

**A NOVEL APPROACH FOR LOCAL TREATMENT OF  
BREAST CANCER**

**DISSERTATION FOR THE DEGREE OF**

**DOCTOR OF PHILOSOPHY**

**BY**

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## CHAPTER 4

# **The novel technique of intra-operative radiotherapy**



## Introduction

We have used a novel technology to deliver therapeutic radiation. The technique employs a miniature



electron-beam driven x-ray source (the Photon Radiosurgery System (PRS) developed by the Photoelectron Corporation in Massachusetts, USA) that delivers low energy (50Kv) x-ray radiation directly to the tumour site/ tumour bed from the tip of a 10cm long, 3.2mm diameter, tube. Being soft x-rays, there is quick attenuation of the radiation within tissues so that the dose is inversely proportional to the 3<sup>rd</sup> power of the distance. Such quick attenuation reduces the damage to surrounding normal tissues and minimises the need for radiation protection to the operating personnel. The x-ray production itself is controlled very precisely and monitored in three ways – one within the X-ray source, one kept on the operating theatre

table and third using thermoluminescent detectors (TLDs). The portability of the device enables radiation treatments to be delivered precisely and directly to the inside of tumours, or the tumour bed, while at the same time, minimising unwanted irradiation of surrounding tissue.

Since the radiation consists of soft X-rays, the beam is rapidly attenuated to reduce the dose to more distant tissue. Full measurements and calibration are carried out in a water phantom and in materials that simulate the radiation absorption properties of the breast. 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 minutes at 1cm from the margins of a 3.5 cm cavity after wide local excision of the tumour.

The whole assembly is small and lightweight (Weight =1.8 Kg, Dimensions: X-ray generator body 7 x 11 x 14 cm; applicator: 16 cm long conical applicator sheath with a 2 to 5 cm applicator sphere at the tip) and hangs dependently from a mobile gantry in perfect balance remaining steady wherever it is positioned. 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 using interstitial implantation of radioactive wires to provide high dose radiotherapy to the tumour bed or the even more complex techniques necessary for conformal radiotherapy by external beams with multi-leaf collimators from a linear accelerator. The quick attenuation of the radiation dose allows the treatment to be carried out

### ***The Physics and Radiobiology***

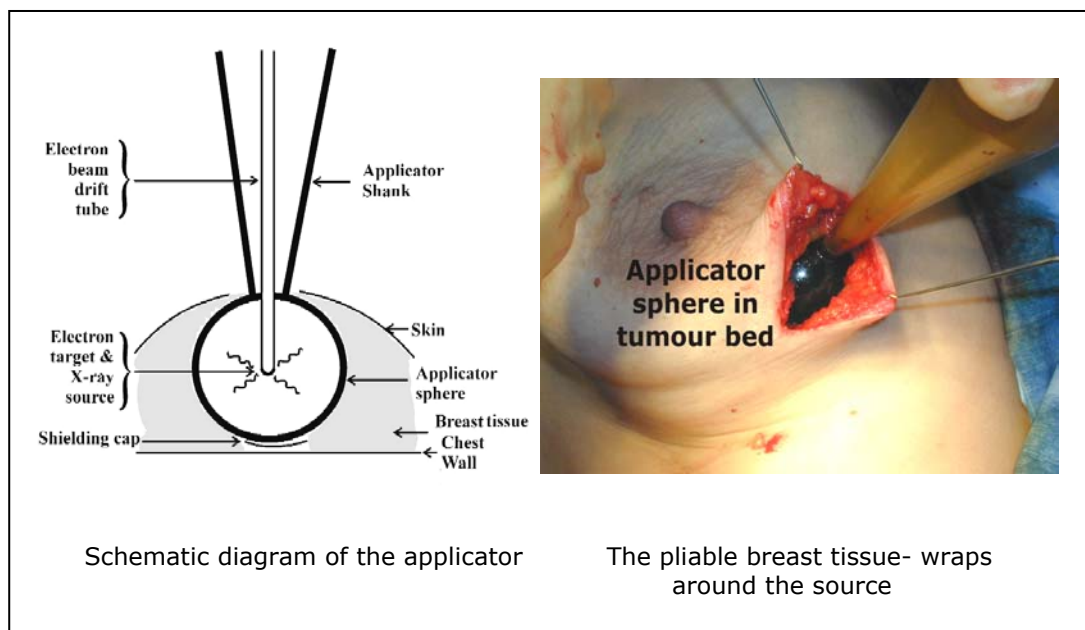
The miniature x-ray source (XRS) developed for the Photon Radiosurgery System contains a proprietary miniature x-ray tube, a high voltage power supply, and the associated electronic circuitry required to control and monitor the operation of the x-ray tube.

The distal end of the x-ray tube is a thin probe extending outside the XRS enclosure. X-rays are emitted from the tip of the probe, which is inserted into the site to be irradiated. Within the XRS, an electron gun accelerates electrons towards a gold

in unmodified operating theatres. The walls usually incorporate shielding for microwave radiation from electronic equipment such as mobile phones and such walls provide enough protection to the staff. Furthermore, the biologically effective dose (BED) attenuates rapidly so that the highest radiation dose is received by tissue nearest the primary tumour and a much lower dose at the skin. Thus in theory, the biological effect and cosmetic outcome could be improved.

target at the tip of the probe.

The last 2cm of the probe are made of beryllium, an x-ray transparent material. When the electrons strike the target, x-rays are generated in a nearly spherical distribution centred at the tip of the probe. The x-ray tube (XRT) is a miniature electron gun and electron accelerator. Electrons are generated and accelerated towards a gold target at the end of a long, thin drift tube or probe. The operation of the x-ray tube requires that the filament be heated which, in turn, heats the cathode and an excess of electrons is generated by thermionic emission. Electrons produced by the gun are accelerated to the desired energy, and with the help of steering



Schematic diagram of the applicator

The pliable breast tissue- wraps around the source

coils, directed down an evacuated field-free tube towards a thin, gold target. Anodes located in the electron gun assembly provide the accelerating potential of the electron beam. The vacuum envelope of the system is composed of a brazed metal/ceramic structure for good thermal and mechanical shock tolerance. The electron optics of the device are designed to provide a highly focused, stable spot of electrons at target. Following acceleration, the electrons enter a 10cm long, 3mm diameter "needle" type, evacuated drift tube. The drift tube or probe passes through the deflection coils and is terminated with a beryllium (Be) window that is transparent to x-rays. The electron beam is directed to a point on the target. When fast electrons interact with matter, part of their energy is converted into electromagnetic radiation in the form of characteristic and bremsstrahlung radiation. The fraction of the electron energy converted into bremsstrahlung increases with increasing electron energy, and is largest for absorbing materials of high atomic number (the atomic number for gold is 79). This is the same process that results in the production of x-rays within conventional x-ray tubes. The result of this is the production of a symmetric distribution of radiation around the tip of the probe.

The physics, dosimetry of this soft x-ray device have been well studied and the probe has already been tested in pre-clinical studies.

Radiobiological experiments [Astor et al., 2000] using cell cultures have suggested that the radiobiological effectiveness (RBE) of the PRS system is between 1.2 and 2.5. This was in agreement with

microdosimetric analysis and modelling [Brenner et al., 1999]. The PRS radiation is found to induce both necrotic and apoptotic cell death in addition to rapid cell death through non-apoptotic pathway.[Kurita et al., 2000]. Animal experiments have demonstrated that PRS can induce well demarcated ablation in canine liver and kidney [Koniaris et al., 2000;Solomon et al., 2001].

Thus, the characteristics of this radiation are:

- **Low energy x-rays** (50keV maximum) used to ensure minimal radiation dose to adjacent normal tissues and critical structures.
- **Low voltage supply**, approximately 12V, ensures no electrical hazard to the operator.
- The XRS is **lightweight and portable**, which makes it easily adaptable to any clinical application.
- The low energy x-rays produced by the XRS are easily shielded, and there are **minimal radiation protection requirements** in the operating room.
- The PRS has been cleared by the FDA after the report of this project, to be marketed for radiotherapy anywhere in the body and also carries a CE Mark allowing it to be marketed in the European Community for radiotherapy applications.



- We have developed a range of applicators from 2.5cm to 5cm for use

in the breast, as detailed in the next section.

- A range of special Quality Assurance tools is supplied with every system to ensure maximum safety and ease-of-use. These are

necessary as a result of the x-ray source's unique treatment geometry.

The radiation dose at various distances from the cavity margin varies as shown in the table, for the simulated assembly.

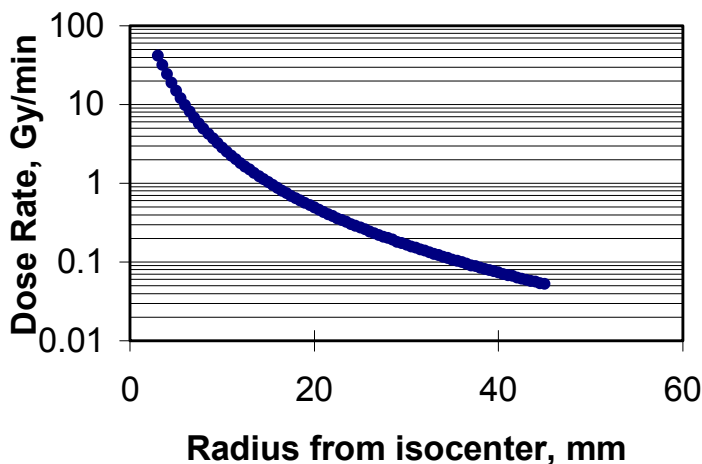
Standard dosimetry table: Calculations for a 3.5 cm diameter spherical applicator and a period of irradiation of 21 min as measured from the periphery of the sphere in a breast phantom. (PRS operating parameters:50Kv)

Distance from the surface of the applicator	PE probe (Gy)		External beam radiotherapy (Gy)		Whole breast radiotherapy (Gy)	
	PD	BED	PD	BED	PD	BED
0.1 cm	15	165	10	12	50	60
0.2 cm	12.5	121	10	12	50	60
0.5 cm	8.75	59	10	12	50	60
1 cm	5	21.7	10	12	50	60

PD= Physical x-ray dose, BED= Biologically effective dose, .

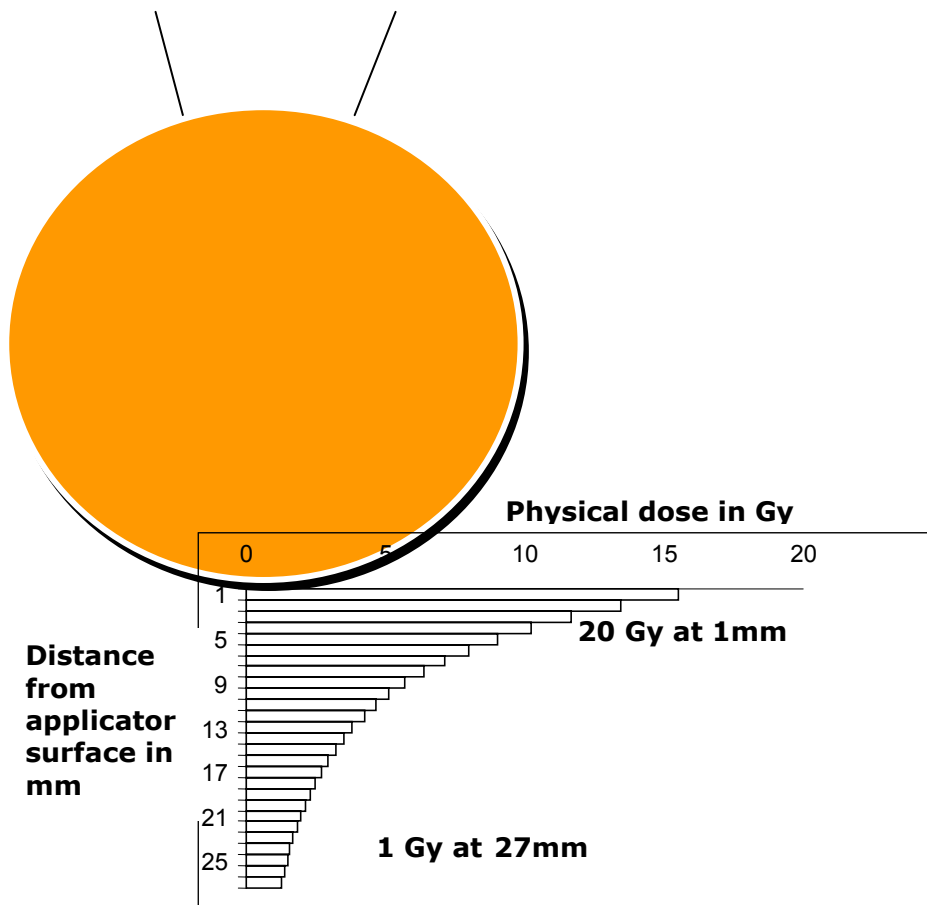
The biologically effective dose (BED) is given by the equation (Dale 1985),  $BED= D \times (1 + (d/(\alpha/\beta)))$ , where D is the total physical dose, d is the physical dose per fraction and  $\alpha/\beta$  is the biological coefficient which is 10 for early and tumour effects when radiotherapy is delivered in fractions of about 2Gy. For a single dose, we have assumed the value of  $\alpha/\beta$  to be equal to 1.5. It could actually range from 1.5 to 4.

Dosimetry around the bare probe in water (in terms of dose rate)





Dosimetry around the applicator (in terms of physical dose with a prescription of 5Gy at 1cm)

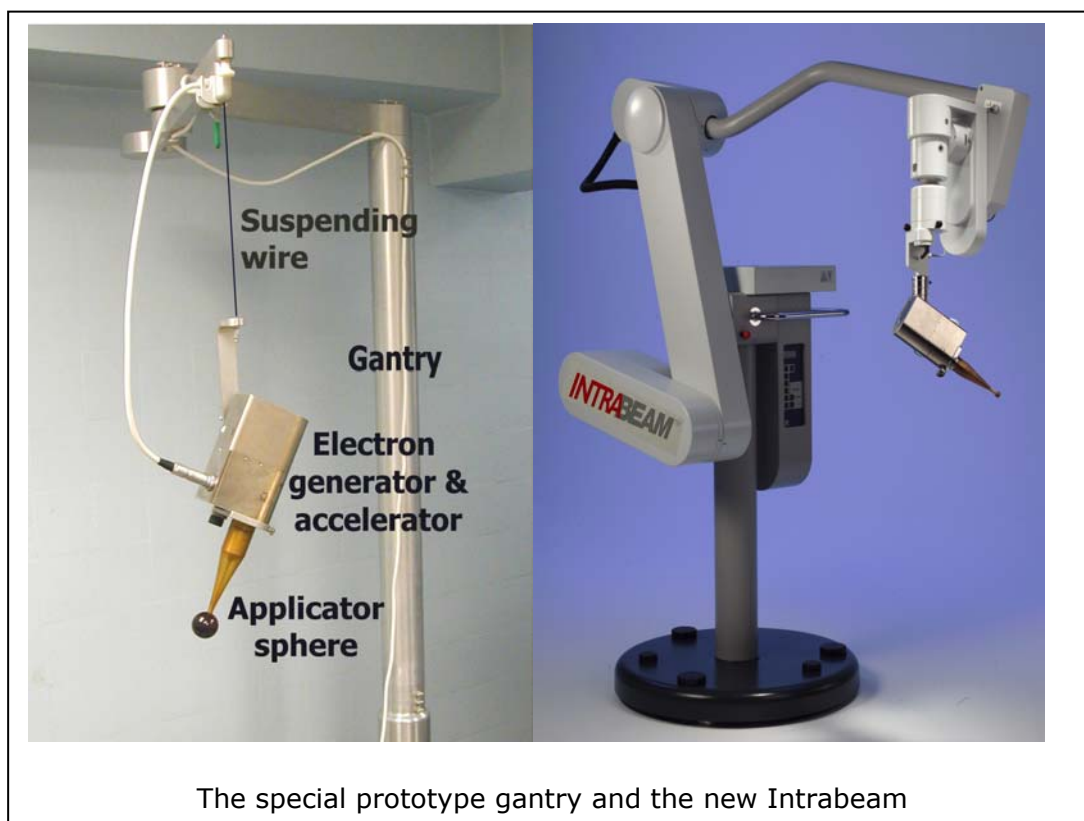


### Positioning the X-ray source

It is important that the x-ray source (XRS) is very stable and does not move at all during the treatment. It was thought that the movement of the chest wall during respiration would cause enough displacement of the x-ray source and the applicator within the tumour cavity to jeopardise the correct dosimetry. Hence a special suspending gantry was designed.

This is a large gantry that suspends the XRS with the help of a hydraulic

counter-balance system such that it remains stable in any position that it is placed. While doing treatments, it was noticed that in actual fact, there is hardly any movement of the XRS during normal respiration and therefore there is no need for the large, heavy and awkward gantry. A simple arm to fix the XRS to the operating table would be adequate. Subsequently, the PeC Company established a strategic alliance with Carl-Zeiss and the commercial device uses a multi-armed device to hold the XRS in position the system being called INTRABEAM.



### **Development of the machine for Brain tumours**

The machine was originally developed for the treatment of brain tumours using stereotactic frames. This development started in 1992 and the machine was used for treatment of brain tumours since 1994. [Butler et al., 1998; Cosgrove et al., 1997; McDermott et al., 1996; Douglas et al., 1996] [Cosgrove et al., 1997; Cosgrove et al., 1999]

### **Conceptualisation and adaptation for the breast: use of special applicators**

In the spring of 1996, we began a dialogue with the company to adapt the machine for use in the breast. This would need to adapt the technique for use in a very different part of body. As opposed to the

brain, where there are bony landmarks whose relationship to neural structures is relatively fixed, breast is a very mobile organ. There are no structures - reference points - that have a constant relationship to a tumour bed. We felt that movement of the chest wall during respiration would also change the configuration the chest wall enough to make a significant difference. So we had to apply a different strategy. Firstly we assessed the shape of the cavity.

### Shape of the cavity after wide local excision

We assessed the shape of the cavity after wide local excision using a fast setting wound dressing material (Cavicare®). Within 15-20 seconds of mixing the two components the foam that is placed into the cavity starts setting and within 1-2 minutes, the cast of the cavity can be removed to be studied. We found the shape of the

cavity to be rather irregular; nevertheless the shape was that of a multisided pyramid with the base resting on the posterior/deep wall. We also realised that 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 and thus get the highest dose of radiation.

### ***The technique of giving intra-operative radiotherapy***

#### **Sterilisation issues**

In the first few cases using the Photoelectron's Photon Radio Surgery (PRS) X-Ray Source (XRS), we sterilised the whole X-ray source. This was done using Plasma sterilisation. Sterilising the XRS meant that it had to be delivered to the Central Sterilisation Department at least 24 hours in advance and, when it was returned, it needed to be re-calibrated in the sterile atmosphere of the operation theatre by the medical physicists team downed in sterile gowns and gloves. This took about 1 hour of additional time of the physicists on the day of the surgery. After the first few cases, we also found that the tip of XRS accumulated an oxidative product of Molybdenum viz., Molybdenum trioxide. Molybdenum trioxide is potentially toxic - irritant to eyes and upper aero-digestive system and there is some evidence of its carcinogenicity in mice and male rats. A solution to these problems was to enclose the XRS in a large sterile plastic bag. We used a large transparent plastic bag (38.1cm

x63.5cm x99cm or 15x25x39 inches, 40 $\mu$  thick) with a pleat on either side - that is ubiquitous in our operation theatres, easy to sterilise and costing almost nothing. The XRS was calibrated on the previous day at the convenience of the medical physicists and kept un-sterilised. The applicators were sterilised, each in separate covers. During surgery, the sterile plastic bag was modified - a hole was cut at its bottom - to accommodate the applicator sphere. Then, the applicator was inserted in plastic bag such that the sphere protruded out of it and the conical sheath remained inside the bag. The edges of the newly created hole were now sealed with sterile tape to the junction of the applicator globe and shaft. The bag was then inverted inside out. The XRS was now lowered into the applicator and locked in and the power supply cord attached. The bag was now lifted over the XRS so that it covered the XRS. The bag was kept in place with sterile plastic tapes. This procedure of covering the XRS was inspected and approved by the Consultant Microbiologist. This adaptation considerably reduced the time the physicists needed to spend in the operating theatre.

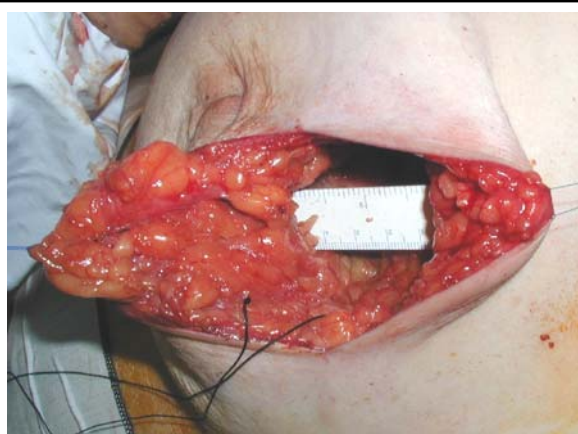
#### **Operative technique**

A single prophylactic dose of intravenous antibiotic (Cefuroxime 1.5gm) is given at induction of anaesthetic. The wide local excision (WLE) is carried out 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

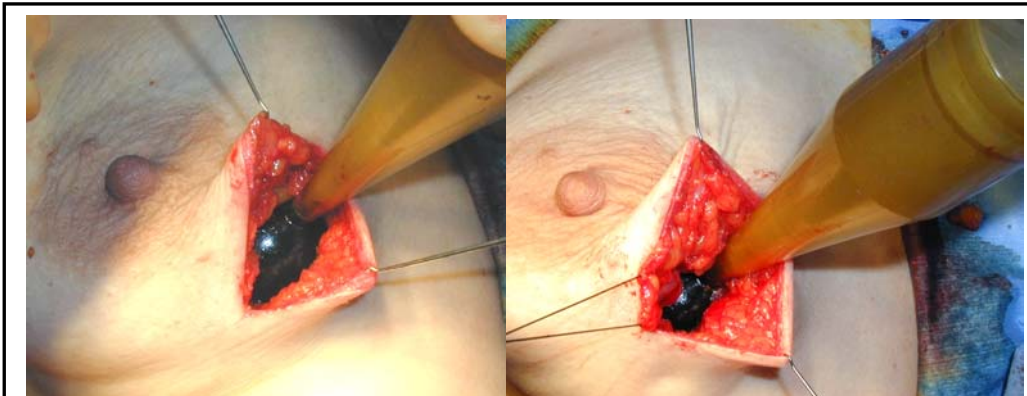
usual axillary dissection or sentinel node biopsy, alone or in combination with axillary dissection as part of another ongoing clinical trial.

Haemostasis of the breast wound is now rechecked. This is very important since, even 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 dilate the blood vessels and cause an ooze. The diameter of the cavity is now measured with a disposable tape measure cut to 4cm or 5cm. This and the judgement of how well the breast

wraps around the applicator – actually inserting the applicators in the wound and visualising the apposition is very useful – will determine the size of the applicator. The usual size of the applicator is either 3.5, 4 or 4.5 cm. We have used the 3 or 5cm applicators only a few times.



Cavity is measured with a cut tape

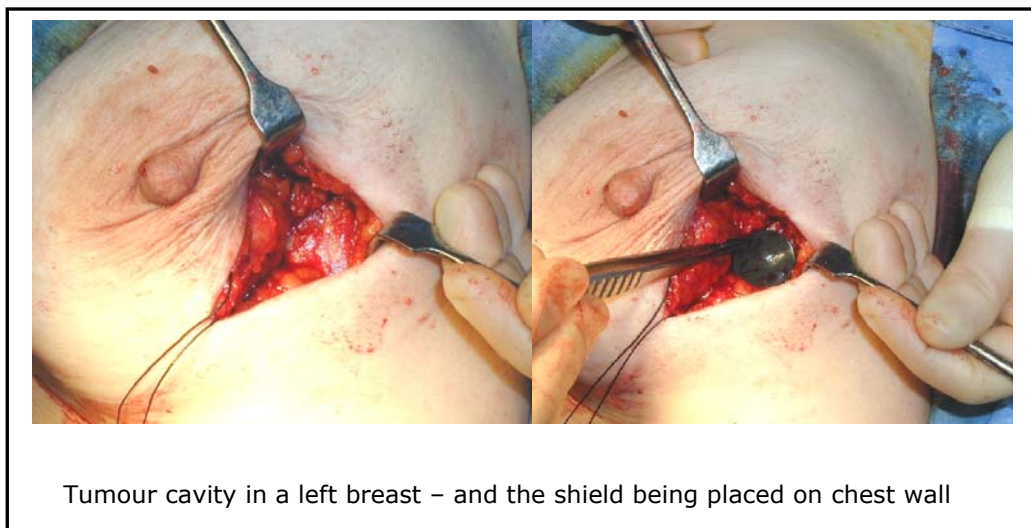
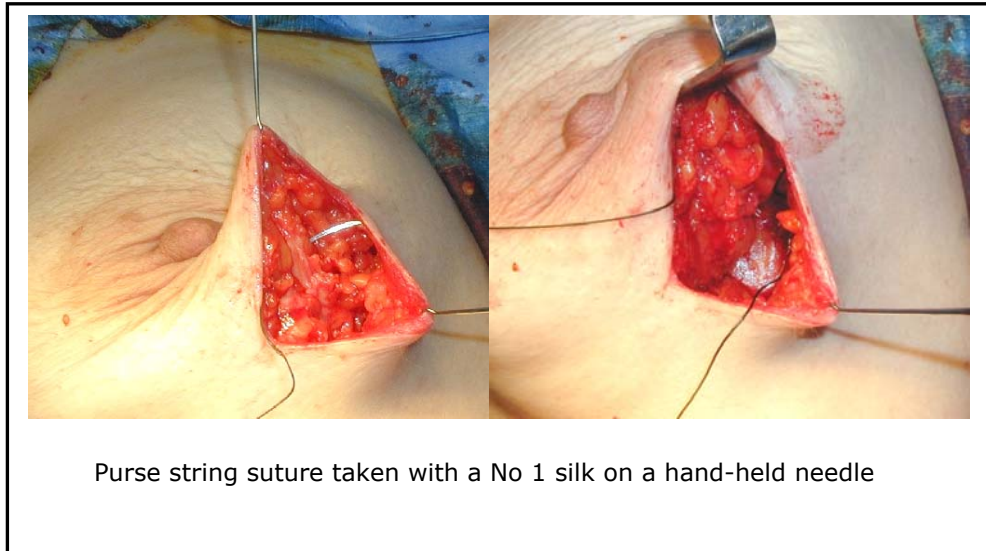


The applicator is inserted in the cavity to assess the closeness of fit

A purse-string suture is now taken with a No 1 silk mounted on a hand-held needle. 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 (<1cm) 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 visualise and ascertain during this phase, how well the target breast tissues appose to the applicator surface. It adheres naturally.

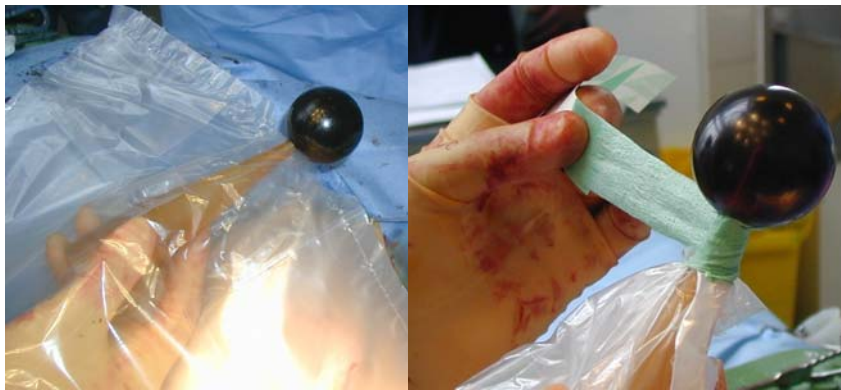
If the tumour is on the left side, a tungsten-impregnated rubber shield is used to cap the applicator, to protect the heart and coronary vessels. The applicator cap needs to be positioned such that it apposes the bare muscle on the chest wall.



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.

The bag is now turned inside out. 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

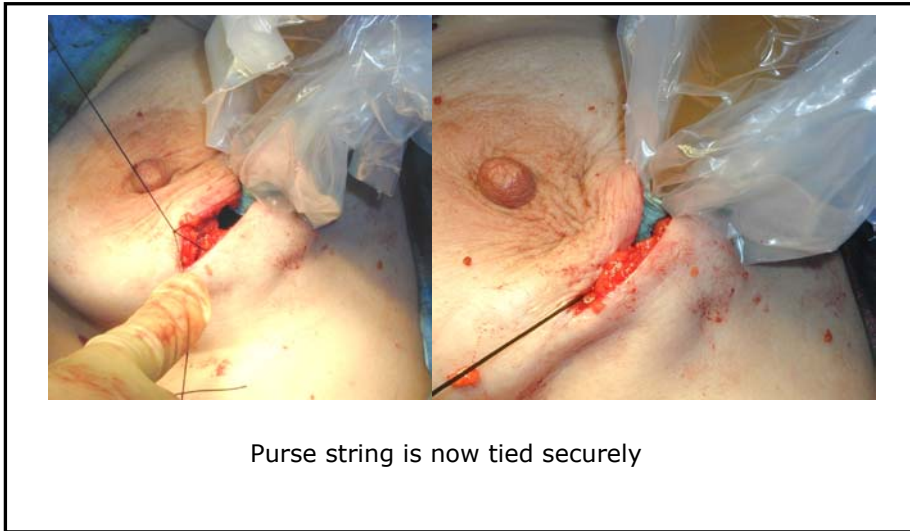
it- and taped in place. In the commercial device- modelled over this prototype is now available with pre-designed holes and tapes to cover the Intrabeam device. Once the applicator is in place, the position of the chest wall shield is ascertained, the purse string is tightened carefully. Care is taken to ensure that all breast tissue in the cavity apposes applicator and no part of skin is less than 1cm from the applicator.



Applicator is wrapped in sterile polyethylene bag and taped



The X-ray source is being inserted into the applicator





The whole assembly





Frequently the skin edge flips over the applicator. In order to avoid this getting excessive radiation dose, a 3-0 Prolene stitch is now taken in the dermis of the 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.

The minimum distance between skin at the site of TLD/RCP and the applicator is measured. All care is taken that this is not less than 1cm. If the cavity is such that the best positioned purse string still draws one part of the skin too close to the

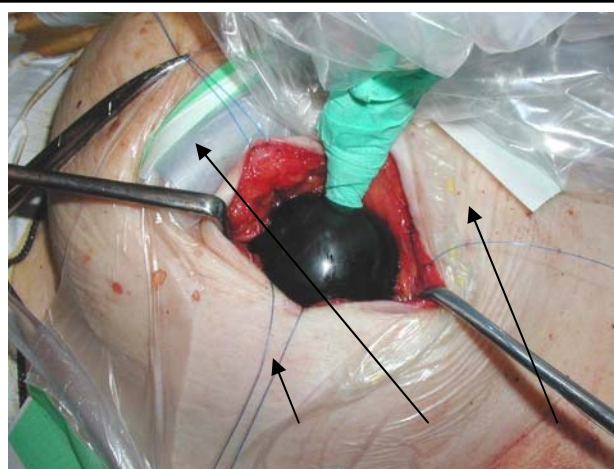
applicator then a small piece of gauze soaked in saline, and 0.5cm to 1cm thick is inserted between the skin and applicator such that the gap between the applicator surface and the skin is at least 1cm. If the tumour is very superficial we have preferred to take a small ellipse of skin that might be involved - as would be the normal oncological practice.

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.

When the XRS is lowered into the breast wound we have found that



Prolene stitch everting skin edges



Placement of purse-string, RCP and TLD

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. 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 anaesthetist wearing a lead gown sits behind a portable lead shield and the physicists are located just outside the operation 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 confirmed and wound closed. We used a 2-0 prolene subcuticular stitch in early cases, leaving it for 14 days before removal. Since the last year 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, the choice based on individual patient. The breast drain is removed within 24 hours to reduce the chance of causing a puckered wound.

Giving IORT increases the operating time by 45 minutes on average (range 34 to 60 minutes).

The prescribed dose is 5Gy at 1cm. This delivers a physical dose of about 20Gy 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 3.5cm applicator, the



time is usually 24-25 minutes and for a 5cm applicator it is usually around 38 minutes. The radiation from the probe varies by a small fraction at every session and is calculated on site – hence the small range of durations even for the same size of the applicator.

### **Postoperative care**

The postoperative 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 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**

- Assess the size
- Achieve meticulous haemostasis
- Prepare the applicator in the plastic bag
- Position the shielding cap if tumour on Left side
- Prolene stitches for reflecting skin edges if required
- Purse string in breast tissues
- Attach the applicator (already in plastic bag) to the XRS
- Lower the applicator in the wound – and pulling the purse string
- Adjust and ascertain close fit of breast-wrap-around the applicator
- Tie the purse string
- Reassess the closeness to skin etc
- Place the TLDs
- Place the shields over the wound
- After radiotherapy- reconfirm haemostasis and close the wound with subcuticular monocryl sutures.

These are the photographs of the first case on 2 July 1998

