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

Burdett S, Rydzewska L, Tierney J, Fisher D, Parmar MKB, Arriagada R, Pignon JP, Le Pechoux C, on behalf of the PORT Meta-analysis Trialists Group

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[Intervention Review]

Postoperative radiotherapy for non-small cell lung cancer

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ABSTRACT

Background

The role of postoperative radiotherapy (PORT) in the treatment of patients with completely resected non-small cell lung cancer (NSCLC) was not clear. A systematic review and individual participant data meta-analysis was undertaken to evaluate available evidence from randomised controlled trials (RCTs). These results were first published in *Lung Cancer* in 2013.

Objectives

To evaluate the effects of PORT on survival and recurrence in patients with completely resected NSCLC. To investigate whether predefined patient subgroups benefit more or less from PORT.

Search methods

We supplemented MEDLINE and CANCERLIT searches (1965 to 8 July 2016) with information from trial registers, handsearching of relevant meeting proceedings and discussion with trialists and organisations.

Selection criteria

We included trials of surgery versus surgery plus radiotherapy, provided they randomised participants with NSCLC using a method that precluded prior knowledge of treatment assignment.

Data collection and analysis

We carried out a quantitative meta-analysis using updated information from individual participants from all randomised trials. We sought data on all participants from those responsible for the trial. We obtained updated individual participant data (IPD) on survival and date of last follow-up, as well as details on treatment allocation, date of randomisation, age, sex, histological cell type, stage, nodal status and performance status. To avoid potential bias, we requested information on all randomised participants, including those excluded from investigators' original analyses. We conducted all analyses on intention-to-treat on the endpoint of survival.

Main results

We identified 14 trials evaluating surgery versus surgery plus radiotherapy. Individual participant data were available for 11 of these trials, and our analyses are based on 2343 participants (1511 deaths). Results show a significant adverse effect of PORT on survival, with a hazard ratio of 1.18, or an 18% relative increase in risk of death. This is equivalent to an absolute detriment of 5% at two years (95% confidence

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interval (CI) 2% to 9%), reducing overall survival from 58% to 53%. Subgroup analyses showed no differences in effects of PORT by any participant subgroup covariate.

We did not undertake analysis of the effects of PORT on quality of life and adverse events. Investigators did not routinely collect quality of life information during these trials, and it was unlikely that any benefit of PORT would offset the observed survival disadvantage. We considered risk of bias in the included trials to be low.

Authors' conclusions

Results from 11 trials and 2343 participants show that PORT is detrimental to those with completely resected non-small cell lung cancer and should not be used in the routine treatment of such patients. Results of ongoing RCTs will clarify the effects of modern radiotherapy in patients with N2 tumours.

PLAIN LANGUAGE SUMMARY

Postoperative radiotherapy for non-small cell lung cancer

Review question

Do patients with non-small cell lung cancer live longer if they are given radiotherapy after surgery?

Background

Non-small cell lung cancer is the most common type of lung cancer. If the tumour is early stage, is not too big and has not spread to other parts of the body, doctors usually operate to remove it. Radiotherapy (treatment with x-rays) is sometimes given after the operation, aiming to kill any remaining cancer cells.

In 1998, we did a systematic review and meta-analysis of individual participant data looking at trials of this treatment - postoperative radiotherapy (PORT). This review brought together information from all patients who took part in similar trials. These trials compared what happened to people with non-small cell lung cancer who were given radiotherapy after surgery and those who had surgery without radiotherapy. Results were first published in *The Lancet* in 1998.

Since this review was completed, many trials have been done. To ensure that available evidence is as up-to-date as possible, we carried out a new systematic review and meta-analysis of individual participant data that included all trials, old and new. As for the 1998 review, this review aimed to find out if giving radiotherapy after surgery (1) helps patients live longer, (2) stops cancer from coming back (recurrence) and (3) stops cancer from spreading to other parts of the body (metastases).

These updated results were first published in *Lung Cancer* in 2013.

Study characteristics

We searched for relevant trials up to 8 July 2016. These studies brought together available trial data from all over the world, with 11 trials and 2343 patients. Trials were carried out between 1966 and 1998.

Key results

Results showed that fewer people given PORT treatment lived for two years after the operation (53 out of every 100 patients) than those not given PORT after the operation (58 out of every 100 patients). Researchers reported no difference in effects of PORT by types of patients included in trials.

Researchers did not routinely collect quality of life information during the trials, and it was unlikely that any benefit of PORT would offset the observed survival disadvantage.

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; however, further research into new types of radiotherapy for patients at higher risk of recurrence is ongoing.

Quality of evidence

These systematic reviews and meta-analyses use individual participant data, which are considered the gold standard for this type of review. We included all eligible trials, if possible, no matter what language they were published in, or whether or not they were published. This meta-analysis included 88% of all participants in eligible trials.

Studies were well designed and conducted and addressed the review question, with consistent effects noted across trials. The impact of any data not included in our analyses is small.

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BACKGROUND

Description of the condition

Worldwide, carcinoma of the lung is the main cause of cancer death. More than 1.5 million new cases are diagnosed each year (Jemal 2011), about 85% of which involve non-small cell lung cancer (American Cancer Society 2007). Surgery is the treatment of choice for early non-small cell lung cancer (NSCLC) (NSCLCCG 1995), but only about 20% of tumours are suitable for potentially curative surgery (Datta 2003). Even for patients with apparently completely resected disease, survival is only around 40% at five years. In an effort to improve local-regional control of the disease and to increase survival, investigators have explored adjuvant postoperative radiotherapy (PORT) as a therapeutic option.

Description of the intervention

This review concentrated on randomised controlled trials (RCTs) that tested surgery alone compared with surgery followed by radiotherapy. Radiotherapy in these trials was given by cobalt therapy, by cobalt therapy and linear accelerators or by linear accelerators only.

How the intervention might work

Radiotherapy may be given after surgery with the aim of killing any remaining cancer cells.

Why it is important to do this review

Despite the conduct of several RCTs (most in the 1980s and 1990s) that recruited a total of more than 2000 patients, the role of PORT in the treatment of patients with NSCLC has remained unclear. Individually, trials showed inconclusive and conflicting results. However, because of their size (74 to 539 participants), individual trials did not have sufficient statistical power to detect the moderate survival differences that might be expected with PORT. We therefore initiated an individual participant data meta-analysis to assess this question. This approach to meta-analysis and systematic review involves the central collection, validation and analysis of original trial data. It does not rely on data extracted from publications. At the outset, the project management group 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* in 1998 (PORT 1998). In 2005, the meta-analysis was updated (PORT 2005) with data from one new trial (Italy 2002). In 2009, the meta-analysis was updated again to include data from another new trial (Korea 2007). However, since this review was last updated, new methods developed to assess treatment by patient covariates that are methodologically more appropriate and less prone to bias have prompted this latest update of the Cochrane review (Fisher 2011). Furthermore, changes over time to the tumour-node-metastasis (TNM) staging system have been taken into account in this update, and although the data did not permit use of the seventh TNM edition, they did allow us to convert tumour stage from the fourth (Mountain 1987) to the fifth/sixth (Mountain 1997) edition.

OBJECTIVES

To evaluate effects of PORT on survival and recurrence in patients with completely resected NSCLC. To investigate whether predefined patient subgroups benefit more or less from PORT.

METHODS

Criteria for considering studies for this review

Types of studies

To be included, both published and unpublished completed trials had to be properly randomised using established methods (not quasi-randomised). Trials could not have been confounded by additional therapeutic differences between the two arms and must have commenced randomisation on or after 1 January 1965. Trials should have aimed to randomise participants with completely resected non-small cell lung cancer between radiotherapy and no immediate further treatment. Trials should not have used orthovoltage radiotherapy.

Types of participants

Eligible trials included individuals with histologically confirmed NSCLC who had undergone a potentially curative resection. We included in the meta-analyses individual participant data from all randomised participants and, when possible, obtained data for individuals who had been excluded from the original trial analyses. We excluded from the meta-analyses, participants with small cell lung cancer, who were included in early trials that randomised all types of lung cancer.

Types of interventions

- Surgery versus surgery + postoperative radiotherapy (PORT).

Types of outcome measures

- Survival.
- Recurrence-free survival.
- Local recurrence-free survival.
- Distant recurrence-free survival.

Primary outcomes

The primary outcome of overall survival was defined as the time from randomisation until death by any cause. Living participants were censored on the date of last follow-up.

Secondary outcomes

Recurrence-free survival was defined as the time from randomisation until first recurrence, or death by any cause. Participants alive without disease were censored on the date of last follow-up. To avoid bias from under-reporting of subsequent events, time to local-regional recurrence was defined as the time from randomisation until first local-regional recurrence, with participants experiencing earlier distant recurrences censored at the time of distant recurrence. Similarly, for time to distant recurrence, participants experiencing earlier local-regional recurrences were censored on that date. Participants who died without recurrence were censored on the date of death. Data on quality of life were not routinely collected in these trials; therefore we could not analyse the data in this review.

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Search methods for identification of studies

To limit publication bias, we included published and unpublished trials with no restrictions based on language. We carried out searches of MEDLINE (Appendix 1) and CANCERLIT from 1965 (using The Cochrane Collaboration's optimal strategy (Lefebvre 2001; Lefebvre 2008). We supplemented searches of trial registers by conducting handsearches of conference proceedings and reference lists of trial publications and review articles. We asked our collaborators if they knew of additional trials. We carried out the most recent searches in July 2016.

In 1997, we identified trials by electronic searches of MEDLINE and CANCERLIT, using a modified version of the optimal search strategy of The Cochrane Collaboration (Dickersin 1995), supplemented by handsearches of Proceedings of the American Society of Clinical Oncology (ASCO) (1990 to 2016) and the World Conference on Lung Cancer (1990 to 2015) and bibliographies of books, reviews and specialist journals. We also searched trial registers (Cochrane Central Register of Controlled Trials (CENTRAL), the National Cancer Institute Physicians Data Query Clinical Protocols and United Kingdom Co-ordinating Committee for Cancer Research)and asked all trialists who took part in the meta-analysis to help to identify additional trials. We regularly updated searches to identify new trials and to assess the status of any ongoing trials. Search updates in October 2002 and August 2003 identified one new eligible trial (Italy 2002), and the search update carried out in 2009 identified two new eligible trials: a Polish trial (Dymek 2003) and a Korean trial published as an abstract (Korea 2007). We last carried out searches in July 2016 and identified no new eligible trials.

Electronic searches

We modified The Cochrane Collaboration's optimum search strategy for retrieving RCTs from MEDLINE (Appendix 1) to specifically retrieve RCTs of radiotherapy for NSCLC, and we used this search strategy to search MEDLINE and CANCERLIT (1965 to 2016).

In addition, we searched the following electronic bibliographic databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (1995 to 8 July 2016) (Appendix 2).
- Proceedings of annual meetings of the American Society for Clinical Oncology (ASCO) (1995 to 2016).

We used the following trial registers to supplement searches of electronic databases with trials that were not (yet) published or were still recruiting patients.

- United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Trials Register.
- ClinicalTrials.gov.
- Physicians Data Query Protocols (open and closed).
- Current Controlled Trials 'metaRegister' of controlled trials.

Searching other resources

Handsearches

We carried out the following handsearches to identify trials that may have been reported only as abstracts, or that might have been missed in the searches described above.

- Proceedings of the American Society for Clinical Oncology (ASCO), 1990 to 1994.
- Proceedings of the International Association for the Study of Lung Cancer (IASLC) World Lung Cancer Conference 1990 to 2015.

Searches of reference lists

We searched the bibliographies of all identified trials and review articles.

Correspondence

We asked all participating trialists to review and supplement a provisional list of trials.

Data collection and analysis

Selection of studies

Two members of the Project Management Group (SB, LR) checked all titles and abstracts identified by electronic searching and handsearching of conference proceedings, and obtained full publications for those thought to be potentially relevant. We sought individual participant data (IPD) from trial authors, including updated follow-up, when available.

Data extraction and management

We sought IPD for all eligible trials, as well as 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.

We used standard checks to identify missing data. We verified data, for example, by checking the order of the dates of randomisation, and assessed data validity and consistency. To assess randomisation integrity, we checked patterns of treatment allocation and balance of baseline characteristics by treatment arm. We checked follow-up of surviving participants to ensure that it was balanced by treatment arm and up-to-date. We resolved queries, and each trial investigator or statistician verified the final database.

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, which has been updated since the original analysis to reflect the TNM sixth edition classification (Table 1; Table 2).

Assessment of risk of bias in included studies

We assessed included studies using the risk of bias tool of The Cochrane Collaboration, as outlined in Table 8.5c of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), two authors (SB, LR) checked these studies. We considered adequate sequence generation and allocation concealment to be most important; therefore a judgement of low risk was desirable for these domains for all trials. Blinding was not appropriate

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owing to the nature of the treatments, and any issues surrounding reporting of incomplete outcome data, selective outcome reporting or attrition bias were overcome by collection of IPD.

Measures of treatment effect

Unless otherwise stated, we prespecified all analyses in the protocols and carried out an intention-to-treat analysis. For each outcome, we used the log-rank expected number of events and variance to calculate individual trial hazard ratios (HRs), which we pooled across trials using the fixed-effect model (Yusuf 1985). We presented overall survival using simple (non-stratified) Kaplan-Meier curves (Kaplan 1958) and computed median follow-up for all participants by using the reverse Kaplan-Meier method (Schemper 1996).

We analysed 'raw' IPD using in-house software (SCHARP), then entered the log-rank summary statistics of these analyses (O-E and variance) into RevMan (RevMan 2014). We presented results as absolute differences at five years, calculated with the HR and baseline event rate on the surgery alone arm; we assumed proportional hazards (Parmar 1995). We similarly calculated confidence intervals for absolute differences from the baseline event rate and the HR at 95% confidence interval boundary values.

To explore any impact of trial characteristics on effects of adjuvant chemotherapy on overall survival, we calculated pooled HRs for each prespecified trial group and used Chi^2 tests for interaction to investigate differences in treatment effect across trial groups.

Dealing with missing data

We outlined all desired variables in a protocol (available on request) and requested missing variables from those who carried out the trials.

Assessment of heterogeneity

We used Chi^2 tests and the I^2 statistic (Higgins 2002) to test for differences in treatment effect across groups of trials or groups of participants.

Assessment of reporting biases

As we collected IPD, we encountered no reporting biases.

Data synthesis

When we could get data, we included all eligible trials in the analyses. We carried out these analyses in SCHARP (in-house software), Stata (Stata 2013) and RevMan (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

To investigate differences in treatment effect across participant subgroups, we undertook Cox regressions, including the relevant treatment by subgroup interaction term within each trial. We pooled these interaction coefficients (HRs) across trials (Fisher 2011) and investigated whether differences in treatment effect could be identified that varied with participant age, sex, histological cell type, tumour stage or performance status.

Sensitivity analysis

We outlined in the protocol that HRs for overall survival would be calculated, excluding any trials that were clear outliers.

RESULTS

Description of studies

We identified 14 eligible trials (one unpublished) and included 11 trials in the review (see Characteristics of included studies). We could not include three trials: Data for two trials were unavailable (Dymek 2003 (150 participants); LCSG 841 (five participants)), and it was unclear whether one study of 155 participants, which was reported as a randomised controlled trial (RCT), was indeed randomised. We were unable to obtain appropriate data for this trial (Austria 1996) (see Characteristics of excluded studies).

Therefore, this update is based on the results of 11 RCTs (Belgium 1966; CAMS 1981; EORTC 08861; GETCB 04CB86; GETCB 05CB88; Italy 2002; Korea 2007; LCSG 773; Lille 1985; MRC LU11; Slovenia 1988) and 2343 individuals. Across these trials, PORT doses ranged from 30 Gy to 60 Gy, given in between 10 and 30 fractions, and considerable diversity was evident in other aspects of radiotherapy planning. All trials included participants with completely resected tumours for which the disease stage was no greater than IIIA. Most trials provided updated follow-up giving a median of 4.4 years for surviving participants (2.3 to 11.4 years for individual trials). Baseline participant characteristics show that most participants were male with stage II/III squamous cell carcinoma (although histology was unknown for a relatively large number of participants) with good performance status (Table 3).

Risk of bias in included studies

We included only trials with adequate methods of randomisation. We excluded trials that used quasi-random methods, such as birth date. We thoroughly checked all raw data received on individual participants to ensure both the accuracy of the meta-analysis database and the quality of randomisation and follow-up. We resolved all queries and verified final database entries through discussion with the responsible trial investigator or statistician. No RCTs were blinded owing to the nature of the intervention, but the primary outcome is not likely to be influenced by lack of blinding. For two trials, allocation concealment was unclear - one trial was unpublished (EORTC 08861), and one was published only as an abstract (Korea 2007) - but checks on IPD and correspondence with those who supplied the data reassured us that the data had been adequate. We received IPD for all outcomes of interest; therefore we considered reporting bias to be low for all RCTs. We considered all included trials to be at low risk of bias (see Figure 1 and Figure 2).

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Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

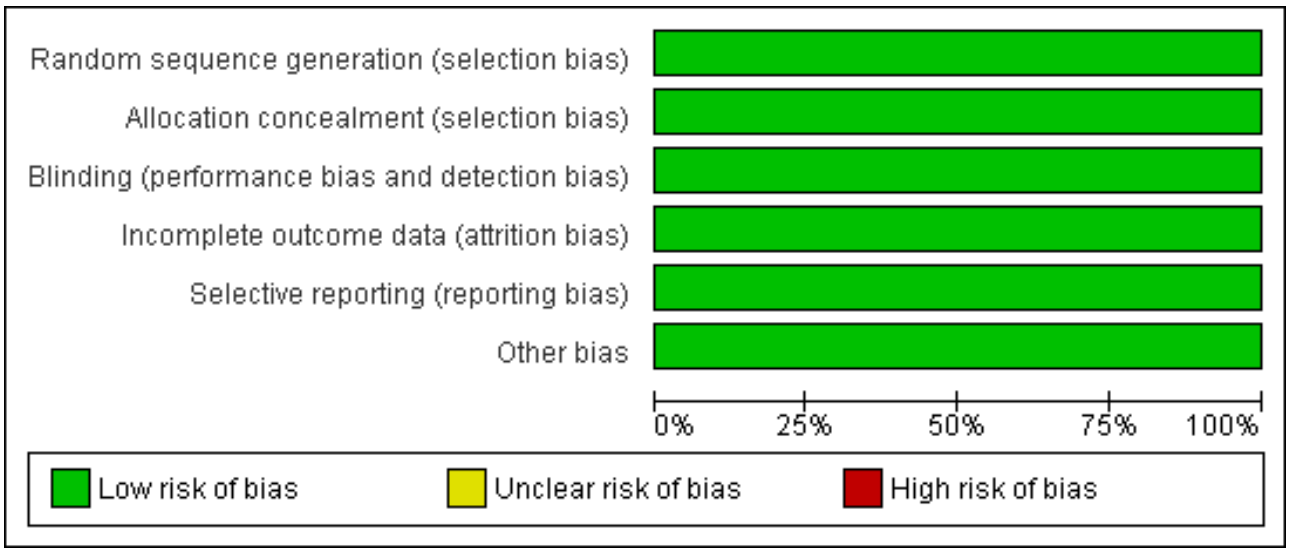

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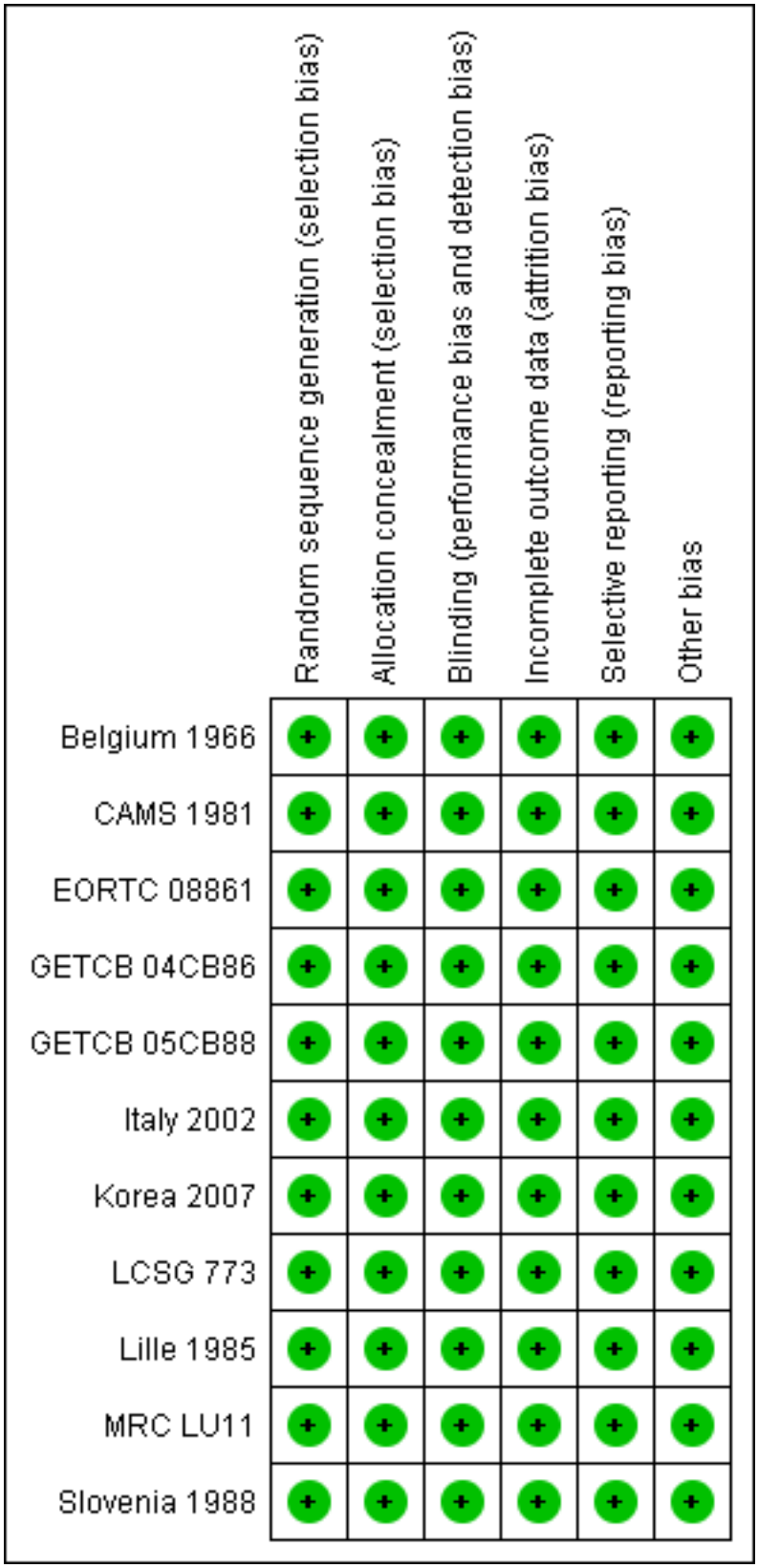
Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



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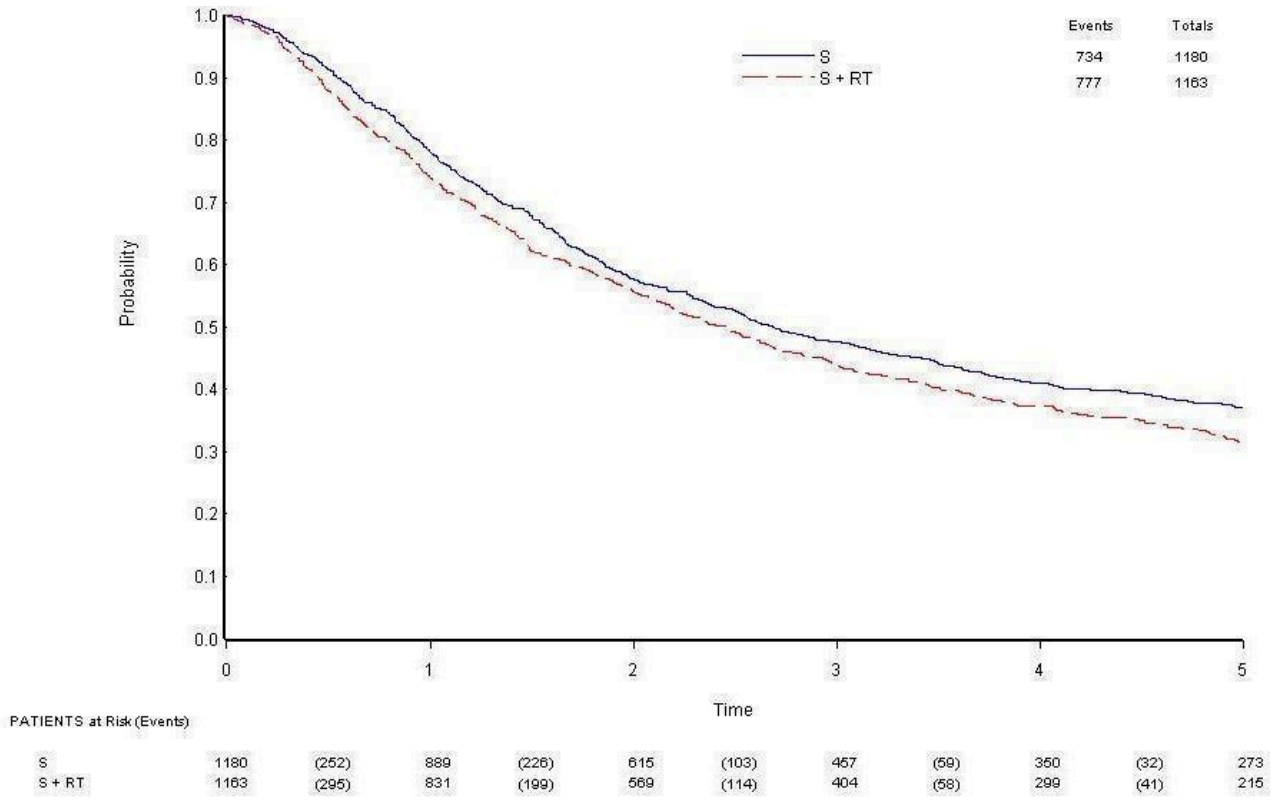
Effects of interventions

Results were based on information from 11 RCTs (2343 participants), representing 88% of individuals from all eligible randomised trials. We collected data for 140 out of 142 participants who had been excluded from the original published trial analyses and were reinstated in this meta-analysis. For one trial, which randomised all histological types of lung cancer (Belgium 1966), we excluded the 20 participants with small cell tumours from the meta-analysis. Survival and recurrence data were available for all trials. All trials provided information on age, sex and stage, and nine trials provided data on histology (Belgium 1966; CAMS 1981; EORTC 08861; Italy 2002; Korea 2007; LCSG 773; Lille 1985; MRC LU11; Slovenia 1988). Performance status data were available for only four trials (EORTC 08861; Italy 2002; MRC LU11; Slovenia 1988) and were insufficient for assessment of treatment by covariate interactions. All but two trials provided cause of death data (coded as NSCLC, treatment-related or other) (Italy 2002; LCSG 773), although the trialists themselves questioned the reliability of this information for many trials.

Survival

Survival data were available for all trials and included information from 2343 participants and 1511 deaths (777 PORT, 734 surgery alone). Although the confidence intervals (CIs) for individual trial results were wide, 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) (Analysis 1.1), or an 18% relative increase in 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 3) 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 evidence of increased statistical heterogeneity between trials in the current update (I^2 = 40%, P = 0.08), compared with the original 1998 meta-analysis. However, the random-effects result is similar (HR 1.17, 95% CI 1.02 to 1.34, P = 0.02), and heterogeneity appears largely driven by the Italian trial (Italy 2002). A sensitivity analysis excluding this trial reduces heterogeneity (I^2 = 31%, P = 0.16) and gives similar fixed-effect (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 3. Overall survival.



Cause of death information coded as NSCLC, treatment related or other was available for nine trials. Of 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-regional recurrence were available from all trials. Analysis of local-regional recurrence-free survival, based on 1556 events (498 local-regional recurrences (200 on PORT, 298 on surgery alone) and 1058 deaths (593 on PORT, 465 on surgery alone)), gave a HR of 1.12 (95% CI 1.01 to 1.24), significantly in favour of surgery alone (P = 0.03) (Analysis 1.2). There was evidence of statistical heterogeneity between trials (I^2 = 47%, P = 0.04), which was not

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apparent in the 1998 analysis (I^2 = 29%, P = 0.19), and for this outcome, the random-effects result is less convincing (HR 1.10, 95% CI 0.95 to 1.27, P = 0.19) than the fixed-effect result. However, 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-effect (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). Results may suggest an increase in local-regional recurrence on the PORT arm, but the number of local-regional recurrences alone shows less local-regional recurrence on the PORT arm and more events when deaths without local-regional recurrence are included.

Distant recurrence-free survival

All trials provided data on distant recurrence. 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 an HR of 1.13 (95% CI 1.02 to 1.24) in favour of surgery alone (P = 0.02) (Analysis 1.3). There was no evidence of gross 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 surgery alone. Of these, 445 first events were deaths, 260 participants had local-regional recurrences and 654 had distant recurrences (238 participants had both local-regional and distant recurrences, of which 110 were recorded on the same date). The overall HR of 1.10 (95% CI 0.99 to 1.21) potentially suggests an adverse effect of PORT (P = 0.07) (Analysis 1.4). This 10% relative increase in 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 with local-regional recurrence-free survival, there was some evidence of increased statistical heterogeneity between trials (I^2 = 44%, P = 0.06) that was 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-effect (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.

Analyses by trial characteristics

We planned analysis for overall survival by trial characteristic based on the planned energy beam delivery method (cobalt only, cobalt and linac, linac only) and radiotherapy dose (< 45 Gy, ≥ 45 Gy). We found no difference in effects of treatment on overall survival depending on delivery method (P = 0.18) (Analysis 1.5). We did find a difference by dose of radiotherapy (P = 0.02) (Analysis 1.6), but 80% of data is in the >=45 Gy group, and the result in the < 45 Gy group subgroup alone is not significant.

Analyses by participant covariates

Based on data from all trials, for survival there was no evidence to suggest that PORT was differentially effective by age (interaction P = 0.67), sex (P = 0.49) or histology (P = 0.38). For analysis by stage, we could not include three trials because all participants were in a single stage category (Italy 2002, Lille 1985 stage I only; Slovenia 1988 stage III only). Data from the remaining eight trials provide no evidence to suggest that PORT was differentially effective by stage within individual trials (Figure 4), but the meta-analysis of these interactions suggests that PORT may be most detrimental in earlier-stage patients, although the result was not significant (HR = 0.87, 95% CI 0.72 to 1.04, P = 0.12) (Figure 5). Similar results were observed whether or not trials included all three stages or only stage II and III participants (Figure 6; Figure 7). Exploratory analyses of how the effect of PORT on local-regional, distant and overall recurrence-free survival varies by stage gave similar results. For analysis by nodal status, we could not include four trials because all participants were in a single subgroup category with N0 (Belgium 1966; Italy 2002; Lille 1985) or N2/3 (Slovenia 1988) disease. Data from the remaining seven trials provided no evidence to suggest that PORT was differentially effective by nodal status within individual trials (Figure 8), nor in a meta-analysis of these interactions (HR = 0.92, 95% CI 0.76 to 1.11, P = 0.39) (Figure 3).

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Figure 4. PORT effect on overall survival by trial according to stage.

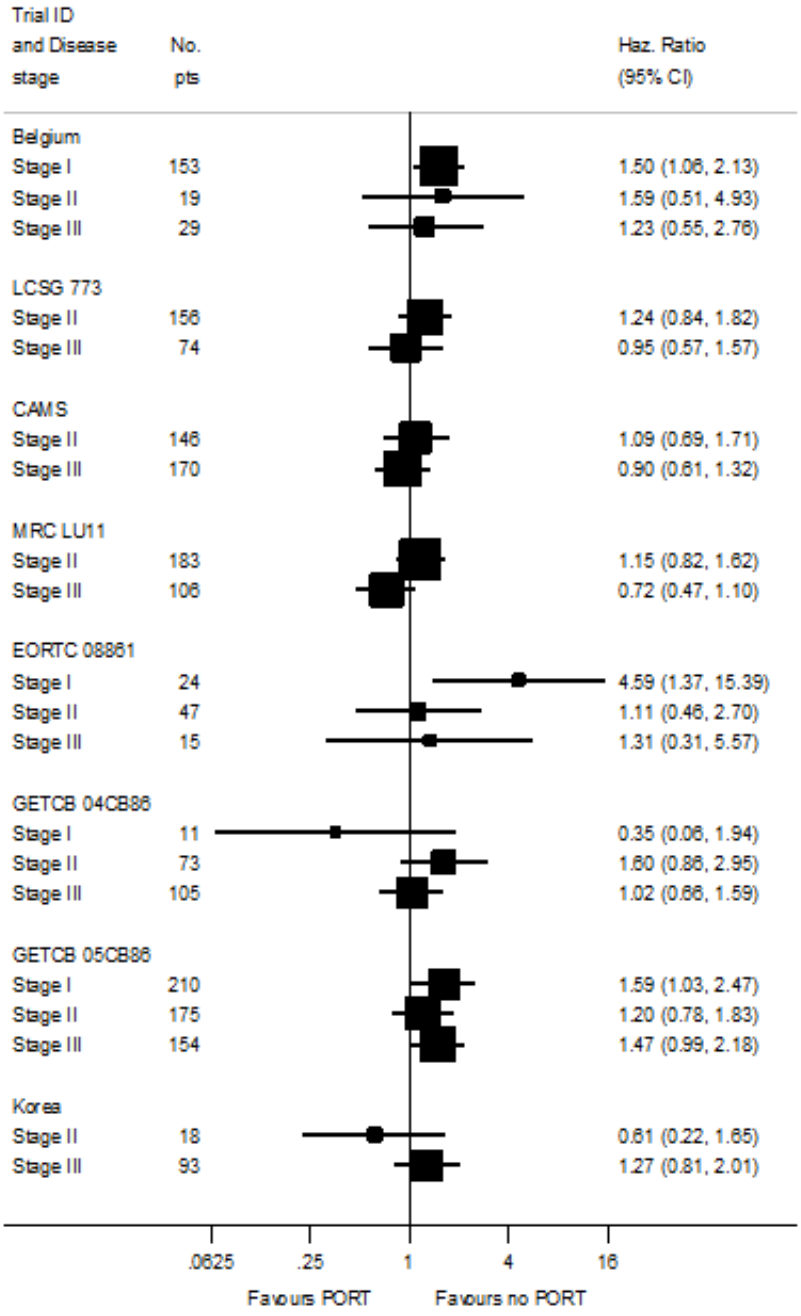

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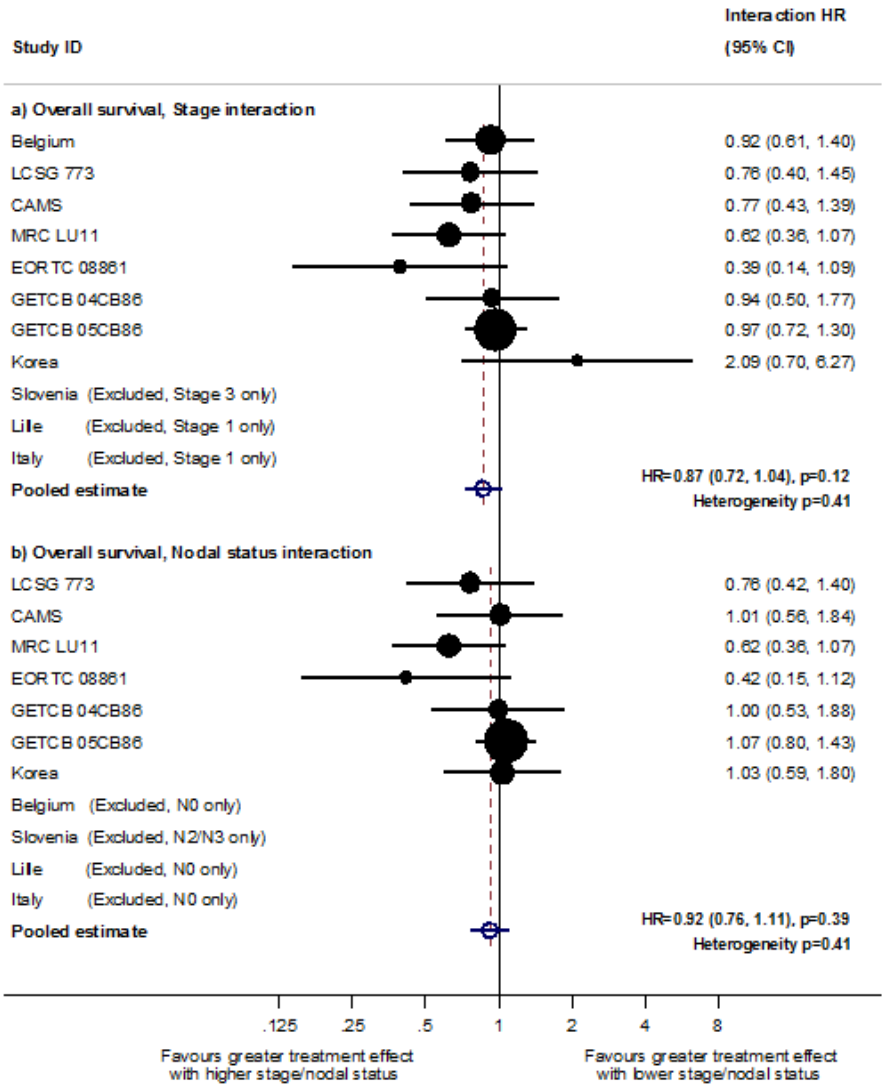
Figure 5. Hazard ratio (HR) for the interaction between the effect of PORT on survival and (a) stage or (b) nodal status.



The centre of each filled circle denoted the HR for the interaction between the effect of chemotherapy and stage or nodal status for each trial, with the horizontal line showing the 95% confidence interval (CI). The size of each circle is directly proportional to the amount of information contributed by a trial. The open circle represents a (fixed effect) meta-analysis of the interaction HRs, again with the horizontal line showing the 95% CI. Results of PORT effect on overall survival by trial according to stage and nodal status are shown in figures 2 and 6 respectively.

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Figure 5. (Continued)

Figure 6. Sensitivity analysis 1: only trials with all stage subgroups included.

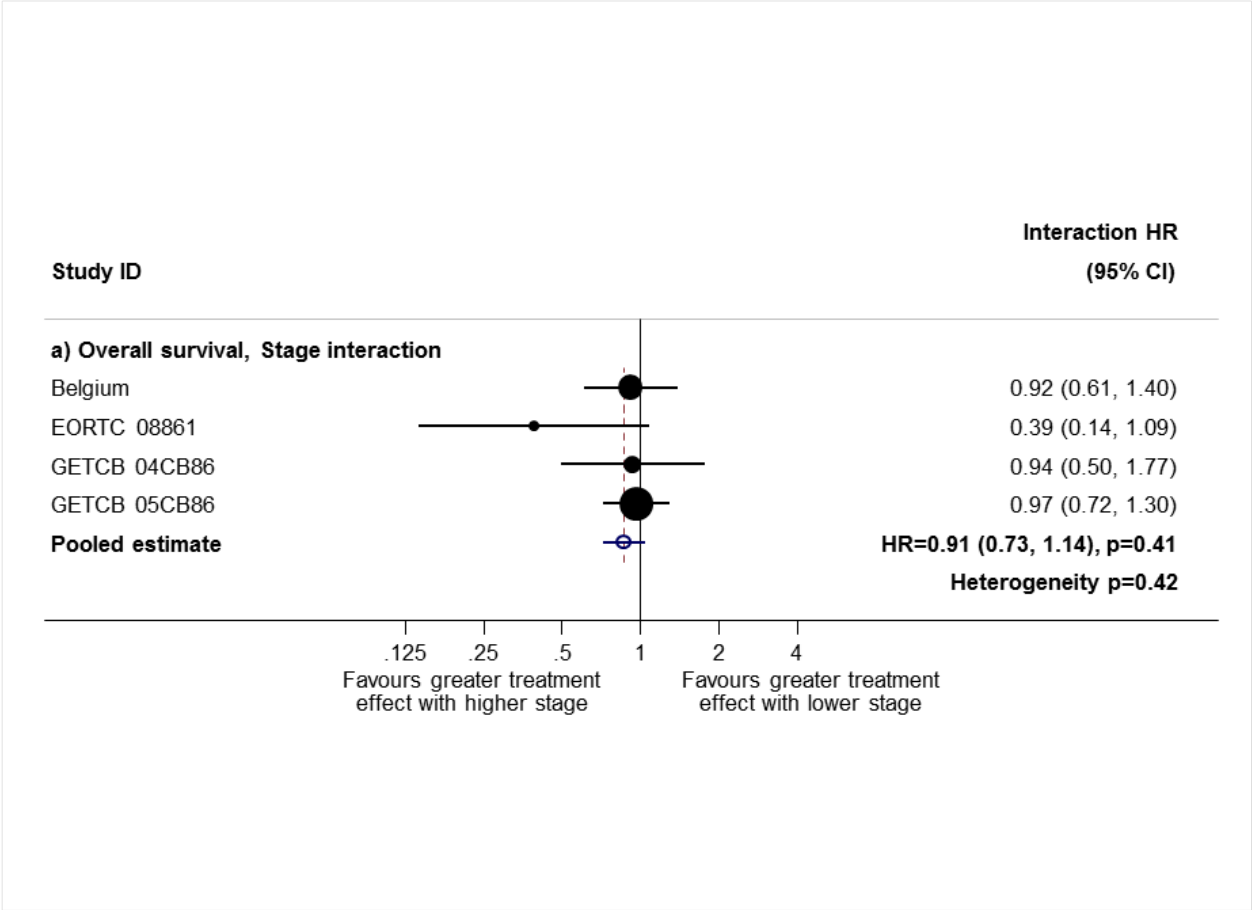

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Figure 7. Sensitivity analysis (2): only trials with stage II and III subgroups represented.

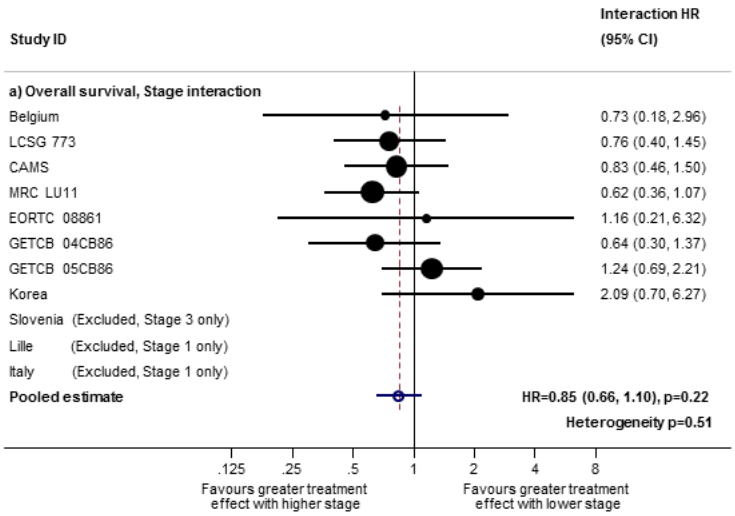

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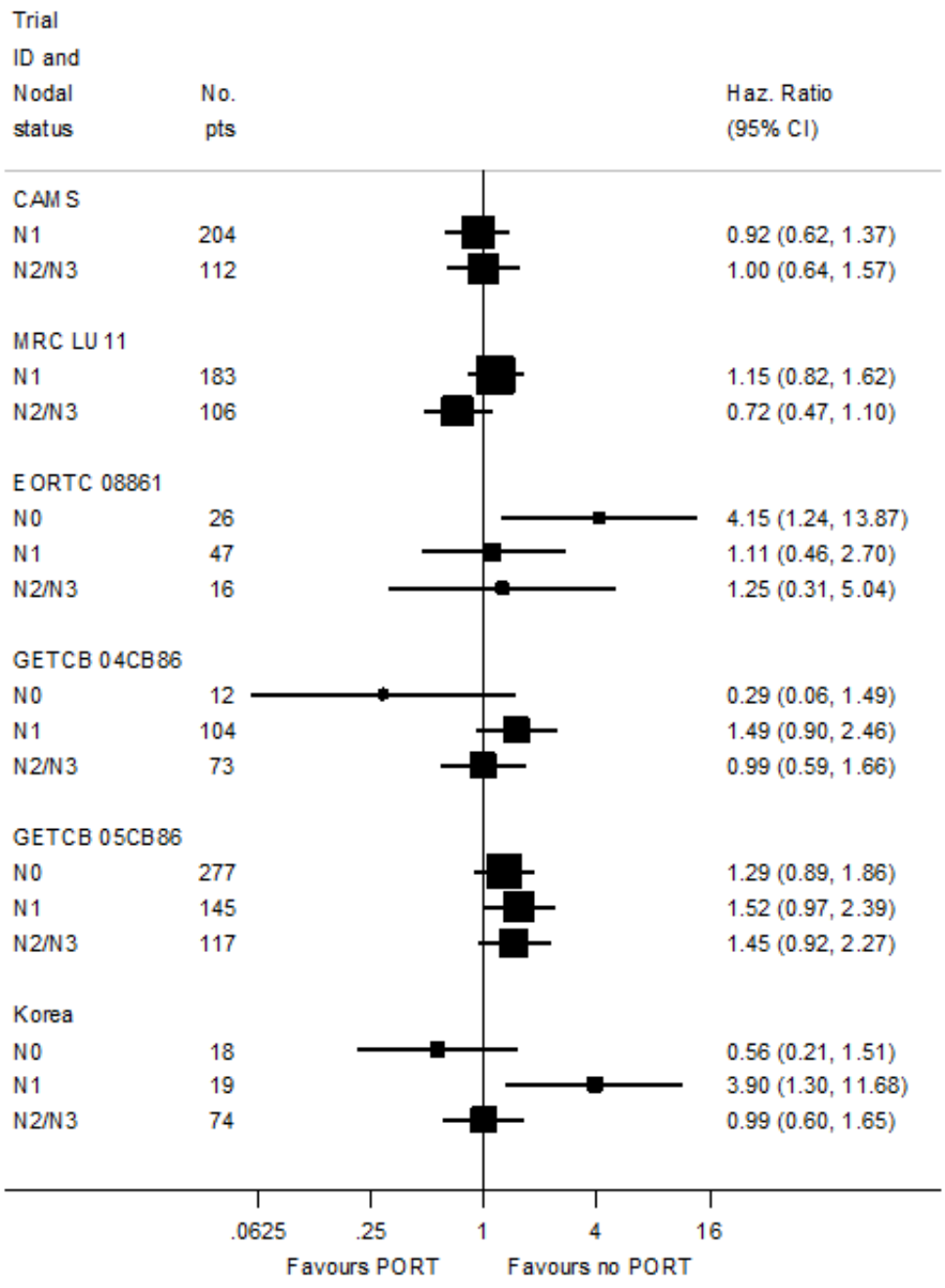
Figure 8. PORT effect on overall survival by trial according to nodal status.



Results for stage and nodal status are different from previously published results (PORT 1998; PORT 2005) largely for two reasons. Here, we have used a method (Fisher 2011) to examine whether the effect of PORT varied by participant covariates that was different from the method used in the original review in 1998 (PORT 1998), and in the previous updates in 2005 and 2009 (PORT 2005). This new method is more appropriate and is less prone to bias. We could not calculate several covariate interactions for trials contributing participants in only a single covariate category; therefore we did not include these studies; this approach, although correct, can provide less power than the methods used previously. Trials not included here also happen to have quite extreme results and have had undue influence on previous analyses.

In this update, we wanted to take account of changes to the TNM staging system; although the data do not allow us to use the

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seventh edition, they do allow us to convert stage from the fourth to the sixth edition; the major impact of this is that patients previously classified as T3N0M0 (stage IIIA) have been reclassified as stage IIB. This change affected 98 participants and Table 4 shows results for stage and nodal status according to the combination of changes made.

DISCUSSION

At the outset of this project, despite enrolment of more than 2000 participants in randomised trials, it remained unclear whether postoperative radiotherapy (PORT) was effective for the treatment of patients with 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% confidence interval (CI) 1.08 to 1.34), or a 21% relative increase in risk of death. We undertook this systematic review and individual participant data meta-analysis to produce a comprehensive, reliable and up-to-date summary of the average effect of PORT in patients with NSCLC, to provide reliable guidance for clinical practice and future research. Therefore, when a new trial of 111 participants was published (Korea 2007), we included this study 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 risk of death associated with PORT, equivalent to an overall reduction in survival from 58% to 53% at five years, represents a considerable hazard for these patients. In contrast to the original meta-analysis and previous updates, this update, using new and more appropriate methods, did not provide evidence that the relative effect of PORT was smaller or larger for patients of any category defined by age, sex or histology. For analysis by stage, PORT tended to be most detrimental in patients with earlier-stage disease, but this result was not significant once 98 patients had been reclassified according to the updated TNM system. Likewise, analysis by nodal status shows a much less convincing relationship between the effect of PORT and nodal status. Also, in the case of both stage and nodal status analyses, trials with participants in only a single stage or nodal status category (Lille 1985; Italy 2002; Slovenia 1988) had a major impact on the original analyses, and so their appropriate exclusion from these analyses is significant. However, this means that despite inclusion of more trials overall, less data were included in this compared with the original analyses so power is more limited.

All analyses of local-regional (P = 0.02), distant (P = 0.02) and overall (P = 0.08) recurrence-free survival (i.e. time to recurrence or death) have suggested an overall adverse effect of PORT. However, the observed detriment was less for these endpoints than for overall survival. For local-regional recurrence-free survival, results were driven largely by survival (as deaths account for the majority of events). This suggests that antitumour activity may be attributable to radiotherapy, and that increased risk of death from PORT may be attributable to other mechanisms. Analysis of the local-regional recurrence-free interval (i.e. the time to local-regional recurrence with death and distant recurrence censored) was not presented because such analysis would be difficult to interpret and would be potentially seriously flawed. This difficulty arose because increased risk of death with PORT may mean that patients treated with PORT die before their tumour has had time to recur locally. Thus, such measurement was likely to be an overestimation of local-regional control.

Inclusion of the most recent trial (Korea 2007) has brought the total number of participants to 2343 across 11 randomised controlled trials (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 in relation to the Italian trial (Italy 2002), which, it should be noted, included only participants with stage I disease.

However, a significant detriment of PORT for survival persists, with similar estimates, irrespective of whether a fixed-effect or a random-effects model is used. Results for local-regional and overall recurrence-free survival are less convincing. Furthermore, although trials have been conducted over a period of 40 years, with changes in diagnosis and assessment of recurrence and radiotherapy, no clear evidence indicates that the effect of PORT has improved over the decades.

In particular, much discussion over the past few years has focused on modern radiotherapy techniques such as those used in some of the trials included here; the suggestion is that modern radiotherapy (delivered by linear accelerator) may be less detrimental than older methods (delivered by cobalt machines). Recent literature-based meta-analyses (Billiet 2014) could not confirm this, providing a reported risk ratio (RR) for overall survival of 0.85 (95% confidence interval (CI) 0.59 to 1.22, P = 0.38) for trials that used only linear accelerators. Indeed when we ran this same analysis using our individual participant data, for those trials that used only linear accelerators (albeit on a different selection of trials), we observed a hazard ratio (HR) for overall survival of 1.02 (95% CI 0.80 to 1.31, P = 0.85; Analysis 1.5). Another recent literature-based meta-analysis (Patel 2014) has suggested benefit of PORT for overall survival when radiotherapy has been given only with linear accelerators (HR = 0.77, 95% CI 0.62 to 0.92, P = 0.02); however, this review used a combination of three RCTs (some of which included chemotherapy) and eight retrospective studies. Results of an ongoing trial may clarify this matter (Lung ART-IGR 2006/1202).

Although this meta-analysis did not directly address quality of life (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

Although the radiotherapy used in most of the included trials is now considered suboptimal, this update still provides the best evidence that postoperative radiotherapy (PORT) has an adverse effect on survival. There is now less compelling evidence that the effect of PORT varies by stage, and in particular nodal status, but PORT should not be used routinely unless supporting evidence can be obtained from an ongoing trial of modern PORT techniques (Lung ART-IGR 2006/1202).

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Implications for research

This meta-analysis has shown a clear adverse effect of postoperative radiotherapy on survival. However, whilst PORT still tends to be detrimental in early-stage disease, the result is no longer significant. Researchers must evaluate PORT using modern radiotherapy techniques. One recent systematic review (Patel 2014) has suggested a benefit of PORT when radiotherapy is given only with the use of linear accelerators; this review used a combination of randomised controlled trials (RCTs) (some of which included chemotherapy) and retrospective studies. Another recent review (Billiet 2014) could not confirm benefit. A trial including participants with N2 disease is currently ongoing (NCT00410683). If further trials are initiated, accurate and detailed information on the cause of death will be important, as will data regarding surgical resection and radiotherapy technique. Collection of such data may help to clarify whether a combination of radiation with surgery or radiation alone is the cause of excess deaths with postoperative radiotherapy.

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GETCB 04CB86 *{published and unpublished data}*

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GETCB 05CB88 *{published and unpublished data}*

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* Indicates the major publication for the study

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CHARACTERISTICS OF STUDIES

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

Belgium 1966

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: stated as randomised in paper; checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "randomisation carried out via sealed envelope"
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently free of other sources of bias

CAMS 1981

Methods	1981 to 1995 RCT

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CAMS 1981 *(Continued)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: stated as randomised in paper; checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "randomisation carried out via sealed envelope"
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently free of other sources of bias

EORTC 08861

Methods	1986 to 1990 RCT
Participants	106 patients Stages II, III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status
Interventions	Surgery + radiotherapy vs 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 × 10

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EORTC 08861 *(Continued)*

	Clinical target volume: hilum, mediastinum Technique: composite plans
Outcomes	Survival
Notes	Unpublished trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: unpublished trial; checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Comment: unpublished, insufficient information provided, but collection of IPD and correspondence with those who supplied the data reassured that data were adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently free of other sources of bias

GETCB 04CB86

Methods	1986 to 1994 RCT
Participants	189 patients Stages I, II, III Trial data used in subgroup analyses for sex, age, stage and nodal status
Interventions	Surgery + radiotherapy vs surgery alone RT details 60 Gy in 24 to 30 fractions in 6 weeks Prescription technique: isocentre Machine used: Co60 and linac (majority linac) Average field size (cm): unavailable 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

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GETCB 04CB86 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned by centralised telephone procedure" Comment: stated as randomised in paper; checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Comment: randomisation by central telephone call
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently free of other sources of bias

GETCB 05CB88

Methods	1988 to 1994 RCT
Participants	539 patients Stages I, II, III Trial data used in subgroup analyses for sex, age, stage and nodal status
Interventions	Surgery + radiotherapy vs surgery alone RT details 60 Gy in 24 to 30 fractions in 6 weeks Prescription technique: isocentre Machine used: Co60 and linac (majority linac) Average field size (cm): unavailable Clinical target volume: bronchial stump, hilum, mediastinum Technique: spinal cord blocks, oblique fields, lateral fields
Outcomes	Survival
Notes	Same publication as GETCB 04CB86

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned by centralised telephone procedure" Comment: stated as randomised in paper; checks run on IPD suggest adequate sequence generation

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GETCB 05CB88 *(Continued)*

Allocation concealment (selection bias)	Low risk	Comment: randomisation by central telephone call
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently free of other sources of bias

Italy 2002

Methods	1989 to 1997 RCT
Participants	104 patients Stage I Trial data used in subgroup analyses for age, sex, histology and stage
Interventions	Surgery + radiotherapy vs surgery alone RT details 50.4 Gy in 1.8 Gy/d 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "by chance" using computer-generated model Comment: stated as randomised in paper; checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Comment: computer-generated randomisation, which was checked by an independent colleague
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely influenced by lack of blinding

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Italy 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently free of other sources of bias

Korea 2007

Methods	1989 to 1998 RCT
Participants	111 patients Stages II, III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status
Interventions	Surgery + radiotherapy vs 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: stated as randomised in paper; checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Comment: insufficient information provided in abstract, but collection of IPD and correspondence with those who supplied the data reassured that data were adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes

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Korea 2007 *(Continued)*

Other bias	Low risk	Comment: study apparently free of other sources of bias

LCSG 773

Methods	1978 to 1985 RCT
Participants	230 patients Stages II, III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status
Interventions	Surgery + radiotherapy vs 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 and 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "permuted block randomisation" Comment: stated as randomised in paper; checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Quote: treatment assigned by central office
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of intervention; outcome not likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently free of other sources of bias

Lille 1985

Methods	1985 to 1991

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Lille 1985 *(Continued)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 (selection bias)	Low risk	Quote: "randomised with a table of randomisation according to Snedecor and Cochran"; insufficient information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently free of other sources of bias

MRC LU11

Methods	1986 to 1993 RCT
Participants	308 patients Stages II, III Trial data used in subgroup analyses for sex, age, histology, stage and nodal status

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MRC LU11 *(Continued)*

Interventions	Surgery + radiotherapy vs surgery alone RT details 40 Gy in 15 fractions in 3 weeks Prescription technique: central axis, at midplane Machine used: Co60 and 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: stated as randomised in paper; checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "treatment assigned by central office"
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently 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 vs 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 × 12 Clinical target volume: hilum, mediastinum Technique: oblique fields, lateral fields
Outcomes	Survival

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Slovenia 1988 *(Continued)*

Notes	Sealed envelope randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: stated as randomised in paper; checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "randomisation carried out via sealed envelope"
Blinding (performance bias and detection bias) All outcomes	Low risk	Comment: trial not blinded owing to the nature of the intervention; outcome not likely influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: individual participant data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Comment: individual participant data obtained and checked for all outcomes
Other bias	Low risk	Comment: study apparently free of other sources of bias

All trials supplied individual participant data for analysis and therefore are defined as unpublished data, even though most are published.
IPD = individual participant data.
RCT = randomised controlled trial.
RT = radiotherapy.1G

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

Study	Reason for exclusion
Austria 1996	Data unavailable/eligibility uncertain Reported to be an RCT. Data provided by trialists, but anomalies evident between reported results and data received, and it was not clear if the trial was randomised. We were unable to resolve these problems with the trialists
Dymek 2003	Eligible Data could not be obtained
LCSG 841	Eligible Data could not be obtained (5 participants)

RCT = randomised controlled trial.

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

Lung ART-IGR 2006/1202

Trial name or title	Essai de phase III comparant une radiothérapie médiastinale conformationnelle post-opératoire à l'absence de radiothérapie après chirurgie complète chez des patients présentant un carcinome bronchique non à petites cellules (CBNPC) avec envahissement médiastinal N2

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Lung ART-IGR 2006/1202 *(Continued)*

Methods	Phase III multi-centric
Participants	
Interventions	
Outcomes	Evaluation de l'impact de la radiothérapie médiastinale conformationnelle sur la survie sans récidive comparé à l'absence de radiothérapie
Starting date	2006
Contact information	Docteur Cécile Le Péchoux - lepechoux@igr.fr
Notes	

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 Local recurrence-free survival	11	2343	Hazard Ratio (95% CI)	1.12 [1.01, 1.23]
3 Distant recurrence-free survival	11	2343	Hazard Ratio (95% CI)	1.13 [1.02, 1.24]
4 Recurrence-free survival	11	2343	Hazard Ratio (95% CI)	1.10 [0.99, 1.21]
5 RT delivery method	11	2343	Hazard Ratio (95% CI)	1.18 [1.07, 1.31]
5.1 Cobalt-60 only	1	202	Hazard Ratio (95% CI)	1.48 [1.09, 2.02]
5.2 Cobalt-60 and linac	6	1746	Hazard Ratio (95% CI)	1.18 [1.05, 1.33]
5.3 Linac only	4	395	Hazard Ratio (95% CI)	1.02 [0.80, 1.31]
6 RT dose	11	2343	Peto Odds Ratio (95% CI)	1.18 [1.07, 1.31]
6.1 < 45 Gy	2	382	Peto Odds Ratio (95% CI)	0.93 [0.75, 1.17]
6.2 ≥ 45 Gy	9	1961	Peto Odds Ratio (95% CI)	1.25 [1.12, 1.40]

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

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
Belgium 1966	88/98	80/104		10.91%	1.48[1.09,2.02]
LCSG 773	84/110	81/120		11%	1.12[0.83,1.53]
CAMS 1981	83/153	100/164		12.04%	1.02[0.76,1.37]
Lille 1985	59/81	45/82		6.88%	1.53[1.04,2.25]
EORTC 08861	26/52	20/54		3%	1.64[0.91,2.94]
MRC LU11	116/154	123/154		15.93%	0.96[0.74,1.24]
GETCB 04CB86	69/99	59/90		8.47%	1.17[0.83,1.66]
Slovenia 1988	30/35	33/39		4.19%	0.85[0.52,1.39]
GETCB 05CB88	152/274	120/265		18%	1.45[1.14,1.85]
Italy 2002	23/51	30/53		3.54%	0.71[0.41,1.22]
Korea 2007	47/56	43/55		6.02%	1.15[0.76,1.73]
Total (95% CI)	**1163**	**1180**		**100%**	**1.18[1.07,1.31]**
Total events: 777 (Surgery + PORT), 734 (Surgery)					
Heterogeneity: Tau^2=0; Chi^2=16.65, df=10(P=0.08); I^2=39.95%					
Test for overall effect: Z=3.2(P=0)					

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

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
Belgium 1966	88/98	80/104		10.61%	1.44[1.06,1.96]
LCSG 773	85/110	81/120		10.74%	1.09[0.8,1.48]
CAMS 1981	91/153	111/164		12.97%	0.94[0.71,1.24]
Lille 1985	59/81	45/82		6.68%	1.5[1.02,2.21]
EORTC 08861	26/52	23/54		3.13%	1.29[0.73,2.26]
MRC LU11	118/154	125/154		15.71%	0.97[0.75,1.25]
GETCB 04CB86	70/99	61/90		8.38%	1.04[0.74,1.47]
Slovenia 1988	30/35	33/39		4.08%	0.94[0.58,1.55]
GETCB 05CB88	156/274	127/265		18.19%	1.39[1.1,1.75]
Italy 2002	23/51	34/53		3.66%	0.55[0.33,0.93]
Korea 2007	47/56	43/55		5.84%	1.05[0.69,1.58]
Total (95% CI)	**1163**	**1180**		**100%**	**1.12[1.01,1.23]**
Total events: 793 (Surgery + PORT), 763 (Surgery)					
Heterogeneity: Tau^2=0; Chi^2=18.86, df=10(P=0.04); I^2=46.97%					
Test for overall effect: Z=2.18(P=0.03)					

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

Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
Belgium 1966	88/98	80/104		10.46%	1.5[1.1,2.04]

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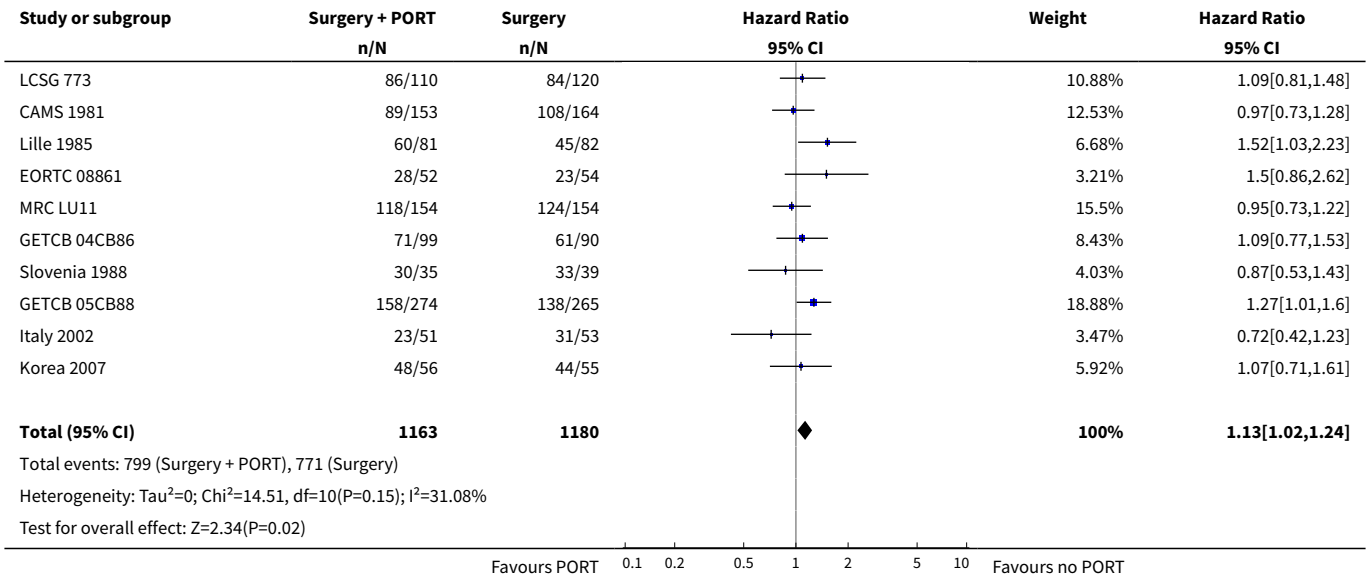
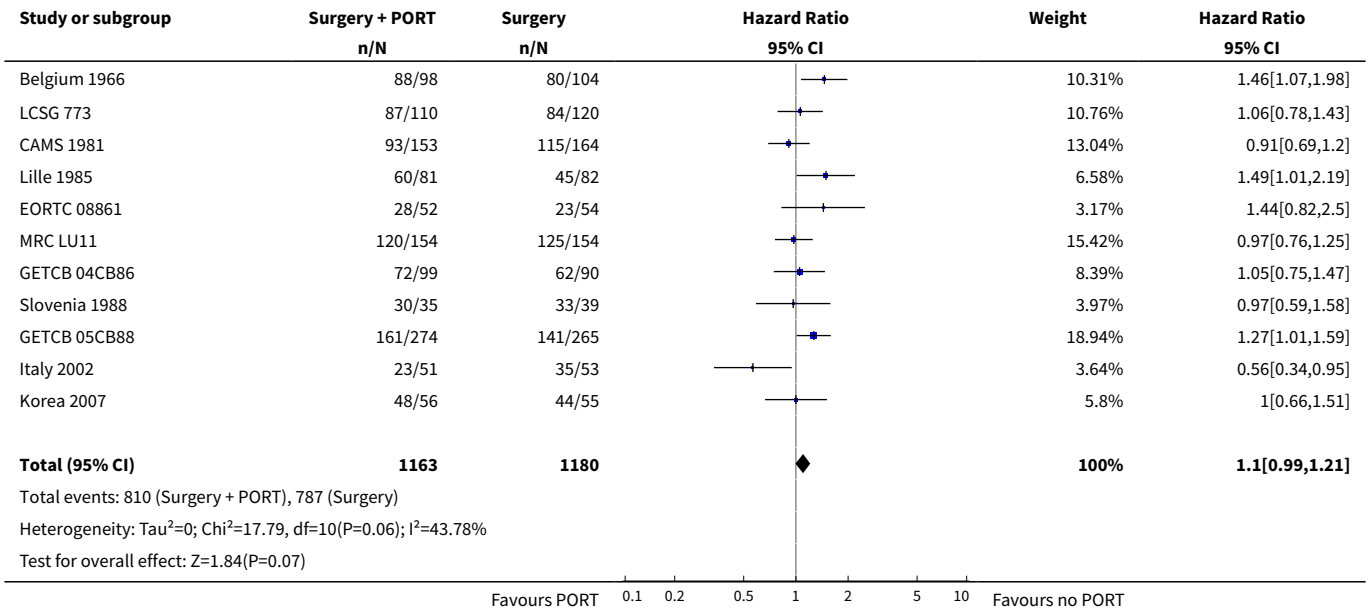


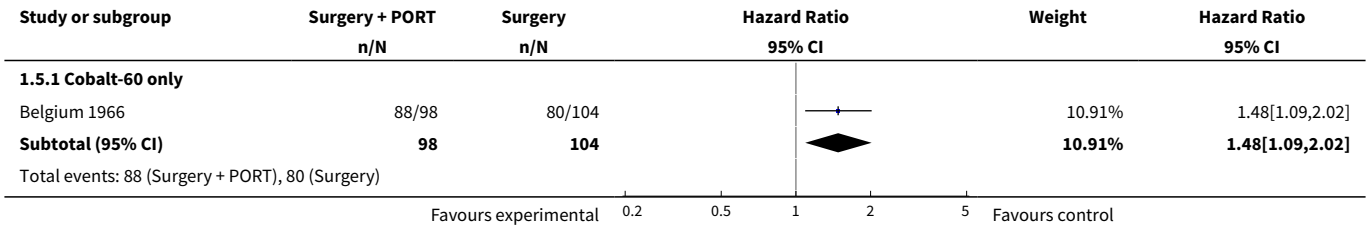
Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
LCSG 773	86/110	84/120		10.88%	1.09[0.81,1.48]
CAMS 1981	89/153	108/164		12.53%	0.97[0.73,1.28]
Lille 1985	60/81	45/82		6.68%	1.52[1.03,2.23]
EORTC 08861	28/52	23/54		3.21%	1.5[0.86,2.62]
MRC LU11	118/154	124/154		15.5%	0.95[0.73,1.22]
GETCB 04CB86	71/99	61/90		8.43%	1.09[0.77,1.53]
Slovenia 1988	30/35	33/39		4.03%	0.87[0.53,1.43]
GETCB 05CB88	158/274	138/265		18.88%	1.27[1.01,1.6]
Italy 2002	23/51	31/53		3.47%	0.72[0.42,1.23]
Korea 2007	48/56	44/55		5.92%	1.07[0.71,1.61]
Total (95% CI)	**1163**	**1180**		**100%**	**1.13[1.02,1.24]**
Total events: 799 (Surgery + PORT), 771 (Surgery)					
Heterogeneity: Tau^2=0; Chi^2=14.51, df=10(P=0.15); I^2=31.08%					
Test for overall effect: Z=2.34(P=0.02)					

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



Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
Belgium 1966	88/98	80/104		10.31%	1.46[1.07,1.98]
LCSG 773	87/110	84/120		10.76%	1.06[0.78,1.43]
CAMS 1981	93/153	115/164		13.04%	0.91[0.69,1.2]
Lille 1985	60/81	45/82		6.58%	1.49[1.01,2.19]
EORTC 08861	28/52	23/54		3.17%	1.44[0.82,2.5]
MRC LU11	120/154	125/154		15.42%	0.97[0.76,1.25]
GETCB 04CB86	72/99	62/90		8.39%	1.05[0.75,1.47]
Slovenia 1988	30/35	33/39		3.97%	0.97[0.59,1.58]
GETCB 05CB88	161/274	141/265		18.94%	1.27[1.01,1.59]
Italy 2002	23/51	35/53		3.64%	0.56[0.34,0.95]
Korea 2007	48/56	44/55		5.8%	1[0.66,1.51]
Total (95% CI)	**1163**	**1180**		**100%**	**1.1[0.99,1.21]**
Total events: 810 (Surgery + PORT), 787 (Surgery)					
Heterogeneity: Tau^2=0; Chi^2=17.79, df=10(P=0.06); I^2=43.78%					
Test for overall effect: Z=1.84(P=0.07)					

Analysis 1.5. Comparison 1 Surgery + PORT versus surgery alone, Outcome 5 RT delivery method.



Study or subgroup	Surgery + PORT n/N	Surgery n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
1.5.1 Cobalt-60 only					
Belgium 1966	88/98	80/104		10.91%	1.48[1.09,2.02]
Subtotal (95% CI)	**98**	**104**		**10.91%**	**1.48[1.09,2.02]**
Total events: 88 (Surgery + PORT), 80 (Surgery)					

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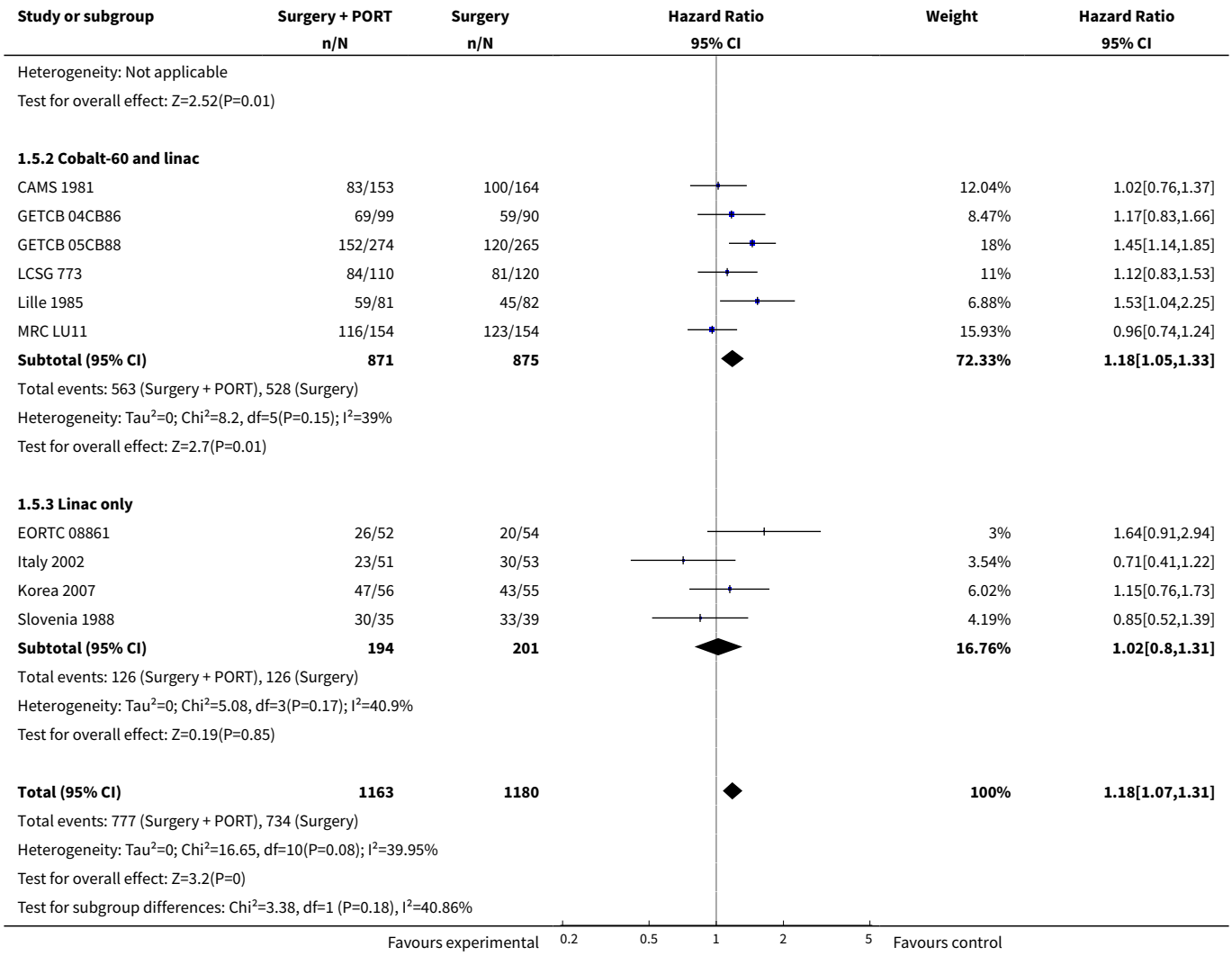
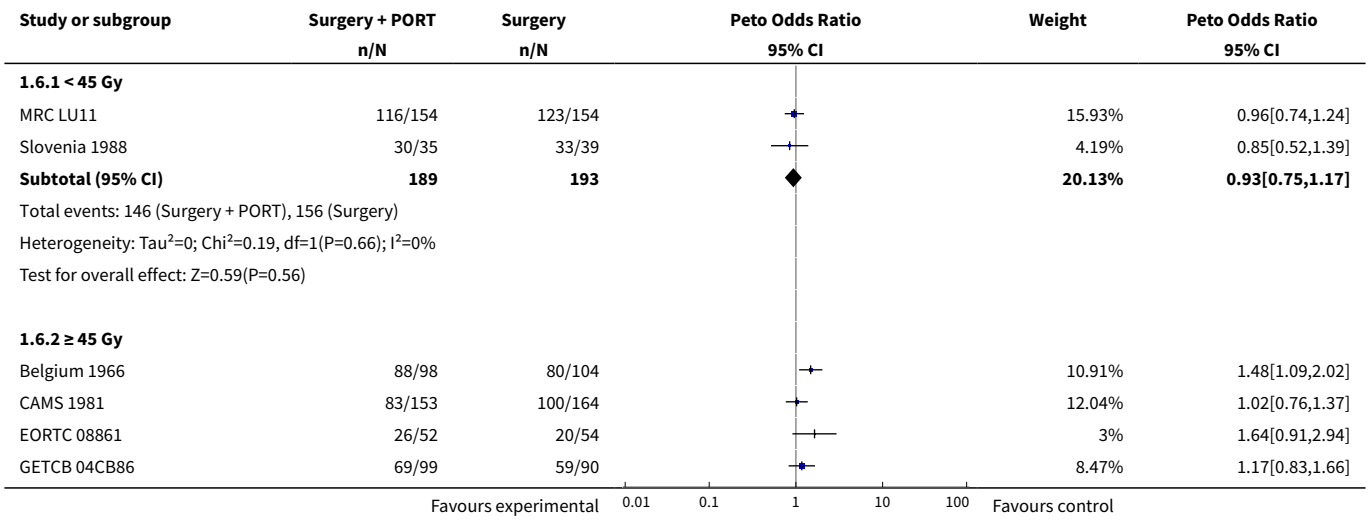


Analysis 1.6. Comparison 1 Surgery + PORT versus surgery alone, Outcome 6 RT dose.



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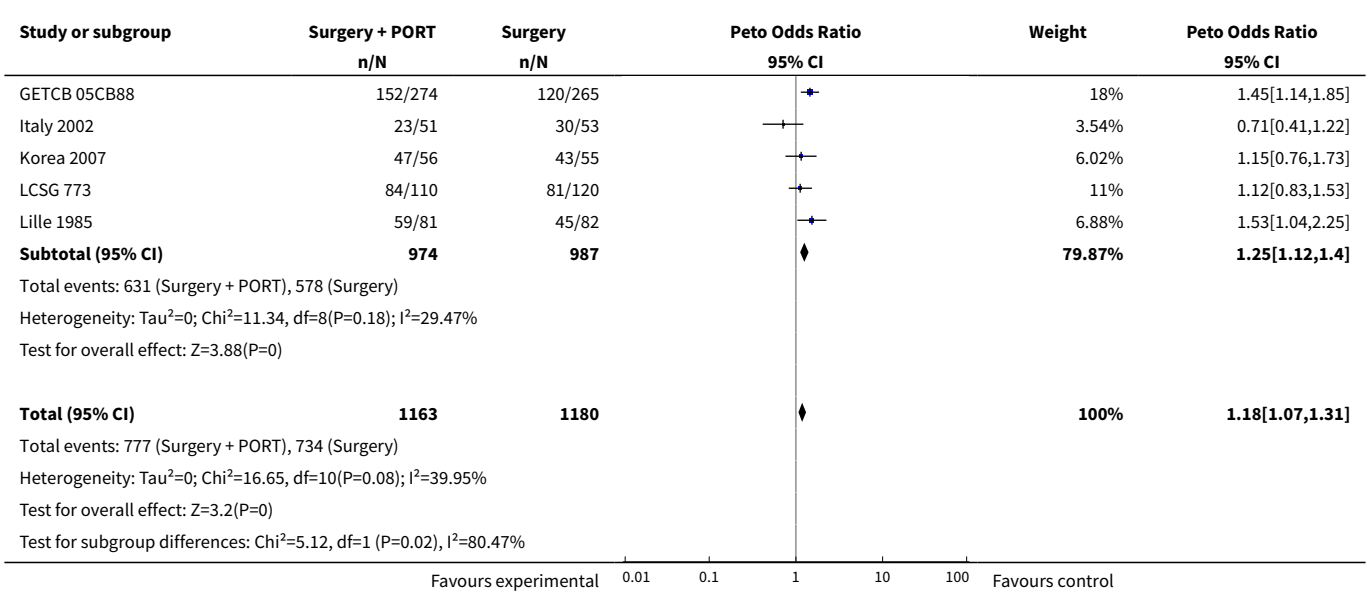

ADDITIONAL TABLES

Table 1. Common meta-analysis stage scale (original analyses - based on TNM 4th edition)

T stage	N stage	M stage	Meta-analysis stage	AJCC stage
0, 1, 2, X, iS	0	0	I	I
0, 1, 2, X, iS	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

AJCC = American Joint Committee on Cancer.

Table 2. Common meta-analysis stage scale (current analysis - based on TNM 6th edition)

T stage	N stage	M stage	Meta-analysis stage
1, 2	0	0	I
1, 2	1	0	II
3	0	0	II
1, 2	2	0	III
3	1, 2	0	III

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Table 2. Common meta-analysis stage scale (current analysis - based on TNM 6th edition) *(Continued)*

Any	Any	1	IV

Table 3. Characteristics of participants in PORT meta-analysis

Characteristic	Postoperative RT	Surgery only	Total
AGE (data from 11 trials)			
< 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 (data from 11 trials)			
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
META-ANALYSIS STAGE (data from 11 trials)			
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; not used)			
Good (0, 1)	195	196	391
Poor (2, 3, 4)	77	83	160

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Table 3. Characteristics of participants in PORT meta-analysis *(Continued)*

Unknown	22	21	43

Table 4. Changes in results over time

	Trend or interaction 1998	Trend or interaction 2005	Trend or interaction 2010 'old' methods	Trend or interaction 2010 'new' methods and TNM changes
Age	P = 0.34	P = 0.44	P = 0.32	P = 0.20
Sex	P = 0.94	P = 0.92	P = 0.84	P = 0.49
Histology	P = 0.75	P = 0.61	P = 0.42	P = 0.38
Stage	P = 0.0003	P = 0.003	P = 0.003	P = 0.12
Nodal status	P = 0.016	P = 0.02	P = 0.03	P = 0.39

APPENDICES

Appendix 1. MEDLINE search strategy (via PubMed)

#1	Search Carcinoma, Non-Small-Cell Lung[MeSH Terms]
#2	Search nsclc[Title/Abstract]
#3	Search lung cancer*[Title/Abstract]
#4	Search lung carcinoma[Title/Abstract]
#5	Search lung neoplasm*[Title/Abstract]
#6	Search lung tumor*[Title/Abstract]
#7	Search lung tumour*[Title/Abstract]
#8	Search non-small cell*[Title/Abstract]
#9	Search nonsmall cell*[Title/Abstract]
#10	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9)
#11	Search Thoracic surgery[MeSH Terms]
#12	Search surg*[Title/Abstract]
#13	Search thoracic surgical procedures[MeSH Terms]

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(Continued)

#14	Search pneumonectomy[MeSH Terms]
#15	Search pneumonectom*[Title/Abstract]
#16	Search lobectom*[Title/Abstract]
#17	Search Lung/surgery[MeSH Terms]
#18	Search thoracotomy[MeSH Terms]
#19	Search Thoracotom*[Title/Abstract]
#20	Search Radiotherapy[MeSH Terms]
#21	Search Radiother*[Title/Abstract]
#22	Search PORT[Title/Abstract]
#23	Search radiation therap*[Title/Abstract]
#24	Search (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) AND (#20 OR #21 OR #22 OR #23)
#25	Search #10 AND #24
#26	Search randomized controlled trial[Publication Type]
#27	Search controlled clinical trial[Publication Type]
#28	Search randomized[Title/Abstract]
#29	Search placebo[Title/Abstract]
#30	Search drug therapy[MeSH Terms]
#31	Search randomly[Title/Abstract]
#32	Search trial[Title/Abstract]
#33	Search groups[Title/Abstract]
#34	Search (#25 OR #26 OR #27 OR #28 OR #29 OR #30OR #31 OR #32 OR #33)
#35	Search animals[MeSH Terms]
#36	Search humans[MeSH Terms]
#37	Search #35 NOT #36
#38	Search #34 NOT #37
#39	Search #25 AND #38

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Appendix 2. CENTRAL search strategy

#1	lung cancer*
#2	non-small cell*
#3	non small cell*
#4	nonsmall cell*
#5	MeSH descriptor: [Lung Neoplasms] explode all trees
#6	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
#7	Nsclc
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	MeSH descriptor: [Thoracic Surgery] explode all trees
#10	surg*
#11	MeSH descriptor: [Thoracic Surgical Procedures] explode all trees
#12	MeSH descriptor: [Pneumonectomy] explode all trees
#13	pneumonectom*
#14	lobectom*
#15	MeSH descriptor: [Lung] explode all trees and with qualifier(s): [Surgery - SU]
#16	MeSH descriptor: [Thoracotomy] explode all trees
#17	thoracotom*
#18	MeSH descriptor: [Radiotherapy] explode all trees
#19	Radiotherap*
#20	radiation therap*
#21	PORT
#22	(#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17) and (#18 or #19 or #20 or #21)

WHAT'S NEW

Date	Event	Description
18 July 2016	New citation required but conclusions have not changed	Changes in authorship

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Date	Event	Description
18 July 2016	New search has been performed	Full update, no new studies - conclusions not changed, some changes to subgroup conclusions as newer, more appropriate methods have been used.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 1, 2000

Date	Event	Description
5 November 2009	Amended	New PLS added
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
25 October 2004	New citation required and conclusions have changed	Substantive amendments made

CONTRIBUTIONS OF AUTHORS

The writing group for the current version of this review consisted of S Burdett, LHM Rydzewska, JF Tierney, MKB Parmar, D Fisher, R Arriagada, JP Pignon and C Le Pechoux, on behalf of the PORT Meta-analysis Trialists Group.

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 [mortality] [*radiotherapy] [surgery]; Combined Modality Therapy; Lung Neoplasms [mortality] [*radiotherapy] [surgery]; Postoperative Care; Radiotherapy, Adjuvant [mortality]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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