02) | | | | | | |
| Test for subgroup differences: chi-square = 0.86; df = 1 (p = 0.35); $I^2$ = 0% | | | | | | |

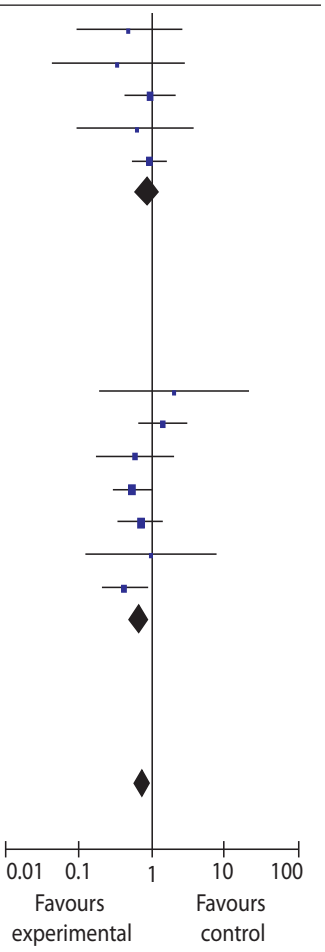


**Figure 4 -** Mortality and initiation of prophylactic cranial irradiation. PCI: prophylactic cranial irradiation.

showed a significant reduction in the incidence of brain metastases and no increase in evident neurological complications in the patients treated with PCI.[6,8-10,12] However, the beneficial effects of PCI on overall survival remained unclear until 1999, when one group of authors performed a meta-analysis of 7 RCTs involving 987 patients in order to guide clinical practice recommendations.[20] The clinical trials included in that meta-analysis met strict inclusion criteria, i.e., trials involving patients who were treated with systemic chemotherapy (with or without thoracic radiation therapy), who had a complete clinical response, and who were subsequently randomized to receive or not to receive PCI. The major finding of that meta-analysis was a significant improvement in the overall survival and disease-free survival of patients submitted to PCI. However, ever since that meta-analysis was published, questions have been raised about the optimal interval between induction chemotherapy and PCI initiation; about whether patients with extensive disease really benefit from PCI; and about the most effective radiation therapy dose. Therefore, the primary objective of our meta-analysis was to determine the subgroups of patients with SCLC that most benefit from PCI. By evaluating 1,983 patients enrolled in 16 RCTs, we found that PCI reduces mortality from SCLC by approximately 4%, particularly in patients who have a complete response to chemotherapy and who undergo PCI after induction chemotherapy, regardless of the disease stage. These findings are similar to those of the meta-analysis published in 1999,

in which the three-year survival rate for patients undergoing PCI was reported to have increased by 5.4%.[20] However, our meta-analysis differs from the 1999 meta-analysis in that we included RCTs involving patients with extensive disease and without response to chemotherapy.

In a meta-analysis published in 2001, Meert et al.[23] evaluated the effects of PCI on patients with SCLC in 12 RCTs (a total of 1,547 patients). The criteria for inclusion in that meta-analysis were similar to ours, allowing the inclusion of RCTs involving patients with extensive disease, with or without a complete response to chemotherapy. However, Meert et al.[23] found that PCI had no beneficial effects on overall survival in patients with extensive disease or in those who had not undergone cranial CT scan before randomization. We also found a reduction in mortality among the patients who received PCI after induction chemotherapy, a finding that was not reported in previous meta-analyses. We believe that this finding should be interpreted with caution, given that it does not reflect the time, in months or days, at which patients should receive PCI; rather, it probably reflects the selection of patients who have good rates of response to the initial treatment and who therefore will benefit from the treatment. Consequently, this finding does confirm the role of partial or complete response to induction chemotherapy as an important prognostic marker for treatment planning and selection. In addition, this finding raises the hypothesis that patients with any response to induction chemotherapy will benefit from PCI in terms of mortality, given that we included patients with any response to induction chemotherapy. Regarding the PCI dose, indirect evidence, derived from the meta-analysis cited above,[20] supports the notion that high PCI doses reduce the incidence of brain metastases. In that study, the PCI dose was analyzed by stratifying PCI into four dose levels (8 Gy; 24-25 Gy; 30 Gy; and 36-40 Gy).[20] We observed a statistically significant trend toward a better control of brain metastases with increasing total doses of radiation. Recently, the PCI dose was directly evaluated in a multicenter phase III clinical trial, in which 720 patients with limited-stage SCLC and complete response to the initial treatment were randomly assigned to receive PCI at a dose of 25 Gy (in 10 daily fractions of 2.5 Gy) or at a dose of 36 Gy (in 18 daily fractions of 2 Gy or in 24 fractions in 16 days with two daily sessions of 1.5 Gy separated by a minimum interval of 6 h).[24] Of the patients randomized to receive treatment with 36 Gy, 78% received PCI once a day. The two-year incidence of brain metastases was found to be 23% among those who received a PCI dose of 36 Gy and 29% among those who received a PCI dose of 25 Gy. The difference was not statistically significant (hazard ratio [HR] = 0.80; 95% CI: 0.57-1.11). However, the 36-Gy dose was associated with significantly lower two-year overall survival (37% vs. 42%; HR = 1.20; 95% CI: 1.00-1.44). To date, there has been no obvious explanation for the increased mortality of the patients who were treated with higher-dose PCI in that study.[24] Regarding the PCI dose, we found no statistically significant differences in patient mortality among the various dose levels used in the studies included in our meta-analysis. However, those results were not evaluated for response to chemotherapy or disease stage, which could mask any effect that an increase in the PCI dose might have on mortality.

In conclusion, the present meta-analysis suggests that PCI reduces mortality in patients with SCLC, especially in those who respond to induction chemotherapy and who undergo PCI after that treatment, regardless of the disease stage. Previous meta-analyses have reported that only patients with a complete response to induction chemotherapy benefit from PCI. However, our findings raise the hypothesis that patients with any response to induction chemotherapy will benefit from PCI. Consequently, PCI should be given as standard treatment in future studies involving such patients.

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