Articles

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

*PORT Meta-analysis Trialists Group**

Summary

Background The role of postoperative radiotherapy in treatment of patients with completely resected non-small-cell lung cancer (NSCLC) remains unclear. We undertook a systematic review and meta-analysis of the available evidence from randomised trials.

Methods Updated data were obtained on individual patients from all available randomised trials of postoperative radiotherapy versus surgery alone. Data on 2128 patients from nine randomised trials (published and unpublished) were analysed by intention to treat. There were 707 deaths among 1056 patients assigned postoperative radiotherapy and 661 among 1072 assigned surgery alone. Median follow-up was 3·9 years (2·3–9·8 for individual trials) for surviving patients.

Findings The results show a significant adverse effect of postoperative radiotherapy on survival (hazard ratio 1·21 [95% CI 1·08–1·34]). This 21% relative increase in the risk of death is equivalent to an absolute detriment of 7% (3–11) at 2 years, reducing overall survival from 55% to 48%. Subgroup analyses suggest that this adverse effect was greatest for patients with stage I/II, N0–N1 disease, whereas for those with stage III, N2 disease there was no clear evidence of an adverse effect.

Interpretation Postoperative radiotherapy is detrimental to patients with early-stage completely resected NSCLC and should not be used routinely for such patients. The role of postoperative radiotherapy in the treatment of N2 tumours is not clear and may warrant further research.

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Introduction

Worldwide, carcinoma of the lung is the main cause of cancer death. More than 500 000 new cases are diagnosed each year,[1] about 80% of which are of non-small-cell histological types.[2] Surgery is the treatment of choice for non-small-cell lung cancer (NSCLC), and about 20% of tumours are suitable for potentially curative resection.[3] However, even for patients with apparently completely resected disease, survival is around only 40% at 5 years. In an effort to improve local control of the disease and to increase survival, adjuvant postoperative radiotherapy has been explored as a therapeutic option.

*Study organisation given at end of paper

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Randomised controlled trials of this issue have recruited a total of more than 2000 patients, but the role of postoperative radiotherapy in the treatment of NSCLC remains unclear. Individually, trials have shown inconclusive and conflicting results. However, because of their size (74–539 patients), individual trials have not had sufficient statistical power to detect the moderate survival differences that might be expected of postoperative radiotherapy. For example, to detect a 10% absolute benefit at 5 years, improving of survival from 50% to 60%, would require that a total of 900 patients were randomised. To detect a 5% improvement to 55% survival would require 3500 patients (90% power, 5% significance level).

A systematic review of all the available randomised evidence and the combination of the results of these trials in a meta-analysis might give sufficient statistical power for a clear decision on whether postoperative radiotherapy is beneficial or not in the treatment of NSCLC. An international meta-analysis of updated individual patient data was therefore initiated by the UK Medical Research Council Cancer Trials Office and conducted on behalf of the PORT Meta-analysis Trialists Group.

Methods

The meta-analysis followed a detailed, prespecified protocol, which set out the inclusion criteria for trials, data to be collected, and analyses to be done (available on request from LAS).

Inclusion criteria

The eligibility criteria for trials were: that the aim was to randomise NSCLC patients, who had undergone a complete surgical resection, between radiotherapy and no immediate further treatment; that there was no confounding; that the method of randomisation precluded prior knowledge of the treatment to be assigned; that orthovoltage radiation was not used; and that recruitment started after 1965 and was completed by Dec 31, 1995.

Identification of trials

To avoid publication bias, both published and unpublished trials were included. Computerised bibliographic searches of MEDLINE and CANCERLIT by a modified version of the

Unpublished trials

Dautzenburg B, Arriagada R, Chammard AB, et al. A controlled study of postoperative radiotherapy in patients with completely resected non-small-cell lung cancer. (GETCB 04CB86, 05CB88)

van Zandwijk N, Gregor A, Rocmans P. EORTC 08861—Phase III randomised trial of adjuvant radiotherapy vs no adjuvant therapy with completely resected non-small-cell lung cancer.

Lung Cancer Study Group (LSCG 841). Phase III randomised study of postoperative radiotherapy vs no radiotherapy following resection of non-small-cell lung cancer.

TNM classification			Meta-analysis stage	AJC stage
T	N	M		
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		
Any	Any	1	IV	Any metastatic

AJC=American Joint Committee. TNM stage and AJC stage were translated to a common stage. No comparison between TNM stage and AJC stage intended.

Table 1: **Common meta-analysis stage scale**

Cochrane Collaboration optimum search strategy[4] were supplemented with hand searches of meetings abstracts, bibliographies of books, reviews, and specialist journals. Trial registers (US National Cancer Institute Physicians Data Query Clinical Protocols and UK Coordinating Committee for Cancer Research) were also searched, and all trialists who took part in the meta-analysis were asked to help to identify trials.

Data

We sought updated information on survival, recurrence, and date of last follow-up, as well as details of treatment allocated, date of randomisation, age, sex, histological cell type, tumour 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.[5] Any queries were resolved and the final database entries verified by the responsible trial investigator or statistician. Since stage was recorded by different classification systems in different trials, for the purposes of this meta-analysis, stage data were translated to a common staging system (table 1).

Definition of endpoints

Local and distant recurrence-free survival were defined 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. Overall recurrence-free survival was taken 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. Overall survival was defined as the time from randomisation until death (from any cause).

Analyses and statistics

All analyses were carried out by intention to treat, that is, patients were analysed according to their allocated treatment, irrespective of whether they received that treatment. Survival analyses were stratified by trial, and the log-rank expected number of deaths and variance were used to calculate individual and overall pooled hazard ratios by the fixed-effects model.[6] Thus, the times to death for individual patients were used within trials to calculate the hazard ratio, representing the overall risk of death for patients who received postoperative radiotherapy compared with those treated by surgery alone. To investigate the effects of postoperative radiotherapy within subgroups, similar stratified analyses were done. Analyses were done for each prespecified category—for example, for male and female patients within each trial. These results were then combined to give overall hazard ratios for men and women.

Results are also presented as absolute differences at 2 years calculated from the hazard ratio and baseline event rate for patients receiving surgery alone;[7] proportional hazards are assumed. Confidence intervals for absolute differences were similarly calculated from the baseline event rate and the hazard ratio at the 95% CI boundary values. χ^2 heterogeneity tests[8] were used to test for gross statistical heterogeneity. These tests (which have low statistical power) mainly aim to detect quantitative differences—that is, differences in size rather than direction—and were chosen because qualitative differences were not expected. Survival curves are presented as simple (non-stratified) Kaplan-Meier curves.[9] All p values are two-sided.

Trial	Recruitment	Patients	Disease stage
Belgium[10]	1966–77	202*	I,II,III
LCSG 773[11]	1978–85	230	II,III
CAMS[12]	1981–95	317	II,III
Lille[13]	1985–91	163	I
EORTC 08861	1986–90	106	II,III
MRC LU11[14]	1986–93	308	II,III
GETCB 04CB86	1986–94	189	I,II,III
Slovenia[15]	1988–92	74	III
GETCB 05CB88	1988–94	539	I,II,III

LSCG=Lung Cancer Study Group, CAMS=Chinese Academy of Medical Sciences, EORTC=European Organization for Research and Treatment of Cancer, MRC=Medical Research Council, GETCB=Groupe d'Etude et de Traitement des Cancers Bronchiques. All trials used TNM staging, except Belgium,[10] which used AJC.
*20 patients with small-cell lung cancer excluded.

Table 2: **Characteristics of trials in PORT meta-analysis**

Results

Preliminary literature searches identified 15 potentially eligible trials[10–20] (plus four unpublished trials) that investigated the role of postoperative radiotherapy in the treatment of NSCLC. Four of these were found to be ineligible: two were conducted before 1965,[17,18] one was not randomised,[19] and one[20] had a trial design and timing of randomisation that precluded an unbiased comparison between surgery alone and postoperative radiotherapy. 11

Trial	Radiotherapy dose				Prescription technique	Machine used	Average field size (cm)	Clinical target volume	Technique
	Total dose (Gy)	Fractions	Duration (weeks)	Gy/day					
Belgium[10]	60	30	6	2	Isodose 90%	Co60	15x9	Bronchial stump, hilum, mediastinum	SCB,OF,LF
LCSG 773[11]	50	25·0–27·5	5·0–5·5	1·8–2·0	Central axis, at midplane	Co60 & linac	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF
CAMS[12]	60	30	6	2	At midplane	Co60 & linac	6x12	Hilum, mediastinum	SCB,OF,LF
Lille[13]	45–60	22·5–30·0	6	2	Isodose 90%	Co60 & linac	12x12	Hilum, upper mediastinum	SCB,OF,LF
EORTC 08861	56	28	5·5	2	Central axis, at midplane	linac	15x10	Hilum, mediastinum	Composite plans
MRC LU11[14]	40	15	3	2·6	Central axis, at midplane	Co60 & linac	*	Hilum, mediastinum, supraclavicular fossae†	SCB,OF,LF
GETCB 04CB86	60	24–30	6	2·0–2·5	Isocentre	Co60 & linac	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF
Slovenia[15]	30	10–12	2	2·5–3·0	Central axis, at midplane	linac	9x12	Hilum, mediastinum	OF,LF
GETCB 05CB88	60	24–30	6	2·0–2·5	Isocentre	Co60 & linac	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF

SCB = spinal cord blocks; OF = oblique fields; LF = lateral fields; linac=linear accelerator; Co60=cobalt-60.
Only one trial (EORTC 08861) used computed tomography for planning, and two trials (EORTC 08861 and Lille) used lung-factor corrections.
*Information not available; †For upper lobe tumours.

Table 3: **Details of radiotherapy**

Trial	Number of events/ number entered PORT	No PORT	O-E	Variance
Belgium (10)	88/98	80/104	16·04	40·67
LCSG 773 (11)	84/110	81/120	4·77	41·02
CAMS (12)	83/153	100/164	1·07	44·88
Lille (13)	59/81	45/82	10·87	25·66
EORTC 08861	26/52	20/54	5·53	11·20
MRC LU11 (14)	116/154	123/154	-2·48	59·39
GETCB 04CB86	69/99	59/90	4·95	31·59
Slovenia (15)	30/35	33/39	-2·56	15·63
GETCB 05CB88	152/274	120/265	25·13	67·08
Total	707/1056	661/1072	63·32	337·12

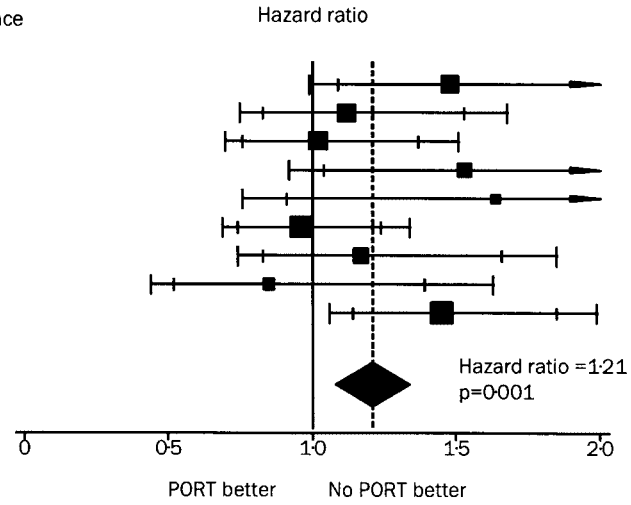

Figure 1: **Hazard ratio plot for survival**

Each individual trial is represented by a square, centre of which denotes hazard ratio for that trial; extremities of horizontal bars denote 99% CI and inner bars mark 95% CI. Size of square is directly proportional to amount of information in trial. Black diamond at foot of plot gives overall hazard ratio for combined results of all trials; centre denotes hazard ratio and extremities 95% CI.Trials are ordered chronologically by date of start of trial (oldest first). PORT=postoperative radiotherapy.

Overall hazard ratio=1·21 (95% CI 1·08–1·34) χ^2_1=11·892, p=0·001; heterogeneity χ^2_8=13·067, p=0·11.

trials potentially eligible for the meta-analysis remained (seven published,[10–16] four unpublished: panel). Results are based on data from nine trials that are known to be randomised. One study[16] of 155 patients is reported to be a randomised controlled trial, but whether it is indeed randomised is not clear, and appropriate data are not yet available from this trial. Data from one unpublished trial (LCSG 841), which accrued only five patients, were no longer available.

Results are therefore based on information from nine randomised controlled trials including 2128 patients, representing 99% of individuals from all identified, eligible trials known to be randomised (table 2). Data were collected for 134 of 136 patients who had been excluded from the original published analyses and were reinstated in the meta-analysis. For the trial that randomised all histological types of lung cancer,[10] the 20 patients with small-cell tumours were excluded from the meta-analysis. Survival and recurrence data were available for all trials. Although trialists were able to provide most of the additional information on patients' characteristics requested, some data were not available. Information on age, sex, and stage was provided for all trials and data on histology for seven trials. Performance-status data were available for only three trials, so were insufficient for subgroup analyses. Data on cause of death (coded as NSCLC, treatment-related, and other) were provided for eight trials, although the trialists themselves questioned the reliability of this information for many of the trials.

Postoperative radiotherapy doses ranged from 30 Gy to 60 Gy, given in 10–30 fractions. There was substantial diversity in other aspects of radiotherapy planning (table

Characteristic	Postoperative radiotherapy	Surgery only	Total
Age (years)			
<54	271	296	567
55–59	240	243	483
60–64	258	252	510
>65	287	280	567
Unknown	0	1	1
Sex			
M	894	901	1795
F	162	170	332
Not recorded	0	1	1
Histology*			
Adenocarcinoma	161	174	335
Squamous	460	488	948
Other	55	47	102
Unknown	380	363	743
Meta-analysis stage†			
I	277	285	562
II	352	366	718
III	408	400	808
IV	1	0	1
Unknown	18	21	39
WHO performance status‡			
Good (0,1)	144	143	287
Poor (2,3,4)	77	83	160
Unknown	20	21	41

*Available from seven trials. † Eight trials used TNM staging, one trial used AJC staging (table 1). ‡ Available from three trials.

Table 4: **Characteristics of patients in PORT meta-analysis**

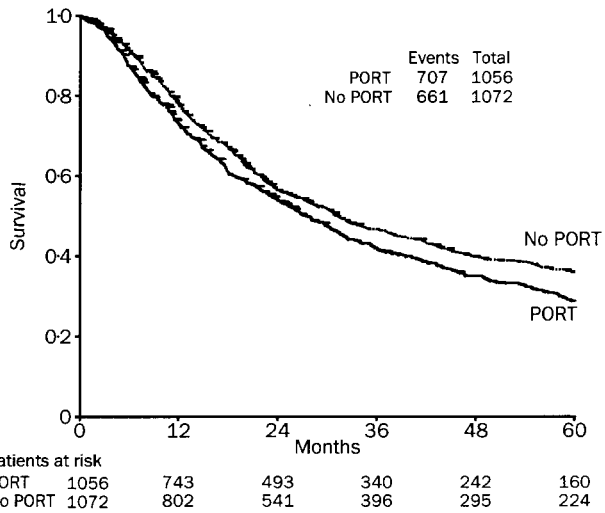

Figure 2: **Kaplan-Meier curve for survival**

Trial	Number of events/ number entered PORT	No PORT	O-E	Variance
Belgium (10)	88/98	80/104	15·39	40·68
LCSG 773(11)	87/110	84/120	2·43	42·46
CAMS(12)	93/153	115/164	-4·88	51·45
Lille (13)	60/81	45/82	10·33	25·95
EORTC 08861	28/52	23/54	4·52	12·50
MRC LU11 (15)	120/154	125/154	-1·67	60·87
GETCB 04CB86	72/99	62/90	1·58	33·10
Slovenia (16)	30/35	33/39	-0·55	15·65
GETCB 05CB88	161/274	141/265	17·68	74·76
Total	739/1056	708/1072	44·82	357·42

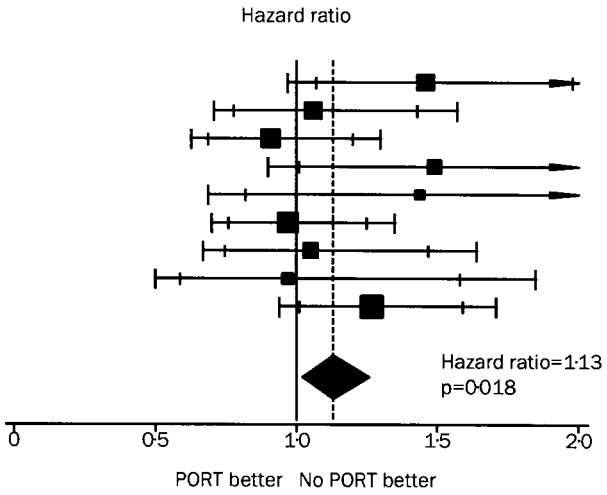

Figure 3: **Hazard ratio plot for recurrence-free survival**
Format as for figure 1. Hazard ratio=1·13 (1·02–1·26) χ^2_1=5·621, p=0·018; heterogeneity χ^2_8=10·867, p=0·209.

3). All trials included patients with completely resected tumours for which disease stage was no greater than stage IIIA (table 2). Follow-up was updated in most trials to give a median of 3·9 years for surviving patients (2·3–9·8 years for individual trials). The patients' characteristics reflect the eligibility criteria of individual trials: most of the patients were male with stage II/III squamous-cell carcinoma (although histology was unknown for a large number of patients) and good performance status (table 4).

Survival

Survival data were available for all trials and included information on 2128 patients and 1368 deaths (707 postoperative radiotherapy, 661 surgery alone). Although the CIs for individual trial results are wide, there is a clear pattern of results in favour of surgery alone (figure 1), and there is no good evidence of statistical heterogeneity (p=0·11) between trials. The combined results show a significant adverse effect of postoperative radiotherapy on survival (p=0·001) with a hazard ratio of 1·21 (95% CI 1·08–1·34), or a 21% relative increase in the risk of death.

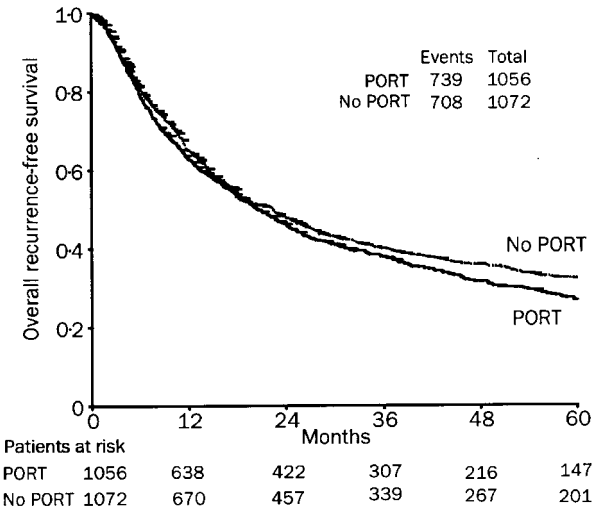

Figure 4: **Kaplan-Meier curve for recurrence-free survival**

This relative increase is equivalent to an absolute detriment of 7% at 2 years (95% CI 3–10), reducing overall survival from 55% to 48%. The survival curves (figure 2) diverge at around 4 months and remain apart for the 5 years to which they can be drawn with reasonable reliability.

Information on cause of death, coded as NSCLC, treatment-related, or other, was available from eight trials. Of the 548 coded deaths among patients assigned postoperative radiotherapy, 81% were attributed to NSCLC, 4% to treatment-related causes, and 15% to other causes. For the 522 coded deaths among patients assigned surgery alone, the corresponding rates were 89%, 2%, and 9%.

Local recurrence-free survival

Data on local recurrence were available from all trials. Analysis of local recurrence-free survival was based on 1409 events (471 local recurrences—195 postoperative radiotherapy, 276 surgery alone; and 938 deaths—528

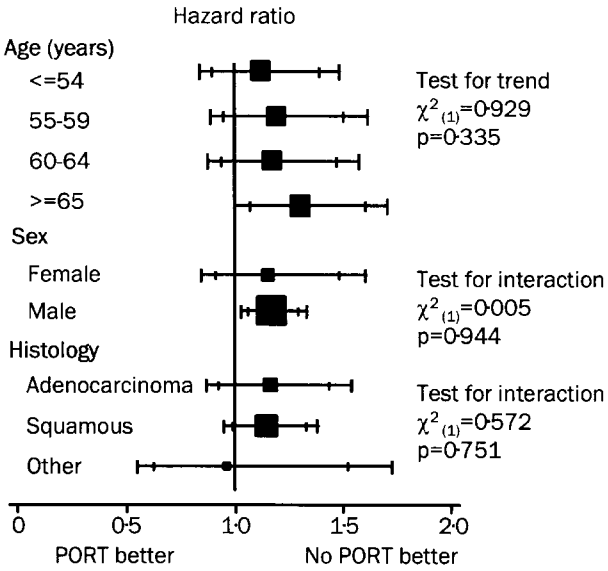

Figure 5: **Age, sex, and histology subgroup analysis for survival**
Format as for figure 1.

postoperative radiotherapy, 410 surgery alone). The hazard ratio was 1·16 (1·05–1·29) significantly in favour of surgery alone (p=0·005). There was no evidence of gross statistical heterogeneity between trials (p=0·19).

Distant recurrence-free survival

Data on distant recurrence were available from all trials. Analysis of distant recurrence-free survival was based on 1424 events (802 distant recurrences—398 postoperative radiotherapy, 404 surgery alone; and 622 deaths—330 postoperative radiotherapy, 292 surgery alone). The hazard ratio was 1·16 (1·04–29), in favour of surgery alone (p=0·007). There was no evidence of gross statistical heterogeneity between trials (p=0·15).

Overall recurrence-free survival

A total of 1447 events were observed, 739 among patients who received postoperative radiotherapy and 708 among those who received surgery alone. Of these, 402 first events were deaths and 252 and 793, respectively, were local and distant recurrences. The overall hazard ratio of 1·13 (1·02–1·26) indicates a significant adverse effect of postoperative radiotherapy (figure 3, p=0·018). There was no evidence of gross statistical heterogeneity between trials (p=0·209). This 13% relative increase in the risk of recurrence or death is equivalent to an absolute detriment of 4% at 2 years (1–8) reducing recurrence-free survival from 50% to 46%. The recurrence-free survival curves (figure 4) diverge at around 2 years and remain apart to 5 years.

Subgroup analyses

We undertook analyses to assess whether there was evidence of a differential effect of postoperative radiotherapy in predefined subgroups of patients. For survival (figure 5), there was no evidence that postoperative radiotherapy was differentially effective in any group of patients defined by age (trend p=0·335), sex (interaction p=0·944), or histology (interaction p=0·751) There was some evidence that the effects of postoperative radiotherapy were more detrimental among patients with stage I disease than among those with stage II disease (figure 6). For stage III patients alone, there was no clear evidence of a detriment (trend across all stages p=0·0005). Similarly, there was a trend that postoperative radiotherapy was increasingly detrimental with lower nodal status (trend p=0·016, figure 6). Results were similar for the endpoints of local, distant, and overall recurrence-free survival (data available from LAS).

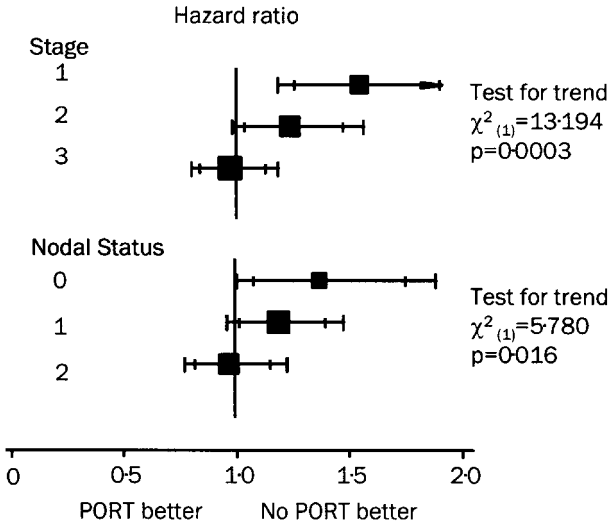

Figure 6: **Stage and nodal status subgroup analysis for survival**
Format as for figure 1.

Discussion

At the outset of this project, despite the enrolment of more than 2000 patients in randomised trials, the question of whether postoperative radiotherapy was effective in the treatment of NSCLC remained unanswered. Current clinical practice varies nationally and internationally. 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 postoperative radiotherapy in NSCLC patients, to provide reliable guidance for clinical practice and future research.

For the primary endpoint of survival, there is clear evidence of a detrimental effect of postoperative radiotherapy for patients with completely resected NSCLC. The 21% relative increase in the risk of death associated with radiotherapy, equivalent to an overall reduction in survival from 55% to 48% at 2 years, represents a substantial hazard for these patients. Exploratory analysis by stage and by nodal status suggested that this effect was greatest for patients with earlier-stage disease and those with lower nodal status. Although the results for stage III and N2 patients were slightly in favour of postoperative radiotherapy (hazard ratios 0·97 and 0·96, respectively), the CIs are wide, indicating no clear evidence of a difference between treatments for these groups of patients. Furthermore, no subgroup of patients defined by stage or nodal status showed evidence of a clear benefit from radiotherapy. The meta-analysis provided no evidence that the relative effect of radiotherapy was smaller or larger for any category of patients defined by age, sex, histology, or performance status.

The analyses of local, distant, and overall recurrence-free survival (that is time to recurrence or death) all indicate an overall adverse effect of postoperative radiotherapy. The observed detriment is, however, less for these endpoints. For local recurrence-free survival, the results were largely driven by survival (since deaths formed the majority of events). This finding suggests that there may be antitumour activity attributable to radiotherapy and that the increased risk of death from postoperative radiotherapy may be attributable to other mechanisms. A competing-risk analysis is planned and will be published elsewhere.

Analysis of local recurrence-free interval (that is, the time to local recurrence with death and distant recurrence being censored) also indicated that the time to local recurrence was significantly reduced in patients assigned postoperative radiotherapy. However, the observed 24% reduction in the overall risk of local recurrence in the analysis of local recurrence-free interval is difficult to interpret and potentially flawed. This difficulty arises because the increased risk of death with postoperative radiotherapy may mean that recipients of radiotherapy die before there is time for the tumour to recur locally. Thus, such measurement is likely to be an overestimation of local control. Taken as a whole, the results suggest that although postoperative radiotherapy may be beneficial in terms of

local recurrence, the effect is likely to be small and easily outweighed by the adverse effect on survival. The cause of this adverse effect is not apparent from these analyses, although the limited information on cause of death suggests that the excess mortality on postoperative radiotherapy may be a result of causes of death other than cancer. There is no convincing evidence from this analysis that the radiation treatment alone increased cancer deaths, especially because few trials were able to provide detailed cause of death information, and because later respiratory events leading to death may well have been wrongly attributed to recurrent cancer. However, the addition of radiation treatment postoperatively may exert an adverse effect by virtue of acute or delayed radiation effects, such as radiation pneumonitis or cardiotoxicity, on lungs likely to be already damaged by smoking and surgery.

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), there is little likelihood that any benefits of postoperative radiotherapy on quality of life 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 quality of life in the short term at least.

Postoperative chemotherapy may offer a more promising approach than radiotherapy. A 1995 meta-analysis[21] suggested that the use of modern chemotherapy regimens may improve survival in the adjuvant setting. An overall reduction in the relative risk of death of 13% for cisplatin-based regimens was observed, equivalent to an absolute improvement of 3% from 70% to 73% at 2 years. Several large international trials to confirm or refute this suggestion are in progress.

Implications for research

This meta-analysis has demonstrated a clear adverse effect of postoperative radiotherapy on survival for patients with completely resected stage I and II tumours, such that further research with similar radiotherapy techniques on similar patients would not be warranted. The results are less clear for stage III (N2) disease, and further research may be justifiable in these patients. Indeed there may still be scope for investigation of more modern radiotherapy techniques, such as conformal radiotherapy or hyperfractionated radiotherapy, in all stages (I, II, and III) of completely resected disease. However, such research should be undertaken only if there is a clear expectation that these newer techniques could provide an overall therapeutic benefit and, in particular, that they would not produce similar adverse effects to those observed in this meta-analysis. If further trials are initiated, collection of accurate and detailed information on the cause of death will be important, since this meta-analysis has suggested that the adverse effect of postoperative radiotherapy may be 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 that is the cause of excess deaths with postoperative radiotherapy.

Implications for practice

This meta-analysis can provide only average estimates of the effect of postoperative radiotherapy. Nevertheless, it is the best available evidence on which to base future treatment policy. Overall, it provides clear evidence of a detrimental effect of postoperative radiotherapy on the survival of patients with stage I or II NSCLC. There was no clear evidence that it was detrimental in those with stage III, N2 disease. However, no group of patients appeared to derive a clear survival benefit from postoperative radiotherapy. Although the meta-analysis was based on data from trials that used different radiotherapy doses and schedules carried out over a long period of time, there is no evidence that the results were influenced by radiotherapy dose and therefore no indication that any one of the individual schedules used was any less detrimental than others. These results therefore indicate that postoperative radiotherapy should not be routinely used to treat patients with completely resected early-stage NSCLC.

PORT Meta-analysis Trialists Group

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An immunological algorithm to predict risk of high-grade rejection in cardiac transplant recipients

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Summary

Background Transplant-related coronary-artery disease (TCAD) develops frequently in cardiac-allograft recipients, and limits long-term survival. We examined the relation between this disorder and cumulative frequency of high-grade rejection, and investigated whether concomitant use of three immunological factors at the time of a low-grade endomyocardial biopsy can predict progression to high-grade rejection.

Methods We investigated the relation between the cumulative annual frequency of high-grade rejection and TCAD in 198 recipients of cardiac transplantation between 1992 and 1996 by means of Kaplan-Meier actuarial life-tables. Endomyocardial biopsy, lymphocyte-growth assays, and anti-HLA antibody measurements were compiled over 12 months in 102 patients during their first post-transplant year. We calculated predictive values for high-grade rejection within 90 days by χ^2, Kaplan Meier survival curves, and by multivariable logistic regression analyses.

Findings We found a direct correlation between cumulative annual frequency of rejection and TCAD onset with highest risk in those with more than 0·75 rejections per year ($p=0·0002$). After a low-grade endomyocardial biopsy (0 or 1A), one or more donor-recipient HLA-DR matches protected against high-grade rejections ($p<0·001$). Among individuals with one or two DR matches, the negative predictive value for progression from a low-grade biopsy to a high-grade rejection was 87% in the presence of a negative lymphocyte-growth assay. Among individuals with no DR matches, the presence of either a positive lymphocyte-growth assay or IgG anti-major-histocompatibility complex (MHC) class II antibodies was independently associated with high probability of progression to rejection (64% and 66%, respectively, $p<0·0005$). When both assays were positive, concomitantly with a low-grade endomyocardial biopsy, the positive predictive value for progression to a high-grade rejection was 86% ($p<0·0001$). For endomyocardial-biopsy grades 1B or 2, a positive lymphocyte-growth assay alone was associated with high-grade rejection in 100% of cases.

Interpretation Use of an algorithm combining three immunological factors at the time of a low-grade endomyocardial biopsy enables prospective stratification of cardiac transplant recipients into risk categories for progression to high-grade rejection. Low-risk individuals require fewer biopsies, moderate-risk individuals require an ongoing schedule of surveillance biopsies, and high-risk individuals require rational organisation of interventional strategies aimed at preventing rejection. Additional predictive factors are needed to identify moderate-risk individuals who will progress to rejection. Ultimately, successful intervention may have an impact on the subsequent complication of TCAD.

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Introduction

The long-term success of cardiac transplantation is currently limited by the high incidence of transplant-related coronary artery disease (TCAD).[1] This complication may be related to the recipient's continuing immune response against donor major-histocompatibility-complex (MHC) antigens, because long-term allograft survival correlates directly with the number of donor-recipient HLA matches,[2–5] and inversely with the development of circulating antibodies against donor HLA molecules.[6–8] Because donor-recipient HLA-DR mismatching is associated with increased cardiac allograft rejection episodes,[9–11] TCAD may be the end result of