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Prophylactic cranial irradiation for preventing brain metastases in patients undergoing radical treatment for non-small cell lung cancer (Review)

Patel N, Lester JF, Coles B, Macbeth F

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[Intervention Review]

Prophylactic cranial irradiation for preventing brain metastases in patients undergoing radical treatment for non-small cell lung cancer

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ABSTRACT

Background

In non-small cell lung cancer (NSCLC), there is a relatively high incidence of brain metastases following radical treatment. At present, the role of prophylactic cranial irradiation (PCI) in this group of patients is not clear. This is an update of the original review published in 2005.

Objectives

To investigate whether PCI has a role in the management of patients with NSCLC treated with radical intent.

Search methods

The electronic databases MEDLINE, EMBASE, CENTRAL (The Cochrane library) and LILACS, along with handsearching of journals, relevant books, and review articles used to identify potentially eligible trials.

Selection criteria

Randomised controlled trials (RCTs) comparing PCI with no PCI in NSCLC patients treated with radical intent.

Data collection and analysis

Two authors independently performed study selection, data extraction and assessment of risk of bias.

Due to the small patient numbers, and variations in radiotherapy (RT) dose, no meta-analysis was attempted.

Main results

Four RCTs have been included in this review. No further trials were found to be eligible in this update. Only one new trial investigating the role of PCI has been carried out since the original review and is only published in the abstract form (RTOG 0214) . PCI may reduce the incidence of brain metastases, but there is no evidence of a survival benefit. There is no evidence that any regimen is superior, and the effect of PCI on quality of life (QOL) is not known.

Authors' conclusions

This update of the review published in 2005 does not contain any new trials published in full. One new trial that has only been published as an abstract, does not show any benefit in overall survival in patients receiving prophylactic cranial irradiation. There is insufficient evidence to support the use of PCI in clinical practice. Where possible, patients should be offered entry into a clinical trial.

PLAIN LANGUAGE SUMMARY

There is no evidence to recommend that patients with non-small cell lung cancer receive prophylactic radiotherapy to the brain following potentially curative treatment with surgery or radiotherapy

Patients with non-small cell lung cancer have a significant risk of developing tumour spread (metastases) to the brain after potentially curative treatment. To date, four research trials have been published in full; they included different groups of patients who had different doses of radiotherapy, and different outcomes were measured. None of the trials showed that patients who had received prophylactic radiotherapy to the brain lived longer than those who had not, although fewer of them developed brain metastases. A fifth trial (RTOG 0214) has not yet been published in full and is discussed in the results section.

BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews Issue 2 2005 (Lester 2005).

Lung cancer is one of the commonest malignant tumours in developed countries, and is an increasing problem in developing countries (Boyle 2000). Between 75% and 85% of patients will have non-small cell lung cancer (NSCLC) (squamous cell carcinoma, adenocarcinoma, large cell carcinoma, undifferentiated carcinoma), and 10% to 20% of these will be potentially curable. Following potentially curative treatment for NSCLC, the brain is a site of first relapse in 6.8% to 19% of cases and the risk of brain metastases is influenced by histological type and tumour stage (LCSG 1988; Perez 1987). Brain metastases are more common in patients with adenocarcinoma or large cell carcinoma, and in those with locally advanced disease. Brain metastases impair quality of life, and survival is poor (Nussbaum 1996). The benefit of prophylactic cranial irradiation (PCI) in small cell lung cancer (SCLC) is well established. At three years, survival is increased by 5.4%, and the cumulative rate of brain metastases reduced by 25.3% in those patients achieving complete remission with chemotherapy (PCIOCG 2000). Despite the relatively high incidence of brain metastases in NSCLC, the role of PCI in patients treated with radical intent has not been established.

OBJECTIVES

1. To establish whether PCI prevents the development of brain metastases and increases survival in NSCLC patients treated with curative intent.
2. To evaluate which is the most effective regimen of radiotherapy (RT).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials (RCTs).

Types of participants

Patients with histologically or cytologically confirmed NSCLC treated with radical intent and no radiological evidence of brain metastases prior to randomisation.

Types of interventions

1. External beam megavoltage RT given to the whole brain (PCI).
2. No PCI.

Types of outcome measures

1. Incidence of brain metastases
2. Overall survival
3. Disease free survival
4. Short and long term toxicity
5. Quality of life (QOL)

Search methods for identification of studies

We ran a search in July 2009 to update the original review. In this update we used an electronic search of the following databases; MEDLINE, EMBASE, CENTRAL (Cochrane library) and LILACS using the following strategy:

1 randomized controlled trial.pt. (276755)

2 controlled clinical trial.pt. (80038)

3 randomized.ab. (192699)

4 placebo.ab. (117063)

5 drug therapy.fs. (1332665)

6 randomly.ab. (142497)

7 trial.ab. (199797)

8 groups.ab. (963935)

9 or/1-8 (2491214)

10 humans.sh. (10885803)

11 9 and 10 (1988830)

12 exp lung neoplasms/ (128374)

13 carcinoma, non-small cell lung/ (19829)

14 nsclc.tw. (10140)

15 (lung$ adj2 (cancer$ or tumo?r$)).tw. (68806)

16 (lung$ adj2 carcinoma$).tw. (12809)

17 (lung$ adj2 neoplas$).tw. (1190)

18 (pulmonary$ adj2 (cancer$ or carcinoma$ or tumo?r$ or neoplas$)).tw. (5917)

19 ((lung$ or pulmonary) adj2 (metast$ or secondar$)).tw. (18208)

20 exp carcinoma, bronchogenic/ (27420)

21 exp bronchial neoplasms/ (9829)

22 (bronch$ adj2 cancer$).ti,ab,rw,sh. (2786)

23 (bronch$ adj2 carcinoma$).ti,ab,rw,sh. (13689)

24 exp pleural neoplasms/ (8960)

25 (lung$ or bronch$ or pulmonary$ or pleura$).tw. (682679)

26 carcinoma, large cell/ (1233)

27 exp carcinoma, squamous cell/ (83247)

28 exp adenocarcinoma/ (222367)

29 ((large adj cell) and (carcinoma$ or cancer$)).tw. (3618)

30 (((squamous adj cell) and carcinoma$) or cancer$).tw. (758277)

31 adenocarcinoma$.tw. (72504)

32 or/26-31 (933845)

33 25 and 32 (112566)

34 or/12-24,33 (188697)

35 Carcinoma, Small Cell/ (15723)

36 35 not (13 and 35) (13691)

37 34 not 36 (176832)

38 exp cranial irradiation/ (3318)

39 whole brain radiation therapy.tw. (298)

40 wbrt.tw. (409)

41 ((brain or crani$ or head$ or skull) adj3 (radiotherapy or irradiat $ or radiat$)).tw. (9356)

42 prophylatic cranial irradiation.tw. (3)

43 pci.tw. (6623)

44 or/38-43 (17845)

45 11 and 37 and 44 (323)

46 limit 45 to 2005 current (118)

Data collection and analysis

The randomised trials identified by the search were assessed to establish if pre-determined inclusion criteria were met by two independent authors (JL, NP).

Assessment of risk of bias in included studies

Two review authors (JL, NP) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We described for each included study the methods used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the methods as:

- adequate (any truly random process e.g. random number table; computer random number generator);
- inadequate (any non random process e.g. odd or even date of birth; hospital or clinic record number);
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study and for each outcome or class of outcomes the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

A fourth domain, blinding of participants (personnel and outcome assessors, a description of measures used to blind study participants and personnel for knowledge of which intervention a participant received) was not assessed. This is because it was impossible to blind participants and health care providers of the intervention, given the nature of the intervention (radiotherapy).

Data synthesis

Data were extracted from included studies using guidelines set out in Higgins 2008. Quantitative outcomes were planned to be evaluated using RevMan 5.0. Time-to-death analysis was planned to be approximated by analysing for different follow-up periods, or by calculating a weighted average of median survival across studies. A fixed-effect model was planned to be used for the primary analysis if appropriate. A decision on if and how to combine quality of life outcomes was to be made once all data had been collected.

Due to the small patient numbers, and variations in radiotherapy (RT) dose, no meta-analysis was attempted.

RESULTS

Description of studies

In the first publication of the review (Lester 2005) the literature search identified four RCTs comparing PCI with observation in NSCLC patients treated with radical intent. All four trials met the inclusion criteria and were included in the review (VALG; SWOG ; RTOG 84-03; Umsawasdi 1984).

The update of the bibliographic search identified 377 unique references. Of those only one new trial was identified since the original review and is only published in the abstract form (RTOG 0214). As it is only published as an abstract it cannot be included in this review formally as we are unable to assess the risk of bias. However, as it is an important trial it will be described in this section. Another trial (Pottgen 2007) was excluded because it was not randomised.

Included studies

The studies included slightly different patient groups. All four trials required histological confirmation of the diagnosis. Three trials (VALG; RTOG 84-03; Umsawasdi 1984) required a normal radionuclide brain scan or CT head prior to randomisation. The VALG trial randomised 410 evaluable male patients not considered

suitable for surgical resection with no evidence of metastases and no spread beyond the regional nodes. Details of disease stage were not given. Eighty-seven patients were excluded with reasons given, leaving 323 evaluable patients. RTOG 84-03 randomised 187 patients with inoperable or unresectable adenocarcinoma or large cell carcinoma confined to the chest and resected carcinomas of the same cell types. There were no exclusions. Over 80% of patients had node-positive disease. Umsawasdi included patients with locally advanced NSCLC of any cell type. One hundred patients were randomised. There were three exclusions with reasons given, leaving 97 evaluable patients. Of these, 84/97 (87%) were stage III and 13/94 (13%) stage I to II. The SWOG study randomised 254 patients with inoperable stage III NSCLC and a Karnofsky performance status of >60. Twenty-eight patients were excluded with reasons given, leaving 226 evaluable cases.

Therefore, a total of 951 patients were randomised in these RCTs, of whom 833 were evaluable and reported. The VALG study included 42 patients with small cell lung cancer and these have been excluded for the purposes of this review, leaving 791 patients in total.

Thoracic treatment differed between the trials. The VALG study randomised patients to one of two radical RT regimens; 50 Gy in 25 fractions over 5 weeks or 42 Gy in 15 fractions over 3 weeks. In RTOG 84-03, patients having primary RT received 55-60 Gy in 30 fractions over 6 weeks or 50 Gy in 25 fractions over 5 weeks to the mediastinum and hilar areas following surgical resection. The thoracic treatment received in the Umsawasdi trial was not clearly stated for all patients. Sixty-three patients received radical chemoradiotherapy (thoracic RT dose 50 Gy in 25 fractions over 5 weeks), the details of which were described in a subsequent publication (Umsawasdi 1987). Thirty-four patients received differing combinations of surgery, RT and chemotherapy given with curative intent. In the SWOG trial, patients were first randomised to either chest RT (58 Gy in 29 fractions) or neoadjuvant chemotherapy followed by chest RT and adjuvant chemotherapy. In all four trials, patients were randomised to PCI or observation irrespective of thoracic response to treatment.

In two trials (RTOG 84-03; Umsawasdi 1984), PCI patients received 30 Gy in 10 fractions over 2 weeks. In the VALG trial, patients received 20 Gy in 10 fractions over 2 weeks. In the SWOG trial, the first 34 patients received 37.5 Gy in 15 fractions, but this was changed to 30 Gy in 15 fractions soon after the trial began recruiting due to concerns about early deaths in the PCI arm.

The studies measured and reported similar outcomes. All four trials reported incidence of brain metastases and survival. Two trials (VALG; Umsawasdi 1984) reported time to brain metastases. The RTOG trial (RTOG 84-03) reported on the prevalence of brain metastases at 12 and 24 months.

Quality of life assessments were not carried out in any of the studies.

One trial (VALG) did not report on PCI-related toxicity. Two trials reported on late complications of PCI (RTOG 84-03; Umsawasdi 1984) and one trial (RTOG 84-03) on acute toxicity. The SWOG trial reported RT toxicity but did not define this further.

Detailed information on the follow-up protocol was provided in two trials (VALG; RTOG 84-03). No study required regular imaging of the head as part of follow up. Three trials (VALG; RTOG 84-03; Umsawasdi 1984) required a CT head or radionuclide scan if intracranial metastases were suspected for any reason. In RTOG 84-03 a CT head was performed in all patients surviving 7.5 months from the completion of PCI.

RTOG 0214 aimed to recruit 1058 patients with Stage III disease following loco-regional treatment and randomise to PCI or observation. Due to slow accrual only 356 patients were recruited and the trial was stopped early. The results show that there is no difference in overall survival or disease free survival in the PCI group compared to the observation arm. However, CNS metastatic rate at 1 year was statistically different with CNS relapse 7.7% vs 18% for PCI vs observation. The trial aims to analyse the impact of PCI on neuropsychological function and QoL.

It is clear that the four published studies were heterogenous in patient selection, thoracic treatment, PCI dose, and the way in which key outcome measures were assessed and reported. Meta-analysis of the data was therefore inappropriate, and only a narrative synthesis was performed.

Excluded studies

We did not exclude any randomised trials in this review. One trial (Pottgen 2007) was excluded but the PCI was not a random allocation. The randomisation was between two local therapy options (Arms A and B). Patients in arm B of the trial all got PCI. This trial did demonstrate a significant reduction in the probability of brain metastases as the first site of failure (7.8% at 5 years v 34.7%).

Risk of bias in included studies

Two trials (RTOG 84-03; VALG) had adequate allocation concealment (central randomisation). The method of allocation concealment was unclear in the other two trials (Umsawasdi 1984; SWOG). The method of sequence generation was adequate in only one trial (RTOG 84-03) which used the randomisation method described by Zelen 1974. The method of sequence generation was unclear in the other three trials (Umsawasdi 1984; SWOG; VALG). Withdrawals and drop-outs were accounted for in all four trials. Two trials (SWOG; RTOG 84-03) carried out intention-to-treat data analysis and had adequately assessed incomplete outcome data. The incomplete outcome data was not adequately assessed in the other two trials (Umsawasdi 1984; VALG)

Additionally, trials were assessed regarding inclusion criteria, PCI treatment details and description of statistical methods.

The entry criteria and PCI treatment details were clearly stated in all four trials. The statistical methods used were described in all four trials.

Effects of interventions

Incidence of brain metastases

PCI did significantly reduce the incidence of brain metastases in three trials (VALG; SWOG; Umsawasdi 1984). In the VALG study, the two thoracic RT schedules used were combined for statistical analysis. The incidence of brain metastases was significantly lower in the PCI arm compared to the observation arm (6% vs 13%, P=0.038, Fisher's exact test). The only specific cell type in which PCI was significantly more effective in reducing the incidence of brain metastases was adenocarcinoma (0% vs 29%, P=0.04). In

the Umsawasdi trial the incidence of brain metastases in the PCI arm was 4% compared to 27% in the observation arm (P=0.02, chi-squared). In the same trial, multivariate analysis suggested the beneficial effect of PCI was only significant in females, patients with a good performance status, weight loss less than 6%, squamous histology and stage III disease. This analysis should be interpreted with caution, as only 97 patients in total were evaluable, and sample sizes may have been too small to reliably detect differences. In the SWOG trial the incidence of brain metastases in the PCI arm was 1% compared to 11% in the observation arm (P=0.003, chi-squared).

In RTOG 84-03, PCI did not significantly reduce the incidence of brain metastases compared to the observation arm (9% vs 19%, P=0.10, chi-squared). A subgroup analysis on the 26 patients who had surgical resection of gross intrathoracic disease followed by mediastinal RT showed PCI did not significantly reduce the incidence of brain metastases (0% vs 25%, P=0.06). The effect of PCI on the incidence of brain metastases in the 161 patients receiving primary thoracic RT was also not significant (10% vs 18%, P=0.34), but in both groups results favoured PCI.

Time to brain metastases

In the VALG trial, the median time to development of brain metastases was 34 weeks in the PCI group and 29 weeks in the observation group. The statistical significance of this result was not stated. In the Umsawasdi trial, PCI was also reported to significantly prolong the median time to central nervous system metastases (50.5 weeks vs 23 weeks, P=0.002, Cox's regression model). The prevalence of brain metastases at 12 and 24 months for PCI versus observation in RTOG 84-03 was not significant (15% vs 17% and 15% vs 31%, P=0.10, log rank test).

Survival

No trial reported a survival advantage with PCI over observation. Three trials reported on median survival (VALG; RTOG 84-03; SWOG). The median survival figures for PCI versus observation in the VALG trial were 35.4 weeks vs 41.4 weeks (P=0.5, Gehan-Wilcoxon test), and in RTOG 84-03, 8.4 months vs 8.1 months (P=0.36, log rank test). In the SWOG trial, median survival was lower in the PCI arm (8 months vs 11 months, P=0.004, log rank test). In the Umsawasdi trial, three-year survival in the PCI and control groups were 22% and 23.5% respectively. No statistical analysis of the survival data was reported. In RTOG 84-03, there was no significant difference between PCI and observation in one and two-year survival (40% vs 44% and 13% vs 21%, P=0.36, log rank test).

Toxicity

Two trials reported no late complications of PCI (RTOG 84-03; Umsawasdi 1984). RTOG 84-03 reported no acute toxicity other than epilation and skin reactions. The SWOG trial reported no excessive neurological toxicity with PCI compared to the observation arm, but the definition of neurological toxicity was not stated.

Quality of life

Quality of life assessments were not carried out in any of the studies.

DISCUSSION

Brain metastases impair quality of life and are associated with a poor prognosis (Nussbaum 1996). The rationale behind PCI is to control or eradicate undetectable micrometastases before they become clinically significant without inducing severe adverse effects. The first objective of the review was to establish whether PCI prevents the development of brain metastases and increases survival in NSCLC patients treated with curative intent. The four trials identified were relatively small, heterogenous in patient selection, thoracic treatment and PCI dose, and this should be considered when interpreting the review. In addition, the overall quality of the trials is low, with only one having adequate allocation concealment.

Three of the four trials did show a significant reduction in the incidence of brain metastases with PCI (VALG; SWOG; Umsawasdi 1984). RTOG 84-03 did not, but with less than 100 patients in each arm it was possible the trial was too small to detect any clinically relevant difference, and the results still favoured PCI.

Two trials (VALG; RTOG 84-03) reported no significant difference in overall survival between the PCI and control arms. The Umsawasdi trial did not publish statistical analysis of the survival data, but three-year survival in the PCI and control arms were very similar (22% vs 23.5%). Only the SWOG trial showed a significantly reduced median survival with PCI. Unlike the other trials, the SWOG trial did give PCI concurrently with thoracic RT, and it may be that the subsequent increased toxicity contributed to the reduced survival. The data presented suggested that PCI may reduce the incidence of brain metastases but this did not lead to a survival advantage. The lack of survival advantage with PCI was not necessarily surprising, however. In all four trials, the majority of patients received RT to the chest as primary treatment, and local control with this modality was only in the region of 50% (Perez 1987).

Response to thoracic treatment was not a requirement in any of the four trials, and patients with uncontrolled thoracic disease would have been unlikely to benefit from PCI. In addition, the thoracic RT dose used in all four trials would not be considered radical by modern standards; higher doses may improve local control, prolong survival, and allow any survival benefit with PCI to be manifest. Finally, any patients in whom brain micrometastases were controlled or eradicated with PCI would almost inevitably have relapsed at other sites because brain metastases are strongly associated with disseminated disease (Cox 1979). The lack of survival advantage may therefore reflect the presence of uncontrolled disease in the chest or at other metastatic sites outside of the brain.

The experience with PCI in SCLC is also worth considering. Several RCTs suggested a reduction in the incidence of brain metastases with PCI, but no convincing improvement in survival. As a consequence, PCI was not considered a standard of care in SCLC. A subsequent meta-analysis of seven RCTs (987 patients) did however, demonstrate a small but significant absolute increase in three-year survival of 5.4% (P=0.01) with PCI (PCIOCG 2000). It was not logical to extrapolate these results to NSCLC patients as SCLC is a more radiosensitive diease with a higher incidence of brain metastases, but it may be that a large enough RCT would demonstrate a survival advantage not seen in the relatively small trials reported to date.

In order to minimise the number of patients treated unnecessarily, it would be beneficial to identify a high risk population which might benefit from PCI. Studies have suggested brain metastases occur in a higher proportion of patients with adenocarcinoma or large cell carcinoma (LCSG 1988; Perez 1987; Salbeck 1990) and it would

be expected that any benefit from PCI would be more pronounced in patients with these histological subtypes. Indeed, the VALG trial showed PCI had a significant effect on reducing the incidence of brain metastases only in patients with adenocarcinoma. The other two trials did not support this hypothesis however. The RTOG 84-03 trial only included patients with adenocarcinoma or large cell carcinoma and did not demonstrate a significant benefit with PCI. The Umsawasdi trial showed that only for patients with squamous histology did PCI significantly reduce the incidence of brain metastases. This may however have been a chance finding from subgroup analysis on small samples.

The incidence of brain metastases depends on the initial disease stage. Salbeck et al (Salbeck 1990) reported no cases of brain metastases on initial CT staging in patients with stage I and II NSCLC. In the same study, CT scanning detected brain metastases in 17.5% of patients thought to have stage III disease, and the rate of brain metastases as a first site of relapse in stage III disease was reported to be as high as 30% at four years (Stuschke 1999). It would seem PCI might be more beneficial in stage III as opposed to early stage disease, but only in the Umsawasdi trial did multivariate analysis suggest a significant beneficial effect in stage III disease compared to stages I and II. Therefore it was not possible using results from the trials included in this review to identify a high risk group which may derive proportionally more benefit from PCI. Again, the number of patients in each trial was relatively small, and a larger RCT would help in establishing the patients at greater risk of brain metastases.

The second objective was to establish the most effective regimen of radiotherapy. The three trials that showed a significant reduction in the incidence of brain metastases with PCI used different regimens. The Umsawasdi trial used 30 Gy in ten fractions over two weeks and the VALG trial 20 Gy in ten fractions over two weeks. The SWOG trial used 37.5 Gy in 15 fractions for the first 34 patients and 30 Gy in 15 fractions for the remaining 77 patients; there was no significant difference in median survival between the two PCI regimens used. The differences in inclusion criteria made any comparison between the trials inappropriate. In addition, no randomised trial had compared these (or any other) PCI regimens head-to-head, so it was not possible to say whether one was more effective.

None of the studies included in this review collected detailed prospective data on the long-term effects of PCI on neuropsychological function. Hopefully RTOG 0214 will provide this information once it is published in full. In the meta-analysis of PCI in SCLC (Auperin 1999), two trials evaluated the effect of PCI on neuropsychological function (Arriagada 1995; Gregor 1997). In the French trial, patients in the PCI group received 24 Gy in 8 fractions over 12 days. There were no significant differences between patients receiving PCI and those in the observation group in terms of neuropsychological function. In the Gregor trial, the majority of patients randomised to PCI received 30Gy in ten fractions over two weeks. In both groups, there was an impairment of cognitive function and QOL before PCI, and further impairment at 6 and 12 months, but no additional impairment in the PCI group compared to the control group. The trials in this review does not provide substantial information on treatment-related toxicity, but is reasonable to assume any effect on function with a given PCI regimen would be the similar in SCLC and NSCLC patients. It is probable, therefore, that both 30Gy in 10 fractions over 2 weeks and 30Gy in 10 fractions over 2 weeks cause little significant brain damage for the first one to two years following PCI, but longer term follow up data is needed to fully assess late toxicity.

AUTHORS' CONCLUSIONS

Implications for practice

This update confirms that there is still insufficient evidence to support the use of PCI in the management of patients with NSCLC treated with curative intent. The trials do demonstrate a potential benefit of PCI, but this evidence is weak and possibly biased. The design and conduct of a proper RCT should also take into account this methodological weakness and avoid or reduce them appropriately.

Implications for research

All trials showed a reduction in the incidence of brain metastases in patients receiving PCI, and there is enough evidence to suggest a large RCT would be justified. More prospective research on the long-term effect of PCI on cognitive function and quality of life is needed, and hopefully RTOG 0214 will provide this information once it is published in full. The patient population most likely to benefit is not clear, nor is the most beneficial radiotherapy schedule. More homogenous entry criteria in future randomised trials would facilitate meta-analysis. The failure of RTOG 0214 to recruit the planned 1000 patients indicates that this question may not ever be fully answered.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

RTOG 84-03

Methods	Randomised 2-arm trial. Clinical assessment 3-monthly. CT head in all patients surviving 7.5 months from PCI completion, and in any patient developing new neurological symptoms. Incidence of brain metastases, median, 1 and 2-year survival reported.
Participants	187 patients with adenocarcinoma or large cell carcinoma confined to the chest; 161 received primary thoracic RT (55-60Gy/30F/6 weeks); 26 received post-operative RT (50Gy/25F/5 weeks) following resection of all gross intrathoracic disease; any age; any PS. Precise stage information not given.
Interventions	30Gy/10F/2 weeks PCI versus observation.
Outcomes	No significant reduction in the incidence of brain metastases with PCI (9% versus 19%, p=0.10).
Notes	Results favoured PCI. Trial probably too small to detect any significant benefit. No formal assessment of toxicity or QOL.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: 'Patients were randomly assigned by RTOG headquarters using the randomisation scheme described by Zelen' Zelen's design is an experimental design for randomised clinical trials proposed by statistician Dr. Marvin Zelen. In this design, patients are randomised to either the treatment or control group before giving informed consent. Because the group to which a given patient is assigned is known, consent can be sought conditionally.
Allocation concealment?	Low risk	Quote 'Patients were randomly assigned by RTOG headquarters'
Incomplete outcome data addressed? All outcomes	Low risk	Quote: 'All the analyses were based upon the intention to treat principle' The proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.

SWOG

Methods	Randomised 4-arm trial. Monthly follow-up for the first year. No details on investigations performed. Incidence of brain metastases and median survival reported.
Participants	254 patients with stage III inoperable NSCLC; Karnofsky>60, any age; randomised to chest RT (58Gy/29F/6 weeks) alone or neoadjuvant chemotherapy plus chest RT plus adjuvant chemotherapy.
Interventions	37.5Gy/15F/3 weeks PCI (first 34 patients) or 30Gy/15F/3 weeks (77 patients) versus observation.
Outcomes	Significant reduction in the incidence of brain metastases with PCI (1% vs 11%, p=0.003). Significant reduction in median survival with PCI (8 months vs 11 months, p=0.004).
Notes	254 patients entered into study. 28 exclusions (all accounted for).

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: Insufficient information to make a judgement of 'yes' or 'no'. No mention of method of randomisation.
Allocation concealment?	Unclear risk	Quote: Insufficient information, but there is concern that allocation concealment is not free of bias. Quote from paper 'Patients were stratified on the basis of performance status and histology. After stratification patients were randomised to receive one of four treatments' Therefore it is feasible that some patients with a poorer performance status may have been excluded from the tougher treatment arm of chemotherapy, chest RT and PCI.
Incomplete outcome data addressed? All outcomes	Low risk	Quote: '254 patients were entered on the study. 28 patients were ineligible' The reasons for ineligibility seem valid and the missing outcome data is unlikely to affect outcome.

Umsawasdi 1984

Methods	Randomised 2-arm trial. Radionuclide/CT brain if neurological symptoms developed. Incidence, time to brain metastases and survival reported.
Participants	97 patients with locally advanced NSCLC(13% stage I/II, 87% stage III); any age; any performance status. Thoracic treatment not clearly described.
Interventions	30Gy/10F/2 weeks PCI versus observation.
Outcomes	Significant reduction in the incidence of brain metastases with PCI (4% versus 27%, p=0.02). PCI significantly prolonged time to brain metastases (50.5 weeks versus 23 weeks, p=0.02).

Umsawasdi 1984 *(Continued)*

	No significant difference in survival.
Notes	100 patients randomised. 3 exclusions (all accounted for). Randomization method not stated. Thoracic treatment not fully described. Follow-up protocol not stated. No formal assessment of toxicity or QOL.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: 'We evaluated the clinical impact of elective brain irradiation (EBI) in a prospective randomised study' No mention of randomisation method.
Allocation concealment?	Unclear risk	Quote: Insufficient information. However, the allocation of treatment appears to be so complicated that it is unlikely to be without bias.
Incomplete outcome data addressed? All outcomes	High risk	Quote: 'Three of 49 patients who were randomised to receive EBI were excluded from the analysis because they did not receive EBI due to a scheduling error. One of these patients had CNS metastasis during the course of their treatment' The exclusion from analysis of these patients in the treatment group (especially of the patient who developed CNS metastasis, a primary outcome of this trial) means that the trial cannot be free of bias.

VALG

Methods	Randomised 4-arm trial. Clinical assessment and Chest X-ray monthly for 6 months, then 2-monthly for 18 months and 3-monthly thereafter. Radionuclide brain scans only if a change in neurological status. Incidence of brain metastases, time to brain metastases and median survival reported.
Participants	281 male patients with non-metastatic inoperable NSCLC. No precise stage detail; Karnofsky>50; any age; randomised to 1 of 2 thoracic radiotherapy schedules (50Gy/25F/5 weeks versus 42Gy /15F/3 weeks).
Interventions	20Gy/10F/2 weeks PCI versus observation.
Outcomes	Significant reduction in the incidence of brain metastases with PCI (6% versus 13%, p=0.038). Time to brain metastases: 34 weeks versus 29 weeks. No significant improvement in median survival with PCI (35.4 weeks versus 41.4 weeks, p=0.5).
Notes	410 patients entered into study. 87 exclusions (all accounted for). 42 patients with SCLC excluded from the review. The 2 thoracic RT schedules were combined for statistical analysis of PCI effect.

VALG *(Continued)*

	Thoracic RT schedules would not be considered radical by modern standards. No formal assessment of toxicity or QOL.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: 'Patients were centrally randomised by telephone call'. This does not specify the method of randomisation. However, patients likely to have been randomised appropriately as central randomisation, but insufficient data to conclude 'yes'
Allocation concealment?	Low risk	Quote: 'Patients were centrally randomised by telephone call to the Statistical Center at Frontier Science and Technology Research Foundation'
Incomplete outcome data addressed? All outcomes	High risk	Quote: 'Eighty seven patients were excluded. 14 refused brain irradiation, 10 never started treatment, 20 had unknown or inconclusive brain scan results' Reason for missing outcome data is likely to be related to true outcome. A significant number of patients refused or did not start brain irradiation, therefore there is likely to be an imbalance in numbers across intervention groups.

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

Study	Reason for exclusion
Pottgen 2007	Not a randomised trial

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

RTOG 0214

Trial name or title	A phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small cell lung cancer.
Methods	
Participants	Patients with newly diagnosed stage IIIa or IIIb NSCLC having completed definitive locoregional therapy with no evidence of progressive disease or metastases at randomisation.
Interventions	Prophylactic cranial irradiation (30Gy/15F/3weeks) versus observation.
Outcomes	Survival, incidence of brain metastases, QOL, neuropsychological function.
Starting date	September 19th 2002.
Contact information	RTOG Headquarters. Tel: 1-800-227-5463 ext 4189
Notes	

WHAT'S NEW

Date	Event	Description
12 May 2010	New search has been performed	A search was run and no further trials were identified.

HISTORY

Protocol first published: Issue 2, 2003
Review first published: Issue 2, 2005

Date	Event	Description
8 January 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Fergus Macbeth initiated the review and helped with the writing. Fergus Macbeth and Jason Lester wrote the protocol and evaluated the quality of the studies in the initial review. Nita Patel and Jason Lester assessed the risk of bias of the studies in this update. Bernadette Coles carried out the literature search. Nita Patel wrote the final version, with the help of Jason Lester. Fergus Macbeth did the final edit of the review.

DECLARATIONS OF INTEREST

None known

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Cranial Irradiation; *Lung Neoplasms; Brain Neoplasms [*prevention & control] [secondary]; Carcinoma, Non-Small-Cell Lung [*prevention & control] [secondary]; Randomized Controlled Trials as Topic

MeSH check words

Humans