



# TARGeted Intraoperative radioTherapy (TARGIT): An Innovative Approach to Partial-Breast Irradiation

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A revolution is challenging the dogma that local treatment for all patients with breast cancer treated with breast conservation therapy must include postoperative radiotherapy delivered to the whole breast. Such prolonged postoperative radiotherapy is a burden to patients and hospitals and forces many women to chose mastectomy instead. Furthermore, for patients receiving chemotherapy, the start of conventional radiotherapy may be delayed so long as to increase the risk of local relapse. These problems might be eliminated if effective radiotherapy could be given as a single treatment intraoperatively, immediately after the surgery. Local recurrence after breast-conserving surgery usually occurs in the portion of the breast in the immediate proximity of the tumor, even when radiotherapy is omitted. Therefore, it should usually be possible to restrict radiotherapy to only the area adjacent to the tumor in selected women. Based on this premise, we have devised a new technique of partial breast irradiation, with the intention of completing all local treatment in a single session. In this article, we elaborate on the rationale and on the different methods of delivering intraoperative radiotherapy. If this approach is validated in ongoing randomized trials, it could save time, money, and breasts.

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The current standard of care for patients with early-stage operable breast cancer is to perform breast-conserving surgery (BCS) followed by a course of postoperative

radiotherapy directed at the whole breast, which requires 3 to 6 weeks of daily treatment, usually given 5 times weekly. This approach, although "conservative" in name, is still "radical" in its spirit; its intent is the same as that of the major extirpative surgery performed by William Halstead over 100 years ago. The paradigm of treating the whole breast has thus far remained unchallenged and today we are faced with the irony of offering radical local therapy to patients with smaller and smaller tumors.

Many patients and surgeons in many parts of the world still prefer mastectomy to breast-conserving therapy. Local culture, distance from radiotherapy facilities, the surgeon's choice, and the patient's preferences, not necessarily in that order, all dictate which operation is chosen. The perceived need for a prolonged course of postoperative radiotherapy is a major barrier against wider acceptance of breast-conserving therapy for several reasons. It adds yet another tiresome course of therapy for patients who may already be facing a 6- to 9-month course of chemotherapy. Many women feel obliged to choose mastectomy because they live too far away from a radiotherapy facility or have difficulty traveling to one. Even many patients treated with BCS may not receive optimal treatment because of living too far from a radiotherapy center. One study in the United States found that when the travel distance was less than 10 miles, 82% of patients received radiotherapy after BCS; when it was 50 to 75 miles, 69% received it; and when it was more than 100 miles, only 42%

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received it.<sup>1</sup> (The proportions of patients in these 3 groups receiving BCS including radiotherapy were 39%, 22%, and 14%, respectively.) Furthermore, in countries with scarce radiotherapy resources, patients treated with BCS may wait a prolonged time before beginning radiotherapy. A recent study of 7,800 patients suggests that delaying the initiation of conventional radiotherapy for 20 to 26 weeks after surgery was associated with decreased survival.<sup>2</sup> The delay imposed by giving chemotherapy before radiotherapy might also increase the risk of local recurrence. Finally, if giving a “boost” dose

to the tumor bed is important, then inaccurate localization of the tumor bed boosts resulting from non-image-guided treatment planning that may still be a norm in many centers means that a portion of the target volume is missed in as much as 24% to 88% of cases.<sup>3,4</sup> Such a “geographical miss” may account for a large proportion of local recurrences.

## New Thinking

We have described<sup>5</sup> the interesting distribution of the location of recurrence in the breast with respect to site of the primary tumor; over 91% are in the same quadrant.<sup>6-12</sup> Bartelink and colleagues reported that only 56% of local recurrences occur in the original tumor bed.<sup>13</sup> However, an additional 27% recurred diffusely throughout the breast, including the tumor bed. Thus, although apparently 29% of recurrences appeared outside the index quadrant, we would argue that this is an artifact because of intensive mammographic follow-up that might have unearthed subclinical occult tumors in other quadrants of unproven clinical significance. For instance the findings of 3-dimensional whole-organ analysis of mastectomy specimens, reveals that 63% of breasts harbored occult cancer foci, of which 80% were situated remotely from the index quadrant.<sup>14</sup> It therefore appears that these widespread and occult multifocal/multicentric cancers in other quadrants of the breast remain dormant for a long time and have a low risk of giving rise to clinically detectable tumors. This is corroborated by the fact that autopsy studies have shown a considerably higher frequency of tumors in examined breasts (20% in young women, with a median age of 39 years, and 33% in women between ages 50 and 55) than the frequency of clinical breast cancer in the population.<sup>15</sup>

We have proposed that local recurrence is a result of the dynamic interaction between the intramammary milieu, the systemic hormonal milieu, background genetic instability in the normal breast tissue surrounding the tumor, and specific tumor factors.<sup>5,16</sup> We have also suggested that perhaps the effect of radiotherapy on the breast stroma is more important than previously supposed.<sup>5</sup> This is based on the finding that local recurrence generally occurs in the index quadrant, whether or not radiotherapy was given and irrespective of margin status.<sup>6,11,17</sup> Of the trials that have tested the effect of radiotherapy after BCS, the NSABP-B06,<sup>18</sup> Ontario,<sup>19</sup> Swedish,<sup>20</sup> and Scottish<sup>21</sup> trials had less extensive surgery compared with the Milan III trial.<sup>12</sup> The recurrence rate in the control arm of the Milan III trial was lower (15%) than in the

other trials (24%-39%), albeit at the cost of worse cosmetic outcome. Nevertheless, patients treated with radiotherapy in the Milan trial had an even smaller risk of local recurrence (3%), with radiotherapy having roughly the same proportional effect in reducing local failure as it did in the other trials. If local recurrence were caused by residual disease only, then radiotherapy should have resulted in a much larger proportional reduction in those patients with less extensive surgery; this observation suggests that radiotherapy may have an effect on the soil, rather than the seed. If radiotherapy has such a dual effect (inhibiting the growth of genetically unstable cells around the primary tumor and making the whole-breast tissue less conducive to growth), then its action would overlap with that of systemic therapies that reduce estrogen concentration in the breast (such as aromatase inhibitors or ovarian suppression). Thus, radiotherapy to the tissues surrounding the primary tumor might be all that is necessary in patients receiving systemic therapy. Such an approach may solve many of the problems associated with conventional postoperative radiotherapy discussed previously, and could increase the rates of BCS, allowing many more women with breast cancer to conserve their breast.<sup>5</sup>

## Tailored Treatment

Irradiation of the index quadrant alone (without whole-breast irradiation) has been tested before. The results of the Christie Hospital trial (performed in Manchester, United Kingdom) are in fact, encouraging.<sup>22</sup> Seven hundred eight patients were randomized to receive either standard wide-field radiotherapy or limited-field radiotherapy (an 8 × 8 cm electron field directed to the index quadrant). Overall, there was a higher recurrence rate in the limited-field arm. However, a single-field size was used for all patients on this arm, irrespective of the tumor size or other characteristics, and this could have resulted in several instances of “geographical miss.” When the results were analyzed according to the type of the primary tumor, it was found that limited-field radiotherapy was inadequate only for patients with infiltrating lobular cancers or cancers with an extensive intraductal component. For the 504 patients with infiltrating duct carcinoma, there was no significant difference in the rates of local recurrence rates between the 2 arms.

## Index Quadrant Irradiation With Conventional Brachytherapy Techniques

Interstitial brachytherapy using catheters and radioactive sources has been used to treat the index quadrant in selected patients with small infiltrating duct cancers with uninvolved nodes. The results as described earlier in this issue have been excellent; the local recurrence rates of these series are between 0% and 4% at 2 to 5 years of follow-up.<sup>5</sup> Early results of a randomized trial (30-month follow-up) have found this approach to give local control equivalent to that achieved

with whole-breast radiotherapy.<sup>23</sup> However, such treatment typically delivers 5 to 10 fractions over 4 to 5 days in the postoperative period. This makes the technique, logistics, and patient perspective regarding brachytherapy techniques fundamentally and conceptually different from intraoperative radiotherapy, which is delivered in a single session at the time of primary surgery.

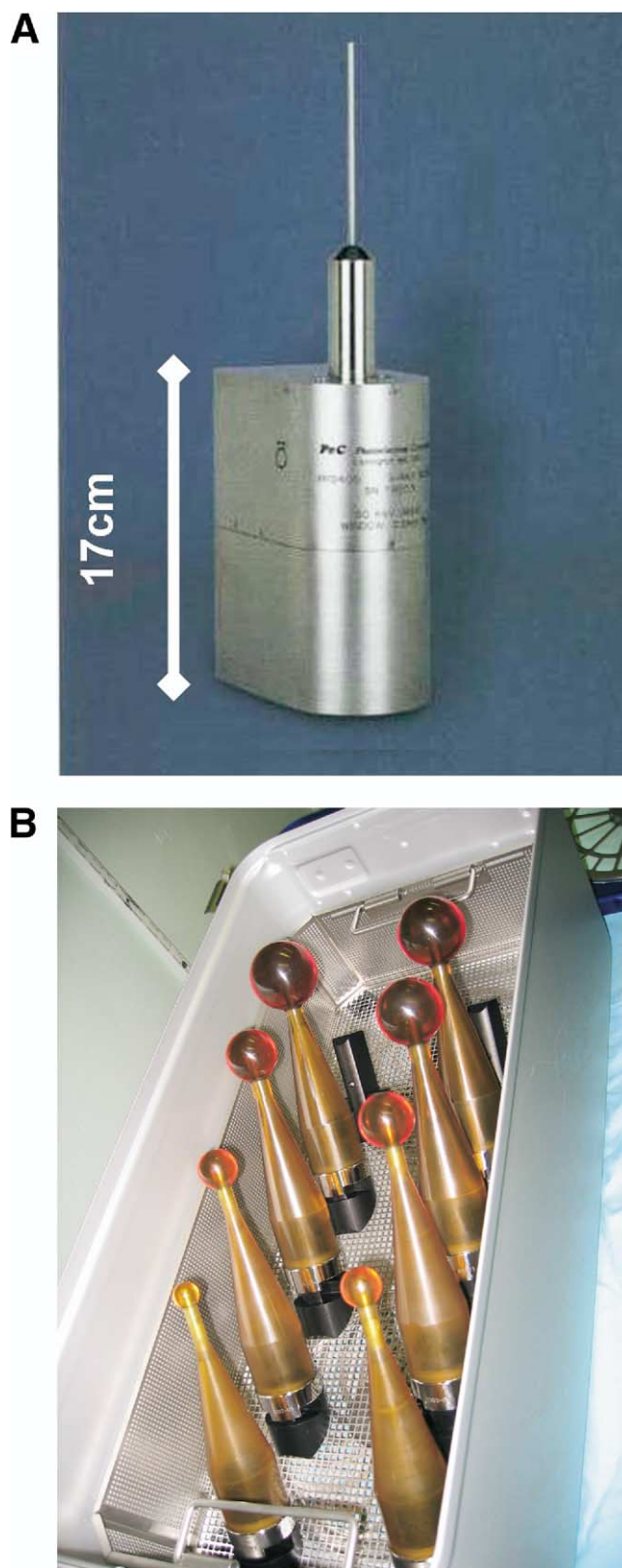
## Intraoperative Radiotherapy

Several attempts have been made to irradiate the breast in a single session intraoperatively. Older intraoperative radiotherapy (IORT) devices were technically cumbersome or required custom-built specially shielded operating rooms. Some institutions performed IORT by transporting the patient from the operating room to the radiotherapy unit during surgery. These limitations have hampered the widespread adoption of IORT.

The technology of miniaturization that has permeated the modern world today has enabled the development of mobile IORT devices. The first device to be used for IORT was the Intrabeam, developed by the Photoelectron Corporation (Lexington, MA), which is currently manufactured by Carl Zeiss AG (Oberkochen, Germany) (Fig. 1). Two mobile linear accelerators have also been developed: the Mobetron System (Oncology Care Systems Group of Siemens Medical Systems, Intraop Medical Inc, Santa Clara, CA) and the Novac 7 System (Hitesys SPA, Aprilia, Italy<sup>24,25</sup>). Some characteristics of these machines are described in Table 1. For the remainder of this article, we will concentrate on the Intrabeam system.

## Radiobiological Aspects of the Intrabeam System

Large single radiotherapy doses, such as those given by the Intrabeam device (eg, a dose of 20 Gy at the applicator surface and 5-6 Gy at 1 cm from the applicator in tissue), should always be used with caution. This is especially important when treating late-reacting tissues like breast, brain, or liver. Cell survival curves of such tissues after single-dose irradiation typically show an increased cell kill at higher doses, compared with acutely reacting tissues, which have a shallower cell survival curve. There is now abundant clinical information about the effects and side effects of high single doses. Radiosurgery doses of 20 to 25 Gy are sufficient to sterilize macroscopic brain metastases with a very low risk of causing brain necrosis or functional damage when the dose is given to a small volume.<sup>26-28</sup> Long-term follow-up of large Swedish<sup>29</sup> and Dutch<sup>30</sup> rectal cancer trials in which 25 Gy given in 5 fractions was prescribed to the pelvis has not shown unacceptable toxicity. Thus, severe long-term side effects would not be expected after administration of 5 Gy to 1 cm of breast tissue surrounding an excision cavity, although caution should be exercised when giving high single doses to skin and ribs.<sup>31</sup>



**Figure 1** (A) The Intrabeam electron generator, accelerator, and x-ray source and (B) applicators. (Color version of figure is available online).

**Table 1** Some Characteristics Of Different Intraoperative Radiotherapy Systems

Device	Radiation Type	Dose	Weight of Treatment Device
Intrabeam	X-rays at 50 kVp	Typical physical dose of 5 Gy at 1 cm or 10 Gy at 0.5 cm or 20 Gy next to the applicator over 25-30 minutes. Setup time is about 10-12 minutes.	1.8 kg
Mobetron	Electrons at 4-12 MeV	20-Gy physical dose in 4-5 minutes. Setup time is about 20-30 minutes.	1275 kg
Novac-7	Electrons at 4-12 MeV	20-Gy physical dose in 4-5 minutes. Setup time is about 20-30 minutes.	650 kg

A detailed analysis of the radiobiological aspects specific to the Intrabeam system requires consideration of the increased relative biologic efficiency (RBE) of the low-energy x-rays, a steep dose dependency of RBE, and the rate of damage repair during radiotherapy delivery (30-50 minutes.) Brenner and coworkers<sup>32</sup> have estimated an RBE of about 1.5 for this type of low-energy x-rays. For a complete modeling of RBE, the introduction of the Lea-Catchside time factor is important.<sup>33</sup> Using this equation, an RBE of 1.0 at the applicator surface, of 1.5 at 10 mm, and about 2.0 at 25 mm can be estimated, with the exact value depending on the size of the applicator. The risk of side effects can also be calculated, although there are insufficient data as to the impact of the volume of treatment to include this as a factor. (However, because the treatment volume is small for IORT, the risk of side effects will probably be lower than that calculated from this model.) Because the TD<sub>50/5</sub> (Tolerance Dose—dose at which there is a 50% chance of complications at 5 years) for pneumonitis is about 9 to 10 Gy, the thickness of the chest wall should ensure that there is virtually no risk of pneumonitis. The same is true for the heart. Because the dose to the heart and lungs during IORT is almost negligible, the mortality from cardiac ischemia that has been observed in some trials using conventional radiation therapy trials should not be seen.<sup>34-37</sup> The TD<sub>50/5</sub> for subcutaneous fibrosis is in the range of 13 Gy. The risk of fibrosis shows a steep decrease with increasing distance from the applicator, reaching nearly zero at about 5-mm tissue depth. The calculated low risk of toxicity is in good agreement with the available clinical data in 13 patients with a maximum follow-up of 4 years.<sup>38</sup>

Another radiobiologic question of importance is whether the tolerable dose is sufficient to prevent local recurrence. We have previously discussed the comparison of how a single IORT treatment of 20 Gy compares with a course of fractionated external-beam radiotherapy (EBRT) of about 50 Gy.<sup>16</sup> One advantage of IORT is that there is no delay between tumor excision and treatment, so there is no loss of efficacy because of tumor-cell proliferation before starting EBRT or during the EBRT course. The RBE of low energy x-rays for early-reacting tissues and tumor cells (alpha-beta ratio of 3 Gy) is higher than for late-reacting tissues (alpha-beta ratio of 10 Gy). As noted earlier, the RBE increases with distance from the applicator.<sup>33</sup> Thus,

one can make a model suggesting that the surviving fraction of tumor cells at the applicator surface will be  $10^{-12}$  and that 99% of the tumor cells 10 mm from the applicator surface should be sterilized. Thus, the tissues immediately next to the applicator would receive a high physical dose (with a low therapeutic ratio), and those further away from the applicator would receive a lower physical dose but with a high therapeutic ratio.<sup>39</sup> This is an advantage of Intrabeam over the systems using electrons to deliver a uniform dose or radiation because its small high (physical)-dose region would be expected to increase tumor cell killing while reducing normal tissue damage and long-term toxicity. In contrast, EBRT has a homogeneous dose distribution, and therefore the spatial distribution of the risk of recurrence depends only on the tumor cell density (which is highest close to the excision cavity). One may therefore expect that there is a “sphere of equivalence” around the excision cavity in which the risk of recurrence for IORT is equivalent to EBRT.<sup>40</sup> The radius of this sphere depends on the details of the model and on the applicator size and is about 15 mm for the most often-used applicators.

Another potential advantage of IORT using Intrabeam is that, because normal tissues can repair their damaged DNA within a few minutes but cancer cells or precancerous cells with poor DNA-repair machinery may be unable to repair as quickly, such treatment (which is given over 25-35 minutes) may have a higher therapeutic index than giving similar doses over 2 to 3 minutes. Laboratory experiments to test this hypothesis are underway.

We have previously described the *in vivo* evidence regarding the effectiveness and toxicity of the Intrabeam system.<sup>5</sup> Intrabeam induces both necrotic and apoptotic cell death, in addition to rapid cell death through non-apoptotic pathways.<sup>41</sup> Animal experiments have shown well-demarcated ablation in canine liver and kidney.<sup>42-44</sup> We have shown its efficacy in ablating tumor tissue with a single application of 6 to 12 minutes in a series of 3 breast cancer patients with tumors from 1 to 2.5 cm in size who were too frail to have surgery, as shown on biopsy and serial contrast-enhanced magnetic resonance imaging.<sup>45</sup> They were treated with the Intrabeam machine without using an applicator but only the sheathed radiograph source (Fig. 1A). (The tumor was localized using a digital stereotactic prone mammography table.)





**Figure 2** The Intrabeam system with the X-ray source in the breast wound (inset) and the electron generator and accelerator held in place by the articulated arm. The inset shows how the target breast tissue wraps around the applicator, giving true conformal radiotherapy. (Color version of figure is available online).

## The Intrabeam Machine and Surgical Technique

The Intrabeam machine contains a miniature electron gun and electron accelerator contained in a radiograph tube, which are powered by a 12-V power supply. “Soft” x-rays (50 kVp) are emitted from the point source. Tissue is kept at a distance from the source by spherical applicators to give a more uniform dose. Depending on the size of the surgical cavity, various sizes of applicator spheres are available. The dose rate depends on the diameter of the applicator and the energy of the beam, both of which may be varied to optimize the radiation treatment. For example, a dose of 5 Gy can be delivered in about 20 minutes at 1 cm from the margins of a 3.5-cm cavity. The quick attenuation of the radiation minimizes the need for radiation protection to the operating personnel. Usually the operating team leaves the room, but the anesthesiologist (and anyone else interested in observing the procedure) sits behind a mobile lead shield that prevents exposure.

The technique has been previously described in detail,<sup>46</sup> and an operative video is available from the authors via the Internet. In the operating room, (Figure 2) wide local excision of the primary tumor is performed in the usual manner, with a margin of normal breast tissue. After the lumpectomy, it is important to achieve complete hemostasis, because even a small amount of bleeding in the 20 to 25 minutes during which radiotherapy is being delivered can distort the cavity enough to considerably change the dosimetry. Different size applicators are tried until one is

found that fits snugly within the cavity. A purse-string suture needs to be skillfully placed; it must pass through the breast parenchyma and appose it to the applicator surface, but at the same time it must not bring the dermis too close to the applicator surface. Sometimes 2 purse-string sutures are required, one deeper and another more superficial. It is important to protect the skin, which should not be brought within 1 cm of the applicator surface. For the edges of the wound, 3 to 0 Prolene stitches that slightly retract the skin away from the applicator are useful. For skin further away from the edge that cannot be effectively retracted for the fear of reducing the dose to target tissues, a customized piece of surgical gauze soaked in saline, 0.5- to 0.9-cm thick, can be inserted deep to the skin; this allows the dermis to be lifted off the applicator, whereas the breast tissue just deep to it still receives radiotherapy. If necessary, the chest wall and skin can be protected by radio-opaque tungsten-filled polyurethane material. These thin rubber-like sheets are supplied as caps that fit on the applicator or that can be cut to size from a larger flat sheet on the operating table so as to fit the area of pectoralis muscle that is exposed and does not need to be irradiated. These provide effective protection (95% shielding) to intrathoracic structures. Because many patients undergo sentinel biopsy with immediate cytological or histological evaluation performed (so that complete axillary clearance can be performed at the same sitting), IORT can often be delivered while the surgical team waits for this result without wasting operating room time.

## Clinical Results and Ongoing Randomized Trials

Based on the hypothesis that irradiation of the index quadrant is sufficient, in July 1998, we introduced the technique of targeted intraoperative radiotherapy (Targit) using the Intrabeam device.<sup>47-49</sup> In the pilot studies in the United Kingdom, the United States, Australia, Germany, and Italy testing the feasibility and safety of the technique, 227 patients underwent Targit as a “boost” dose and also received whole-breast EBRT; for 22 patients, Targit was the sole modality of radiotherapy. The median follow-up is 22 months (maximum, 72 months). Apart from 2 patients treated early in these studies, wound healing has been excellent. There were 2 local relapses: one was a second primary in a separate quadrant at 42 months, and the other patient developed diffuse involvement of the entire breast 2 months after surgery. The cosmetic outcome was assessed formally by a surgeon and a nurse not involved in the trial in available patients treated in the United Kingdom at a median follow-up of 42 months.<sup>38</sup> On a scale of 1 to 5 (with 5 being best), mean scores for appearance, texture, and comfort of the breast given by these observers were 3.5, 2.7, and 3.7. The corresponding scores given by the patient herself were 4, 3.1, and 3.5.

The multicenter randomized trial “TARGIT” using the Intrabeam system is now recruiting patients in the United Kingdom, Germany, Italy, the United States, and Australia.<sup>5,49,50</sup> Patients are enrolled before tumor excision to receive either IORT or conventional whole-breast radiotherapy. However, each center may decide that patients randomized to IORT who are found to have certain pathologic findings (eg, lobular carcinoma or an extensive intraductal component) may subsequently receive whole-breast irradiation in addition.

It is well recognized (as in every adjuvant situation) that postoperative whole-breast radiotherapy is an overtreatment 60% to 70% of the time because only 30% to 40% of patients will ever develop local recurrence after surgery alone. Our approach using IORT intends to refine the treatment of breast cancer patients by introducing a risk-adapted strategy. For example, perhaps the elderly patient with a T1, grade 1 tumor should be treated with Targit only, whereas a young patient with a T2, grade 3 tumor would benefit from having a more accurate boost using Targit in addition to whole-breast radiotherapy. The TARGIT trial is testing exactly such a strategy. Hence, the TARGIT trial should not be mistaken for a trial solely designed to compare intraoperative with postoperative radiotherapy, when actually it is testing 2 different treatment approaches: the conventional “one size fits all” approach versus the new approach of tailored treatment. Endpoints include local recurrence, cosmetic outcome, patient satisfaction, and cost analysis. The first patient was randomized in March 2000, with an accrual goal of 2,232; it is expected that the first results of this trial will be available in 2007.

The Milan trial using the Novac 7 has also been recruiting since November 2000 at a fast rate. Their preliminary results are encouraging.<sup>51,52</sup>

## It Is Cheaper as Well!

Delivering IORT with the Intrabeam prolongs the primary operation by 5 to 45 minutes (the shorter extra time when it is performed in conjunction with immediate analysis of the sentinel lymph node). In addition, approximately 1 hour of a radiotherapy physicist’s time is needed to prepare the device. EBRT requires about 9 man hours of planning, 6 hours of radiotherapy-room time, and 30 to 60 hours of patient time. If the cost of conventional radiotherapy were £2400, using the most conservative estimates, then considering only the 66% saving of man hours, this novel technique would save £1800 per patient. If we assume that 25% of the 40,000 breast cancer patients diagnosed every year in the United Kingdom might be treated by BCS and IORT instead of conventional EBRT, the yearly savings for the National Health Service would be 18,000,000 pounds. This does not include the substantial saving of expensive time on the linear accelerators, enabling a reduction in waiting lists and, most importantly, the saving of time, effort, and inconvenience for patients. Thus, unlike most other “new” treatments, this one could be significantly less expensive than the current standard!

## The Future Is in Sight

Using the Intrabeam device to deliver single-treatment IORT has many advantages compared with other forms of radiation therapy. With this elegant approach, the target, the pliable breast tissue around the cavity of surgical excision, is “conformed” to the radiation source. It avoids the need for using tedious techniques of interstitial radioisotope implantation or expensive technology for complex computed tomography-guided planning of conformal EBRT using linear accelerators. It eliminates the possibility of irradiating the wrong site and delivers radiotherapy at the earliest possible time after surgery. The quick attenuation of the radiation dose protects normal tissues and allows the treatment to be performed in unmodified operating rooms. Thus, in theory, the biological effect and cosmetic outcome of breast-conserving therapy could be improved.

As we have previously warned, we must not be attracted to mere novelty and the convenience of the this new technology.<sup>5,16</sup> Randomized clinical trials are essential to test this revolutionary approach. We believe that the future for local treatment of breast cancer is bright. The patient, the surgeon, and the radiation oncologist will be able to choose from several well-tested approaches. This may mean not just wider availability of breast-conserving therapy but also that small incremental benefits from targeted and tailored treatment could reduce morbidity and even mortality.

## References

1. Athas WF, Adams-Cameron M, Hunt WC, et al: Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. *J Natl Cancer Inst* 92:269-271, 2000
2. Mikeljevic JS, Haward R, Johnston C, et al: Trends in postoperative

- radiotherapy delay and the effect on survival in breast cancer patients treated with conservation surgery. *Br J Cancer* 90:1343-1348, 2004
3. Sedlmayer F, Rahim HBK, Kogelnik HD, et al: Quality assurance in breast cancer brachytherapy: geographic miss in the interstitial boost treatment of the tumor bed. *Int J Radiat Oncol Biol Phys* 34:1133-1139, 1996
  4. Machtay M, Lanciano R, Hoffman J, et al: Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys* 30:43-48, 1994
  5. Vaidya JS, Tobias JS, Baum M, et al: Intraoperative radiotherapy for breast cancer. *Lancet Oncol* 5:165-173, 2004
  6. Clark R, Wilkinson R, Mahoney L: Breast cancer: a 21 year experience with conservative surgery and radiation. *Int J Rad Oncol Biol Phys* 8:967-975, 1982
  7. Schnitt SJ, Connolly JL, Harris JR, et al: Pathologic predictors of early local recurrence in stage I and II breast cancer treated by primary radiation therapy. *Cancer* 53:1049-1057, 1984
  8. Boyages J, Recht A, Connolly J, et al: Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. *Radiother Oncol* 19:29-41, 1990
  9. Kurtz JM, Jacquemier J, Torhorst J, et al: Conservation therapy for breast cancers other than infiltrating ductal carcinoma. *Cancer* 63:1630-1635, 1989
  10. Fisher ER, Anderson S, Redmond C, et al: Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP Protocol B-06. *Semin Surg Oncol* 8:161-166, 1992
  11. Clark RM, McCulloch PB, Levine MN, et al: Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst* 84:683-689, 1992
  12. Veronesi U, Luini A, Del Vecchio M, et al: Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 328:1587-1591, 1993
  13. Bartelink H, Horiot JC, Poortmans P, et al: Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 345:1378-1387, 2001
  14. Vaidya JS, Vyas JJ, Chinoy RF, et al: Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer* 74:820-824, 1996
  15. Nielsen M, Thomsen JL, Primdahl S, et al: Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. *Br J Cancer* 56:814-819, 1987
  16. Vaidya JS, Tobias J, Baum M, et al: Intraoperative radiotherapy: the debate continues. *Lancet Oncol* 5:339-340, 2004
  17. McCulloch PG, MacIntyre A: Effects of surgery on the generation of lymphokine-activated killer cells in patients with breast cancer. *Br J Surg* 80:1005-1007, 1993
  18. Fisher B, Anderson S, Redmond CK, et al: Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 333:1456-1461, 1995
  19. Clark RM, Whelan T, Levine M, et al: Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst* 88:1659-1664, 1996
  20. Liljegren G, Holmberg L, Bergh J, et al: 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol* 17:2326-2333, 1999
  21. Forrest AP, Stewart HJ, Everington D, et al: Randomized controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet* 348:708-713, 1996
  22. Ribeiro GG, Magee B, Swindell R, et al: The Christie Hospital breast conservation trial: an update at 8 years from inception. *Clin Oncol* 5:278-283, 1993
  23. Polgár C, Sulyok Z, Fodor J, et al: Sole brachytherapy of the tumor bed after conservative surgery for T1 breast cancer: five-year results of a phase I-II study and initial findings of a randomized phase III trial. *J Surg Oncol* 80:121-128, 2002
  24. Veronesi U, Orecchia R, Luini A, et al: A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. *Eur J Cancer* 37:2178-2183, 2001
  25. Intra M, Gatti G, Luini A, et al: Surgical technique of intraoperative radiotherapy in conservative treatment of limited-stage breast cancer. *Arch Surg* 137:737-740, 2002
  26. Flickinger JC, Kondziolka D, Lunsford LD: Radiosurgery of benign lesions. *Semin Radiat Oncol* 5:220-224, 1995
  27. Flickinger JC, Kondziolka D, Lunsford LD: Radiobiological analysis of tissue responses following radiosurgery. *Technol Cancer Res Treat* 2:87-92, 2003
  28. Wenz F, Steinvorth S, Wildermuth S, et al: Assessment of neuropsychological changes in patients with arteriovenous malformation (AVM) after radiosurgery. *Int J Radiat Oncol Biol Phys* 42:995-999, 1998
  29. Improved survival with preoperative radiotherapy in resectable rectal cancer. *Swedish Rectal Cancer Trial. N Engl J Med* 336:980-987, 1998
  30. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 345:638-646, 2001
  31. Reitsamer R, Peintinger F, Kopp M, et al: Local recurrence rates in breast cancer patients treated with intraoperative electron-boost radiotherapy versus postoperative external-beam electron-boost irradiation. A sequential intervention study. *Strahlenther Onkol* 180:38-44, 2004
  32. Brenner DJ, Leu CS, Beatty JF, et al: Clinical relative biological effectiveness of low-energy x-rays emitted by miniature x-ray devices. *Phys Med Biol* 44:323-333, 1999
  33. Herskind C, Steil V, Tiefenbacher U, et al: Radiobiological aspects of intraoperative radiotherapy (IORT) with isotropic low energy X-rays for early stage breast cancer. *Radiat Res* in press
  34. Rutqvist LE, Johansson H: Mortality by laterality of the primary tumor among 55,000 breast cancer patients from the Swedish Cancer Registry. *Br J Cancer* 61:866-868, 1990
  35. Lind DS, Kontaridis MI, Edwards PD, et al: Nitric oxide contributes to adriamycin's antitumor effect. *J Surg Res* 69:283-287, 1997
  36. Venables K, Miles EA, Deighton A, et al: Irradiation of the heart during tangential breast treatment: a study within the START trial. *Br J Radiol* 77:137-42, 2004
  37. Meinardi MT, van Veldhuisen DJ, Gietema JA, et al: Prospective evaluation of early cardiac damage induced by epirubicin-containing adjuvant chemotherapy and locoregional radiotherapy in breast cancer patients. *J Clin Oncol* 19:2746-2753, 2001
  38. Vaidya JS, Wilson A, Houghton J, et al: Cosmetic outcome after targeted intraoperative radiotherapy (Targit) for early breast cancer. *Breast Cancer Res Treat* 82:S180, 2003 (abstr, suppl 1)
  39. Astor MB, Hilaris BS, Gruerio A, et al: Preclinical studies with the photon radiosurgery system (PRS). *Int J Radiat Oncol Biol Phys* 47:809-813, 2000
  40. Early Breast Cancer Trialists' Collaborative Group: Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 355:1757-1770, 2000
  41. Kurita H, Ostertag CB, Baumer B, et al: Early effects of PRS-irradiation for 9L gliosarcoma: characterization of interphase cell death. *Minim Invasive Neurosurg* 43:197-200, 2000
  42. Chan DY, Koniaris L, Magee C, et al: Feasibility of ablating normal renal parenchyma by interstitial photon radiation energy: study in a canine model. *J Endourol* 14:111-116, 2000
  43. Koniaris LG, Chan DY, Magee C, et al: Focal hepatic ablation using interstitial photon radiation energy. *J Am Coll Surg* 191:164-174, 2000
  44. Solomon SB, Koniaris LG, Chan DY, et al: Temporal CT changes after hepatic and renal interstitial radiotherapy in a canine model. *J Comput Assist Tomogr* 25:74-80, 2001
  45. Vaidya JS, Hall-Craggs M, Baum M, et al: Percutaneous minimally invasive stereotactic primary radiotherapy for breast cancer. *Lancet Oncol* 3:252-253, 2002
  46. Vaidya JS, Baum M, Tobias JS, et al: The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. *Eur J Surg Oncol* 28:447-454, 2002
  47. Vaidya JS, Baum M, Tobias JS, et al: Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Ann Oncol* 12:1075-1080, 2001

48. Vaidya JS: A novel approach for local treatment of early breast cancer doctoral (PhD) thesis. London, England, University of London, 2002
49. Vaidya JS, Baum M, Tobias JS, et al: Protocol 99PRT/47 Targeted Intraoperative radiotherapy (Targit) for breast cancer. 1999. Available at: <http://www.thelancet.com/info/info.isa?n1=authorinfo&n2=Protocol+review&uid=9920>. Accessed July 18, 2004
50. Vaidya JS, Joseph D, Hilaris BS, et al: Targeted intraoperative radiotherapy for breast cancer (Targit): an international trial. *Radiother Oncol* 64:S136, 2002 (abstr, suppl 1)
51. Orecchia R, Ciocca M, Lazzari R, et al: Intraoperative radiation therapy with electrons (ELIOT) in early-stage breast cancer. *Breast J* 12:483-490, 2003
52. Veronesi U, Gatti G, Luini A, et al: Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery. *Arch Surg* 138: 1253-1256, 2003