



Intraoperative Radiotherapy with the Use of Low Energy X-Rays for the Treatment of Early Breast Cancer

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Abstract

The present study shows the experience, with the use of partial accelerated Intraoperative Radiation Therapy (IORT) to the breast, by the use of 50kV X-ray system (Karl Zeiss Intrabeam), after conservative surgery, for patients with early breast cancer, describing the short-term results in relation to the tolerance and complications of treatment, and in the medium and long term in relation to tumor relapse and overall survival. 230 patients were included in a period of more than 6 years, median age was 57 years (range 40-86 years), and the median tumor size was 1.4cm (range 0.4 cm – 3.2 cm), criteria of ASTRO and ESTRO were applied for the selection of cases. The median follow-up was 48 months (range 12-89 months), 31 patients (13.5%) required complementary external radiotherapy, for adverse prognostic factors, acute complications presented in 23% of the cases, the vast majority (94%), were minor complications resolved spontaneously or by a simple procedure in the office (seroma, small dehiscence, edema, mild radioepithelitis). Local recurrence occurred in 4 patients (1.7%), 3 in the surgical bed or scar, and one axillary, in three of four relapses, breast conservation was possible, since they were resolved with local resection and external radiotherapy. Two patients had distant relapse, one bone and one pulmonary, the latter died 10 months after the relapse was documented, and is the only death in the current series. IORT can be considered as an alternative to external total radiotherapy for well-selected patients, who meet criteria of partial radiation therapy to the breast.

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Introduction

Conservative surgery followed by total radiotherapy to the breast, is the treatment of choice in patients with early breast cancer, and it provides a locoregional control, similar to that of total mastectomy, but with the aesthetic and psychological benefit of the breast conservation. Patients receiving postoperative radiation therapy, require treatment 5 days a week for 3 to 6 weeks [1-3]. Up to a third of the patients treated with conservative surgery in North America, do not receive postoperative radiotherapy, because of the distance they must travel from their homes to the radiation center, and cannot go daily. This fact affects women with breast cancer throughout the world, mainly elderly women [4-5]. In some countries, doctors and patients occasionally reject conservative surgery and choose a total mastectomy in order to avoid radiotherapy [6-8]. Related to this, Intraoperative Radiotherapy (IORT), and some other shorter and localized forms of radiotherapy have been evaluated. It has been shown, that local relapse after conservative surgery, occurs in the majority of cases (around 90%) near the surgical site, and tumors that appear in a different quadrant, are often classified as a second primary, and these events, apparently occur with the same frequency after the removal of the primary tumor regardless of whether or not, the patient received total radiation therapy to the breast [9-11]. Therefore, it has been established, that some patients can be safely treated with partial radiation therapy to the breast, in which only the surgical site after the removal of the primary tumor is irradiated. Such management can be done through different systems, that include brachytherapy techniques with interstitial implants or balloon catheters, IORT with electrons or with 50 kV X-rays or three-dimensional conformal external radiotherapy [12]. The aim of the present study is to show the experience, with the use of partial accelerated IORT to the breast, by the use of 50 kV X-ray system (Karl Zeiss Intrabeam), after conservative surgery, describing the short-term results in relation to the tolerance and complications of treatment, and in the medium and long term in relation to tumor relapse and overall survival.

Table 1,2: Describe the general characteristics of the population, and related variables to the primary tumor and prognostic factors involved in recurrence.

Variable	Median	Range
Age (years)	57	40 – 86
Body mass index	29	20 - 57
Tumor size (cm)	1.4	0.4 – 3.2
Surgical margin (mm)	7	0 - 30
<i>In situ</i> component (%)	10	0 – 70

Table 2:

Variable	n	%
Grade		
1	47	20
2	136	58
3	51	22
Linfovascular invasion		
No	177	76
Yes	57	24
Lymphnode status		
N0	174	74
N1	60	26
Micrometastasis	25	42
Macrometastasis	35	58
Estrogen receptor		
Positive	214 (Median 90%, range 1% - 100%)	91
Negative	20	9
Progesterone receptor		
Positive	176 (Median 40%, range 2% – 100%)	75
Negative	58	25
Her 2 neu over expression	14	6
Triple negative	20	9
Ki 67	Median 5% (range 1-74)	

Material and Method

This is a retrospective study, which included patients diagnosed with early breast cancer (AJCC clinical stages I and IIA), treated primarily with breast-conserving surgery and lymphatic mapping with sentinel lymph node biopsy (+/- radical axillary dissection, in the case of positive sentinel lymph node in intraoperative examination) which received post tumorectomy, IORT with the 50 kV X-ray system (Karl Zeiss Intrabeam) a dose between 20 and 22 Gy, from February 2010 to July 2016. All the patients underwent imaging studies to rule out multifocality. They were initially evaluated with digital mammography and ultrasound, and in some of them, with magnetic resonance, tomosynthesis (three-dimensional mammography) and/or high-resolution ultrasound scan, and only those patients, in whom the absence of multifocality was demonstrated, were eligible for RTIO.

The procedure is carried out in the following way:

a) Breast tumor is removed, with intraoperative radiological and histopathological evaluation of the specimen, to guarantee negative surgical margins. Lymphatic mapping with sentinel lymph node

Table 3: Describes the adjuvant treatment that patients received.

Adjuvant treatment	Patients (%)
Hormonotherapy only	140 (60.8)
Chemotherapy only	18 (7.8)
Chemo + hormonotherapy	41 (17.8)
Chemo + hormo + external radiotherapy	15 (6.5)
Chemo + external radiotherapy	4 (1.7)
Hormono + radiotherapy	12 (5.2)

Table 4:

Variable	n (%)
Loco regional relapse	4 (1.7%)
Median (range) time to relapse	45 months (range 32 - 55 months)
Distant relapse	2 (0.86%)
Breas cancer deaths	1 (0.43%)

biopsy for axillary staging is also performed.

b) Once negative surgical margins are obtained, the tumor bed is prepared, to allow the entire spherical device of the equipment to adapt breast tissue of the surgical bed; suture is made in the surgical bed and upper margin to completely enclose the spherical device.

c) The dose to be administered is calculated and the spherical device is installed in the energy source, to subsequently apply it in the lumpectomy site, the sutures are "closed" and sonographic control is carried out, verifying that the surgical bed is completely in contact with the spherical device and the planned dose is applied.

d) The equipment is removed, and the primary repair or oncological procedure of the surgical bed is performed.

Patients with adverse pathological prognostic factors received complementary external radiotherapy, taking the dose received intraoperatively as the boost in the tumor bed.

Patients with ductal carcinoma in situ, or infiltrating lobular carcinoma were excluded from the present study, since there is no clear evidence of its benefit of partial breast irradiation, in these histological varieties. The clinical and histopathological characteristics of each patient were evaluated, including age, body mass index, tumor size, surgical margins of resection, histological grade, lymphovascular invasion, intraductal component, lymph node involvement, hormonal receptors, Her-2 neu and Ki 67, as well as the adjuvant treatment received after surgery (chemotherapy, antiHer-2 treatment, complementary external radiotherapy, hormone therapy).

Results

A total of 230 patients with breast cancer, with 234 tumors (4 patients with bilateral cancer) were included between February 2010 and July 2016. (Table 1, 2), describe the general characteristics of the population, and related variables to the primary tumor and prognostic factors involved in recurrence. Conservative surgery with IORT, was performed bilaterally in the same surgery in 4 cases, and in combination with oncological procedures in 34 cases. All patients received adjuvant treatment according to stage, and biological subtype. (Table 3) describes the adjuvant treatment that patients received, 31 (13.5%) of them were eligible for complementary external radiotherapy, for adverse prognostic factors detected in the final surgical piece, taking the dose received intraoperatively, as

boost. Ten patients required another surgery for positive margins (4.3%), 7 of them underwent total mastectomy, and 3 re-excision and complementary external radiotherapy. There was an incidence of acute complications in 23% of the cases, of them, the vast majority (94%), were minor complications resolved spontaneously or by a simple procedure in the office (seroma, small dehiscence, edema, mild radioepithelitis) and without sequelae for the patients, only 3 patients (6%) presented severe complications, two of them attended with infection manifested with fever, skin edema and extensive erythema, requiring in-hospital management with antimicrobials, and one patient presented breast tissue radionecrosis, being necessary surgical remove and repaired by vertical mammoplasty with contralateral symmetry. Regarding the late sequelae of the treatment, 15 patients (6.5%) presented fibrosis with breast retraction and apparent aesthetic defect, only one of them required an aesthetic procedure with placement of prosthesis for breast remodeling. The median follow-up was 48 months (range 12-89 months), there were 4 locoregional relapses, (Table 4) three in the surgical bed or scar, and one axillary, in three of four relapses, breast conservation was possible, since they were resolved with local resection and external radiotherapy. The median time from initial treatment to relapse was 45 months (range of 32 to 55 months). Two patients had distant relapse, one bone and the other pulmonary, the latter died 10 months after the relapse was documented and is the only death in the current series of patients. Thus, the overall survival, with a median follow-up of 48 months, was 99.5% and the local recurrence was 1.7%.

Discussion

The American Society for Radiation Oncology (ASTRO), and the European Society for Therapeutic Radiology and Oncology (ESTRO), have issued recommendations for the selection patients who can be treated with partial breast irradiation (intraoperative or postoperative) after conservative surgery, there are selection criteria known as appropriate or for patients with low risk, cautionary or intermediate risk, and high risk of recurrence. In general, it is recommended for women older than 50 years (although it is feasible at 40 years, as a cautionary criteria), with tumors of 3 cm or less, unifocal, infiltrating ductal histology and other varieties of good prognosis (mucinous, tubular, medullary or colloid), luminal subtype, absence of lymph node metastases, and negative surgical margins [13,14]. The justification for the use of partial breast irradiation, is based on the fact that most relapses after breast-conserving surgery occur at the lumpectomy site. In the present study, we used the 50 kV X-ray system (Intrabeam of Karl Zeiss) for IORT, the pivotal study with the use of this therapeutic modality is the TARGIT A, published by Vaidya and cols, in which randomized 3,451 patients to receive standard treatment with total external radiotherapy to the breast, or IORT, including patients ≥ 45 years, with tumors of ≤ 3.5 cm, N0-1, M0 and unifocal infiltrating ductal carcinoma, demonstrating only a slight increase in risk of local relapse at 5 years (1.3 vs. 3.3%) for the group treated with IORT, without a significant impact on overall survival [15]. Factors related to local relapse after partial breast irradiation have been described, in a study published by Shah [16] in which 1,961 patients were included; the absence of expression of estrogen receptors was found as the only factor associated with local recurrence, a major tendency (but not significant) in women under 50 years of age. The risk of local recurrence in early breast cancer is higher in the first 5 years after treatment, regardless of baseline prognostic factors, 30% of local recurrences occurs within 36 months after initial treatment. Different series have reported that patients

whose develop local recurrence within the first two years, have a significantly worse prognosis than those who recur after 5 years. The longer interval between initial treatment and the occurrence of local relapse, the better the prognosis [17-19]. In the present study, 1.7% of locoregional relapses occur, with median of 48 months of primary treatment at the time of relapse, the patients included in the present study, most of them meet "appropriate" selection criteria for partial radiotherapy, and only some with "cautionary" criteria, of the latter, most of them, received external radiotherapy additional to the IORT (13%).

Zhang et al. [20] in a meta-analysis of 5415 patients, which included, in addition to others, TARGIT A [15] and ELIOT [21] trials, and in which the comparison was made between IORT and external total radiotherapy in early breast cancer, finding a significant difference in the relative risk of ipsilateral tumor recurrence in patients treated with IORT (RR=2.83, 95% CI: 1.23-6.51), it should be noted that patient selection, was not homogeneous and therefore these results should be interpreted with caution. There was no significant difference between the two groups in relation to overall mortality, mortality from breast cancer and distant metastases. Several reports, documented that in some patients, it is decided to perform a total mastectomy, even being candidates for breast conservation, due to the time it takes to travel to distant sites, where they may receive adjuvant radiotherapy, total radiotherapy, involves 3 to 6 weeks to complete an adequate dose. Additionally, in the developing countries there is not a sufficient number of radiotherapy equipment's to cover their healthcare needs [22-24]. In a study published by Bargallo-Rocha [25], clearly describes the beneficial impact of the use of IORT in the saving of transfer time and the number of visits to the radiotherapy center, leading to a cost reduction of 12% per patient. IORT offers as an additional benefit that in most cases is offered as a single treatment, in a single dose shortening time and guaranteeing a complete locoregional treatment. It can also be accompanied by oncologic procedures with adequate oncological control and a good cosmetic result, offering then in a single operative time, the extirpation of the primary tumor, the radiation to the surgical bed and the remodeling of the breast shape, even with contralateral breast symmetry. On the other hand, adequate tolerance to IORT has been demonstrated, with no increase in postoperative local complications (infection, dehiscence or necrosis). Other additional advantage of IORT is the direct application on the tumor bed, without the risk of having a topographical mistake; the irradiation of the skin is avoided, minimizing radiation skin damage. The field to be irradiated is smaller and the dose is very homogeneous, the late effect is minimal in terms of fibrosis, and the cosmetic result is usually very good [26].

Conclusion

In conclusion, IORT can be considered as an alternative to external total radiotherapy for well-selected patients, who meet criteria of partial radiation therapy to the breast.

References

1. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, 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. *N Engl J Med.* 2002;347(16):1233-41.
2. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347(16):1227-32.

3. Van Donge JA, Bartelink H, Fentiman IS, Lerut T, Mignolet F, Olthuis G, et al. Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 Trial. *J Natl Cancer Inst Monogr.* 1992;(11):15-8.
4. Tuttle TM, Jarosek S, Habermann EB, Yee D, Yuan J, Viming BA. Omission of radiation therapy after breast-conserving surgery in the United States: a population-based analysis of clinicopathologic factors. *Cancer.* 2012;118(8):2004-13.
5. Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR. Travel distance to radiation therapy and receipt of radiotherapy following breast conserving surgery. *J Natl Cancer Inst.* 2000;92(3):269-71.
6. Kirby RM, Baist A, Manimaran N. Patient choice significantly affects mastectomy rates in the treatment of breast cancer. *Int Semin Surg Oncol.* 2008;5:20.
7. Lazovich DA, White E, Thomas DB, Moe RE. Underutilization of breast-conserving surgery and radiation therapy among women with stage I or II breast cancer. *JAMA.* 1991;266(24):3433-8.
8. Nold RJ, Beamer RL, Helmer SD, McBoyle MF. Factors influencing a woman's choice to undergo breast-conserving surgery versus modified radical mastectomy. *Am J Surg.* 2000;180(6):413-8.
9. Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. *Int J Radiat Oncol Biol Phys.* 1990;19(4):833-42.
10. Kurtz JM, Amalric R, Brandone H, Ayme Y, Jacquemier J, Pietra JC, et al. Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. *Cancer.* 1989;63(10):1912-7.
11. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol.* 2001;12(7):997-1003.
12. Njeh CF, Saunders MW, Langton CM. Accelerated Partial Breast Irradiation (APBI): A review of available techniques. *Radiat Oncol.* 2010;5:90.
13. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol.* 2017;7(2):73-9.
14. Polgár C, Van Limbergen E, Pötter R, Kovács G, Polo A, Lyczek J, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast conserving surgery: recommendations of the Groupe Européenne Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO breast cancer working group based on clinical evidence (2009). *Radiat Oncol.* 2010;94(3):264-73.
15. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A Trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet.* 2010;376(9735):91-102.
16. Shah C, Wilkinson JB, Lyden M, Beitsch P, Vicini FA. Predictors of local recurrence following accelerated partial breast irradiation: a pooled analysis. *Int J Radiat Oncol Biol Phys.* 2012;82(5):825-30.
17. Galper S, Blood E, Gelman R, Abner A, Recht A, Kohli A, et al. Prognosis after local recurrence after conservative surgery and radiation for early stage breast cancer. *Int J Radiat Oncol Biol Phys.* 2005;61(2):348-57.
18. Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch P, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst.* 1996;88(22):1659-64.
19. Freedman GM, Fowble BL. Local recurrence after mastectomy or breast-conserving surgery and radiation. *Oncology.* 2000;14(11):1561-81.
20. Zhang L, Zhou Z, Mei X, Yang Z, Ma J, Chen X, et al. Intraoperative radiotherapy versus whole-breast external beam radiotherapy in early-stage breast cancer: A systematic review and meta-analysis. *Medicine (Baltimore).* 2015;94(27):e1143.
21. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol.* 2013;14(13):1269-77.
22. Pawlik TM, Buchholz TA, Kuerer HM. The biologic rationale for and emerging role of accelerated partial breast irradiation for breast cancer. *J Am Coll Surg.* 2004;199(3):479-92.
23. Schroen AT, Brenin DR, Kelly MD, Knaus WA, Slingluff CL Jr. Impact of patient distance to radiation therapy on mastectomy use in early-stage breast cancer patients. *J Clin Oncol.* 2005;23(28):7074-80.
24. Hébert-Croteau N, Brisson J, Latreille J, Blanchette C, Deschênes L. Compliance with consensus recommendations for the treatment of early stage breast carcinoma in elderly women. *Cancer.* 1999;85(5):1104-13.
25. Bargallo-Rocha JE, Soto-Pérez-de Celis E, Pico-Guzman FJ, Quintero-Rodríguez CE, Almog D, Santiago-Concha G, et al. The impact of the use of intraoperative radiotherapy on costs, travel time and distance for women with breast cancer in the Mexico City Metropolitan Area. *J Sur Oncol.* 2017;116(6):683-9.
26. Tuschy B, Berlit S, Romero S, Sperk E, Wenz F, Kehl S, et al. Clinical aspects of intraoperative radiotherapy in early breast cancer: short-term complications after IORT in women treated with low energy X-rays. *Radiat Oncol.* 2013;8:95.