PERGAMON

European Journal of Cancer 38 (2002) 1107–1110

European Journal of Cancer

www.ejconline.com

Postoperative radiotherapy following mastectomy for high-risk breast cancer: a randomised trial

D.A.L. Morgan*, J. Berridge, R.W. Blamey

Department of Clinical Oncology, Nottingham City Hospital, Nottingham NG5 1PB, UK

Received 20 September 2001; received in revised form 13 November 2001; accepted 18 January 2002

Abstract

Grade III, node-positive breast cancer carries a high risk of loco-regional relapse after simple mastectomy. A randomised trial was conducted to assess whether this would be significantly reduced by postoperative radiotherapy. Between 1985 and 1991, 76 patients who had undergone a simple mastectomy and axillary sampling, and whose tumours had been found to be grade III and node-positive, were randomised to receive postoperative radiotherapy to the chest wall and axilla or no further loco-regional treatment. Radiotherapy was delivered with 8 MV X-rays to the axilla and supraclavicular fossa and with 8 MeV electrons to the chest wall, to a dose of 45 Gy in 15 fractions over 3 weeks. All patients have been followed-up until death, or for a minimum of 10 years. All loco-regional recurrences occurred within the first 4 years after mastectomy. There were 26 such events in the 40 patients randomised to the 'watch' policy (65%), as opposed to 9 out of 36 (25%) who received radiotherapy ($P<0.01$). Ten-year survival was 39% in the radiotherapy arm as opposed to 25% in the no radiotherapy arm. Recruitment to the trial was closed in 1991, when a preliminary safety analysis revealed the size of the effect of radiotherapy, and from then on all node-positive patients with grade III tumours have routinely been given this treatment. Further follow-up has confirmed this finding, as borne out by these 10-year results, which shows that radiotherapy has a significant impact on reducing loco-regional recurrence in patients at high risk after mastectomy. There is an apparent survival benefit although, because of the small numbers in this trial, this has not reached statistical significance.

Keywords: Breast neoplasms; Mastectomy; Neoplasm recurrence, local; Radiotherapy, adjuvant; Randomised controlled trials

1. Introduction

The use of postmastectomy radiotherapy had declined in the United Kingdom during the 1970s and early 1980s following the publication of the Cancer Research Campaign (CRC) and National Surgical Adjuvant Breast and Bowel Project (NSABP) trials [1,2]. In these, no significant survival advantage was seen for patients receiving radiotherapy after mastectomy, although there was a striking reduction in the incidence of locoregional recurrence in the irradiated patients.

In Nottingham, from 1973 to 1986, most patients with breast cancer were treated by simple mastectomy alone. Triple node biopsy was used for staging. Breast conserving surgery by wide local excision followed by radiotherapy steadily replaced mastectomy during the 1980s, but lymph node sampling remained.

In 1985, we showed that factors predictive of a high risk of local recurrence of breast cancer after mastectomy were the grade of tumour and histological evidence of nodal involvement [3]. The extent to which patients with these adverse factors might benefit, particularly with regard to loco-regional control, by receiving chest wall and axillary radiotherapy, needed testing and we embarked on a trial.

2. Patients and methods

Between September 1985 and February 1991, 76 patients were entered into the trial.

2.1. Surgery and pathology

Eligible patients were those who had newly diagnosed, operable (stage I or II) primary breast cancer, with no previous history of any other cancer, were aged 70 years or less, and had been treated by a simple

* Corresponding author. Tel.: +44-115-969-1169x47301; fax: +44-115-962-8027.

E-mail address: david.morgan@nottingham.ac.uk (D.A.L. Morgan).

0959-8049/02/$ - see front matter
PII: S0959-8049(02)00038-2

mastectomy and node sampling. The node sampling procedure consisted of a triple node biopsy—one low axillary, one apical and one internal mammary node. In all patients, the tumour was grade III [4], with at least one node histologically involved.

Patients entering the trial were randomly assigned to receive either postoperative radiotherapy or no further loco-regional treatment.

2.2. Radiotherapy technique

Patients given radiotherapy were treated on a linear accelerator, with an 8 MV X-ray field encompassing the axilla and ipsilateral supraclavicular fossa. To the lower edge of this field an 8 MeV electron field was matched, the other limits of which were chosen to encompass the area previously covered by breast tissue [5]. A dose of 45 Gy (prescribed at D_{max}) was given in 15 fractions to both fields.

Radiotherapy was given once a day, 5 days a week, unless holidays, machine breakdowns or service days intervened, in which case, for each day missed, an additional day of treatment was added at the end of the schedule. For the great majority of patients, the overall treatment time was slightly greater than 3 weeks (a small minority, who started on a Monday, and whose treatment had no interruptions, completed the treatment in less than 3 weeks).

2.3. Systemic treatment

At the time the trial started, adjuvant systemic treatment was not in routine use in our clinic, but a policy of using adjuvant tamoxifen for postmenopausal patients and 'classical' cyclophosphamide, methotrexate, 5-fluorouracil (CMF) (Bonadonna) [6] for premenopausal patients was introduced at the end of 1987 for patients at high risk, by definition including those in this trial. In total, 13 patients in each arm received adjuvant systemic therapy: 19 patients in the trial received adjuvant tamoxifen, 11 of whom were given radiotherapy, and 8 were not; 7 patients received CMF chemotherapy, 2 of whom had radiotherapy and 5 did not.

2.4. Follow-up and analysis

As long as clinically disease-free, patients were followed-up at 3-monthly intervals for 18 months after the completion of local treatment, then 6 monthly until 5 years, and yearly thereafter, indefinitely. In patients who developed recurrent disease, follow-up intervals were determined by clinical need.

The major endpoint of the study was loco-regional control, i.e. freedom from recurrence on the chest wall and adjacent (axillary and supraclavicular) lymph nodes. Survival, disease-free interval and incidence of uncontrolled loco-regional disease were secondary endpoints. Loco-regional recurrence was recorded and included in the analysis whether it occurred before, after or synchronously with metastatic disease.

A preliminary safety analysis was performed in 1991, which showed a highly significant reduction in loco-regional recurrences in the irradiated patients. Although the number that had been entered was small, entry to the trial was closed [7]; all patients with grade III, node-positive tumours since then have received postoperative radiotherapy to the axilla, supraclavicular fossa and chest wall after mastectomy.

3. Results

36 patients were assigned postoperative radiotherapy and 40 were controls (Fig. 1). All patients have been followed-up until death or for a minimum of 10 years (median just under 12 years), at the time of analysis. The main findings are summarised in Table 1 and are as follows.

3.1. Loco-regional recurrence

9 of 36 patients who received radiotherapy developed loco-regional recurrence, compared with 26 of 40 in the control arm. The recurrences were all within the first 4 years and 33 of the 35 patients who developed such recurrence have subsequently died of breast cancer. As none of the patients has been lost to follow-up, this gave absolute 10-year recurrence rates of 25 and 65% in the

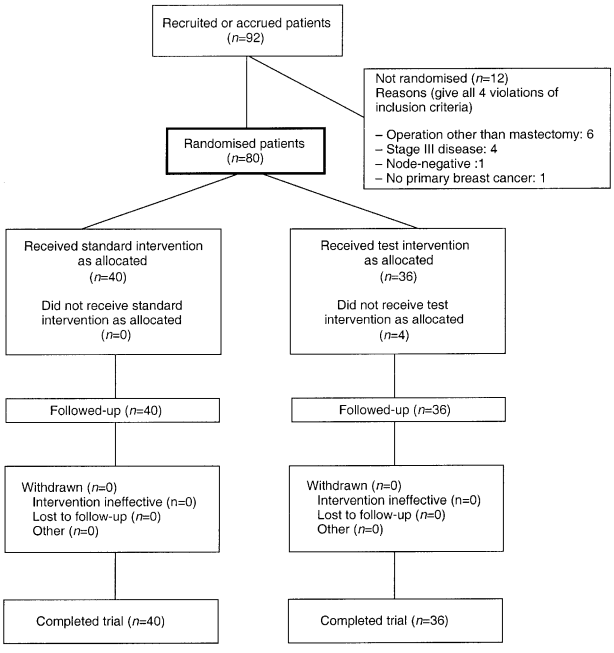

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Ref. [12]).

Table 1
Summary of main findings

	RT arm	No-RT arm	Statistical significance
Loco-regional recurrences in 10 years	9/36 (25%)	26/40 (65%)	$P<0.001$
Actuarial disease-free survival at 10 years	39%	15%	$P=0.043$
Survival at 10 years	14/36 (39%)	10/40 (25%)	NS
Uncontrolled loco-regional disease at death	6/36 (17%)	16/40 (40%)	$P=0.047$

RT, radiotherapy; NS, non-significant.

radiotherapy and control arms, respectively (Chi-square with Yates' correction 10.65, degrees of freedom (df) = 1, $P<0.001$).

As noted earlier, this marked difference became evident rapidly, and led us to close entry to the trial in 1991.

3.2. Uncontrolled loco-regional recurrence

Of the loco-regional recurrences that occurred, further treatment was able to achieve lasting control in only a minority in either arm. This resulted in 6 patients of the 36 (17%) in the treated arm having uncontrolled loco-regional disease at death, whereas this was seen in 16 of 40 (40%) in the untreated arm. This difference just achieves conventional statistical significance (Chi-square with Yates' correction = 3.95, df = 1, $P=0.047$).

3.3. Disease-free survival (DFS)

Two early deaths occurred in women in the control arm without known recurrence. In calculating disease-free survival, these two deaths have been included as 'censored' data, so the analysis of this group is actuarial. Kaplan–Meier analysis shows a 15% disease-free survival at 10 years in the control group, compared with 39% in the irradiated patients, which is statistically significant (Cox, $P=0.043$).

3.4. Overall survival

At 10 years, 22 of the 36 patients (61%) who had been given radiotherapy had died, compared with 30 of the 40 (75%) who did not receive radiotherapy (not statistically significant).

33 of the 35 patients who developed loco-regional recurrence died, whereas only 16 of the 40 patients without such recurrence died of breast cancer (Chi-square with Yates' correction = 22.59, df = 1, $P<0.0001$).

3.5. Radiation-associated morbidity

In this trial, we have seen little in the way of serious sequelae from the radiotherapy used. None of the deaths has been attributed to cardiac disease, and no clinically significant cardiac problems have been found in any of the long-term survivors, to date; none of the irradiated patients has developed significant pulmonary fibrosis, nor have there been any cases of radiation-induced brachial plexus damage. Clinically significant lymphoedema, in the absence of recurrence, has occurred in two of the irradiated patients, but in both this has been recorded as 'mild' or 'moderate'.

4. Discussion

That the selection criteria identified a group at high risk of local and/or regional recurrence, is confirmed by the 65% incidence of such recurrence in the control arm. The relative reduction of both local and regional recurrence achieved by radiotherapy in this study is comparable to that found in other trials that have addressed the same question and published in the most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 'meta-analysis' [8]. Having selected a particularly high-risk group for the trial, the impact of treatment in terms of absolute numbers spared local and regional recurrence is large. Several other trials have evaluated the effect of radiotherapy in high-risk patients [9,10]; they too have found a large absolute impact on local and regional recurrence. The significant effect on uncontrollable recurrence that we found demonstrates an important impact of radiotherapy upon the burden of illness; even so, uncontrolled recurrence is high even in the irradiated patients. This study cannot provide evidence on how this might be avoided.

The EBCTCG meta-analysis also showed a statistically significant reduction in breast cancer deaths for irradiated patients. Again, in our small study, there was a trend towards a survival benefit, falling short of statistical significance, but within the confidence intervals of the other studies. We suggest that this shows again that radiotherapy reduces the relative risk of recurrence and death, and that the level of absolute reduction in these high-risk patients is of real clinical relevance. Cardiovascular risk has been shown in previous studies to be linked to radiotherapy. The extent to which this occurs one must assume is dependent upon radiotherapy technique, as this will determine the amount of radiation received by the myocardium. In the patients we treated, an 8 MeV electron field covered the chest wall, so the dose to the underlying myocardium would

be minimal. This accords with the observation that so far no deaths have been attributed to heart disease, although in this respect, the follow-up is still short.

A few words might be added about the choice of dose and fractionation for the radiotherapy schedule used. This study opened in 1985, at which time 3-week schedules, as popularised by Paterson, were the usual treatment for most 'radical' schedules in Nottingham's Radiotherapy Centre. As the study was designed to ascertain whether radiotherapy would be useful for these patients, we elected to use a relatively high dose, which we had hitherto found acceptable in day-to-day clinical practice. The concept of 'Biological Effective Dose' (BED) was also not in widespread use at that time, although it is interesting to evaluate the schedule in hindsight using the formula [11]:

$$\mathrm{BED} = D\left[1 + \frac{\mathrm{d}}{(\alpha/\beta)}\right],$$

where D is the total dose, d the dose per fraction, and α and β are the constants used in the linear-quadratic formula that together indicate the fractionation sensitivity of a given tissue.

Even today, considerable uncertainty exists as to what a representative value for α/β should be for breast cancer. If we take a reasonably-guessed figure of 10 Gy, we find from the above formula that 45 Gy in 15 fractions gives a BED of 58.5, which is not greatly different from the BED of 60 obtained for the more widely-used (and now the 'standard' in our department) schedule of 50 Gy in 25 fractions. By contrast, if we consider the effect on adjacent normal tissue, for which there is more reliable data on α/β ratios, with a value of around 3 being widely accepted, our schedule gives a BED of 90 compared with 83.3 for 50 Gy/25 fractions.

These calculations would lead us to expect that the schedule would be fairly close to the 'conventional' 50 Gy in 25 fractions in terms of tumour control, but perhaps a little more damaging to normal tissue. The first of these predictions is borne out by our results; the latter will be the subject of a separate report.

In summary, this study is in line with the general understanding that radiotherapy reduces the risk of local and regional recurrence. Since a group at a high risk of such recurrence was selected for the trial, the absolute effect was large. Overall disease-free survival was improved by the use of radiotherapy; the reduction in breast cancer deaths in the radiotherapy arm is of the same degree as that demonstrated in larger trials, even though in this small trial it does not reach statistical significance. Nearly all patients suffering loco-regional recurrence died from breast cancer, suggesting that prevention of this event led to an improvement in survival.

References

1. Cancer Research Campaign Working Party. Cancer Research Campaign (King's/Cambridge) trial for early breast cancer. *Lancet* 1980, **ii**, 55–60.
2. Fisher B, Montague E, Redmond C, *et al*. Comparison of radical mastectomy with alternative treatments for primary breast cancer: a first report of results from a prospective randomized clinical trial. *Cancer* 1977, **39**, 2827–2839.
3. Williams MR, Hinton CP, Todd JH, Morgan DAL, Elston CW, Blamey RW. The prediction of local and regional recurrence after simple mastectomy for operable breast cancer. *Br J Surg* 1985, **72**, 721–723.
4. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991, **19**, 403–410.
5. Magee B, Ribeiro GG, Williams P, Swindell R. Use of an electron beam for post-mastectomy radiotherapy: 5-year follow-up of 500 cases. *Clin Radiol (Royal Coll Radiol)* 1991, **3**, 310–314.
6. Bonadonna G, Brusamolino E, Valagussa P, *et al*. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976, **294**, 405–410.
7. Morgan DAL, Galea NH, Berridge J, Blamey RW, Elston CW, Ellis IO. Post-mastectomy radiotherapy in patients at high risk of locoregional recurrence: a randomised trial. *Breast* 1992, **1**, 165 (abstr).
8. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000, **355**, 1757–1770.
9. Overgaard M, Hansen PS, Overgaard J, *et al*. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who received adjuvant chemotherapy. *N Engl J Med* 1997, **337**, 949–955.
10. Ragaz J, Jackson SM, Le N, *et al*. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997, **337**, 956–962.
11. Fowler JF. The linear quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989, **62**, 679–694.
12. Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639.