Partial breast irradiation: when less could be more

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Abstract: Breast cancer is the most commonly diagnosed cancer in Brazilian women and the leading causing of cancer death among them. Breast-conserving surgery (BCS) followed by whole breast radiotherapy has become the standard care for early breast cancer. Although the omission of adjuvant breast radiotherapy has been associated with worse oncological outcomes, distance from treatment centers directly affects the employment of adjuvant breast irradiation. In addition to distance, patients from low- and middle-income countries suffer from a paucity of radiotherapy centers. It was estimated that 46.6% of the oncological patients requiring radiation therapy for a new primary cancer in 2016 did not receive this treatment in the Brazilian public health system. Accelerated partial breast irradiation significantly reduces the treatment time and has the potential to overcome the logistics and social barriers related to adjuvant breast irradiation. During the last 30 years, 8 randomized phase III clinical trials showed that partial breast irradiation is a safe, effective, and convenient treatment for selected early breast cancer patients. At AC Camargo Cancer Center experience, for selected patients, partial breast irradiation achieved a 10 years local control of 95.6%. At Angelina Caron Hospital, a regional reference for cancer treatment in the state of Paraná, the median traveled distance from patients home to the radiotherapy department is 24 Km (11–287 Km). The implementation of partial breast irradiation, specially the intraoperative technique, could save patients a median of 1,440 traveled distance.

Keywords: Breast cancer; partial breast irradiation; radiotherapy

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Introduction

Since the 90s, breast-conserving surgery (BCS) has become the mainstay treatment for early breast cancer. BCS followed by whole breast irradiation (WBI) with or without regional nodal irradiation has the same overall and disease-free survival as mastectomy (1-6), while is associated with better cosmesis, benefit in body image and treatment satisfaction (2).

The absolute benefit of adding WBI after BCS varies according to age, nodal status, tumour grade, oestrogen-receptor, systemic therapy, extent of surgery (7). Even lower-risk patients benefit from adjuvant breast radiotherapy (7,8).

Despite its efficacy and low toxicity profile, WBI can have major social impact since its comprises 6 weeks treatment in the protracted schedule or 3 weeks in the hypofractionated course (9). For patients who are elderly or live a significant distance from treatment centers, logistical problems can prove to be prohibitive. An analysis of TARGIT-A trial (10) showed that the patients treated in intraoperative radiotherapy (IORT) arm were saved, on average, a travel distance of 491 kilometers. Even in high-income countries the travel distance to radiation therapy facilities impacts in prevalence.
of mastectomies in early stage breast cancer (11) and the receipt of radiotherapy following BCS (12).

In Brazil, breast cancer is the most common malignant disease in women. About 59,700 new cases were estimated for 2018 (13). As in others middle incoming countries, Brazil suffers from a paucity of radiotherapy centres (14). It was estimated that 46.6% (111,432 patients) of the oncological patients requiring radiation therapy for a new primary cancer in 2016 did not receive this treatment in the Brazilian public health system (15).

IORT and others forms of accelerated partial breast irradiation (APBI) significantly shortens the treatment time and have the potential to overcome the logistics and social barriers related to adjuvant breast irradiation.

In this paper, we make a descriptive review of the randomized controlled trials published in the last 30 years about APBI, report the authors institutional experience and the potential impact in traveled distance for every fraction omission.

The clinical basis for APBI

APBI has been investigated in randomized phase III trials since the 80’s. To date, a simple electronic search on MEDLINE and LILACS database for studies assessing APBI compared with WBI retrieves more than 200 references, but with only 8 randomized phase III trials: Ribeiro, 1993 (16); Dodwell, 2005 (17); Tarig A, 2010 (18); Budapest trial, 2013 (19); ELIOT, 2013 (20); Livi, 2015 (21); Strnad, 2016 (22); IMPORT-LOW, 2017 (23). Table 1 synthesizes the main characteristics of each trial.

In Ribeiro et al. (16) series, all patients were submitted to breast conserving surgery but the axilla was not sampled nor dissected. No adjuvant systemic therapy were permitted. APBI technique was direct electron beam field with energy of 8–14 MeV. Limited breast irradiation were associated with higher local and regional recurrence rate than WBI, but with the same overall survival (OS). At subgroup analysis, lobular histology and the presence of extensive intraductal component were associated with higher local recurrence rate. APBI resulted in higher incidence of marked fibrosis and telangiectasia.

Dodwell et al. (17) recruited patients with initial breast cancer who were submitted to local excision and axillary dissection. Adjuvant systemic therapy were mandatory. For APBI, a variety of techniques were used, including a direct cobalt or caesium beam, electrons or a “small” megavoltage tangential pair. APBI was associated with higher regional recurrence rate, but without a negative impact on loco control, systemic control or OS. No data regarding cosmesis were published.

At Tarig A (18), patients were treated with wide local excision of primary tumour plus definitive sentinel node biopsy and/or axillary dissection. Patients allocated to APBI whose histopathology showed adverse criteria (invasive lobular carcinoma, extensive intraductal component, grade 3, node involvement or lymphovascular invasion, involved margins), received additional WBI. APBI technique consisted of IORT with Intrabeam. There were no significant difference regarding locoregional control or OS between the two arms. IORT was associated with wound seroma needing more than three aspirations, whereas RTOG skin toxicity grade 3 or 4 was more frequent in the external beam radiotherapy group.

In Budapest Trial (19), women with unilateral breast cancer underwent BCS with axillary dissection or sentinel node biopsy. Patients with pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; lymphovascular invasion; or the presence of an extensive intraductal component were excluded. Adjuvant systemic therapy was given according to institutional protocol. There were no significant difference regarding locoregional control or OS between the two arms. APBI was associated with a higher rate of excellent-good cosmetic result.

ELIOT trial (20) experimental arm utilized an intraoperative technique with electrons beam. All patients with a positive sentinel biopsy specimen received axillary dissection. For patients with four or more positive axillary nodes, additional irradiation was given as conventional fractionation of 2 Gy to a total dose of 50 Gy. Although APBI were associated with a higher locoregional recurrence rate, it was not associated with a worse OS. For patients in the intraoperative group, a tumour size greater than 2 cm, four or more positive lymph nodes, poorly differentiated tumour and triple negative subtype doubled the risk of breast recurrence. For patients with none of those risk factors, the ipsilateral breast recurrence at 5 years were 1.5%. Although APBI were associated with a higher occurrence of fat necrosis, lower rates of erythema, dryness, hyper-pigmentation, pruritus and pulmonary fibrosis were observed.

Livi et al. (21) chose external beam radiotherapy with IMRT for its experimental arm. The adopted fractionation was 30 Gy/5 Fx delivered every other day. There were no significant difference regarding locoregional control or OS between the two arms. The clinical target volume (CTV) was drawn with a uniform 1 cm three-dimensional margin around the surgical clips. A second uniform three-dimensional 1 cm margin was added to the CTV to obtain the planning target volume (PTV). Concerning acute and
late adverse events, the APBI group displayed significantly better safety considering grade 2 or higher skin toxicity.

Strnad and colleagues (22) used multicatheter brachytherapy for its experimental arm. For patients with invasive carcinoma, either an axillary dissection with minimum of six nodes in the specimen or a negative sentinel node was required. Adjuvant systemic therapy was given according to institutional protocol. There were no significant difference regarding locoregional control or OS between the two arms. APBI resulted in a slightly higher incidence of breast pain. Late skin toxicity was similar in the two arms of the study.

At UK IMPORT-LOW (23), patients were allocated to three treatment arms: standard whole breast radiotherapy with 40 Gy/15 Fx (control), reduced dose whole breast radiotherapy (reduced-dose group), partial breast radiotherapy (partial-breast group). The protocol specified forward-planned field-in-field intensity-modulated radiation therapy (IMRT) delivered by standard medial and lateral tangential beams. The CTV was drawn with a uniform 1.5 cm three-dimensional margin around the tumour bed, bound by 5 mm from the skin surface and should not extended beyond the pectoral fascia posteriorly. A second 1 cm margin was added to the CTV to obtain the PTV. Adjuvant systemic therapy was given according to institutional protocol. There were no significant difference regarding locoregional control or OS between the two arms. Clinical assessment of late normal-tissue effects showed a low occurrence of events across all treatment groups.

### Table 1 Randomized clinical trials comparing partial breast irradiation and whole breast irradiation

| Trial          | Patients (n) | Median follow-up | Inclusion criteria                                                                 | Control arm                | Investigational arm                        | Ipsilateral breast recurrence (control vs. APBI) | Ipsilateral axilar recurrence (control vs. APBI) |
|---------------|--------------|------------------|------------------------------------------------------------------------------------|---------------------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Ribeiro et al. (16) | 708          | 65 months        | cN0; <70 years; tumour <4 cm                                                      | WBI 40 Gy/15 Fx           | 40 Gy/8 Fx (electrons)                    | 11 % vs. 19.6 % (P=0.0008)                  | 10 % vs. 23 %                                 |
| Dodwell et al. (17) | 174          | 8 years          | pT1/T2 pN0/pN1                                                                     | WBI 40 Gy/15 Fx + boost   | 55 Gy/20 Fx                               | 4% vs. 11% (P=0.07)                         | 9% vs. 24%                                    |
| Target A (18)    | 3,451        | 4 years          | >45 years; unifocal ductal carcinoma; pT1/T2.                                     | WBI 40-56 Gy + boost      | 20 Gy/1 Fx (Intrabeam)                    | 0.4% vs. 0.5 % (P=NS)                       | 0.2% vs. 0.3%                                 |
| Budapest Trial (19) | 258          | 10.2 years       | >40 years; pT1 pN0/ pN1mic; unifocal tumours; histologic grade I/II.               | WBI 50 Gy/25 Fx           | 36.4 Gy/7 Fx (interstitial brachytherapy)  | 5.1% vs. 5.9 % (P=NS)                       | 1.7% vs. 2.4%                                 |
| ELIOT (20)      | 1,305        | 5.8 years        | >48 years; tumour <2,5 cm;                                                        | WBI 50 Gy/25 Fx + boost   | 21 Gy/1 Fx (IORT)                         | 0.4% vs. 4.4 % (P<0.0001)                   | 0.3% vs. 1%                                   |
| Livi et al. (21) | 520          | 5 years          | >40 years; tumour <2,5 cm; unifocal; no extensive intraductal component            | WBI 50 Gy/25 Fx + boost   | 30 Gy/5 Fx (IMRT)                         | 1.4% vs. 1.5 % (P=NS)                       | 1.9% vs. 1.5 %                                |
| Strnad (22)     | 1,328        | 6.6 years        | ≥40 years; in situ carcinoma; tumour ≤3 cm; pN0/N1mic; negative resection margins; no lymph or blood-vessel invasion | WBI 50 Gy/25 Fx + boost   | 32 Gy/8 Fx (interstitial brachytherapy)    | 0.92% vs. 1.44% (P=NS)                      | 0.18% vs. 0.48%                               |
| IMPORT-LOW (23) | 2,018        | 6 years          | ≥50 years; unifocal ductal WBI 40 Gy/15 Fx                                         | WBI 40 Gy/15 Fx           | 40 Gy/15 Fx (forward-planned IMRT)        | 1.1% vs. 0.5 % (P=NS)                       | <1% on both arms                              |

WBI, whole breast irradiation; Gy, Gray; Fx, fractions; NS, non-significant; IORT, intraoperative radiotherapy; IMRT, intensity-modulated radiation therapy.

Accelerated partial breast irradiation experience in a Cancer Center

At AC Camargo Cancer Center IORT with electrons beam has been implemented since 2005. By that time, results of phase III studies were not available, and treatment inclusion criteria was not consensual worldwide. The inclusion criteria
were: histology (Ductal, Medullary, Papilliferous, Mucinous or Tubular Carcinoma); size <3 cm; up to 3 positive lymph nodes; M0; unilateral cancer; no extensive intraductal component; free margins; no previous history of neoplasia.

A total of 147 patients were treated between September 2005 and January 2016. Median follow-up of these patients was of 6.9 years (0.1–11.5 years). Local control of the cohort in 5 years, using the Kaplan Meier method, in the median follow-up and in 10 years was of 96%, 94.9% and 89.5%, respectively.

Two risk groups were formed for local recurrence. The low risk group included patients with positive estrogen and progesterone hormone receptors, node negative axilla, with no angio-lymphatic invasion and with free surgical margins; the high risk group comprised patients with estrogen or progesterone negative receptors, node positive axilla, angio-lymphatic invasion or positive surgical margins. Local control in 5 years and in 10 years, was of 95.6x92.5% and 95.6x62.3% (P=0.016) in the low and high risk groups, respectively. Late side effects occurred in few cases. Six patients developed mild local fibrosis, two reported local breast retraction, and one patient developed necrosis in the irradiated area.

Impact of implementation of accelerated partial breast irradiation in traveled distance

Angelina Caron Hospital is localized in Campina Grande do Sul (metropolitan region of Curitiba) and plays an important role in oncological assistance for patients of public health system in the state of Paraná.

By March 2019, 100 patients were receiving daily radiotherapy at our department. Eighteen of those patients were at adjuvant breast irradiation. A search in all breast cancer patients’ medical record for their home address were made. The travel distance were estimated using “Google Maps” software (24).

The most frequent radiotherapy schedule was 50 Gy in 25 fractions followed by tumor bed boost and 40 Gy in 15 fractions with or without tumor bed boost. The median travel distance from patients house to the radiotherapy department were 24 Km (11–287 Km). The implementation of APBI, specially IORT, could save patients a median of 1,440 traveled distance (compared with conventional fraction schedule).

Conclusions

Breast-conserving treatment was one of the most successful advances of Oncology in the 20th Century. Adjuvant radiotherapy enhances local control and OS in breast cancer after conservative surgery (7). Nevertheless, treatment with conventional fractionation may be challenging to patients and to the health system and attempts have been made to reduce its time.

Longer distances from treatment facilities may represent emotional, social and financial challenges, specially for elderly patients who are more likely to have a limited budget.

Hypofractionated radiotherapy (9) represented a step forward for overcoming social barriers on the adjuvant therapy of breast cancer. But, there is still a necessity to reduce the treatment time in our clinical practice, since our patients dislocates a median of 48 Km for each day of treatment.

The perception that in the absence of WBI after quadrantectomy almost 90% of local failures presented in the scar area (5,25), led to the development of focal breast irradiation.

Randomized clinical trials have been accumulating evidence for APBI since 1982 (17). We have reported the results of 8 published trials with a minimum follow-up of 4 years and a total of 9,762 patients. Despite the diversities on APBI techniques, surgery template and systemic treatment protocol, focal breast irradiation were associated with good local control and aesthetic results.

The APBI arm of three of the eight aforementioned trials (16,17,20), resulted in worse local control, but included patients with high number of axilar micrometastasis (17,20), without axilar pathologic evaluation (16) or systemic treatment (16). Although the IMPORT-LOW (23) also included N1 patients, they represented <5% of the patients.

Rigorous patient selection is crucial for IORT treatment. Important international consensuses (26) are published to assist oncologists to select patients carefully. Leonardi et al. (27) demonstrated that, of the 1,797 patients treated with IORT at the European Oncology Institute, local relapse in 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.

The authors institutional experience also showed great local control for selected patients.

Two important trials were recently presented at San Antonio Breast Cancer Symposium 2018. The NSABP B-39/RTOG 0413 (28) and RAPID trial (29).

NSABP B-39/RTOG 0413 (28) randomly assigned 4,216 patients who had recently received a lumpectomy with none to three positive axillary nodes to treatment with WBI or APBI. APBI arm was defined as twice daily treatment with 34–38.5 Gy in 10 fractions delivered via.
3D external beam radiation or brachytherapy. APBI were associated with a statistical higher ipsilateral breast tumor recurrence rate (4.8% vs. 4.1%), but without a negative impact on disease free survival or OS.

The RAPID trial (29) randomized 2,135 women ≥40 years of age with axillary node-negative invasive ductal carcinoma, or ductal carcinoma in situ (DCIS) ≤3 cm treated by BCS with clear margins to WBI or APBI. APBI arm consisted of 3D radiotherapy with 38.5 Gy in 10 fractions delivered twice daily. APBI and WBI resulted in the same locoregional control.

Those two trials (28,29) represents a landmark on partial breast irradiation since their protocols consisted of a simple radiotherapy technique (three-dimensional conformal radiotherapy) and concise fraction schedule which could be implemented in low- and middle-income countries.

Based on all published trials and AC Camargo Cancer Center experience, our team from Angelina Caron Hospital is seeking to implement APBI with 3-dimensional conformal radiation therapy for patients ≥50 years old, tumors ≤3 cm, clear margins, favorable histology (invasive ductal carcinoma, DCIS, medullary, mucinous, tubular or papilliferous carcinoma), estrogen/progesterone positive receptors, negative axillary lymph nodes.

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