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## Original Paper

# Inadequacy of Iridium Implant as Sole Radiation Treatment for Operable Breast Cancer

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**In order to avoid a prolonged course of external irradiation as part of breast conservation therapy, 27 patients received an iridium implant to the primary tumour bed as sole radiation treatment. Surgery was standardised comprising tumourectomy and axillary clearance. Using a rigid implant afterloading with iridium$^{192}$ wires, 55 Gy was delivered on a continuous basis over 5 days. After 6 years median follow-up, relapse of cancer within the treated breast has occurred in 10 of the 27 patients (37%). Compared with historical controls treated by similar surgery and iridium$^{192}$ implant (20 Gy) with external radiotherapy (46 Gy), there was a significantly increased breast relapse rate in those treated by iridium implant alone. However, the incidence of distant metastases and overall survival was similar. Thus, a continuous iridium$^{192}$ implant delivering 55 Gy in 5 days is not an effective means of achieving local control in patients with operable breast cancer.** 

**Key words: breast cancer, brachytherapy, conservation, iridium implant**
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## INTRODUCTION

THERE IS general agreement that selected patients with operable breast cancer can be treated safely by breast conservation therapy (BCT). Three large trials have compared radical or modified radical mastectomy with BCT and shown similar relapse-free and overall survival for patients treated by either treatment [1–3]. Although the extent of surgery to the primary tumour varied between tumourectomy (with clear margins) through to quadrantectomy, in all three trials patients had an axillary clearance and a course of external therapy (46–50 Gy). The exception to this was NSABP B-06, in which half the patients treated by breast conservation, with histologically confirmed tumour-free excision margins, received no post-operative radiotherapy [3]. After a median follow-up of 8 years, the breast relapse rate in the non-irradiated group was 40% as compared with 11% among those who received breast irradiation.

A recent trial compared radiation versus no radiation in patients treated by tumourectomy and axillary clearance in whom the axillary nodes were negative [4]. After a median follow-up of 43 months, breast relapse occurred in 6% of the irradiated group but in 26% of those who received no radiotherapy. Although the overall survival of both groups was similar, there was a trend towards an increase in distant metastases in the non-irradiated group.

To simplify irradiation, it was decided at Guy's Hospital, London, U.K., that a prospective study would evaluate the role of a synoperative iridium$^{192}$ implant to the excised tumour bed as the sole method of radiation delivery. It was hoped that such an approach might simplify treatment leading to a wider availability of breast conservation therapy, particularly for older patients, and additionally might improve cosmetic outcome and allow more prompt delivery of adjuvant chemotherapy for appropriate patients. Preliminary results were encouraging [5], but this report gives the results after longer follow-up.

## PATIENTS AND METHODS

The characteristics of the treated patients were as previously reported [5]. All were aged less than 70 years and had single operable breast tumours. Although it was planned to treat patients with primary cancers measuring no more than 4 cm diameter (clinically), there were three with larger tumours. Routine staging investigations carried out prior to definitive treatment included full blood count, biochemical screen, chest

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X-ray, radio-isotopic bone scan and bilateral mammography. All surgical and brachytherapy procedures were performed in the same hospital by the same operators. No systematic quality assurance procedure was in use at this time, but this was a commonly used technique, with over 600 brachytherapy procedures having been carried out on patients with breast cancer at Guy's Hospital.

*Surgery*

The technique was as previously described and included tumourectomy, with no attempt to achieve wide excision either grossly or microscopically. An axillary clearance was performed in all cases.

*Radiotherapy*

Under the same general anaesthetic during which axillary clearance was performed, a rigid implant was inserted into the breast tissue at the excision site using a multiplane triangular array. A 2 cm margin of normal breast was aimed for, with the deep plane close to or upon the pectoralis minor muscle. Manual afterloading with iridium$^{192}$ wires was carried out the following day and the implant remained in place for 5–6 days to deliver 55 Gy to 85% of the basal dose as defined by the Paris System.

*Follow-up*

Patients were seen every 3 months for 3 years, then 6 monthly for 2 years, and thereafter annually unless relapse occurred. Locoregional recurrence was confirmed histologically and salvage mastectomy was performed when appropriate.

*Statistical tests*

Students *t*-test, chi-square and Fisher's exact test were used as appropriate. Multivariate analysis of local relapse was performed with Cox's proportional hazards model.

## RESULTS

There were 27 patients in the study and, after a median follow-up of 6 years, breast relapse occurred in 10 (37%). In all except 1 case the site of relapse was within the irradiated field. The clinical features of those cases with and without relapse are shown in Table 1. The relapsed group was slightly younger than the non-relapsers (48.4 versus 53.3 years, $t = 1.56$, $P = 0.13$). Similar proportions of both groups were premenopausal (40 versus 41%). The maximum diameter of the primary tumour was slightly greater in the relapsed group (3.5 versus 3.0 cm, $t = 0.91$, $P = 0.37$).

Pathological features of the two groups of patients are given in Table 2. Of the patients who relapsed, axillary nodal metastases were confirmed histologically in 70% but in only 29% of the non-relapsed group (Fisher's exact test, $P = 0.057$). In the relapsed group, 90% of patients had invasive ductal carcinoma compared with 71% of those in the non-relapsed group. There were more grade III ductal carcinomas and fewer grade II lesions in the relapsed group, but this did not achieve statistical significance. There were no significant differences in terms of margin involvement of the biopsy nor in relation to the presence of extensive *in situ* carcinoma. Figure 1 gives the time to breast relapse in those with involved and non-involved biopsy margins and shows no significant difference ($\chi^2 = 0.25$, $P = 0.62$).

Lymphatic permeation was present in two biopsies from those patients who relapsed, but in only one of those without relapse (Fisher's exact test, $P = 0.53$). Necrosis was present with significantly increased frequency among those who relapsed (50 versus 0%; Fisher's exact text, $P = 0.004$).

Figure 2 gives the comparative relapse-free survival of patients treated by iridium$^{192}$ implant alone compared with a historical control group of women treated by our standard breast conservation technique including iridium$^{192}$ implant boost and external radiotherapy (C10 trial). There have been significantly more relapses in the iridium alone group ($\chi^2 = 9.1$, $P = 0.0026$). Survival, shown in Figure 3, was not significantly different in the standard conservation group to the iridium only group ($\chi^2 = 1.08$, $P = 0.34$).

*Table 1. Clinical features of patients with or without breast relapse*

| | Breast relapse | No relapse |
|---|---|---|
| Number | 10 | 17 |
| Mean age (years) | 48.4 | 53.2* |
| Premenopausal | 4 (40%) | 7 (41%)† |
| Tumour size (cm) | 3.5 | 3.0‡ |

* *t*-test = 1.56, $P = 0.13$. † Fisher's exact test = 1.00. ‡ *t*-test = 0.91, $P = 0.37$.

*Table 2. Pathological features of patients who developed breast relapse and cases who remained relapse-free*

| | Breast relapse | No relapse |
|---|---|---|
| Number | 10 | 17 |
| Axillary nodes | | |
| Positive | 7 (70%) | 5 (29%) |
| Negative | 3 (30%) | 12 (71%) |
| Tumour type | | |
| Ductal | 9 (90%) | 12 (71%) |
| Other | 1 (10%) | 5 (29%) |
| Ductal grade | | |
| I | 1 (11%) | 2 (17%) |
| II | 4 (44%) | 7 (58%) |
| III | 4 (44%) | 3 (25%) |
| Margins | | |
| Involved | 6 (60%) | 9 (53%) |
| Clear | 3 (30%) | 7 (41%) |
| Not known | 1 (10%) | 1 (6%) |
| Lymphatic permeation | | |
| Yes | 2 (20%) | 1 (6%) |
| No | 6 (60%) | 14 (82%) |
| Unknown | 2 (20%) | 2 (12%) |
| Tumour necrosis | | |
| Yes | 5 (50%) | 0 (0%) |
| No | 5 (50%) | 16 (94%) |
| Unknown | 0 (0%) | 1 (6%) |
| Extensive *in situ* | | |
| Yes | 5 (50%) | 6 (35%) |
| No | 0 (0%) | 5 (29%) |
| Unknown | 5 (50%) | 6 (35%) |

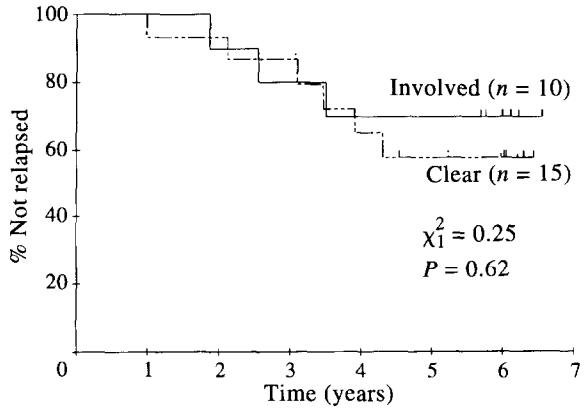


**Figure 1. Comparison of time to local relapse in patients treated by iridium implant alone with pathological involvement and non-involvement of tumour margins. Note that the margin involvement was not known for 2 patients (1 relapse, 1 no relapse).**

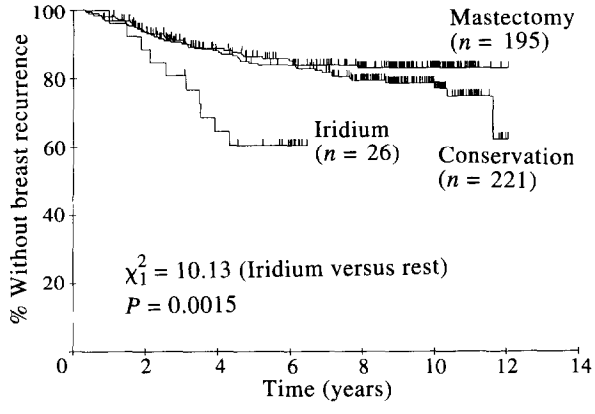


**Figure 2. Comparison of breast relapses in patients treated by iridium implant alone compared with women treated by either mastectomy or breast conservation in EORTC 10801.**

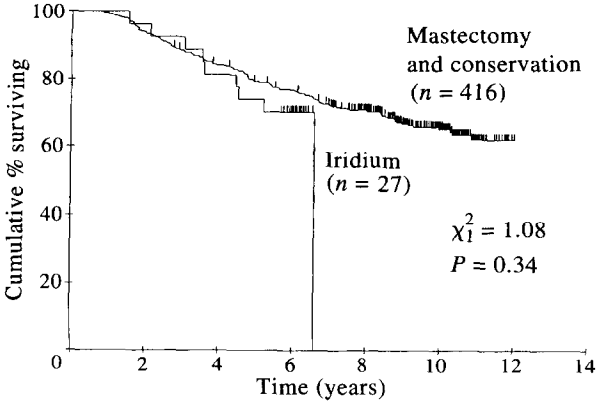


**Figure 3. Comparison of survival of patients treated by iridium implant alone compared with women treated in EORTC 10801.**

*Table 3. Significant variables in multivariate analysis*

| Variable | $\chi^2$ | *P* value |
|---|---|---|
| Number of positive axillary nodes* | 28.59 | <0.0001 |
| Menopausal status | 16.19 | <0.0001 |
| Iridium implant alone | 5.66 | 0.017 |
| Tumour type | 5.16 | 0.023 |

* 0 versus 1–9 versus ⩾ 10.

To examine possible factors responsible for the high relapse rate in the iridium only group, a multivariate analysis was conducted comparing the two study groups with those who had been treated by modified radical mastectomy, or tumourectomy, axillary clearance, iridium implant and whole breast irradiation as the Guy's Hospital component of EORTC 10801 [3].

Variables which emerged as significant in the model are shown in Table 3 and these comprised axillary nodal status, menopausal status, method of treatment and tumour type. Of these, axillary node positivity proved to be the major factor determining risk of breast relapse, followed by perimenopausal nodal status, iridium only, and least important, tumour type.

Normal tissue side-effects were monitored. One patient developed a local skin reaction with subsequent telangiectasia at the site of a superficially placed iridium wire. None of the patients had breast fibrosis, nor was peau d'orange observed.

## DISCUSSION

The results of this study are both interesting and perplexing. The high rate of brease relapse which occurred among those treated by iridium$^{192}$ who had received 55 Gy in 5 days was similar to that reported in studies where no postoperative radiotherapy had been given [2, 4]. The dose of 55 Gy was selected because of worries that higher doses (60–70 Gy) would lead to late radiation damage with a severe cosmetic penalty. No serious side-effects in normal tissue were seen in the patients in this study. No previous study has compared interstitial treatment with interstitial and external irradiation, but Ribeiro and associates compared quadrant irradiation with whole breast irradiation using external radiotherapy [6]. At 6 years, the actuarial breast recurrence rate was 38% in the limited irradiation group and 16% in those who had whole breast irradiation [7].

It is possible that the high recurrence rate in our study was due to an over-representation of young patients with unsuitable tumours, namely lymphatic permeation, necrosis and axillary nodal involvement. For whatever reason, a continuous iridium$^{192}$ implant delivering 55 Gy in 5 days did not achieve the good tumour control which was observed in patients treated by iridium$^{192}$ 20 Gy and external beam 46 Gy in EORTC Trial 10801. Similar encouraging results of combined radiotherapy have also been reported in a series of 51 patients deemed to be at high risk of local relapse who were given external irradiation and an iridium boost of 25 Gy who had an actual breast recurrence-free survival of 88% after 8 years (data from G.G. Ribeiro). This therefore raises the question of a role of an interstitial boost in breast conservation treatment, which is currently being addressed in EORTC Trial 10882. Implant of an excised breast tumour site is at best a clinical estimate of the tissue at risk. Others have shown the difficulty of defining accurately the boost target [8].

If localised irradiation is to be used in the management of early breast cancer, very careful selection of patients will be required if good tumour control is to be obtained. Until such evidence has emerged, whole breast irradiation with fractionated external beam radiotherapy is likely to remain the mainstay of breast conservation therapy.


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