Postoperative radiotherapy for non-small cell lung cancer (Review)

PORT Meta-analysis Trialists Group

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[Intervention Review]

Postoperative radiotherapy for non-small cell lung cancer

PORT Meta-analysis Trialists Group[1]

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Editorial group: Cochrane Lung Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.
Review content assessed as up-to-date: 18 January 2009.

Citation: PORT Meta-analysis Trialists Group. Postoperative radiotherapy for non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD002142. DOI: 10.1002/14651858.CD002142.pub2.

ABSTRACT

Background

The role of postoperative radiotherapy (PORT) in the treatment of patients with completely resected non-small cell lung cancer was not clear. A systematic review and quantitative meta-analysis were therefore undertaken to evaluate the available evidence from randomised trials.

Objectives

To evaluate the effect of postoperative radiotherapy on survival and recurrence in patients with completely resected non-small cell lung cancer. To investigate whether or not pre-defined patient subgroups benefit more or less from PORT.

Search methods

We supplemented MEDLINE and CANCERLIT searches with information from trial registers, by handsearching relevant meeting proceedings and by discussion with relevant trialists and organisations.

Selection criteria

Both published and unpublished trials were eligible for inclusion provided the patients had undergone a complete resection; had been randomised between radiotherapy and no immediate further treatment; that the method of randomisation precluded prior knowledge of the treatment to be assigned; and that recruitment was after 1965.

Data collection and analysis

We carried out a quantitative meta-analysis using updated information from individual patients from all available randomised trials. We sought data from all patients randomised in all eligible trials directly from those responsible. We obtained updated information on survival, recurrence and date of last follow up. To avoid potential bias, we requested information for all randomised patients including those who had been excluded from the investigators' original analyses.

Main results

We included 2343 patients from 11 trials (median follow up of 4.4 years). The results showed a significant adverse effect of PORT on survival with a hazard ratio of 1.18 or an 18% relative increase in the risk of death. This is equivalent to an absolute detriment of 5% at two years (95% CI 2% to 9%), reducing overall survival from 58% to 53%. Exploratory subgroup analyses suggested that this detrimental effect was most pronounced for patients with stage I/II, N0-N1 disease, whereas for stage III, N2 patients there was no clear evidence of an adverse effect.

Authors' conclusions

PORT is detrimental to patients with early stage completely resected non-small cell lung cancer and should not be used in the routine treatment of such patients. The role of PORT in the treatment of N2 tumours is not clear and may justify further research.

PLAIN LANGUAGE SUMMARY

Postoperative radiotherapy for non-small cell lung cancer

Non-small cell lung cancer is the most common type of lung cancer. If this type of lung cancer has not spread, standard treatment is an operation to remove the tumour. Trials of a treatment called Post-Operative Radiotherapy Treatment (PORT), which involves giving x-ray treatment after the operation, have been carried out. These trials have been combined in this review, which found that giving PORT did not help people live longer. Fewer people given PORT treatment lived for two years after the operation (53%) than those who were not given PORT (58%). The treatment seemed to be harmful to patients in the early stages of the disease whose cancer had not spread. For those with more advanced disease, the evidence is less clear. However, even for these patients there is no indication that PORT is beneficial. Radiotherapy given after successful removal of tumour at operation is not beneficial for patients with non-small cell lung cancer and should not be used as routine treatment. Further research with new types of radiotherapy may be justified.

BACKGROUND

Worldwide, carcinoma of the lung is the main cause of cancer deaths. Over half a million new cases are diagnosed annually (Parkin 1993), about 80% of which are of non-small cell histological type (Rankin 1986). Surgery is the treatment of choice for non-small cell lung cancer (NSCLC) (NSCLCCG 1995) and about 20% of tumours are suitable for potentially curative surgery (Silverberg 1990). However, even for patients with apparently completely resected disease, survival is only around 40% at five years. In an effort to improve local control of the disease and to increase survival, adjuvant postoperative radiotherapy (PORT) has been explored as a therapeutic option.

Despite the conduct of a number of randomised controlled trials (RCTs) which have recruited a total of over 2000 patients, the role of PORT in the treatment of NSCLC remains unclear. Individually, trials have shown inconclusive and conflicting results. However, because of their size (74 to 539 patients), individual trials have not had sufficient statistical power to detect the moderate survival differences that might be expected of PORT. The Meta-analysis Group of the British Medical Research Council (MRC) Clinical Trials Unit (CTU) therefore initiated an individual patient data meta-analysis to assess this question. This approach to meta-analysis and systematic review involves the central collection, validation and analysis of the original trial data. It does not rely on data extracted from publications. At the outset, the secretariat contacted the investigators responsible for each trial and established the PORT Meta-analysis Trialists Group, under whose auspices the meta-analysis was conducted and published. This review was first published in *The Lancet* on 25 July 1998 (PORT 1998). In 2004, data from one new trial (Italy 2002) were added and the meta-analysis was updated. This update was published in *Lung Cancer* in 2005 (PORT 2005). In 2008, this meta-analysis was updated again to include data from another new trial (Korea 2007) and the results are reported here.

OBJECTIVES

To compare surgery plus PORT with surgery alone in completely resected non-small cell lung cancer patients. To investigate whether or not predefined patient subgroups benefit more or less from PORT.

METHODS

Criteria for considering studies for this review

Types of studies

Both published and unpublished trials were eligible for inclusion. Trials should have been properly randomised in a way which precluded prior knowledge of treatment assignment (trials which allocated treatment by pseudo-random methods such as birth date

were excluded). Trials should have aimed to randomise patients with completely resected non-small cell lung cancer between radiotherapy and no immediate further treatment. Recruitment should have started after 1 January 1965. Trials should not have used orthovoltage radiotherapy.

Types of participants

Eligible trials included individuals with histologically confirmed non-small cell lung cancer who had undergone complete resection. We included individual data from all randomised patients in the meta-analysis and where possible obtained data for individuals who had been excluded from the original trial analyses. These individuals were included in the meta-analysis. We excluded from the meta-analysis patients with small cell lung cancer that were included in an early trial which randomised all types of lung cancer.

Types of interventions

- Surgery versus surgery + postoperative radiotherapy (PORT).

Types of outcome measures

- Survival.
- Recurrence-free survival.

Search methods for identification of studies

In 1997, we identified trials by computerised bibliographic searches of MEDLINE and CANCERLIT using a modified version of the Cochrane Collaboration optimal search strategy (Dickersin 1995), supplemented with handsearches of meetings abstracts, bibliographies of books, reviews and specialist journals. We also searched trial registers (National Cancer Institute Physicians Data Query Clinical Protocols and United Kingdom Coordinating Committee for Cancer Research) and asked all trialists who took part in the meta-analysis to help to identify trials. Searches are updated annually to identify new trials and to assess the status of any ongoing trials. Searches updated in October 2002 and August 2003 yielded one new eligible trial (Italy 2002) and the search update carried out in 2008 identified a further two new eligible trials; a Polish trial (Dymek 2003) and a Korean trial published as an abstract (Korea 2007).

Data collection and analysis

This review was based on individual patient data obtained directly from the responsible trialist or data centre. The methods used were prespecified in a protocol.

We sought data for all patients randomised in all eligible randomised trials (published or unpublished). We sought updated information on survival, recurrence and date of last follow up, and details of treatment allocated, date of randomisation, age, sex, histological cell type, stage and performance status. To avoid potential bias, we requested information for all randomised patients including those who had been excluded from the investigators' original analyses. All data were thoroughly checked for consistency, plausibility and integrity of randomisation and follow up. We resolved any queries and the responsible trial investigator or statistician verified the final database entries. As stage was recorded using different classification systems, for the purposes of this meta-analysis we translated all stage data to a common staging system (see Table 1).

All analyses were based on intention-to-treat. We stratified survival analyses by trial, and used the log rank expected number of deaths and variance to calculate individual and pooled hazard ratios (HRs) using the fixed-effect model (Yusuf 1985). Thus, the times to death for individual patients were used within trials to calculate the hazard ratio (HR), representing the overall risk of dying when receiving PORT compared with surgery alone. We defined local and distant recurrence-free survival as the time from randomisation until the first event: death (from any cause) or local or distant recurrence, respectively. Patients alive without recurrence were censored at the time of last follow up. We took overall recurrence-free survival as the time from randomisation until the first recurrence or death (by any cause), whichever happened first. Patients alive without recurrence were censored on the date of last follow up. We also calculated HRs for prespecified subgroups of patients using similar stratified methodology. We performed analyses for each prespecified category, for example, for males and for females, within each individual trial. We then combined these results to give overall HRs for males and females.

We analysed the 'raw' individual patient data using an in-house program (SCHARP). For transferring to *The Cochrane Library*, we entered the log rank summary statistics of these analyses (o-e and variance) into RevMan (RevMan 2008) under the individual patient data category. We also presented results as absolute differences at two years, calculated using the HR and baseline event rate on the surgery alone arm; proportional hazards were assumed (Parmar 1995). We similarly calculated confidence intervals for absolute differences from the baseline event rate and the HR at the 95% confidence interval boundary values. We used Chi^2 tests to test for gross statistical heterogeneity over all trials in a comparison, and between subgroups, using the test for interaction or trend as appropriate (EBCTCG 1990). These tests (which have low statistical power) are aimed primarily at detecting quantitative differences - that is, differences in size rather than direction - and were chosen because qualitative differences were not anticipated. Survival curves were drawn as simple (non-stratified) Kaplan-Meier curves (Kaplan 1958). All P values quoted are two-sided and unless otherwise specified Chi^2 values are on one degree of freedom. We used the I^2 statistic to assess consistency between trials (Higgins 2002).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Initially, 15 potentially eligible trials (four unpublished), which investigated the role of PORT in the treatment of NSCLC, were identified by preliminary literature searches. Four of these were found to be ineligible; two because they were conducted before 1965 (Paterson 1962; Bangma 1972), one because it was not randomised (INT 1991) and one was excluded because the trial design and timing of randomisation precluded an unbiased comparison between surgery alone versus PORT (EORTC 08741). Of the remaining 11 trials potentially eligible for the meta-analysis (seven published, four unpublished), 1998 results were based on data from nine trials which were known to be randomised. Data from one trial (LCSG 841) which accrued only five patients were no longer available. It was unclear whether one study of 155 patients, which was reported as a randomised controlled trial (RCT), was indeed randomised and we were unable to obtain appropriate data for this trial (Austria 1996).

In 2002 we identified a further eligible trial (Italy 2002), sought data from this trial and updated the meta-analysis in 2005. In 2008, another two new trials were identified (Dymek 2003; Korea 2007). Unfortunately, data from the Polish trial were unavailable at the time of this update and so have not been included in the current meta-analysis. However, it is hoped it may be possible to include this trial in a future update. The meta-analysis was therefore based on the results of 11 RCTs and 2343 individuals. In these trials PORT doses ranged from 30 to 60 Gy, given in between 10 and 30 fractions, and there was considerable diversity in other aspects of radiotherapy planning. All trials included patients with completely resected tumours where the disease stage was no greater than IIIA. Follow up was updated in most trials giving a median of 4.4 years for surviving patients (2.3 to 11.4 years for individual trials). The patient characteristics showed that patients were mostly male with stage II/III squamous cell carcinoma (though histology was unknown for a relatively large number of patients) and with good performance status (see Table 2).

Risk of bias in included studies

We only included trials with adequate methods of randomisation (those which did not allow prior knowledge of treatment assignment). We checked all data received thoroughly to ensure both the accuracy of the meta-analysis database and the quality of randomisation and follow up. We resolved any queries and the responsible trial investigator or statistician verified the final database entries.

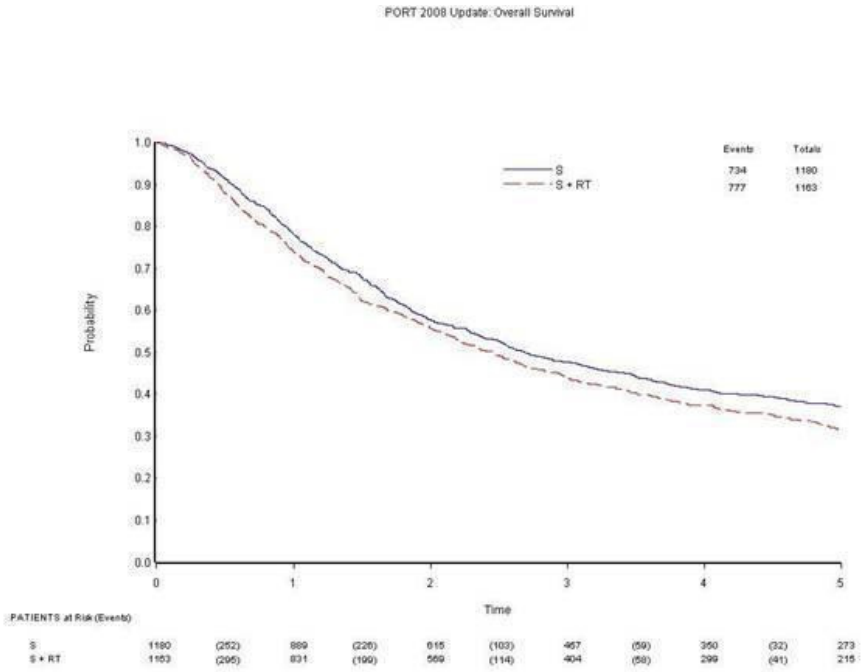
Effects of interventions

Results were based on information from 11 RCTs including 2343 patients, representing 99% of individuals from all eligible trials known to be randomised. Data were collected for 140 of 142 patients who had been excluded from the original published analyses and were reinstated in the meta-analysis. In the trial which randomised all histological types of lung cancer (Belgium 1966), the 20 patients with small cell tumours were excluded from the meta-analysis. Survival and recurrence data were available for all trials. Although trials were able to provide most of the additional patient characteristic data requested, some data were unavailable. Information on age, sex and stage was provided for all trials and data on histology for nine trials (Belgium 1966; LCSG 773; CAMS 1981; MRC LU11; EORTC 08861; Slovenia 1988; Lille 1985; Italy 2002; Korea 2007). Performance status data were only available for four trials (MRC LU11; EORTC 08861; Slovenia 1988; Italy 2002) and so were insufficient for subgroup analyses. Cause of death data (coded as NSCLC, treatment related and other) were provided for all but two trials (LCSG 773; Italy 2002), although the trialists themselves questioned the reliability of this information for many of the trials.

Survival

Survival data were available for all trials and included information from 2343 patients and 1511 deaths (777 PORT, 734 surgery alone). Although the confidence intervals (CIs) for individual trial results were wide, there was a clear pattern of results in favour of surgery alone. The combined results showed a significant adverse effect of PORT on survival (P = 0.001), with a hazard ratio (HR) of 1.18 (95% CI 1.07 to 1.31), or an 18% relative increase in the risk of death. This was equivalent to an absolute detriment of 5% at two years (95% CI 2% to 9%) reducing overall survival from 58% to 53%. Survival curves (Figure 1) appeared to diverge at around four months and remained apart for the five years to which they could be drawn with reasonable reliability. There was some minimal evidence of statistical heterogeneity between trials in 1998 which is greater in the current analysis (I^2 = 40%, P = 0.08). However, the random-effects result is similar (HR 1.17, 95% CI 1.02 to 1.34, P = 0.02). The heterogeneity is largely driven by the Italian trial (Italy 2002) as shown by a sensitivity analysis excluding this trial which reduces heterogeneity (I^2 = 31%, P = 0.16) and gives similar fixed- (HR 1.20, 95% CI 1.08 to 1.33, P = 0.0005) and random-effects results (HR 1.20, 95% CI 1.06 to 1.37, P = 0.005).

Figure 1. Overall survival curve for PORT meta-analysis.



Cause of death information coded as NSCLC, treatment related or other was available from nine trials. Of the 595 coded deaths on PORT, 82% were attributed to NSCLC, 4% to treatment related causes and 14% to other causes. For the 565 coded deaths on surgery alone, these figures are 89%, 2% and 9% respectively.

Local recurrence-free survival

Data on local recurrence were available from all trials. Analysis of local recurrence-free survival, based on 1556 events (498 local recurrences (200 on PORT, 298 on surgery alone) and 1058 deaths (593 on PORT, 465 surgery alone)), gave a HR of 1.12 (95% CI 1.01 to 1.23), significantly in favour of surgery alone (P = 0.03). There was evidence of statistical heterogeneity between trials (I^2 = 47%, P = 0.04) which was not apparent in the 1998 analysis (I^2 = 29%, P = 0.19), and the random-effects result is less convincing (HR 1.10, 95% CI 0.95 to 1.27, P = 0.19). Exclusion of the Italian trial (Italy 2002) again reduces heterogeneity to non-significant levels (I^2 = 22%, P = 0.23), as well as giving similar fixed- (HR 1.15, 95% CI 1.04 to 1.27, P = 0.008) and random-effects estimates (HR 1.15, 95% CI 1.02 to 1.29, P = 0.02).

Distant recurrence-free survival

Data on distant recurrence were available from all trials. Analysis of distant recurrence-free survival based on 1570 events (892 distant recurrences (438 on PORT, 454 on surgery alone) and 678 deaths (361 on PORT, 317 on surgery alone)) gave a HR of 1.13 (95% CI 1.02 to 1.24) in favour of surgery alone (P = 0.02). There was only modest evidence of statistical heterogeneity between trials (I^2 = 31%, P = 0.15).

Overall recurrence-free survival

A total of 1597 events were observed, 810 on PORT and 787 on the surgery alone arms. Of these, 445 first events were deaths, 260 patients had local recurrences and 654 had distant recurrences (238 patients had both local and distant recurrences of which 110 were recorded the same date). The overall HR of 1.10 (95% CI 0.99 to 1.21) only suggested an adverse effect of PORT (P = 0.07). This 10% relative increase in the risk of recurrence or death was equivalent to an absolute detriment of 3% at two years (95% CI 0% to 7%), reducing the recurrence-free survival rate from 48% to 45%. As for local recurrence-free survival, there was some evidence

of increased statistical heterogeneity between trials (I^2 = 44%, P = 0.06) not present in the 1998 analysis (I^2 = 26%, P = 0.21) and a random-effects analysis produces a less convincing result (HR 1.09, 95% CI 0.95 to 1.25, P = 0.23). However, a sensitivity analysis excluding the Italian trial (Italy 2002) not only reduces heterogeneity (I^2 = 20%, P = 0.26), but also gives similar fixed- (HR 1.13, 95% CI 1.02 to 1.24, P = 0.02) and random-effects (HR 1.13, 95% CI 1.00 to 1.26, P = 0.04) results.

Subsidiary analyses in patient subgroups

Analyses were performed to determine whether there was evidence of a differential effect of PORT in predefined subgroups of patients. For survival there was no evidence to suggest that PORT was differentially effective in any group of patients defined by age (trend P = 0.32), sex (interaction P = 0.84) or histology (interaction P = 0.42). There was some evidence that the effects of PORT were more detrimental in those patients with stage I than with stage II disease; considering the results for stage III patients alone there was no clear evidence of a detriment (trend across all stages P = 0.004). Similarly, there was a trend that PORT was increasingly detrimental with lower nodal status (trend P = 0.03). Results were similar for the endpoints of local, distant and overall recurrence-free survival.

DISCUSSION

At the outset of this project, despite the enrolment of over 2000 patients in randomised trials, it remained unclear whether or not postoperative radiotherapy (PORT) was an effective therapy in the treatment of non-small cell lung cancer (NSCLC). The original 1998 meta-analysis found a significant adverse effect of PORT on survival (P = 0.001) with a hazard ratio (HR) of 1.21 (95% CI 1.08 to 1.34), or a 21% relative increase in the risk of death. The aim of this systematic review and meta-analysis was to provide a comprehensive, reliable and up-to-date summary of the average effect of PORT in NSCLC patients, in order to provide reliable guidance for clinical practice and future research. Therefore, when a new trial of 111 patients was published (Korea 2007), it was included in an update of the analyses.

Overall, for the primary endpoint of survival, there was clear evidence of a detrimental effect of PORT for patients with completely resected NSCLC. The 18% relative increase in the risk of death associated with PORT, equivalent to an overall reduction in survival from 58% to 53% at two years, represents a considerable hazard for these patients. Exploratory analysis by stage and by nodal status suggested that this detrimental effect was most pronounced for earlier stage patients and those with lower nodal status. For stage III and N2 patients HRs were 0.99 and 0.97 respectively, but with wide confidence intervals indicating no clear evidence of a difference between treatments for these groups of patients. Further, no patient subgroup defined by stage or nodal status showed clear evidence of a benefit from PORT. The meta-analysis did not provide evidence that the relative effect of PORT was smaller or larger for any category of patients defined by age, sex, histology or performance status.

The analyses of local (P = 0.03), distant (P = 0.02) and overall (P = 0.07) recurrence-free survival (that is, time to recurrence or death) all suggested an overall adverse effect of PORT. However, the observed detriment was less for these endpoints. For local recurrence-free survival, the results were largely driven by survival (since deaths provide the majority of events). This suggested that there may be anti-tumour activity attributable to radiotherapy and that the increased risk of death from PORT may be attributable to other mechanisms. Analysis of local recurrence-free interval (that is, the time to local recurrence with death and distant recurrence being censored) was not presented because such analysis would be difficult to interpret and potentially seriously flawed. This difficulty arose because the increased risk of death on PORT may mean that PORT patients die before their tumour has had time to recur locally. Thus, such measurement was likely to be an overestimation of local control.

Taken as a whole, the results suggested that although PORT may be beneficial in terms of local recurrence, the effect was likely to be small and easily outweighed by the deleterious effect on survival. The cause of this detrimental effect was not apparent from these analyses, although the limited cause of death information available suggested that the excess mortality on PORT may be a result of causes of death other than cancer. There was certainly no convincing evidence from this analysis that radiation treatment alone increased cancer deaths, especially as most trials were unable to provide detailed cause of death information and later respiratory events leading to death may well have been wrongly attributed to recurrent cancer. However, the addition of radiation treatment postoperatively may exert a deleterious effect by virtue of the acute or delayed radiation effects, such as radiation pneumonitis or cardiotoxicity, on lungs likely to be already damaged by surgery and smoking.

The inclusion of this new trial (Korea 2007) has brought the total number of patients to 2343 from 11 RCTs. As would be expected, the addition of this modestly sized trial has not substantially changed the overall effect of PORT on survival. As evidence from new trials has accumulated, there has been some increase in heterogeneity, particularly relating to the Italian trial (Italy 2002). However, a significant detriment of PORT on survival persists, with similar estimates irrespective of whether a fixed-effect or random-effects model is used. Results for local, distant and overall recurrence-free survival are less convincing unless the Italian trial (Italy 2002) is excluded, although it is not clear why the results of this trial should differ. Furthermore, although the trials have been conducted over a period of 40 years, with changes in diagnosis,

assessment of recurrence and radiotherapy treatment, there was no evidence that the effect of PORT on survival differed by decade.

Although quality of life was not addressed directly in this meta-analysis (none of the trials collected data on patient-reported quality of life measures) it was unlikely that any benefits of PORT would offset the observed survival disadvantage. Indeed the additional time spent undergoing treatment and the side effects of radiation could reasonably be expected to impair at least short-term quality of life.

AUTHORS' CONCLUSIONS

Implications for practice

This meta-analysis can only provide average estimates of the effect of PORT. Nevertheless, it is still the best available evidence on which to base future treatment policy. Overall, it provides clear evidence of a detrimental effect of PORT on the survival of stage I and II NSCLC patients. There is no clear evidence that it is detrimental or beneficial in those with stage III, N2 disease.

Implications for research

The role of PORT in the treatment of N2 tumours is not clear so further research with new types of radiotherapy may be justified. If further trials of newer chemotherapy and radiotherapy regimens are initiated then it may be important to collect accurate and detailed information on the cause of death, as this meta-analysis has suggested that the adverse effect of PORT may be attributable to deaths from causes other than cancer. Collection of such data may also help to clarify whether it is the combination of radiation with surgery or the radiation alone which is the cause of excess deaths on the PORT arm.

ACKNOWLEDGEMENTS

The following investigators, groups and secretariat* form the PORT Meta-analysis Group and participated in this meta-analysis:

R Arriagada, Instituto de Radiomedicina (IRAM), Santiago, Chile; AH Brichet, JJ Lafitte, Hôpital Calmette, CHRU, Lille, France; S Burdett*, DJ Girling, MKB Parmar*, LHM Rydzewska*, RJ Stephens, LA Stewart*, MRC Cancer Trials Office, Cambridge, UK; B Dautzenberg, Groupe d'Etude et de Traitement des Cancers Bronchiques (GETCB); M Debevec, V Kovac, Institute of Oncology, Zaloska 2 , Ljublijana, Slovenia; A Gregor, European Organization for Research and Treatment of Cancer, Brussels, Belgium; JH Park, Korea Cancer Center, Seoul, Korea; S Piantadosi, Lung Cancer Study Group, USA; JP Pignon, Institut Gustave-Roussy, Villejuif, France; P Rocmans, Dept of Thoracic Surgery, Hôpitaux St Pierre et Erasme, Brussels, Belgium; R Souhami*, University College London, Medical School, UK; V Torri, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy; P Van Houtte, Dept of Radiotherapy, Institut Jules Bordet, Brussels, Belgium; L Trodella, Department of Radiation Oncology, Università Cattolica del S. Cuore, Rome; M Wang, Dept of Radiation Oncology and Surgery, Chinese Academy of Medical Sciences, Beijing, China.

The co-ordination of the meta-analysis and the collaborators' meeting was funded by the UK National Health Service Research and Development Cancer Programme (Project grant NCP/U03). We would like to thank all those patients who took part in the trials and contributed to this research. The meta-analysis would not have been possible without their help or without the collaborating institutions who kindly supplied their trial data. We are particularly grateful to Jayne Tierney and Desmond Curran for comments and assistance at all stages of the project. For their helpful comments on the 1998 manuscript we also thank Stanley Dische and Michele Saunders.

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EORTC 08861 *{unpublished data only}*

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GETCB 04CB86 *{unpublished data only}*

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GETCB 05CB88 *{unpublished data only}*

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z age <= 54 years *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zb age 55-59 years *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zc age 60-64 years *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zd age >= 65 years *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

ze female *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zf male *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zg adenocarcinoma *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zh squamous *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zi other histology *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zj stage 1 *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zk stage 2 *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zl stage 3 *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zm nodal status 0 *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zn nodal status 1 *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

zo nodal status 2 *{unpublished data only}*

Subgroup analysis using individual patient data from all trials.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Belgium 1966

Methods	1966 to 1977 RCT
Participants	224 patients Stage I, II, III Trial data used in subgroup analyses for sex, age and histology
Interventions	Surgery + radiotherapy versus surgery alone RT details 60 Gy in 30 fractions in 6 weeks Prescription technique: isodose 90% Machine used: Co60 Average field size (cm): 15 x 9 Clinical target volume: bronchial stump, hilum, mediastinum Technique: spinal cord blocks, oblique fields, lateral fields
Outcomes	Survival
Notes	20 small cell patients excluded from meta-analysis Unable to supply data for 2 patients

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Yes	Quote: "randomisation carried out via sealed envelope"
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

CAMS 1981

Methods	1981 to 1995 RCT
Participants	317 patients Stage II, III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status
Interventions	Surgery + radiotherapy versus surgery alone RT details 60 Gy in 30 fractions in 6 weeks Prescription technique: at midplane Machine used: Co60 & linac Average field size (cm): 6 x 12 Clinical target volume: hilum, mediastinum Technique: spinal cord blocks, oblique fields, lateral fields
Outcomes	Survival
Notes	Abstract only

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Yes	Quote: "randomisation carried out via sealed envelope"
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: Individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: Individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

EORTC 08861

Methods	1986 to 1990 RCT
Participants	106 patients Stage II, III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status

EORTC 08861 (*Continued*)

Interventions	Surgery + radiotherapy versus surgery alone RT details 56 Gy in 28 fractions in 5.5 weeks Prescription technique: central axis, at the midplane Machine used: linac Average field size (cm): 15 x 10 Clinical target volume: hilum, mediastinum Technique: composite plans
Outcomes	Survival
Notes	Unpublished trial

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Comment: unpublished trial, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Unclear	Comment: insufficient information provided
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

GETCB 04CB86

Methods	1986 to 94 RCT
Participants	189 patients Stage I, II, III Trial data used in subgroup analyses for sex, age, stage and nodal status
Interventions	Surgery + radiotherapy versus surgery alone RT details 60 Gy in 24 to 30 fractions in 6 weeks Prescription technique: isocentre Machine used: Co60 & linac Average field size (cm): unavailable

GETCB 04CB86 (*Continued*)

	Clinical target volume: bronchial stump, hilum, mediastinum Technique: spinal cord blocks, oblique fields, lateral fields
Outcomes	Survival
Notes	Same publication as GETCB 05CB88

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "randomly assigned by centralised telephone procedure" Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Unclear	Comment: insufficient information provided
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

GETCB 05CB88

Methods	1988 to 1994 RCT
Participants	539 patients Stage I, II, III Trial data used in subgroup analyses for sex, age, stage and nodal status
Interventions	Surgery + radiotherapy versus surgery alone RT details 60 Gy in 24 to 30 fractions in 6 weeks Prescription technique: isocentre Machine used: Co60 & linac Average field size (cm): unavailable Clinical target volume: bronchial stump, hilum, mediastinum Technique: spinal cord blocks, oblique fields, lateral fields
Outcomes	Survival

GETCB 05CB88 (*Continued*)

Notes	Same publication as GETCB 04CB86

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomly assigned by centralised telephone procedure" Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Unclear	Comment: insufficient information provided
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

Italy 2002

Methods	1989 to 1997 RCT
Participants	104 patients Stage 1 Trial data used in subgroup analyses for age, sex, histology and stage
Interventions	Surgery + radiotherapy versus surgery alone RT details 50.4 Gy in 1.8 Gy/day in 5 weeks and 3 days Prescription technique: angled field technique machine used: linac Average field size (cm): unavailable Clinical target volume: bronchial stump, hilum, mediastinum Technique: unavailable
Outcomes	Survival
Notes	-

Risk of bias

Item	Authors' judgement	Description

Italy 2002 (*Continued*)

Adequate sequence generation?	Yes	Quote: "by chance" using computer generated model Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Unclear	Comment: insufficient information provided
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

Korea 2007

Methods	1989 to 1998 RCT
Participants	111 patients Stage III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status
Interventions	Surgery + radiotherapy versus surgery alone RT details 50.4 to 55.8 Gy in 1.8 to 2 Gy fractions, 5 times a week Prescription technique: at midplane Average field size: defined inferiorly by a point 5 cm below the carina and superiorly by the suprasternal notch Clinical target volume: tumour bed, bronchial stump, ipsilateral hilum, vascular shadows of the bilateral mediastinum Technique: combination of parallel opposed, and anterior and posterior oblique fields, or any combination chosen at the discretion of the chest radiation oncologist
Outcomes	Survival
Notes	Abstract only

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation

Korea 2007 (*Continued*)

Allocation concealment?	Unclear	Comment: insufficient information provided
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

LCSG 773

Methods	1978 to 1985 RCT
Participants	230 patients Stage II, III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status
Interventions	Surgery + radiotherapy versus surgery alone RT details 50 Gy in 25 to 27.5 fractions in 5 to 5.5 weeks Prescription technique: central axis, at midplane Machine used: Co60 & linac Average field size (cm): unavailable Clinical target volume: bronchial stump, hilum, mediastinum Technique: spinal cord blocks, oblique fields, lateral fields
Outcomes	Survival
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "permuted block randomisation" Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Yes	Quote: treatment assigned by central office
Blinding? All outcomes	Unclear	Comment: insufficient information provided

Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

Lille 1985

Methods	1985 to 1991 RCT
Participants	163 patients Stage I Trial data used in subgroup analyses for sex, age, histology, stage and nodal status
Interventions	Surgery + radiotherapy versus surgery alone RT details 45 to 60 Gy in 22.5 to 30 fractions in 6 weeks Prescription technique: isodose 90% Machine used: Co60 & linac Average field size (cm): 12 x 12 Clinical target volume: hilum, upper mediastinum Technique: spinal cord blocks, oblique fields, lateral fields
Outcomes	Survival
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "randomised with a table of randomisation according to Snedecor and Cochran" Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Unclear	Comment: insufficient information provided
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes

Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

MRC LU11

Methods	1986 to 1993 RCT
Participants	308 patients Stage II, III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status
Interventions	Surgery + radiotherapy versus surgery alone RT details 40 Gy in 15 fractions in 3 weeks Prescription technique: central axis, at midplane Machine used: Co60 & linac Average field size (cm): unavailable Clinical target volume: hilum, mediastinum, supraclavicular fossae for upper lobes Technique: spinal cord blocks, oblique fields, lateral fields
Outcomes	Survival
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Yes	Quote: "treatment assigned by central office"
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

Slovenia 1988

Methods	1988 to 1992 RCT
Participants	74 patients Stage III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status
Interventions	Surgery + radiotherapy versus surgery alone RT details 30 Gy in 10 to 12 fractions in 2 weeks Prescription technique: central axis, at the midplane Machine used: linac Average field size (cm): 9 x 12 Clinical target volume: hilum, mediastinum Technique: oblique fields, lateral fields
Outcomes	Survival
Notes	Sealed envelope randomisation

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Comment: stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment?	Yes	Quote: "randomisation carried out via sealed envelope"
Blinding? All outcomes	Unclear	Comment: insufficient information provided
Incomplete outcome data addressed? All outcomes	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of selective reporting?	Yes	Comment: individual patient data obtained and checked for all outcomes
Free of other bias?	Yes	Comment: study appears to be free of other sources of bias

z age <= 54 years

Methods	Subgroup Analysis by age
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone

z age <= 54 years (*Continued*)

Outcomes	-
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zb age 55-59 years

Methods	Subgroup Analysis by age
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zc age 60-64 years

Methods	Subgroup Analysis by age
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias

Item	Authors' judgement	Description

zc age 60-64 years (*Continued*)

Allocation concealment?	Unclear	D - Not used

zd age >= 65 years

Methods	Subgroup Analysis by age
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

ze female

Methods	Subgroup Analysis by sex
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zf male

Methods	Subgroup Analysis by sex
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zg adenocarcinoma

Methods	Subgroup Analysis by histology
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zh squamous

Methods	Subgroup Analysis by histology
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

zh squamous (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zi other histology

Methods	Subgroup Analysis by histology
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zj stage 1

Methods	Subgroup Analysis by tumour stage
Participants	
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zk stage 2

Methods	Subgroup Analysis by tumour stage
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zl stage 3

Methods	Subgroup Analysis by tumour stage
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

zm nodal status 0

Methods	Subgroup Analysis by nodal status
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

zm nodal status 0 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zn nodal status 1

Methods	Subgroup Analysis by nodal status
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

zo nodal status 2

Methods	Subgroup Analysis by nodal status
Participants	-
Interventions	Surgery + radiotherapy versus surgery alone
Outcomes	-
Notes	-

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

All trials supplied individual patient data for analysis and are therefore defined as unpublished data, even though most are published.
IPD = individual patient data

RCT = randomised controlled trial
RT = radiotherapy

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

Study	Reason for exclusion
Austria 1996	Eligibility uncertain: Reported to be a RCT. Data provided by trialists but there are as yet unresolved problems with these data. It is not clear whether it is indeed randomised
Bangma 1972	Ineligible: Pre-1965
EORTC 08741	Ineligible: Excluded because trial design and timing of randomisation precluded an unbiased comparison between surgery alone and PORT
INT 1991	Ineligible: Not randomised
LCSG 841	Eligible: Data could not be obtained (4 patients)
Paterson 1962	Ineligible: Pre-1965

RCT = randomised controlled trial

DATA AND ANALYSES

Comparison 1. Surgery + PORT versus surgery alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	11	2343	Hazard Ratio (95% CI)	1.18 [1.07, 1.31]
2 Recurrence-free survival	11	2343	Hazard Ratio (95% CI)	1.10 [0.99, 1.21]
3 Local recurrence-free survival	11	2343	Hazard Ratio (95% CI)	1.12 [1.01, 1.23]
4 Distant recurrence-free survival	11	2343	Hazard Ratio (95% CI)	1.13 [1.02, 1.24]
5 Survival subgroup analysis - age	4		Hazard Ratio (95% CI)	Totals not selected
6 Survival subgroup analysis - sex	2		Hazard Ratio (95% CI)	Totals not selected
7 survival subgroup analysis - histology	3		Hazard Ratio (95% CI)	Totals not selected
8 survival subgroup analysis - stage	3		Hazard Ratio (95% CI)	Totals not selected
9 Survival subgroup analysis - nodal status	3		Hazard Ratio (95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Surgery + PORT versus surgery alone, Outcome 1 Survival.

Review: Postoperative radiotherapy for non-small cell lung cancer

Comparison: 1 Surgery + PORT versus surgery alone

Outcome: 1 Survival

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
Belgium 1966	88/98	80/104		10.9 %	1.48 [1.09, 2.02]
LCSG 773	84/110	81/120		11.0 %	1.12 [0.83, 1.53]
CAMS 1981	83/153	100/164		12.0 %	1.02 [0.76, 1.37]
Lille 1985	59/81	45/82		6.9 %	1.53 [1.04, 2.25]
EORTC 08861	26/52	20/54		3.0 %	1.64 [0.91, 2.94]
MRC LU11	116/154	123/154		15.9 %	0.96 [0.74, 1.24]
GETCB 04CB86	69/99	59/90		8.5 %	1.17 [0.83, 1.66]
Slovenia 1988	30/35	33/39		4.2 %	0.85 [0.52, 1.39]
GETCB 05CB88	152/274	120/265		18.0 %	1.45 [1.14, 1.85]

(*Continued* . . .)

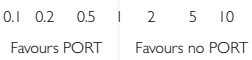
(. . . *Continued*)

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
Italy 2002	23/51	30/53		3.5 %	0.71 [0.41, 1.22]
Korea 2007	47/56	43/55		6.0 %	1.15 [0.76, 1.73]
Total (95% CI)				**100.0 %**	**1.18 [1.07, 1.31]**

Heterogeneity: Chi^2 = 16.65, df = 10 (P = 0.08); I^2 =40%

Test for overall effect: Z = 3.20 (P = 0.0014)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Surgery + PORT versus surgery alone, Outcome 2 Recurrence-free survival.

Review: Postoperative radiotherapy for non-small cell lung cancer

Comparison: 1 Surgery + PORT versus surgery alone

Outcome: 2 Recurrence-free survival

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
Belgium 1966	88/98	80/104		10.3 %	1.46 [1.07, 1.98]
LCSG 773	87/110	84/120		10.8 %	1.06 [0.78, 1.43]
CAMS 1981	93/153	115/164		13.0 %	0.91 [0.69, 1.20]
Lille 1985	60/81	45/82		6.6 %	1.49 [1.01, 2.19]
EORTC 08861	28/52	23/54		3.2 %	1.44 [0.82, 2.50]
MRC LU11	120/154	125/154		15.4 %	0.97 [0.76, 1.25]
GETCB 04CB86	72/99	62/90		8.4 %	1.05 [0.75, 1.47]
Slovenia 1988	30/35	33/39		4.0 %	0.97 [0.59, 1.58]
GETCB 05CB88	161/274	141/265		18.9 %	1.27 [1.01, 1.59]
Italy 2002	23/51	35/53		3.6 %	0.56 [0.34, 0.95]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
Korea 2007	48/56	44/55		5.8 %	1.00 [0.66, 1.51]
Total (95% CI)				**100.0 %**	**1.10 [0.99, 1.21]**

Heterogeneity: Chi^2 = 17.79, df = 10 (P = 0.06); I^2 =44%

Test for overall effect: Z = 1.84 (P = 0.065)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Surgery + PORT versus surgery alone, Outcome 3 Local recurrence-free survival.

Review: Postoperative radiotherapy for non-small cell lung cancer

Comparison: 1 Surgery + PORT versus surgery alone

Outcome: 3 Local recurrence-free survival

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
Belgium 1966	88/98	80/104		10.6 %	1.44 [1.06, 1.96]
LCSG 773	85/110	81/120		10.7 %	1.09 [0.80, 1.48]
CAMS 1981	91/153	111/164		13.0 %	0.94 [0.71, 1.24]
Lille 1985	59/81	45/82		6.7 %	1.50 [1.02, 2.21]
EORTC 08861	26/52	23/54		3.1 %	1.29 [0.73, 2.26]
MRC LU11	118/154	125/154		15.7 %	0.97 [0.75, 1.25]
GETCB 04CB86	70/99	61/90		8.4 %	1.04 [0.74, 1.47]
Slovenia 1988	30/35	33/39		4.1 %	0.94 [0.58, 1.55]
GETCB 05CB88	156/274	127/265		18.2 %	1.39 [1.10, 1.75]
Italy 2002	23/51	34/53		3.7 %	0.55 [0.33, 0.93]
Korea 2007	47/56	43/55		5.8 %	1.05 [0.69, 1.58]

(*Continued* . . .)

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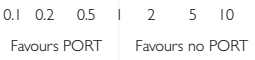
Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
Total (95% CI)				**100.0 %**	**1.12 [1.01, 1.23]**

Heterogeneity: Chi² = 18.86, df = 10 (P = 0.04); I² =47%

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Surgery + PORT versus surgery alone, Outcome 4 Distant recurrence-free survival.

Review: Postoperative radiotherapy for non-small cell lung cancer

Comparison: 1 Surgery + PORT versus surgery alone

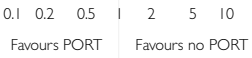
Outcome: 4 Distant recurrence-free survival

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
Belgium 1966	88/98	80/104		10.5 %	1.50 [1.10, 2.04]
LCSG 773	86/110	84/120		10.9 %	1.09 [0.81, 1.48]
CAMS 1981	89/153	108/164		12.5 %	0.97 [0.73, 1.28]
Lille 1985	60/81	45/82		6.7 %	1.52 [1.03, 2.23]
EORTC 08861	28/52	23/54		3.2 %	1.50 [0.86, 2.62]
MRC LU11	118/154	124/154		15.5 %	0.95 [0.73, 1.22]
GETCB 04CB86	71/99	61/90		8.4 %	1.09 [0.77, 1.53]
Slovenia 1988	30/35	33/39		4.0 %	0.87 [0.53, 1.43]
GETCB 05CB88	158/274	138/265		18.9 %	1.27 [1.01, 1.60]
Italy 2002	23/51	31/53		3.5 %	0.72 [0.42, 1.23]
Korea 2007	48/56	44/55		5.9 %	1.07 [0.71, 1.61]
Total (95% CI)				**100.0 %**	**1.13 [1.02, 1.24]**

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
Heterogeneity: Chi² = 14.51, df = 10 (P = 0.15); I² =31%					
Test for overall effect: Z = 2.34 (P = 0.019)					
Test for subgroup differences: Not applicable					



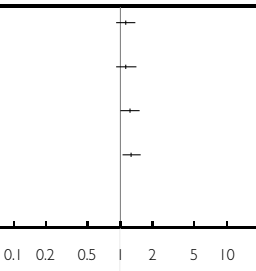
Analysis 1.5. Comparison 1 Surgery + PORT versus surgery alone, Outcome 5 Survival subgroup analysis - age.

Review: Postoperative radiotherapy for non-small cell lung cancer

Comparison: 1 Surgery + PORT versus surgery alone

Outcome: 5 Survival subgroup analysis - age

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
z age <= 54 years	182/294	196/327		1.12 [0.91, 1.37]
zb age 55-59 years	178/267	159/261		1.13 [0.91, 1.41]
zc age 60-64 years	191/290	173/276		1.22 [0.99, 1.51]
zd age >= 65 years	226/312	205/315		1.27 [1.04, 1.54]



Analysis 1.6. Comparison 1 Surgery + PORT versus surgery alone, Outcome 6 Survival subgroup analysis - sex.

Review: Postoperative radiotherapy for non-small cell lung cancer

Comparison: 1 Surgery + PORT versus surgery alone

Outcome: 6 Survival subgroup analysis - sex

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
ze female	113/175	113/187		1.21 [0.92, 1.59]
zf male	664/988	621/992		1.17 [1.05, 1.31]

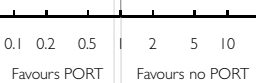
Analysis 1.7. Comparison 1 Surgery + PORT versus surgery alone, Outcome 7 survival subgroup analysis - histology.

Review: Postoperative radiotherapy for non-small cell lung cancer

Comparison: 1 Surgery + PORT versus surgery alone

Outcome: 7 survival subgroup analysis - histology

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
zg adenocarcinoma	147/195	158/218		1.21 [0.96, 1.52]
zh squamous	360/522	353/545		1.14 [0.98, 1.32]
zi other histology	44/66	37/54		0.85 [0.54, 1.36]



Analysis 1.8. Comparison 1 Surgery + PORT versus surgery alone, Outcome 8 survival subgroup analysis - stage.

Review: Postoperative radiotherapy for non-small cell lung cancer

Comparison: 1 Surgery + PORT versus surgery alone

Outcome: 8 survival subgroup analysis - stage

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
zj stage 1	203/327	181/338		1.42 [1.16, 1.75]
zk stage 2	226/352	212/366		1.26 [1.04, 1.52]
zl stage 3	334/464	331/455		0.99 [0.85, 1.15]

Analysis 1.9. Comparison 1 Surgery + PORT versus surgery alone, Outcome 9 Survival subgroup analysis - nodal status.

Review: Postoperative radiotherapy for non-small cell lung cancer

Comparison: 1 Surgery + PORT versus surgery alone

Outcome: 9 Survival subgroup analysis - nodal status

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
zm nodal status 0	142/252	120/257		1.33 [1.03, 1.71]
zn nodal status 1	265/417	261/450		1.24 [1.05, 1.48]
zo nodal status 2	246/627	234/297		0.97 [0.81, 1.16]

ADDITIONAL TABLES

Table 1. Common meta-analysis stage scale

T stage	N stage	M stage	Meta-analysis stage	AJCC stage
0, 1, 2, X, S	0	0	I	I
0, 1, 2, X, S	1	0	II	II
Any	2, 3	0	III	III non-metastatic
3, 4	Any	0	III	III non-metastatic
Any	Any	1	IV	Any metastatic

Table 2. Characteristics of patients in PORT meta-analysis

Characteristic	Postoperative RT	Surgery only	Total
AGE			
< 54 years	294	327	621
55 to 59 years	267	261	528
60 to 64 years	290	276	566
> 65 years	312	315	627
Unknown	0	1	1
SEX			
Male	988	992	1980
Female	175	187	362
Not recorded	0	1	1
HISTOLOGY (data from 9 trials)			
Adenocarcinoma	195	218	413
Squamous	522	545	1067
Other	66	54	120
Unknown	380	363	743

Table 2. Characteristics of patients in PORT meta-analysis (*Continued*)

META-ANALYSIS STAGE			
I	328	338	666
II	353	366	719
III	463	455	918
IV	1	0	1
Unknown	18	21	39
WHO PERFORMANCE STATUS (data from 4 trials)			
Good (0, 1)	195	196	391
Poor (2, 3, 4)	77	83	160
Unknown	22	21	43

WHAT'S NEW

Last assessed as up-to-date: 18 January 2009.

Date	Event	Description
5 November 2009	Amended	New PLS added

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 1, 2000

Date	Event	Description
12 May 2009	Amended	Name of Group author slightly changed
19 January 2009	New search has been performed	Full update, new trial data included
22 May 2008	Amended	Converted to new review format

(*Continued*)

25 October 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All aspects of the meta-analysis were carried out under the auspices of the PORT Meta-analysis Trialists group: R Arriagada; AH Brichet, JJ Lafitte, B Dautzenberg, M Debevec, V Kovac, DJ Girling, RJ Stephens, A Gregor, S Piantadosi, P Rocmans, L Trodella, JH Park, P Van Houtte, M Wang collated and supplied the individual patients' data, contributed to the discussions of the results, and commented on the drafts of the report. The project was organised by the advisory group (R Arriagada, DJ Girling, JP Pignon, V Torri) and the secretariat (S Burdett, M K B Parmar, L A Stewart, L Rydzewska), who were responsible for formulating the questions, developing the protocol, and discussing the preliminary results. The secretariat were responsible for receiving, checking and analysing the data and drafting the report.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Medical Research Council, UK.

External sources

- NHS R&D programme project grant NCP/U03, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Carcinoma, Non-Small-Cell Lung [*radiotherapy; surgery]; Lung Neoplasms [*radiotherapy; surgery]; Radiotherapy, Adjuvant; Randomized Controlled Trials as Topic

MeSH check words

Humans