Clinical Study

Intraoperative Full-Dose of Partial Breast Irradiation with Electrons Delivered by Standard Linear Accelerators for Early Breast Cancer

Alfredo Carlos S. D. Barros,1,2 Samir A. Hanna,3 Heloísa A. Carvalho,3,4 Eduardo Martella,5 Felipe Eduardo M. Andrade,1 José Roberto M. Piatto,1 and José Luiz B. Bevilacqua1

1Mastology Center, Hospital Sírio Libanês, Rua Dona Adma Jafet 91, 01308-050 São Paulo, SP, Brazil
2LIM 02, Discipline of Human Structural Topography, University of São Paulo Medical School, Avenida Dr. Arnaldo 455, 01246-903 São Paulo, SP, Brazil
3Department of Radiotherapy, Hospital Sírio Libanês, Rua Dona Adma Jafet 91, 01308-050 São Paulo, SP, Brazil
4Radiotherapy Service, Hospital das Clínicas, University of São Paulo Medical School, Rua Dr. Enéas de Carvalho Aguiar 225, 05403-000 São Paulo, SP, Brazil
5Hospital Perola Byington, Avenida Brigadeiro Luís Antônio 683, 01317-000 São Paulo, SP, Brazil

Correspondence should be addressed to Alfredo Carlos S. D. Barros; clinab@terra.com.br

Received 30 May 2014; Accepted 25 November 2014; Published 17 December 2014

Academic Editor: Debra A. Tonetti

Copyright © 2014 Alfredo Carlos S. D. Barros et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Purpose. To assess feasibility, efficacy, toxicity, and cosmetic results of intraoperative radiotherapy (IORT) with electrons delivered by standard linear accelerators (Linacs) during breast conserving surgeries for early infiltrating breast cancer (BC) treatment. Materials and Methods. A total of 152 patients with invasive ductal carcinoma (T ≤ 3.0 cm) at low risk for local relapses were treated. All had unicentric lesions by imaging methods and negative sentinel node. After a wide local excision, 21 Gy were delivered on the parenchyma target volume with electron beams. Local recurrences (LR), survival, toxicity, and cosmetic outcomes were analyzed. Results. The median age was 58.3 years (range 40–85); median follow-up was 50.7 months (range 12–101.5). There were 5 cases with LR, 2 cases with distant metastases, and 2 cases with deaths related to BC. The cumulative incidence rates of LR, distant metastases, and BC death were 3.2%, 1.5%, and 1.5%, respectively. Complications were rare, and the cosmetic results were excellent or good in most of the patients. Conclusions. IORT with electrons delivered by standard Linacs is feasible, efficient, and well tolerated and seems to be beneficial for selected patients with early infiltrating BC.

1. Introduction

It is well known that whole breast irradiation (WBI) after breast conserving surgeries for patients with early infiltrating breast carcinoma (BC) significantly reduces the likelihood of local recurrence (LR) [1]. There are several evidences that LR is a predisposing factor for systemic metastasis [2–4] and, within this scope, radiotherapy (RT) is very useful for treating residual tumor cells after the surgery. The most used schedule for WBI is 50 Gy delivered in 5 weeks using conventional fractionation.

There is no consensus, however, regarding whether the entire breast needs to be irradiated [5]. The accelerated partial breast irradiation (APBI) concept, based on confining the irradiation to the vicinity of the tumour bed, shortening the course of the treatment and allowing more convenience for patients, has contributed to changes in the RT paradigms [6, 7].

A variety of APBI techniques, including low- or high-dose rate brachytherapy, balloon brachytherapy, localized external beam RT (using either three-dimensional or intensity-modulated), and intraoperative electron or photon
beam treatments, have been used with encouraging results [8–13].

Nondedicated linear accelerators (Linacs) capable of delivering treatment with electrons have been used for intraoperative irradiation of many other tumors [14, 15]. These types of equipment are available in almost every RT facility and are used for daily patients’ treatments. The possibility of delivering intraoperative radiotherapy (IORT) with electrons, without dedicated equipment, is very attractive. Addressing this issue, the purpose of our paper was to assess the efficacy, toxicity, and cosmetic outcomes of IORT delivered by standard Linacs, during breast conserving surgeries for the treatment of early breast cancer.

2. Materials and Methods

A prospective phase II cohort study started in May 2004 at the Sirio Libanes Hospital in Sao Paulo, Brazil. As of July 2012, 187 women with diagnosis of BC by percutaneous biopsy were enrolled. The research protocol was approved by the Ethics Committee of the hospital.

Patients were eligible if they had unicentric invasive ductal carcinoma, with less than 3.0 cm at the largest diameter confirmed by mammography, ultrasonography, and magnetic resonance imaging (MRI).

Patients were considered ineligible if any of the following features were present: skin involvement, history of BC in the contralateral breast, or intraoperative microscopic findings of involvement of surgical margins or sentinel node (SN). Invasive lobular carcinoma subtype was also an exclusion criterion due to its high rate of multicentricity and multifocality.

2.1. Surgery. The breast conserving surgeries were performed at an operating theater located inside the Radiotherapy Department, contiguous to the Linac suite. The quadrantectomy consisted of an “en bloc” resection of the parenchyma and pectoralis fascia, with at least a 2 cm macroscopic margin around the tumor. The skin over the tumor was generally removed by a circular incision, with its conservation being possible in small, deeply located tumours (T ≤ 1.0 cm).

After verification of clear margins by intraoperative histopathologic and cytologic exams, SN radioguided biopsy was generally performed by the unique breast incision, as previously described [16, 17]. SN was analyzed by means of cytology.

As for surgical aspects, the same maneuvers standardized for electron intraoperative therapy (ELIOT) by Veronesi et al. were adopted [9, 18]. Once the wide local excision and the SN biopsy were performed, the glandular tissue was detached from the pectoralis major muscle, to an extension of 3 cm margin around the resected area, and the skin flaps were detached from the parenchyma at the level of the adipose lamina for 2 cm circumferentially.

The surgical bed was filled with a wet compress, the wound was covered, and the patient was transferred to the RT room, where all of the materials needed for maintaining anaesthesia, including gases, were available.

A three-layer disk made of lead (down), aluminium (middle), and silicon (up) was inserted underneath the gland over the muscle, to protect the normal tissue below the irradiated area and absorb the backscattered radiation. The shielding disks (0.5 cm thick each) were available in three diameters (6, 8, or 10 cm), and the largest one fitting the space was placed. The parenchyma was approximated over the disk by separated stitches, exposing the area to the electron beam.

2.2. Radiotherapy. Irradiation was performed using one of two standard models of Siemens linear accelerators: Primus or KD2. Both machines produce electrons and are able to generate photon and electron beams with energy ranging between 6 and 21 MeV. A single total dose of 21 Gy prescribed at the 90% isodosism was delivered directly to the parenchyma at a rate of 300 cGy/min.

The electron beam energy was chosen after measuring the gland thickness by inserting a needle perpendicularly to the parenchyma. A sterile, round collimator was connected to the gantry of the Linac and gently placed into the surgical bed by appropriated mobilization of the couch and gantry (Figure 1). The choice of collimator diameter was made according to each case but was usually up to 6 cm.

A portal film was taken placing the film below the accelerator couch, orthogonally to the collimator, to guarantee the exact positioning of the disks. This procedure was repeated, if necessary, until the disk was considered well positioned. Afterwards, the staff left the room; the irradiation was delivered during in average 8 minutes, according to the chosen energy, under video surveillance of the vital signs of the anaesthetized patient (Figure 2). Subsequently, the collimator and the disk were removed. The breast tissue was then reconstructed using oncoplastic techniques, preferentially outside the Linac room, in the operating room [19–21].

The whole irradiation procedure lasted approximately 30 minutes, including patient transfer.

2.3. Adjuvant Treatment and Follow-Up. Adjuvant systemic therapy was at the discretion of the physician, in accordance with current guidelines [22]. More than half of the patients received hormone therapy alone (51.3%), 8.5% of the patients received only chemotherapy, 38.1% had both, and 1.9% patients had no adjuvant systemic therapy.

Follow-up was performed every 3 months in the first year and every 6 months thereafter. Mammography and ultrasonography were performed at the 6-month visit and annually thereafter.

The primary outcome of the study was LR as the first unfavorable event. Secondary outcomes were local toxicity and cosmesis.

LR was considered as a true relapse (TR), which represents regrowth of residual malignant cells in the same region of the primary tumour, or a second primary tumour (SPT), representing tumor growth in another quadrant, suggesting a distinct clonal origin.

The presence of seromas, hematomas, fat necrosis, wound infections, and dehiscences was investigated at all time points after surgery. Events that occurred until one month after the
treatment were considered as “early” and after 6 months as “late.”

Cosmesis evaluation was scored by the physician at least 12 months after irradiation, in accordance with the Harvard criteria [23]. Briefly, the treated breast is compared with the contralateral one and the result is classified as excellent (minimal or no difference in the size or shape); good (mild asymmetry in the size or shape); fair (obvious differences in the size and/or shape); and poor (marked change in the appearance involving more than 1/4 of the breast).

2.4. Statistical Analysis. Descriptive and frequencies analysis were performed. The cumulative incidence of LR, overall survival, and BC survival were calculated using the Kaplan-Meier method. The SPSS package version 17.0 (Chicago II) MedCalc package, 11.3.3.0 version (Mariakerke, Belgium), was used for statistical analysis.

3. Results

Of the 187 enrolled patients, 35 (18.7%) were intraoperatively excluded because of SN positivity (18 patients), difficulty in obtaining clear margins (11 patients), multicentricity/multifocality (3 patients), muscle infiltration (1 patient), $T > 3.0$ cm (1 patient), and no SN identification (1 patient).

A total of 152 patients received IORT with electrons and were analyzed. The median age of the patients was 58.3 years (range 40–85). Table 1 summarizes the patients and tumours characteristics. The median follow-up time was 50.7 months (12–110.5).

Five of the 152 patients presented LR (TR or SPT). The cumulative incidence of LR as the first unfavorable event was 3.2% (95% CI: 0.8–8.1) (Figure 3). Among the 5 cases of LR in the entire cohort 4 were considered to be a TR, and one had a failure in a quadrant other than the index lesion at 30-month follow-up, consistent with SPT. Regarding other failures, two patients (1.3%) developed distant metastases, three had axillary failure (1.9%), and one patient had a contralateral tumor (0.6%). It is worth noting that among the cases with TRs one had SN micrometastasis and one
Table 1: Characteristics of the patients.

| Age (years)    | n  | (%)  |
|---------------|----|------|
| <50           | 45 | 29.6 |
| 50–59         | 39 | 25.6 |
| ≥60           | 68 | 44.7 |

| Menopausal status    | n  | (%)  |
|----------------------|----|------|
| Before menopause     | 36 | 23.6 |
| After menopause      | 116| 76.4 |

| Tumor size | n  | (%)  |
|------------|----|------|
| pT1        | 133| 87.5 |
| pT2        | 19 | 12.5 |

| Estrogen receptor        | n  | (%)  |
|--------------------------|----|------|
| Positive                 | 140| 92.1 |
| Negative                 | 12 | 7.9  |

| Progestrone receptor      | n  | (%)  |
|---------------------------|----|------|
| Positive                  | 140| 92.1 |
| Negative                  | 12 | 7.9  |

| Grading | n  | (%)  |
|---------|----|------|
| G1      | 14 | 9.2  |
| G2      | 79 | 51.9 |
| G3      | 59 | 38.8 |

Table 2: Incidence of first unfavorable events.

| Event                           | n  | (%)  |
|---------------------------------|----|------|
| Local recurrence                | 5  | 3.3  |
| True local recurrence           | 4  | 2.6  |
| Second primary tumor            | 2  | 1.3  |
| Axillary relapse                | 2  | 1.3  |
| Distant metastasis              | 2  | 1.3  |
| Contralateral tumor             | 1  | 0.6  |

Table 3: The 3-year actuarial rates of recurrence. Data of the 109 patients with at least 36 months of follow-up.

| Pattern of failure | 3-year actuarial rate (%) |
|--------------------|---------------------------|
| Local recurrence   | 4.6                       |
| True local recurrence | 0.9                     |
| Second primary tumor within treated breast | 1.8 |
| Axillary relapse   | 1.8                       |
| Distant metastasis | 1.8                       |
| Contralateral tumor | 0.9                     |

4. Discussion

Breast conserving surgery followed by external WBI is a well-established treatment for most women with early infiltrating BC [24, 25]. Currently, more sophisticated RT techniques are available, allowing better target coverage with better normal tissue sparing [26]. In this context, APBI is a rapidly evolving strategy, with a widespread support for its use [7, 27, 28].

The main biologic rationale for intraoperative partial breast irradiation is that 85% of the LR (almost 100% of TR) occurs in the vicinity of the tumour, next to the scar, as a consequence of the persistence of neoplastic cells that most likely possess aggressive cancer stem cell properties [29, 30]. Experimental data indicate hierarchical organisation of BC with a small number of cancer-initiating cells (CICs) that had lobular carcinoma, both identified only in the definitive histopathological analysis.

One hundred and nine cases were followed up for at least 36 months with an estimated LR rate of 4.6%. Thus, the TR cumulative incidence at 36 months was 2.6%. Kaplan-Meier estimates of efficacy at three years were LR of 4.6%, contralateral breast tumor 0.9%, distant failure 1.8%, cancer specific survival 98.2%, and overall survival 98.0%. The cumulative incidences of first unfavorable events are outlined in Table 2, and the 3-year actuarial rates of recurrences are presented in Table 3.

There were three deaths (1.9%): two related to breast cancer (one secondary to pulmonary metastasis and another due to chemotherapy toxicity) and one nononcologically related death. Overall survival is shown in Figure 4.

In the first month after surgery, 6 cases of skin erythema (3.9%), 2 wound dehiscences (1.3%), and 1 case of hematoma (1.9%) were observed. These events were considered as early postoperative complications. Evidence of late toxicity, observed after at least 6 months of follow-up, was seen in 45 patients (29.6%) in a median time of 8 months (range 8–24). There were 21 cases (13.8%) of breast fibrosis (13 mild and 8 severe) and 15 cases of fat necrosis (9.8%). Among these cases, 6 patients required punctons and other 6, surgical drainage. There were also 3 cases of breast lymph edema and 2 cases of nipple retraction.

The esthetic outcomes have shown 70.3% excellent, 14.4% good, 3.9% regular, and 3.2% of bad results. From the entire cohort, 7.8% of patients were not cosmetically evaluated. Cosmetic outcomes are listed in Table 4. In Figure 5 a case with an excellent esthetic result four years after the procedure is shown.
have ability to self-renew and exhibit multilineage potential [31]. CICs, in contrast to their tumorigenic counterparts, can survive fractions of sublethal doses of RT, retaining self-renewal capacity over several generations [32–34]. Some properties of CICs could make them a more vulnerable target to a single lethal irradiation dose, soon after the breast resection, without allowing postoperative hypoxia and time for cell repopulation [35]. Effects of IORT on tumor microenvironment could improve outcomes, as it impairs local proliferation caused by surgical manipulation, inflammation, and simulation of the epithelial mesenchymal transition [36,37].

Different RT techniques can be used with this purpose and, given that intraoperative RT with standard Linacs has previously been used to treat abdominal tumors, we decided to use this form of treatment during breast conserving surgeries. The surgeries were performed at an operating theatre in the RT department, close to the Linac room where the patients were transferred to receive the irradiation. This urban characteristic by itself turned out to be a feature that helped the better feasibility of the method. However, it is still possible to transport the patient from an operative theatre far from the Linac suite (usually out of business hours), previously prepared to be used as an operating room [38].

The patient transport from the operating room to the Linac may be regarded as a disadvantage of the method, when compared to the treatment with a dedicated Linac. But one must realize that the use of a nondedicated Linac, mainly in developing countries, may represent a cost-benefit strategy. We have previously reported our outcomes with focus on technical aspects, and the highlights of the use of nondedicated machine were to explore its capability of producing higher electron beam energies rather than dedicated machines and to check the possibility of misalignment between the collimator and the shielding disks by obtaining portal films using photon beams [39].

Other advantages of IORT with electrons are accurate targeting of RT and a precise definition of the tumour bed volume under direct guidance, offering very good dose homogeneity and more effectively sparing of the heart and lungs when compared to external beam RT [35].

At the moment there are two published randomised trials focusing on single dose of RT during breast-conserving surgeries. Vaidya et al., using localized photon beams delivered by the Intrabeam device (Carl Zeiss Meditec, Oberkochen, Germany), concluded that such approach is as efficient as conventional fractioned external beam RT for carefully selected patients [40]. Veronesi et al. did a study with ELIOT at the European Institute of Oncology [41]. They employed two types of dedicated linear accelerators: NOVAC7 (Hitesys, Latina, Italy) and Liac (Info and Tech, Rome, Italy). Although they found that the rate of LR in the ELIOT group was within the prespecified equivalence margin of results, it was observed that this rate was significantly greater than with external radiotherapy, pointing out the necessity of defining the optimal patient selection criteria.

By far, the most important benefit of IORT with electrons is shortening the RT duration from the traditional 5–6 weeks to 5–8 minutes, thereby eliminating the delay in receiving RT, alleviating emotional distress, avoiding logistical difficulties in travelling to the radiation facility and ensuring 100% compliance. The rate of undertreated patients due to incomplete fractioned adjuvant WBI is far from ideal, especially in developing countries, being such women exposed to a higher risk of BC recurrence [42,43].

The key feature for the development of ELIOT by the Italian group was the estimation of dose equivalence between the standard 60 Gy divided into 30 fractions and the single dose of 21 Gy [44]. In a landmark paper, Veronesi et al. presented a large phase II study that included 1,822 cases treated with ELIOT using dedicated machines [45]. After a mean follow-up period of 36.1 months, 42 women (2.3%) developed a TR, 24 women (1.3%) had a new primary ipsilateral tumour, and 26 women (1.4%) had distant metastases as the first event. Five- and 10-year survival rates were 97.4 and
The widespread use of APBI motivated the American Society of Therapeutic Radiology and Oncology to define a suitable group of patients for whom APBI is acceptable outside of clinical trials, including the following: women older than 60 years, with T1 IDC, clear margins, and the absence of multicentricity, multifocality, and axillary nodes involvement [27]. The European Society for Therapeutic Radiology and Oncology also proposed suitable conditions for APBI: age \( \geq 50 \) years, unicentric and unifocal \( T_{1-2} \) (\( \leq 3.0 \) cm), pN0 nonlobular invasive cancer, the absence of an extensive intraductal component and lymphovascular invasion, and negative surgical margins of at least 2 mm [28]. Currently it is also known that estrogen receptor negativity is associated with increased risk of LR following APBI [46].

This study has started before the publication of these recommendations, and part of our cases should be considered not suitable for APBI. However, some other results have pointed out that even patients who do not meet the ideal conditions may be locally treated with success [47, 48]. Anyway, since the publication of the recommendations (2009), women under 50 years of age were no longer accepted in our study.

Although it might be tempting to offer IORT to a large number of patients, at this time, a careful selection of suitable patients is paramount. For this reason we advocate preoperative MRI which was performed in all of our patients, to better select the cases for partial breast irradiation. Most likely, the traditional WBI reduces the rate of SPT in the treated breast solely if they were present and occult at the time of the primary treatment. MRI could potentially contribute to the more precise detection of multifocal or multicentric disease, with improvement of operative outcomes and decreased recurrence rates [49], although, besides the MRI high diagnostic accuracy, it is always desirable to have pathological verification of the findings because of the MRI high false-positive rates [50].

The confirmation of intraoperative clear surgical margins is also mandatory, since the objective of IORT is to reduce LR by treating residual malignant cells that may persist in tumour-bearing areas.

With regard to efficacy, the incidence of LR in this cohort was low and acceptable. Moreover, complications due to local toxicity were scarce, and this form of IORT led to a favorable impact on body image, as already observed by other authors [51]. Also, when oncoplastic maneuvers are required, including immediate breast reconstruction with prostheses, they are feasible and safe [19, 21].

We consider as limitations of this study the facts that there was not a control group and that it was performed at a single institution on relatively small number of patients. In spite of these caveats, the technique was demonstrated to be feasible and was successfully implemented, with a very short learning curve. IORT with electrons delivered by conventional Linacs, immediately after a wide local excision, presented the expected results until now, with very good local control and cosmetic outcomes and a low toxicity rate. Selected patients with early infiltrating breast carcinomas may benefit from the technique, which may represent an interesting option for developing countries.

**Conflict of Interests**

The authors declare that there is no conflict of interests.

**Acknowledgments**

The authors thank the following study collaborators: surgeons Adriana A. Yoshimura, Carlos A. Del Roy, Carlos A. Valente, Donizetti R. Santos, Jorge S. Souen, José Roberto Filassi, Lincon Jo Mori, Luis H. Gebrim, Maria Aparecida C. Barros, Marianne Pinotti, and Paula Tambellini; radiation oncologists Agamedes Paduan, Carlos Eduardo Vita Abreu, Carlos R. Montenegro, Fernando Arruda, João Luís F. Silva, Juliana D. Panichella, Romualdo Dalle Molle, and Sebastião Correa; physicists Cecília Maria K. Haddad and Edilson Pelosi; pathologist Cristiane da Costa B. A. Nimir; nuclear medicine specialist Paulo Aguirre Costa.

**References**

[1] Early Breast Cancer Trialists’ Collaborative Group (EBCTCG), “Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials,” The Lancet, vol. 378, pp. 1707–1716, 2011.

[2] E. Botteri, V. Bagnardi, N. Rotmensz et al., “Analysis of local regional recurrences in breast cancer after conservatur surgery,” Annals of Oncology, vol. 21, no. 4, pp. 723–728, 2009.

[3] J. R. Benson and K. A. T. Teo, “Breast cancer local therapy: what is its effect on mortality?” World Journal of Surgery, vol. 36, no. 7, pp. 1460–1474, 2012.

[4] A. C. S. D. Barros, L. C. Teixeira, A. C. Nisida, M. Pinotti, and A. Pinotti, “Prognostic effects of local recurrence after conservational treatment for early infiltrating breast carcinoma,” Tumori, vol. 88, no. 5, pp. 376–378, 2002.

[5] E. Huang, T. A. Buchholz, F. Meric et al., “Classifying local disease recurrences after breast conservation therapy based on location and histology: new primary tumors have more favorable outcomes than true local disease recurrences,” Cancer, vol. 95, no. 10, pp. 2059–2067, 2002.

[6] J. A. Cox and T. A. Swanson, “Current modalities of accelerated partial breast irradiation,” Nature Reviews Clinical Oncology, vol. 10, no. 6, pp. 344–356, 2013.

[7] M. Barry, A. Ho, and M. Morrow, “The evolving role of partial breast irradiation in early-stage breast cancer,” Annals of Surgical Oncology, vol. 20, no. 8, pp. 2534–2540, 2013.

[8] J. S. Vaidya, D. J. Joseph, and J. S. Tobias, “Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, noninferiority phase 3 trial,” The Lancet, vol. 376, no. 9735, p. 90, 2010.

[9] U. Veronesi, R. Orecchia, A. Luini et al., “A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated,” European Journal of Cancer, vol. 37, no. 17, pp. 2178–2183, 2001.
[10] C. Polgár, J. Fodor, T. Major, Z. Sulyok, and M. Kásler, “Ten-year results of the Budapest randomized trial. Breast-conserving therapy with partial or whole breast irradiation,” *Radiotherapy & Oncology*, vol. 108, no. 2, pp. 197–202, 2013.

[11] K. J. Baatjes and J. P. Apfelstaedt, “7-year follow up of intraoperative radiotherapy for early breast cancer in a developing country,” *Breast*, vol. 21, no. 3, pp. 326–329, 2012.

[12] C. Shah, J. B. Wilkinson, M. Lyden et al., “Comparison of survival and regional failure between accelerated partial breast irradiation and whole breast irradiation,” *Brachytherapy*, vol. 11, no. 4, pp. 311–315, 2012.

[13] A. J. Zauls, J. M. Watkins, A. E. Wahlquist et al., “Outcomes in women treated with MammoSite brachytherapy or whole breast irradiation stratified by ASTRO accelerated partial breast irradiation consensus statement groups,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 82, no. 1, pp. 21–29, 2012.

[14] J.-B. Dubois, “Intraoperative radiotherapy: back to the future?” *Cancer/Radiotherapy*, vol. 13, no. 5, pp. 423–427, 2009.

[15] A. R. Skandarajah, A. C. Lynch, J. R. MacKay, S. Ngan, and A. G. Heriot, “The role of intraoperative radiotherapy in solid tumors,” *Annals of Surgical Oncology*, vol. 16, no. 3, pp. 735–744, 2009.

[16] A. C. S. D. Barros, M. A. C. Barros, F. E. Andrade et al., “Combined radioguided nonpalpable lesion localization and sentinel lymph node biopsy for early breast carcinoma,” *Annals of Surgical Oncology*, vol. 14, no. 4, pp. 1472–1477, 2007.

[17] A. Barros, M. Pinotti, M. D. Ricci, A. C. Nisida, and J. A. Pinotti, “Immediate effects of intraoperative evaluation of surgical margins over the treatment of early infiltrating breast carcinoma,” *Tumori*, vol. 89, no. 1, pp. 42–45, 2003.

[18] M. Intra, A. Luini, G. Gatti et al., “Surgical technique of intraoperative radiation therapy with electrons (ELIOT) in breast cancer: a lesson learned by over 1000 procedures,” *Surgery*, vol. 140, no. 3, pp. 467–471, 2006.

[19] A. M. Munhoz, J. R. Filassi, C. Aldrighi et al., “Bilateral reduction mammoplasty for immediate breast conservation surgery reconstruction and intraoperative radiotherapy: a preliminary report,” *Aesthetic Plastic Surgery*, vol. 31, no. 1, pp. 94–100, 2007.

[20] M. Rietjens, F. De Lorenzi, P. Veronesi et al., “Breast conserva-
tive treatment in association with implant augmentation and intraoperative radiotherapy,” *Journal of Plastic, Reconstructive and Aesthetic Surgery*, vol. 59, no. 5, pp. 532–535, 2006.

[21] F. de Lorenzi, V. Lohsiriwat, B. Barbieri et al., “Immediate breast reconstruction with prostheses after conservative treatment plus intraoperative radiotherapy. Long term esthetic and oncological outcomes,” *Breast*, vol. 21, no. 3, pp. 374–379, 2012.

[22] A. Goldhirsh, J. H. Glick, R. D. Gelber, A. S. Coates, B. Thurlimann, and H. J. Senn, “Meeting highlights: international expert consensus on the primary therapy of early breast cancer,” *Annals of Oncology*, vol. 16, pp. 1569–1583, 2005.

[23] A. L. Abner, A. Recht, F. A. Vicini et al., “Cosmetic results after surgery, chemotherapy, and radiation therapy for early breast cancer,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 21, no. 2, pp. 331–338, 1991.

[24] U. Veronesi, N. Cacinelli, L. Mariani et al., “Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer,” *The New England Journal of Medicine*, vol. 347, no. 16, pp. 1227–1232, 2002.

[25] B. Fisher, S. Anderson, J. Bryant et al., “Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer,” *The New England Journal of Medicine*, vol. 347, no. 16, pp. 1233–1241, 2002.

[26] P. Poortmans, M. Aznar, and H. Bartelink, “Quality indicators for breast cancer: revisiting historical evidence in the context of technology changes,” *Seminars in Radiation Oncology*, vol. 22, no. 1, pp. 29–39, 2012.

[27] B. D. Smith, D. W. Arthur, T. A. Buchholz et al., “Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO),” *International Journal of Radiation Oncology Biology Physics*, vol. 74, no. 4, pp. 987–1001, 2009.

[28] C. Polgár, E. V. Limbergen, R. Pötter et al., “Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curie thérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009),” *Radiotherapy and Oncology*, vol. 94, no. 3, pp. 264–273, 2010.

[29] D. T. Miyamoto and J. R. Harris, “Molecular predictors of local tumor control in early-stage breast cancer,” *Seminars in Radiation Oncology*, vol. 21, no. 1, pp. 35–42, 2011.

[30] T. Yoshida, H. Takei, M. Kurosumi et al., “True recurrences and new primary tumors have different clinical features in invasive breast cancer patients with ipsilateral breast tumor relapse after breast-conserving treatment,” *Breast Journal*, vol. 16, no. 2, pp. 127–133, 2010.

[31] M. Al-Hajj, M. S. Wicha, A. Benito-Hernandez, S. J. Morrison, and M. F. Clarke, “Prospective identification of tumorigenic breast cancer cells,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 7, pp. 3983–3988, 2003.

[32] C. Lagadec, E. Vlashi, L. D. Donna et al., “Survival and self-renewing capacity of breast cancer initiating cells during fractionated radiation treatment,” *Breast Cancer Research*, vol. 12, article R13, 2010.

[33] N. P. Nguyen, F. S. Almeida, A. Chi et al., “Molecular biology of breast cancer stem cells: potential clinical applications,” *Cancer Treatment Reviews*, vol. 36, no. 6, pp. 485–491, 2010.

[34] R. Orecchia, G. B. Ivaldi, and M. C. Leonardo, “Integrated breast conservation and intraoperative radiation therapy,” *Breast*, vol. 18, supplement 3, pp. S98–S102, 2009.

[35] R. Orecchia and U. Veronesi, “Intraoperative electrons,” *Seminars in Radiation Oncology*, vol. 15, no. 2, pp. 76–83, 2005.

[36] B. Belletti, J. S. Vaidya, S. D'Andrea et al., “Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cells,” *Clinical Cancer Research*, vol. 14, no. 5, pp. 1325–1332, 2008.

[37] S. C. Formenti and S. Demaria, “Local control by radiotherapy: is that all there is?,” *Breast Cancer Research*, vol. 10, no. 6, article 215, 2008.

[38] A. L. Frasson, F. P. Zerwes, A. P. B. Filho, F. S. Barbosa, and H. A. Koch, “Intraoperative radiotherapy in the conventional linear accelerator room for early breast cancer treatment: An alternative choice in developing countries,” *Journal of Experimental & Clinical Cancer Research*, vol. 26, no. 3, pp. 379–384, 2007.

[39] S. A. Hanna, A. C. S. D. Barros, F. E. M. Andrade et al., “Intraoperative radiation therapy in early breast cancer using a linear accelerator outside of the operative suite: an “image-guided”
approach,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 89, no. 5, pp. 1015–1023, 2014.

[40] J. S. Vaidya, F. Wenz, M. Bulsara et al., “Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5 years results for local control and overall survival from the TARGIT—a randomised trial,” *The Lancet*, vol. 383, pp. 603–613, 2014.

[41] U. Veronesi, R. Orecchia, P. Maisonneuve et al., “Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial,” *The Lancet Oncology*, vol. 14, no. 13, pp. 1269–1277, 2013.

[42] W. F. Athas, M. Adams-Cameron, W. C. Hunt, A. Amir-Fazli, and C. R. Key, “Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery,” *Journal of the National Cancer Institute*, vol. 92, no. 3, pp. 269–271, 2000.

[43] A. E. Dragun, B. Huang, T. C. Tucker, and W. J. Spanos, “Disparities in the application of adjuvant radiotherapy after breast-conserving surgery for early stage breast cancer,” *Cancer*, vol. 117, no. 12, pp. 2590–2598, 2011.

[44] M. Ciocca, R. Orecchia, C. Garibaldi et al., “In vivo dosimetry using radiochromic films during intraoperative electron beam radiation therapy in early-stage breast cancer,” *Radiotherapy and Oncology*, vol. 69, no. 3, pp. 285–289, 2003.

[45] U. Veronesi, R. Orecchia, A. Luini et al., “Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons,” *Breast Cancer Research and Treatment*, vol. 124, no. 1, pp. 141–151, 2010.

[46] C. Shah, J. B. Wilkinson, M. Lyden, P. Beitsch, and F. A. Vicini, “Predictors of local recurrence following accelerated partial breast irradiation: a pooled analysis,” *International Journal of Radiation Oncology Biology Physics*, vol. 82, no. 5, pp. e825–e830, 2012.

[47] F. Vicini, D. Arthur, D. Wazer et al., “Limitations of the American society of therapeutic radiology and oncology consensus panel guidelines on the use of accelerated partial breast irradiation,” *International Journal of Radiation Oncology, Biology, Physics*, vol. 79, no. 4, pp. 977–984, 2011.

[48] M. C. Leonardi, P. Maisonneuve, M. G. Mastropasqua et al., “Accelerated partial breast irradiation with intraoperative electrons: using GEC-ESTRO recommendations as guidance for patient selection,” *Radiotherapy and Oncology*, vol. 106, no. 1, pp. 21–27, 2013.

[49] F. Sardanelli, C. Boetes, B. Borisch et al., “Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group,” *European Journal of Cancer*, vol. 46, no. 8, pp. 1296–1316, 2010.

[50] M. N. Planas, C. Carreira, A. Muriel et al., “Magnetic resonance imaging in the preoperative assessment of patients with primary breast cancer: systematic review of diagnostic accuracy and meta-analysis,” *European Radiology*, vol. 22, no. 1, pp. 26–38, 2012.

[51] S. Mussari, W. S. della Sala, L. Busana et al., “Full-dose intraoperative radiotherapy with electrons in breast cancer: first report on late toxicity and cosmetic results from a single-institution experience,” *Strahlentherapie und Onkologie*, vol. 182, no. 10, pp. 589–595, 2006.