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EDUCATIONAL SECTION

The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer

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Aim: We believe that conservative treatment of early breast cancer may not require radiotherapy that encompasses the whole breast in all patients. We have developed a novel therapeutic approach that allows targeted intraoperative radiotherapy (Targit) to be safely and accurately delivered in a standard operating theatre. We are currently recruiting for a randomized trial testing whether Targit can replace the whole 6 weeks of post-operative radiotherapy after breast conserving surgery.

Methods: This paper describes the operative technique. It employs a miniature electron-beam-driven X-ray source called INTRABEAM^{TM}(PeC) that emits soft X-rays (50 kV) from within the breast. The X-rays are emitted from the tip of a 10 cm $\times$ 3.2 mm diameter probe, that is enclosed in a spherical applicator (available in 2.5–5 cm diameter sizes), which in turn is inserted in the tumour bed and intraoperative radiotherapy is delivered in about 25 min. The prescribed dose is 5 and 20 Gy at 1 cm and 0.2 cm respectively, from the tumour bed.

Results: The biologically effective dose is 7–53 Gy for $\alpha/\beta = 10$ and 20–120 Gy for $\alpha/\beta = 1.5$. The quick attenuation of the radiation reduces the damage to normal tissues and allows radiotherapy to be delivered in a standard operating theatre. Tungsten impregnated rubber sheets, cut to size, are placed on the chest wall to protect the heart/lungs and over the wound to stop stray radiation. The skin dose is monitored with thermoluminescent detectors (TLDs). After wide local excision of the tumour and good haemostasis, a spherical applicator is inserted in the tumour bed and the target breast tissues are wrapped around it with a purse-string suture. Thus, true conformation of the target around the applicator source is achieved in real time.

Conclusion: As a tumour bed boost, this technique has the potential to reduce local recurrence by avoiding geographical misses and achieving excellent dosimetry. In patients with low risk of local recurrence, it has the potential to replace the full 6 weeks of post-operative radiotherapy with considerable implications to patients and hospitals.
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Key words: breast cancer; breast conserving surgery; intraoperative radiotherapy; IORT; TARGIT

INTRODUCTION

We believe that conservative treatment of early breast cancer may not require radiotherapy that encompasses the whole breast in all patients. We have already presented the clinico-pathological basis for this

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view and the results of the pilot study of the novel therapeutic approach that allows *targeted intra*-operative radiotherapy (Targit) to be safely and accurately delivered to the target tissues in a standard operating theatre.[1] In this pilot study we substituted the boost radiation with Targit in 25 patients. At the median follow up of 34 months there has been no local recurrence and the cosmetic outcome is good. There was one wound breakdown at 3 months in our third patient – attributable to the radiotherapy applicator being too close to the skin. The cosmetic outcome as judged by the patient and the clinician is good. We calculated the satisfaction index by dividing the score out of 10 given by the patient to her own observed look and feel of the breast/scar to her own expectation. This was 1.2 (95% CI 1.1–1.4) for appearance and 1.2 (95% CI 1.0–1.4). We are currently recruiting for a randomized trial testing whether Targit can replace the whole 6 weeks of post-operative radiotherapy after breast conserving surgery.[2] As of July 2001, we have randomized 29 patients. Centres from USA, Australia, Germany, UK and India are in the process of collaborating to make this a multicentre randomized trial. If the randomized study demonstrates that this technique can replace the usual six-week course of external beam radiotherapy for early breast cancer the implications are considerable. Many women from the developing world and remote areas of the developed world (e.g. Outback of Australia) cannot benefit from breast conserving therapy because of the large distances between their home and the radiotherapy centre. All too frequently they have to choose mastectomy because they cannot stay in or travel daily to the metropolis for the six weeks of post-operative radiotherapy. With the novel approach these women could have breast-conserving therapy in one sitting. For more privileged women, the avoidance of six weeks of daily visits to a radiotherapy centre would still be a great advantage. Furthermore, in our pilot study we have found that in terms of operational expenses the novel technique costs about half to one third the man-hours compared with the conventional six-week course of post-operative radiotherapy, without taking into account patient time. If the cost of conventional radiotherapy is £5000, considering only the 66% saving of man-hours the novel technique would save £3750 per patient. So if we assume that 60% of the 27 000 breast cancer patients diagnosed every year in the UK are treated by conservative surgery, the novel technique could potentially save over £60 million ($0.60 \times 27\,000 \times 3750$) per year for the NHS. This does not take into account the much cheaper machinery and maintenance.

In this paper we shall describe the operative technique. The learning curve for this technique, as for any new operative technique, is unavoidable, but we expect it to be a steep one. A video demonstrating the technique is available from the authors.

THE TECHNOLOGY

The technique employs a miniature electron-beam driven X-ray source that emits soft X-rays (50 kV) from within the breast. There is quick attenuation of the radiation within tissues so that the dose is inversely proportional to the third power of the distance and this reduces the damage to surrounding normal tissues and minimizes the need for radiation protection to the operating personnel. This is important since it allows radiotherapy to be delivered in a standard operating theatre. The machine has been used for the treatment of brain tumours using stereotactic frames since 1994.[3–5] We have been the first to use it for breast cancer. The details of the radiotherapy device have already been discussed.[1] It is a very portable machine – small and lightweight (Weight 1.8 kg. Dimensions: X-ray Source (XRS) body $7\frac{3}{4} \times 11\frac{3}{4} \times 14$ cm; applicator: 16 cm long

Figure 1 Various sizes of applicators for use in the breast (2–5 cm with 0.5 cm increments).

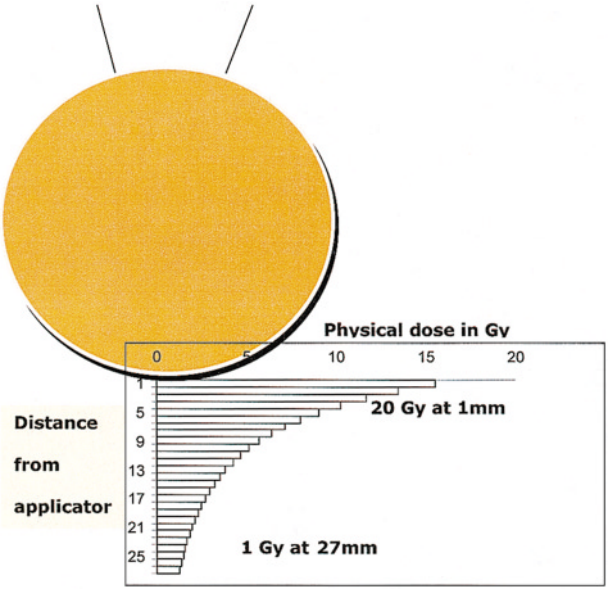

Figure 2 Dosimetry around a 3.5 cm applicator in terms of physical dose with a prescription of 5 Gy at 1 cm.

conical applicator sheath with 2 to 5 cm applicator sphere at the tip). This system is called Photon Radio Surgery System (PRS400) and has been cleared by the Food and Drug Administration (USA) and also carries a CE mark permitting the distribution of products in the European Union as well. Since it is not a radioactive source, it does not have any special storage requirements and its maintenance is little more than an X-ray machine. The quality assurance tools are supplied by the company and the local medical physics team can easily learn to use it. More information is available on the company's website (www.photoelectron.com)

A range of applicators from 2.5 cm to 5 cm have been developed for use in the breast (Fig. 1). The dosimetry around a 3.5 cm diameter applicator is shown in Figure 2. We have found the shape of the cavity after wide local excision resembles a multisided pyramid with the base resting on the posterior/deep wall. However, this cavity could easily be made spherical if the pliable breast tissue were wrapped around a rigid applicator so that the tissue immediately beyond the surgical excision would be closely applied to the surface of the applicator (Fig. 3) and thus get the highest dose of radiation. The prescribed dose is 5 Gy at 1 cm. This delivers a physical dose of about 20 Gy at the surface of the applicator. The time to deliver this dose depends upon the size of the applicator – generally larger the applicator, longer the duration. For a 3.5 cm applicator, it usually takes 24–25 minutes and for a 5 cm applicator about 38 minutes. It is important that the X-ray source (XRS) does not move at all during the treatment since even a millimetre movement can change the dosimetry. The original special suspending gantry that we have used (Fig. 4) has a hydraulic counter-balance system designed to maintain the XRS stable in any position that it is placed. Subsequently, the manufacturing company (Photoelectron Corporation (PeC), 5 Forbes Road, Lexington, MA 02421-7305, USA) has established a strategic alliance with Carl-Zeiss and the current commercial device uses a multi-armed device to hold the XRS in position. The whole system is now being marketed as 'Intrabeam'.

Sterilization issues

In the first few cases using the Photoelectron's Photon Radio Surgery (PRS) X-ray Source (XRS), we sterilized the whole X-ray source using plasma sterilization. This required it to be re-calibrated in the sterile atmosphere of the operating theatre by the medical physicists team taking about 1 hour of additional time. In addition, the tip of XRS accumulated molybdenum trioxide which is potentially toxic. So we stopped sterilizing the whole XRS, instead enclosed it in a large sterile plastic bag. We used a large transparent plastic bag (38.1 cm × 63.5 cm × 99 cm or 15 × 25 × 39 inches, 40 μ thick) with a pleat on either side – that is ubiquitous in our operation theatres, easy to sterilize and costing almost nothing. The XRS is now calibrated on the previous day at the convenience of the medical physicists and kept un-sterilized. The applicators are sterilized, each in separate covers. During surgery, the sterile plastic bag is modified – a hole was cut at its bottom – to accommodate the applicator sphere. Then, the applicator is inserted in plastic bag such that the sphere protrudes out of it and the conical sheath remains inside the bag. The edges of the newly created hole are now sealed with

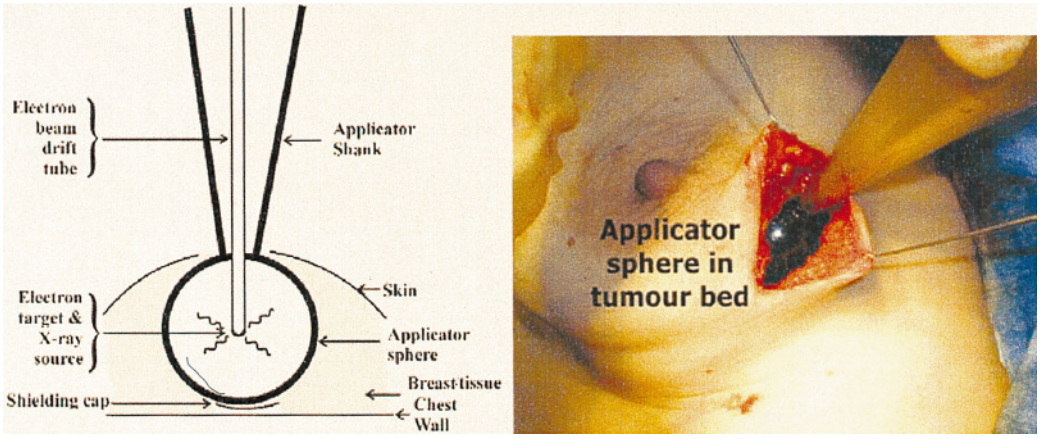

Figure 3 Positioning the applicator in the breast. Schematic diagram of the applicator (left) and a photograph showing how the pliable breast tissue wraps around the source (right). The electrons are generated and accelerated in the main unit (seen in Fig. 4) and travel via the electron beam drift tube which is surrounded by the conical applicator sheath such that its tip lies at the epicentre of the applicator sphere. Once the electrons hit the inner surface of the hemisphere at the tip, X-rays are generated. Thus, a uniform radiation dose rate is available at the surface of the applicator sphere. There is a small very high dose region close to the applicator which attenuates quickly (α 1/r3). Hence we expect a low risk of long term fibrosis. Reproduced from Vaidya et al., *Ann Oncol* 2001; 12(8): 1075–80, by kind permission of the European Society of Medical Oncology (ESMO).

Figure 4 The special gantry to hold the applicator and the new Intrabeam. Left half reproduced from Vaidya et al., *Ann Oncol* 2001; 12(8): 1075–80, by kind permission of the European Society of Medical Oncology (ESMO).

sterile tape to the junction of the applicator globe and shaft. The bag is then inverted inside out. The XRS is now lowered into the applicator and locked in and the power supply cord attached. The bag is now lifted over the XRS so that it covers it and is secured with sterile plastic tapes. This procedure of covering the XRS has been inspected and approved by our consultant microbiologist. This adaptation has considerably reduced the time the physicists needed to spend in the operating theatre.

Operative technique

A single prophylactic dose of intravenous antibiotic (Cefuroxime 1.5 gm) is given at induction of anaesthetic. The wide local excision (WLE) is carried out in the usual way and immaculate haemostasis achieved. The depth of excision always includes the pectoralis fascia so that there is no breast tissue beyond the deep margin. This is especially important on the left side. One or two gauze pieces are left in the breast wound and axillary surgery is performed. This consists of either the usual axillary dissection or sentinel node biopsy, alone or in combination with axillary dissection as part of another ongoing clinical trial.

Haemostasis of the breast wound is now rechecked. This is very important because even a tiny ooze from capillaries can collect significant amount of blood over the duration of radiotherapy and this could potentially cause a distortion of the cavity around the applicator. Distortion of the cavity can change the dose that the target tissues receive. In addition we have found that the temperature of the cavity rises by 2°C from an average of 32°C that is present in the operative cavity in the operating theatre. This increase in temperature could induce bleeding so it is important that meticulous haemostasis is achieved.

The diameter of the cavity is now measured with a disposable tape measure cut to 4 cm or 5 cm (Fig. 5). This and the judgement of how well the breast wraps around the applicator – actually inserting the applicators in the wound and visualizing the apposition is very useful – will determine the size of the applicator. The usual size of the applicator is 3.5, 4 or 4.5 cm. We have used the 3 or 5 cm applicators only a few times.

A purse-string stitch is now taken with a No 1 silk mounted on a hand-held needle (Fig. 6). This step is very important and needs to be taken very carefully because the dose to the target tissues depends on how well it is taken. This stitch should be taken deep to the whole cavity edges, through the breast tissue and not in the subcutaneous tissues, such that on tightening the purse string, the skin should not get pulled too close ($<$1 cm) to the applicator; at the same time, on pulling the purse-string, the breast tissue should appose to the surface of the applicator and wrap around it. It is important to visualize and ascertain during this phase, how well the target breast tissues appose to the applicator surface. It adheres naturally. If the tumour is on the left side, a tungsten-impregnated rubber shield is used to cap the applicator, to protect the heart and coronary vessels

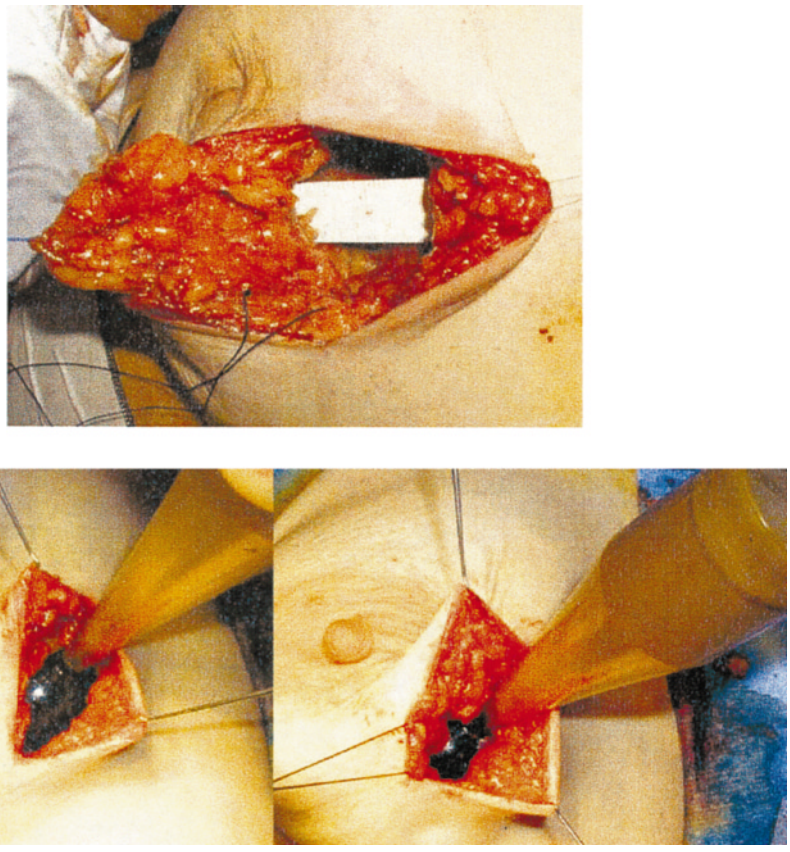

Figure 5 Cavity is measured with a cut tape (above) and the applicator is inserted in the cavity to assess the closeness of fit (below).

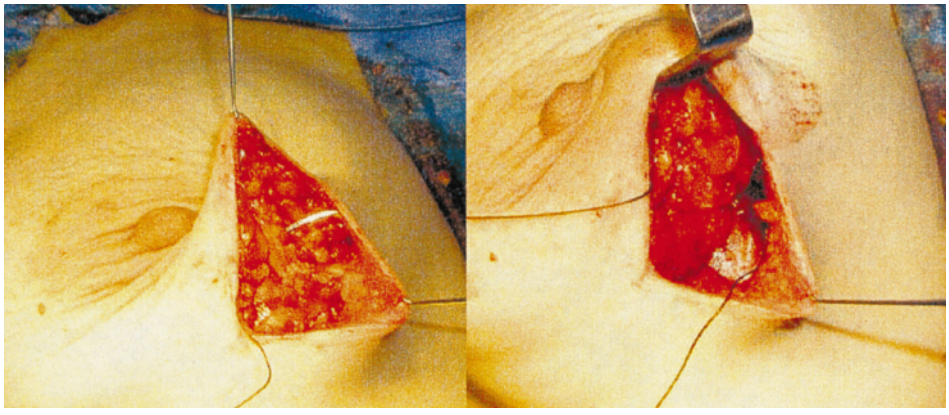

Figure 6 Purse string suture taken with a No 1 silk on a hand-held needle.

(Fig. 7). The applicator cap needs to be positioned such that it apposes the bare muscle on the chest wall. Since the Intrabeam device is not sterile, it is wrapped in a sterile polyethylene bag. At first, a hole is cut at the closed end of the bag for the applicator sphere to come out which is taped at its neck (Fig. 8). The bag is now turned inside out (Figs 9 and 10). Once the purse string and position of the gantry is ready, Intrabeam is attached to the applicator and the bag reversed over the Intrabeam to cover it – and taped in place. A commercial device – modelled over this prototype – is now available with pre-designed holes and tapes to cover the Intrabeam device. Once the applicator is in place, the position of the chest wall shield is ascertained, the purse string is tightened carefully (Fig. 11). Care is taken to ensure that all breast tissue in the cavity apposes applicator and no part of skin is less than 1 cm from the applicator. Frequently the skin edge flips over the applicator. In order to avoid this getting an excessive radiation dose, a 3-0 Prolene stitch is now taken (Fig. 12) in the dermis of the

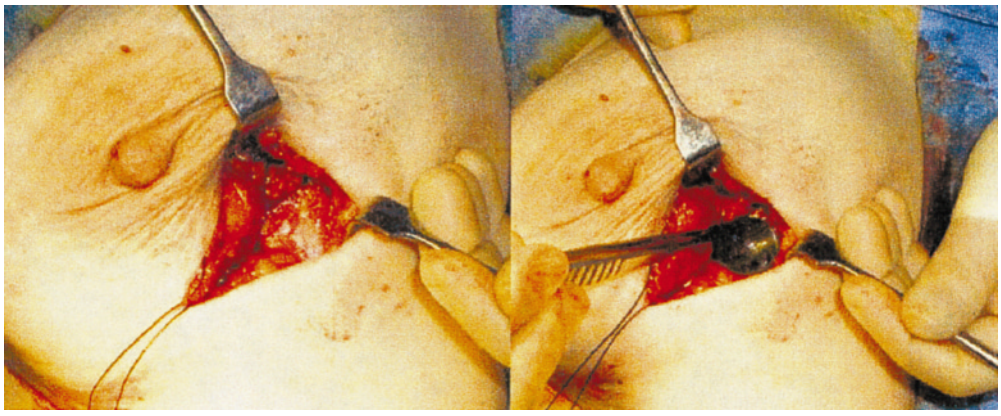

Figure 7 Tumour cavity in a left breast – and the shield being placed on chest wall.

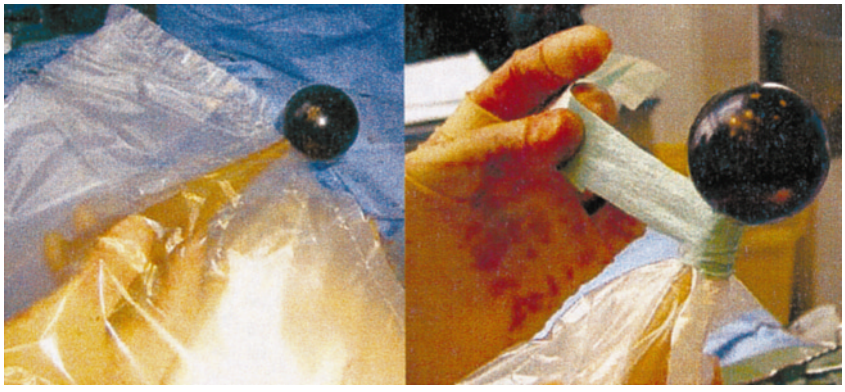

Figure 8 Applicator is wrapped in sterile polyethylene bag and taped.

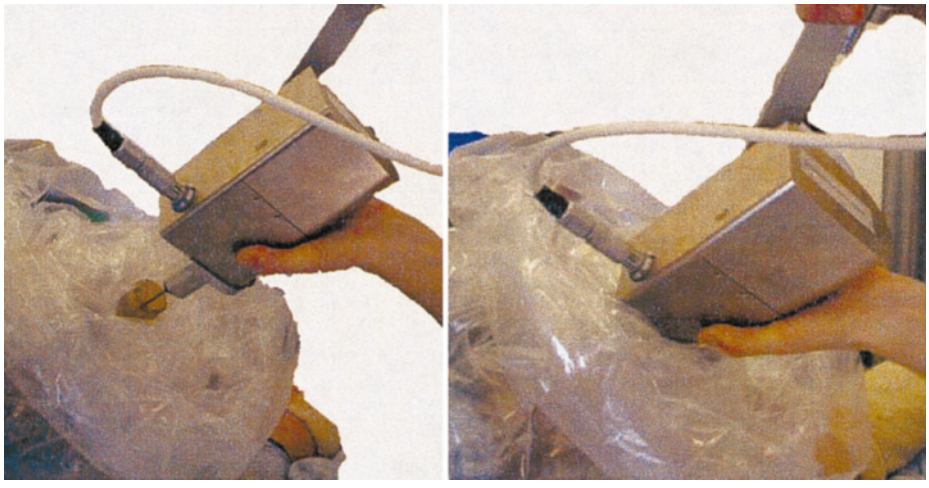

Figure 9 The X-ray source is being inserted into the applicator.

skin edge in order to pull it away from the shaft of the applicator so that it does not come in direct contact with the applicator or in direct line of the applicator with only an air gap in between. Three Thermo-Luminescent Detectors (TLD) and a sheet of Radio-chromatic paper (RCP) is placed adjacent to the skin edges and kept in place with transparent tapes (Fig. 13). The minimum distance between skin at the site of TLD/RCP and the applicator is measured. Care is taken that this is not less than 1 cm. If the cavity is such that the best positioned purse string still draws one part of the skin too close to the applicator then a small piece of gauze soaked in saline, and 0.5 cm to 1 cm thick is inserted between the skin and applicator such that the gap between the applicator

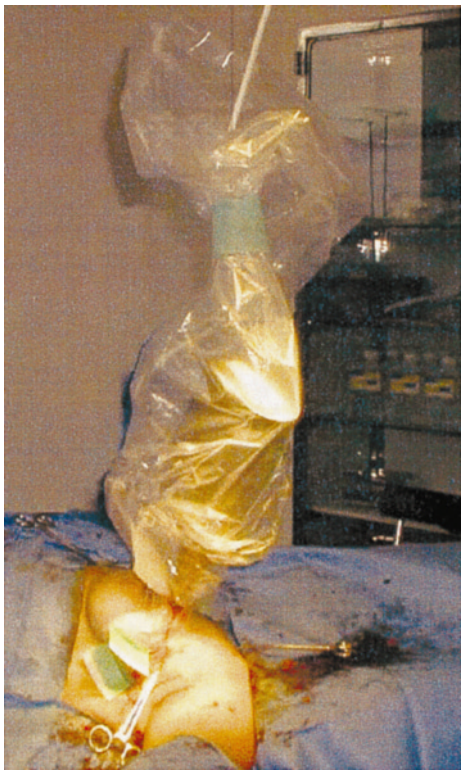

Figure 10 The whole assembly.

surface and the skin is at least 1 cm. If the tumour is very superficial we have preferred to take a small ellipse of skin that might be involved – as would be the normal oncological practice.

When the XRS is lowered into the breast wound we have found that lowering the operation table to the lowest level, helps in balancing the XRS in the most stable position. The position of the XRS should be usually vertical and stay in its position once it is left free to hang. Once the XRS and the applicator is inserted and well balanced, a Tungsten impregnated sheet covers the wound around the applicator (Fig. 14). This blocks 95% of radiation and reduces the amount of radiation in the operating theatre to very low levels and that in the corridor to near zero levels.

The anaesthesiologist wearing a lead gown sits behind a portable lead shield and the physicists are located just outside the operating theatre, along with the portable computer and monitoring equipment. The surgeons and nurses un-scrub and go out of the theatre.

Once the radiotherapy is completed, the shield is removed, the purse-string cut and the XRS delivered to the Physics team. The TLDs and Radiochromatic paper is handed over, carefully mapping the position of each of the TLD. Haemostasis is re-confirmed and wound closed. We used a 2-0 prolene subcuticular stitch

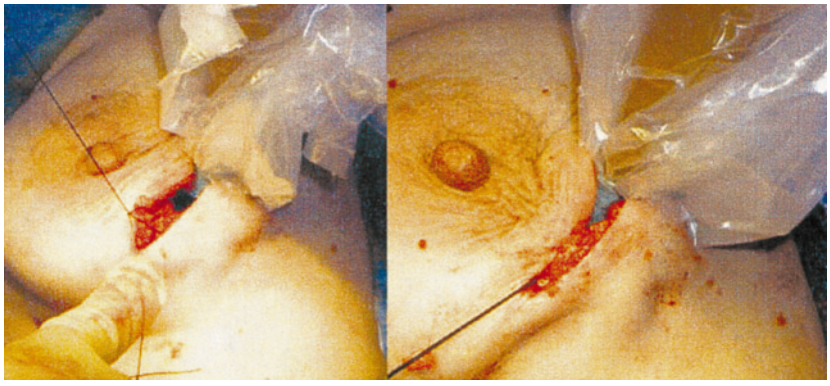

Figure 11 Purse string is now tied securely.

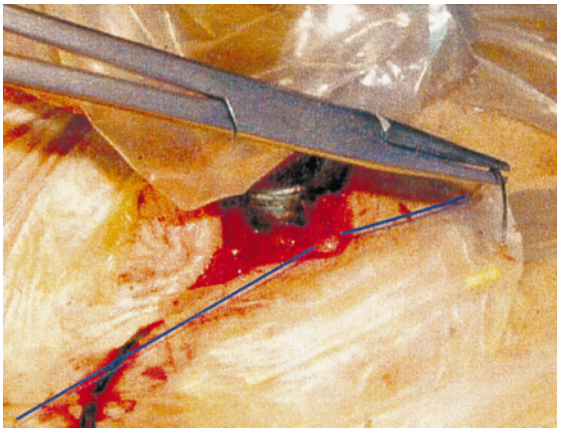

Figure 12 Prolene stitch everting skin edges.

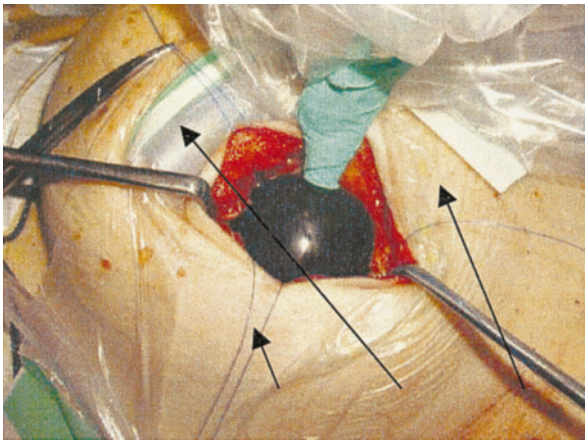

Figure 13 Placement of purse-string, RCP and TLD.

Figure 14 Intrabeam in place and site covered with protective shield.

in early cases, leaving it for 14 days before removal. Since January 2000 we have used 3-0 monocryl absorbable monofilament suture which is absorbable and does not need to be removed, but the steristrips are left in place for 14 days, unless there is need to remove them earlier.

The axillary wound is always drained with a Redivac drain and the breast wound sometimes, drained depending on the individual patient. The breast drain is removed within 24 hours to reduce the chance of causing a puckered wound. Delivering Targit increases the operating time by 45 minutes on average (range 34 to 60 minutes).

Post-operative care

The post-operative care is not different from the usual. If there was a breast drain, it is removed at 24 hours and the patient is usually home after removal of axillary drain within 3–6 days.

Radiation safety

The operation and radiotherapy are carried out in the usual operating theatres with no special shielding apart from the portable lead shield and lead aprons. The measurement of radiation dose on the anaesthetist's body is nearly undetectable.

Summary of the operative technique

- Assess the size.
- Secure haemostasis.
- Prepare the applicator in the plastic bag.
- Insert a shielding cap if tumour on left side.
- Take a purse-string suture in breast tissues (not dermis).
- Attach the applicator (already in plastic bag) to the XRS.
- Lower the applicator in the wound – and pull the purse string.
- Adjust and ascertain close fit of breast-wrap-around the applicator.
- Tie the purse string.
- Take the conforming prolene stitches for reflecting skin edges.
- Reassess the closeness to skin.
- Place the TLD and radio-chromatic paper.
- Place the tungsten impregnated shields over the wound.
- After radiotherapy – meticulous haemostasis and closure.

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The video demonstrating this technique is available online at http://www.idealibrary.com on IDEAL®.