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ORIGINAL ARTICLE

PROSPECTIVE TRIAL OF INTRAOPERATIVE RADIATION TREATMENT FOR BREAST CANCER

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Background: A new device, Intrabeam, is available for intraoperative radiotherapy. We have prospectively examined its feasibility and tolerability in delivering adjuvant breast cancer treatment.

Methods: Thirty-five patients undergoing breast-conserving surgery received targeted tumour bed irradiation consisting of 5 Gy (at 10 mm) in a single fraction. This single intraoperative treatment was used to replace the external beam radiotherapy 'boost' that would usually be given in 10 daily treatments following 5 weeks of whole breast irradiation. Patients later completed external beam radiotherapy as usual. Potential toxicities were prospectively assessed fortnightly prior to external beam radiotherapy, weekly during it, and 3 monthly subsequently.

Results: The intraoperative radiotherapy was able to be delivered without difficulty, either at time of initial cancer surgery or as a second procedure. When performed as a separate procedure the median operating time was 56 min. The treatment was well tolerated, with only one patient experiencing any grade 3 or 4 toxicities – this was acute grade three itch. There was an overall early breast infection rate of 17%. No unexpected toxicities were seen.

Conclusions: This simple and well-tolerated treatment delivers a useful radiation dose to the area of highest risk of tumour recurrence. The early infection rate is similar to that reported in the literature, for treatments without intraoperative radiotherapy. Whether such a treatment may adequately replace the entire adjuvant radiation therapy treatment for low-risk patients is now being studied in a randomized trial.

Key words: breast cancer, intraoperative procedures, radiotherapy.

Abbreviations: EBRT, external beam radiation treatment; IORT, intraoperative radiation treatment; RT, radiation therapy; RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

INTRODUCTION

Breast conserving surgery with postoperative radiotherapy has been shown to be as effective as mastectomy in terms of overall survival, but with improved cosmesis.[1–5] Adjuvant radiation treatment is usually given 5 days each week, over a 5–7 week period. This may be a significant inconvenience to women, particularly those who reside some distance from a treatment centre, have difficulties with transport, or a full-time career. In addition, adjuvant breast irradiation makes up to 30% of radiation oncology department workloads, at a time when radiation staff and machine time are scarce in both Australia and New Zealand. Unfortunately, trials attempting to omit radiotherapy in selected women after breast conserving surgery have shown unsatisfactory local recurrence rates.[1,6–10] Even women with small mammographically detected breast cancers should be offered adjuvant irradiation.

An X-ray source small enough to be placed inside a tumour bed to deliver its treatment has been developed (Intrabeam, initially from Photoelectron Corporation, now produced by Carl Zeiss). In the USA, the device has received approval from the Food and Drug Administration for use at any body site. It has a number of potential applications, and although it has mainly been studied as a neuro-oncological treatment, it seems ideally suited for therapy of breast cancer.[11–17] A series of applicators of varying diameters are available, which allows the correct size to be chosen for any surgical cavity after breast conservation surgery. Low energy 50 kV X-rays are produced that have limited penetration, and so deliver a dose that is relatively high at the surface of the applicator but which falls off rapidly with distance. We prescribe a 5 Gy dose at 10 mm depth from the applicator surface, given in a single treatment. The procedure lengthens theatre times but otherwise there are few logistical issues (e.g. no purpose built room shielding is required). The pilot experience with Intrabeam for breast cancer in the UK, has been reported recently.[18–20]

Such intraoperative radiation treatment (IORT) may be effective as the sole adjuvant radiotherapy for selected low risk patients. Prior to testing this in a randomized trial, we performed a prospective feasibility trial using the IORT as a method replacing the 1–2 week tumour bed 'boost' component of a standard external beam radiation treatment (EBRT) course. This allowed us to test whether this IORT treatment was possible in routine practice in Australia, and whether acute toxicity was acceptable when EBRT was also used – as might be required if final pathology results were less favourable than expected.

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METHODS

Patients and surgical treatment

Between July 2001 and October 2003, patients planned to undergo breast-conserving surgery for breast cancer were offered participation in this phase II prospective trial. Here the radiation therapy boost that would have been delivered over a 2-week period was given instead by a single dose of IORT delivered by Intrabeam. Initially the study was open to all patients, but the eligibility criteria were later changed to allow only low risk patients who would meet the eligibility criteria for an upcoming randomized trial (this is described in more detail in the discussion). Institutional ethics approval was granted, and written informed consent obtained from each patient. Patients underwent whatever breast conservation and axillary surgery they would otherwise have received, in addition to the intrabeam treatment. The IORT could be performed either at time of other surgery or as separate procedure at a later date. The operating times and total duration of the procedures, were prospectively recorded.

Intraoperative radiation treatment

The Intrabeam device is fitted to a mobile stand, on an arm that is movable and in perfect balance when a button is depressed but otherwise stable. The device is calibrated prior to each treatment, and a range of sizes of sterilized spherical applicators is available. Once adequate wide local excision has been performed and haemostasis achieved, the appropriate size applicator is selected – that is, the size that fits comfortably without producing tension in the surrounding tissue. The device and its stand are wrapped in a sterile clear plastic cover, and the applicator attached. The applicator, now attached to the device, is positioned in the surgical cavity and a purse string suture is used to conform the target breast tissue to the surface of the applicator. The skin is gently everted and two stay sutures are used to prevent direct contact with the applicator. Five Gray is prescribed at a depth of 10 mm, and the physicist calculates the appropriate treatment duration to deliver this. The treatment takes approximately 20 min, but varies with the size of the applicator selected. During treatment the anaesthetist, oncologist and physicist remain in theatre behind a mobile shielded screen, while other staff leave the room (Fig. 1). Treatment can be interrupted if, for example, the anaesthetist needs to attend to the patient. After completion of radiation, the temporary stitches are removed and the wound is closed in the usual manner. Prophylactic antibiotics (a single injection at the time of surgery) were used for none of the first 16 patients, but all of the remaining patients.

Fig. 1. The Intrabeam device sited in the surgical cavity prior to treatment.

Other adjuvant therapies

Following the definitive surgical procedure and IORT, patients went on to receive appropriate systemic treatment and postoperative adjuvant radiotherapy. EBRT of 45 Gy in 25 fractions to the whole breast was usual.

Assessment of complications and radiation toxicity

Following surgery, patients were assessed fortnightly (until EBRT commenced) by a research nurse or radiation oncologist, for any complication of surgery or the Intrabeam treatment. In addition, patients were assessed for complications and acute radiation toxicity weekly during each of the 5 weeks of radiation therapy (RT), then at 1 month. Patients were then assessed for late radiation complications, at 3 monthly intervals, beginning 3 months after completing EBRT, by the radiation oncologist. Particular note was made of any breast haematoma, seroma or infection, or axillary infection or lymphocoele requiring intervention. An infection was defined by the commencement of an antibiotic. Early breast infections were defined as those occurring within 30 days of IORT. Any acute radiation toxicity was graded according to the National Cancer Institutes' Common Toxicity Criteria (version 2.0) for radiation dermatitis, breast pain or other radiation toxicity.[21] Any late radiation toxicity was scored using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) Late Radiation Morbidity Scoring Scheme.[22] Patients also completed cosmesis, quality of life (EORTC QLQ C30 and BR23 breast cancer specific modules) and body image assessments, which will be reported with additional follow up.

RESULTS

Thirty-five patients, one with bilateral disease, were treated using the Intrabeam device. Patient and cancer details are shown in Table 1. Fourteen of the patients usually reside more than a 1-h drive away, but seven relocated to Perth to receive their EBRT. Half of the cancers would be considered low-risk. Details of the surgical and postoperative adjuvant treatments are shown in Table 2. Although breast-conserving surgery had been planned, three patients went on to mastectomy, due to findings on their pathology. Postoperative radiotherapy was planned in all but four patients, including two of the patients treated with mastectomy. Two patients had relative contraindications to EBRT, so were planned to have IORT alone – one patient had previously undergone mantle irradiation for Hodgkin's disease, and one patient had Systemic Lupus Erythematosus. Seven patients have yet to complete EBRT. Radiation treatment was to breast tangents alone (45 Gy in 25 fractions over 5 weeks) in most cases. One of the mastectomy patients had her chest wall treated. Three patients had four field radiotherapy (i.e. regional nodal treatment in addition to their breast/chest wall irradiation) because of extensive

nodal involvement. The median time between IORT and commencement of EBRT was 93 days (range 37–221 days).

Details of the IORT are shown in Table 3. The procedures were performed by one of five surgeons, in conjunction with one of two radiation oncologists. IORT was performed at the time of definitive wide local excision in 24 cases, with a re-excision in three cases, or as separate procedure in nine cases. None of the patients undergoing re-excision had received prior IORT. In 22 cases, both breast and axillary surgery were performed at the same procedure as the Intrabeam treatment. The applicator sizes used were smaller when Intrabeam was performed as separate procedure, as the cavity contracts following initial surgery. When performed as a separate procedure applicators 25 mm or less were usual, compared to 40 mm or more when Intrabeam was performed earlier. The median time to deliver the IORT, not including the time to set-up or take down the device (i.e. the 'beam-on' time) was 19 min. The median operating time and total duration of general anaesthesia, when IORT alone was performed, was 56 and 79 min, respectively.

Table 4 shows the radiation toxicities of the IORT and/or EBRT. The median follow up is 8.9 months, with a range of 0.2–27.7 months. Twenty-seven patients have been followed up for at least 4 weeks following completion of EBRT (or 1 month post IORT if no EBRT was planned), while 11 patients have been followed up for over 1 year post IORT. The worst National Cancer Institute Common Toxicity Criteria (NCI CTC) grade of acute radiation toxicity experienced by each patient included only one grade 3 or 4 toxicity, this was grade 3 itch. No patients experienced RTOG/EORTC grade 3 or 4 late toxicity.

Six patients experienced either a breast haematoma or seroma requiring management (e.g. aspiration) following IORT but before EBRT. One patient required aspiration of an axillary lymphocoele prior to IORT, and an additional 10 patients required such treatment between IORT and EBRT. A number of patients developed breast and/or axillary infections, which are shown in detail in Table 5. Six patients (17%) developed a breast infection within 30 days of the IORT procedure. However, 17 patients in all (over the total duration of follow-up) experienced a breast or axillary infection requiring antibiotics. Two patients experienced both an axillary infection and a breast infection. Two patients required admission, and two patients required treatment with antibiotics on more than one occasion. The rate of early breast infections in those not given prophylactic antibiotics was 25% (four of 16 patients), while in those given prophylactic antibiotics it was 11% (two of 19 patients). Two patients had axilla infections prior to IORT and later also went on to have prophylactic antibiotics at the time of the IORT procedure. None of the cases in which Intrabeam alone was given as second procedure have developed an infection. No patients have had a local recurrence,

Table 1. Patient and cancer details

Number of patients	35
Number of breasts treated	36
Age (years)	58 (range, 42–82)
Reside more than 1 h away	14 (40%)
Screen detected	27 (75%)
Prior hormone replacement therapy	13 (36%)
Contraindications to EBRT	2 (6%)
Cancer details	
Size (mm)	10 (range, 1–30)
Grade	
1	18 (50%)
2	14 (39%)
3	4 (11%)
Hormone receptor positive	34 (94%)
Nodes	
N0	25 (69%)
N1	6 (17%)
NX	5 (14%)
Low risk†	16 (46%)

†For the randomized trial this is defined as a postmenopausal patient with a unifocal tumour, <20 mm, grade ≤2, of ductal or special type, and N0. For the purposes of this study we have also included NX patients. EBRT, external beam radiation treatment.

Table 2. Treatment details other than Intrabeam

Final breast surgery	
Breast conservation	33
Mastectomy	3
Axillary management	
None	4
SLNB only	12†
Axillary dissection	13
SLNB and axillary dissection	7
Adjuvant systemic treatment	
Tamoxifen	28
Chemotherapy	5
Both	3
Adjuvant EBRT	
Nil	4
Breast (Tangents) only	22‡
Breast and SCF-axilla	2
Chest wall and SCF-axilla	1

†Includes one failed SLNB (NX); ‡An additional seven patients are planned to have breast tangents alone, but have not completed this. SCF, Supra-clavicular fossa; SLNB, sentinel lymph node biopsy.

Table 3. Intrabeam treatment – by concurrent breast surgery procedure

IORT performed with:	WLE	Re-excision	Alone
Total number	24	3	9
Applicator size (mm)			
20	–	–	4
25	–	–	2
30	–	–	1
35	11	1	2
40	7	1	0
45	3	–	–
50	3	1	–
Duration of IORT (min)			
Median	22	23	17
Range	18–34	19–36	13–23
Ax. surgery at time of IORT	30	2	0
Operating time (min)			
Median	143†	171	56
Range	62–222†	85–187	46–69
Total duration GA (min)			
Median	179†	192	79
Range	70–267†	110–201	57–96

†Two patients had additional measurements (e.g. ultrasound) performed intraoperatively during WLE, and one patient underwent bilateral breast WLE and axillary dissections. IORT, intraoperative radiation treatment; WLE, wide local excision.

although this is not an endpoint of the study because of the small numbers of patients involved.

DISCUSSION

We have demonstrated that breast IORT delivered by the Intrabeam device is feasible in an Australian hospital. In this study, Intrabeam was used to replace only the 2-week boost in an otherwise conventional course of adjuvant radiation treatment. Such treatment may be able to be used as sole treatment for favourable tumours, but this needs to be assessed in a randomized trial. It was associated with some complications, and does require an investment in the cost of the machine and the time of the personnel using it. This typically included almost an hour of operating time per patient, at least during the learning stage. The cost of the Intrabeam device and floor stand is approximately $A590 000. This treatment is unlikely to be economical simply as a routine method of tumour bed boost delivery, but may be cost-effective if it were able to replace entire courses of EBRT. The benefits to patients, including reductions in time off work, transport and accommodation costs might be substantial, as in the case of the 14 women in our series who usually live over 1 h drive away from the nearest radiotherapy centre. In addition, freeing space on linear accelerators allows other patients to be treated with shorter waiting times. We plan to carry out a detailed cost–benefit analysis with a health economist.

The actual treatments themselves went smoothly. We have now moved to performing the IORT as a separate procedure rather than at the time of other breast or axillary surgery. This appears easier to schedule, and allows the final pathology to be available prior to IORT – avoiding problems such as close margins at initial resection requiring further surgery.

We assessed patients closely for complications, and found minimal radiation reactions. There was, however, an acute breast infection rate of 17%. As we noted a possible increased risk of breast infections in the early part of this study, we moved to using prophylactic antibiotics given at the time of the procedure. This resulted in an apparent decrease in the rate of infections from 25% to 11%. This reduction may also be related to the use of a separate procedure list. The rate of early breast infection is similar to the 4–21% reported in the literature for these types of operation.[23–27] Reid *et al*. recently reported a prospective audit of the first 30 postoperative days following clean general surgical wounds. Assessment included inpatient review by a research nurse, and subsequent outpatient follow up by patient telephone interview. With this method of assessment – similar to ours, they found the rate for acute breast infection was 16%.[28] The investigators noted that the overall wound-infection rate was higher than previously described, and felt this was due to the finding that two-thirds of infections occur after discharge from hospital. In our study, there was a rate of late infections of 14%, but there is little comparative data available in the literature. The rate of severe late infections has recently been estimated at 3–5% for patients undergoing breast-conserving surgery and irradiation.[29–36] The relatively high rate of infections we have noted, may be due to the inclusion of milder infections and closer follow up. In addition, as an infection was defined by the use of antibiotics, and as there may have been a low threshold for starting treatment, this may overestimate the true infection rate. Our follow up is not long enough to demonstrate all potential late effects of radiation, but we will continue to monitor for them.

Vaidya *et al.* have recently reported their experience on 25 patients where, like this study, they replaced the routine boost to the tumour bed with IORT using the Intrabeam device.[18–20] They

Table 4. Acute and late radiation toxicity grading

Grade	0	1	2	3	4
Acute radiation toxicity – worst NCI CTC grade					
RT dermatitis	17	29	13	0	0
Pain	18	28	13	0	0
Other	18	4	1	1	0
Late radiation toxicity – worst RTOG/EORTC grade					
Skin	9	6	0	0	0
Lung	14	1	0	0	0
Subcutaneous	11	4	0	0	0
Other	0	0	0	0	0

NCI CTC, National Cancer Institute Common Toxicity Criteria; RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

Table 5. Patients experiencing breast or axillary infections (by time following IORT)

	Early (≤30 days)	Late (>30 days–1 year)	Total
Breast	6	5	11
Axilla	5†	1	6†
Both	1	1	2

†Two additional patients developed axillary infection prior to IORT.

Table 6. Randomized trials of breast conservation surgery with and without adjuvant radiation therapy

Trial	Max. tumour size (cm)	Local recurrence RT *vs*	No RT	Reporting method
NSABP[1]	4	10%	35%	12-year actuarial
Uppsala-Orebro[6]	2	9%	24%	10-year actuarial
Ontario[7]	4	11%	35%	8-year crude
Scottish[8]	4	6%	25%	68-month crude
British[9]	5	13%	35%	71-month crude
Milan[10]	2.5	6%	24%	10-year crude

RT, radiation therapy.

had no major complications and no patients had developed local recurrence at the time of the report. One minor complication was a problem with wound healing due to radio-necrosis caused by the applicator being positioned too close to the skin. This had been reported prior to our study, and we incorporated changes to our IORT technique to avoid this.

As mentioned, trials attempting to omit radiotherapy in selected women after breast conserving surgery, summarized in Table 6, have given unsatisfactory results.[6–10] However, there has been interest in giving more limited radiotherapy (i.e. to the tumour bed rather than treating the entire breast). This has been tested in a randomized trial with patients receiving EBRT to either standard fields or EBRT to the involved quadrant only. Overall there was a higher local recurrence rate in patients treated with the limited field, but among the 504 cases of infiltrating duct carcinoma there was no significant difference.[37] This suggests that in selected patients, EBRT could reasonably be limited to part of the breast; however, this treatment requires the same time and resources as standard EBRT. Other complicated approaches to limit treatment to the tumour bed, using brachytherapy or IORT with a mobile linear accelerator have been reported.[38–43]

Curative EBRT is given in multiple fractions, as this relatively spares the normal tissues from late radiation effects. Single treatments to curative doses with EBRT are not tolerated, but with this form of IORT we make use of the fact that the radiation dose falls off exponentially with the distance from the surface of the applicator. Using the linear-quadratic model and assuming an alpha–beta ratio of three, we can calculate the equivalent dose for normal tissue late effects.[44] At 1 cm from the applicator, the dose is 5 Gy in a single fraction – in terms of late effects this is approximately equivalent to only 8 Gy in 2-Gy fractions. A small volume receives higher doses, but there is significant 'volume effect' for normal tissue reactions, so the effect will be less than would be expected if a large volume were irradiated to the same dose.[45]

Equivalent doses in terms of cancer treatment can also be estimated using the linear quadratic model, assuming an alpha–beta ratio of 10.[44] For example, the dose at the surface of the applicator is nominally equivalent to 50 Gy in 2-Gy fractions (i.e. similar to an entire course of EBRT). Although the linear quadratic model accounts for fractionation effects, IORT as described may be more biologically effective than predicted due to advantages such as immediate treatment (which avoids tumour repopulation).[46,47] The actual biological effectiveness of this treatment will depend on the 3-dimensional distribution of the tumour clonogens. Such treatment may be more effective for more favourable pathology tumours.

We have recently commenced enrolment into an international randomized multicentre trial comparing targeted IORT delivered using the Intrabeam with conventional postoperative radiotherapy. All patients randomized will receive some adjuvant radiation therapy (either IORT or EBRT), and in addition any appropriate systemic therapies. It is possible the local recurrence rate with IORT alone may be slightly higher (than with a full course of EBRT), but lower than with no RT at all. This trade off may be acceptable to patients, and we are studying this in a separate 'patient preference' study. This randomized study is part of an international collaboration; however, we will be entering only lower risk patients (postmenopausal women, with unifocal tumours, <20 mm, Grade ≤2, of ductal or special type and node negative).

Adjuvant breast IORT with the Intrabeam device is feasible and non-toxic when used to replace an EBRT boost. Care should be taken not to stretch skin over the applicator, and prophylactic antibiotics should probably be used. IORT may be better used to replace an entire 5–7 weeks of EBRT, in highly selected patients. This simple, effective technique is to be tested in a randomized trial, which has already started accrual.

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