Original paper

Accelerated partial breast irradiation in a single 18 Gy fraction with high-dose-rate brachytherapy: preliminary results

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Abstract

Purpose: To evaluate the feasibility of acute and chronic toxicity in patients suitable for accelerated partial breast irradiation (APBI) in a single 18 Gy fraction with multicatheter high-dose-rate (HDR) brachytherapy, as well as cosmetic and oncological outcomes.

Material and methods: Between September 2014 and March 2016, twenty consecutive patients with low-risk invasive and ductal carcinoma in situ were treated with interstitial multicatheter HDR brachytherapy in a single 18 Gy fraction.

Results: Median age was 63.5 years (range, 51-79). Acute toxicity was observed in seven patients, while the pain during following days and hematoma were seen in four patients. With a median follow-up of 24 months, late toxicity was found in one patient with fat necrosis g2 and fibrosis g2 in another patient. The overall survival (OS) and locoregional control (LC) was 100%. Disease-free survival (DFS) and distant control was 95%. Good to excellent cosmetic outcomes were noted in 80% of patients and fair in 4 patients (20%).

Conclusions: This is the first report in the medical literature that focuses on feasibility and acute and chronic toxicity, with a median follow-up of 24 months (range, 20-40). The protocol is viable and convenient. However, a longer follow-up is needed to know chronic toxicity and oncologic outcomes.

J Contemp Brachytherapy 2018; 10, 1: 58–63
DOI: https://doi.org/10.5114/jcb.2018.73994

Key words: APBI, brachytherapy, breast cancer, morbidity.

Purpose

Whole breast irradiation (WBI) followed by breast conserving surgery (BCS) is one of the standards of care for breast cancer treatment, called breast conserving therapy (BCT). Several randomized trials have shown the equivalence of BCT with disease-free survival (DFS) and overall survival (OS), and modified radical mastectomy with a more than 20-year follow-up [1,2,3]. WBI typically requires a 5 to 8-week treatment, delivering 45-50 Gy to the entire breast and 10-16 Gy to the tumor bed. The use of hypofractionated radiotherapy is currently growing as it allows the administration of treatment in 3-5 weeks (40,05 Gy plus a 10-16 Gy boost) [4]. However, in several countries such as the United States, up to 50% of patients are treated with mastectomy to avoid radiation therapy because of the distances to the site of treatment, and due to other factors, such as the fear of keeping the breast [5]. In the last few years, the use of accelerated partial breast irradiation (APBI) has increased. It has been established as an attractive option due to administration of radiation to the tumor bed at a higher dose per fraction in one week or less [6]. In addition, while using APBI, organs at risk (lung, skin, and the rest of the breast) receive less radiation with a subsequent decrease in toxicity, except for the heart in certain situations [7,8].

There are several modalities of APBI such as multicatheter interstitial brachytherapy, intracavitary brachytherapy (balloon or hybrid applicators), external beam radiotherapy, 3D conformal radiotherapy (3D RT), intensity modulated radiation therapy (IMRT), and intraoperative radiation therapy (IORT). Some treatment schemes have been tested according to the irradiation technique, ranging from 10 fractions in one week with EBRT to just

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Received: 29.11.2017
Accepted: 22.01.2018
Published: 28.02.2018

1 fraction with IORT. The purpose of the present study is to determine acute and late toxicity (during the follow-up) and cosmetic results after APBI with multicatheter interstitial brachytherapy in one fraction (18 Gy). Furthermore, dose volume histograms were analyzed and dosimetric parameters were correlated with toxicity.

Material and methods

Patient selection and characteristics

Between September 2014 and March 2016, a total of 20 patients with histologically proven invasive breast carcinoma or ductal breast carcinoma in situ were treated. The median follow-up was 24 months (range, 20-40). Patients were staged according to the American Joint Committee on Cancer, 6th edition of clinical staging guidelines [9], using a directed history, physical examination, mammography, ultrasound (US), and/or magnetic resonance imaging and a blood test.

Patients aged 50 years or older, with a ≤ 3 cm of diameter lesion (invasive or intraductal), pN0, and M0 breast cancer were considered eligible for APBI. They underwent lumpectomy with microscopically clear margins, and had no lymph nodes or blood-vessels invasion. Positive estrogen receptors were mandatory. Neither neoadjuvant or adjuvant chemotherapy were permitted. The interval time between lumpectomy and the radiation treatment had to be under 12 weeks. At least 4 clips in the tumor cavity placed during surgery were mandatory. Tumor and patients' characteristics are shown in Table 1.

Patients with a history of other tumors (except nonmelanoma skin cancer), previous thoracic radiotherapy, pregnancy, a Karnofsky index ≤ 70, or a multicentric/multifocal tumor were excluded from the study. We also excluded patients with a PTV in the pre-implant computerized tomography (CT) > 40 cc. All patients signed an informed consent form.

Brachytherapy implant

All patients received one implant and a single 18 Gy fraction of high-dose-rate (HDR) brachytherapy. Brachytherapy procedures were completed under locoregional anesthesia. All patients underwent pre- and post-implant CT. First, the tumor bed was localized with clinical examination and with an ultrasound, and then the first needle was placed and checked fluoroscopically its position regarding the clips to plan the implant. After the implantation, patients underwent a CT for treatment planning in the Oncentra®Brachy (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden).

The tumor bed, including all clips and seroma/hematoma (if present) were the target volume. The CTV was tumor bed with a 1 cm margin, CTV = PTV. Based on the dose volume histogram (DVH) data, the quality of plans and implant was evaluated using the following indicators: 1. Dose to 0.1 cc of the skin was limited to < 12.5 Gy; 2. Dose to 0.1 cc of the chest wall was limited to < 12.5 Gy; 3. The % of PTV receiving 90% of the prescription dose had to be more than 90% (V_{90} > 90%); 4. V_{150} and V_{200} (% receiving 150% and 200% of the prescription dose) were recorded. They had to be as low as possible.

The dose non-uniformity ratio, V_{150}/V_{100}, (DNR) should be < 0.35. The dose homogeneity index (DHI), $1 - V_{150}/V_{100}$ should be > 0.75, and the coverage index (CI) > 0.90.

All patients were discharged from the center in the same day of the procedure, between 2-4 hours from the implantation.

Follow-up

Follow-up visits were arranged the following day after completion of the treatment, the following week, the fourth week, every three months during the first year, every 6 months the second year, and then annually. A photograph was taken at each visit with the patient's permission. None of the patients were lost in follow-up.

Follow-up mammography was scheduled at 6 and 12 months, and then annually.

Toxicity

Toxicity was reported according to the Common Toxicity Criteria for Adverse Event, version 4.0 (CTAE v. 4.02) by the National Cancer Institute. Cosmesis was qualitatively evaluated by the treating radiation oncologist by comparing the treated breast with the untreated breast using the Harvard breast cosmesis 4-point scale: "0" excellent result (no difference), "1" good result (small difference), "2" fair result (moderate difference), "3" poor result (large difference) [10]. We also compared changes before and after the radiation treatment. Late toxicity was defined as symptoms that persisted or appeared beyond 6 months after completion of the treatment.

Table 1. Patient and tumor characteristics (*n* = 20)

Characteristics	*N*; %
Age (years)	Median 63.5 (range 51-79) 50-60: 7 (35%) 61-70: 11 (55%) > 70: 2 (10%)
Menopausal status	Postmenopausal: 20 (100%)
Karnofsky index	90: 20 (100%)
Tumor size (mm)	≤ 5 mm: 6 (30%) 5-10 mm: 7 (35%) 11-20 mm: 6 (30%) 20-30 mm: 1 (5%)
Grading	1: 13 (65%) 2: 2 (10%) 3: 3 (15%) No data: 2 (10%)
Histological subtype	Ductal: 15 (75%) Lobular: 1 (5%) Tubular: 3 (15%) Ductal in situ: 1 (5%)
Systemic treatment	Antihormonal: 20 (100%) Trastuzumab: 1 (5%)

Statistical considerations

Descriptive statistical considerations included absolute and relative frequencies for categorical variables, and the mean and standard deviation for quantitative variables. Distant metastases disease was defined by an imaging study or physical examination that demonstrated cancer outside of the breast and its regional nodes. Failure in disease-free survival (DFS) analyses was represented as detection of local, regional, and/or systemic tumor relapse. To assess the local relapse, biopsies were needed in patients without metastatic disease prior consent on their behalf. Estimated likelihood of events was calculated by the Kaplan-Meier method from the time of completion of radiotherapy. The statistical significance of the difference between estimated event-free curves was calculated with the log rank test. Multivariate analysis was performed using logistic regression. Statistical analysis was assessed with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

This is the first report in medical literature that focuses on acute/chronic toxicities and cosmetic result in early breast cancer treated with APBI with HDR brachytherapy in a single 18 Gy fraction. All 20 patients successfully received 18 Gy HDR brachytherapy in one fraction.

Median of catheters implanted were 10 (range, 7-15), with three planes in all cases. Dosimetric values are shown in Table 2. For the entire treatment, patients remained in hospital for 5-7 hours. The mean duration for the treatment was 90 min. Median patient age was 63.5 years (range, 51-79). Median volume at implant was 15.5 cc (7.05-28.00). The median follow-up was 24 months (range, 20-40). A total of 95% of the patients had invasive carcinoma. All patients were discharged from the center on the same day of the procedure between 3-4 hours after implantation.

Acute toxicity

In our series of 20 patients, we found no g ≥ 3 toxicity. Seven patients (35%) had pain g1 the following days, but none of them had to take analgesic drugs. None of the patients suffered epidermitis. Four patients had hematoma g1 (20%) at the point of insertion/exit of the needles, which was auto-limited. No infections were observed. One patient had a contact dermatitis due to the template, which was treated successfully with a topic corticosteroid.

Chronic toxicity

With a median follow-up of 24 months, none of the patients had g ≥ 3 toxicity. One patient was diagnosed of fat necrosis (six months after the implantation), occasionally taking ibuprofen 400 mg. One patient (5%) had fibrosis g2. None of the patients had neither epidermitis, hyper/hypopigmentation, nor edema during analysis. We found no correlation between toxicity and dosimetric values.

Cosmesis

Good-to-excellent cosmetic outcomes were noted in 80% of patients and fair in 4 patients (20%). There were no differences between cosmetic result before and after brachytherapy.

Oncological outcomes

At 24-months follow-up, in the cohort of 20 patients, no patients had a local or regional recurrence, and 1 patient had distant metastases (bone). That patient was 79 years-old and had a luminal B Her2 tumor. She received antihormonal and antiHer2 treatment, but no chemotherapy. None of them died from breast cancer or another cause. The overall survival (OS) and locoregional control according to Kaplan-Meier was 100%. Disease-free survival (DFS) and distant control was 95% (Figure 1).

Discussion

Treatment with APBI was studied for the first time in 1982 at Christie's hospital (Manchester) throughout external beam radiotherapy. After a median follow-up of 8 years, no differences were found in overall survival,

Table 2. Dosimetric values

	Median	Minimum	Maximum
Skin (0.2 cc)	7.755 Gy	4.6 Gy	10.9 Gy
Chest wall (0.2 cc)	5.85 Gy	2.5 Gy	10.5 Gy
$V_{90\%}$	97.45%	91.3%	99.9%
V_{100cc}	27.1 cc	6.1 cc	54 cc
V_{150cc}	9.95 cc	4.6 cc	29.5 cc
V_{200cc}	4.6 cc	0.95 cc	18.7 cc
DHI	0.645	0.32	0.82
CI	0.9	0.72	0.99

$V_{90\%}$ – percentage volume of the PTV receiving 90% of the prescribed dose, V_{100cc} – volume of the PTV receiving 100% of the prescribed dose, V_{150cc} – volume of the PTV receiving 150% of the prescribed dose, V_{200cc} – volume of the PTV receiving 200% of the prescribed dose, DHI – dose homogeneity index, CI – coverage index

and the recurrence rate was 25% versus 13%. They analysis concluded that APBI needed more stringent selection of patients [11].

Other trials have attempted to select patients in appropriate manner, and have also explored different techniques of irradiation and fractionations. Brachytherapy is the most explored technique for APBI treatment. At the beginning, it was made with low-dose-rate (LDR), pulsed-dose-rate (PDR), and high-dose-rate (HDR). Nowadays, HDR technique is the most used with similar schedules on 10 days restricted treatment. Acute and chronic toxicity, as well as oncological results are very similar in all trials comparing the different techniques of brachytherapy [12,13,14,15]. As a result, different recommendations have been published [16].

Polgar *et al*. published the results of the phase III trial. Two hundred fifty-eight patients were randomized to receive whole breast irradiation (WBI) or APBI. 80 patients received APBI with HDR brachytherapy (7 fractions of 5.2 Gy). The results for local recurrence were similar in both groups, with 10 years of follow-up (5.9% APBI group and 5.1% in the WBI) [17]. Prior to this study, acute toxicity was reported on a phase I/II trial, in which there was only one case of arterial bleeding and one hematoma after removing a catheter [18]. After this trial, the GEC-ESTRO reported acute toxicity and therapeutic compliances in a phase III trial. 1,328 patients were randomized to receive multicatheter brachytherapy versus WBI. The patients treated with APBI received 7 fractions of 4.3 Gy, or 8 fractions of 4 Gy with HDR. The results in both groups turned out to be excellent. No grade 4 side effects were reported. Grade 3 epidermitis was 7% in WBI versus 0.2% in APBI ($p < 0.0001$). In the WBI group, epidermitis toxicity grade 1-2 was reported in 86% compared to 21% for APBI ($p < 0.0001$), being significantly smaller in the hematoma toxicity g1-2 (2% vs. 20%, $p = 0.01$) and infection (2% vs. 5%, $p = 0.01$). No differences were found in pain g1-2 (26% vs. 29%, $p = 0.23$) or infection (0% vs. 0.2%, p = ns). Chronic toxicity as well as OS, DFS, and LC to 5 years were similar for APBI and WBI [19,20].

Other therapeutic schedules involving more hypofractionated brachytherapy were tested. A Japanese group published the results of a multi institutional study that included 46 patients treated with HDR brachytherapy. A 36 Gy dose at 6 Gy per fraction was administered. With a 26-month median follow-up, only one case of g3 toxicity was registered, with pain in 2% and g3 fibrosis in 4% of the patients. The other toxicities were g1-2 (dermatitis 7%, fibrosis 11%, fractures 2%, and fat necrosis 6%). The cosmetic results were very good or excellent in 81% of the patients [21]. Aliyer *et al*. conducted a retrospective analysis with 44 patients treated with 8 fractions of 4 Gy (32 Gy) or 7 fractions of 5 Gy (35 Gy) with HDR brachytherapy. The median follow-up was 37 months, and the authors found no differences between both groups in cosmesis or chronic toxicity [22].

Recently, William Beaumont's group has published the results of a 6-year follow-up of APBI with HDR brachytherapy, delivering 28 Gy in 4 fractions during two days. In the first publication, acute toxicity was analyzed, and none of the 30 treated patients suffered pain,

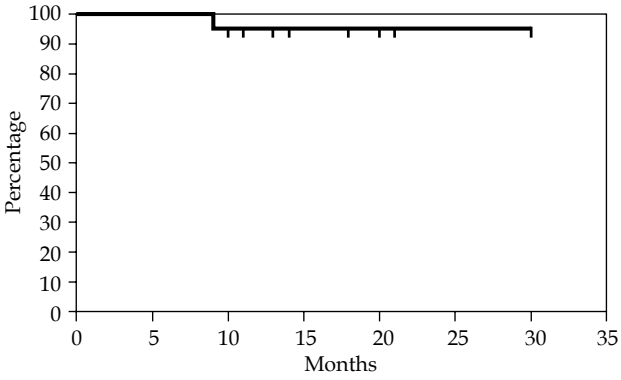

Fig. 1. Actuarial analysis of all 20 patients for disease-free survival

one had an infection, two had symptomatic seroma, and six hyper/hypopigmentation as acute toxicity [23]. After 6.2 years of follow-up, a grade 3 toxicity with telangiectasia (2%) form was registered. The rest were grade 1-2 (11% asymptomatic fat necrosis, 13% asymptomatic seroma). The cosmetic result was excellent in 91% of cases. DFS, CSS, and OS were of 96%, 100%, and 93% respectively [24]. A new strategy, consisting of the administration of three 8.25 Gy fractions is currently being investigated.

Hannoun-Lévi *et al*. have recently published the results of a trial, with 26 patients older than 69 years, treated with APBI (HDR brachytherapy) and delivering a dose of 16 Gy. The implementation of the implant was done intraoperatively, and the treatment was administered after definitive results of pathological anatomy were known. The oncological outcomes were excellent and the toxicity in the last follow-up was very low (15.4% with g1 toxicity and 3.9% of the patients with g2 toxicity). The CTV were larger than in our work (median, 41 cc), and the doses reached in OAR also (maximum skin dose of 19 Gy and chest wall of 30 Gy), which is probably the reason for greater acute toxicity (70% of patients). However, longer follow-up is needed to evaluate whether these two factors will have a long-term toxicity consequence [25]. Horton *et al*. published the results of phase I trial, in which external preoperative radiotherapy in a single dose of 15 Gy to 8 patients was administered, 18 Gy to 8 patients, and 21 Gy to 16 patients. With a 23 months median of follow-up, no grade 3 toxicity was reported. Acute toxicity reported was pain (g1 in 16%, g2 in 6%), dermatitis (g1 29 %, g2 10%), fibrosis (g1 23%), g2 infection, and g1 seroma in 32% of cases [26]. In addition to this study, the biggest experience on high-dose administration is intraoperative radiotherapy (IORT). There is data from two researches with more than 2,000 patients. In the TARGIT trial, a spherical applicator was used to administer 20 Gy dose (to the surface), with 50 Kv X-ray. The dose reached within 1 cm, resulted in 5 Gy. 1,113 patients were randomized to receive IORT, and 1,119 to receive WBI. Grade 3 or 4 toxicity were similar in both groups. One local recurrence was noticed in the experimental arm, even though the breast cancer mortality was less in this group [27]. On the ELIOT trial, 1,305 patients were randomized to receive APBI with electrons IORT, versus the standard treatment of external radiother-

apy (50 Gy and 10 Gy boost). The administered dose was 21 Gy in a single fraction. The experimental group resulted in less skin toxicity but more incidence of fat necrosis. The local recurrence in the experimental group was higher than on the standard group (4.4% vs. 0.4%, $p < 0.0001$) without any differences in overall survival [28].

In our study, the dose was estimated to expect the radiobiological isoeffect of 50 Gy, followed by a surgical bed boost of 16 Gy in 2 Gy per fraction, BED = 99 Gy ($\alpha/\beta = 4$). Brown *et al*. concluded that above 10 Gy per fraction, the lineal quadratic (LQ) model is expected to become progressively less accurate [29]. However, it is not currently possible to identify an alternative high-dose model that performs better than the LQ for predicting cell killing [30]. Therefore, the equivalent dose in one fraction was calculated using the LQ model without considering the repopulation factor and the large heterogeneities of interstitial implants in brachytherapy, which also would affect the radiobiological effect [31].

Our results regarding acute toxicity have been very positive; the appearance self-limited superficial hematoma was found to be the most frequent toxicity. During the follow-up period, we did not observe any g3-4 toxicity, only one patient suffered g2 fat necrosis. No chronic/acute toxicity or rib fracture occurred during follow-up. This is probably justified by the restrictions used, evaluating the skin and the chest wall as risk organs. No infections were declared as a probable relation, except only one procedure that included antibiotic prophylaxis. We have been very restrictive with the dose allowed for skin and the chest wall. Akhtari *et al*. analyzed a group of patients treated with Contura® (Contura® Multi-Lumen Balloon, SenoRx, Inc., Aliso Viejo, CA, USA) or Savi® (Strut-Adjusted Volume Implant, Cianna Medical, Aliso Viejo, CA, USA). When the distance to skin was smaller or equal to 3 mm, up to 128.8% of the dose prescribed have reached the skin, increasing acute and chronic toxicity [32].

None of the patients had a worsening of cosmesis after the surgery. The cosmetic result at last visit has been good or very good in 80%, and excellent in 20%. Higher than 40 cc volumes were not allowed to avoid the high-dose irradiation to the breast tissue. In cases, in which PTV was lower, we had difficulties to obtain more homogenic dose distributions.

The recommended margin according to different guidelines is 1-1.5 cm. When we administered high doses, we decided to restrain margins to 1 cm. In addition, it has been demonstrated that significative volume variations can be produced in 5 days treatments [33].

As an advantage of IORT, it could be emphasized that we designed the treatment with full knowledge of the surgical margins and the node status. Also, thanks to this technique, we were able to treat all the cases in our reference area, regardless of the hospital where the patients had been treated surgically.

The main disadvantage of this technique is that two invasive procedures are needed in each patient, instead of performing all the local treatment at one time with IORT. Gurram *et al*. reported no differences in implant quality between intraoperative placement of catheters and postoperative implants [34].

This treatment has been done in all cases in an ambulatory way, always discharging the patients a few hours after the implantation.

We are aware of our work limitation. It is a study with a follow-up and patient limited number. In spite of this, we consider this treatment to be safe and effective based on the follow-up acute toxicity, which has been very low, with a cosmetic result comparable to other historical series.

It would be interesting to analyze the quality of life impact in patients treated with this scheme. Bitter *et al*. found greater satisfaction in cosmesis and quality of life in 80 patients treated with APBI, in opposition to 26 patients treated with WBI with similar characteristics [35].

Furthermore, a cost-effectiveness analysis comparing APBI in a single fraction versus WBI or even APBI in several fractions could be performed. In fact, in a cost-effectiveness analysis of Harat *et al*., a greater cost-effectiveness was found for APBI [36].

Conclusions

This is the first report in medical literature that focuses both on feasibility and acute toxicity, and the appearance of secondary effects with a monitoring median of 24 months. This protocol is feasible and well tolerated, showing advantages when compared to IORT and other HDR brachytherapy protocols, like APBI treatment. However, a longer follow-up is needed to evaluate chronic toxicity and oncological outcomes.

Disclosure

Authors report no conflict of interest.

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