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Intra-operative radiotherapy for breast cancer

Over the last century, the treatment of breast cancer has evolved as the biology of the disease is better understood. In the mid-19th century, the humoral theory of breast cancer was overturned by a mechanistic model *viz.*, 'it arises in the breast and spreads centrifugally to regional lymph nodes and thence to rest of the body'. Charles Moore, (1821–1879) a surgeon from the Middlesex Hospital in London, among others, believed that the only way to cure breast cancer was very extensive surgery, in which the tumour was not violated.¹ The belief in this mechanistic model resulted in development of the Halsted radical mastectomy for the 'cure of the cancer of the breast', at the end of the 19th century.² Unfortunately, only 23% of patients treated by Halsted survived 10 years.³ Even more radical surgery,⁴ including the internal mammary lymph nodes, did not make a difference.^{5,6} Prompted by the failures of radical operations to cure patients of breast cancer, Fisher⁷ and others postulated that cancer spreads via blood stream even before its clinical detection, with the outcome determined by the biology of tumour–host interactions. This concept of 'biological predeterminism' suggested that:

1. Adjuvant systemic treatment of apparently localised tumours would be beneficial and may offer a chance of cure; this is now proven in the Oxford overview and, although the effect is only modest, the absolute number of lives saved is considerable, given that breast cancer is a common disease.
2. The extent of local treatment would not affect survival. Again, it was the genius of the Oxford overview^{8,9} of 26,000 women from 36 trials resolved the controversy. In 1995, it concluded that postoperative radiotherapy had a substantial effect on reducing local recurrence rates (from 27.2% to 8.8% overall), but more radical local treatment, whether surgery or adjuvant

radiotherapy, did not have any influence on appearance of distant disease and overall survival. At a 20-year follow-up,⁹ it was found that radiotherapy reduced breast cancer mortality by 4–5% but other mortality, mainly cardiovascular was increased by an equivalent amount. This has resulted in acceptance of breast-conserving therapy as the standard of care.

One must realise that breast-conserving therapy in the form of wide local excision of the primary tumour, axillary surgery followed by a 6-week course of whole-breast radiotherapy including a tumour bed boost actually has the same radical intent as was achieved by the extirpative surgery of Halsted more than 100 years ago. In that respect, it is not really a change in the paradigm.

PROBLEMS WITH THE CURRENT STANDARD OF CARE

Nevertheless, properly delivered breast-conserving therapy (BCT) is now taken as equivalent to mastectomy and the current standard of care for early operable breast cancer is wide local excision and a 6-week course of whole-breast postoperative radiotherapy usually including a tumour bed boost. In spite of this concept being established for more than a decade, the rates of mastectomy in various populations are still very high, and this cannot be accounted for by a late stage of disease. Local culture and geography, surgeon's choice and patient preference, not necessarily in that order, all dictate which operation is chosen.

The disadvantages of the current practice of 6 weeks of postoperative radiotherapy after breast conservative surgery are:

1. The long course is a considerable strain on women especially when it comes after a 6-month course of chemotherapy.
2. Many women are forced to choose mastectomy because they live far away from a radiotherapy facility. This problem is not restricted to non-industrialised countries. In a study in the US, it was found that the farther the patient lives, the less is the likelihood that she will receive BCT and radiotherapy after breast conserving surgery (BCS). When the travel distance was less than 10 miles, 82% (*i.e.* 39% of total) of patients received radiotherapy after BCS; when it was 50–75 miles, 69% (22% of total) received it and when it was more than 100 miles, only 42% (14% of total) received it.¹⁰
3. Many women fail to complete the 6-week course and thus may be receiving sub-optimal treatment.
4. It takes up scarce resources of the radiotherapy centres and in many countries leads to long waiting lists.
5. Delay in delivery of radiotherapy either because of long waiting time or because chemotherapy is given first, may jeopardise its effectiveness and the window of opportunity to sterilise the target tissues of tumour cells/potential tumour cells may be lost.
6. It has been estimated that the externally delivered boost dose misses target volume in 24–88% of cases.^{11,12} Thus a large proportion of local recurrences could be attributed to this 'geographical miss' alone.

Key point 1

- The usual 6-week course of postoperative radiotherapy after breast conserving surgery has several disadvantages that reduces its general applicability to a wide population, even amongst the most advanced health economies.

LOCAL RECURRENCE AFTER BREAST CONSERVING THERAPY AND RATIONALE BEHIND INTRA-OPERATIVE RADIOTHERAPY

Local recurrence of breast cancer can cause considerable psychological morbidity which may include a sense of failure. There are various theories to explain local recurrence. It may arise from tumour cells left behind or occur because of seeding of circulating metastatic cells in the surgical field rich in growth factors. The latter is supported by the fact that patients with early local recurrence have a relatively poor prognosis (RR, 0.34).¹³ Recent data suggest that local recurrence may be facilitated by a local field defect. First, the morphologically normal cells surrounding breast cancer demonstrate a loss of heterozygosity, which is often identical to that of the primary tumour.¹⁴ So these 'normal' cells are already on the brink of becoming cancer. In addition, aromatase activity in the index quadrant is higher than other quadrants¹⁵ and via oestrogen has the potential to stimulate mutagenesis, growth and angiogenesis.^{16,17} Young age appears to be a risk factor for local recurrence after breast conserving therapy¹⁸ and radiotherapy seems to have a differential effect according to age.¹⁹ Patients with ipsilateral breast tumour recurrence (IBTR) have an increased risk of carrying a mutant p53 gene (23% *versus* 1%) and young patients (< 40 years) with IBTR have a disproportionately increased risk (40%) of carrying a deleterious BRCA1/2 gene mutation.²⁰ This suggests that such local recurrence is probably related more to the background genetic instability rather than a different tumour biology at younger age. It appears that a dynamic interaction between the local factors (such as aromatase) present in the breast parenchyma, systemic hormonal milieu and genetic instability will determine the risk of local recurrence, in addition to the biology of the excised primary tumour.

Table 1 The site of local recurrence in large studies of breast conserving therapy

Study	Patients (n)	Proportion of recurrences in the index quadrant
Clark <i>et al.</i> ²¹ 1982	680	96%
Schnitt <i>et al.</i> ²² 1984	231	83%
Boyages <i>et al.</i> ²³ 1990	783	81%
Kurtz <i>et al.</i> ²⁴ 1990	1593	86%
Fisher <i>et al.</i> ¹³ 1992 (RT)	488	100%
Clark <i>et al.</i> ²⁵ 1992 (RT arm)	416	(19/23) 83%
Clark <i>et al.</i> ²⁵ 1992 (no RT arm)	421	(103/108) 86%
Veronesi <i>et al.</i> ²⁶ 1993	570	90%
Total	5182	91%

The location of recurrence in the breast with respect to site of the primary tumour has been analysed in large series of breast conservation studies (Table 1). It is seen that 81–100% of early breast recurrences occur in the quadrant that harboured the primary tumour.^{13,21–26} Bartelink²⁷ has reported that only 56% (47% in ‘tumour bed’ and 9% in scar) of local recurrences occurred in the original tumour bed. In addition, 27% recurred diffusely throughout the breast including the tumour bed – so that 29% recurred outside the index quadrant. However, these patients had intensive mammographic follow-up protocol which might have unearthed the subclinical occult tumours (see below) in other quadrants that may never have surfaced clinically.

It appears that local recurrence occurs in the index quadrant, whether or not radiotherapy is given.^{21,25,28} That suggests that, whatever the cause of local recurrence, its location remains in the index quadrant and is not affected by radiotherapy. Second, we also know that local recurrence occurs in the index quadrant irrespective of clear margins. Of the breast conserving trials that have tested the effect of radiotherapy, the NSABP-B06,²⁹ Ontario,³⁰ Swedish,³¹ and Scottish³² trials had less extensive surgery compared with the Milan III trial.²⁶ The recurrence rate in the control arm of the Milan III trial, in which the tumours were smaller and excision was considerably wider, was low (8.8% *versus* 24–27% in other trials) even in the control group albeit at the cost of cosmesis. Nevertheless, radiotherapy reduced it even further and at the same proportional rate as in other trials. If local recurrence is caused by residual disease, then radiotherapy should have affected a much larger proportional reduction in those patients with positive margins or less extensive surgery. However, radiotherapy also reduces the rate of local recurrence in those patients with negative margins, which further suggests that local recurrence does not arise only from residual disease and that radiotherapy probably inhibits the growth of genetically unstable cells around the primary tumour. This is in contrast to the findings of whole-organ analysis of mastectomy specimens performed in three dimensions³³ which reveals that 63% of breasts harbour occult cancer foci and 80% of these are situated remote from the index quadrant. It, therefore, appears that these wide-spread and occult multifocal/multicentric cancers in other quadrants of the breast probably remain dormant for a long time and have a low risk of causing clinical tumours. This is corroborated by the high frequency (20% in young women [median age, 39 years] and 33% in women aged 50–55 years) of occult tumours found in ‘normal’ breasts when analysed in detail in autopsy studies.³⁴

It is, therefore, hypothesized that radiotherapy to the tissues that surround the primary tumour is all that is probably necessary. Such an approach may solve many of the problems of postoperative radiotherapy mentioned earlier, and may increase the rates of breast-conserving surgery.

This approach of irradiating the index quadrant alone has been tested in the Christie Hospital trial³⁵ and, contrary to the popular myth, its findings are encouraging. A total of 708 patients were randomised to receive either the standard wide field (WF) radiotherapy or a limited field (LF) radiotherapy to the index quadrant. Overall, there was a higher recurrence rate in the latter (LF) arm. In the limited field arm, a constant size of radiotherapy field was used, irrespective of the tumour size, and this could have resulted in several instances of ‘geographical misses’. More importantly, when the results were

Key point 2

- Since local recurrence after breast-conserving surgery occurs mainly in the area around the original primary tumour, it may be sufficient to target adjuvant radiotherapy to peri-tumoural tissues.

analysed according to the type of the primary tumour, it was found that limited field radiotherapy was inadequate only in infiltrating lobular cancers or cancers with extensive intraductal component (EIC). In the 504 cases of infiltrating duct carcinoma, there was no significant difference in the local recurrence rates of the two arms.

BRACHYTHERAPY

When patients with small infiltrating duct cancers with uninvolved nodes are treated with interstitial brachytherapy with radioactive wires, the recurrence rate is 0–4% at 2–5-year follow-up (see Table 2). It is important to note that the patients in these series have small tumours and have a low risk of local recurrence. In a recently published randomised trial,³⁶ this technique was found to be equivalent to whole-breast radiotherapy at 30-month follow-up. This is a very important result and is a proof of the principle of treating the

Table 2 Index field interstitial brachytherapy series – good prognosis patients at low risk of local recurrence

Institution	Radiotherapy technique	Median follow-up	Crude local recurrence rate (actual numbers)
Ninewells Hospital, Dundee, UK ³⁷	LDR	5.6	0% (0/11)
Ochsner Clinic, USA ³⁸	LDR/HDR	3.8	1.3% (2/150)
London Regional Cancer Center, Canada ³⁹	HDR	1.7	2.6% (1/39)
William Beaumont Hospital, USA ⁴⁰	LDR/HDR	3	0% (0/174)
Orebro Medical Centre, Sweden ⁴¹	PDR	2.8	2.3% (1/43)
University of Kansas, USA ⁴²	LDR	4	0% (0/24)
National Institute of Oncology, Hungary ³⁶	HDR	4.5	4.4% (2/45)
Tufts University, USA ⁴³	HDR	2	0% (0/30)

LDR, low dose rate; HDR, high dose rate; PDR, pulsed dose rate; IORT, intra-operative (electrons) radiotherapy.

Table 3 Some characteristics of intra-operative radiotherapy systems

Device Company	Radiation type [*Wt of device]	Dose
INTRABEAM Photoelectron Corporation, Lexington, MA, USA	Soft X-rays at 50 kV [*1.8 kg]	Typical physical dose of 5 Gy at 1 cm or 10 Gy at 0.5 cm or 20 Gy next to the applicator over 25–30 min. Setting-up time ~10–12 min
MOBITRON Oncology Care Systems Group of Siemens Medical Systems, Intraop Medical Inc., Santa Clara, CA, USA	Electrons at 4–12 MeV [*1275 kg]	20 Gy physical dose in 3–5 min. Setting-up time ~20 min
NOVAC-7 Hitesys SpA, Italy	Electrons at 4–12 MeV [*650 kg]	20 Gy physical dose in 3–5 min. Setting-up time ~20 min

*Weight of treatment device (kg)

index quadrant. However, these studies employ standard high-dose rate brachytherapy delivered with a radioactive source (such as iridium, caesium wires, or radioactive pellets within a saline-filled balloon, *e.g.* Mammosite™) placed intra-operatively to cover a large field in the breast. These techniques need after-loading of the radioactive source in the wire or balloon templates. This typically is done in 5–7 fractions delivered in the postoperative period, over 4–5 days. This makes it fundamentally and conceptually different in terms of technique from the intra-operative radiotherapy which is delivered in one sitting at the time of primary surgery, although sharing the basic premise of treating only the index quadrant.

TECHNIQUES OF INTRA-OPERATIVE RADIOTHERAPY

We shall now consider the techniques of delivering intra-operative radiotherapy as a single fraction delivered in the operating theatre immediately after wide excision of the primary tumour. While brachytherapy using interstitial implants necessitated the treatment to be carried out in a specially shielded room, the other, older, intra-operative radiotherapy devices were technically cumbersome and often relied on transporting the patient from the operating theatre to the radiotherapy unit during surgery. Alternatively, operating theatres with built-in IORT systems were used in some centres. These technical and financial limitations to IORT delivery placed a substantial constraint on the wide-spread adoption of IORT in a variety of hospital settings. Recent advances in miniaturisation technology have enabled the development of mobile IORT devices. The first device to be used for IORT is the Intrabeam™ (Photoelectron Corporation, Lexington, MA, USA). The two

Key point 3

- Modern technology has allowed development of portable, powerful radiotherapy devices that can be used in standard unmodified operation theatres.

other systems are mobile linear accelerators – the Mobetron System (Oncology Care Systems Group of Siemens Medical Systems, Intraop Medical Inc., Santa Clara, CA, USA) and the Novac-7 System (Hitesys SpA, Italy). Some of the characteristics of these machines are given in Table 3.

RADIOBIOLOGY OF INTRA-OPERATIVE RADIOTHERAPY

Whether IORT has an identical biological effect on tissue compared with external beam radiotherapy is not known; but, because it is more conformational, the same physical dose of IORT is equivalent to a much higher dose of external beam radiotherapy. With regards to the specific mobile IORT systems currently being used in early breast cancer, the Intrabeam IORT system delivers a physical dose of 5.0 Gy administered at a distance of 1.0 cm from the breast tumour cavity for a period of 21 min that is equivalent to a biologically effective dose of 21.7 Gy. Using Novac-7 IORT technology, Veronesi *et al.*²⁶ have estimated that an external beam dose of 60 Gy delivered in 30 fractions at 2 Gy/fraction is equivalent to a single IORT fraction of 20–22 Gy (using an α/β ratio at 10 Gy, typical for tumours and acute reacting tissues). Using this same equation, but calculating the tolerance of late responding tissues (α/β ratio at 3 Gy) this equivalent value rises to at least 110 Gy. Radiobiological experiments⁴⁴ using cell cultures have suggested that the radiobiological effectiveness (RBE) of the Intrabeam system is 1.2–2.5. This was in agreement with microdosimetric analysis and modelling.⁴⁵ The PRS radiation is found to induce both necrotic and apoptotic cell death in addition to rapid cell death through non-apoptotic pathways.⁴⁶ Animal experiments have demonstrated that PRS can induce well-demarcated ablation in canine liver and kidney.^{47–49} As a demonstration of its efficacy of ablating tumour tissue, 3 patients were treated with a PRS 400 (bare probe only, *i.e.* without the applicators, but with the same Intrabeam machine that is used for intra-operative radiotherapy). The tumour was localised on the Mammotest™, a digital, stereotactic, prone mammaryography table. The tumours (range, 1–2.5 cm) were ablated with a single dose of radiotherapy as demonstrated on biopsy and serial, contrast-enhanced MRI.⁵⁰

There are no biological models or experimental evidence yet available to estimate the radiobiological effect of a single, large fraction of radiotherapy. The linear quadratic equations that are usually used for these estimates are

Key point 4

- Radiobiology of single-dose, intra-operative radiotherapy is still being studied and the optimum dose has not been established as yet.

reliable up to a single dose of 2–3 Gy, but not higher. It has been proposed (Prof. Frederik Wenz Mannheim, Germany; personal communication) that the low energy X-rays emitted by a system such as the Intrabeam™ may have special properties with respect to tumour and normal cells. Since the radiotherapy delivered by Intrabeam (called TARGIT for targeted intra-operative radiotherapy⁵¹) is over a period of 25–30 min and the normal tissue DNA repair mechanism takes only 10 min, there is ample time for normal tissues to repair whereas the tumour cells, being poor at DNA repair, would not survive. Thus the radiobiological effect of such a single fraction of radiotherapy may actually be paradoxically higher at greater depth.⁴⁴ Thus, the tissues immediately next to the applicator would have a high physical dose with low therapeutic ratio and those away from the applicator would have lower physical dose, but a high therapeutic ratio. This is an advantage of Intrabeam™ over the systems delivering electrons because the treatment time is short and the high (physical) dose region is small – it is expected that this would increase acute tumour effects while reducing long-term toxicity. The specific laboratory experiments to test this concept are already underway.

As yet, there is no firmly established, standardised IORT dose or dose rate for use in early breast cancer. IORT doses investigated for use in early breast cancer have ranged from 5 Gy to 22 Gy using a variety of different IORT systems.

EARLY RESULTS

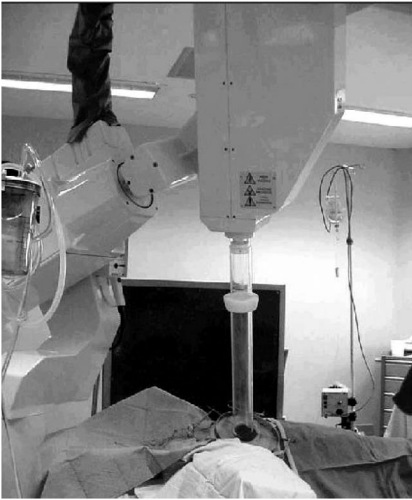
Based on the hypothesis that index quadrant irradiation is sufficient and equipped with modern technology, in July 1998 we introduced the technique of intra-operative radiotherapy^{52–54} that is delivered as a single-dose treatment using low energy X-rays, targeted to the peri-tumoural tissues from within the breast. In patients with small breast cancers (now the majority), this could be the sole treatment. In those with high risk of local recurrence, it would avoid any geographical miss and, in combination with external beam radiotherapy, may further reduce local recurrence.

The results of pilot studies using one such device that uses soft X-rays (Intrabeam™) are encouraging and a randomized trial (TARGIT)^{51,55} is under way in the UK, Europe, USA and Australia. The Milan group is also testing the same approach,⁵⁶ using a mobile linear accelerator (Novac-7™) in a randomized trial (ELIOT). The completion of these trials is eagerly awaited. If proven effective, these novel approaches have the potential to save time and money, and enable many more women to conserve their breasts.

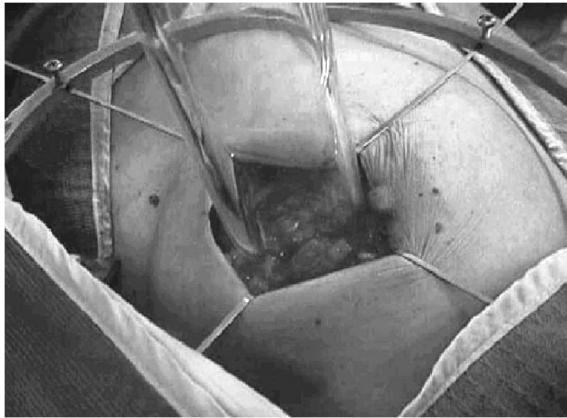
THE NOVAC-7 SYSTEM

Novac-7 (Hitesys SpA, Italy) is a mobile, dedicated, linear accelerator. Its radiating head can be moved by an articulated arm which can work in an existing operating room. It only delivers electron beams at four different nominal energies – 3, 5, 7, and 9 MeV radiation (Fig. 1).

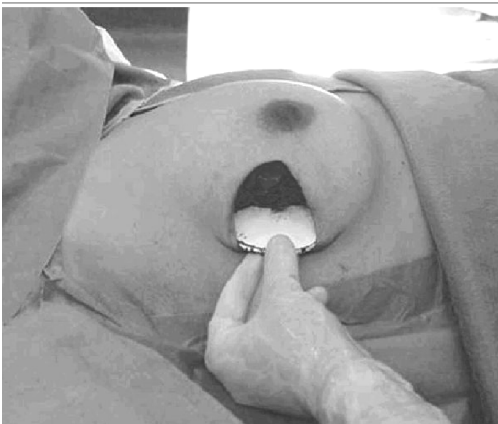
Beams are collimated by means of a hard-docking system, consisting of cylindrical perspex applicators available in various diameters (4, 5, 6, 8, and 10 cm). The source-to-surface distance is 80–100 cm. For reasons of radiation



A



B



C

Fig. 1 The Novac-7 system – the arm of the mobile linear accelerator (A) is attached to a perspex cylinder that is introduced in the breast wound (B). The breast tissue is mobilized from the chest wall and overlying skin and apposed in the wound after placing a lead shield between the breast and pectoralis muscle (C). Figures taken from Veronesi *et al.*⁵⁶ with kind permission from Prof. Umberto Veronesi.

protection, a primary beam stopper (consisting of a lead shield, 15 cm thick) mounted on a trolley and three mobile barriers (100 cm length, 150 cm height and 1.5 cm lead thickness) are provided. Electron beams delivered by Novac-7 have very high dose/pulse values compared with those supplied by conventional medical linacs. Once the breast resection has been performed, the breast is mobilised off the pectoral muscle for 5–10 cm around the tumour bed and also separated from the skin for 3–5 cm in every direction. In order to minimise the irradiation of the thoracic wall, dedicated aluminum–lead disks (4 mm Al + 5 mm Pb) of various diameters (4–10 cm) are placed between the deep face of the residual breast and the pectoralis muscle. The breast is now sutured so as to obliterate the tumour bed and bring the target tissues together. The thickness of the target volume is measured by a needle and a ruler in at least three points and averaged. The skin margins are stretched out of the radiation using a home-made device consisting of a metallic ring furnished with four hooks. The cylindrical applicator (4–10 cm diameter) is now placed through the skin incision and in contact with the breast. The source cylinder is now 'docked' onto the upper end of the applicator. The optimal energy of the electron beam is selected on the basis of the previously measured target thickness. The primary beam stopper and the three mobile barriers are positioned, below and around the operating table, in order to provide good shielding from stray radiation, and all medical personnel leave the operating room. Once the radiotherapy is finished, the wound is closed in the usual manner.

THE INTRABEAM SYSTEM

In the Intrabeam, the X-ray tube (XRT) is powered by a 12 V supply, a miniature electron gun and electron accelerator (Figs 2 & 3). Radiation in the form of soft X-rays (low energy 50 kV) is emitted from the point source and is modulated by spherical applicators to give a uniform dose of radiotherapy in a spherical field in the tumour bed. There is quick attenuation of the radiation within tissues which reduces the damage to surrounding normal tissues and minimises the need for radiation protection by the operating personnel. Depending upon the size of the surgical cavity, various sizes of applicator spheres are available and, for each size, the radiation received is proportional to the time the machine is switched on and left *in situ*. The precise dose rate depends on the diameter of the applicator and the energy of the beam, both of which may be varied to optimise the radiation treatment. For example, a dose of about 5 Gy can be delivered in about 20 min at 1 cm from the margins of a 3.5 cm cavity after wide local excision of the tumour.

If necessary, the chest wall and skin can be protected (95% shielding) by radio-opaque, tungsten-filled polyurethane caps, which can be cut to size on the operation table – another advantage of using soft X-rays. With this elegant approach, the pliable breast tissue around the cavity of surgical excision wraps around the radiotherapy source (*i.e.* the target is 'conformed' to the source). This simple, effective technique avoids the unnecessarily complex and sophisticated techniques of interstitial implantation of radioactive wires or the even more complex techniques necessary for conformal radiotherapy by external beams with multi-leaf collimators from a linear accelerator. It eliminates 'geographical miss' and delivers radiotherapy at the earliest possible time after surgery. The

quick attenuation of the radiation dose protects normal tissues and allows the treatment to be carried out in unmodified operating theatres. Thus, in theory, the biological effect and cosmetic outcome could be improved. The median follow-up time of the UK pilot feasibility study is now 36 months and there has been no

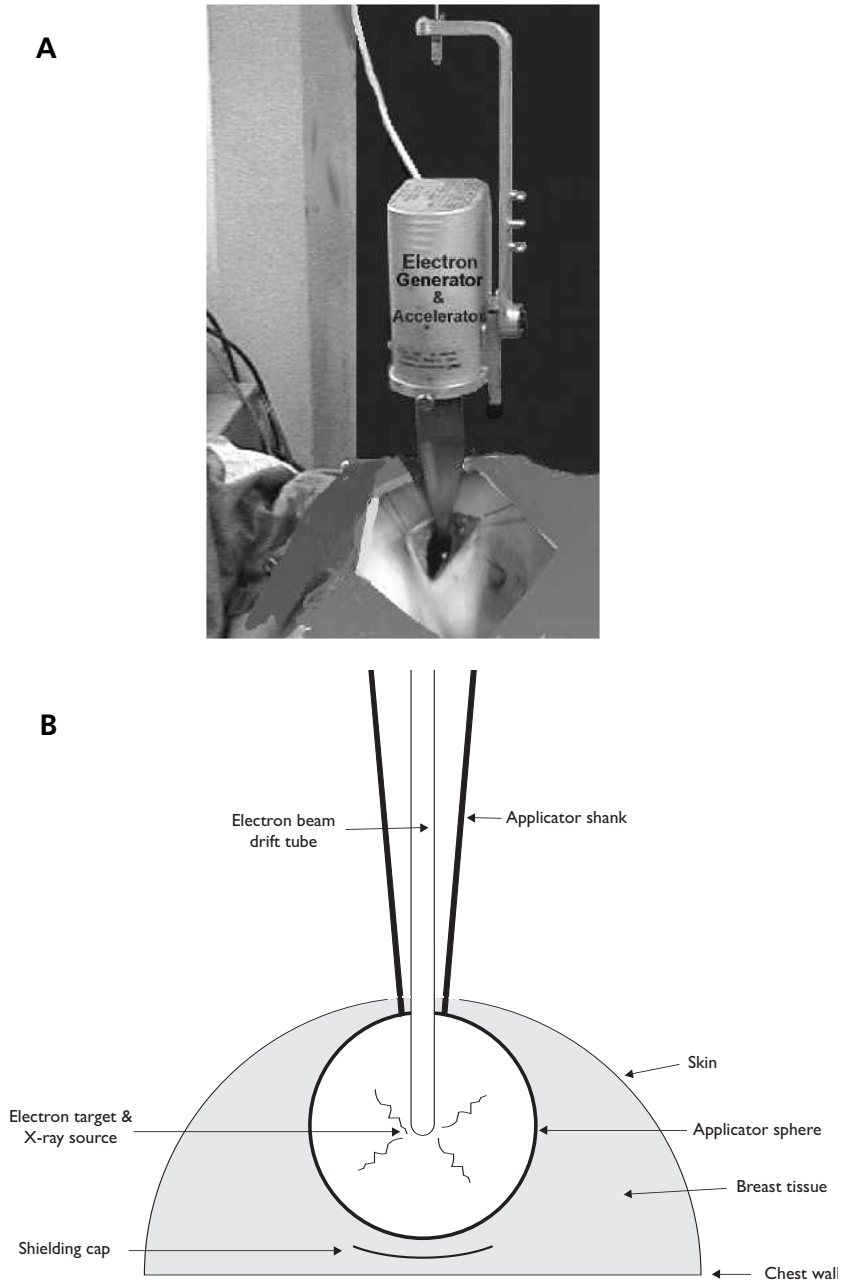


Fig. 2 (A) The Intrabeam system, with the X-ray source in the breast wound (tumour bed), and the electron generator and accelerator held by the gantry. The schematic diagram (B) shows how the target tissues are irradiated from within the breast and how the intrathoracic structures can be protected with a thin shield.

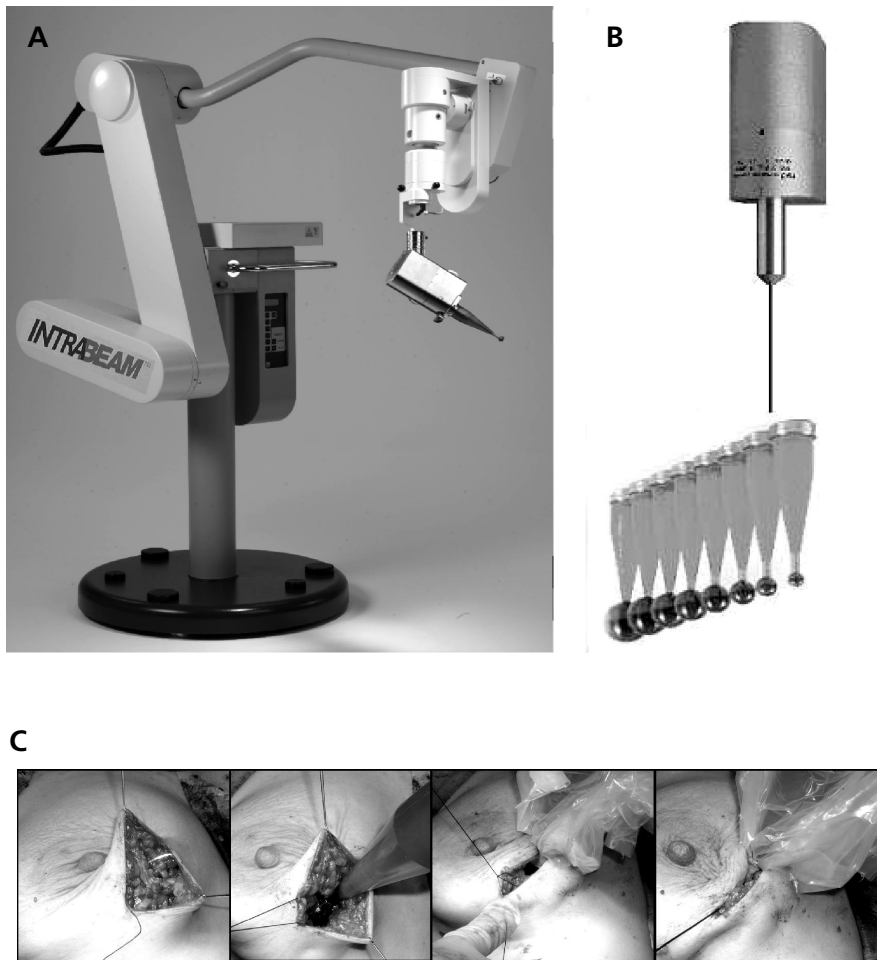


Fig. 3 The Intrabeam system (A), X-ray source and applicators (B). In (C), the figures demonstrate how the target breast tissue wraps around the applicator giving true conformal brachytherapy.

local recurrence. Including the US and Australian data,⁵⁵ a total of more than 100 patients have been treated with good short-term results.

The randomised trial TARGIT, which has collaboration of centres from the UK, Europe, USA, India and Australasia, is designed to test the hypothesis that the strategy of delivering targeted intra-operative radiotherapy in patients eligible for breast-conserving therapy with a facility to add whole breast radiotherapy in those patients who are at high risk of recurrence elsewhere in the breast (*e.g.* lobular cancers, EIC) is equivalent to the standard 6-week postoperative radiotherapy. In this pragmatic trial, each centre will have the ability to decide the level of uncertainty and, therefore, the trial will be stratified according to each centre's decision on which group of patients will receive whole breast radiotherapy in addition to the intra-operative dose. It is expected that the first results of this trial will be available in 2007.

Key point 5

- Results of pilot studies using modern intra-operative radiotherapy techniques are encouraging and several collaborating international groups are recruiting patients in randomised trials.

Key point 6

- Used as a boost, targeted intra-operative radiotherapy can avoid geographical miss and has the potential to reduce local recurrence. Used as a sole treatment for good prognosis breast cancers, it could replace the whole 6-week course of postoperative radiotherapy.

HEALTH ECONOMICS

Delivering intra-operative radiotherapy with Intrabeam™ prolongs the primary operation by 15–45 min and adds 1–2 h of radiotherapy physicists' time in preparation of the device. External beam radiotherapy, on the other hand, costs about 9 man-hours, 6 h of radiotherapy room time and 30–60 h of patient time. If the cost of conventional radiotherapy were £1200, considering only the 66% saving of man-hours the novel technique would save £900 per patient. So, assuming that 60% of the 27,000 breast cancer patients diagnosed every year in the UK are treated by conservative surgery and intra-operative radiotherapy, the novel technique would potentially save about £15 million ($0.60 \times 27,000 \times 3750$) per year for the NHS in the UK. This does not include the substantial saving of expensive resource time on linear accelerators and, most importantly, the saving of time, effort and inconvenience to patients. This is a very attractive aspect of novel technology that is, unlike most other 'new' treatments, actually less expensive than the current standard.

Key point 7

- Unlike most modern medical technology, some intra-operative systems may actually save money for the health system.

Key points for clinical practice

- The usual 6-week course of postoperative radiotherapy after breast conserving surgery has several disadvantages that reduces its general applicability to a wide population, even amongst the most advanced health economies.

Key points for clinical practice (continued)

- Since local recurrence after breast-conserving surgery occurs mainly in the area around the original primary tumour, it may be sufficient to target adjuvant radiotherapy to peri-tumoural tissues.
- Modern technology has allowed development of portable, powerful radiotherapy devices that can be used in standard unmodified operation theatres.
- Radiobiology of single-dose, intra-operative radiotherapy is still being studied and the optimum dose has not been established as yet.
- Results of pilot studies using modern intra-operative radiotherapy techniques are encouraging and several collaborating international groups are recruiting patients in randomised trials.
- Used as a boost, targeted intra-operative radiotherapy can avoid geographical miss and has the potential to reduce local recurrence. Used as a sole treatment for good prognosis breast cancers, it could replace the whole 6-week course of postoperative radiotherapy.
- Unlike most modern medical technology, some intra-operative systems may actually save money for the health system.

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