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INTRAOPERATIVE RADIOTHERAPY (IORT) FOR BREAST CANCER USING THE INTRABEAM™ SYSTEM

Uta Kraus-Tiefenbacher[1], Antonella Scheda[1], Volker Steil[1], Brigitte Hermann[1], Tanja Kehrer[1], Lelia Bauer[2], Frank Melchert[2], and Frederik Wenz[1]

[1]Department of Radiation Oncology, [2]Department of Gynecology, Mannheim Medical Center, University of Heidelberg, Germany

Introduction: **Intraoperative radiotherapy (IORT) with low-energy X-rays (30-50 KV) is an innovative technique that can be used both for accelerated partial breast irradiation (APBI) and intraoperative boosting in patients affected by breast cancer. Immediately after tumor resection the tumor bed can be treated with low-distance X-rays by a single high dose. Whereas often a geographic miss in covering the boost target occurs with external beam boost radiotherapy (EBRT), the purpose of IORT is to cover the tumor bed safely. This report will focus on the feasibility and technical aspects of the Intrabeam™ device and will summarize our experience with side effects and local control.**
Materials and methods: **Between February 2002 and June 2003 57 breast cancer patients, all eligible for breast conserving surgery (BCS), were treated at the Mannheim Medical Center with IORT using the mobile X-ray system Intrabeam™. The patient population in this feasibility study was not homogeneous consisting of 49 patients with primary stage I or II breast cancer, seven with local recurrence after previous EBRT and one with a second primary in a previously irradiated breast. The selection criteria for referral for IORT included tumor size, tumor cavity size, margin status and absence of an extensive intraductal component. The previously irradiated patients with local recurrences and 16 others received IORT as single modality. In all other cases IORT was followed by EBRT with a total dose of 46 Gy in 2-Gy fractions. The intraoperatively delivered dose after tumor resection was 20 Gy prescribed to the applicator surface. EBRT was delivered with a standard two-tangential-field technique using linear accelerators with 6- or 18-MV photons. Patients were assessed every three months by their radiation oncologist or surgeon during the first year after treatment and every six months thereafter. Breast ultrasound for follow-up was done every six months and mammographies once yearly. Acute side effects were scored according to the CTC/EORTC score and late side effects according to the Lent-Soma classification.**
Results: **Twenty-four patients received IORT only; eight patients because they had received previous radiotherapy, 16 because of a very favorable risk profile or their own preference. Thirty-three patients with tumor sizes between 1 and 30 mm and no risk factors were treated by IORT as a boost followed by EBRT. The Intrabeam™ system was used for IORT. The Intrabeam source produces 30-50 KV X-rays and the prescribed dose is delivered in an isotropic dose distribution around spherical applicators. Treatment time ranged between 20 and 48 minutes. No severe acute side effects or complications were observed during the first postoperative days or after 12 months. One local recurrence occurred 10 months after surgery plus IORT followed by EBRT. In two patients distant metastases were diagnosed shortly after BCS.**
Discussion: **IORT with the Intrabeam system is a feasible method to deliver a single high radiation dose to breast cancer patients. As a preliminary boost it has the advantage of reducing the EBRT course by 1.5 weeks, and as APBI it might be a promising tool for patients with a low risk of recurrence. The treatment is well tolerated and does not cause greater damage than the expected late reaction in normal tissue.**

Key words: breast cancer, IORT, X-rays.

Introduction

The conventional treatment for early breast cancer is breast conserving surgery (BCS) followed by radiotherapy[1]. The standard technique is to treat the entire breast up to a total dose of 50-56 Gy with or without a boost to the tumor bed. Several studies showed that omission of radiotherapy after complete surgery, even in highly selected small and well-differentiated tumors, leads to a significant increase in local relapse[2-4]. However, due to patient preference or logistic problems such as traveling distance, only 80-85% of all patients receive radiotherapy after BCS.

Despite the well-known benefit of adjuvant radiotherapy, there is ongoing debate about the treatment volume and especially about the necessity of whole breast irradiation in every patient. In agreement with the pathological findings of Holland *et al.*[5], results of large controlled studies showed that more than 90% of local in-breast tumor recurrences after BCS occurred in the vicinity of the primary tumor[6,7], whereas differently located breast recurrences after conservative treatment were reported in a range of 1.5-5.8%[6,8-14]. These results suggest that radiotherapy limited to the tumor bed with a reasonable safety margin may provide, in selected patients, similar local control rates as conventional radiotherapy[15,16].

Shortening of the overall treatment time by accelerated partial breast irradiation (APBI) could contribute to solving the logistic and psychological problems of undergoing 5-7 weeks of daily radiation, particularly for elderly patients and those living far from a radiation oncology center. APBI can be delivered with different techniques including external beam radiotherapy (EBRT), brachytherapy and intraoperative radiotherapy (IORT). In breast cancer IORT can be given both as an intraoperative boost and as a single radical treatment[17].

The European brachytherapy society (GEC-ESTRO)

Correspondence to: Dr Uta Kraus-Tiefenbacher, Department of Radiation Oncology, Mannheim Medical Center, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. Tel +49-621-3833530; fax +49-621-3832476; e-mail uta.kraus-tiefenbacher@radonk.ma.uni-heidelberg.de

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recommended in June 2001 that all patients with a five-year local recurrence rate after breast-conserving surgery and whole-breast RT of more than 5% should be boosted. The high-risk subset of patients includes all women aged less than 50 years, as well as patients with positive or narrow resection margins and with an extensive intraductal component in their tumors[18]. For the correct delivery of a boost, precise demarcation of the excision cavity is mandatory: it has been estimated that the externally delivered boost misses the target volume in 24-88% of cases[19].

The purpose of this report is to describe the experience with a novel mobile X-ray system used for IORT in patients with early breast cancer who underwent breast conserving surgery and axillary dissection from February 2002.

Materials and methods

Since 2002 the mobile X-ray system Intrabeam™ (manufactured by Carl Zeiss, Oberkochen, Germany) has been used for IORT at the Department of Radiation Oncology of the Mannheim Medical Center, University of Heidelberg, Germany. The system is composed of a miniature, light-weight (1.6 kg) X-ray source (PRS-400), combined with a balanced floor stand with six degrees of freedom to gain access to target sites throughout the body (Figure 1). This floor stand has been optimized to balance the miniature X-ray source during positioning and treatment delivery including ergonomic features for guiding the source to the target with ease.

The miniature X-ray source has a probe of 10 cm length and 3.2 mm diameter. Within this device electrons are accelerated to the desired energy level and focused down the probe to strike a gold target. This results in the production of an isotropic dose distribution of radiation around the tip of the probe. Various spherical applicators with a diameter ranging from 1.5 to 5 cm are available. They are fixed to the end of the source and placed in the excision cavity to obtain a homogeneous dose distribution on the surface of the applicator and consequently on the surface of the tumor cavity (Figure 2).

The X-ray system produces low-energy photons (30-50 KV) with a steep dose falloff in soft-tissue; no special shielding is therefore required in the room. Treatment can be carried out in unmodified operating rooms with minimal exposure of patient and staff. The rapid dose falloff in the tissue around the applicator guarantees minimal exposure of the surrounding tissue such as the lung and cardiac tissue in the case of breast cancer.

Before each use of the Intrabeam system, a standardized quality assurance program has to be run to ensure homogeneous dose distribution and dose rate. This is done by the physicists early in the morning of a day with a scheduled case in front of the operating rooms in a non-dedicated room. The equipment for the procedure comes with the Intrabeam device. The quality procedure consists of a defined sequence with four levels. For a complete check-up all steps have to be carried out care-

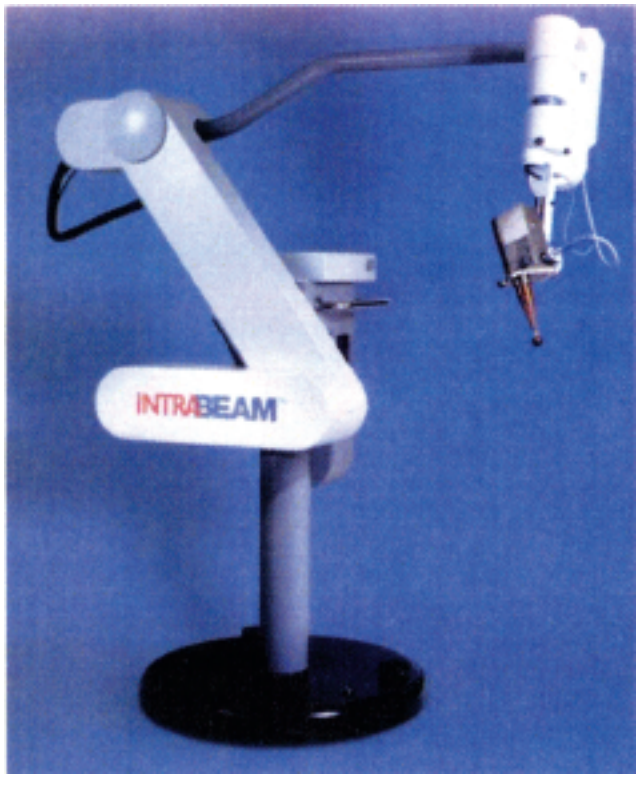

Figure 1 - Intrabeam device with miniature X-ray source (PRS 400).

Figure 2 - Spherical applicators.

fully. The mechanical stability of the probe and the external radiation console are tested first, followed by a check of the dose rate by means of an external ionization chamber. Then the dose distribution is optimized. If the quality of all these items is acceptable, the device can be moved to the operating room.

After resection of the tumor and before delivery of IORT, all resected specimens were radiographically examined for assessment of the surgical margins. In case of uncertainties further resection was performed before IORT was started. Following confirmation of 1-cm tumor-free margins, an appropriate spherical applicator was placed into the tumor bed, its size depending on the size of the surgical cavity. The Intrabeam was then completely wrapped in a sterile plastic cover with a hole for the sterile applicator. Before final fixation of the applicator, a purse-string suture was made within the previously mobilized breast tissue and was tightened around the applicator. With this technique at least 1-1.5 cm of the remaining breast tissue around the tumor cavity covered the spherically shaped applicator surface as target volume. For cardiac shielding we put a 1.0-cm-thick perspex disc with a diameter of 4.0 cm under the applicator at the pectoral muscle in left-sided cases. No special shielding was used for right-sided cases. In IORT with low-KV X-rays the lungs were not affected on either side due to the dose falloff in the tissue and the anatomic protection of the thoracic wall. After fixation of the whole system, the skin was everted by one or two distractors to avoid the presence of skin tissue at less than 0.5-1 cm from the surface of the applicator (Figure 3). The electric clutches and braking system ensured safe and accurate delivery from the probe to the target.

The dose rate and dose distribution were defined for ongoing IORT using the given dose tables, and the treatment time for the prescribed dose was calculated. We prescribed a physical dose of 20 Gy to the applicator surface, which yielded a physical dose of about 6 Gy at a tissue depth of 1 cm depending on the diameter of the applicator. Low-energy X-rays have an increased relative biological equivalence (RBE) compared to megavoltage radiation. The dose falloff in the tissue is less steep because of the increasing RBE with decreasing physical dose. The RBE reaches values up to 2.0 for tumor cells.

Before starting treatment we covered the patient with a tungsten sheet for radiation protection. The control console weighed 18 kg and had a length, width and height of 47 cm, 39.4 cm and 20.3 cm, respectively. Treatment duration depended on the chosen applicator size and ranged from 20 minutes to 48 minutes (Table 1). After treatment, the applicator was carefully removed and the wound was closed as usual.

In this feasibility study some patients, who were preoperatively diagnosed with tumors of less than 1.0-1.5 cm and favorable factors such as tubular-invasive histology, age around 70 years and/or tumor grade 1, were treated with a single IORT treatment after having given their informed consent. All other patients with early, localized breast cancer, selected by tumor size less than 3.5 cm with a tumor cavity size less than 4.5 cm, were treated with IORT as a boost followed by consecutive EBRT.

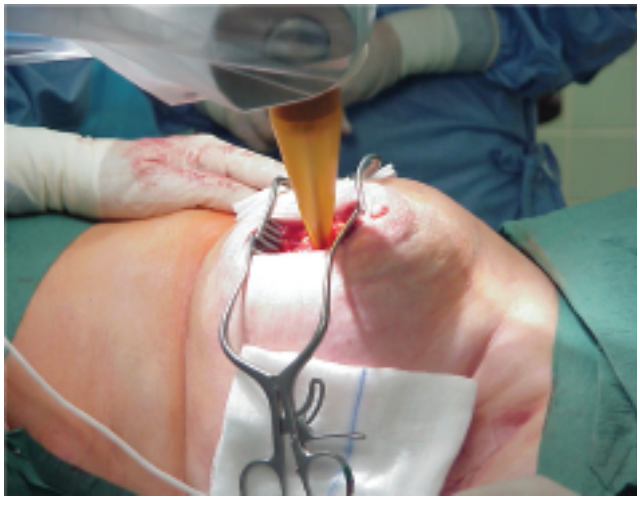

Figure 3 - Positioning of distractors after fixation of the mobilized breast tissue close to the applicator surface by means of a purse-string suture.

Table 1 - Patient characteristics

Characteristics	No. of cases treated with IORT (n = 24)	No. of cases treated with IORT as only intraoperative boost (n = 33)	Total number of cases (n = 57)
Tumor stage			
T1a	1	-	1
T1b	7	5	12
T1c	12	17	29
T2	3	11	14
Tmic	1	-	1
Nodal status			
Node positive	5	8	13
Node negative	19	25	44
Grading			
G1	11	12	23
G2	11	15	26
G3	2	6	8
Histology			
Invasive ductal carcinoma	13	14	27
Invasive lobular carcinoma	6	11	17
Invasive tubular carcinoma	1	1	2
Adenoid-cystic carcinoma	1	1	2
Medullary carcinoma	1	1	2
Invasive tub-lob. carcinoma	2	4	6
Invasive duct-lob. carcinoma	-	1	1
Hormone receptor status			
Estrogen receptor positive	21	27	48
Estrogen receptor negative	3	6	9
Progesterone receptor positive	19	27	46
Progesterone receptor negative	5	6	11

Patients were assessed every three months by their radiation oncologist or surgeon during the first year after treatment and every six months thereafter.

Results

From February 2002 to June 2003, 57 breast cancer patients eligible for breast conserving treatment were enrolled for IORT. The average age of the patients was 63 years (range, 43-83 years). They were all affected by invasive carcinomas of different types with a diameter equal to or less than 3 cm on mammography and ultrasonography. Seven of the 57 patients had local recurrences after previous BCS and EBRT. All seven could be treated with a second breast conserving procedure in combination with IORT. Disease recurrence was diagnosed 3-13 years after primary BCS. Whereas histology in all seven recurrences was the same as in the primary tumor, one patient had a second primary with another histology in the previously irradiated breast; she was also submitted to tumor excision and IORT.

Twenty-four patients received IORT to the tumor bed and no consecutive EBRT of the whole breast. There were different reasons for giving single IORT: seven patients with local recurrences and one patient with a second primary had had previous EBRT and therefore IORT was the only radiotherapeutic option in secondary breast conserving treatment. Sixteen additional patients received IORT as a single modality because of a very low risk profile related to old age and/or a very small tumor and/or low tumor grade and/or favorable histology; other reasons were randomization to the single-IORT arm of our ongoing multicenter trial TARGIT and the patient's own preference.

Thirty-three patients received IORT as a preliminary boost followed by conventional fractionated external beam irradiation. Selection criteria for referral to IORT included tumor size, tumor cavity size (because of a maximum applicator diameter of 5.0 cm), margin status and absence of an extensive intraductal component. EBRT was started 3-5 weeks after surgery. In patients receiving adjuvant chemotherapy, EBRT was started between 8 and 13 weeks from surgery, depending on the chemotherapy regimen. Thirty-seven of the 57 patients (65%) received adjuvant hormonal therapy, 5/57 patients (9%) chemotherapy and 6/57 (10%) chemotherapy followed by hormonal therapy; 9/57(16%) did not receive any adjuvant systemic treatment. In all cases where IORT was delivered as a boost, EBRT was performed two to four weeks after BCS with two individually shaped tangential opposing fields using the isocentric technique after CT-based three-dimensional treatment planning. We treated patients with 2 Gy per fraction up to a total dose of 46 Gy using linear accelerators with energies from 6- to 18-MV photons. The characteristics of the patients are shown in Table 1.

The average treatment time of IORT was 30 minutes, with different treatment times for each applicator (Table 2). Positioning of the applicators took about 5-10 minutes. The median applicator size used was 4.0 cm (range, 3.5 to 5.0 cm) (Table 3).

Table 2 - Treatment time for 20 Gy at the applicator surface according to applicator size

Applicator (mm)	Treatment time (minutes)
15	7.07
20	11.53
25	17.43
30	24.98
35	18.57
40	26.8
45	36.58
50	48.82

The follow-up time of the 57 patients varied from 7 months to 35 months with a median of 18 months. Patients submitted to IORT were clinically evaluated 1-2 weeks after surgery, then every three months for the first year and every six months thereafter. Ultrasound of the breast was performed every six months for the first year and mammographies were done yearly. Acute side effects were scored according to the CTC/EORTC score and late side effects according to the Lent-Soma classification.

Postoperative side effects

No severe complications occurred early after surgery. In three patients (5%), one from the IORT plus EBRT group (applicator size for IORT 4.5 cm) and two from the IORT only group (applicator size 4.0 cm), delayed wound healing was observed. Two (3%) patients from the IORT plus EBRT group developed hematomas requiring puncture. The applicators used for IORT in these cases had a diameter of 3.5 and 4.5 cm. Grade 2 erythema was observed one day after surgery in a patient from the IORT plus EBRT group; it disappeared two days later without any therapy. In this case an applicator with a diameter of 3.5 cm was used for IORT. No fistulae, skin necrosis or abscesses were observed in either patient group.

Late side effects

During a median follow-up of 18 months two patients, who received IORT plus EBRT, presented with grade II fibrosis within the tumor bed four and six months after surgery. The diameter of the applicators used for IORT was 5.0 cm in both cases. Three patients

Table 3 - Applicator sizes and frequencies of the use of each applicator (total of 57 IORT cases)

Applicator (mm)	Frequency
30	2
35	13
40	13
45	17
50	12

from the IORT plus EBRT group (applicator size 4.5, 4.0 and 5.0 cm) and one patient from the IORT only group (applicator size 4.5 cm) developed seromas.

Four patients who had all been treated with combined IORT plus EBRT developed erythemas: three (applicator sizes for IORT of 3.5, 4.0 and 4.5 cm) sufferred from grade I erythema three months after EBRT and one (applicator size for IORT 4.5 cm) had grade II erythema three months after EBRT. All erythemas had disappeared completely at six months of follow-up.

Except in these cases the cosmetic outcome was excellent. No radiation-induced pneumonitis occurred. In all seven cases with locally relapsed breast cancer, patients could be treated with a second breast-conserving procedure combined with IORT, despite prior EBRT.

We did not observe any correlation between the occurrence and grade of side effects, either acute or late, and the different applicator sizes.

Tumor control

Fifty-six of the 57 patients showed no evidence of local recurrent disease during follow-up. In one patient with a ductal invasive carcinoma (pT1cN1biM0, G2, L1, receptor negative) a local recurrence occurred during follow-up after combined treatment consisting of IORT, adjuvant chemotherapy and EBRT. The patient developed an in-breast recurrence with simultaneous multiple skin metastases 10 months after surgery. In two other patients distant metastases (liver, cervical lymph nodes) were diagnosed shortly after BCS.

Discussion

The current standard of care for early operable breast cancer is breast-conserving surgery followed by postoperative radiotherapy. Due to better screening methods, breast cancers are detected more frequently at very early stages so that the question arises whether all patients have to be uniformly treated with whole-breast radiotherapy. Since local recurrences after breast-conserving surgery occur mainly in the area around the primary tumor site[6-14], localized radiotherapy delivered to the peritumoral tissue as accelerated partial breast irradiation could be an appropriate method to control local recurrence in selected patients with early stage breast cancer. This issue has recently generated significant interest because several brachytherapy studies demonstrated excellent five-year results[20]. One modality to deliver APBI is intraoperatively, when the tumor bed is clearly visible. This can be done by means of mobile IORT devices in the operating room. An ongoing trial, ELIOT, is comparing intraoperatively delivered electrons covering the 90% isodose volume of the remaining breast tissue after lumpectomy with conventional external beam radiotherapy of the whole breast; it will be closed in 2005 with 900 patients enrolled[21].

The goal of the intraoperative procedure with the Intrabeam™ device is to deliver a high dose to the tissue around the tumor cavity up to a depth of 1-2 cm. In contrast to brachytherapeutic approaches with high-dose radiotherapy or intraoperative electron devices, where the dose is prescribed to a defined depth margin or to the 90% isodose line around the tumor cavity, in this low-energy X-ray device the dose is not prescribed to a defined depth. The highest dose is at the applicator surface and it decreases with increasing tissue distance from the applicator. A detailed analysis of the radiobiological aspects specific to the Intrabeam system requires careful consideration of the increased relative biological efficiency of the low-energy X-rays, a steep dose dependence of RBE, and the rate of damage repair during radiotherapy delivery (30-50 minutes). Brenner has estimated an RBE of about 1.5 for low-energy X-rays of this type[22]. After using a special time factor for radiobiological modeling, an RBE of 1.0 at the applicator surface, 1.5 at 10 mm and about 2.0 at 25 mm can be estimated, with the exact value depending on the applicator size[23]. There is still a physical dose of about 6 Gy at a tissue depth of 1 cm, depending on the diameter of the applicator. The dose falloff into the tissue is less steep because of the increasing RBE with decreasing physical dose. One advantage of IORT is that there is no delay between tumor excision and treatment, and therefore no loss of efficacy because of tumor cell proliferation before the start of or during EBRT. The RBE of low-energy X-rays for early-reacting tissue and tumor cells (α/β, ratio of 3 Gy) is higher than for late-reacting tissue (α/β, ratio of 10 Gy). Due to a higher RBE with increasing distance from the applicator, radiobiological modeling suggests that the surviving fraction of the tumor cells at the applicator surface will be 10^{-12}, and that 99% of the tumor cells 10 mm away from the applicator surface should be sterilized. Thus, while the tissue close to the applicator surface receives a high physical dose with a low therapeutic ratio, the tissue further away from the applicator receives a lower physical dose but with a high therapeutic ratio[23].

Due to the increased RBE compared to megavoltage radiation, low energy X-rays can be used for the breast tissue around the tumor cavity immediately following complete tumor excision with a clear margin. Together with the excised lumpectomy margin of at least 5-10 mm, this approximates a quadrant. Holland and coworkers were able to demonstrate that the highest probability of tumor cell spread within the breast was close to the primary tumor[5]. According to Vicini a margin of 10 mm around the tumor bed should be adequate in covering any disease remaining in the breast after lumpectomy in more than 90% of patients treated with APBI, clear margins presumed[24].

Due to the increased RBE of low-energy X-rays it may be argued that intraoperative radiation with the PRS source may cause more than the expected late reactions in normal tissue, especially at greater distances from the applicator where the dose decreases. Since the irradiation produced by the Intrabeam system is delivered during an interval of 20-55 mins, there is ample time for normal tissue to repair during the procedure, assuming that the half-time for recovery from sublethal damage is about 15 minutes. The effect of recovery re-

sults in a reduction of the effective RBE, so that the spatial extent of late damage is decreased[23].

Our experience with 57 patients treated at the University Hospital Mannheim with the Intrabeam device allows positive preliminary conclusions. The procedure was well accepted and tolerated by all patients. After a median follow-up of 18 months there were no severe complications for patients treated in our institution and the cosmetic outcome was excellent.

Due to a lack of evidence and patient data, only preliminary results can be shown regarding posttherapeutic complications in general[25]. Overall, only a few studies on breast-conserving treatment reported on this subject. Bartelink of the EORTC "boost *versus* no boost" trial, however, does report hematoma rates of 13%[26]. Romestaing *et al*. observed in their CRLC trial a 12.4% rate of postoperative teleangiectasia[27]. The only comparison that is currently possible is an indirect comparison of wound infection rates: whereas Bartelink *et al*. observed a wound infection rate of 17% in their 5318 patients, who were treated by breast conserving surgery, only 4% occurred in IORT patients[15].

The IORT procedure prolongs the operation time by a maximum of 60 minutes and adds one to two hours of radiotherapy physicist's time in the preparation of the device. EBRT, on the other hand, costs about nine man hours, six hours of radiotherapy room time and 30-60 hours of patient time.

No final conclusion in terms of survival and equivalence to the standard six-week postoperative radiotherapy can be drawn, since the follow-up and the number of patients in our study are limited. Only the results of the multicenter randomized trial TARGIT designed to test the hypothesis of equivalence between the two treatment arms will provide an answer[15,28]. It is expected that the first results of this trial will be available in 2007.

For the moment we can conclude that with the Intrabeam system a radiation boost can be delivered without the risk of geographic misses associated with external beam boost techniques. The follow-up is still too short to draw any further conclusions.

In the ongoing international randomized trial TARGIT the use of low-energy X-rays as the only intraoperative irradiation treatment delivered to selected breast cancer patients with a good prognosis and no risk factors is compared to conventional external beam radiotherapy of the whole breast. It has to be proved whether IORT can eventually contribute to reduce some disadvantages of conventional radiation treatment such as the psychological distress of undertaking a 5-6 week course of external beam radiotherapy and the financial burden to both patient and health care system. IORT might be an alternative treatment option for many radiotherapy centers where long waiting lists due to scarce resources lead to delay in the delivery of radiation therapy or even omission of breast-conserving strategies.

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