Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial

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Summary

Background The use of radiotherapy after therapeutic lymphadenectomy for patients with melanoma at high risk of further lymph-node field and distant recurrence is controversial. Decisions for radiotherapy in this setting are made on the basis of retrospective, non-randomised studies. We did this randomised trial to assess the effect of adjuvant radiotherapy on lymph-node field control in patients who had undergone therapeutic lymphadenectomy for metastatic melanoma in regional lymph nodes.

Methods This randomised controlled trial included patients from 16 hospitals in Australia, New Zealand, the Netherlands, and Brazil. To be eligible for this trial, patients had to be at high risk of lymph-node field relapse, judged on the basis of number of nodes involved, extranodal spread, and maximum size of involved nodes. After lymphadenectomy, randomisation was done centrally by computer and patients assigned by telephone in a ratio of 1:1 to receive adjuvant radiotherapy of 48 Gy in 20 fractions or observation, with institution, lymph-node field, number of involved nodes, maximum node diameter, and extent of extranodal spread as minimisation factors. Participants, those giving treatment, and those assessing outcomes were not masked to treatment allocation. The primary endpoint was lymph-node field relapse (as a first relapse), analysed for all eligible patients. The study is registered at ClinicalTrials.gov, number NCT00287196. The trial is now closed and follow-up discontinued.

Findings 123 patients were randomly allocated to the adjuvant radiotherapy group and 127 to the observation group between March 20, 2002, and Sept 21, 2007. Two patients withdrew consent and 31 had a major eligibility infringement as decided by the independent data monitoring committee, resulting in 217 eligible for the primary analysis (109 in the adjuvant radiotherapy group and 108 in the observation group). Median follow-up was 40 months (IQR 27–55). Risk of lymph-node field relapse was significantly reduced in the adjuvant radiotherapy group compared with the observation group (20 relapses in the radiotherapy group *vs* 34 in the observation group, hazard ratio [HR] 0·56, 95% CI 0·32–0·98; p=0·041), but no differences were noted for relapse-free survival (70 *vs* 73 events, HR 0·91, 95% CI 0·65–1·26; p=0·56) or overall survival (59 *vs* 47 deaths, HR 1·37, 95% CI 0·94–2·01; p=0·12). The most common grade 3 and 4 adverse events were seroma (nine in the radiotherapy group *vs* 11 in the observation group), radiation dermatitis (19 in the radiotherapy group), and wound infection (three in the radiotherapy group *vs* seven in the observation group).

Interpretation Adjuvant radiotherapy improves lymph-node field control in patients at high risk of lymph-node field relapse after therapeutic lymphadenectomy for metastatic melanoma. Adjuvant radiotherapy should be discussed with patients at high risk of relapse after lymphadenectomy.

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Introduction

Standard treatment protocols for many solid tumours include adjuvant radiotherapy on the basis of data that show improved local control and, in some situations, improved survival. For primary cutaneous melanoma, the commonest and usually first site of recurrence after definitive excision of the primary tumour is in the draining lymph-node field. After therapeutic lymphadenectomy for isolated lymph-node field relapse, patients with substantial disease burden in the regional lymph-node field have a high risk of recurrence,[1–3] which can cause morbidity including pain, ulceration, malodour, lymphoedema, and impaired function, particularly in the leg. Further lymph-node field relapse is predicted by extranodal spread of melanoma, increased number of tumour-positive lymph nodes, and increasing size of involved nodes.[4–6] The use of adjuvant radiotherapy after lymphadenectomy to reduce the risk of further relapse is controversial. In many centres it is recommended in patients considered to be at high risk of further relapse; however, evidence from randomised studies is scarce. In 1993, the Radiation Therapy Oncology Group initiated a randomised trial of post-operative adjuvant radiotherapy (RTOG 93.02), but the trial was halted after failure to accrue sufficient patients, with no results reported. Some retrospective single institution studies and several reviews suggest that

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radiotherapy after therapeutic lymphadenectomy improves lymph-node field control; however, the effect of radiotherapy on survival is much less clear.[7–19]

In 1996, the Trans-Tasman Radiation Oncology Group (TROG) initiated a phase 2 trial[20] (TROG 96.06) of adjuvant radiotherapy for melanoma patients with completely resected lymph-node disease judged to be at substantial risk of further melanoma relapse. Regional control was good, with few toxic effects.[20,21]

With the same radiotherapy regimen as TROG 96.06, we did a randomised trial to compare adjuvant radiotherapy with observation alone in patients at high risk of lymph-node field relapse who had undergone therapeutic lymphadenectomy for metastatic melanoma in regional lymph nodes. The study was started in 2002, by the Australian and New Zealand Melanoma Trials Group and TROG (ANZMTG 01.02/TROG 02.01).

Methods

Patients

Patients from 16 hospitals in Australia, four in New Zealand, one in the Netherlands, and one in Brazil were considered for inclusion. Patients were eligible if they had palpable metastatic lymph-node field disease; had a complete cervical, axillary, or inguinal lymphadenectomy; were at high risk of further lymph-node field relapse; had an ECOG performance status of 0 or 1; were aged 18 years or older; had a life expectancy in the absence of melanoma of 2 years or more; were staged (by CT scan of lymph node field, chest, abdomen, or pelvis, and CT or MRI of brain); had a serum lactate dehydrogenase (LDH) concentration of less than 1·5-times the upper limit of normal; had normal full blood count and biochemistry; and had given informed consent. High risk of further lymph-node field relapse was defined as any one of the following factors: one or more involved parotid nodes, two or more involved cervical or axillary nodes, or three or more involved inguinal nodes; presence of extranodal tumour spread; or the maximum diameter of the largest metastatic lymph node was 3 cm or more (for a cervical node) or 4 cm or more (for an axillary or inguinal node). The ethics committees of all participating centres approved the study. Before randomisation the involved lymph-node field (including the nodal basin and the tissues to be targeted for radiotherapy) was photographed, with protocol-defined anatomical boundaries drawn on the skin. The photograph assisted definition of subsequent lymph-node field relapse versus non-lymph node field relapse (local, in transit, or distant).

Patients were ineligible if they had a concurrent or previous history of local, in transit, or distant relapse; had impalpable (including detected by sentinel-node biopsy) lymph-node field relapse; or had had cancer previously (unless diagnosed more than 5 years before with an estimated risk of recurrence of less than 10%). PET scanning was permitted in centres where it was routine practice. Adjuvant systemic therapy, including interferon, was permitted although the protocol stipulated that no cytotoxic drugs be given during, or close to radiotherapy.

	Adjuvant radiotherapy group (n=17)	Observation group (n=24)
Previous local or in-transit relapse	5	8
Non-palpable nodes	5	7
Local or in-transit relapse at randomisation	1	5
Two node fields involved	3	1
Distant metastases at randomisation	2	1
Incompletely resected nodal disease	1	0
Previous nodal surgery	0	1
No melanoma in lymph nodes	0	1

Table 1: **Major eligibility infringements**

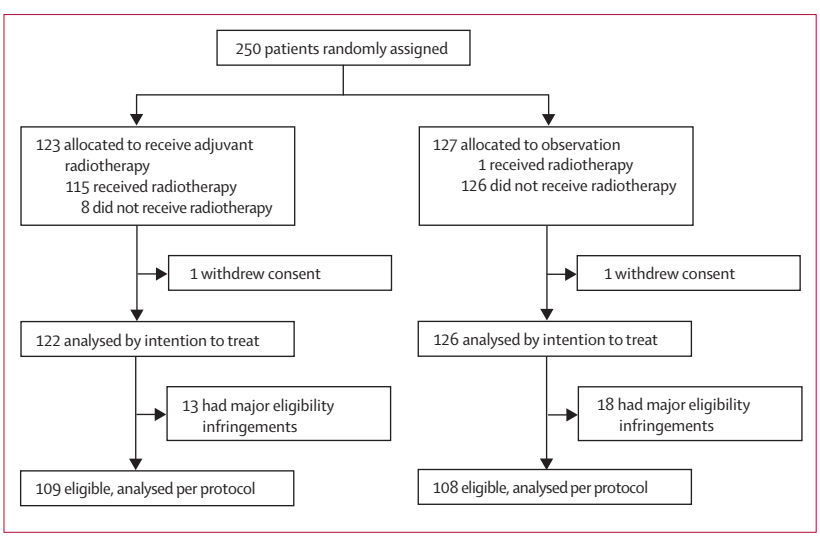

Figure 1: **Trial profile**

Randomisation and masking

We randomly assigned eligible patients centrally with a computer program (with our own algorithm, constructed in Microsoft Access) in a 1:1 ratio to receive adjuvant radiotherapy or observation by a telephone call to the trial centre. Randomisation was done with minimisation using a random component, with balancing factors of institution, lymph-node field (parotid and cervical, axilla, or groin), number of involved nodes (≤three or >three), involved node maximum diameter (≤4 cm or >4 cm), and extent of extranodal spread (none, limited, or extensive).

Procedures

Adjuvant radiotherapy was started within 12 weeks of lymphadenectomy. The dose was 48 Gy given in 20 fractions over 4 weeks. Treatment was given over a maximum of 30 days, by different techniques for each nodal site. The planned treatment volume had prespecified boundaries that included the dissected

	Intention-to-treat population		Eligible population	
	Adjuvant radiotherapy group (n=122)	Observation group (n=126)	Adjuvant radiotherapy group (n=109)	Observation group (n=108)
Sex				
Male	92 (75%)	92 (73%)	83 (76%)	81 (75%)
Female	30 (25%)	34 (27%)	26 (24%)	27 (25%)
Age at randomisation (years)				
Median (IQR; range)	58 (46–69; 22–80)	56 (45–68; 22–87)	59 (47–69; 22–80)	56 (45–68; 25–87)
ECOG performance status				
0	88 (72%)	90 (71%)	77 (71%)	74 (69%)
1	34 (28%)	36 (29%)	32 (29%)	34 (31%)
Lymph-node field				
Head and neck	31 (25%)	34 (27%)	29 (27%)	30 (28%)
Axilla	52 (43%)	52 (41%)	45 (41%)	44 (41%)
Groin	39 (32%)	40 (32%)	35 (32%)	34 (31%)
Node maximum diameter				
≤4 cm	75 (61%)	80 (63%)	64 (59%)	66 (61%)
>4 cm	47 (39%)	46 (37%)	45 (41%)	42 (39%)
Number of positive nodes				
Head and neck				
Mean (SD)	1·90 (1·60)	3·32 (5·43)	1·93 (1·65)	3·53 (5·75)
Median (IQR; range)	1 (1–2; 1–9)	2 (1–3; 1–31)	1 (1–2; 1–9)	2 (1–3; 1–31)
Axilla				
Mean (SD)	3·79 (4·38)	4·23 (7·07)	3·96 (4·69)	4·55 (7·57)
Median (IQR; range)	3 (1–4; 1–25)	2 (1–4; 1–47)	3 (1–5; 1–25)	2 (1–4; 1–47)
Groin				
Mean (SD)	3·54 (2·26)	3·35 (2·25)	3·66 (2·35)	3·18 (2·19)
Median (IQR; range)	3 (2–4; 1–12)	3 (2–4·25; 1–10)	3 (2–4·5; 1–12)	2·5 (2–4; 1–10)
Extent of extranodal spread				
None	61 (50%)	62 (49%)	51 (47%)	56 (52%)
Limited	37 (30%)	44 (35%)	36 (33%)	35 (32%)
Extensive*	24 (20%)	20 (16%)	22 (20%)	17 (16%)
Primary site				
Head and neck	19 (16%)	22 (17%)	18 (17%)	20 (19%)
Trunk	37 (30%)	27 (21%)	30 (28%)	22 (20%)
Arm	17 (14%)	22 (17%)	15 (14%)	16 (15%)
Leg	29 (24%)	30 (24%)	26 (24%)	25 (23%)
Unknown	20 (16%)	25 (20%)	20 (18%)	25 (23%)
Use of interferon				
None	118 (97%)	120 (95%)	105 (96%)	103 (95%)
Planned or started at randomisation	4 (3%)	6 (5%)	4 (4%)	5 (5%)

*Matted nodes, multiple node extracapsular spread, or multiple deposits of lymphovascular space invasion or multiple deposits of tumour in fat or connective tissue unrelated to nodes or vessels.

Table 2: **Baseline characteristics of the intention-to-treat and eligible populations**

lymph-node field and lymphadenectomy scar. For the axillary and ilio-inguinal lymph-node fields multiple photon fields were recommended, but in the head and neck region both photon and electron plans were allowed. Maximum doses were stipulated for the spinal cord (40 Gy), brachial plexus (45 Gy), and femoral neck (40 Gy). In patients who were assigned to observation and later developed isolated lymph-node field relapse, resection with postoperative radiotherapy was permitted.

Patients were followed up once every 3 months for 2 years, then every 6 months until 5 years, and annually thereafter. We assessed surgical morbidity, quality of life, and limb circumference at baseline and at each visit. Patients assigned to radiotherapy were assessed for acute radiation toxic effects with the Radiation Therapy Oncology Group criteria[22] at 2 and 6 weeks after completion of radiotherapy, and at the first 3 month follow-up visit. A full blood cell count, serum urea and

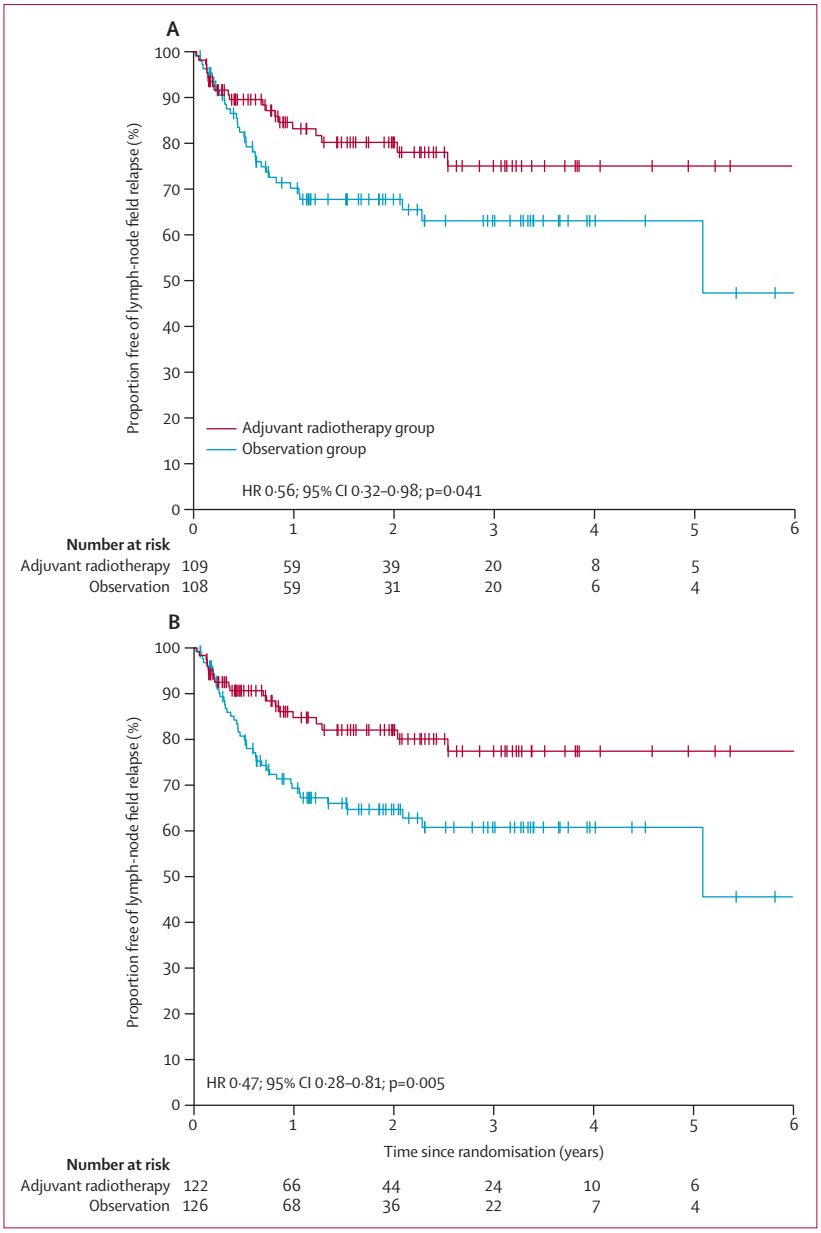

Figure 2: **Kaplan-Meier curves of time to lymph-node field relapse by treatment group**
In the eligible population (A) and the intention-to-treat population (B). Hazard ratios are for adjuvant radiotherapy versus observation.

creatinine concentrations, liver function tests, and CT scans of the head, chest, abdomen, pelvis, and involved lymph-node field were done by the treating clinician annually.

The trial was overseen by an independent data monitoring committee, which consisted of a surgeon, a radiation oncologist, and a statistician. Quality assessments of the trial data were done throughout the trial. These reviews included eligibility criteria, pathology reports, operation reports, photographs of the lymph-node field taken before randomisation (inadequate photographs were retaken), informed consent forms, primary melanoma details, lymph-node field relapse (using original and relapse photographs), other sites of relapse (local, in transit, and distant), and verification of date and cause of death.

The primary endpoint was lymph-node field relapse (as first relapse). Secondary objectives were measurement of acute toxic effects, relapse-free survival, and overall survival. Late toxic effects, quality of life, and long-term survival will be assessed in later reports.

Statistical analysis

The trial was designed to have a target sample size of 270 patients, but included a planned reassessment of the sample size on the basis of the lymph-node field relapse rate in both groups. This reassessment (overseen by two independent experienced clinical researchers) resulted in a decrease of the target sample size because of a slower accrual rate than was expected and because the lymph-node field relapse rate for both groups combined was higher than expected. Consequently, we amended the protocol twice: the first introduced an interim analysis for efficacy based on the primary endpoint. The interim α was 0·048, based on the proportion of the total number of lymph-node field relapses and the O'Brien-Fleming spending function. After the interim analysis, the data monitoring committee recommended continuation of the trial to full accrual. The second amendment occurred after the identification of eligibility infringements and permitted an increase in the sample size accordingly.

The final target sample size was 250 patients, on the basis of the assumption that 40% of patients in the observation group would have a lymph-node field relapse according to an exponential distribution and that 70% of these relapses would occur within 1 year. The trial was designed to have 80% power to detect a 20% difference in the proportion of patients with lymph-node field relapse beween groups (20% in the radiotherapy group *vs* 40% in the observation alone group), corresponding to a hazard ratio (HR) of 0·437. 48 lymph-node field relapses were needed to ensure adequate power. We initially planned to do efficacy analyses in the intention-to-treat population. However, during the course of the trial, the independent data monitoring committee identified several eligibility infringements. On the advice of the committee, a formal independent, external review was done for all patients for whom eligibility concerns existed. The eligibility review panel consisted of a radiation oncologist and a surgical oncologist who were masked to the patient's institution, assignment, and outcome. This review identified 41 major eligibility infringements in 31 patients (table 1). The committee recommended that these patients be excluded from the primary analysis. Thus, two study populations were analysed; the intention-to-treat population, and the eligible population.

We used the Kaplan-Meier method to estimate curves for time to lymph-node field relapse, overall survival,

and relapse-free survival. The start date for all time-to-event outcomes was the date of randomisation. Time to lymph-node field relapse was defined as time from start date to lymph-node field relapse, either alone or concurrent with relapse at any other site. Time to lymph-node relapse was censored by relapse in other sites, the cutoff date, and loss to follow-up. Overall survival was defined as time from start date to death from any cause and relapse-free survival was defined as relapse at any site or death without previous relapse. Both measures were censored by the cutoff date and loss to follow-up. We used a cutoff date for follow-up of Nov 15, 2008, and all living patients were followed up to this date; any follow-up after this date was ignored to minimise reporting bias. Potential follow-up time was defined for each patient as time from entry to the trial to the cutoff date, or to the last follow-up date for patients lost to follow-up. We analysed time-to-event with unadjusted and stratified log-rank tests and Cox regression methods, including testing model assumptions. We did two-sample comparisons with unadjusted and stratified exact log-rank tests based on hypergeometric probabilities. We analysed patterns of failure with a competing risks method, presented with cumulative incidence curves and compared with Gray's test.

To assess the effects of potential prognostic factors in the eligible population for lymph-node field relapse and overall survival we did a multivariable analysis including lymph-node field site (head and neck, axilla, or groin), status of primary lesion (known or unknown primary), extranodal spread (none, limited, or extensive; coded as 0, 1, or 2 and analysed as a continuous variable), and number of positive nodes (one, two or three, or four or more; coded as 1, 2, or 3 and analysed as a continuous variable).

All p values are two sided. All analyses were done with the R statistical package (version 2.14.0). This study is registered with ClinicalTrials.gov, number NCT00287196.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From March 20, 2002, to Sept 21, 2007, 250 patients from 16 institutions (six did not accrue any patients) in Australia (222 patients), New Zealand (14 patients), the Netherlands (12 patients), and Brazil (two patients) were randomly assigned. The accrual rate (average 3·7 patients per month) was generally uniform throughout the accrual period. Two patients (one from each group) withdrew consent soon after randomisation and were excluded from all analyses (figure 1). The intention-to-treat population thus consisted of 248 patients, while the eligible population consisted of 217 patients.

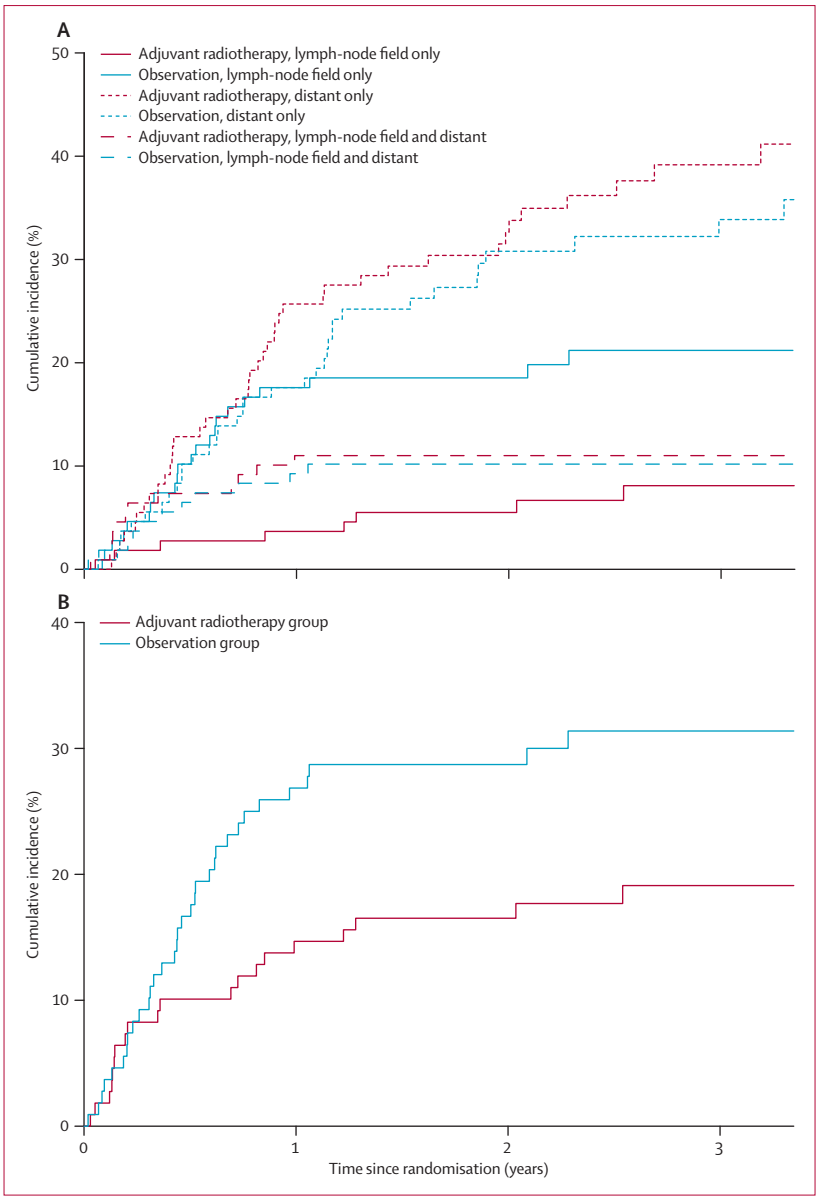

Figure 3: **Cumulative incidence curves of relapse**
(A) Curves of competing events: isolated lymph-node field relapse, isolated distant relapse, and concurrent lymph node and distant relapse in each group in the 217 patients in the eligible population. Additionally (data not shown), nine patients had isolated local or in-transit disease and one patient died without relapse (local or in-transit disease concurrent with lymph-node field and distant relapse are included in presented curves). (B) Curves for lymph-node field relapse, with or without concurrent relapse in other sites, as a first relapse, in each group in the eligible population.

Median potential follow-up in the intention-to-treat population was 40 months (IQR 27–55) and, in patients not lost to follow-up, ranged from 14 to 80 months. Two patients in the observation group were lost to follow-up, after 13 and 21 months. Table 2 shows baseline characteristics, including patient demographics, for the eligible and intention-to-treat populations. Characteristics were much the same in both groups and in both analysis populations. Median time from primary melanoma

For the **statistical package** see http://www.R-project.org/

	Intention-to-treat population		Eligible population	
	Adjuvant radiotherapy group (n=122)	Observation group (n=126)	Adjuvant radiotherapy group (n=109)	Observation group (n=108)
Lymph-node field only	8	26	8	23
Local or in-transit only	7	3	7	2
Lymph-node field and local or in-transit	0	2	0	0
Distant only	49	39	42	37
Lymph-node field and distant	11	11	11	9
Distant and local or in-transit	0	1	0	0
Lymph-node field and distant and local or in-transit	1	3	1	2
Total relapsed	76	85	69	73
No relapse	46	41	40	35

Of the 161 patients in the intention-to-treat population who had a first relapse, 132 relapsed in one site only (64 in the radiotherapy group *vs* 68 in the observation group) and 29 relapsed in multiple sites (two sites, 11 *vs* 14; or all three sites, 1 *vs* 3). Of the 142 patients in the eligible population who had a first relapse, 119 relapsed in one site only (57 *vs* 62) and 23 relapsed in multiple sites (two sites, 11 *vs* 9; or all three sites, 1 *vs* 2).

Table 3: **Sites of first relapse**

diagnosis to diagnosis of isolated lymph-node field relapse in the eligible population was 16 months (IQR 5–41).

Of the 122 patients due to to receive adjuvant radiotherapy in the intention-to-treat population, seven did not (four refused and three developed progressive disease before starting radiotherapy). Of the remaining 115, 109 (95%) received the prescribed dose of 48 Gy, five (4%) received less than 48 Gy, and one (<1%) received more than 48 Gy. 99 patients (86%) received their treatment without interruption and 16 (14%) had interruptions of 1–11 days because of machine malfunction, public holidays, personal circumstances, concurrent interferon administration, or unplanned hospital admissions for other disorders. 54 patients had their compliance to the radiotherapy protocol reviewed; compliance (defined as complete adherence to the radiotherapy protocol) was 79%.

In the eligible population, 54 of 217 patients had lymph-node field relapse as a first relapse. Fewer patients in the radiotherapy group (20 of 109) relapsed than did those in the observation group (34 of 108; HR 0·56, 95% CI 0·32–0·98; p=0·041; figure 2A). Results were similar for the analysis adjusted for lymph-node field (head and neck, axilla, or groin; HR 0·56, 95% CI 0·33–0·96; p=0·041). Higher risk of lymph-node field relapse in the observation group than in the radiotherapy group was consistent across all nodal sites (data not shown). The risk of lymph-node field relapse in the intention-to-treat population was comparable with that in the eligible population (HR 0·47, 95% CI 0·28–0·81; p=0·005; figure 2B). Of 23 eligible patients in the observation group who had an isolated lymph-node field relapse as a first relapse, 18 received salvage therapy and seven of these patients have died. Survival from first relapse in all eligible patients who relapsed at any site was 44% (95% CI 36–53) at 1 year, 24% (17–34) at 2 years, and 18% (11–27) at 3 years; median survival was 10 months (IQR 7–13).

Of the 217 eligible patients, 142 relapsed with melanoma (69 in the radiotherapy group, 73 in the observation group) and one assigned to the radiotherapy group died without having relapsed. Figure 3A shows cumulative incidence curves for different first relapse sites in the eligible population, and sites of relapse are shown in table 3. At 3 years, the cumulative incidence of lymph node relapse was 19% (95% CI 11–27) in the radiotherapy group and 31% (20–40) in the observation group. Relapse-free survival did not differ between in the radiotherapy group compared with the observation group (HR 0·91, 95% CI 0·65–1·26; p=0·56; figure 4A). Median recurrence-free survival was 15 months (95% CI 11–27) in the radiotherapy group and 14 months (95% CI 9–23) in the observation group. The results for relapse-free survival were similar in the intention-to-treat population (HR 0·90, 95% CI 0·66–1·22; p=0·53); 163 of the 248 patients had a relapse at any site (n=161; table 3) or death without relapse (two patients in the radiotherapy group). Time to distant relapse (as a first relapse) for the eligible patients did not differ significantly between treatment groups (HR 1·06, 95% CI 0·72–1·57; p=0·77). Time to any distant relapse was almost identical for the two groups (HR 1·00, 0·71–1·41; p=0·8). Results were much the same for the intention-to-treat population (data not shown).

106 eligible patients died by the data cutoff, 59 in the radiotherapy group and 47 in the observation group (including three deaths that were not from melanoma). This difference was not statistically significant (HR 1·37, 95% CI 0·94–2·01; p=0·12; figure 4B). Median survival was 32 months (95% CI 20 to not yet reached) for patients in the radiotherapy group and 47 months (95% CI 30 to not yet reached) for patients in the observation group. 120 patients in the intention-to-treat population died, 66 in the radiotherapy group and 55 in the observation group, all but two (one in each group) of melanoma; the difference was not statistically significant (HR 1·35, 95% CI 0·94–1·92; p=0·12).

The most common early surgery-related adverse events were seroma formation in the groin or axilla, infection, nerve damage, wound necrosis, and local pain (table 4). For patients in the radiotherapy group, the most commonly early reported toxic effects were radiation dermatitis, and pain (table 4).

In a multivariable analysis of potential prognostic factors, extranodal spread (none *vs* limited *vs* extensive) was the only independent risk factor for lymph-node field relapse (HR 1·77 per degree of spread, 95% CI 1·26–2·49; p=0·001 [HR lymph-node field relapse for adjuvant radiotherapy *vs* observation 0·53, 95% CI 0·30–0·92; p=0·025]). Seven of 51 patients (14%) in the radiotherapy group with no extranodal spread had lymph-node field relapse, compared with six of 36 (17%) with limited extranodal spread, and seven of 22 (32%)

with extensive extranodal spread. Extranodal spread (HR 1·66 per degree of spread, 95% CI 1·30–2·13, p=0·0001) and number of positive nodes involved (one *vs* two to three *vs* four or more; HR 1·45 per level, 95% CI 1·13–1·86, p=0·004) were independently predictive of poor overall survival. Treatment group, adjusting for these two factors, was not significantly related to survival (HR 1·36, 95% CI 0·92–2·00; p=0·12).

Discussion

The results of our study suggest that the use of adjuvant radiotherapy after complete surgical resection for isolated lymph-node field melanoma relapse in patients at high risk of relapse substantially reduced the risk of further lymph-node field relapse, although there was no effect on overall survival. As used in this trial, adjuvant radiotherapy was associated with acceptable early toxic effects.

The first study to investigate the role of adjuvant radiotherapy in melanoma patients with resected lymph-node field recurrences was a randomised study of 56 patients done in 1978.[23] The duration of follow-up was short, the radiation therapy used was suboptimum by current standards, and the rate of lymph-node field relapse was not reported. The investigators attributed the trend towards improved survival in patients receiving radiotherapy to an imbalance of prognostic factors between the two groups (age and the number of lymph nodes involved), leading them to conclude that radiotherapy had no effect on outcome. Since this report, several groups have published retrospective reviews which, in most but not all cases, indicate improved lymph-node field control with adjuvant radiotherapy compared with surgery alone.[10–21] Results of several systematic reviews have also shown that adjuvant radiotherapy reduces lymph-node field relapse.[24,25] However, other reports indicate no significant improvement in lymph-node field control for radiotherapy after lymphadenectomy (panel).[26,27]

The evidence supporting a survival benefit for patients receiving adjuvant radiotherapy is even more controversial and conflicting.[17] Although many major melanoma treatment centres around the world offer adjuvant radiotherapy for selected patients, many others are still cautious because of the absence of a clear survival benefit in patients with a very high risk of succumbing to the disease and concerns about the possibility of long-term morbidity associated with radiotherapy. Lymphoedema is the most common long-term problem, affecting many patients receiving adjuvant radiotherapy after axillary or inguinal lymphadenectomy.[10,11,13,21] No comprehensive, prospective assessments of long-term radiotherapy-associated complications or effects of radiotherapy on quality of life exist. Our study closed in November, 2011, and analyses of long-term toxic effects and quality-of-life outcomes are not yet complete.

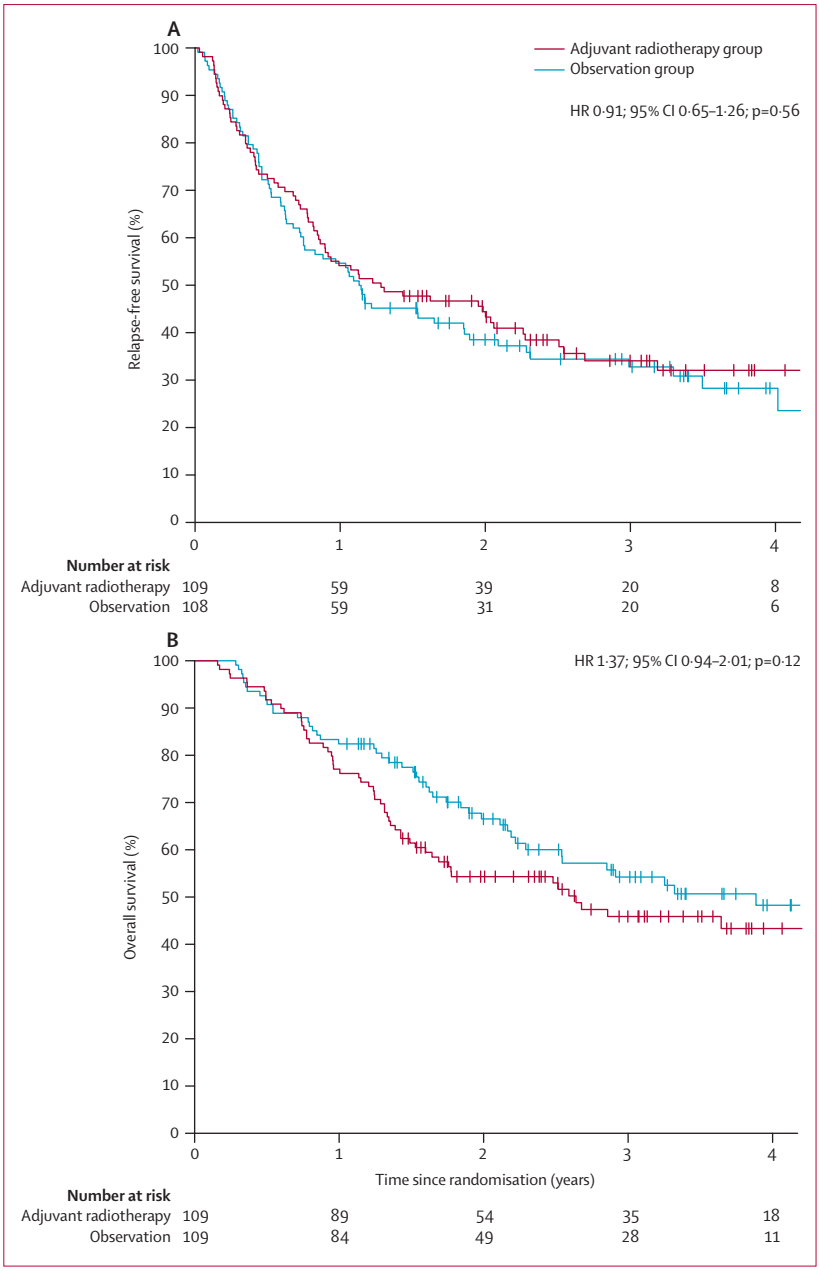

Figure 4: **Survival by group in the eligible population**
Relapse-free survival (A) and overall survival (B). Hazard ratios are for adjuvant radiotherapy versus observation.

Concerns about long-term morbidity caused by radiotherapy restricts the use of adjuvant radiotherapy in most centres to patients at high risk of lymph-node field relapse after lymphadenectomy. These risks are well documented; they are principally related to the number and maximum size of tumour-involved nodes, and the presence of extranodal tumour extension.[4–6] Our results show that radiotherapy affects the timing and pattern of first relapse and reduces the risk of lymph-node field relapse. Overall survival was not significantly different between groups.

	Head and neck		Axilla		Ilio-inguinal	
	Adjuvant radiotherapy group	Observation group	Adjuvant radiotherapy group	Observation group	Adjuvant radiotherapy group	Observation group
Related to surgery*						
Seroma	0	0	5	4	4	7
Wound infection	1	0	0	1	2	6
Nerve damage	1	1	0	0	0	0
Wound necrosis	0	0	0	0	0	1
Pain	0	0	0	0	0	1
Related to radiation therapy†						
Dermatitis	3	..	10	..	6	..
Pain	0	..	2	..	0	..

Based on the common toxicity criteria version 2.0.[22] *At registration. †2 weeks after radiotherapy.

Table 4: **Early adverse events (grade 3 and 4)**

Panel: Research in context

Systematic review

To assess the evidence supporting the use of adjuvant radiotherapy in melanoma, we searched Cochrane, PubMed, and Medline with the terms "melanoma, regional recurrence, lymph-node field recurrence and melanoma", for studies in English published between 1970, and 2001. We did not identify any completed randomised trials with the primary endpoint of lymph-node field relapse. Data from retrospective studies and one prospective study suggest reduction in the risk of lymph-node field relapse by about 50%. Three reviews published after 2001 support this assessment.

Implications

This report confirms that adjuvant radiotherapy reduces the risk of further lymph-node field relapse after lymphadenectomy in patients at high risk of relapse, although it had no significant effect on overall survival. Early toxic effects related to radiotherapy were infrequent and minor. If the intention of treatment is to reduce the risk of regional recurrence, adjuvant radiotherapy is a treatment option that should be discussed with patients at high risk of lymph-node field relapse after lymphadenectomy.

Some centres use hypofractionated regimens for melanoma rather than traditional standard fractionation schedules, largely on the basis of radiobiological data from in-vitro studies, which suggested that melanoma was relatively radioresistant compared with other types of cancer, but might respond to higher dose-per-fraction schedules.[28] However, more recent radiobiological and clinical studies suggest that most melanomas are radiosensitive.[29] Hypofractionated regimens have not been directly compared with standard fraction regimens in the adjuvant setting. Hypofractionation regimens might be associated with increased risk of long-term tissue effects, notably lymphoedema.[10,11] Improved selection of patients for adjuvant systemic therapies or adjuvant radiotherapy is clearly a priority. High standard uptake values in FDG-PET and raised serum S100 concentration are useful predictors of outcome and potential of metastasis in operable stage 3 melanoma.[30] Several new targeted therapies—eg, ipilimumab and verumafenib—are highly effective in patients with advanced melanoma. These agents will likely be investigated in adjuvant studies of patients at high risk of locoregional and distant recurrence.

A limitation of our study was the high number of ineligible patients, which reduced the power of the study. Our future studies are centred on further exploring the role of radiotherapy in the preoperative setting in which modern imaging modalities are able to identify high risk patients before surgery.

Contributors

BHB, MAH, and JFT designed the study, developed the protocol, recruited patients, and drafted the Article. JA designed the study, developed the protocol, and recruited patients. RF designed the study, developed the protocol, analysed data, and drafted the Article. JDI coordinated the trial and collected data, was involved in quality assurance, and drafted the Article. BMS, KS, SC, BJC, SB, JD, and HJH were involved in patient accrual. AH was involved in patient accrual and developed the protocol. RAS was involved in pathology review.

Conflicts of interest

We declare that we have no conflicts of interest.

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