important donors are: the Arab Gulf Programme, Australia, Bangladesh, Belgium, Canada, Denmark, the Ford Foundation, France, Holland, Japan, the Norwegian Agency for International Development, Saudi Arabia, Switzerland, the United Kingdom, Unicef, the United Nations Development Programme, USAID, the World Health Organisation, and the World Bank. We thank Dr A Foster and Dr J Menken for their help and advice in the statistical analysis and Drs R Eeckels, V Fauveau, A Hall, and F Henry (ICDDR,B) for their help and encouragement during the preparation of the manuscript.

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(Accepted 7 April 1989)

Postoperative radiotherapy and late mortality: evidence from the Cancer Research Campaign trial for early breast cancer

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Abstract

***Objective*—To identify any excess mortality caused by adjuvant radiotherapy for early breast cancer.**

***Design*—Prospective randomised clinical trial. Two thousand subjects needed for study to have a 90% chance of detecting a difference in survival rate of 7% with 95% significance. Patients were followed up until June 1988, giving follow up of 158-216 months.**

***Setting*—A multicentre trial mainly drawing patients from centres in the United Kingdom.**

***Patients*—2800 Women presenting with clinical stage I or II carcinoma of the breast from June 1970 to April 1975.**

***Interventions*—One group of women (n=1376) had simple mastectomy followed by immediate postoperative radiotherapy (1320 to 1510 rets). The remaining women (n=1424) had simple mastectomy with subsequent careful observation of the axilla, radiotherapy being delayed until there was obvious progression or recurrence of disease locally.**

***End point*—Increased mortality in patients treated with radiotherapy from causes other than breast cancer.**

***Measurements and main results*—Survival was measured from time of first treatment to death or last follow up. Deaths from any cause and from specified causes were counted as events. Comparison over the whole follow up showed a slight excess mortality in the group treated with radiotherapy (relative risk 1·04; 95% confidence interval 0·94 to 1·15). The relative risk of death from breast cancer was 0·97 (0·87 to 1·08) but that of death from other causes was 1·37 (1·09 to 1·72), the increase mainly being in women who had had tumours of the left breast (1·61 (1·17 to 2·24)) and had been treated with orthovoltage (1·85 (1·27 to 2·71)). Analysis of causes of death after five years showed a relative risk of 2·11 (1·25 to 3·59) for new malignancies and of 1·65 (1·05 to 2·58) for cardiac disease, the increase in cardiac mortality being most pronounced in patients who had had tumours of the left breast and whose treatment had included orthovoltage radiation (relative risk 2·67 (1·28 to 5·55)).**

***Conclusions*—Adjuvant radiotherapy after simple mastectomy for early breast cancer produces a small excess late mortality from other cancers and cardiac disease. The risk has to be balanced against the higher risk of local recurrence when immediate postoperative radiotherapy is not given. The balance has to be assessed for each patient, and for many patients radiotherapy will still be desirable in the initial treatment of their early breast cancer.**

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Br Med J 1989;**298**:1611-4

Introduction

Postoperative radiotherapy reduces the rate of local recurrence after treatment for early breast cancer.[1,2] No significant improvement in rates of survival has been shown after radiotherapy, and some critics have claimed that it has a deleterious effect.[3] Cuzick *et al* carried out an overview of 10 randomised trials in which the difference between the two groups was solely whether patients had been irradiated postoperatively.[4] This overview showed no significant effect on survival up to 10 years, but beyond 10 years the mortality in the irradiated patients was signficantly increased. This finding was greatly influenced by the earlier trials, which contributed most to the long term follow up and tended to use orthovoltage rather than supervoltage radiation.

The largest trial in Cuzick *et al*'s overview was the Cancer Research Campaign (King's/Cambridge) trial, which compared simple mastectomy and postoperative radiotherapy with simple mastectomy followed by a watch policy. This trial started in 1970 and had a maximum follow up at the time of the overview of 14 years. Of all deaths after 10 years' follow up included in the overview, only one fifth were from the Cancer Research Campaign trial. Nevertheless, Cuzick *et al* reported that on its own the data showed an increased risk of death in the group treated with radiotherapy after 10 years, the relative risk being 1·50 (95% confidence interval 1·07 to 2·11). They also reported a similar trend from five to 10 years with a relative risk of 1·21 (1·01 to 1·44).

If increased late mortality in patients given radiotherapy is a true effect several questions arise concerning the reasons for this. Is it due to late failure of treatment as would be shown by increased deaths from cancer of the breast? Is it due to the carcinogenic effect of radiation causing an increase in deaths from other cancers? Or is it due to other effects of radiation on normal tissues causing late changes in those tissues that precipitate death?

We tried to answer these questions by detailed analysis of the data from the Cancer Research Campaign trial on causes of death in the two groups.

Patients and methods

The dataset consisted of all randomised patients: 1376 treated by simple mastectomy and postoperative radiotherapy and 1424 treated by simple mastectomy followed by a watch policy. The results at 10 years were reported in 1980 and showed a significant decrease in the rate of local recurrence in the group treated with radiotherapy but no difference in mortality between the two groups.[2] The recommended radiotherapy regimens delivered doses in the range 1320 to 1510 rets. A detailed analysis of the radiotherapy treatments and the sites of local recurrence has been given by Brinkley *et al*.[5]

Entry into the trial took place from June 1970 to April 1975. We have analysed the data as at 30 June 1988, when follow up varied from 158 to 216 months. Thus follow up was longer than when analysed by Cuzick *et al*.[4]

Causes of death were determined from information given on the death report form, copies of death certificates, and, in some cases, correspondence with treating clinicians and examination of the patient's notes. Deaths were first classified as due or not due to breast cancer. Deaths not due to breast cancer were then subdivided into deaths from other malignant disease; deaths related to cardiac disease—that is, heart failure, myocardial infarct, coronary thrombosis; and deaths from all other causes. Included in this last group were all cardiovascular deaths not recorded in the second group. A few patients could not be classified, and for some others there was considerable uncertainty about the correct classification.

Statistical comparisons between the two groups were made with logrank tests,[6] counting as events all deaths or one particular classification of death—for example, deaths due to breast cancer and deaths related to cardiac disease.

Results

Figure 1 shows the survival curves in the two groups over the 18 years of follow up. Mortality was slightly higher in the group treated with radiotherapy (relative risk 1·04; 95% confidence interval 0·94 to 1·15), but this was not significant. When only deaths due to breast cancer were counted as events the curves were

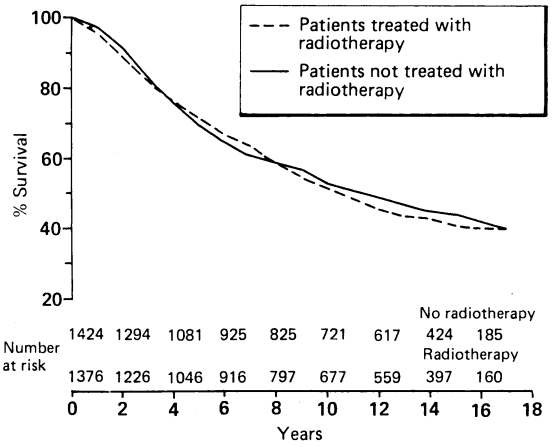

FIG 1—*Survival curves for two treatment groups. Number at risk is number of patients alive at entry and every two years thereafter; this decreases in later years as fewer patients had been in trial for relevant length of time* $\chi^2=0{\cdot}57$ *(NS)*

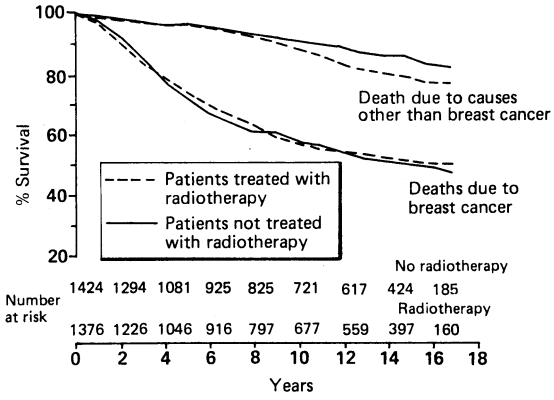

FIG 2—*Survival curves according to cause of death. When only deaths from breast cancer were counted as events* $\chi^2=0{\cdot}28$ *(NS); when only deaths from causes other than breast cancer were counted as events* $\chi^2=7{\cdot}69$, $p=0{\cdot}006$. *For definition of numbers at risk see figure 1*

TABLE I—*Deaths due to causes other than breast cancer in patients who had had breast cancer treated with and without postoperative radiotherapy by affected breast and type of radiation*

Type of radiation	Affected breast	Deaths in patients given radiotherapy: Observed	Deaths in patients given radiotherapy: Expected	Variance of observed minus expected	Relative risk* (95% confidence interval)
Supervoltage	Left	19	18·11	9·47	1·10 (0·58 to 2·08)
	Right	29	23·55	12·22	1·56 (0·89 to 2·74)
Orthovoltage or mixed	Left	66	49·50	26·74	1·85 (1·27 to 2·71)
	Right	55	54·21	25·93	1·03 (0·70 to 1·51)
All	Left	85	67·61	36·21	1·61 (1·17 to 2·24)
	Right	84	77·76	38·15	1·18 (0·86 to 1·62)
All	Either breast	169	145·37	74·36	1·37 (1·09 to 1·72)

*Log (relative risk)=(observed-expected)/variance. Relative risk >1·0 indicates higher mortality in group given radiotherapy.
Tests for interaction: between left and right overall χ^2 1·86; p=0·17; between left and right in orthovoltage χ^2 4·53; p=0·03.

almost superimposed (fig 2) and again the difference was not significant (relative risk 0·97; 0·87 to 1·08). When only deaths due to causes other than breast cancer were counted as events (fig 2), however, the curves began to separate in the second quinquennium, and, over the whole period of follow up mortality from these causes was significantly higher in the group treated with radiotherapy (relative risk 1·37; 1·09 to 1·72). No significant interactions were detected when the data were divided according to age or stage or size of tumour.

An unexpected finding was that the increase in deaths due to causes other than breast cancer in the group treated with radiotherapy was mainly in patients who had had tumours of the left breast (see table I), in whom the relative risk was 1·61 (1·17 to 2·24), though a test for interaction between tumours of the left and right breasts was not significant (p=0·18). As noted above, the earlier trials in which orthovoltage radiation was used contributed most of the data after 10 years in the overview by Cuzick *et al.*[4] In the Cancer Research Campaign trial some centres used only supervoltage, others only orthovoltage, and some both. When both were used orthovoltage was almost invariably used for the pectoral fields, supervoltage being used for treatment outside the pectoral area. Table I stratifies deaths due to causes other than breast cancer not only by which breast was affected but also by type of radiation —that is, only supervoltage and only or some orthovoltage. The overall relative risk confirmed the result of the unstratified comparison given above, but two thirds of the excess deaths due to causes other than breast cancer in the group treated with radiotherapy were in patients who had had tumours of the left breast treated by orthovoltage. This, of course, is a finding in a subset and must be viewed with some caution, but the p value was significant (p=0·0014) and a test for interaction between left and right sides in the patients treated with orthovoltage was also significant (p=0·03).

As the excess deaths in patients with tumours of the left breast may have been due to irradiation of the heart region, and especially as orthovoltage, with its more lateral scatter, gives a higher dose of radiation to this region, we examined in more detail the deaths due to causes other than breast cancer after five years, when the excess mortality became apparent (fig 2). Table II shows the breakdown by cause of death after five years in the two groups of the trial. More deaths related to cardiac disease and other malignancies were seen in the group treated with radiotherapy. Table III shows the distribution of the deaths related to cardiac disease according to which breast was affected and the type of radiation. The excess deaths in the group treated with radiotherapy occurred mainly in patients with tumours of the left breast whose treatment included orthovoltage radiation (relative risk 2·67; 1·28 to 5·55), though a test for interaction between tumours of the left and right breasts treated by orthovoltage was not significant (p=0·15).

The increased deaths from other malignancies in the patients treated with radiotherapy followed an increased incidence of new malignancies (table IV). There were also more new malignancies in the opposite breast, which were not allowed for in any of the analyses of cause of death as determining whether deaths from breast cancer were due to the first or second primary was impossible. Table V gives details of the second malignancies responsible for the deaths after five years. The excess in the group treated with radiotherapy was not confined to sites in the upper part of the body where higher radiation doses might have been delivered, nor was it particularly associated with tumours of the left breast or treatment with orthovoltage radiation (table VI).

TABLE II—*Causes of death after five years in patients who had had breast cancer treated with or without postoperative radiotherapy*

Cause of death	Patients given radiotherapy	Patients not given radiotherapy	Relative risk*	p Value (logrank comparison)
Breast cancer	271	278	1·02 (0·86 to 1·20)	0·84
Other malignancies	37	18	2·11 (1·25 to 3·59)	0·006
Cardiac related	46	30	1·65 (1·05 to 2·58)	0·03
Other	44	36	1·30 (0·84 to 2·01)	0·24
Not known	3	2		

*See footnote to table I.

TABLE III—*Deaths related to cardiac problems in patients who had had breast cancer treated with or without postoperative radiotherapy at least five years previously by affected breast and type of radiation*

Type of radiation	Affected breast	Deaths in patients given radiotherapy: Observed	Deaths in patients given radiotherapy: Expected	Variance of observed minus expected	Relative risk* (95% confidence interval)
Supervoltage	Left	5	4·33	2·25	1·35 (0·36 to 4·98)
	Right	8	7·20	3·74	1·24 (0·45 to 3·41)
Orthovoltage or mixed	Left	20	12·99	7·15	2·67 (1·28 to 5·55)
	Right	13	12·04	5·74	1·18 (0·52 to 2·67)
All	Left	25	17·32	9·40	2·26 (1·19 to 4·29)
	Right	21	19·24	9·48	1·20 (0·64 to 2·28)
All	Either breast	46	35·79	18·88	1·65 (1·05 to 2·59)

*See footnote to table I.
Tests for interaction: between left and right overall χ^2 1·88; p=0·17; between left and right in orthovoltage χ^2 2·11; p=0·15.

TABLE IV—*Incidence of new malignancies throughout follow up in patients who had had breast cancer treated with or without postoperative radiotherapy*

Site	Patients given radiotherapy	Patients not given radiotherapy	Relative risk* (95% confidence intervals)	p Value (logrank comparison)
Opposite breast	73	58	1·33 (0·97 to 1·88)	0·10
Other	67	51	1·30 (0·98 to 2·02)	0·06

*See footnote to table I.

TABLE V—*Deaths from other malignancies after five years in patients who had had breast cancer treated with and without postoperative radiotherapy*

	Patients given radiotherapy	Patients not given radiotherapy
Site of cancer:		
Lung	4	4
Stomach	1	2
Jejunum	1	
Caecum	1	
Colon-rectum	6	1
Pancreas	4	2
Kidneys	1	
Ovary	6	2
Uterus	2	2
Cervix	3	2
Type of malignancy:		
Fibrosarcoma	1	
Melanoma	1	
Myeloma	1	1
Lymphoma	1	
Acute myeloblastic leukaemia		1
Chronic lymphocytic leukaemia	1	
Total	37	18

TABLE VI—*Mortality from other malignancies after five years in patients who had had breast cancer treated with or without postoperative radiotherapy by affected breast and type of radiation*

	Deaths in patients given radiotherapy		Variance of observed minus expected	Relative risk* (95% confidence interval)
	Observed	Expected		
Affected breast:				
Left	20	12·99	6·95	2·74 (1·30 to 5·77)
Right	17	13·78	6·74	1·61 (0·76 to 3·43)
Type of radiation:				
Supervoltage	9	6·22	3·24	2·35 (0·79 to 7·00)
Orthovoltage	28	20·58	10·49	2·03 (1·11 to 3·72)
All patients	37	26·72	13·73	2·20 (1·29 to 3·73)

*See footnote to table I.
Tests for interaction: between left and right χ^2 0·96; p=0·33; between orthovoltage and supervoltage χ^2 0·06; p=0·81.

Discussion

This analysis of the Cancer Research Campaign (King's/Cambridge) trial confirms that late mortality was significantly increased in patients treated with radiotherapy, as reported by Cuzick *et al*[4]; this was due to an excess of deaths from causes other than breast cancer, which was significant even when the analysis was made over the whole follow up. More detailed examination of the causes of the excess mortality showed that there was an increased risk of death from other cancers and cardiac disease.

These findings lend some support to the suggestion that radiotherapy may adversely affect the immune system.[3] In previous studies of the excess risk of cancer associated with radiotherapy the malignancies were predominantly in or close to the parts of the body that received the highest radiation. Thus, for example, patients irradiated for ankylosing spondylitis or an artificial menopause showed the excess of malignancies after long follow up predominantly in the heavily irradiated sites.[7-9] The fact that the excess malignancies in our study were not predominantly in or close to the parts of the body that would have received the highest dose of radiation, however, might indicate that the long term adverse systemic effect is mediated by irradiation of the lymphocytes recirculating in the thoracic duct. Our results are also at variance with those of Jones and Ribeiro, who did not find a significant excess of deaths from other cancers in the patients treated with radiotherapy in trials in Manchester in 1949-55.[10]

The other main contribution to the excess mortality in the group treated with radiotherapy was from deaths related to cardiac disease in patients who had had tumours of the left breast (table III). This would be consistent with radiation damaging the heart and its associated structures. Irradiation of the heart would arise mainly from the tangential pectoral fields used in the usual postoperative technique, and because of increased sideways scatter the dose would be higher with orthovoltage than with supervoltage radiation. The fact that the excess mortality seems to have been mainly in patients who had had tumours of the left breast treated by orthovoltage radiation supports this hypothesis. Caution is needed, however, in interpreting these analyses of subgroups and the hypotheses derived from the data: the observation concerning orthovoltage radiotherapy (which was not a randomised option) may be a statistical artefact. Nevertheless, the same tendency for more deaths due to cardiac disease in patients who had had tumours of the left breast was reported in the Manchester trials, in which orthovoltage was used, though a test for interaction between tumours of the left and right breasts was not significant.[10]

What are the implications of our results for the current use of adjuvant radiotherapy to treat early breast cancer? As always, the harmful effects of treatment have to be weighed against its benefits. Radiotherapy reduces the risk of local recurrence and the consequent distress this may cause a patient due to uncontrolled local disease at the time of death.[11] It may also be considered an essential part of any treatment aimed at conserving the breast, an option that many patients consider highly desirable. On the debit side are the immediate trauma and inconvenience caused by radiotherapy, and to these must now be added the increased risk of death after long follow up.

The risk of death, however, must be put in perspective. The number of excess deaths is small in relation to the total number of patients treated. In the total follow up period (to 1988) of the Cancer Research Campaign trial 56·9% (783/1376) of the irradiated group died, compared with 55·5% (791/1424) of the group allocated to a watch policy. Cuzick *et al* in their overview reported for all follow up a mortality of 52·6% (2071/3935) in those given radiotherapy compared with 51·8% (2077/4006) in those not given radiotherapy. The risk-benefit analysis, therefore, has to be assessed for each patient individually, but on present evidence we think that for many patients radiotherapy is still a desirable part of their initial treatment. In undertaking such treatment radiotherapists should try particularly to minimise the dose to the cardiac region.

Finally, those patients at the highest risk of local recurrence—for example, those with large, poorly differentiated primary cancers with affected axillary nodes—for whom postoperative radiotherapy is most justified are the ones likely to die of breast cancer within 10 years and therefore less likely to experience the delayed toxic effects of this treatment. In contrast, those women with small breast cancers, perhaps detected by mammography, have an excellent chance of living beyond 10 years and would then be at greatest hazard of developing the long term unwanted effects of radical radiotherapy. For this reason the need for postoperative radiotherapy in patients treated conservatively is being assessed with other forms of adjuvant treatment in randomised controlled trials organised by the Cancer Research Campaign group.

We thank all who took part in this trial; Mrs J Reeley for typing the manuscript; and the Cancer Research Campaign for the continued financial support.

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(Accepted 10 April 1989)