Annals of Oncology **12**: 1075–1080, 2001.

Original article

*Targ*eted *i*ntra-operative radio*t*herapy (*Targit*): An innovative method of treatment for early breast cancer

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Summary

Introduction: We believe that conservative treatment of early breast cancer may not require radiotherapy that encompasses the whole breast. We present here 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 1 cm and 0.2 cm from the tumour bed over about 22 min. The pliable breast tissue – the target – wraps around the source, providing perfect conformal radiotherapy. Being soft X-rays, the dose attenuates rapidly ($\alpha \sim 1/r^3$), reducing distant damage.

Results: In our pilot study of 25 patients (age 30–80 years, T = 0.42–4.0 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, at 24 months.

Conclusion: It is safe and feasible to deliver *targ*eted *i*ntra-operative radio*t*herapy (*Targit*) for early breast cancer. We have begun a randomised trial – the first of its kind – comparing *Targit* with conventional six-week course of radiotherapy. If proven equivalent in terms of local recurrence and cosmesis, it could eliminate the need for the usual six-week course of post-operative radiotherapy.

Key words: breast cancer, breast conserving therapy/surgery, IORT, pilot, randomised trial, targeted intra-operative radiotherapy, Targit

Introduction

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 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 terms of overall survival (EBCTCG 1995) [1]. 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. We propose that this approach be reappraised and have already suggested the biological and clinico-pathological basis for avoiding unnecessary treatment to the whole breast* [2]. One part 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[3] and whether or not the margins are involved [4]. 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 [5]. 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 heterozyocity in these 'normal' cells within the index

* Presented by JSV at the Hong Kong International Cancer Congress, Nov. 1995.

quadrant [6]. 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 [4]. This approach of irradiating the index quadrant alone has been tested in two clinical trials and the results seem to support our hypothesis. The Christie Hospital Trial [7] randomised 708 patients to receive either the standard wide field radiotherapy or a limited field radiotherapy to the index quadrant. They found that overall there was a higher recurrence rate in the latter arm. However when the results were analysed according to the type of the primary tumour, it was found that limited field radiotherapy is 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 [8], a single continuous application of an iridium-192 implant delivering 55 Gy over 5–6 days replaced the standard radiotherapy regimen including whole breast radiotherapy plus tumour bed boost. The authors found a 20% increase in local recurrence compared with historical controls. However, as discussed in a letter in response to the study [9], it was pointed out that the Biologically Effective Dose (BED) was 20% lower than conventional radiotherapy and this almost completely explained the difference. In addition 12/27 patients were node positive and 15/27 had involved margins – putting these patients at high risk of local recurrence anyway.

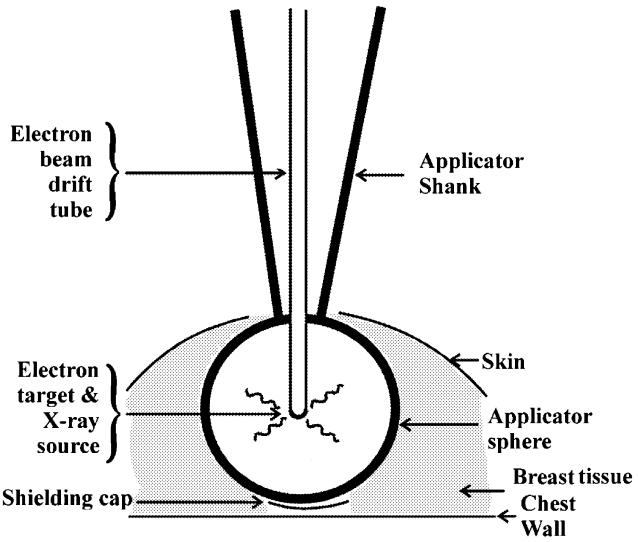

Figure 1. The Photon-Radiosurgery System (PRS). The electrons are generated and accelerated in the main unit (seen in Figure 3) and travel via the electron beam drift tube which is surrounded by the conical applicator sheath such that its tip lies at the epicentre of the applicator sphere. Once the electrons 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 ($\alpha \sim 1/r^3$).

The new radiotherapy technique: *Targeted intra-operative radiotherapy* (*Targit*)

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 Photon Radiosurgery System (PRS) developed by the Photoelectron Corporation in Massachusetts, USA is a simple and ingenious device which in essence is a miniature electron-beam driven X-ray source which provides a point source of low energy X-rays (50 kV maximum). The unit is connected, via a low-voltage cable, to a control box housing a rechargeable NiCd battery. Within the unit itself, electrons are produced from a barium oxide thermionic cathode, accelerated to the desired energy (up to 50 kV) by a multi-stage anode, and directed down a 10 cm long, 3.2 mm diameter evacuated drift tube towards a thin-film hemispherical gold target at its tip. The resultant spectrum of X-rays is emitted isotropically. Accurate steering of the electron beam is achieved using two sets of X-Y deflection coils, and by the incorporation of magnetic shielding.

The radiation source can be inserted into the area of interest, to provide intra-operative interstitial irradiation. The physics, dosimetry and early clinical applications of this soft X-ray device have been well studied and the probe has already been used for treatment of malignant brain tumours in man [10, 11], though treatment of breast has not previously been attempted. For use in the breast, the radiation source is surrounded by a conical sheath with a sphere at the tip (see Figures 1, 2 and 3). The sphere is specially designed to produce an accurately calculated uniform dose rate at its surface, enabling delivery of a uniform dose of radiation to a prescribed depth. Since the radiation consists of soft X-rays, the beam is rapidly attenuated to reduce the dose to more distant tissue (Figure 4). Full measurements and calibration are carried out in a water phantom and in materials which 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. The radiation dose at various distances from the cavity margin varies as shown for the simulated assembly in Table 1. For example, a dose of about 5 Gy can be delivered in about 20 min 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 × 11 × 14 cm; applicator: 16 cm long conical applicator sheath with a 2 to 5 cm applicator sphere at the tip) and hangs

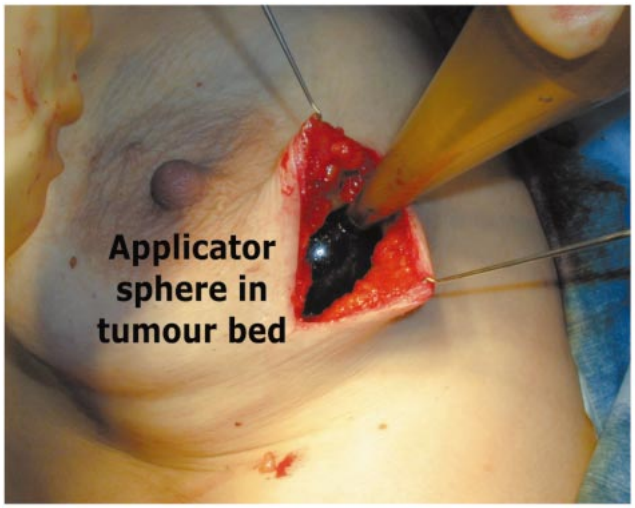

Figure 2. The applicator being placed in the tumour bed, immediately after the excision of the tumour.

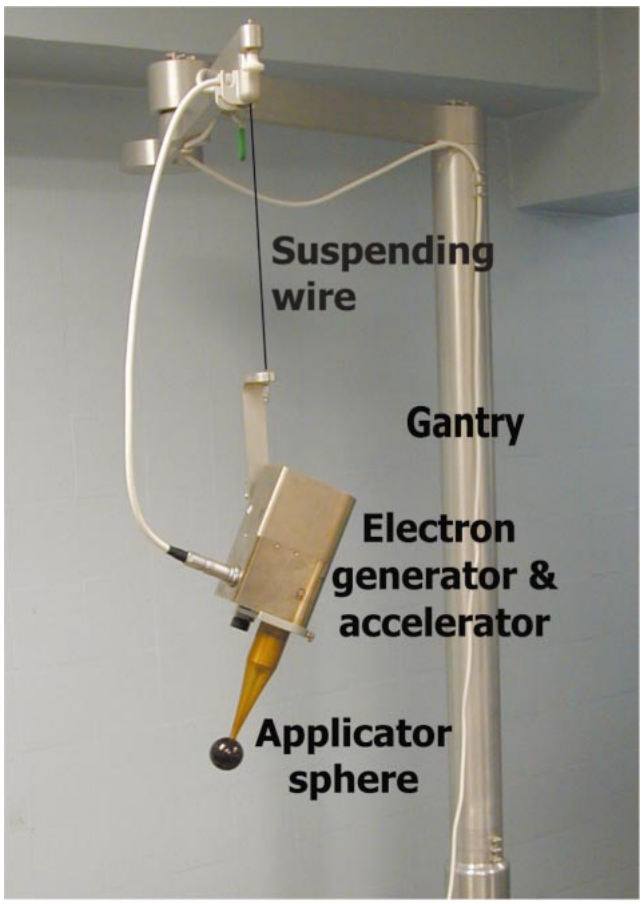

Figure 3. The PRS assembly. The whole assembly is suspended on a counter balance system so that the position of the applicator remains steady irrespective of the respiratory movements. Once the applicator is positioned, the electron beam drift tube with the electron generator and accelerator is inserted in the applicator and maintained by a spring-loaded system.

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 from a linear accelerator. The quick attenuation of the radiation dose allows the treatment to be carried out in unmodified operating theatres. The walls usually incorporate shielding for microwave radiation from electronic equipment such as mobile phones, and provide sufficient staff protection. Furthermore, the biologically effective dose (BED) attenuates rapidly (see Table 1), 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.

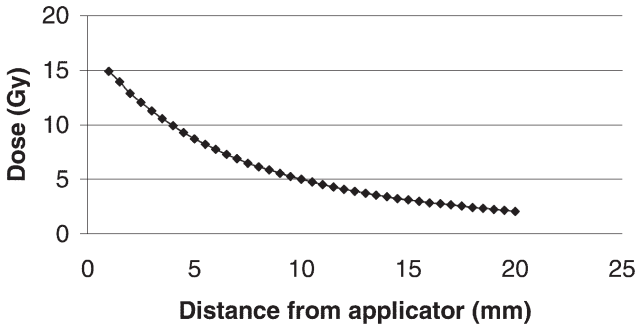

Figure 4. The physical X-ray dose at various distances in a breast phantom for the typical applicator of 3.5 cm diameter and a prescription of 5 Gy at 1 cm.

The operative procedure

Patients who were diagnosed to have operable breast cancer suitable for conservative breast surgery were recruited in the pilot study, after a full informed consent.

Each patient underwent wide local excision and axillary clearance. After haemostasis was achieved, the tumour bed was assessed and the appropriate applicator was attached to the X-ray source (XRS) and inserted in the wound. In the first three 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 fourth case onwards, we wrapped up the XRS in a 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 team in the operation theatre. Since this modification, the average time required to set-up the

Table 1. Standard dosimetry table. Calculations for a 3.5 cm diameter spherical diameter and a period of irradiation of 21 min as measured from the periphery of the sphere in a breast phantom. (PRS operating parameters: 50 kV). Radial doses are stated for a treatment prescription on 5 Gy at 1 cm.

	PE probe (Gy)		External beam radiotherapy tumour bed boost		Whole breast radiotherapy	
Distance from the surface of the applicator	Physical X-ray dose (Gy)	BED	Physical X-ray dose (Gy)	BED	Physical X-ray Dose (Gy)	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	5.0	21.7	10	12	50	60

Biologically effective dose (BED) is given by the equation (Dale, 1985 [12]): $BED = D \times (1 + (d/(\alpha/\beta))$ where D is the total physical dose, d is the physical dose per fraction and α/β is the biological coefficient which is 10 for early and tumour effects for tumour tissues when the radiotherapy is delivered in fractions of about 2 Gy. For the single dose we have assumed the value of α/β to be equal to 1.5.

system at the end of excision was only 12 min. When the lesion is on the left side, the chest wall is protected by thin polyurethane-tungsten impregnated sheets that can either be applied to the applicator or custom-made to fit on the chest wall. This reduces the radiation by 95% and protects the heart and coronary vessels. The applicator sphere is inserted into the breast cavity, and a deep surgical purse-string suture is 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 (Figures 2 and 3). 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 3–0 prolene stitches and ensuring that no part of skin is less than 1 cm from the applicator surface. Essentially these 'conforming' stitches allow real-time hands-on-accurate conformation of the target to the source of radiation. The radiation needs to be switched on for 21 to 28 min depending upon the size of the applicator sphere, and using an energy of 50 kV a dose of 5 Gray (Gy) is delivered at 1 cm distance from the cavity margins. After completion of radiation, the 'conforming' stitches are removed and the skin is sutured in the usual manner with a subcuticular prolene stitch which is left in place for 14 days.

The prescribed dose of 5 Gy at 1 cm (obviously with a much higher dose at the tumour bed margin), was selected as likely to be a safe exposure from a single fraction bearing in mind that the commonest radiotherapy boost programmes provide a small boost of external beam irradiation to a dose of 10 Gy over 5 fractions over a week.

We assessed the cosmetic results of the patients with photographs and by comparing the 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, and the satisfaction index was calculated by dividing the observed by expected.

Results

We began the pilot study on 2 July 1998 and have treated 25 patients. They all had 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. Twenty-two tumours were infiltrating duct carcinomas (4 grade 1, 7 grade 2 and 11 grade 3) with one of them being the tubular variant and three were invasive lobular carcinomas (2 grade 1, and 1 grade 2). Twenty-two patients had axillary node dissection and three had sentinel node biopsy only. All sentinel nodes were negative and three patients had involved lymph nodes (1, 2 and 1 each). The applicator size was 3.5 cm in 13 cases, 4 cm and 4.5 cm in 4 cases each, 3 cm in 3 cases and 2.5 cm in 1 case. In all except the first case, the operating voltage was 50 kV at 40 microamperes. The mean treatment time required to treat the prescribed dose of 5 Gy at 1 cm was 26.5 min (95% confidence interval (95% CI): 24.3–28.8) The total mean operation time for the wide local excision, axillary clearance and intraopeartive radiotherapy was 1 h 57 min (95% CI: 1 h 47 min – 2 h 7 min). In the first case, we used a 40 kV voltage and took 36.8 min.

Three patients received intraoperative radiotherapy as the only form of radiotherapy. One patient was blind, 80 years old, and keen to avoid daily postoperative visits for external beam radiotherapy. In a joint decision, she was prescribed 7.5 Gy (150% of the usual dose) at 1 cm 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 mid-line, she was prescribed 6 Gy at 1 cm, giving 20 Gy to the cavity margin as the only radiotherapy. The third patient (patient 21 in the pilot study) was a lady who well understood the rationale of our subsequent randomised study and chose not to undergo the five-week 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 (50 Gy over 5 weeks).

No patient has had major operative or postoperative complications either in general or in respect of the wound. Two patients had some problem with wound healing and one had wound infection. We believe that one of these was due to excessive radiation and radionecrosis. This was our third patient as mentioned before, who had radionecrosis of a 1 cm area of skin close the applicator. The skin breakdown occurred three months after an initial good healing and resulted in delayed healing by secondary intention. In the 80-year-old blind lady, both the axillary and primary wound had delayed wound healing. Both these patients were very satisfied with the final appearance and/or texture of the breast. In the patient who developed a wound infection, the wound healed satisfactorily within two weeks without delay to her adjuvant treatment. Some short-term erythema around the scar was seen in three patients.

The longest follow up is 35 months, with a median of 24 months and a minimum of 16 months. No patient has had a local recurrence. None of the patients who were eligible (essentially all those who were suitable for breast conserving therapy) 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' was also 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 12–16 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 the tumour bed in conjunction with external beam irradiation to the whole breast, saving a week of radiotherapy treatment time and travelling for each patient. In those patients undergoing sentinel node excision with immediate frozen section, intra-operative radiotherapy could even be delivered during the time waiting for the frozen section results. In the next phase, we need to test whether giving targeted localised radiotherapy in this manner is equivalent to the routine six-week course of postoperative radiotherapy, since this technique has the potential to save six weeks of external beam radiotherapy time for both the patient and the overstretched resources of radiotherapy departments. 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 Iridium-192 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. The present technique provides a simple form of brachytherapy, which could potentially provide equivalent benefit with a lesser demand on professional time expended. Although other groups have now started using intra-operative radiotherapy, 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; yet it achieves excellent dosimetry. The other methods employing massive and expensive linear accelerators can require relocation of the operation theatre in the radiotherapy suite.

We recognise that the follow up of this study is relatively short (median 24 months and longest 35 months) for assessing local recurrence rates, but this was a phase II pilot 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. We have already received ethics approval and began, on 29 March 2000, the randomised trial (called *Targit – Targ*eted *i*ntraoperative radio*t*herapy) comparing conventional radiotherapy to radiotherapy delivered to the index quadrant alone, using the PRS (http://www.thelancet.com/info/info.isa?n1=authorinfo&n2=Protocol+review&uid=9920). This is a pragmatic trial, planned to be a multicentre trial, in which patients suitable for breast conserving therapy undergoing wide local excision and axillary clearance are randomised to either receive the intra-operative radiotherapy only, or the usual six-week course of post-operative radiotherapy. If on final histopathology, the tumour is found to be lobular cancer or harbours extensive intraductal component (>25%, EIC), then they will receive in addition, a course of post-operative whole breast radiotherapy, excluding the tumour bed boost.

In the pilot study we only had one patient with a positive margin – the deep margin. Since this was the blind lady who had received the higher (7.5 Gy at 1 cm) dose of radiotherapy, the area adjacent to the tumour bed would have received about 23 Gy, which was thought to be adequate therapy, and a decision to give no further treatment was taken jointly in the multidisciplinary meeting and with the patient. In the randomised trial, the protocol includes the provision to re-excise those patients with grossly positive margins, and to re-irradiate the revised tumour bed if they were randomised to the intra-operative radiotherapy arm. Previous intra-operative radiotherapy should not contra-indicate this because the previously radiated area would have been excised in the re-excision.

Future implications

The national and international implications of avoiding a six-week course of external beam radiotherapy for early breast cancer would be considerable. Treatment of breast carcinoma often represents a third or more of the total case-load of radiotherapy units worldwide. 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. If proven equal to the standard treatment, the novel approach would allow these women to 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 needs about three man-hours and 45 min each of operation theatre time and patient time. The conventional six-week course of post-operative radiotherapy on the other hand, costs about nine man-hours, six hours of radiotherapy room time and 30–60 h of 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 27000 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 × 27000 × 3750) per year for the NHS. *In addition*, the saving of expensive resource time on linear accelerators would of course be very substantial.

Acknowledgements

We wish to thank Mr Michael Douek, for comments on the manuscripts and Ms Vardhini Vijay for helping with illustrations.

Funding

The project is funded by the University College London Hospitals Trust and the Photoelectron Corporation.

Conflict of interest

Professor Michael Baum is on the scientific advisory committee of the Photoelectron Corporation (PeC), with share options. Dr Jayant S. Vaidya was partly funded by the Research Grant from Photoelectron Corporation. Ken Harte, Alan Sliski and Euan Thomson are employees of the Photoelectron Corporation.

References

1. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. N Engl J Med 1995; 333: 1444–55.
2. Baum M, Vaidya JS, Mittra I. Multicentricity and recurrence of breast cancer. Lancet 1997; 349: 208.
3. Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: Pathological findings from NSABP protocol B-06. Sem Surg Oncol 1992; 8: 161–6.
4. Vaidya JS, Baum M. Clinical and biological implications of the Milan Breast conservation trials. Eur J Cancer 1998; 34: 1143–4.
5. Vaidya JS, Vyas JJ, Chinoy RF et al. Multicentricity of breast cancer: Whole organ analysis and clinical implications. Br J Cancer 1996; 74: 820–4.
6. Deng G, Lu Y, Zlotnikov G et al. Loss of heterozygosity in normal tissue adjacent to breast carcinomas. Science 1996; 274: 2057–9.
7. Ribeiro GG, Magee B, Swindell R et al. The Christie Hospital breast conservation trial: An update at eight years from inception. Clin Oncol (R Coll Radiol) 1993; 5: 278–83.
8. Fentiman IS, Poole C, Tong D et al. Inadequacy of iridium implant as sole radiation treatment for operable breast cancer [see comments]. Eur J Cancer 1996; 32A: 608–11.
9. Dale RG, Jones B, Price P. Comments on inadequacy of iridium implant as sole radiation treatment for operable breast cancer, Fentiman et al. Eur J Cancer 1996; 32A: 608–11; Eur J Cancer 1997; 33: 1707–8.
10. Cosgrove GR, Hochberg FH, Pardo FS et al. Interstitial irradiation of brain tumors using a miniature radiosurgery device: Initial experience. Neurosurgery 1997; 40: 518–25.
11. Douglas RM, Beatty J, Gall K et al. Dosimetric results from a feasibility study of a novel radiosurgical source for irradiation of intracranial metastases. Int J Radiat Oncol Biol Phys 1996; 36: 443–50.
12. Dale RG. The application of the linear quadratic dose effect equation to fractionated and protracted radiotherapy. Br J Radiol 1985; 58: 515–28.

Received 30 December 2000; accepted 2 April 2001.

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