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# Intraoperative breast radiotherapy: survival, local control and risk factors for recurrence

*Guilherme Rocha Melo Gondim*, *Fabiana Baroni Alves Makdissi*, *Ricardo Cesar Fogaroli*, *Juan Bautista Donoso Collins*, *Hirofumi Iyeyasu*, *Douglas Guedes de Castro*, *Maria Letícia Gobo Silva*, *Michael Jenwei Chen*, *Tharcisio Machado Coelho*, *Henderson Ramos*, *Antônio Cássio Assis Pellizzon*

*AC Camargo Cancer Center* □ *R. Prof. Antônio Prudente, 211 - Liberdade, São Paulo, Brazil*

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ABSTRACT

*Background:* Whole breast irradiation reduces loco-regional recurrence and risk of death in patients submitted to breast-conserving treatment. Data show that radiation to the index quadrant alone may be enough in selected patients.

*Aim:* To report the experience with intra-operative radiotherapy (IORT) with Electron-beam Cone in Linear Accelerator (ELIOT) and the results in overall survival, local control and late toxicity of patients submitted to this treatment.

*Materials and Methods:* 147 patients treated with a median follow up of 6.9 years (0.1□11.5 years). The actuarial local control and overall survival probabilities were estimated using the Kaplan Meier method. All tests were two-sided and $p \leq 0.05$ was considered statistically significant.

*Results:* Overall survival of the cohort in 5 years, in the median follow up and in 10 years was of 98.3%, 95.1% and 95.1%, respectively, whereas local control in 5 years, in the median follow up and in 10 years was of 96%, 94.9% and 89.5%, respectively. Two risk groups were identified for local recurrence depending on the estrogen or progesterone receptors, axillary or margin status and lymphovascular invasion (LVI) ($p = 0.016$).

*Conclusions:* IORT is a safe and effective treatment. Rigorous selection is important to achieve excellent local control results.



□ Corresponding author.
E-mail addresses: guilherme.gondim@accamargo.org.br (G.R.M. Gondim), fabiana.makdissi@accamargo.org.br (F.B.A. Makdissi), rcfogaroli@terra.com.br (R.C. Fogaroli), juan.collins@accamargo.org.br (J.B.D. Collins), hiroiyeyasu@hotmail.com (H. Iyeyasu), dougguedes@uol.com.br (D.G. de Castro), mlgobo@yahoo.com.br (M.L.G. Silva), michaelchen@outlook.com.br (M.J. Chen), tharcisio.coelho@accamargo.org.br (T.M. Coelho), hendersonramos@uol.com.br (H. Ramos), acapellizzon@accamargo.org.br (A.C.A. Pellizzon).

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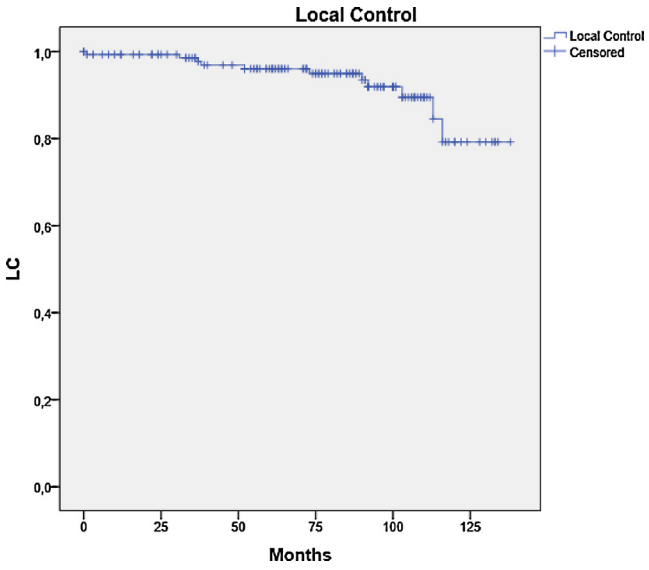


**Fig. 1 – Local control.**

## 1. Background

Breast cancer treatment requires a multimodal approach. Identification of tumor heterogenicity, new drug development and improvement of adjuvant therapy permitted a more personalized treatment to breast cancer patients, in some cases de-escalated, and with less side effects.[1]

Although breast cancer incidence has increased globally, mortality remains stable, evidencing better control of the disease.[2] Whole breast irradiation reduces loco-regional recurrence and risk of death in patients submitted to breast-conserving treatment.[3] Recurrence usually occurs close to the surgical bed in patients who do not receive whole breast irradiation and this observation was the rationale for intraoperative and partial radiation trials.[4]

Different techniques of intraoperative radiotherapy (IORT) and Accelerated Partial Breast Irradiation (APBI) are available and, regardless of the technique employed, data show that radiation to the index quadrant alone may be enough in selected patients.[5–7] Performing radiotherapy (RT) during surgery eliminates patient's daily journey to hospital, decreases emotional stress of medical appointments and can reduce treatment costs.[8]

## 2. Aim

Based on evidence that IORT can be beneficial to patients, in 2005 our Institution introduced this technique, initially in a research protocol, with Electron-beam Cone in a Linear Accelerator (ELIOT).

The aim of this paper is to demonstrate the experience of a single Cancer Center with ELIOT, as well as the results in local control of patients submitted to this treatment.

## 3. Materials and methods

A total of 147 patients were treated with ELIOT between September 2005 and January 2016. Median follow up of these patients was 6.9 years (0.1–11.5 years).

In the ELIOT technique, a lumpectomy/conservative surgery is performed; tumor is removed with free margins, always through an 8 cm incision, regardless of the size of the tumor. During the surgical procedure, frozen section analysis is performed and, if any risk factor is present, IORT is contraindicated. The 8 cm incision is necessary to allow a led disc to be inserted to protect the chest wall. Breast tissue is sutured over the disc and the electron cone is carefully placed under direct vision over the disc so as to maintain chest wall protection; tissue thickness is then measured and the electron beam energy chosen. The patient is then transported under general anesthesia from the operating room to the Linear Accelerator for this technique to be performed. All patients were treated with 21 Gy dose with electron beam's energies between 6 and 15 MeV in the 2100C Varian® Linear Accelerator and all node positive patients were submitted to axillary nodal dissection.

When we started our IORT program in 2005, the results of phase 3 studies were not available, and treatment inclusion criteria were not consensual worldwide. Thus, we included patients in a research protocol, which was approved by the appropriate institutional review committee (approval number 213715) and met the guidelines of the responsible governmental agency, as per the criteria below:

INCLUSION CRITERIA

1 Women
2 Ductal, Papilliferous, Mucinous or Tubular Carcinoma
3 cT1 or cT2 stages ≤3 cm
4 up to 3 positive lymph nodes
5 M0
6 Unilateral
7 No extensive intraductal component (DCIS occupying at least 25% of the invasive tumor)
8 Free margins (no ink on tumor)
9 No previous history of neoplasia
10 Informed consent (Surgeon and Radiation Oncologist)

EXCLUSION CRITERIA

1 Patients with previous breast cancer treatment
2 Invasive Lobular Carcinoma
3 Suspicious diffuse microcalcifications
4 Inappropriate tumor location
5 Small breasts

Statistical calculations were made using SPSS 20.0 software. The actuarial local control and overall survival probabilities were estimated using the Kaplan–Meier method,[9] and groups were compared using a log-rank test. All tests were two-sided and $p \leq 0.05$ was considered statistically significant. Local control was calculated from the date of surgery to the date of recurrence. Any recurrence in the treated breast, including recurrences in the other quadrants, was considered

**Table 1 – Patient Characteristics.**

| | All patients (147 patients) | Low risk group (87 patients) | High Risk group (60 patients) |
|---|---|---|---|
| Median Age (years) | 59 (35□87) | 60 (35□84) | 58 (40□87) |
| Age ≥50 years | 80.3% | 82.7% | 76.7% |
| Median Tumor Size (mm) | 12 (3□37) | 12 (3□37) | 12 (4□25) |
| Tumor ≤2cm | 83.9% | 85.1% | 83.3% |
| Node positive axilla | 13.6% | 0.0% | 33.3% |
| Free Margins | 95.9% | 100.0% | 90.0% |
| Unifocality | 94.5% | 94.3% | 95.0% |
| Estrogen Receptor positive | 90.8% | 100.0% | 78.3% |
| Progesterone Receptor positive | 77.9% | 100.0% | 53.5% |
| Positive Lymphovascular Invasion | 12.3% | 0.0% | 30.0% |
| Extensive Ductal Carcinoma In Situ component | 1.4% | 0.0% | 3.3% |
| ESTRO □Suitable□ group | 66.4% | 94.3% | 25.0% |
| ASTRO □Suitable□ group | 37.7% | 54.0% | 15.0% |
| Hormonotherapy | 85.7% | 93.1% | 75.0% |
| Chemotherapy | 46.3% | 40.2% | 55.0% |

local recurrence. Overall survival was calculated from the date of surgery to the date of death.

In this study, two risk groups were identified for local recurrence. The low risk group included patients with positive estrogen and progesterone hormone receptors, node negative axilla, with no lymphovascular invasion (LVI) and with free surgical margins; the high risk group comprised patients with estrogen or progesterone negative receptors, node positive axilla, LVI or positive surgical margins (Table 1□Patient Characteristics).

## 4. Results

Overall survival of the cohort at 5 years, in the median follow up of 6.9 years and at 10 years was 98.3%, 95.1% and 95.1%, respectively, whereas local control at 5 years, in the median follow up and at 10 years was 96%, 94.9% and 89.5%, respectively (Fig. 1□Local Control). 59.1% and 6.8% of patients were followed for more than 5 and 10 years, respectively.

Local control at 5 years, in the median follow up and at 10 years, was 98.6% ÿ 92.5%, 98.6% ÿ 89.8% and 95.6% ÿ 62.3% (p = 0.016) in the low and high-risk groups, respectively. (Fig. 2□Local Control per Risk Group).

In our cohort, 4 nodal recurrences occurred, all of them in the axilla and 2 were synchronic with local recurrence in the breast. In this study, 8 patients developed distant metastasis.

## 5. Discussion

Breast-conserving treatment was one of the most successful advances of Oncology in the 20th century. Adjuvant RT enhances local control and overall survival in breast cancer after conservative surgery.[3] Nevertheless, treatment with conventional fractionation may be challenging to patients and to the health system and attempts have been made to reduce treatment time. Currently, many studies support the use of APBI[5,7,13] and various techniques of IORT are available in clinical practice.

Randomized adjuvant RT trials, such as Milan III and NSABP B06, show recurrence rates in the other quadrants in patients submitted to External Beam Radiotherapy (EBRT) of 0.6□3.2% at 10-year follow up.[4] This observation was the rationale for intraoperative and partial radiation trials.

The British study IMPORT LOW[10] is a non-inferiority trial in which 2018 patients were randomized in 3 groups. EBRT was performed with 40 Gy dose in the whole breast, 36 Gy in the whole breast followed by boost of 40 Gy or partial breast EBRT up to 40 Gy in 15 fraction treatment. With a median 72-month follow up, local relapse occurred only in 1.1, 0.2 and 0.5% of the patients, respectively, demonstrating non-inferiority of the partial breast RT in local control. Patients treated with partial breast RT also demonstrated less change in appearance and hardening of the treated breast.

The ELIOT[6] study randomized 1305 patients for whole breast or partial breast RT treatment with the intraoperative technique with a portable electron accelerator. Greater local relapse occurred in the group submitted to IORT at 5 years (4.4 ÿ 0.4% - p < 0.0001). Nevertheless, 27% of the patients in this study had the node positive axilla and 10% had triple negative tumors. Currently, it is known that these are not ideal patients to be treated with IORT. In our experience with ELIOT, patients classified in the low risk group had local control of 95.6% at 10 years.

The TARGIT A[7] trial is a non-inferiority study in which patients were randomized for whole breast RT or IORT with INTRABEAM and, if any risk factor was present in the final anatomopathological report after surgery, as defined according to each participating Institution, additional EBRT was performed to the whole breast (Risk-Adapted Radiotherapy). In this trial, 3439 patients were randomized to EBRT or IORT with INTRABEAM. Local relapse at 5 years occurred in 2.1 and 1.1% (p = 0.31) of the patients submitted to IORT during surgery or EBRT of the whole breast, respectively. Smaller non-cancer

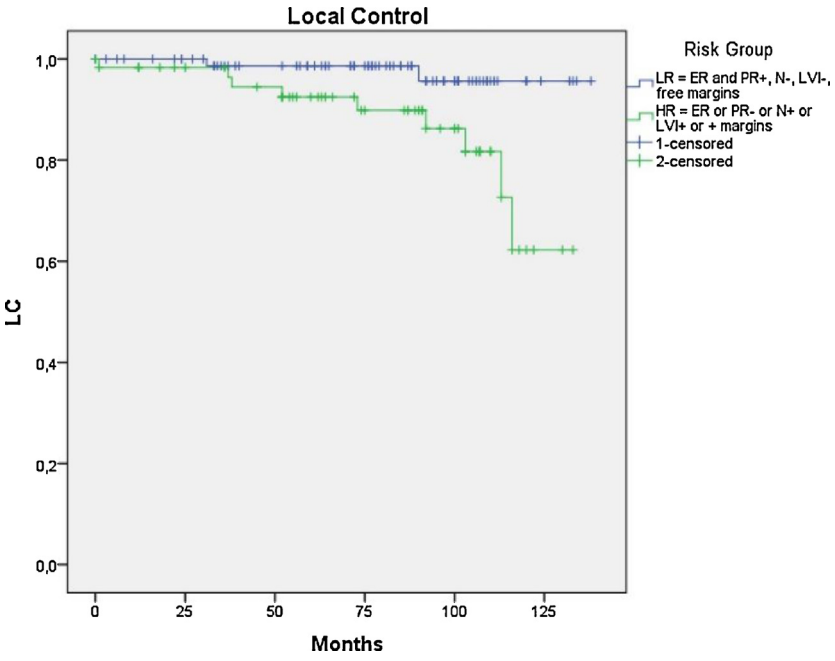


**Fig. 2 – Local control per risk group.**

specific mortality occurred in the INTRABEAM treated group due to a smaller incidence of cardiovascular events at 5 years (1.4 ÿ 3.5%, p = 0.0086). Additional EBRT after INTRABEAM was necessary in 14% of patients.

The phase 3 GEC-ESTRO[5] study was another non-inferiority trial in which 1184 patients were randomized to EBRT of the whole breast or APBI with the interstitial Brachytherapy technique. Local relapse at 5 years occurred in 1.44 ÿ 0.92% (p = 0.42) of the patients submitted to Brachytherapy or EBRT, demonstrating once again the non-inferiority of partial breast irradiation.

Compared to the IMPORT LOW,[10] ELIOT,[6] TARGIT A[7] and GEC-ESTRO[5] trials, our cohort was composed of a more unfavorable group of patients as 60 of 147 patients (40.8%) presented at least one of the following risk factors for recurrence: estrogen or progesterone negative receptors, node positive axilla, LVI or positive surgical margins. In this high-risk group of patients, local control was 89.8% in the median follow up of 6.9-years in this study,

Rigorous patient selection is crucial for IORT treatment. Important international consensuses[11,12] are published to assist oncologists to select patients carefully. Leonardi et al.[13] demonstrated that of the 1797 patients treated with IORT at the European Oncology Institute local relapse at 5 years occurred in 1.5%, 4.4% and 8.8% of those classified according to ASTRO criteria in the *Suitable*, *Cautionary* or *Unsuitable* groups, respectively. Cannon et al.[14] demonstrated in multivariate analyses that negative estrogen receptor, LVI, extensive ductal carcinoma in situ and histology of invasive lobular carcinoma are variables which increase local recurrence after partial breast RT. When we started our research protocol with ELIOT, these data were not available, and we also noticed higher local recurrence in the group of patients treated with negative estrogen or progesterone receptors, with LVI, node positive axilla or positive margins. In our patients who did not present these risk factors, an excellent local control of 98.6% after IORT was achieved in the median follow up.

In summary, many studies currently demonstrate the safety and efficacy of partial breast RT. Many techniques are available and, regardless of the technique employed, strict selection criteria are crucial for successful treatment. Risk-Adapted strategy of the TARGIT A trial to perform EBRT after the definitive anatomopathological report may be necessary for an excellent result in some patients. Reduced cutaneous reaction and greater convenience are definite advantages of partial breast RT. These benefits and the possible reduction in the risk of cardiovascular events should encourage the use of APBI in the future.

## 6. Conclusions

IORT is a safe and effective treatment. Rigorous selection is important to achieve excellent local control results.

## Conflict of interest

None declared.

## Financial disclosure

None declared.

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