APBI with 50 kV Photons: Targeted Intraoperative Radiotherapy (TARGIT)

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19.1 Individualizing Local Treatment for Breast Cancer

It took the mammoth effort of the 26,000 women in 36 randomized trials that were meta-analyzed in the Oxford overview (Early Breast Cancer Trialists' Collaborative Group 1995, 2000) to make the move from the radical mastectomy described by William Halsted more than 100 years ago (Halsted 1894) to breast-conserving therapy that is considered the norm today. Standing on the shoulders of these giants, the next step—the real paradigm shift to a local therapy truly localized to the tumor and its environs in selected patients may be an easier one.

In this chapter, I will provide a synopsis of its rationale followed by details about the intraoperative approach to delivering partial breast radiotherapy.

The dogma of 3–6 weeks of postoperative radiotherapy after breast-conservative surgery for all patients is one of the main obstacles to the widespread utilization of breast-conserving surgery. The radiotherapy schedule is inconvenient for patients and contributes substantially to the unacceptable waiting lists experienced in many oncology departments worldwide. When making decisions about which operation to choose, recurrence, radiation therapy, and quick recovery are the main factors women are concerned about (Katz et al. 2005). Consequently, if radiation can be completed at the time of the surgery, then two large concerns will be taken care of and perhaps fewer women will feel obliged to choose mastectomy just because they live far from a radiotherapy facility (Athas et al. 2000) or to avoid prolonging their treatment.

It has been estimated that the externally delivered boost dose misses the target volume in 24–88% of cases (Sedlmayer et al. 1996; Machtay et al. 1994). Thus a large proportion of local recurrences could be attributed to this "geographical miss." This could be even more important today, in the age of oncoplastic surgery, when there is extensive

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remodeling of the breast in order to achieve a better cosmetic result. In this situation, it is very difficult to delineate the tumor bed, even with markers such as gold seeds. This can result either in completely missing the target or "precautionary" overtreatment achieved by enlarging the boost field. Delivering radiotherapy immediately after tumor excision with the TARGIT approach before remodeling occurs could ensure that the radiotherapy (boost or alone) is delivered to the correct target.

A delay in the delivery of radiotherapy, either because of a long waiting list or because chemotherapy is given first, may jeopardize its effectiveness (Wyatt et al. 2003; Mikeljevic et al. 2004), although this has been difficult to substantiate. The really important delay may however be the one that occurs immediately after surgery. We have found that the tumor bed is a rich microenvironment that promotes proliferation, migration and invasion (Massarut et al. 2006; Baldassarre et al. 2007). Targeting this microenvironment at the right time could be crucially important. I would like to call missing this window of opportunity a "temporal miss," analogous to its spatial counterpart. Finally, whole breast irradiation carries the risks of acute and long-term complications such as erythema, fatigue, prolonged discomfort, radiation pneumonitis, rib fracture, cardiovascular effects and carcinogenesis, which could compromise the long-term benefit of postoperative radiotherapy (Rutqvist and Johansson 1990; Early Breast Cancer Trialists' Collaborative Group 2000).

Recent data suggest that local recurrence may be facilitated by a local field defect. The morphologically normal cells surrounding the breast cancer demonstrate a loss of heterozygosity that is often identical to that of the primary tumor (Deng et al. 1996). In addition, aromatase activity in the index quadrant is higher than in other quadrants (O'Neill et al. 1988), and has the potential via estrogen to stimulate mutagenesis, growth and angiogenesis (Nakamura et al. 1996; Lu et al. 1996). Patients with ipsilateral breast tumor recurrence (IBTR) have an increased risk of carrying the mutant p53 gene (23% vs. 1%) (Turner et al. 2000), and young patients (<40 years) with IBTR have a disproportionately increased risk (40%) of carrying a deleterious BRCA1/2 gene mutation (Turner et al. 1999). This suggests that local recurrence is probably related more to background genetic instability than to a different tumor biology at a younger age. It appears that a dynamic interaction between the local factors (such as aromatase) present in the breast parenchyma, the systemic hormonal milieu and genetic instability will determine the risk of local recurrence, in addition to the biology of the excised primary tumor.

The location of recurrence in the breast with respect to site of the primary tumor shows an interesting distribution. Between 80 and 100% of early breast recurrences occur in the quadrant that harbored the primary tumor. This is in contrast to the findings of 3D analysis of mastectomy specimens (Vaidya et al. 1996), which reveal that 63% of breasts harbor occult cancer foci, and 80% of these are situated remote from the index quadrant. 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 causing clinical tumors. This is corroborated by the fact that although there is a high frequency—20% in young (median age 39) women and 33% in women between 50 and 55—of tumors found in breasts when analyzed in autopsy studies (Nielsen et al. 1987), the frequency of clinical breast cancer in the population is considerably lower.

Arguably, in the EORTC study (Bartelink et al. 2001), only 56% of local recurrences are reported to have occurred in the original tumor bed. In fact, a further 27% recurred diffusely throughout the breast including the tumor bed, leaving 29% recurrences outside the index quadrant. However, patients in this study received intensive mammographic follow-up, which might have unearthed subclinical occult tumors in other quadrants of unproven clinical significance.

19.2 Radiotherapy Has a Dual Benefit: On the Seed and On the Soil!

It appears that local recurrence occurs in the index quadrant, whether or not radiotherapy is given (Clark et al. 1982, 1992; McCulloch and MacIntyre 1993) and irrespective of clear margins. Of the breast-conserving trials that have tested the effect of radiotherapy, patients in the NSABP-B06 (Fisher et al. 1995), Ontario (Clark et al. 1996), Swedish (Liljegren et al. 1999) and Scottish (Forrest et al. 1996) trials had less extensive surgery compared with the Milan III trial (Veronesi et al. 1993). The recurrence rate in the control arm of the Milan III trial, in which the tumors were smaller and excision was considerably wider, was low (8.8% vs. 24–27% in other trials), albeit at the cost of cosmesis. Nevertheless, radiotherapy reduced it even further and at the same proportional rate as in other trials. If local recurrences were caused by residual disease only, then radiotherapy should have effected a much larger proportional reduction in those patients with positive margins or less extensive surgery; but radiotherapy is as effective in patients with negative margins, suggesting that radiotherapy may have an effect on the soil rather than the seed (Vaidya et al. 2004b).

Thus, radiotherapy may have a dual effect of inhibiting the growth of genetically unstable cells around the primary tumor and of making the breast tissue less conducive to growth (Vaidya et al. 2004b). This idea has been vindicated by translational research during intraoperative radiotherapy. This study, performed at the Centro di Riferimento di Oncologia, Aviano, Italy (Belletti et al. 2008), demonstrated for the first time that radiotherapy could exert its beneficial effects by affecting the tumor microenvironment. We found that the wound fluid collected in the 24 hours following surgical wide local excision of cancer stimulates breast cancer cell lines to proliferate, migrate and invade Matrigel. On the other hand, the fluid collected from wounds that had received targeted intraoperative radiotherapy did not have such an effect (Fig. 19.1). Thus, if radiotherapy is delivered immediately after the operation using TARGIT, it could be superior to conventional radiotherapy that suffers from a “temporal miss.”

Systemic therapies such as aromatase inhibitors or ovarian suppression may achieve a similar effect on the microenvironment by reducing the estrogen concentration in the breast, and may have a synergistic effect with radiotherapy (Azria et al. 2005). Thus, with the increasing use of systemic therapy, intraoperative radiotherapy to the tissues surrounding the primary tumor might be all that is necessary, and such an approach may solve many of the problems of postoperative radiotherapy discussed earlier and may allow many more women with breast cancer to conserve their breast.

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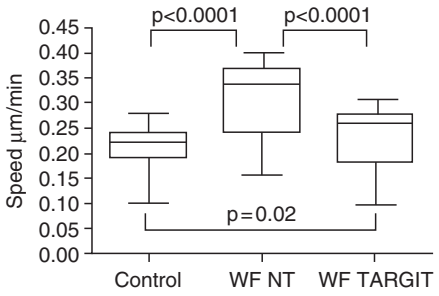

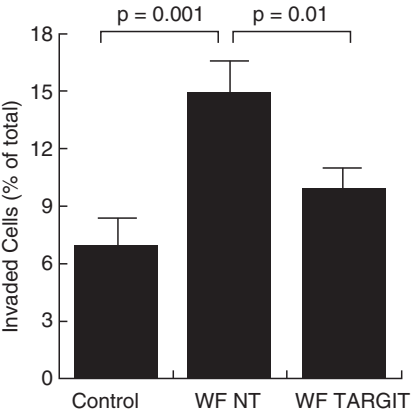

Decreased by TARGIT	Increased by TARGIT
Angiogenin	AgRP
Flt-3 ligand	EFGR
IL-10	FAS/TNFRSF6
IL-6	FGF-4
IL-7	G-CSF
Leptin	IFGBP-6
MCP-1	IL-13
MCP-2	IL-4
RANTES	IL-5
PDGF-BB	Mip-1d
GRO	
HGF	
IL-8	
Mip-1a	
sTNFR-II	
sTNFR-I	
uPAR	
VEGF-R3	
Tie-1	
Tie-2	

Fig. 19.1 TARGIT treatment impairs the WF-induced cancer cell migration and invasion, and changes the tumor microenvironment. Mammary carcinoma-derived cell lines MDA-MB 231 and MDA-MB 453 were tested in a Transwell-based chemotaxis assay and via video endoscopy for their ability to migrate toward the indicated treatment. Preoperative serum (PS) and wound fluid (WF) pools were used at 2.5% in serum-free medium (SFM). The *figure on the left* shows the single-cell speed of MDA-MB 453 immersed in a three-dimensional collagen I matrix and treated as indicated (*NT*, surgery only; *IORT*, surgery + TARGIT). The *figure on the right* shows the percentage of MDA-MB 231 cells invading a three-dimensional Matrigel in a Transwell-based chemotaxis assay in response to the indicated WF, used at a concentration of 2.5%. The box lists the results of the proteomic assay, showing the factors in the wound fluid that are modified by intraoperative radiotherapy (TARGIT). Modified from Belletti et al. (2008)

19.3 Radiobiology of Intraoperative Radiotherapy

The main basis of intraoperative radiotherapy is that a single dose of IORT could have a biological effect on tissue that is equivalent to a full course of fractionated external-beam radiotherapy (EBRT). This is therefore being tested in randomized trials. There is already some evidence suggesting the safety and effectiveness of a single dose of radiotherapy in achieving tumor cell kill (Vaidya et al. 2004b, 2005b, 2006a, 2008). The theoretical basis for calculating the biological effects of a given dose of radiation is the linear–quadratic model. This model is based on the different shapes of cell survival curves of acute and late-reacting tissues. It is assumed that large single doses of radiation are more effective on late-responding tissues as compared to acute reacting tissues. However, the LQ model is reliable for single doses up to 6–8 Gy only, and may therefore not be appropriate for modeling the effects of the high single doses (~20 Gy) that are used in IORT or radiosurgery. There is now abundant clinical information about the effects and side effects of high single doses on a variety of cancers. Radiosurgery doses of 20–25 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 (Flickinger et al. 1995, 2003; Wenz et al. 1998). Long-term follow-up of large Swedish (Swedish Rectal Cancer Trial 1997) and Dutch (Kapiteijn et al. 2001) rectal cancer trials in which 25 Gy, given in five 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 (Reitsamer et al. 2004).

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, the steep dose-dependency of RBE, and the rate of damage repair during radiotherapy delivery (30–50 min). Brenner et al. (1999) have estimated an RBE of about 1.5 for this type of low-energy X-rays. To achieve a complete model of RBE, the introduction of the Lea–Catchside time factor (Herskind et al. 2004) is important. Using this equation, RBEs 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 calculated, although there are insufficient data as to the impact of the volume of treatment to include this as a factor. (However, since the treatment volume is small for IORT, the risk of side effects will probably be lower than that calculated from this model.) Since the $TD_{50/5}$ for pneumonitis is about 9–10 Gy, the thickness of the chest wall should ensure that virtually no risk of pneumonitis is expected. The same is true for the heart. Since 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 (Rutqvist and Johansson 1990; Lind et al. 1997; Bates and Evans 1995; Meinardi et al. 2001) should not be seen. The $TD_{50/5}$ 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 from patients treated with

TARGIT (Vaidya et al. 2003, 2006a; Kraus-Tiefenbacher et al. 2006a, b; Joseph et al. 2004). The single dose of radiation is administered using Intrabeam over 25–35 min. Since normal tissues can repair their DNA within a few minutes, a large proportion of radiation-induced DNA damage is repaired in normal tissues during this long duration of IORT. On the other hand, cancer cells or precancerous cells with poor DNA-repair machinery are unable to do so. Thus, radiation administered using Intrabeam over 25–35 min would have a high therapeutic index, and would induce lesser normal tissue damage than similar doses given over 2–3 min (Herskind et al. 2005, 2006), as used when electrons are employed (ELIOT trial).

We have developed a mathematical model (Enderling et al. 2006, 2007) to estimate the effect of a single dose of radiotherapy as given with Intrabeam in the TARGIT trial. We hypothesize that the therapeutic effectiveness or not of radiotherapy is influenced by the fact that breast cancers are surrounded by morphologically normal cells that already show a loss of heterozygosity in critical genes (Deng et al. 1994, 1996). These cells would be able to repair their DNA in response to fractionated radiotherapy, just like normal cells. Continuing survival and subsequent transformation of these cells may be a large factor in the development of local recurrence. This mathematical model (which can be accessed at https://www.cvit.org/spotlight/RT_applet/) is the first to offer an explanation for the observation that conventional radiotherapy is effective in only two-thirds of cases of early breast cancers. This proportional reduction in recurrence by conventional radiotherapy (of 66%) is constant across tumor sizes and excision extents. However, when a subjected to a single large dose of radiotherapy (as in TARGIT), these cells would succumb and thus the source of local recurrence would be eliminated. Furthermore, the radiobiological effect of a single fraction of radiotherapy may actually be paradoxically higher at greater depth (Astor et al. 2000). This idea gained recent support from the results of the START trials (Bentzen et al. 2008a, b), which suggested that the breast cancer tissue may be more sensitive to fraction size, and delivery in a small number of larger fractions could be a valid option. Thus, the tissues immediately next to the applicator would have a high physical dose with low therapeutic ratio, while those away from the applicator would have a lower physical dose but a high therapeutic ratio. This is an advantage of Intrabeam over the systems that use electrons to deliver a uniform dose or radiation, because its high (physical) dose region is small and it is expected that this would increase acute tumor effects while reducing normal tissue damage and long-term toxicity.

The radiation produced by Intrabeam (the X-ray source is called PRS: Photon Radiosurgery System) is found to induce both necrotic and apoptotic cell death in addition to rapid cell death through nonapoptotic pathways (Kurita et al. 2000). Animal experiments have demonstrated that PRS can induce well-demarcated ablation in canine liver and kidney (Chan et al. 2000; Koniaris et al. 2000; Solomon et al. 2001). As a demonstration of its efficacy at ablating tumor tissue, a series of three breast cancer patients (T = 1–2.5 cm) have been treated with a PRS 400 (bare probe only; i.e., without the applicators, but with the same Intrabeam machine that is used for intraoperative radiotherapy, as shown in the left lower part of Fig. 19.3). These patients were too frail to have surgery. The tumor was localized on the Mammotest, a digital stereotactic prone mammography

table. The tip of the probe was placed in the center of the tumor and radiation was delivered in about 6–12 min. The tumors, ranging in size from 1 to 2.5 cm, were ablated with a single dose of radiotherapy, as demonstrated on biopsy and serial contrast-enhanced MRI (Vaidya et al. 2002c).

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 to a course of fractionated external-beam radiotherapy (EBRT) of about 50 Gy (Vaidya et al. 2004a). One advantage of IORT is that there is no delay between tumor excision and treatment, so there is no loss of efficacy due to 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 (α/β ratio of 3 Gy) is higher than for late-reacting tissues (α/β ratio of 10 Gy). As noted above, the RBE increases with distance from the applicator (Herskind et al. 2004). Thus, the surviving fraction of tumor cells at the applicator surface will be 10^{-12}; 99% of the tumor cells 10 mm from the applicator surface should be sterilized. The tissues immediately next to the applicator would thus 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 (Astor et al. 2000). 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 death 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" (Herskind et al. 2008 and Vaidya et al. 2009) around the excision cavity in which the risk of recurrence for IORT is equivalent to that obtained by EBRT (Early Breast Cancer Trialists' Collaborative Group 2000). The radius of this sphere depends on the applicator size and is about 15 mm for the applicators used most often.

As yet, there is no firmly established standardized IORT dose or dose rate for use in early breast cancer. IORT doses investigated for use in early breast cancer have ranged from 5 to 22 Gy using a variety of different IORT systems. The Intrabeam IORT system delivers a physical dose of 18–20 Gy administered to the tumor bed and about 5–7 Gy at a distance of 1.0 cm from the breast tumor cavity for a period of 20–25 min. Using their Novac7 IORT technology, Veronesi et al. have estimated that an external-beam dose of 60 Gy delivered in 30 fractions at 2 Gy/fraction is equivalent to a single IORT fraction of 20–22 Gy (using an α/β ratio at 10 Gy, typical for tumors and acute reacting tissues). The doses delivered by other methods of partial breast irradiation such as intraoperative systems such as Novac7 have been criticized as being large (Pawlik and Kuerer 2005), and while that dose is uniform, the dose distribution delivered using the TARGIT approach theoretically approximates the geographic distribution of risk of recurrence within the breast.

There has been some discussion about the gap between the IORT and EBRT when TARGIT is delivered as a boost. From the long-term data, it appears that it is safe (Kraus-Tiefenbacher et al. 2006b) and effective (Vaidya et al. 2008). It also appears that the gap is

necessary to avoid late toxicity (Wenz et al. 2008), and we believe at least a five- to six-week gap could be ideal.

19.4 Intraoperative Radiotherapy: An Elegant Method of Partial Breast Irradiation

Modern intraoperative radiotherapy devices derive benefit from miniaturization technology. No longer do we need to transport the patient to the purpose-built radiotherapy suite; the (mini) radiotherapy suite comes to the patient right in the operating room! The first device to be used for IORT was the Intrabeam (Photoelectron Corporation, Lexington, MA, USA) (Vaidya et al. 1999, 2001), which is now manufactured by Carl Zeiss AG (Oberkochen, Germany) (Fig. 19.2). The two other systems of mobile linear accelerators are the Mobetron System (Oncology Care Systems Group of Siemens Medical Systems, Intraop Medical Inc., Santa Clara, CA, USA) and the Novac7 System (Hitesys SPA, Italy). Some of the characteristics of these machines are given in Table 19.1 (taken from Vaidya et al. 2004b).

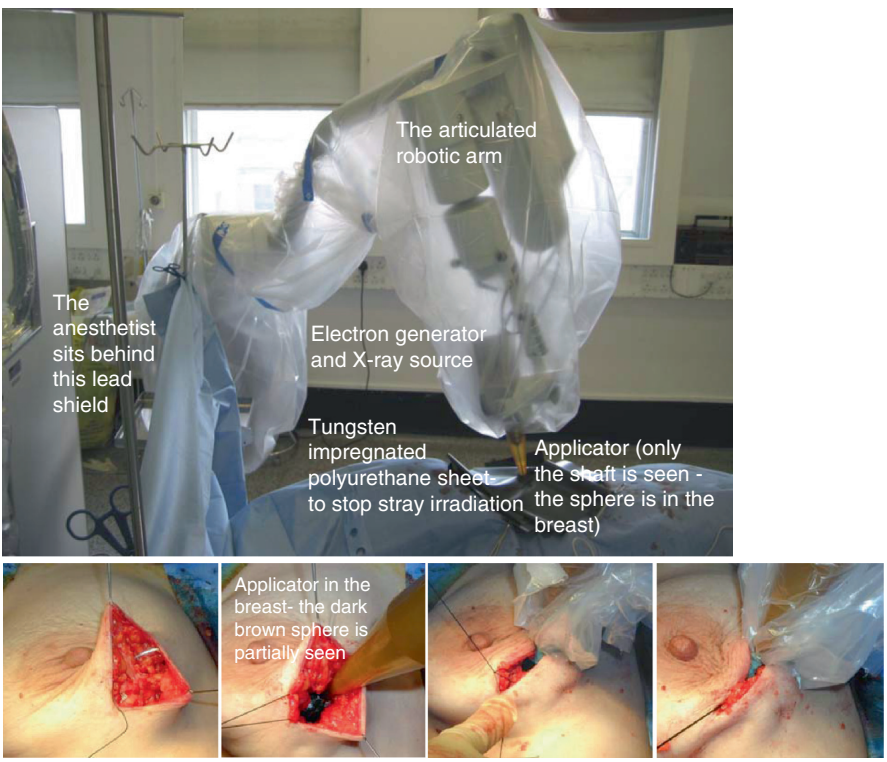

Fig. 19.2 The Intrabeam system (with the X-ray source in the breast wound) and the electron generator and accelerator held by the articulated arm. The figures below demonstrate how the target breast tissue wraps around the applicator, giving true conformal brachytherapy. Modified from Vaidya et al. 2004b.

Table 19.1 Some characteristics of intraoperative radiotherapy systems

Device	Company	Radiation type	Dose	Weight (kg)	Modification of operating room
Intrabeam	Carl Zeiss AG, Germany	Soft X-rays at 50 kV	Physical dose of 20 Gy next to the applicator (with a quick attenuation) over 25–30 min. Setting-up time is about 10–12 min	1.8	Not usually required
Mobitron	Intraop Medical Inc., USA	Electrons at 4–12 MeV	20 Gy physical dose in 3–5 min. Setting-up time is about 20 min	1,275	Necessary
Novac7	Hitesys SPA, Italy	Electrons at 4–12 MeV	20 Gy physical dose in 3–5 min. Setting-up time is about 20 min	650	Necessary

19.5 The Intrabeam Machine and Surgical Technique

The Intrabeam machine contains a miniature electron gun and electron accelerator contained in an X-ray tube 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 in order to give a uniform dose. Various sizes of applicator spheres are available to suit the size of the surgical cavity. The precise 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 18–20 Gy at the applicator surface (i.e., the tumor bed) can be delivered in about 25–35 min with a 3.5 cm applicator. 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 anesthetist (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 (Vaidya et al. 2002a), and an operative video is available from the authors via the Internet.

In the operating room, wide local excision of the primary tumor is carried out 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 20–25 min during which radiotherapy is being delivered can distort the cavity enough to considerably change the dosimetry. Applicators of different sizes 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. It is important to protect the

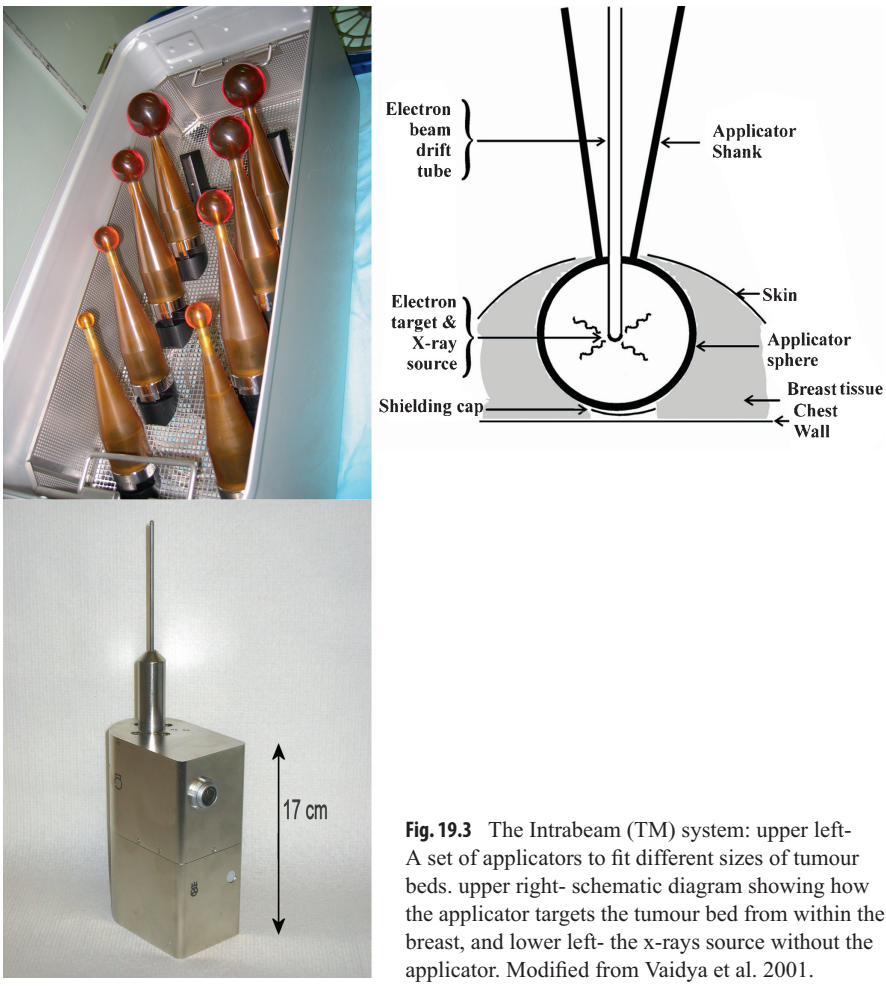

Fig. 19.3 The Intrabeam (TM) system: upper left- A set of applicators to fit different sizes of tumour beds. upper right- schematic diagram showing how the applicator targets the tumour bed from within the breast, and lower left- the x-rays source without the applicator. Modified from Vaidya et al. 2001.

dermis, which should not be brought to within 1 cm of the applicator surface. Fine prolene sutures can be used to slightly retract the skin edge away from the applicator. However, complete eversion of the skin or the use of self-retaining retractors will increase the separation from the applicator so much that it would jeopardize the radiation dose and risk under treatment. For skin further away from the edge that cannot be effectively retracted for fear of reducing the dose to target tissues, a customized piece of surgical gauze soaked in saline, 0.5–0.9 cm thick, can be inserted deep to the skin. This allows the dermis to be lifted off the applicator while ensuring that the breast tissue just deep to it still receives radiotherapy. If necessary, the chest wall and skin can be protected by radiopaque tungsten-filled polyurethane material. These thin rubber-like sheets are supplied as caps that fit on

the applicator or 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 (95% shielding) protection to intrathoracic structures. In patients undergoing sentinel node sampling with immediate cytological or histological evaluation (so that complete axillary clearance can be carried out at the same sitting), TARGIT can often be delivered while the surgical team waits for this result without wasting operating room time. 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 or the even more complex techniques needed for conformal radiotherapy by external beams with multileaf collimators from a linear accelerator. It eliminates "geographical miss" 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 carried out in unmodified operating theaters. Thus, in theory, the biological effect and cosmetic outcome can be improved.

The surgical part of the TARGIT technique is simple and does *not* require extensive dissection around the breast, separating it from the skin anteriorly and the chest wall posteriorly, which is necessary to perform intraoperative radiotherapy with other devices such as the Novac7 used in the ELIOT trial. This means that it can be administered even under local anesthetic (Vaidya et al. 2006b), especially when it is being given as a second procedure a few days after the primary tumor is excised. This latter approach is useful when it is logistically easier and when the primary operation is not performed at a center equipped with the Intrabeam machine. We have found that about 10% of patients get additional EBRT and about 25% of patients are given TARGIT as a second procedure.

19.6 Results of Clinical Trials with the Intrabeam System

Based on the hypothesis that index quadrant irradiation is sufficient, in July 1998 we introduced the technique of targeted intraoperative radiotherapy (TARGIT) (Vaidya et al. 2001, 2002b, 2004b; Vaidya 2002) radiotherapy delivered as a single dose using low-energy X-rays targeted to the peritumoral tissues from within the breast using the Intrabeam device. In patients with small, well-differentiated breast cancers, which are now becoming the majority, this could be the sole radiotherapy treatment.

In pilot studies performed in the United Kingdom, the United States, Australia, Germany, and Italy testing the feasibility and safety of the technique, TARGIT was used as a "boost" dose (Vaidya et al. 2005a, 2006a, 2008) and whole breast EBRT was also given. The median follow-up is 49 months, and the first patient was treated over ten years ago. This was not a low-risk group. A third of the patients were younger than 51 years, 57% of cancers were between 1 and 2 cm (21% > 2 cm), 29% had a grade 3 tumor and 29% were node positive. Amongst these 300 patients, five patients had a local recurrence (five-year actuarial recurrence rate = 1.52%, SE = 0.76%). This compares very favorably with the recurrence rates achieved in recent radiotherapy trials (see Table 19.2)

Table 19.2 Comparison of TARGIT boost with recent clinical trial data

High-risk factors	EORTC boost[8]	START-B trial[9]	TARGIT boost
Young age	37% (< = 50)	21% (<50)	32% (<50)
% >1 cm	75%	86%	78%
% Grade 3	N/A	23%	29%
% Node +ve	21%	23.6%	29%
Recurrence rate at 5 years	4.3%	2.8%	1.52%

despite having a cohort of patients with a worse prognosis. It appears that, given as a boost, TARGIT yields very low recurrence rates.

TARGIT is already used a standard option for the routine tumor bed boost in many centers, and is included in the German radiation oncology guidelines since 2008. While we recognize that a TARGIT boost is at least equivalent to a conventional EBRT boost, we believe that there is pathological, biological (geographical and temporal accuracy), mathematical-modeling, and clinical evidence to suggest that it is likely to be superior. Hence, we have recently launched the TARGIT boost trial that is aimed at ascertaining whether it yields a lower recurrence rate than EBRT in higher-risk (especially young) patients who still suffer a 8–13% local recurrence rate.

During this pilot phase, and for some time later on, a few highly selected patients received TARGIT as the sole modality of radiotherapy (Vaidya et al. 2005b). The updated report on such patients who could not otherwise be given EBRT or entered into the TARGIT trial now includes 78 patients (Keshtgar et al. 2008) with a median follow up of 2–3 years and with excellent local control, giving us reassurance that an inferior result is unlikely.

Over 1,300 patients have been treated with the TARGIT technique. Apart from two patients treated early in these studies, wound healing has been excellent. The cosmetic outcome was assessed formally in available patients treated in the United Kingdom at a median follow-up of 42 months by a surgeon and a nurse not involved in the trial (Vaidya et al. 2003). On a scale of 1–5 (with five 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 of TARGIT (Vaidya et al. 1999, 2002d, 2004b; Vaidya 2002) using the Intrabeam system is now recruiting patients at 23 centers in the United Kingdom, Germany, Italy, Denmark, Poland, Switzerland, the United States, Canada, and Australia. Over 1,600 patients have already been randomized.

In this trial, patients with invasive breast cancer over the age of 45 and suitable for breast-conserving therapy are enrolled prior to tumor excision to receive either IORT or conventional whole breast radiotherapy. Patients with a preoperative diagnosis of invasive lobular carcinoma are excluded because this is indicative of a higher risk of recurrence away from the tumor bed. The pragmatic design of the trial means that if factors such as lobular carcinoma, extensive intraductal component and positive margins are found only postoperatively, then whole breast EBRT can be added safely without jeopardizing the trial analysis. In addition, each center can choose (at the outset) to give additional EBRT in patients in whom they feel it is needed (e.g., those who are found to have multiple lymph

node involvement or extensive lymphovascular invasion). We have found that EBRT was added for 10% of the ~1,600 patients randomized to date. This facility allows pragmatic management of patients with an equipoise that can be decided by each individual center before they start to recruit in the trial. Furthermore, the trial allows the radiotherapy to be delivered at a second procedure, after the final histopathology is available and eligibility criteria are met satisfactorily. Initially at University College London, we were exclusively delivering intraoperative radiotherapy at the time of the primary operation. Our Australian collaborators administered TARGIT as a second procedure for logistic reasons and found that it is indeed safe. In Dundee, Scotland, for example, both approaches are being used, and this allows the recruitment of patients from another hospital that is part of the same NHS trust but is situated some distance away in Perth.

The first patient was randomized in the TARGIT trial in March 2000. Twenty-three centers are now recruiting in this trial. The outcome measures are local recurrence, cosmetic outcome, patient satisfaction and cost analysis, and it is expected that the first results of this trial will be available in 2010/11.

It is well recognized, as in every adjuvant situation, that postoperative whole breast radiotherapy is an overtreatment 60–70% of the time, since only 30–40% of patients will ever get a local recurrence after surgery alone. Our approach to intraoperative radiotherapy intends to refine the treatment of breast cancer patients by introducing a risk-adapted strategy; the elderly patient with a T1G1a tumor should perhaps be treated with a different kind of therapy, such as targeted intraoperative radiotherapy (TARGIT) only, whereas to the young patient with a T2G3 tumor, would have a more accurate boost with TARGIT in addition to whole breast radiotherapy. The TARGIT trial is testing just such a strategy. Hence, the TARGIT trial should not be mistaken for a trial that is solely designed to compare intraoperative with postoperative radiotherapy when actually it is testing two different treatment approaches: the conventional blanket approach versus the new approach of tailored treatment. Endpoints include local recurrence, cosmetic outcome, patient satisfaction and cost analysis.

19.7 Health Economics

Delivering IORT with the Intrabeam prolongs the primary operation by 5–45 min (the shorter extra time when it is performed in conjunction with immediate analysis of the sentinel lymph node). In addition, approximately 1 h of a radiotherapy physicist's time is needed to prepare the device. External-beam radiotherapy requires about nine man-hours of planning, 6 h of radiotherapy-room time, and 30–60 h of patient time. If the cost of conventional radiotherapy was £2,400, using the most conservative estimates, then considering only the 66% saving in man-hours, this novel technique would save £1,800 per patient. If we assume that 25% of the 27,000 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 £12,150,000. This does not include the substantial saving of expensive time on the linear accelerators, which would allow reduced waiting lists and—most importantly—the saving of time, effort, and inconvenience

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for patients. Thus, unlike most other "new" treatments, this one may be actually be less expensive than the current standard! The results of the START trials (Bentzen et al. 2008a) have now resulted in an increase in the popularity of a three-week course of radiotherapy in the UK, although this has not been widely adapted elsewhere in the world. Reducing the radiotherapy duration would change the magnitude of the economic benefit, but TARGIT will still maintain its potential advantages in terms of avoiding geographical and temporal misses and reducing the duration from 15 to 20 postoperative fractions to a single intraoperative fraction of radiotherapy, while also retaining its promise of significantly improving the accessibility to breast-conserving surgery in remote areas around the world.

As we have reiterated before (Vaidya et al. 2004a, b), mere novelty and the convenience of this new technology should not stand in the way of its proper scientific assessment before it is used for standard care. Randomized clinical trials are essential to test this revolutionary approach. We believe that in the future, local treatment of breast cancer could be tailored to the needs of the patient and the tumor. The patient, the surgeon and the radiation oncologist will be able to choose from several well-tested approaches. This may mean not only a wider availability of breast-conserving therapy, but also that small, incremental benefits from targeted and tailored treatment may reduce morbidity and even mortality.

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