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The Prophylactic Cranial Irradiation Overview Collaborative Group.
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[Intervention Review]

Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

The Prophylactic Cranial Irradiation Overview Collaborative Group[1]

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ABSTRACT

Background

Prophylactic cranial irradiation halves the rate of brain metastases in patients with small cell lung cancer. Individual randomized trials conducted on patients in complete remission were unable to clarify whether this treatment improves survival.

Objectives

This study aims to test whether prophylactic cranial irradiation prolongs survival of patients with small cell lung cancer in complete remission.

Search methods

Published and unpublished trials were eligible. Electronic databases (Medline, Cancerlit, Excerpta Medica, Biosis from 1965 to 1998), reference lists of trial publications, review articles and relevant books were used to identify potentially eligible trials. The search was also guided by discussions with investigators and experts, and the examination of meeting proceedings and of the Physician Data Query clinical trial registry.

Selection criteria

Randomized trials comparing prophylactic cranial irradiation with no prophylactic cranial irradiation in patients with small cell lung cancer in complete remission.

Data collection and analysis

Meta-analysis based on updated individual data. The main endpoint was survival.

Main results

Seven trials with a total of 987 participants were included. The relative risk of death in the treatment group compared to the control group was 0.84 (95% confidence interval=0.73 to 0.97, P=0.01), corresponding to a 5.4 percent increase in the 3-year survival rate (from 15.3 percent in the control group to 20.7 percent in the treatment group). Prophylactic cranial irradiation also increased disease-free survival (relative risk=0.75, 95% confidence interval=0.65 to 0.86, P<0.001) and decreased the risk of brain metastases (relative risk=0.46, 95% confidence interval=0.38 to 0.57, P<0.001). Increasing doses of irradiation decreased the risk of brain metastases when

four groups (8 Gy, 24-25 Gy, 30 Gy, 36-40 Gy) were analyzed [trend test, P=0.02], but the effect on survival did not differ significantly according to the dose. We found a trend (P=0.01) for a decrease in the brain metastasis risk in favour of earlier administration of cranial irradiation after the initiation of induction treatment.

Authors' conclusions

Prophylactic cranial irradiation significantly improves survival and disease-free survival for patients with small cell lung cancer in complete remission. Further clinical trials are needed to confirm the potential greater benefit on brain metastasis rate suggested when cranial irradiation is given earlier or at higher doses.

PLAIN LANGUAGE SUMMARY

Prophylactic cranial irradiation improves survival rate of patients with small-cell lung cancer in complete remission

Small-cell lung cancer accounts for 20-25% of lung cancer. Treatment with chemotherapy and thoracic radiotherapy yields complete response rates of 50-85%. But, due to relapses, only 15% of patients who achieved complete response survived at 3 years since treatment. Tumour spread to brain (metastasis) is one of the main types of relapse, occurring in more than 50% of patients. Several clinical trials showed that prophylactic cranial irradiation (X-ray treatment of the brain for preventing brain metastasis) halves the rate of brain metastasis but they did not show whether this treatment can help people to live longer. This review found that prophylactic cranial irradiation given to patients in complete remission after initial treatment improves survival. At 3 years since treatment 20.7% of patients who received prophylactic cranial irradiation survived, compared to 15.3% for those who did not received this irradiation. Prophylactic cranial irradiation should now be considered part of the standard treatment of patients with small-cell lung cancer in complete remission.

BACKGROUND

In limited small cell lung cancer, chemotherapy combined with thoracic radiotherapy yields 50 to 85 percent complete response rates, a median survival duration of 12 to 20 months and 2-year disease-free survival rates of 15 to 40 percent (Albain 1990; Arriagada 1992; Turrisi 1999). Five-year survival rates may exceed 20 percent for complete responders (Turrisi 1999).

The risk of a thoracic recurrence decreases while brain metastasis becomes one of the main causes of treatment failure. Although only 10 percent of patients present brain metastases at the time of diagnosis, clinical series have reported a cumulative incidence at 2 years of more than 50 percent (Komaki 1985; Arriagada 1992), consistent with the rate found in autopsy series (Hirsch 1982). In the early 1970's, the brain was assumed to be a pharmacological sanctuary where subclinical metastases were protected from cytotoxic drugs by the blood-brain barrier (Hansen 1973), and it was suggested that cranial irradiation might prevent the development of clinically evident brain metastases.

These hypotheses led to several clinical trials evaluating the role of prophylactic cranial irradiation. Early small trials showed a decrease in the rate of brain metastasis but no evidence of improvement in survival (Kristjansen 1993). Rosen et al (Rosen 1983) reviewed retrospective data and suggested the potential prolongation in survival would be restricted to patients in complete remission because patients with residual extra-cranial cancer die of systemic cancer. In the early 1980's, some investigators (Catane 1981; Johnson 1990; Lee 1986; Lishner 1990; Frytak 1989) reported possible toxic effects on neuropsychological functions. However, most of them were seen in patients who had received prophylactic cranial irradiation concurrently with potentially neurotoxic drugs. A new generation of trials was conducted in patients in complete remission, and some of them included neuropsychological assessment. The results of these trials are consistent and show a significant decrease in the rate of brain metastases without an increase in neuropsychological complications (Arriagada 1992; Gregor 1997). These results however remain inconclusive as to the benefit on overall survival.

The Prophylactic Cranial Irradiation Overview (PCIO) collaborative group was created to undertake a meta-analysis based on individual patient data, with overall survival as the main endpoint. This review was first published in the New England Journal of Medicine on the 12th August 1999 (Aupérin 1999). Since then no further relevant trials have been published.

OBJECTIVES

To test whether prophylactic cranial irradiation might lead to a moderate improvement of survival of patients with small cell lung cancer in complete remission.

METHODS

Criteria for considering studies for this review

Types of studies

Eligible trials were those that randomized patients with small cell lung cancer in complete remission to receive prophylactic cranial irradiation (treatment group) or no prophylactic cranial irradiation (control group). Trials had to have been adequately randomized (randomization procedures in which clinicians could not know in advance which treatment would be allocated). Patient accrual had to have been completed between January 1965 and December 1995.

Types of participants

Patients with histologically proven small cell lung cancer, having achieved a complete response after induction treatment, with no brain metastasis before randomization and no previous cranial irradiation.

Types of interventions

Prophylactic cranial irradiation versus no prophylactic cranial irradiation.

Types of outcome measures

The main endpoint was overall survival, defined as the time from randomization until death due to any cause.

Secondary endpoints were disease-free survival (time from randomization until first event including death or relapse), the cumulative rate of brain metastasis, the cumulative rate of other metastases and the cumulative rate of loco-regional recurrence (patients who died without the event considered were censored at the date of death).

Search methods for identification of studies

The meta-analysis aimed to include both published and unpublished trials. There was no linguistic exclusion criteria. Electronic databases (Medline, Cancerlit, Excerpta Medica, Biosis, searching for small cell lung cancer/tumor/neoplasm, prophylactic cranial irradiation, randomized/phase 3 clinical trial, from 1965 to 1998), reference lists of trial publications, review articles and relevant books were used to identify potentially eligible trials. The search was also guided by discussions with investigators and experts, and the examination of meeting proceedings (American Society of Clinical Oncology, International Association for the Study of Lung Cancer) and the Physician Data Query clinical trial registry. After this search, no additional trials were found in the Cochrane Registry of clinical trials.

Data collection and analysis

Individual patient data were collected from the principal investigators for all patients randomized, including those who had been excluded from the investigator's own analyses. The following data were requested: identifiers, gender, age, performance status at the time of randomization, initial disease stage, induction treatment that led to a complete response, start date of induction treatment, randomization date, treatment allocated, and updated information on survival, brain metastasis, other metastases and loco-regional recurrence.

The quality of the trials was assessed. The quality of randomization was checked. Data were checked for internal consistency and compared with the trial protocol and published results. Range checks were performed and extreme values were verified with the trialists. As necessary, data were amended through correspondence with the investigators. Each trial was analysed individually, and the resulting survival analyses along with trial data were sent to the trialists for review.

All analyses were conducted on an intention-to-treat basis, that is, all randomized patients were included in the analyses according to the allocated treatment, irrespective of whether they received the treatment or whether they were excluded from the investigator's original analysis. Follow-up was quantified by the reverse Kaplan-Meier method (Schemper 1996).

The statistical method used has been described elsewhere (EBCTCG 1990). Analyses were performed with the logrank test adjusted for trials. Cox's model, stratified for trials, was used to adjust the analyses for the covariables.

For each trial, the relative risk (RR) of death in the treatment group to that in the control group was calculated. The pooled relative risk was estimated, with a 95% confidence interval. On the graphs, the relative risk is named Peto OR but it refers to the same concept. The percent reduction in the risk of death was estimated as 100 [1 - RR] and indicates the proportional reduction in mortality produced by treatment. Chi-square heterogeneity tests were used to test for statistical heterogeneity among trials. The absolute difference in the 3-year survival rate was calculated using the pooled relative risk and the survival rate in the control group; proportional hazards were assumed (Stewart 1993). Crude (non-

stratified for trial) Kaplan-Meier survival curves were plotted. The curves are not currently reproducible in the Cochrane Library but can be found in the original meta-analysis publication (Aupérin 1999). The same analyses were performed for the other endpoints. Indirect comparison of four subsets of trials defined according to the total dose of prophylactic cranial irradiation: 8 Gy, 24-25 Gy, 30 Gy, and 36-40 Gy was performed by a trend test taking into account the ordinal nature of the dose categories (EBCTCG 1990). In this analysis, the 36 patients randomized in the control group during the first period of the UKCCCR/EORTC trial (Gregor 1997) were counted twice: once as control to the patients who received prophylactic cranial irradiation at 24 Gy and once as control to the patients who received prophylactic cranial irradiation at 36 Gy.

Subgroup analyses were planned according to gender, age, performance status, initial disease stage, the type of induction treatment and time interval between initial treatment and randomization. All p values are two-tailed.

RESULTS

Description of studies

Searches identified 17 trials that randomized patients with small cell lung cancer between prophylactic cranial irradiation and observation.

Ten trials (Beiler 1979; Cox 1978; Eagan 1981; Hansen 1980; Jackson 1977; Katsensis 1982; Maurer 1980; Mountain 1982; Niiranen 1989; Seydel 1985) involving a total of 929 patients, were excluded from the analysis for one or more of the following reasons: the patients were randomized before the response to induction treatment was evaluated, one randomized prophylactic cranial irradiation versus mannitol (Eagan 1981), one used an inadequate randomization method (Beiler 1979), and one included patients with inoperable carcinoma of the lung, without stratification for the histologic diagnosis (Cox 1978).

Seven trials (Aroney 1983; Arriagada 1992; Gregor 1997; Laplanche 1998; Ohonoshi 1993; Wagner 1996; Danish/NCI) including 987 patients were eligible. Four trials were small, with 55 or fewer patients. The remaining three trials accounted for 84 percent of all patients. The PCI-88 trial (Laplanche 1998) was a simplified trial, without neuropsychological assessment, conducted in parallel with the PCI-85 trial (Arriagada 1992). The policy to determine complete remission differed in each trial, some required a simple chest X-ray and others a bronchoscopy and/or a chest CT-scan and/or a brain CT-scan. In all trials, except for the UKCCCR/EORTC trial (Gregor 1997), the recommended total dose of prophylactic cranial irradiation ranged from 24 Gy to 40 Gy given in 8 to 20 fractions, corresponding to a dose range per fraction of 2 to 3 Gy. The UKCCCR/EORTC trial (Gregor 1997) had two inclusion periods. During the first period, patients were randomized to three treatment arms: control group, prophylactic cranial irradiation at 24 Gy in 12 fractions and at 36 Gy in 18 fractions. During the second period, there were only two treatment arms: control group and prophylactic cranial irradiation group with a randomization ratio of 2 to 3. The recommended total dose was between 20 and 36 Gy, but the choice was left to individual centers. One center chose 8 Gy in one fraction. Since 120 patients were randomized in the control group and 194 in the treatment group, the overall number of patients included in the meta-analysis is different in the two arms (461 versus 526).

The characteristics of the 987 patients are shown in Table 1. Because the UKCCCR/EORTC trial (Gregor 1997) included only patients with limited disease and included more patients in the treatment group than in the control group, overall there were significantly more patients with extensive initial disease in the control group (P=0.02). This difference was no longer significant after adjustment for trial.

Risk of bias in included studies

All included trials were adequately randomized. Most patients were included after 1985, which accounts for the high quality of the data available. Only eight patients had been excluded from the investigator's original analyses: six had brain metastasis at randomization, one was not in complete remission and one refused irradiation after randomization. The analysis of survival in these meta-analysis was based on all patients.

Effects of interventions

Eight hundred and forty-six patients have died. The follow-up did not differ between the two groups: the median was 5.3 years in the control group and 5.9 years in the treatment group.

The combined result showed a significant survival benefit in the group assigned to prophylactic cranial irradiation as compared with the control group (P=0.01) with a pooled relative risk of 0.84 (95% confidence interval=0.73 to 0.97). Cox's model, adjusted for the extent of disease, gender and age led to the same relative risk value (0.83, P=0.009). Additional adjustment for the performance status, induction treatment and time between induction and randomization produced similar results. There was no evidence of statistical heterogeneity among trials. The result corresponded to a 16 percent (SD=6) reduction in the risk of death and to an absolute increase in survival of 5.4 percent at 3 years after randomization, from 15.3 percent to 20.7 percent. The survival benefit persisted beyond 3 years.

Other endpoints

The combined result showed that prophylactic cranial irradiation was significantly beneficial in reducing the rate of brain metastasis with a pooled relative risk of 0.46 (95% confidence interval=0.38

to 0.57, P<0.001). This result corresponded to a 54 percent (SD= 7) reduction in the risk of brain metastasis and to an absolute decrease in the cumulative rate of brain metastasis of 25.3 percent at 3 years, from 58.6 percent to 33.3 percent.

Data on the occurrence of metastases at other sites and loco-regional recurrences were available for only 67 percent of patients. Prophylactic cranial irradiation significantly improved disease-free survival (RR=0.75, 95% confidence interval=0.65 to 0.86) and did not have a significant effect on other metastases or on loco-regional recurrences. The results of analyses of the four secondary endpoints after adjustment for the covariables, particularly for the extent of disease, were similar.

Indirect comparison

Trials were subdivided into four categories according to radiation doses: 8 Gy in one fraction (Gregor 1997 period 2: one center), 24 to 25 Gy in 8 to 12 fractions (Gregor 1997 period 1; Arriagada 1992; Danish/NCI; Laplanche 1998; Wagner 1996), 30 Gy in 10 fractions (Aroney 1983; Gregor 1997 period 2), and 36 or 40 Gy in 18 or 20 fractions (Gregor 1997 period 1; Ohonoshi 1993). The effect of treatment on survival did not differ significantly according to the total dose (P=0.89). However, there was a significant trend (P=0.02) for reducing the risk of developing brain metastases as the radiation dose increased.

Subgroup analyses

Predefined subgroups of patients were analyzed to determine whether the treatment effect varied in size across subgroups. Data on gender, age and extent of initial disease were available for all randomized patients. Data on the performance status, induction treatment, and on the time interval between initial treatment and randomization were available for 641 (65 percent), 742 (75 percent) and 634 (64 percent) patients respectively. There was no evidence that any subgroup of patients benefited more or less from treatment, except for gender and the time interval between initial treatment and randomization.

There was some evidence of a differential effect on survival according to gender: the interaction test between the two relative risks was of borderline significance (P=0.07). Results for the 755 men were in favour of prophylactic cranial irradiation, whereas results for the 232 women showed no effect of prophylactic irradiation. There was some heterogeneity among trials in women (P=0.11): the relative risk of death were higher than one in three trials (Aroney 1983; Arriagada 1992; Laplanche 1998) which randomized 72 women. The relative risks of brain metastasis did not differ (P=0.87) between women and men but the rate of other metastases was lower in the control group than in the treatment group among women.

There was a significant trend (P=0.01) towards a greater effect of prophylactic cranial irradiation on the brain metastasis rate in patients randomized earlier than in those randomized later. However, the time interval between initial treatment and randomization had no effect on the relative risk of death.

DISCUSSION

This meta-analysis of seven randomized trials evaluating prophylactic cranial irradiation in 987 patients with small cell lung cancer in complete remission demonstrates that prophylactic cranial irradiation leads to a significant 16 percent reduction in mortality, even after adjustment for the extent of initial disease. The absolute impact on overall survival at 3 years is 5.4 percent. Prophylactic cranial irradiation not only significantly reduces the risk of developing brain metastases, as previously shown in individual trials, but overall and disease-free survival are also improved. This meta-analysis also confirms that prophylactic cranial irradiation prevents and not simply delays the emergence of brain metastases: the brain metastases curves plateau and become parallel after 2 years of follow-up. As the examinations required to determine complete response were heterogeneous among the trials included, one can speculate that prophylactic cranial irradiation might also be beneficial in patients with a good partial response assessed with the diagnostic methods used nowadays. The benefit was consistent across subgroups defined according to age, performance status, extent of initial disease and the type of induction therapy. However, prophylactic cranial irradiation seems to be less effective on survival in women than in men. There was no differential effect on brain metastasis but the rate of other metastases was lower in the control group than in the treatment group for women. As this is a subgroup analysis, which is moreover of borderline significance, this result should be interpreted with caution. Moreover, there is some heterogeneity across trials among women. Although women have better survival than men (data not shown), there is no hypothesis to explain this difference in effect.

In the 1980's, several non randomized studies reported neuropsychological impairment and abnormalities on brain CT-scan that were potentially related to prophylactic cranial irradiation (Catane 1981; Johnson 1990; Lee 1986; Lishner 1990; Frytak 1989). Recently, a study on patients treated by prophylactic cranial irradiation given concomitantly with chemotherapy suggested that this association had a negative impact on cognitive function assessed immediately after the end of treatment (Ahles 1998). The randomized trial is the only context allowing valid comparisons of the neuropsychological functions between patients receiving prophylactic cranial irradiation and patients not receiving prophylactic cranial irradiation, as many confounding factors such as age, chronic tobacco abuse, paraneoplastic syndromes, micro-metastases and the neurotoxicity of anticancer drugs may produce effects that may erroneously be attributed to prophylactic irradiation. Whether prophylactic cranial irradiation leads to neuropsychological sequelae could not be addressed in this meta-analysis as only two randomized trials conducted a neuropsychological evaluation (Arriagada 1992; Gregor 1997). The initial neuropsychological assessment, performed in 350 patients in these trials before randomization, revealed that many patients in the two groups had abnormalities initially (from 24 to 60 percent according to the neuropsycholog-

ical test). The results within the first years of follow-up showed no significant difference in neuropsychological modifications nor in the rate of brain CT-scan abnormalities between treated and untreated patients. These results partly dissipated concern about neuropsychological sequelae even though a longer follow-up would be highly desirable for a definitive conclusion. Prophylactic cranial irradiation could be well tolerated provided small fractions are used (< 3 Gy) and without concomitant chemotherapy.

The duration of survival has increased with more effective systemic chemotherapy combined with thoracic radiotherapy (Arriagada 1992; Murray 1993; Johnson 1996), so the cumulative risk of developing brain metastases has become higher, accompanied by distressing, debilitating symptoms (Arriagada 1992; Gregor 1997; Johnson 1996). As the mean duration of survival is brief after developing brain metastases, approximately 4.5 months, despite treatment with cranial irradiation at full doses (Arriagada 1992), the overriding objective at this point is prevention. Moreover, one potential advantage of prophylactic cranial irradiation is improved quality of life (Rosen 1983).

The magnitude of the effect of prophylactic cranial irradiation on survival found in this meta-analysis (5.4 percent from 15.3 percent without prophylatic cranial irradiation to 20.7 percent with prophylactic cranial irradiation at 3 years after randomization for prophylactic cranial irradiation) is similar to that previously found for thoracic radiotherapy in small cell lung cancer (5.4 percent from 8.9 percent without thoracic radiotherapy to 14.3 percent with thoracic radiotherapy at 3 years after start of induction chemotherapy) (Pignon 1992). Most of the patients in the present meta-analysis received thoracic radiotherapy. As the mechanisms of action of these two modalities are different, it is likely that both of the beneficial effects can be summed.

Although no significant difference was found in survival according to the total dose of irradiation, this meta-analysis suggested that the observed reduction in the risk of brain metastases increased with total dose. A dose-response relationship was also found in a recent review (Suwinski 1998). The dose-response curve was almost linear within the 20 to 35 Gy dose range. Furthermore, when prophylactic cranial irradiation was delayed to over 60 days after initiating induction treatment, higher doses were necessary. In our study, there was a significant trend towards a greater reduction in the brain metastasis rate among patients who received prophylactic cranial irradiation earlier. Only one small randomized trial has prospectively investigated the impact of the timing of prophylactic cranial irradiation. However this factor was confounded with the timing of chemotherapy and the study failed to show a difference in the frequency of brain metastases according to whether prophylactic irradiation was delivered at the start of induction treatment or 6 weeks later (Perez 1981).

AUTHORS' CONCLUSIONS

Implications for practice

Prophylactic cranial irradiation should now be considered as part of the standard treatment of patients with small cell lung cancer in complete remission.

Implications for research

Establishing the optimal dose and timing of treatment so as to reduce further the incidence of brain metastases with minimal and acceptable toxicity should be the aim of future clinical trials.

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UKCCCR/EORTC trial (Gregor 1997): Anna Gregor, Richard J. Stephens

UMCC trial (Aroney 1983): Joseph Aisner, Margaret Whitacre

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aroney 1983

Methods	1977-1980 Parallel design Unblinded	
Participants	29 patients 62 years median FU 18.5 years	
Interventions	RT 30 Gy / 10 fractions	
Outcomes	Brain metastasis Survival Local recurrence Other metastasis	
Notes	Induction therapy CT	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Arriagada 1995

Methods	1985-1993 Parallel design Unblinded	
Participants	300 patients 56 years median FU 8.4 years	
Interventions	RT 24 Gy / 8 fractions	
Outcomes	Brain metastasis Survival Local recurrence Other metastasis	
Notes	Induction therapy CT or CT plus RT	
Risk of bias		

Arriagada 1995 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Danish/NCI

Methods	1985-1991 Parallel design Unblinded
Participants	55 patients 59 years median FU 8.8 years
Interventions	RT 24 Gy / 8 fractions
Outcomes	Brain metastasis Survival Local recurrence Other metastasis
Notes	Induction therapy CT

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Gregor 1997

Methods	1987-1995 Parallel design Unblinded
Participants	314 patients 59 years Limited disease median FU 3.5 years
Interventions	RT 8-36 Gy /1-18 fractions
Outcomes	Brain metastasis Survival Neuropsychological assessment
Notes	Induction therapy CT or CT plus RT

Gregor 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Laplanche 1998

Methods	1988-1994 Parallel design Unblinded
Participants	211 patients 57 years median FU 5.1 years
Interventions	RT 24 Gy / 8 fractions
Outcomes	Brain metastasis Survival Local recurrence Other metastasis Neuropsychological assessment
Notes	Induction therapy CT or CT plus RT

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Ohonoshi 1993

Methods	1981-1986 Parallel design Unblinded
Participants	46 patients 63 years median FU 11.7 years
Interventions	RT 40 Gy / 20 fractions
Outcomes	Brain metastasis Survival Local recurrence

Ohonoshi 1993 (*Continued*)

	Other metastasis	
Notes	Induction therapy CT or CT plus RT	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Wagner 1996

Methods	1991-1994 Parallel design Unblinded	
Participants	32 patients median FU 3.9 years	
Interventions	RT 24 Gy / 8 fractions	
Outcomes	Brain metastasis Survival Local recurrence Other metastasis	
Notes	Induction therapy CT or CT plus RT	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

FU Follow up
RT Radiotherapy

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beiler 1979	Randomized patients before the response to induction therapy was evaluated. Inadequate randomization method.
Cox 1978	Randomized patients before the response to induction therapy was evaluated. Included patients with inoperable carcinoma of the lung, without stratification for the histologic diagnosis
Eagan 1981	Randomized patients before the response to induction therapy was evaluated. Randomized prophylactic cranial irradiation versus mannitol.
Hansen 1980	Randomized patients before the response to induction therapy was evaluated
Jackson 1977	Randomized patients before the response to induction therapy was evaluated
Katsensis 1982	Randomized patients before the response to induction therapy was evaluated
Maurer 1980	Randomized patients before the response to induction therapy was evaluated
Mountain 1982	Randomized patients before the response to induction therapy was evaluated
Niiranen 1989	Randomized patients before the response to induction therapy was evaluated
Seydel 1985	Randomized patients before the response to induction therapy was evaluated

DATA AND ANALYSES

Comparison 1. Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	7	987	Peto Odds Ratio (95% CI)	0.84 [0.73, 0.97]
2 Brain metastasis	7	981	Peto Odds Ratio (95% CI)	0.46 [0.38, 0.57]
3 Disease-free survival	7	987	Peto Odds Ratio (95% CI)	0.75 [0.65, 0.86]
4 Other metastasis	6	657	Peto Odds Ratio (95% CI)	0.89 [0.69, 1.15]
5 Local or regional recurrence	6	657	Peto Odds Ratio (95% CI)	0.97 [0.75, 1.26]
6 Survival by total dose of cranial irradiation	7	1023	Peto Odds Ratio (95% CI)	0.85 [0.74, 0.97]
6.1 8 Gy	1	42	Peto Odds Ratio (95% CI)	0.69 [0.35, 1.37]
6.2 24-25 Gy	5	670	Peto Odds Ratio (95% CI)	0.88 [0.75, 1.04]
6.3 30 Gy	2	201	Peto Odds Ratio (95% CI)	0.81 [0.59, 1.12]
6.4 36-40 Gy	2	110	Peto Odds Ratio (95% CI)	0.81 [0.54, 1.20]
7 Brain metastasis by total dose of cranial irradiation	7	1017	Peto Odds Ratio (95% CI)	0.47 [0.38, 0.58]
7.1 8 Gy	1	42	Peto Odds Ratio (95% CI)	0.76 [0.28, 2.10]
7.2 24-25 Gy	5	667	Peto Odds Ratio (95% CI)	0.52 [0.41, 0.67]
7.3 30 Gy	2	198	Peto Odds Ratio (95% CI)	0.34 [0.19, 0.59]
7.4 36-40 Gy	2	110	Peto Odds Ratio (95% CI)	0.27 [0.14, 0.51]
8 Survival by age	7	987	Peto Odds Ratio (95% CI)	0.85 [0.74, 0.98]
8.1 <=54 years	7	305	Peto Odds Ratio (95% CI)	0.84 [0.65, 1.08]
8.2 55-64 years	7	435	Peto Odds Ratio (95% CI)	0.90 [0.73, 1.11]
8.3 >=65 years	7	247	Peto Odds Ratio (95% CI)	0.79 [0.60, 1.03]
9 Brain metastasis by age	7	981	Peto Odds Ratio (95% CI)	0.48 [0.39, 0.59]
9.1 <=54 years	7	304	Peto Odds Ratio (95% CI)	0.55 [0.39, 0.77]
9.2 55-64 years	7	432	Peto Odds Ratio (95% CI)	0.49 [0.35, 0.68]
9.3 >=65 years	7	245	Peto Odds Ratio (95% CI)	0.37 [0.24, 0.59]
10 Survival by extend of initial disease	7	987	Peto Odds Ratio (95% CI)	0.84 [0.73, 0.97]
10.1 Limited	7	847	Peto Odds Ratio (95% CI)	0.85 [0.73, 0.99]
10.2 Extensive	7	140	Peto Odds Ratio (95% CI)	0.77 [0.54, 1.11]
11 Brain metastasis by extend of initial disease	7	981	Peto Odds Ratio (95% CI)	0.46 [0.38, 0.57]
11.1 limited	7	844	Peto Odds Ratio (95% CI)	0.48 [0.38, 0.61]
11.2 Extensive	7	137	Peto Odds Ratio (95% CI)	0.38 [0.23, 0.64]
12 Survival by performance status	5	641	Peto Odds Ratio (95% CI)	0.83 [0.70, 0.98]
12.1 PS 0	5	427	Peto Odds Ratio (95% CI)	0.85 [0.69, 1.05]
12.2 PS 1-3	5	214	Peto Odds Ratio (95% CI)	0.78 [0.58, 1.04]
13 Brain metastasis by performance status	5	638	Peto Odds Ratio (95% CI)	0.48 [0.37, 0.61]
13.1 PS 0	5	425	Peto Odds Ratio (95% CI)	0.47 [0.35, 0.63]
13.2 PS 1-3	5	213	Peto Odds Ratio (95% CI)	0.50 [0.32, 0.78]
14 Survival by induction therapy	5	742	Peto Odds Ratio (95% CI)	0.86 [0.74, 1.01]
14.1 Chemotherapy plus thoracic radiotherapy	4	562	Peto Odds Ratio (95% CI)	0.86 [0.71, 1.03]

14.2 Chemotherapy without thoracic radiotherapy	5	180	Peto Odds Ratio (95% CI)	0.88 [0.64, 1.21]
15 Brain metastasis by induction therapy	5	736	Peto Odds Ratio (95% CI)	0.43 [0.33, 0.54]
15.1 Chemotherapy plus thoracic radiotherapy	4	562	Peto Odds Ratio (95% CI)	0.43 [0.33, 0.57]
15.2 Chemotherapy without thoracic radiotherapy	5	174	Peto Odds Ratio (95% CI)	0.40 [0.23, 0.67]
16 Survival by sex	7	987	Peto Odds Ratio (95% CI)	0.82 [0.71, 0.94]
16.1 Male	7	755	Peto Odds Ratio (95% CI)	0.77 [0.66, 0.90]
16.2 Female	7	232	Peto Odds Ratio (95% CI)	1.05 [0.78, 1.42]
17 Brain metastasis by sex	7	981	Peto Odds Ratio (95% CI)	0.48 [0.38, 0.59]
17.1 Male	7	749	Peto Odds Ratio (95% CI)	0.47 [0.37, 0.60]
17.2 Female	7	232	Peto Odds Ratio (95% CI)	0.50 [0.32, 0.78]
18 Survival by time between start of induction therapy and randomization	5	633	Peto Odds Ratio (95% CI)	0.88 [0.75, 1.05]
18.1 <4months	5	161	Peto Odds Ratio (95% CI)	0.92 [0.66, 1.29]
18.2 4-6 months	5	279	Peto Odds Ratio (95% CI)	0.79 [0.61, 1.02]
18.3 >6 months	4	193	Peto Odds Ratio (95% CI)	1.01 [0.74, 1.38]
19 Brain metastasis by time between start of induction therapy and randomization	5	627	Peto Odds Ratio (95% CI)	0.48 [0.37, 0.62]
19.1 <4 months	5	158	Peto Odds Ratio (95% CI)	0.27 [0.16, 0.46]
19.2 4-6 months	5	276	Peto Odds Ratio (95% CI)	0.50 [0.35, 0.72]
19.3 >6 months	4	193	Peto Odds Ratio (95% CI)	0.69 [0.44, 1.08]

Analysis 1.1. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 1 Survival.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

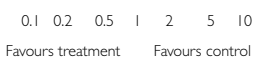
Outcome: 1 Survival

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
Aroney 1983	14/15	13/14		3.3 %	1.06 [0.50, 2.26]
Arriagada 1995	133/149	135/151		32.5 %	0.87 [0.69, 1.11]
Danish/NCI	24/28	24/27		5.8 %	0.86 [0.49, 1.52]
Gregor 1997	154/194	106/120		29.5 %	0.85 [0.66, 1.09]
Laplanche 1998	80/100	94/111		21.1 %	0.84 [0.62, 1.13]
Ohonoshi 1993	21/23	21/23		4.9 %	0.69 [0.37, 1.27]
Wagner 1996	14/17	13/15		3.0 %	0.59 [0.27, 1.31]
Total (95% CI)				**100.0 %**	**0.84 [0.73, 0.97]**

Heterogeneity: Chi^2 = 1.64, df = 6 (P = 0.95); I^2 =0.0%

Test for overall effect: Z = 2.45 (P = 0.014)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 2 Brain metastasis.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 2 Brain metastasis

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
Aroney 1983	0/14	5/12		1.4 %	0.10 [0.02, 0.56]
Arriagada 1995	46/149	87/151		37.1 %	0.41 [0.29, 0.58]
Danish/NCI	10/27	13/25		6.5 %	0.67 [0.30, 1.53]
Gregor 1997	46/194	54/120		26.0 %	0.44 [0.29, 0.66]
Laplanche 1998	32/100	44/111		21.6 %	0.71 [0.45, 1.12]
Ohonoshi 1993	5/23	11/23		4.4 %	0.32 [0.12, 0.87]
Wagner 1996	4/17	8/15		3.0 %	0.23 [0.07, 0.76]
Total (95% CI)				**100.0 %**	**0.46 [0.38, 0.57]**

Heterogeneity: Chi² = 9.71, df = 6 (P = 0.14); I² =38%

Test for overall effect: Z = 7.18 (P < 0.00001)

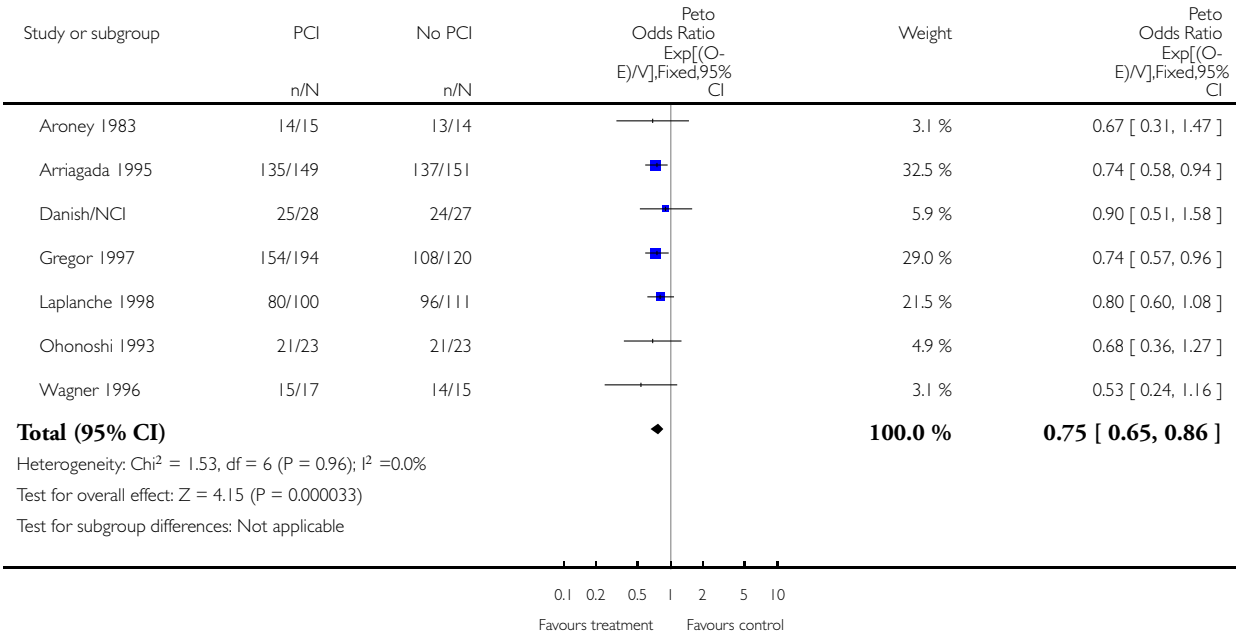
Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 3 Disease-free survival.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 3 Disease-free survival

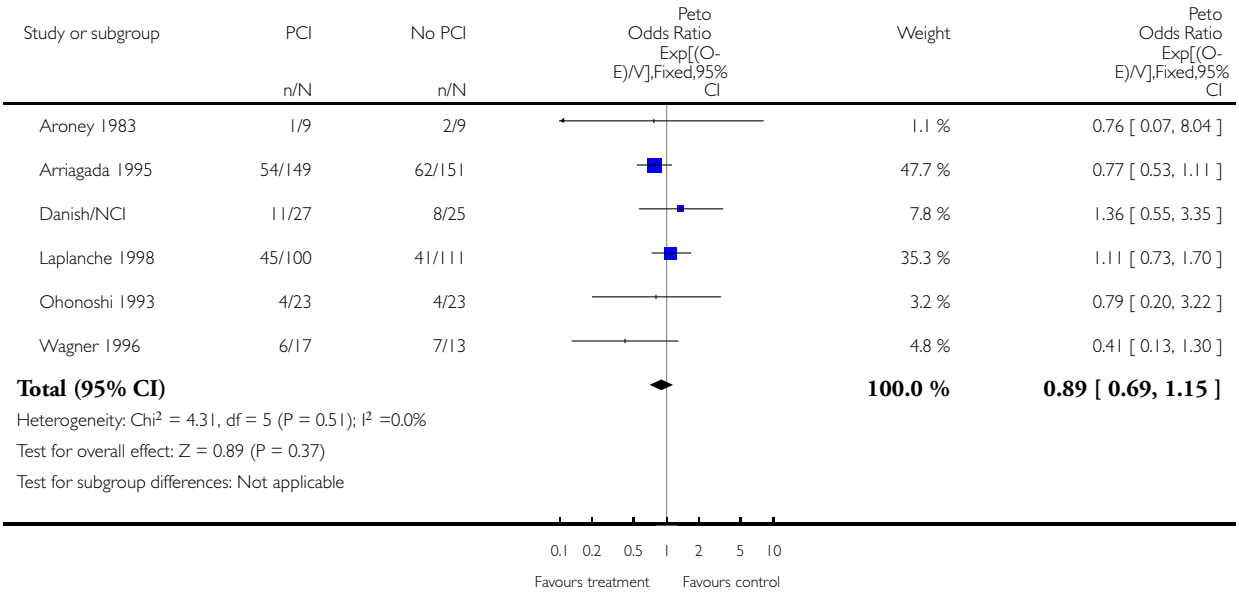


Analysis 1.4. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 4 Other metastasis.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 4 Other metastasis

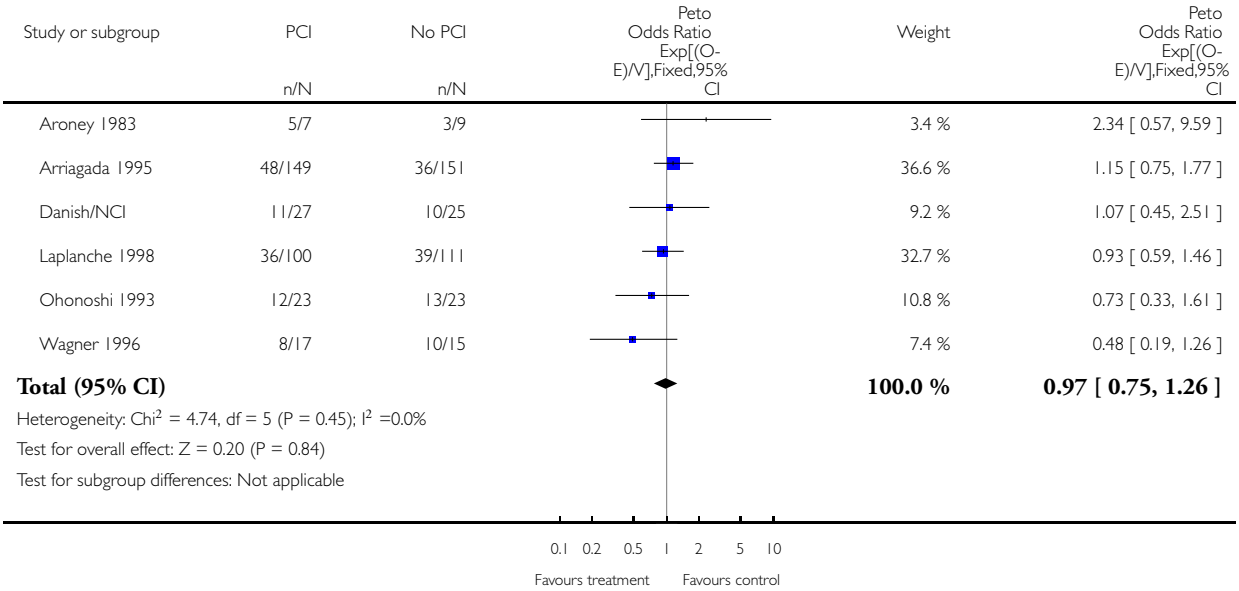


Analysis 1.5. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 5 Local or regional recurrence.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 5 Local or regional recurrence



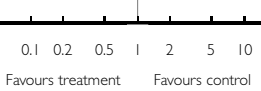
Analysis 1.6. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 6 Survival by total dose of cranial irradiation.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 6 Survival by total dose of cranial irradiation

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 8 Gy					
Gregor 1997	21/26	16/16		3.9 %	0.69 [0.35, 1.37]
Subtotal (95% CI)	**26**	**16**		**3.9 %**	**0.69 [0.35, 1.37]**
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
2 24-25 Gy					
Arriagada 1995	133/149	135/151		31.2 %	0.87 [0.69, 1.11]
Danish/NCI	24/28	24/27		5.5 %	0.86 [0.48, 1.52]
Gregor 1997	31/36	34/36		7.4 %	1.21 [0.74, 1.98]
Laplanche 1998	80/100	94/111		20.2 %	0.84 [0.62, 1.13]
Wagner 1996	14/17	13/15		2.9 %	0.59 [0.27, 1.31]
Subtotal (95% CI)	**330**	**340**		**67.3 %**	**0.88 [0.75, 1.04]**
Heterogeneity: Chi^2 = 2.65, df = 4 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.54 (P = 0.12)					
3 30 Gy					
Aroney 1983	14/15	13/14		3.1 %	1.06 [0.50, 2.26]
Gregor 1997	78/104	56/68		14.4 %	0.77 [0.54, 1.09]
Subtotal (95% CI)	**119**	**82**		**17.5 %**	**0.81 [0.59, 1.12]**
Heterogeneity: Chi^2 = 0.58, df = 1 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 1.28 (P = 0.20)					
4 36-40 Gy					
Gregor 1997	24/28	34/36		6.6 %	0.91 [0.54, 1.53]
Ohonoshi 1993	21/23	21/23		4.7 %	0.68 [0.37, 1.27]
Subtotal (95% CI)	**51**	**59**		**11.3 %**	**0.81 [0.54, 1.20]**
Heterogeneity: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 1.05 (P = 0.29)					
Total (95% CI)				**100.0 %**	**0.85 [0.74, 0.97]**
Heterogeneity: Chi^2 = 4.34, df = 9 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 2.36 (P = 0.018)					
Test for subgroup differences: Chi^2 = 0.64, df = 3 (P = 0.89), I^2 =0.0%					

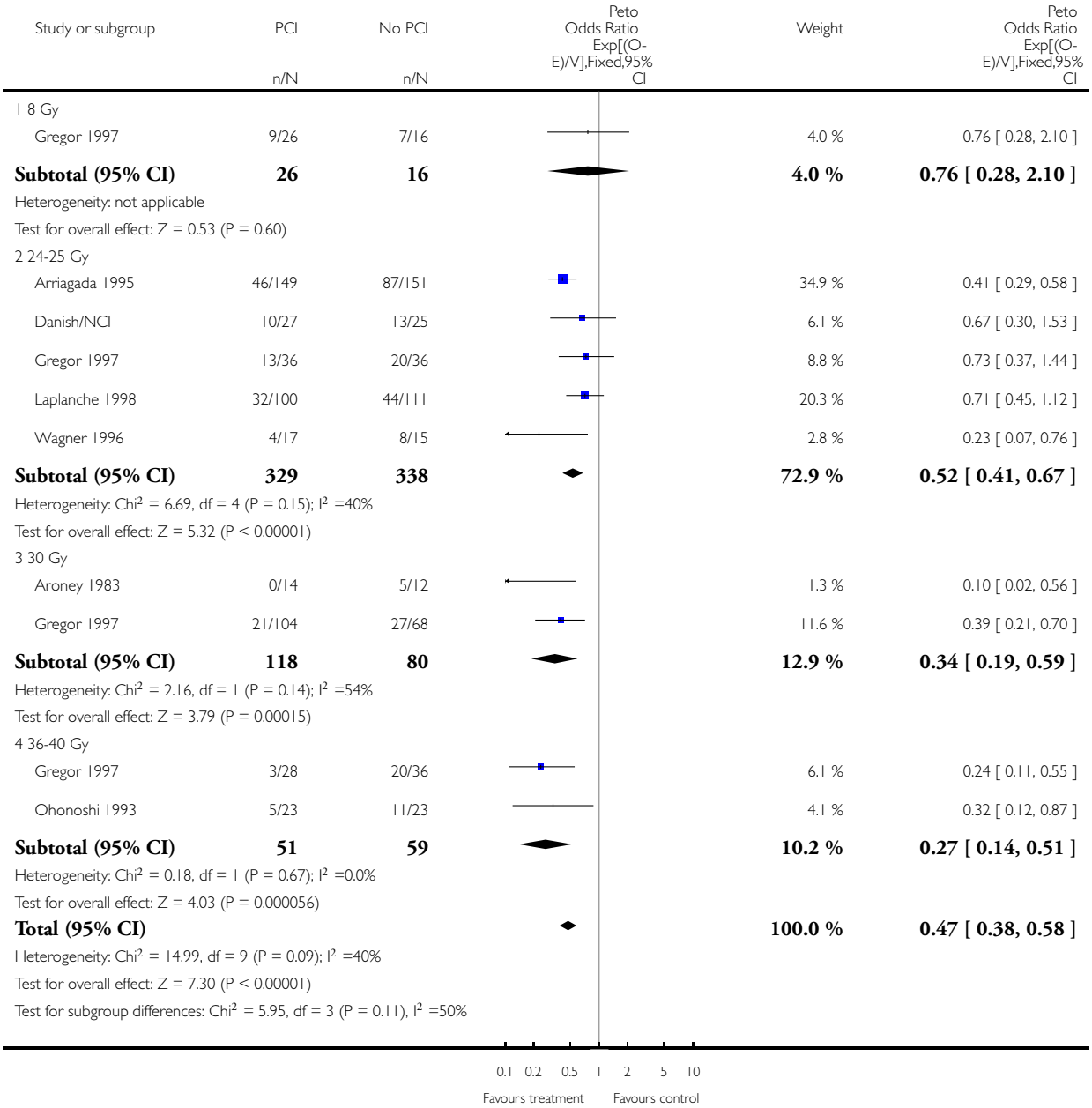


Analysis 1.7. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 7 Brain metastasis by total dose of cranial irradiation.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 7 Brain metastasis by total dose of cranial irradiation



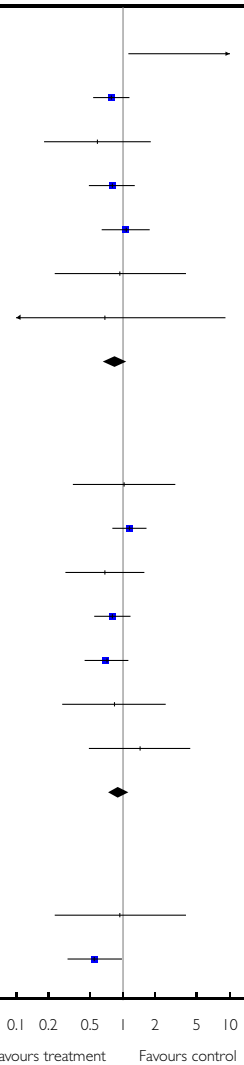
Analysis 1.8. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 8 Survival by age.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 8 Survival by age

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 <=54 years					
Aroney 1983	1/1	4/4		0.1 %	148.41 [1.11, 19928.58]
Arriagada 1995	42/50	59/64		12.7 %	0.78 [0.53, 1.15]
Danish/NCI	5/8	7/9		1.5 %	0.57 [0.18, 1.81]
Gregor 1997	34/47	30/35		7.8 %	0.79 [0.48, 1.30]
Laplanche 1998	26/33	31/40		7.1 %	1.06 [0.63, 1.79]
Ohonoshi 1993	4/4	4/5		1.0 %	0.94 [0.23, 3.85]
Wagner 1996	3/4	1/1		0.3 %	0.68 [0.05, 9.12]
Subtotal (95% CI)	**147**	**158**		**30.4 %**	**0.84 [0.65, 1.08]**
Heterogeneity: Chi^2 = 5.73, df = 6 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 1.34 (P = 0.18)					
2 55-64 years					
Aroney 1983	7/8	6/6		1.6 %	1.03 [0.34, 3.08]
Arriagada 1995	69/75	50/59		14.8 %	1.15 [0.80, 1.65]
Danish/NCI	12/13	11/12		2.7 %	0.68 [0.29, 1.60]
Gregor 1997	74/96	44/50		13.0 %	0.79 [0.54, 1.17]
Laplanche 1998	33/43	38/43		8.6 %	0.70 [0.44, 1.13]
Ohonoshi 1993	5/6	8/8		1.6 %	0.83 [0.27, 2.54]
Wagner 1996	8/9	5/7		1.6 %	1.44 [0.48, 4.31]
Subtotal (95% CI)	**250**	**185**		**43.9 %**	**0.90 [0.73, 1.11]**
Heterogeneity: Chi^2 = 4.42, df = 6 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 0.99 (P = 0.32)					
3 >=65 years					
Aroney 1983	6/6	3/4		1.0 %	0.94 [0.23, 3.91]
Arriagada 1995	22/24	26/28		5.6 %	0.54 [0.30, 0.98]



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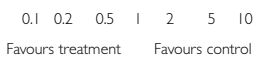
Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
Danish/NCI	7/7	6/6		1.1 %	4.02 [1.09, 14.85]
Gregor 1997	46/51	32/35		9.3 %	1.02 [0.64, 1.60]
Laplanche 1998	21/24	25/28		5.7 %	0.78 [0.43, 1.39]
Ohonoshi 1993	12/13	9/10		2.1 %	0.50 [0.19, 1.34]
Wagner 1996	3/4	7/7		0.9 %	0.17 [0.04, 0.73]
Subtotal (95% CI)	**129**	**118**		**25.7 %**	**0.79 [0.60, 1.03]**
Heterogeneity: Chi^2 = 13.82, df = 6 (P = 0.03); I^2 =57%					
Test for overall effect: Z = 1.72 (P = 0.086)					
Total (95% CI)				**100.0 %**	**0.85 [0.74, 0.98]**
Heterogeneity: Chi^2 = 24.56, df = 20 (P = 0.22); I^2 =19%					
Test for overall effect: Z = 2.27 (P = 0.023)					
Test for subgroup differences: Chi^2 = 0.59, df = 2 (P = 0.74), I^2 =0.0%					

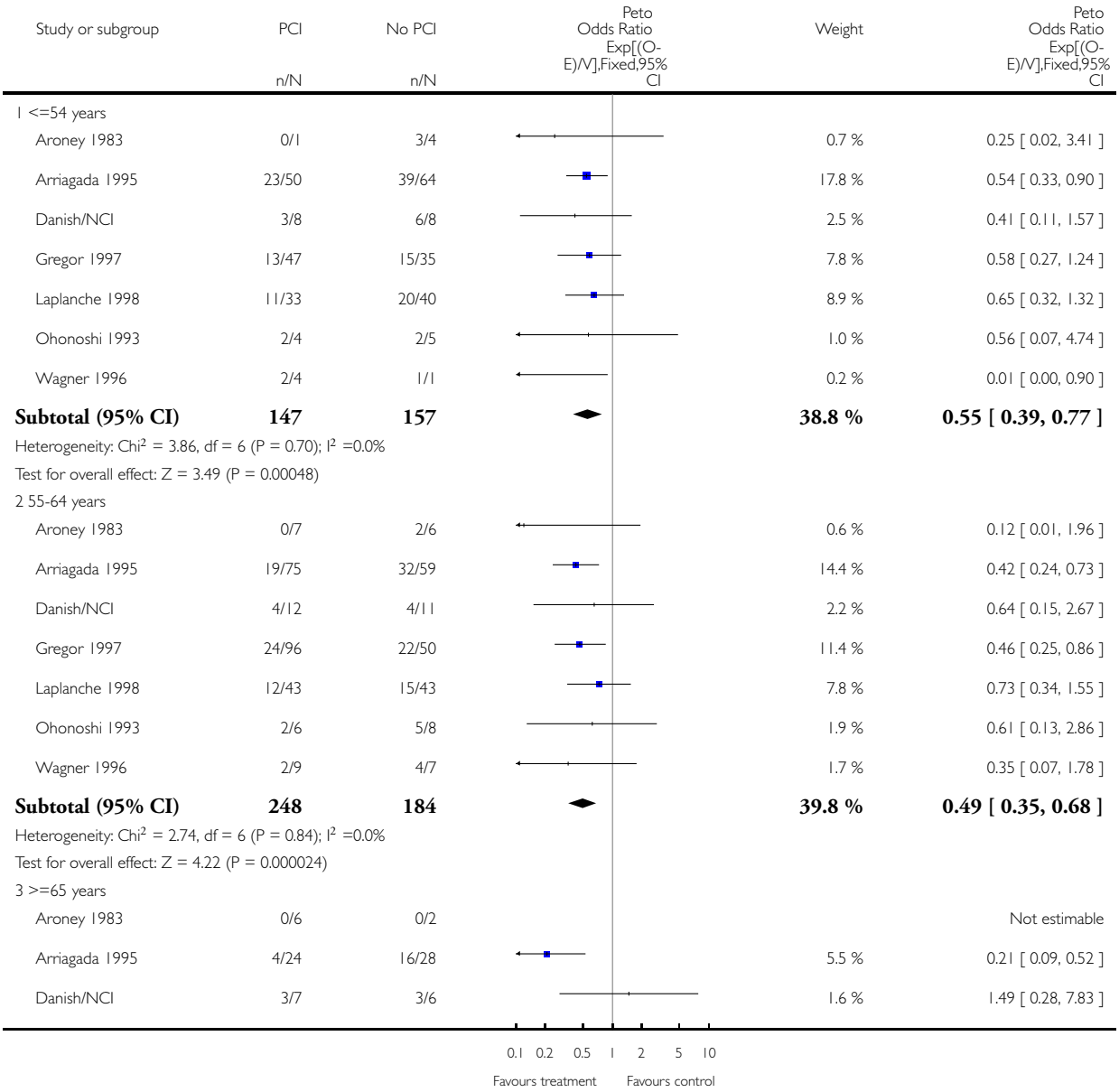


Analysis 1.9. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 9 Brain metastasis by age.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 9 Brain metastasis by age



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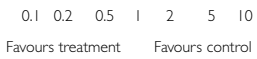
Study or subgroup	PCI	No PCI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
	n/N	n/N			
Gregor 1997	9/51	17/35		7.0 %	0.30 [0.13, 0.66]
Laplanche 1998	9/24	9/28		5.2 %	0.92 [0.36, 2.32]
Ohonoshi 1993	1/13	4/10		1.2 %	0.11 [0.02, 0.73]
Wagner 1996	0/4	3/7		0.8 %	0.17 [0.02, 1.65]
Subtotal (95% CI)	**129**	**116**		**21.4 %**	**0.37 [0.24, 0.59]**
Heterogeneity: Chi² = 10.20, df = 5 (P = 0.07); I² =51%					
Test for overall effect: Z = 4.25 (P = 0.000022)					
Total (95% CI)				**100.0 %**	**0.48 [0.39, 0.59]**
Heterogeneity: Chi² = 18.56, df = 19 (P = 0.49); I² =0.0%					
Test for overall effect: Z = 6.81 (P < 0.00001)					
Test for subgroup differences: Chi² = 1.77, df = 2 (P = 0.41), I² =0.0%					



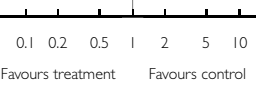
Analysis 1.10. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 10 Survival by extend of initial disease.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 10 Survival by extend of initial disease

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 Limited					
Aroney 1983	11/12	5/6		1.8 %	1.26 [0.45, 3.52]
Arriagada 1995	108/124	105/120		26.5 %	0.90 [0.69, 1.18]
Danish/NCI	19/23	17/18		4.4 %	0.90 [0.46, 1.74]
Gregor 1997	152/192	105/119		29.9 %	0.84 [0.65, 1.08]
Laplanche 1998	64/83	78/95		17.6 %	0.83 [0.60, 1.16]
Ohonoshi 1993	14/16	12/14		3.2 %	0.88 [0.40, 1.92]
Wagner 1996	11/14	10/11		2.1 %	0.40 [0.15, 1.05]
Subtotal (95% CI)	**464**	**383**		**85.5 %**	**0.85 [0.73, 0.99]**
Heterogeneity: Chi^2 = 3.16, df = 6 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 2.08 (P = 0.037)					
2 Extensive					
Aroney 1983	3/3	8/8		0.6 %	3.38 [0.56, 20.39]
Arriagada 1995	25/25	30/31		6.8 %	0.82 [0.48, 1.39]
Danish/NCI	5/5	7/9		1.3 %	1.27 [0.38, 4.28]
Gregor 1997	2/2	1/1		0.2 %	5.85 [0.34, 101.99]
Laplanche 1998	16/17	16/16		3.6 %	0.61 [0.29, 1.27]
Ohonoshi 1993	7/7	9/9		1.2 %	0.15 [0.04, 0.53]
Wagner 1996	3/3	3/4		0.7 %	1.53 [0.29, 8.06]
Subtotal (95% CI)	**62**	**78**		**14.5 %**	**0.77 [0.54, 1.11]**
Heterogeneity: Chi^2 = 12.70, df = 6 (P = 0.05); I^2 =53%					
Test for overall effect: Z = 1.39 (P = 0.16)					
Total (95% CI)				**100.0 %**	**0.84 [0.73, 0.97]**
Heterogeneity: Chi^2 = 16.11, df = 13 (P = 0.24); I^2 =19%					
Test for overall effect: Z = 2.45 (P = 0.014)					
Test for subgroup differences: Chi^2 = 0.24, df = 1 (P = 0.62), I^2 =0.0%					



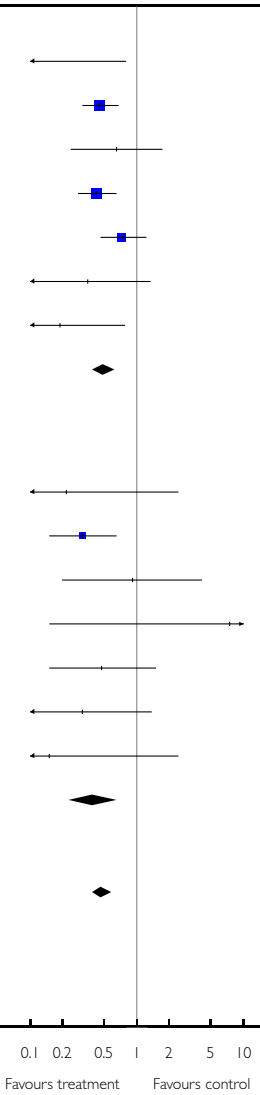
Analysis 1.11. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 11 Brain metastasis by extend of initial disease.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 11 Brain metastasis by extend of initial disease

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 limited					
Aroney 1983	0/11	2/5		0.5 %	0.04 [0.00, 0.80]
Arriagada 1995	39/124	65/120		29.2 %	0.45 [0.31, 0.67]
Danish/NCI	7/22	9/18		4.6 %	0.65 [0.24, 1.75]
Gregor 1997	45/192	54/119		25.8 %	0.42 [0.28, 0.64]
Laplanche 1998	27/83	37/95		18.3 %	0.74 [0.46, 1.22]
Ohonoshi 1993	3/16	6/14		2.5 %	0.35 [0.09, 1.34]
Wagner 1996	4/14	6/11		2.2 %	0.19 [0.05, 0.78]
Subtotal (95% CI)	**462**	**382**		**83.1 %**	**0.48 [0.38, 0.61]**
Heterogeneity: Chi^2 = 8.40, df = 6 (P = 0.21); I^2 =29%					
Test for overall effect: Z = 6.19 (P < 0.00001)					
2 Extensive					
Aroney 1983	0/3	3/7		0.8 %	0.22 [0.02, 2.43]
Arriagada 1995	7/25	22/31		8.1 %	0.31 [0.15, 0.64]
Danish/NCI	3/5	4/7		2.0 %	0.92 [0.20, 4.10]
Gregor 1997	1/2	0/1		0.3 %	7.39 [0.15, 372.38]
Laplanche 1998	5/17	7/16		3.3 %	0.47 [0.15, 1.50]
Ohonoshi 1993	2/7	5/9		1.9 %	0.31 [0.07, 1.39]
Wagner 1996	0/3	2/4		0.6 %	0.15 [0.01, 2.46]
Subtotal (95% CI)	**62**	**75**		**16.9 %**	**0.38 [0.23, 0.64]**
Heterogeneity: Chi^2 = 4.68, df = 6 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 3.67 (P = 0.00024)					
Total (95% CI)				**100.0 %**	**0.46 [0.38, 0.57]**
Heterogeneity: Chi^2 = 13.73, df = 13 (P = 0.39); I^2 =5%					
Test for overall effect: Z = 7.15 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.64, df = 1 (P = 0.42), I^2 =0.0%					

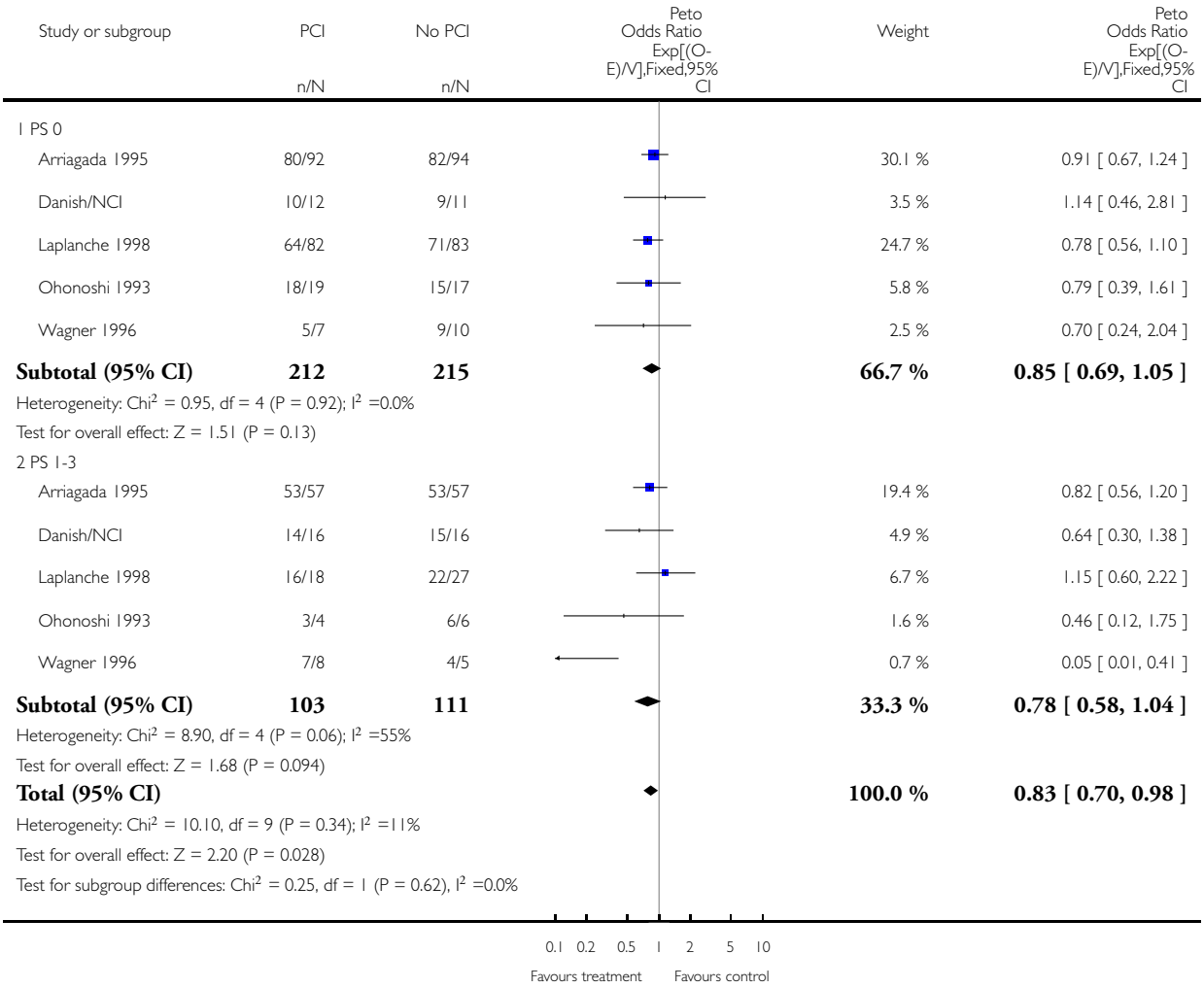


Analysis 1.12. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 12 Survival by performance status.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 12 Survival by performance status



Analysis 1.13. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 13 Brain metastasis by performance status.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 13 Brain metastasis by performance status

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 PS 0					
Arriagada 1995	31/92	59/94		35.2 %	0.43 [0.28, 0.65]
Danish/NCI	4/11	4/10		3.1 %	1.02 [0.25, 4.11]
Laplanche 1998	26/82	38/83		25.1 %	0.59 [0.36, 0.96]
Ohonoshi 1993	3/19	9/17		4.5 %	0.22 [0.07, 0.70]
Wagner 1996	1/7	5/10		2.4 %	0.24 [0.05, 1.21]
Subtotal (95% CI)	**211**	**214**		**70.3 %**	**0.47 [0.35, 0.63]**
Heterogeneity: Chi^2 = 4.46, df = 4 (P = 0.35); I^2 =10%					
Test for overall effect: Z = 5.06 (P < 0.00001)					
2 PS 1-3					
Arriagada 1995	15/57	28/57		16.6 %	0.39 [0.21, 0.72]
Danish/NCI	6/16	9/15		5.8 %	0.51 [0.18, 1.43]
Laplanche 1998	6/18	6/27		4.6 %	1.50 [0.47, 4.76]
Ohonoshi 1993	2/4	2/6		1.6 %	0.96 [0.13, 6.89]
Wagner 1996	2/8	3/5		1.2 %	0.07 [0.01, 0.68]
Subtotal (95% CI)	**103**	**110**		**29.7 %**	**0.50 [0.32, 0.78]**
Heterogeneity: Chi^2 = 7.42, df = 4 (P = 0.12); I^2 =46%					
Test for overall effect: Z = 3.02 (P = 0.0025)					
Total (95% CI)				**100.0 %**	**0.48 [0.37, 0.61]**
Heterogeneity: Chi^2 = 11.93, df = 9 (P = 0.22); I^2 =25%					
Test for overall effect: Z = 5.88 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.05, df = 1 (P = 0.82), I^2 =0.0%					

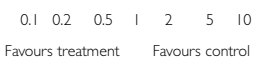
Analysis 1.14. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 14 Survival by induction therapy.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 14 Survival by induction therapy

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 Chemotherapy plus thoracic radiotherapy					
Arriagada 1995	121/135	125/141		40.0 %	0.91 [0.70, 1.16]
Danish/NCI	4/4	2/2		0.8 %	1.06 [0.17, 6.45]
Gregor 1997	129/164	89/99		32.4 %	0.78 [0.59, 1.03]
Ohonoshi 1993	9/11	4/6		1.9 %	1.19 [0.38, 3.78]
Subtotal (95% CI)	**314**	**248**		**75.1 %**	**0.86 [0.71, 1.03]**
Heterogeneity: Chi² = 1.00, df = 3 (P = 0.80); I² =0.0%					
Test for overall effect: Z = 1.66 (P = 0.097)					
2 Chemotherapy without thoracic radiotherapy					
Aroney 1983	14/15	13/14		4.4 %	1.06 [0.50, 2.26]
Arriagada 1995	12/14	10/10		3.0 %	0.54 [0.22, 1.37]
Danish/NCI	20/24	22/25		6.8 %	0.87 [0.47, 1.60]
Gregor 1997	25/29	16/20		6.5 %	1.40 [0.75, 2.61]
Ohonoshi 1993	12/12	17/17		4.2 %	0.51 [0.23, 1.09]
Subtotal (95% CI)	**94**	**86**		**24.9 %**	**0.88 [0.64, 1.21]**
Heterogeneity: Chi² = 5.44, df = 4 (P = 0.24); I² =26%					
Test for overall effect: Z = 0.78 (P = 0.43)					
Total (95% CI)				**100.0 %**	**0.86 [0.74, 1.01]**
Heterogeneity: Chi² = 6.46, df = 8 (P = 0.60); I² =0.0%					
Test for overall effect: Z = 1.83 (P = 0.067)					
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² =0.0%					



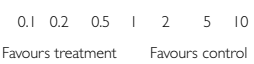
Analysis 1.15. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 15 Brain metastasis by induction therapy.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 15 Brain metastasis by induction therapy

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 Chemotherapy plus thoracic radiotherapy					
Arriagada 1995	45/135	82/141		47.6 %	0.45 [0.32, 0.64]
Danish/NCI	2/4	1/2		0.9 %	0.68 [0.05, 9.12]
Gregor 1997	39/164	48/99		29.5 %	0.38 [0.25, 0.60]
Ohonoshi 1993	2/11	0/6		0.6 %	4.48 [0.22, 92.23]
Subtotal (95% CI)	**314**	**248**		**78.6 %**	**0.43 [0.33, 0.57]**
Heterogeneity: Chi² = 2.72, df = 3 (P = 0.44); I² =0.0%					
Test for overall effect: Z = 6.00 (P < 0.00001)					
2 Chemotherapy without thoracic radiotherapy					
Aroney 1983	0/14	5/12		1.9 %	0.10 [0.02, 0.56]
Arriagada 1995	1/14	5/10		2.0 %	0.11 [0.02, 0.58]
Danish/NCI	8/23	12/23		7.6 %	0.65 [0.27, 1.57]
Gregor 1997	7/29	6/20		4.8 %	0.86 [0.29, 2.58]
Ohonoshi 1993	3/12	11/17		5.1 %	0.26 [0.09, 0.75]
Subtotal (95% CI)	**92**	**82**		**21.4 %**	**0.40 [0.23, 0.67]**
Heterogeneity: Chi² = 8.59, df = 4 (P = 0.07); I² =53%					
Test for overall effect: Z = 3.47 (P = 0.00052)					
Total (95% CI)				**100.0 %**	**0.43 [0.33, 0.54]**
Heterogeneity: Chi² = 11.40, df = 8 (P = 0.18); I² =30%					
Test for overall effect: Z = 6.92 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² =0.0%					



Analysis 1.16. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 16 Survival by sex.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 16 Survival by sex

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 Male					
Aroney 1983	9/10	7/8		1.9 %	0.80 [0.29, 2.22]
Arriagada 1995	116/129	120/130		28.8 %	0.76 [0.59, 0.98]
Danish/NCI	18/21	13/15		3.6 %	0.94 [0.45, 1.95]
Gregor 1997	102/125	69/74		19.2 %	0.77 [0.56, 1.05]
Laplanche 1998	71/89	90/102		19.9 %	0.78 [0.57, 1.06]
Ohonoshi 1993	17/19	14/15		3.6 %	0.72 [0.35, 1.50]
Wagner 1996	8/10	7/8		1.7 %	0.57 [0.19, 1.67]
Subtotal (95% CI)	**403**	**352**		**78.7 %**	**0.77 [0.66, 0.90]**
Heterogeneity: Chi^2 = 0.65, df = 6 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 3.31 (P = 0.00093)					
2 Female					
Aroney 1983	5/5	6/6		0.9 %	3.70 [0.84, 16.28]
Arriagada 1995	17/20	15/21		3.8 %	1.70 [0.83, 3.46]
Danish/NCI	6/7	11/12		2.0 %	0.76 [0.28, 2.01]
Gregor 1997	52/69	37/46		10.7 %	0.96 [0.63, 1.46]
Laplanche 1998	9/11	4/9		1.6 %	1.91 [0.63, 5.74]
Ohonoshi 1993	4/4	7/8		1.3 %	0.50 [0.15, 1.69]
Wagner 1996	6/7	6/7		1.1 %	0.36 [0.10, 1.31]
Subtotal (95% CI)	**123**	**109**		**21.3 %**	**1.05 [0.78, 1.42]**
Heterogeneity: Chi^2 = 10.36, df = 6 (P = 0.11); I^2 =42%					
Test for overall effect: Z = 0.33 (P = 0.74)					
Total (95% CI)				**100.0 %**	**0.82 [0.71, 0.94]**
Heterogeneity: Chi^2 = 14.33, df = 13 (P = 0.35); I^2 =9%					
Test for overall effect: Z = 2.78 (P = 0.0054)					
Test for subgroup differences: Chi^2 = 3.33, df = 1 (P = 0.07), I^2 =70%					

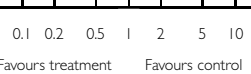
Analysis 1.17. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 17 Brain metastasis by sex.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 17 Brain metastasis by sex

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 Male					
Ohonoshi 1993	4/19	9/15			Not estimable
Aroney 1983	0/9	1/6		0.3 %	0.08 [0.00, 4.49]
Arriagada 1995	39/129	77/130		33.4 %	0.36 [0.25, 0.52]
Danish/NCI	6/20	7/13		3.8 %	0.62 [0.21, 1.89]
Gregor 1997	34/125	32/74		17.5 %	0.51 [0.30, 0.85]
Laplanche 1998	28/89	41/102		20.6 %	0.67 [0.42, 1.08]
Wagner 1996	1/10	2/8		0.8 %	0.28 [0.03, 2.96]
Subtotal (95% CI)	**401**	**348**		**76.3 %**	**0.47 [0.37, 0.60]**
Heterogeneity: Chi^2 = 5.57, df = 5 (P = 0.35); I^2 =10%					
Test for overall effect: Z = 6.06 (P < 0.00001)					
2 Female					
Aroney 1983	0/5	4/6		1.2 %	0.14 [0.02, 0.98]
Arriagada 1995	7/20	10/21		5.0 %	1.15 [0.44, 2.99]
Danish/NCI	4/7	6/12		2.8 %	0.93 [0.26, 3.36]
Gregor 1997	12/69	22/46		9.6 %	0.33 [0.17, 0.66]
Laplanche 1998	4/11	3/9		2.1 %	1.13 [0.26, 5.01]
Ohonoshi 1993	1/4	2/8		0.8 %	0.48 [0.04, 5.43]
Wagner 1996	3/7	6/7		2.2 %	0.21 [0.05, 0.87]
Subtotal (95% CI)	**123**	**109**		**23.7 %**	**0.50 [0.32, 0.78]**
Heterogeneity: Chi^2 = 9.43, df = 6 (P = 0.15); I^2 =36%					
Test for overall effect: Z = 3.06 (P = 0.0022)					
Total (95% CI)				**100.0 %**	**0.48 [0.38, 0.59]**
Heterogeneity: Chi^2 = 15.07, df = 12 (P = 0.24); I^2 =20%					
Test for overall effect: Z = 6.79 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.08, df = 1 (P = 0.78), I^2 =0.0%					

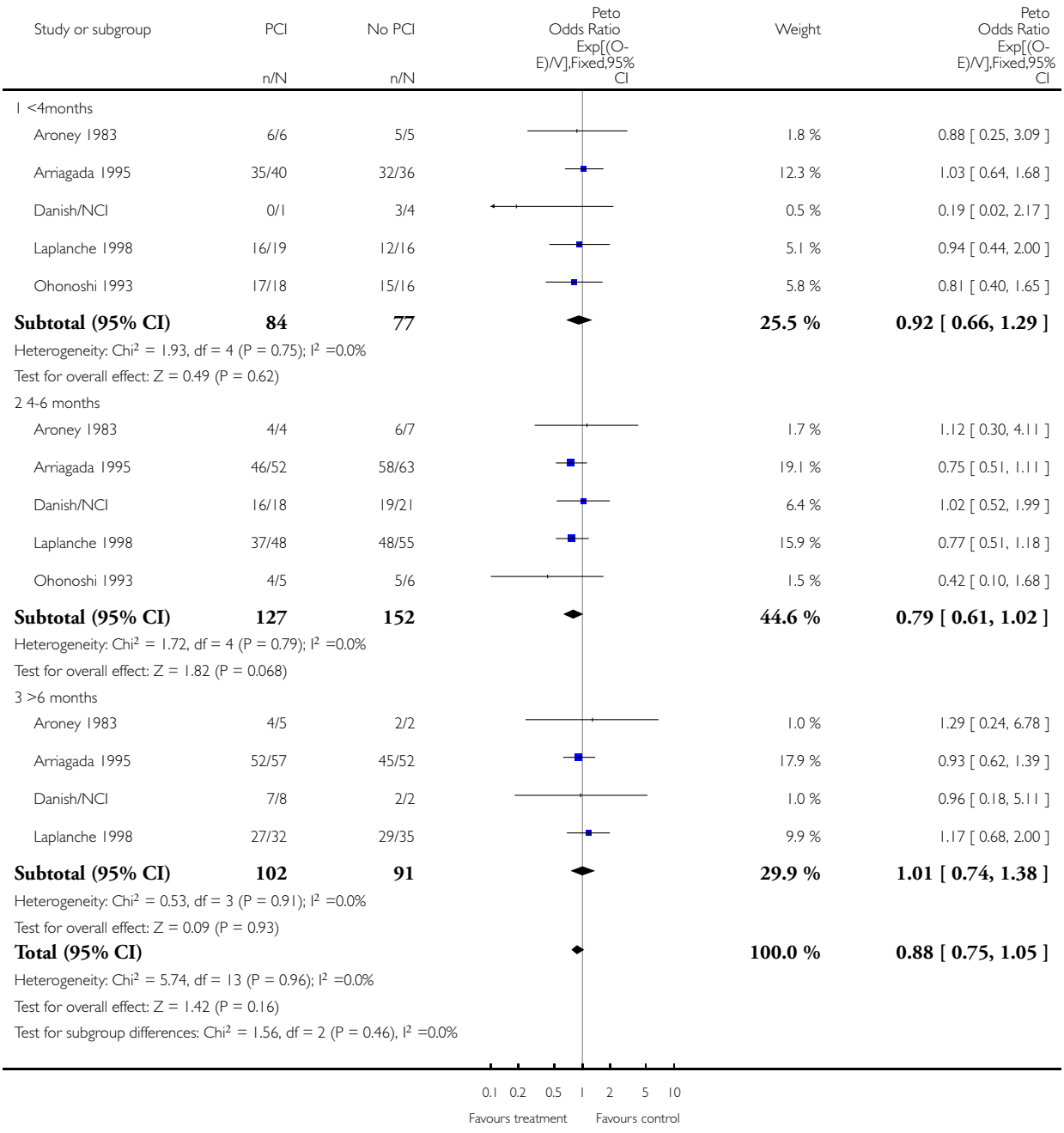


Analysis 1.18. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 18 Survival by time between start of induction therapy and randomization.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 18 Survival by time between start of induction therapy and randomization



Analysis 1.19. Comparison 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 19 Brain metastasis by time between start of induction therapy and randomization.

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

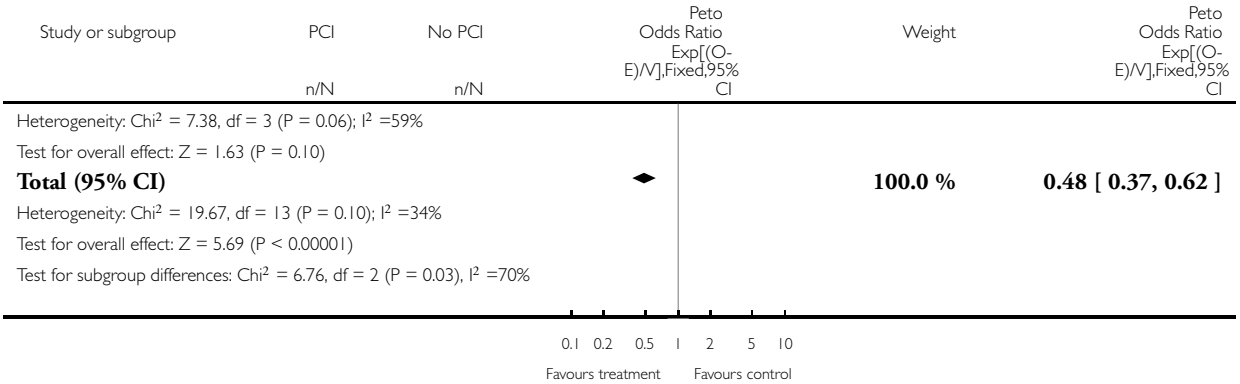
Comparison: 1 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 19 Brain metastasis by time between start of induction therapy and randomization

Study or subgroup	PCI n/N	No PCI n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 <4 months					
Aroney 1983	0/5	2/4		0.8 %	0.08 [0.00, 1.45]
Arriagada 1995	7/40	22/36		11.6 %	0.26 [0.13, 0.55]
Danish/NCI	0/1	2/3		0.8 %	0.17 [0.01, 2.98]
Laplanche 1998	5/19	8/16		4.7 %	0.28 [0.09, 0.88]
Ohonoshi 1993	4/18	7/16		4.4 %	0.40 [0.12, 1.33]
Subtotal (95% CI)	**83**	**75**		**22.2 %**	**0.27 [0.16, 0.46]**
Heterogeneity: Chi² = 1.16, df = 4 (P = 0.89); I² =0.0%					
Test for overall effect: Z = 4.77 (P < 0.00001)					
2 4-6 months					
Aroney 1983	0/4	1/6		0.4 %	0.19 [0.00, 10.32]
Arriagada 1995	17/52	40/63		23.1 %	0.38 [0.23, 0.64]
Danish/NCI	7/17	9/20		6.5 %	0.87 [0.32, 2.32]
Laplanche 1998	15/48	22/55		15.2 %	0.69 [0.36, 1.31]
Ohonoshi 1993	1/5	4/6		1.9 %	0.20 [0.03, 1.22]
Subtotal (95% CI)	**126**	**150**		**47.1 %**	**0.50 [0.35, 0.72]**
Heterogeneity: Chi² = 4.37, df = 4 (P = 0.36); I² =9%					
Test for overall effect: Z = 3.70 (P = 0.00021)					
3 >6 months					
Aroney 1983	0/5	2/2		0.6 %	0.01 [0.00, 0.30]
Arriagada 1995	22/57	25/52		18.8 %	0.64 [0.36, 1.15]
Danish/NCI	3/8	2/2		1.5 %	0.42 [0.05, 3.28]
Laplanche 1998	12/32	13/35		10.0 %	1.06 [0.48, 2.36]
Subtotal (95% CI)	**102**	**91**		**30.8 %**	**0.69 [0.44, 1.08]**

(*Continued . . .*)

(. . . *Continued*)



ADDITIONAL TABLES

Table 1. Characteristics of the 987 patients with small cell lung cancer in CR

Characteristic	Group PCI (n=526)	Group No PCI (n=461)
Male sex - no. (%)	403 (77)	352 (76)
Age - median (range) - yr	59 (26-80)	59 (21-79)
Performance status -no. (%)		
0	212 (67)	215 (66)
1	96 (30)	105 (32)
2-3	7 (2)	6 (2)
Extensive initial disease - no. (%)	62 (12)	78 (17)
Induction treatment with chemotherapy plus thoracic radiotherapy - no (%)	314 (77)	248 (74)
Time between start of induction therapy and randomization - no (%)		
<4 months	84 (27)	77 (24)
4-6 months	127 (41)	152 (48)

Table 1. Characteristics of the 987 patients with small cell lung cancer in CR (*Continued*)

>6 months	102 (33)	91 (28)

WHAT'S NEW

Last assessed as up-to-date: 24 November 2003.

Date	Event	Description
18 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 4, 2000

Date	Event	Description
29 July 2000	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Association pour la Recherche sur le Cancer, France.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cranial Irradiation; Brain Neoplasms [*prevention & control; *secondary]; Carcinoma, Small Cell [*secondary]; Lung Neoplasms [*pathology]; Meta-Analysis as Topic; Proportional Hazards Models; Randomized Controlled Trials as Topic; Remission Induction; Survival Analysis

MeSH check words

Humans