

Immediate versus delayed palliative thoracic radiotherapy in patients with unresectable locally advanced non-small cell lung cancer and minimal thoracic symptoms: randomised controlled trial

Stephen J Falk, David J Girling, Roger J White, Penelope Hopwood, Angela Harvey, Wendi Qian, Richard J Stephens on behalf of the Medical Research Council Lung Cancer Working Party



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Abstract

Objective To determine whether patients with locally advanced non-small cell lung cancer unsuitable for resection or radical radiotherapy, and with minimal thoracic symptoms, should be given palliative thoracic radiotherapy immediately or as needed to treat symptoms.

Design Multicentre randomised controlled trial.

Setting 23 centres in the United Kingdom, Ireland, and South Africa.

Participants 230 patients with previously untreated, non-small cell lung cancer that is locally too advanced for resection or radical radiotherapy with curative intent, with minimal thoracic symptoms, and with no indication for immediate thoracic radiotherapy.

Interventions All patients were given supportive treatment and were randomised to receive palliative thoracic radiotherapy either immediately or delayed until needed to treat symptoms. The recommended regimens were 17 Gy in two fractions one week apart or 10 Gy as a single dose.

Main outcome measures Primary—patients alive and without moderate or severe cough, chest pain, haemoptysis, or dyspnoea six months from randomisation, as recorded by clinicians.

Secondary—quality of life, adverse events, survival.

Results From December 1992 to May 1999, 230 patients were randomised. 104/115 of the patients in the immediate treatment group received thoracic radiotherapy (90 received one of the recommended regimens). In the delayed treatment group, 48/115 (42%) patients received thoracic radiotherapy (29 received one of the recommended regimens); 64 (56%) died without receiving thoracic radiotherapy; the remaining three (3%) were alive at the end of the study without having received the treatment. For patients who received thoracic radiotherapy, the median time to start was 15 days in the immediate treatment group and 125 days in the delayed treatment group. The primary outcome measure was achieved in 28% of the immediate treatment group and 26% of patients from the delayed treatment group (27/97 and 27/103, respectively; absolute difference 1.6%, 95% confidence interval -10.7% to 13.9%). No evidence of a difference was observed between the two treatment groups in terms of activity level, anxiety, depression, and psychological distress, as recorded by the patients. Adverse events were more common in the immediate treatment group. Neither group had a survival advantage (hazard ratio 0.95, 0.73 to 1.24; $P=0.71$). Median survival was 8.3 months and 7.9 months, and the survival rates were 31% and

29% at 12 months, for the immediate and delayed treatment groups, respectively.

Conclusion In minimally symptomatic patients with locally advanced non-small cell lung cancer, no persuasive evidence was found to indicate that giving immediate palliative thoracic radiotherapy improves symptom control, quality of life, or survival when compared with delaying until symptoms require treatment.

Introduction

A minority of patients with unresectable non-small cell lung cancer whose lesions are confined to the thorax are selected for immediate, radical radiotherapy aimed at cure or prolonging survival. For the remainder, however, advanced disease within the chest, the presence of distant metastases, or poor performance status preclude such potentially curative treatment.

Within this latter group, in the United Kingdom, patients with symptomatic disease, good performance status, no evidence of metastases, and who are considered able to tolerate a high dose palliative regimen are likely to be offered 39 Gy in 13 fractions or an equivalent regimen.¹ For patients who are unsuitable for a high dose palliative regimen—for example, because of poor performance status or metastatic disease—but who have thoracic symptoms requiring palliation, one or two fractions of palliative thoracic radiotherapy is the most commonly applied treatment. Some patients, however, are unsuitable for high dose palliative radiotherapy and have no, or only minimal, thoracic symptoms. For this group, the course of action is unclear—should they be offered immediate palliative thoracic radiotherapy or should a wait and see policy be adopted, with radiotherapy not being given until needed to treat thoracic symptoms?

We undertook the present randomised trial in patients with unresectable non-small cell lung cancer, with no, or only minimal, thoracic symptoms, in whom there was no compelling indication for immediate radiotherapy and who were not suitable for radical radiotherapy with curative intent. Our aim was to compare, in terms of chest symptoms, quality of life, and survival, (a) supportive treatment together with immediate, palliative, thoracic radiotherapy and (b) supportive treatment, radiotherapy not being given until indicated.

Methods

The main eligibility criteria were previously untreated, microscopically confirmed non-small cell lung cancer, locally too advanced for surgical resection or radical

Editorial by Hansen

Department of Oncology, Bristol Oncology Centre, Bristol BS2 8ED
Stephen J Falk
clinical oncologist

Cancer Division, MRC Clinical Trials Unit, London NW1 2DA

David J Girling
senior scientist

Angela Harvey
clinical trials manager

Wendi Qian
medical statistician

Richard J Stephens
research scientist

Department of General Medicine, Frenchay Hospital, Bristol BS16 1LE

Roger J White
respiratory physician

Christie Hospital NHS Trust, Manchester M20 4BX

Penelope Hopwood
consultant in psychiatry and psycho-oncology

Correspondence to: R J Stephens
rs@ctu.mrc.ac.uk

BMJ 2002;325:465-8

radiotherapy with curative intent; minimal thoracic symptoms; performance status of any World Health Organization (WHO) grade²; and no compelling indication for immediate thoracic radiotherapy. Local ethics committee approval of the protocol and individual patient consent were required.

Treatment allocation

Patients were randomly allocated to supportive treatment plus either immediate or delayed thoracic radiotherapy. Supportive treatment consisted of active symptom control using whatever treatment was considered to be most appropriate. The choice of radiotherapy regimen was left to the local radiotherapist, but the two regimens shown in previous Medical Research Council trials to have good palliative effect were recommended.^{3,4} These were 17 Gy given as two 8.5 Gy fractions one week apart, or 10 Gy as a single dose. In the delayed treatment group, thoracic radiotherapy was held in reserve until needed to control symptoms arising from disease within the chest.

Reports and investigations

Patients were assessed at randomisation, one month and two months after randomisation, then every two months up to 12 months, and then every six months thereafter.

Statistical methods

All analyses were conducted on the basis of intention to treat. The primary outcome measure was the percentage of patients alive and without moderate or severe cough, chest pain, haemoptysis or shortness of breath as recorded by clinicians at six months from randomisation. Secondary outcome measures were quality of life,⁵⁻⁷ adverse events, and survival. We anticipated that the failure rate in achieving the primary outcome measure in the delayed treatment group would be 70%. To detect a reduction to 50% in the immediate treatment group at the 5% significance level with 90% power would require a total of 300 patients. We intended to accrue this total over two years. However, we stopped the intake in May 1999—when 230 patients had been randomised during 6.5 years—on the recommendation of an independent data monitoring and ethics committee on the grounds that the trial had achieved a reliable result.

Results

Patients

Between December 1992 and May 1999, 230 patients (115 immediate treatment, 115 delayed treatment) were randomised from 23 centres in the United Kingdom, Ireland, and South Africa. The two groups were well matched at randomisation (see bmj.com). Although, according to the eligibility criteria, all patients were unsuitable for radical radiotherapy, only 27 (12%) had distant metastases, and 157 (68%) had a performance status of grade 0 or 1. As recorded by clinicians, slight or moderate cough and shortness of breath were common, but few patients had severe symptoms, and chest pain, dysphagia, and haemoptysis were uncommon.

Treatment received

The thoracic radiotherapy regimens we used to treat the patients are shown in detail on bmj.com. In the immediate treatment group, 104 of the 115 patients received thoracic radiotherapy (90 with one of the recommended regimens). Subsequently, 12 patients received additional thoracic radiotherapy and five received radiotherapy to metastatic sites. Only one patient received cytotoxic chemotherapy. In the delayed treatment group, 48 (42%) of the 115 patients were treated with thoracic radiotherapy (29 with one of the recommended regimens), 64 (56%) died without having received the thoracic radiotherapy, and the remaining three (3%) were still alive without having received it. Seven patients were given radiotherapy to metastatic sites, one of whom also received cytotoxic chemotherapy. For patients who received the thoracic radiotherapy, the median time to the start of the treatment was 15 days in the immediate treatment group and 125 days in the delayed treatment group.

Outcome

The outcome at all assessments up to six months, the predefined time for assessment of the primary outcome measure, is shown in table 1. None of the differences between the two treatment groups was statistically significant; the differences in success rates were 4.8% (95% confidence interval -10.8% to 20.5%) in favour of immediate treatment at one month, 13.0% (-3.3% to 29.3%) at two months, -8.4% (-21.6% to 4.7%) at four months, and 1.6% (-10.7% to 13.9%) at six months. At months 1-4, the most common reason

Table 1 Outcome at all assessments as recorded by clinicians. Values are numbers (percentages)

Patient group	1 month		2 months		4 months		6 months	
	Immediate treatment (n=115)	Delayed treatment (n=115)	Immediate treatment (n=115)	Delayed treatment (n=115)	Immediate treatment (n=115)	Delayed treatment (n=115)	Immediate treatment (n=115)	Delayed treatment (n=115)
Inadequate data for assessment:								
Missing items on forms	4	1	1	1	2	2	3	0
No form at specified time-point	45	21	40	46	14	15	15	12
Total	49	22	41	47	16	17	18	12
Evaluable patients*	66	93	74	68	99	98	97	103
Successful outcome†	38 (58)	49 (53)	39 (53)	27 (40)	29 (30)	37 (38)	27 (28)	27 (26)
Failed outcome:								
Death before specified time-point	2 (3)	4 (4)	8 (11)	14 (21)	29 (29)	29 (30)	46 (47)	45 (44)
Moderate or severe symptoms	26 (39)	40 (43)	27 (36)	27 (40)	41 (41)	32 (33)	24 (25)	31 (30)
Total	28 (42)	44 (47)	35 (47)	41 (60)	70 (71)	61 (62)	70 (72)	76 (74)

*Some patients treated immediately were still receiving radiotherapy, which led to an imbalance at 1 month.

†Defined as alive and without moderate or severe cough, chest pain, haemoptysis, or shortness of breath.

for failure was the presence of moderate or severe symptoms, whereas at six months it was death.

The analysis shown in table 1 was repeated in patients with no symptoms or only mild symptoms at randomisation. None of these differences was statistically significant, but a delay in the appearance of moderate or severe symptoms is suggested in the immediate treatment group (see [bmj.com](#)).

Activity level, anxiety depression, and psychological distress

On the Rotterdam symptom checklist subscale of activity level, scores range from 7 (best) to 28 (worst). The median scores (table 2) were similar in the two treatment groups.

Levels of anxiety and depression assessed from hospital anxiety and depression scale scores were similar between the treatment groups and did not change with time (see [bmj.com](#)).

Main adverse effects of treatment

Adverse effects of any type were reported more commonly in the immediate treatment group (24 patients) than in the delayed treatment group (12 patients). Dysphagia was the most common adverse effect, being reported in 14 patients from the immediate treatment group and in six patients in the delayed treatment group. One case of radiation pneumonitis occurred, in the delayed treatment group.

Survival

Overall, 112 patients in the immediate treatment group and 110 in the delayed treatment group have died. No evidence of a survival advantage to either group was found (hazard ratio 0.95, 0.73 to 1.24; $P=0.71$) (figure). Median survival was 253 days (8.3 months) in the immediate treatment group and 240 days (7.9 months) in the delayed treatment group, and the survival rates at 12 months were 31% and 29%, respectively.

Discussion

This trial has provided no persuasive evidence that immediate palliative thoracic radiotherapy improves the outcomes for patients with unresectable, locally advanced non-small cell lung cancer and minimal thoracic symptoms. The trial supports a policy of offering short courses of thoracic radiotherapy when appreciable symptoms develop in patients with advanced non-

Table 2 Activity level scores, as recorded by patients using the Rotterdam symptom checklist, during the first six months of patients receiving palliative thoracic radiotherapy treatment immediately or delayed until needed to treat symptoms

Month	No of evaluable patients		Median score (range)	
	Immediate treatment	Delayed treatment	Immediate treatment	Delayed treatment
0	109	110	9 (7-22)	9 (7-27)
1	59	81	11 (7-23)	9 (7-27)
2	61	51	9 (7-24)	10 (7-27)
4	59	58	10 (7-28)	10 (7-28)
6	45	49	10 (7-28)	12 (7-26)

small cell lung cancer for whom no other interventions are planned. Short schedules using one or two fractions of radiotherapy are efficient at relieving the local symptoms of lung cancer, without detriment in terms of either survival time or the toxicity of therapy compared with other longer schedules.^{3 4} Only 42% of patients in the delayed group received thoracic radiotherapy, at a median of 125 days after randomisation. This suggests that, for many patients in whom major thoracic symptoms are not the presenting feature, firstly, a minority will develop significant local thoracic symptoms, which clinicians feel it appropriate to treat with local radiotherapy and, secondly, there should be an emphasis on the management of the more systemic symptomatic manifestations of the disease.

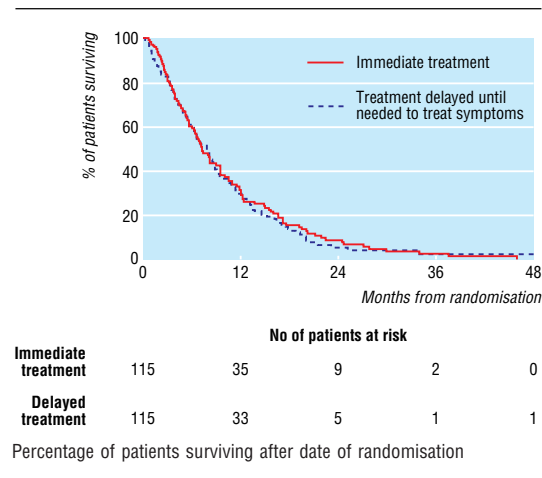
Although palliative radiotherapy is predominantly used for the relief of local symptoms, sometimes it is used as a psychological support. This trial shows, however, that the levels of anxiety, depression, psychological distress, and physical activity recorded by patients were not affected by delaying treatment.

Patterns of care

This trial was designed in the late 1980s and early 1990s and opened in December 1992. At that time, many respiratory physicians in the United Kingdom did not refer patients for treatment with radiotherapy unless there were appreciable local symptoms such as haemoptysis, chest pain, breathlessness, or cough. Such practice is now changing as a result of the widespread introduction of multidisciplinary teams, with a national requirement that the care of each new patient with lung cancer—whatever the extent of disease or severity of symptoms—be discussed within this framework. Such patterns of care should increase the frequency with which patients are offered treatments that alter the course of the disease, most particularly surgical resection or radical radiotherapy. Radical radiotherapy can be curative in selected cases, especially when the CHART (continuous hyperfractionated accelerated radiation therapy) regimen is used.⁸

Chemotherapy has now reliably been shown to prolong survival in patients with metastatic non-small cell lung cancer and good performance status, and to improve long term survival when used as an adjunct to radiotherapy in locally advanced disease.^{9 10} Indeed, most of the patients in the present trial were of reasonable functional status (WHO performance status 0-2), and may now justifiably be considered for systemic chemotherapy. This emphasises again the need for therapeutic plans to be discussed within multidisciplinary teams.

See [bmj.com](#) for the consultants and their colleagues who entered patients into the trial, and for the members of the Medi-



What is already known on this topic

Radiotherapy is commonly given to patients with inoperable non-small cell lung cancer in the United Kingdom

One or two fractions of palliative radiotherapy can control thoracic symptoms

What this study adds

In the group of patients with no symptoms or only minimal symptoms, palliative thoracic radiotherapy can be safely deferred until significant thoracic symptoms appear

Compared with immediate, palliative radiotherapy, no evidence exists that such a policy affects patients' survival or levels of activity, anxiety, or depression

cal Research Council Lung Cancer Working Party.

We are grateful to the data manager, Hannah Brooks, and to all the local coordinators.

Contributors: see bmj.com

Funding: The Medical Research Council (MRC) funded the planning, design, conduct, data collection, analysis and reporting, and provided payments on a per patient basis to collaborating hospitals to assist with local costs. The MRC is a public sector non-profit-making body and has no financial or other interest in the treatments evaluated.

Competing interests: None declared.

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(Accepted 22 January 2002)



The full version of this article appears on bmj.com

Editorial by MacAuley and Best

School of Physiotherapy, University of Sydney, PO Box 170, Lidcombe, New South Wales 1825, Australia
Rob D Herbert senior lecturer
Michael Gabriel physiotherapist

Correspondence to: R D Herbert
R.Herbert@fhs.usyd.edu.au

BMJ 2002;325:468-70

Effects of stretching before and after exercising on muscle soreness and risk of injury: systematic review

Rob D Herbert, Michael Gabriel

Abstract

Objective To determine the effects of stretching before and after exercising on muscle soreness after exercise, risk of injury, and athletic performance.

Method Systematic review.

Data sources Randomised or quasi-randomised studies identified by searching Medline, Embase, CINAHL, SPORTDiscus, and PEDro, and by recursive checking of bibliographies.

Main outcome measures Muscle soreness, incidence of injury, athletic performance.

Results Five studies, all of moderate quality, reported sufficient data on the effects of stretching on muscle soreness to be included in the analysis. Outcomes seemed homogeneous. Stretching produced small and statistically non-significant reductions in muscle soreness. The pooled estimate of reduction in muscle soreness 24 hours after exercising was only 0.9 mm on a 100 mm scale (95% confidence interval -2.6 mm to 4.4 mm). Data from two studies on army recruits in military training show that muscle stretching before exercising does not produce useful reductions in injury risk (pooled hazard ratio 0.95, 0.78 to 1.16).

Conclusions Stretching before or after exercising does not confer protection from muscle soreness. Stretching before exercising does not seem to confer a practically useful reduction in the risk of injury, but

the generality of this finding needs testing. Insufficient research has been done with which to determine the effects of stretching on sporting performance.

Introduction

Many people stretch before or after engaging in athletic activity. Usually the purpose is to reduce muscle soreness after exercising, to reduce risk of injury, or to improve athletic performance.¹⁻⁷

This systematic review synthesises research findings of the effects of stretching before and after exercising on delayed onset muscle soreness, risk of injury, and athletic performance.

Methods

Inclusion and exclusion criteria

The review included English language randomised or quasi-randomised studies that investigated the effects of any stretching technique, immediately before or after exercising, on delayed onset muscle soreness, risk of injury, or athletic or sporting performance. Studies were included only if stretching was conducted before or after exercising.

Search strategy

Relevant studies were identified by searching Medline (1966 to February 2000), Embase (1988 to February 2000), CINAHL (1982 to January 2000), SPORTDiscus