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Iridium Implant Treatment without External Radiotherapy for Operable Breast Cancer: a Pilot Study

I. S. Fentiman, C. Poole, D. Tong, P. J. Winter, H. M. O. Mayles, P. Turner, M. A. Chaudary and R. D. Rubens

A pilot study has been conducted to examine a new approach to the treatment of operable breast carcinoma. 27 patients with tumours measuring up to 4 cm in diameter have been treated by tumourectomy, axillary clearance and high dose iridium-192 implant (55 Gy) without any external beam radiotherapy. This enabled the entire local primary treatment of the breast carcinoma to be given in five days. The technique was compatible with adjuvant chemotherapy for those with involved axillary nodes. Local complications have been few and locoregional control has to date been satisfactory. With a relatively short median follow-up of 27 months, cosmesis was objectively rated as good or excellent in over 80% of cases and subjectively rated good/excellent in 96%. High dose brachytherapy now requires testing in a prospective clinical trial to determine whether it is as effective as standard breast conservation techniques for management of early breast cancer.
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INTRODUCTION

THERE IS little doubt that for selected patients breast conserving therapy is a safe alternative to mastectomy. Apart from several uncontrolled historical studies there are now data from prospective randomised trials which have shown similar relapse free survival and overall survival rates in patients with tumours up to 4 cm in diameter treated by either mastectomy or breast conservation [1–3]. However, both the Guy's Hospital wide excision trial and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 have shown that either suboptimal or no radiotherapy will lead to an unacceptably high rate of local relapse [2, 4]. In the Guy's wide excision trial this local failure rate was followed by the earlier appearance of distant metastases and reduced survival in patients treated by conservative means.

The need for effective radiotherapy can create problems. In Britain radiotherapy centres serve large catchment areas so that some patients have to travel long distances. Megavoltage equipment is expensive and resources are finite. Many district hospitals do not have easy access to a radiotherapy unit. External beam radiotherapy is given over a 4 to 6 week period which can be very tiring for patients, particularly the elderly, who are therefore not usually recommended to receive this form of therapy. Both interstitial and external beam radiotherapy can lead to local complications such as skin oedema, breast fibrosis and telangiectases which can adversely affect cosmesis. These changes may occur more frequently if the number of fractions is reduced, unless the time/dose relationships are carefully corrected. Older forms of orthovoltage radiotherapy may lead to an increase in late deaths from other causes as a result of myocardial or pulmonary fibrosis [5]. Use of postoperative radiotherapy also influences the ability to deliver adjuvant chemotherapy, with a significant reduction in dosage among those so treated [6].

The rationale for external beam radiotherapy is to treat multifocal disease which has not been encompassed by either surgery or interstitial treatment. However, in the NSABP trial, in which patients had histologically confirmed complete excision of primary tumour, almost all the relapses in the non-irradiated group occurred in the original quadrant. This indicates that the major problem of early local relapse relates to the primary tumour rather than multifocal disease. Thus whole breast irradiation might not be necessary for patients with unifocal breast cancer. Because other quadrants would not be irradiated there might be an increase in incidence of new primary tumours, but the magnitude of this effect is not known. Experience with contralateral breast cancers after mastectomy suggests an annual 0.8% risk of a new primary and this figure might be doubled after breast conservation [7].

At Guy's Hospital Breast Unit, the standard breast conserving treatment comprises tumourectomy, axillary clearance, low dose rate iridium implant (20 Gy) followed by external beam megavoltage radiotherapy to the breast (46 Gy in 23 fractions over 31 days). Since there has been considerable experience in this unit with implant therapy, increasing the interstitial irradiation from 20–55 Gy and omitting the external beam component was considered to be worth testing. A pilot study in 27 patients has been conducted.

PATIENTS AND METHODS

Eligible patients were aged less than 70 years and had a unifocal primary carcinoma which measured clinically no greater than 4 cm in diameter. All had routine staging investigations including full blood count, biochemical screen, chest radiograph, bone scan and bilateral mammography. All patients were judged suitable psychologically for 5-day interstitial treatment.

Surgical technique

Under a general anaesthetic an axillary clearance was performed through an excision along the lateral border of pectoralis major. The pectoralis minor muscle was excised as was the axillary tail and the complete axillary fat and node contents. After completion of the procedure a vacuum drain was inserted and the wound closed. In the majority of patients the histological diagnosis had been made by needle biopsy. If an excision biopsy of a primary tumour had not been performed previously, the tumour was then locally excised through a skin crease incision. Only gross tumour excision was performed and no attempt was made to carry out wide excision. A vacuum drain was inserted and the wound closed in layers. For most patients the primary surgical treatment of tumourectomy and axillary clearance was performed under one general anaesthetic.

Rigid implant technique

In this pilot study, suitability for a rigid implant was determined by the presence of sufficient breast tissue in the quadrant, after surgery, so that an implant was technically possible.

Hollow stainless steel needles were then implanted into the tumour bed in a multiplane triangular array according to the Paris system. A margin of 2 cm was allowed with the deep plane close to or upon the pectoralis major muscle. The patient was then transferred to a side room equipped with lead bed shields.

On the following day the implanted lengths were measured and the necessary lengths of iridium wire calculated. Individual dose calculations were not performed in most cases but tables were used to calculate the activity of the iridium wire and the treatment time needed to give a dose of 55 Gy in 5.5 days to 85% of the basal dose rate as defined by the Paris system. Tables for two-plane implants were drawn up using data by Casebow [8] and those for three-plane implants were drawn up by doing calculations with an ADAC radiation therapy planning system and in house software [9]. The tables assumed that wires were symmetrical about the midplane and if measurements showed that the asymmetry of a wire exceeded 1 cm then an individual calculation was performed.

The iridium wires were then prepared and loaded into the hollow needles. During treatment patients were confined to the side room, apart from visits to the bathroom, and nursing procedures were kept to a minimum. At the end of the treatment time the active sources, needles and templates were removed.

Follow-up

After discharge from hospital patients were seen at 1 month and subsequently at 3 montly intervals. Routine follow-up investigations included bilateral mammography and bone scan. Premenopausal patients with axillary lymph node involvement were given six cycles of chemotherapy cyclophosphamide, methotrexate, 5-fluorouracil (CMF) and postmenopausal patients were given adjuvant tamoxifen if they had axillary nodal involvement.

Cosmetic evaluation

Cosmetic outcome has been assessed by two different groups; firstly, by a radiotherapist (PJW) and a surgeon (ISF). The second evaluation was performed by a panel of 5, none of whom were directly concerned with the running of the pilot study. The panel comprised a male medical oncologist, a female radiographer and 3 female nurses, 2 of whom worked on the ward and 1 of whom was a nurse counsellor. The ratings were performed on photographs taken 23–25 months posttreatment. Ratings were categorised as follows: excellent = no difference seen between treated and non-treated breast; good = slight skin pigmentation or puckering; fair = obvious tissue deficit, skin pigmentation or oedema; and poor = major distortion or loss of breast tissue.

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Table 1. Complications of high dose iridium implant

Wound infection	4
Erythema/pigmentation	7
Skin necrosis from template	1
Skin necrosis from sources	2
Frozen shoulder	2
Claustrophobia	1

No. of patients.

Table 2. Outcome of treatment (median follow-up 26 months)

Alive without relapse	23 (85%)
Locoregional relapse	2 (7.5%)
Locoregional and distant relapse	2 (7.5%)

RESULTS

27 patients were included within the study with a mean age of 51 years. 9 were premenopausal, 4 had had a hysterectomy, and 14 were postmenopausal. The mean tumour diameter measured clinically was 3 cm. 20 patients had infiltrating ductal and 5 had infiltrating lobular carcinomas. Of the 2 with other types, 1 had a medullary carcinoma and 1 had an adenoid cystic carcinoma. Axillary nodes were histologically positive in 12 cases (44%). For 17 patients a two-plane implant was used with a median of 9 wires. In 10 patients a three-plane implant was used with a median of 12 wires. Complications of treatment are shown in Table 1. Wound infection occurred in 4 patients. There was temporary erythema and pigmentation in 7 cases. 1 patient had localised skin necrosis as a result of pressure from the template. This occurred in an early case with rapid healing and subsequently this complication was not observed. However, 2 other patients had radiation skin changes at the needle points of the superficial sources because the iridium wires had been placed too close to the skin. These healed slowly leaving a small amount of skin scarring.

Of the 27 patients, 23 (85%) are alive without relapse after a median follow-up of 27 months (range 24–32, mean 27.8) as shown in Table 2. 4 patients have relapsed, 2 with recurrence in the breast, and 2 with a combination of local relapse and distant metastases. Up to the time of relapse the cosmetic outcome had been good in all 4 cases. The mean tumour diameter of those that relapsed was 2.95 cm. 1 patient had a ductal grade II tumour and 2 had grade III tumours and 1 a lobular carcinoma. 3 out of 4 of the patients who relapsed had axillary nodal involvement. All 3 received ajuvant therapy, the premenopausal patients being given CMF and the postmenopausal patient receiving tamoxifen.

The assessments of cosmetic outcome by the panel of observers are given in Table 3. These comprised 24 patients who had not relapsed. No cases were rated as having poor cosmesis. It is of interest that the two ward nurses were more stringent in terms of assessment than the other observers. The median number of cases rated as fair was 4 (17%), good 7 (29%), and excellent 13 (54%). When the patients themselves were asked to assess their own cosmetic outcome this was rated as good/excellent by 22/23 (96%).

Table 3. Assessment of cosmetic outcome

	Poor	Fair	Good	Excellent
Radiotherapist	0	4	7	13
Surgeon	0	4	7	13
Medical oncologist	0	3	7	14
Radiographer	0	4	8	12
Nurse	0	4	7	13
Nurse	0	7	14	5
Nurse	0	6	12	4
Median	0	4	7	13

DISCUSSION

This study has shown that it is possible to replace external radiotherapy by interstitial irradiation as part of the primary treatment of early breast cancer without untoward early side effects. No major sequelae of high dose irradiation have yet been observed although further follow-up will be necessary to exclude later development of telangiectasia and breast fibrosis. Omission of external radiotherapy has meant that so far none of the patients has developed long-term skin oedema.

The rate of relapse, 4/27 (15%) after 27 months of follow-up is similar to that reported after other methods of breast conservation but clearly it will be necessary to study larger numbers of patients in order to be more confident about the efficacy of the treatment. Recently reported results of a trial from the Christie Hospital, Manchester, lend support to the concept of limited irradiation [10]. Patients with breast cancers measuring no more than 4 cm and without clinical evidence of axillary nodal metastases were treated by tumourectomy and then randomised to receive either whole breast irradiation (42.5 Gy) or limited field irradiation to the tumour bed. After a median follow-up of 37 months there were 708 evaluable patients. Breast relapse occurred in 30 (8%) of those receiving limited irradiation compared with 13 (4%) of those given whole breast irradiation. There were no significant differences between the two groups in terms of distant metastases or overall survival.

These preliminary data suggest that the technique appears to achieve satisfactory local control, with a good cosmetic outcome within the first three years of treatment the major determinant of cosmetic results appeared to be the extent of surgery. Thus it was tissue deficit that was largely responsible for patients being graded as having fair rather than good or excellent cosmetic results.

A high dose implant in a hospital side room may not be possible because it requires radiation protection for other patients and staff. The need for 5 days of continuous treatment with relative isolation causes problems for the patient which could be avoided by intermittent treatment.

At present the technique is being modified to use caesium-137 instead of iridium-192 sources, and to give a fractionated treatment over a 4-day period using a medium dose rate "Microselectron" remote control afterloading system installed in a fully shielded treatment room. The biological effects of changing from continuous low dose rate to intermittent medium dose rate have yet to be determined. Once this has been carried out it may form the foundations for a trial to compare standard low dose rate irridium-192 implant (20 Gy) and external beam radiotherapy against intermittent medium dose rate interstitial radiation alone, using caesium-137 to give 45 Gy, fractionated over 4 days, in patients who will have had tumourectomy and axillary clearance.

If the treatments are found to have similar efficacy this could

lead to a form of breast conservation which will not only ease pressure on external beam megavoltage treatment facilities but also achieve good radiation protection of staff. It should prove more acceptable to the patient as all her radiotherapy will be given during a brief hospital stay. These benefits, together with the possibility of better cosmetic outcome, and less interference with subsequent scheduling of chemotherapy make this a treatment worth testing.

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Reasons for Non-entry of Patients with DCIS of the Breast into a Randomised Trial (EORTC 10853)

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In EORTC trial 10853, patients with histologically confirmed surgical clearance of ductal carcinoma *in situ* (DCIS) are being randomised to observation alone or to receive external radiation to the breast (50 Gy). So far, 190 patients have been entered from 27 centres. An analysis has been conducted of patients with DCIS presenting to 6 of the participating hospitals. Within these centres there was a total of 216 patients with biopsy confirmed DCIS, without invasion, between 1985 and 1989. However only 77 (36%) were entered into the trial. The major reason for non-entry was that DCIS was too extensive (76/139, 55%), so that *in situ* disease extended to the margins of excision. Other reasons for exclusion included prior breast cancer (18%), delay in histological diagnosis (6%) and a lump measuring more than 3 cm in diameter (4%). Only 6 patients (4%) refused to take part in the trial. Thus the eventual results of the trial may be applicable only to a minority of patients with DCIS.
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BACKGROUND

THE PARADOX of randomised clinical trials of cancer treatment is that non-specific eligibility criteria can give uninterpretable results because of heterogeneity, whereas stringent requirements may make the conclusions of the study unapplicable to the majority of patients with that particular tumour type. This may be amplified as a result of multicentre trials studying less common problems, of which an example is ductal carcinoma *in situ* (DCIS) of the breast.

Of symptomatic patients who are found to have DCIS, without evidence of invasion, up to 40% will go on to develop infiltration in the ipsilateral breast after biopsy alone [1, 2]. Among screen detected cases with lesions measuring less than 2.5 cm treated by wide excision, the progression rate to invasion has been reported to be as low as 5%. The aim of EORTC trial 10853 was to determine whether the rate of progression could be inhibited by radiotherapy [4]. As part of this study ineligible cases were also registered and the reasons for non-entry have been examined.

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