A NOVEL APPROACH FOR LOCAL TREATMENT OF BREAST CANCER

DISSERTATION FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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CHAPTER 5

The pilot study of intra-operative boost radiotherapy

Time course : events leading up to the setting up of the pilot study

After completion of the study of whole organ analysis of mastectomy specimens (Chapter 2) the paper was presented at the Hong Kong International Cancer Congress in November 1995. This was the time when I proposed that radiotherapy to the index quadrant alone is probably sufficient for early breast cancer.

The paper was submitted to British Journal of Cancer for consideration for publication and was finally accepted in April 1996. In April 1996, I started clinical work with Professor Michael Baum at the Royal Marsden Hospital. Between April 1996 to October 1996 the protocol for intra-operative radiotherapy was developed based on the pathological /biological rationale described in the BJC paper.

Photoelectron corporation agreed to sponsor a part of the Research fellow's salary to develop the machine and adapt it for treatment of breast cancer. As discussed in the chapter on technique, we developed the various applicators for use in the breast. There was considerable delay caused by the Medical Devices Agency before these were approved for clinical use.

We proposed a long-term strategy for improving the local treatment of breast cancer in early 1997 as follows:

Long-term strategy for improving the delivery of local treatment for breast cancer

Pathological basis of localised radiotherapy.

Spatial distribution of dormant cancers in the breast

Clinical evidence of sites of local recurrence

The Hypothesis

Radiotherapy to the quadrant alone might be as good as radiotherapy to the whole breast in selected patients

The tools and methods for easier delivery of treatment

Intra operative radiotherapy

Interstitial stereotactic radiotherapy of small cancers

Establishing the efficacy and safety of the tools

Effect of interstitial radiotherapy in elderly women who would otherwise not undergo surgery. (Outcome measure: local control)

Effect of Intra-operative radiotherapy immediately after wide local excision as a substitute for the routine local boost. (Outcome measure: feasibility and local recurrence)

Planning randomised trials (multicentre and in India)

Early breast cancers: WLE + AD + localised RT vs. WLE + AD + Standard RT

Elderly women: Interstitial RT + Tam vs. Tam only

Small breast cancers including screen detected cancers: Interstitial RT only vs. standard Surgery + standard RT

Depending upon the results of the trials, application of the new techniques to benefit women world-wide

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The ethical approval for the intra-operative boost radiotherapy project was given in October 1996. However, the medical devices agency (MDU) did not approve of the new device until June 1998.

During this period I tried to perform several experiments with Comet assay to evaluate the radiation dose and its effects at various distances. However, the dose from the PeC x-ray source fell off very quickly- so that the cells placed on a single microscope glass-slide received a differential dose. These were therefore not analysable using the Comet assay.
The first clinical trial using the PRS device was aimed to test its safety and feasibility and was commenced on 2 July 1998.

Background

Over the past 30 years, there has been a dramatic change in the local management of breast cancer from very radical to more conservative surgical operations, with the widespread use of radiotherapy in conjunction with wide local excision of the tumour itself. This shift away from radical surgery has been prompted by randomised clinical trials that have clearly demonstrated that conservative breast surgery followed by radiotherapy is equivalent to more radical procedures in overall survival [Early Breast Cancer Trialists' Collaborative Group, 1995]. However, although the outcome is 'conservative' the intention is 'radical' with the radiotherapy fields encompassing virtually all of the tissues previously excised by radical mastectomy. This approach needs to be reappraised. A component of the rationale for the less radical approach is that in large studies of breast conservative therapy more than 90% of early breast recurrences have been found to occur at the site of the original primary tumour. This is true whether or not radiotherapy is given [Fisher et al., 1986] and whether or not the margins are involved [Vaidya and Baum, 1998]. Furthermore, this is the case in spite of the fact that, when mastectomy specimens are examined by detailed radiological-histological correlational methods, small additional invasive or *in situ* cancer foci are found in over 60% of patients, with 80% of these situated remote from the index quadrant. The relative distribution of primary tumour and these foci in the four breast quadrants is significantly different [Vaidya et al., 1996]. Hence it appears that these additional cancer foci do not in general give rise to local recurrence which more probably develops from the cells that surround the primary tumour. These may be overtly malignant or morphologically normal, yet capable of malignant progression, as evident by the loss of heterozygosity in these 'normal' cells within the index quadrant [Deng et al., 1996]. We have suggested that the next step is a clinical trial to test whether radiotherapy to the index quadrant alone can achieve as good a local control as radiotherapy to the whole breast [Baum et al., 1997] [Vaidya and Baum, 1998].
This approach of irradiating the index quadrant alone has been tested in two clinical trials and in fact (contrary to the popular myth) the results of these trials are encouraging. The Christie Hospital Trial [Ribeiro et al., 1993] randomised 708 patients to receive either the standard wide field (WF) radiotherapy or a limited field (LF) radiotherapy to the index quadrant. They found that 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 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. In the much smaller (n=27) Guy’s Hospital Study [Fentiman et al., 1991] [Fentiman et al., 1996], a single continuous application of an iridium-192 implant delivering 55 Gy over 5-6 days replaced the standard radiotherapy regimen of whole breast radiotherapy plus tumour bed boost. The authors found a 20% increase in local recurrence compared to historical controls. However, as discussed in a letter in response to the study [Dale et al., 1997], it was pointed out that the Biologically Effective Dose (BED) of the implant-only arm was 20% lower than the conventional radiotherapy arm and this almost completely explained the difference. In addition 12/27 patients in this study were node positive and 15/27 had involved margins - putting these patients at high risk of local recurrence anyway.

Methods and Design

We report here the pilot study approved by the University College London Hospitals Ethics Committee in which a novel method of radiotherapy is used to deliver therapeutic radiation to the tissues around the primary tumour immediately following excision, with a degree of precision impossible with an external beam. The novel technology is called the Photon Radiosurgery System (PRS) developed by the Photoelectron Corporation in Massachusetts, USA and is now commercially available as Intrabeam.
The detailed technical details of the device and the operative technique have already been described in the preceding chapter.

Patients diagnosed using triple assessment (physical examination, imaging and cytology or histology), to have operable breast cancer and suitable for breast conserving surgery were recruited in the pilot study, after a full informed consent. In every case Dr Jeffrey Tobias, the consultant clinical oncologist, obtained the informed consent.

Each patient underwent wide local excision and axillary clearance. The details of the technique have been described in the preceding chapter. In the first 3 cases, the complete PRS device was sterilised. This required the Quality Assurance analysis to be done on the previous day before sterilisation and repetition in the operating theatre under sterile conditions. From the 4th case onwards, we wrapped up the XRS with sterile plastic bag, with a hole for the sterile applicator to pass through. Not only has this made the operation streamlined, it has also significantly reduced the time spent by the medical physics teams in the operation theatre. Since this modification, the average time needed to set-up the system at the end of excision was 12 minutes. When the lesion was on the left side, the chest wall was protected by thin polyurethane- tungsten impregnated sheets that could either be applied to the applicator or custom-made to fit on the chest wall. This reduced the radiation by 99% and protected the heart and

coronary vessels. The applicator sphere was inserted into the breast cavity and a deep surgical purse-string suture was inserted in the subcutaneous plane to bring together the target breast tissue so that it applies well to the surface of the PRS applicator sphere and holds it in place during radiotherapy, as described in detail in the preceding chapter. Our third patient had radionecrosis of the skin close to the scar, which we believe was the site of one of these subcutaneous stitches. Since then we have been retracting the skin with a 3-0 prolene stitch and ensuring that no part of skin is less than 1cm from the applicator surface. Essentially these 'conforming' stitches allowed hands-on-conformation of the target to the source of radiation. The radiation was switched on for 21 to 28 minutes depending upon the size of the applicator sphere, and using an energy of 50kV a dose of 5 Gray (Gy) was delivered at 1cm distance from the cavity margins. After completion of radiation, the 'conforming' stitches were removed and the skin was sutured in the usual manner with a subcuticular prolene stitch, which was left in place for 14 days.

The follow up of these patients was as usual with 3 monthly visits to the outpatients clinic and yearly mammograms. Any other investigations such as ultra-sonography or fine needle aspiration cytology were performed if prompted by symptoms or signs.

We assessed the cosmetic results of the patients with photographs and by comparing patient's own assessment of the cosmetic result. We asked the patients to score the appearance and texture of the breast on an analogue scale of 1 to 10, 10 being the best. We also asked her at the same time, to give a similar score to what she would have expected the appearance and texture to be, again on an analogue scale of 1 to 10, 10 being the best. The satisfaction index was calculated by dividing the patient's score for the actual (observed) appearance (and texture) by her score for what she would have expected it to be (expected). We felt that ultimately, it is the patient's own assessment that is more accurate depiction of the 'real' cosmetic outcome. For comparison with other studies, the 'objective' assessment of photographs by an independent panel would of course be more relevant.

Results

We have completed 26 cases of intra-operative radiotherapy for breast cancer. The patients were diagnosed to have early operable breast cancer suitable for breast conserving surgery. The age ranged from 30 –80 years (Mean 51.5). The pathological tumour size ranged from 0.42 cm to 4.0 cm. The applicator size was 3.5 cm in 15 cases, 4cm and 3cm in 3 cases each, and 4.5 cm in 3 cases and 2.5 cm in 1 case. In all except the first case, the operating voltage was 50Kv @ 40microamperes. The time required to treat the prescribed dose of 5Gy at 1cm ranged from 21.1 min to 28.7 minutes. In the first case, we used a 40 kV voltage and took 36.8 minutes.

Three patients received intraoperative radiotherapy as the only form of radiotherapy. One patient was blind and 80 year old and not very suitable for daily postoperative visits for external boost radiotherapy. In a joint decision, she was prescribed 7.5 Gy at 1cm effectively giving about 23 Gy to the

cavity margin as the only radiotherapy. Another patient had a contralateral breast cancer treated 14 years ago with interstitial wire boost and whole breast radiotherapy. In order not to overlap radiation beams in the sternal region, she was prescribed 6 Gy at 1cm giving 20Gy to the cavity margin as the only radiotherapy. The third patient (Patient number 21 in the pilot study) was a lady who well understood the rationale of our subsequent randomised study and chose not to undergo the 5-wk course of whole breast radiotherapy, although we had not yet started the randomised trial to test this approach. All other patients received the routine external beam radiotherapy to the whole breast (50Gy over 5 wks, 25 fractions).

No patient has had major operative or postoperative complications, in general as well as regards the wound. Two patients had some problem with wound healing one of which we believe was due to excessive radiation and radionecrosis. This was our third patient as mentioned before, who had radionecrosis of an area of skin close the applicator. This resulted in delayed wound healing by secondary intention. After this case, we measured the skin dose using Thermoluminscent detectors (TLD). The mean of the highest dose of radiation at the skin surface was 4.6 Gy (95% CI 3.6 – 5.6, median 3.7). It has been between 5-10 Gy in 4 patients but has never reached about 10Gy. None of these 4 patients has had any complications.

In the 80-year-old blind lady, both the axillary and primary wound had delayed wound healing that was probably age related. One other patient had wound infection - but the wound healed satisfactorily within 2 weeks and did not delay her adjuvant treatment. Some non-tender transient erythema around the scar was seen in 3 patients.

The longest follow up is 45 months, with a median of 34 months and a minimum of 27 months. No patient has had a local recurrence. None of the patients whom we found suitable have refused to participate in the study. Many patients found the technique logical and could immediately see the practical advantage of fewer visits to the radiotherapy department. The concept of giving the radiotherapy to the tumour bed ‘there and then’ also was very attractive.

The actual score of appearance of breast and texture of breast, as judged by the patients themselves, either matched or exceeded their expected score in 21 out of 25 patients. At 12-24 months after surgery, the satisfaction index (observed/expected score) was 1.2 (95% CI 1.1-1.4) for breast appearance, and 1.2 (95% CI 1.0- 1.4) for breast texture.

Discussion

In the present protocol, the PRS was used for boosting of the tumour bed in conjunction with external beam irradiation to the whole breast which provided a saving of 1 week of radiotherapy treatment time and travelling for the patient. In those patients undergoing sentinel node excision with immediate frozen section, intra-operative radiotherapy could actually be delivered during the time waiting for the frozen section results.

In addition, the PRS technique has advantages over other types of brachytherapy. At present, both low-dose-rate and high-dose-rate brachytherapy are employed in order to

maximise local dosage for improved local control, but the techniques are time-consuming and expensive. Careful placement of semi-flexible I^{192} IR wires probably represents the "gold standard" brachytherapy technique at present but geometrical accuracy is important and the implant must be removed at a later date, increasing the workload and creating additional problems of radiation protection.

Intraoperative radiotherapy has been explored in the past, employing massive and expensive linear accelerators that required relocation of the operation theatre in the radiotherapy suite. Mobile linear accelerators are now being used by several groups in the world, most notably Professor Umberto Veronesi's group. The advantage of using the linear accelerator (e.g. NOVAC–7) high-energy electrons is that the actual treatment time is reduced to a few minutes. However, the positioning of the equipment takes much longer and the total time for treatment is about 25 to 35 minutes. Furthermore, the shape of the radiation is different from the one which we use – it is in the form of a radiation beam- so that the target tissue – the breast cavity - needs to be brought facing the radiation source. With the Intrabeam device, the radiation is delivered from within the breast, which intuitively appears a much more elegant approach.

Nevertheless, whichever technique is able to accurately and relatively inexpensively deliver radiotherapy to the target tissues in the operating theatre in a reasonable time would revolutionise the local management of breast cancer.

We believe we are the first to use this approach and the technique we use is simple, portable, and can be used in a routine operation theatre. It provides a simple form of brachytherapy, which could potentially provide equivalent benefit with a lesser demand on professional time expended. We recognise that the follow up of this study is relatively short (median 34 months and longest 45 months) for assessing local recurrence rates, but this study was a pilot phase II study mainly testing the feasibility, safety and acceptability of the technique to the patient and not local control, which will be tested in the next phase- the randomised trial. Nevertheless, it is encouraging to have a 0% local recurrence rate at nearly 3 years of follow up.

Another important value of the pilot project is that it has demonstrated that it is safe, at least in the relatively short term, to deliver a very high dose of radiotherapy –the Intraoperative dose in one fraction followed by 50Gy of postoperative whole breast radiotherapy. The lack of side effects until now is probably due to the fact that the high dose is small and for the same reason, we expect that the late fibrosis, if any, will not be disfiguring.

This method of delivery of radiotherapy offers excellent radiation dosimetry and does not have the risk of a "geographical miss". The treatment is delivered at the earliest possible time after the surgery. It has been suggested that a large proportion of local recurrence after breast conserving therapy is because of a geographical miss of the boost dose. It has been estimated that the boost dose could miss between 24% to 88% of the target volume [Sedlmayer et al., 1996;Hunter

et al., 1996;Krawczyk and Engel, 1999;Machtay et al., 1994]. Thus a large proportion of local recurrences could be attributed to geographical miss alone.

In patients with high risk of local recurrence (e.g. larger tumours with high nuclear grade and with involved nodes) this approach can offer the most optimal mode of delivery of radiotherapy, and may have the potential to reduce the local recurrence rate substantially.

It is the next phase, that we would test whether giving targeted localised radiotherapy in this manner is equivalent to the routine 6-weeks course of postoperative radiotherapy in selected patients; then this technique has a potential to save 6 weeks of external beam radiotherapy time for both the patient and the overstretched resources of radiotherapy departments.

We received ethics approval and have begun in March 2000, a randomised trial (called Targit-Targeted Intraoperative Radiotherapy) comparing conventional radiotherapy to radiotherapy delivered to the index quadrant alone using the PRS – this is described in the chapter 7.

Summary

Introduction: We believe that conservative treatment of breast cancer may not require radiotherapy that encompasses the whole breast. This chapter discusses the clinico-pathological basis for this view as well as a novel therapeutic approach that allows intra-operative radiotherapy to be safely and accurately delivered to the target tissues in a standard operating theatre. **The Rationale**: Whole-organ analysis of mastectomy specimens reveals that 80% of occult cancer foci are situated *remote* from the index quadrant. In contrast, over 90% of local recurrences after breast conservative therapy occur *near* the original tumour- even when radiotherapy is not given. Therefore, the remote occult cancer foci may be clinically irrelevant and radiotherapy to the index quadrant alone might be sufficient. **A Novel Technique** The Photon Radiosurgery System (PRS) is an ingenious portable electron-beam driven device that can typically deliver, intra-operative doses of 5 - 20 Gy, respectively, to 1cm and 0.2cm from the tumour bed over about 22 minutes. The pliable breast tissue - the target - wraps around the source providing optimal conformal radiotherapy. Being soft x-rays, the dose attenuates rapidly ($\alpha \sim 1/r^3$), reducing distant damage. **Results** In our pilot study of 26 patients (age 30-80 years, T=0.42-4 cm), we replaced the routine post-operative tumour bed boost with *targ*eted *i*ntra-operative radio*t*herapy. There have been no major complications and no patient has developed local recurrence although the median follow-up time is short 34 months. **Conclusion** It is safe and feasible to deliver ***targ***eted ***i***ntra-operative radio***t***herapy (*Targit*) for early breast cancer. This novel method of delivery of radiotherapy, used alone, could be used in a randomised trial testing the hypothesis that index quadrant irradiation alone may be adequate local treatment for selected cases of breast cancer. In other patients, in whom whole breast irradiation is deemed necessary, this method can be used to accurately deliver the tumour bed boost at a high therapeutic ratio, without the risk of a geographical miss, with a potential to reduce the overall local recurrence rate.