



# Chronic toxicity and long-term outcome in intraoperative electron radiotherapy as boost followed by whole-breast irradiation

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Received: 6 December 2020 / Accepted: 12 January 2021 / Published online: 3 February 2021  
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## Abstract

**Purpose** The administration of a dose boost to the tumor bed after breast-conserving surgery has proven to reduce local recurrence. Intra-operative electron radiotherapy (IOERT) offers an alternative method to deliver a boost with several advantages, such as direct visualization of the tumor bed, less inter- and intrafraction motion and a reduction in the number of medical appointments. The objective of our study is to assess chronic toxicity and long-term outcome for our patients after IOERT boost.

**Material and methods** Forty-six patients treated at our institution between July 2013 and June 2020 with IOERT boost during Breast-Conserving Surgery and consecutive whole breast irradiation were prospectively analyzed. A 10–12 Gy boost was prescribed to 42 patients and 4 patients received a 20 Gy boost. An analysis for overall survival, local relapse and distant progression was performed. Acute and chronic toxicity was assessed by CTCAE 4.0.

**Results** The median age was 64.5 years (40–90). The median follow-up was 62 months (4–86). We had no local recurrences but 2 patients (4.3%) presented a distant recurrence. Mean pathological tumor size was 16 mm (6–52). 84.8% (39) of the patients had invasive ductal carcinoma. 52.2% (24) presented histological grade II. 52.2% (24) were Luminal A like, 21.7% (10) Luminal B like, 13% (6) HER2 positive, 13% (6) triple negative. No Grade 3–4 chronic toxicity was observed. Grade 1–2 fibrosis was evidenced in 13% (6) of the patients, 4.3% (2) patients presented fat necrosis, 6.5% (3) presented seroma, 4.3% (2) had localized pain, 2.2% (1) presented localized hematoma and 2.2% (1) presented localized edema.

**Conclusions** IOERT boost in breast cancer treatment during BCS is a safe option with low chronic toxicity. The recurrence rates are comparable to published data and emphasize that IOERT as boost is an effective treatment.

**Keywords** Breast cancer · Boost radiotherapy · Intraoperative electron radiotherapy · Chronic toxicity · IOERT

## Introduction

Breast-Conserving Surgery (BCS) followed by whole-breast irradiation (WBI) is the current standard of care for early-stage breast cancer patients. WBI shows a significant benefit regarding the oncological outcome by reducing recurrence rates and breast cancer-related deaths [1].

About 71% of local recurrences (LR) are located in or near the primary tumor bed [2]. By adding an additional dose of 16 Gy to the tumor bed, the EORTC ‘boost versus no boost’- trial reported a reduction of the 10- years LR rate from 10.2 to 6.2%. However, a benefit on overall survival was not observed [3]. The boost can be applied with several techniques, such as an external electron or photon radiation therapy, interstitial or intraoperative radiotherapy, either with kV photons (kV-IOERT) or with electrons (IOERT). The criteria to choose the best boost technique remains unclear in the literature. A number of studies have compared boost techniques in terms of local recurrences. Most of these studies demonstrated equal local control rates for different boost techniques [4–9]. Adding a boost over the tumor bed is recommended for younger patients or for patients with

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other risk factors related to a higher risk of local recurrence [10–13].

According to literature an IOERT-boost plus WBI resulted in high in-breast control rates consistently, with observed 6- and 10-year local recurrence rates (LRR) of 0.8 and 2.7%, respectively [14, 15]. In the subgroups at “higher risk” for in breast recurrences (IBR), e.g. patients with locally advanced breast cancer (LABC) after primary systemic therapy (PST) or triple-negative subtypes (TN), IOERT-Boost data compared favorably to those that received other boost methods (boost with external radiotherapy) [16, 17]. In addition, with the increased utilization of oncoplastic techniques, IOERT boost represents a strategy where the tumor bed boost can be delivered before the oncoplastic procedure distorts the anatomy of the breast, allowing higher-risk patients to receive a boost while maximizing their cosmetic outcomes in cases where the boost offers a large potential LC benefit [18, 19]. Regarding the combination of IORT-boost and hypofractionated WBI after BCS, data from the first prospective multicenter trial has recently been published and, after 3 years of follow-up, acute and late treatment tolerance was excellent in short/mid-term assessment [20].

The present study aims to report chronic toxicity and long term outcome in women enrolled prospectively at our institution who received IOERT-boost during BCS followed by WBI.

## Materials and methods

Forty-six patients were recruited between July 2013 and June 2020 to receive IOERT boost. The inclusion criteria were: patients over 18 years of age, histological diagnosis of unifocal breast carcinoma, suitable for BCS and free surgical margins. Any histological grade, lymphovascular invasion, tumor necrosis, molecular subtype, or axillary stage were allowed. Neoadjuvant chemotherapy treatment was also allowed. Previous irradiation of the affected breast was considered as exclusion criteria. Each case was previously evaluated in a multidisciplinary oncologic committee.

## Surgery and radiotherapy

Lumpectomy was performed with an incision centered over the tumor. Sentinel node or axillary lymph node dissection was performed according to the current guidelines [1]. A mammogram of the removed tumor is performed and the radiologist macroscopically reports the tumor margins. Then, intraoperative assessment of histology margins is performed by the pathologist, reporting the nearest margin distance to the tumor. After the excision of the tumor, the surgeon mobilizes the part of the remaining breast around

the tumor bed by separating the deep side from the fascia of the major pectoral muscle and the superficial side from the subcutaneous tissue at the level of the anterior adipose lamina, to expose the target volume to the radiation beam. The surgical margins are then temporarily sutured together to restore the anatomy of the gland. Indicated in Fig. 1.

A dedicated 10 meV mobile electron linear accelerator LIAC (S.I.T. Sordina IORT Technologies S.p.A, Italy) was used to deliver IOERT. The electron beam is delivered through applicators (tubes) with different diameters, ranging from 3 to 10 cm. To spare underlying tissues from radiation, a shielding disc, available in various diameters, was inserted between the surface of the pectoralis muscle and the posterior side of the reconstructed mammary gland. The protective disc consists of a steel disc that is inserted in a PTFE (Polytetrafluoroethylene) sleeve. The orientation of the disc is such that the sleeve is facing upwards (towards the tumor bed) to efficiently shield backscattered electrons produced in the steel disc and avoid undesired overdosage of the surrounding tissue. The size of the shielding disc used was, for the majority of the cases, 1 cm larger in diameter than the applicator selected according to the tumor size. While the median applicator size used was 5 cm (range 4–6), the median size of the shielding disc used was 6 cm (range 5–8). Only flat tubes were used. The sterile applicator was placed directly in contact with the target volume. The applicator size was chosen to ensure the proper coverage of a given target volume around the surgical sutured breach, depending on the tumor size and location. The Planning Target Volume was defined as a 3D volume of 2 cm beyond the former macroscopic tumor edge. Median energy of electron beams used was 6 meV (range 4–10), and it was chosen according to the depth of the tumor bed which was measured with a needle before IOERT. The docking was first performed by rigid tube attached to the linear accelerator and later



Fig. 1 Disc insertion and positioning

by moving the gantry until it reached the proper position through manual alignments. The dose was prescribed at the 90% isodose [21]. For patients over 60 years, only those with poor prognostic factors received a boost. The dose of 10 Gy was chosen based on the bibliography reported. The dose of 12 Gy was selected based on the poor prognostic factors and resection margins [17]. With the 20 Gy dose, four patients who had been selected for IOERT-exclusive (without external radiotherapy) were treated, but given the poor prognostic factors, they were converted from IOERT-exclusive to IOERT-boost. We prescribed a median dose of 10 Gy (range 10–20).

After IOERT, the sutures used to put together the surrounding tissue were removed, and the surgeon completed the remaining surgical procedure. Tumor cavity remodeling was done with oncoplastic techniques according to the surgeon's preference. After wound healing, WBI was initiated. This entailed giving a hypofractionated scheme in 15 fractions over 3 weeks (each fraction dose being 2.67 Gy) or normofractionated scheme in 25 fractions over 5 weeks (with a fraction dose of 1.8–2 Gy). Each radiation oncologist decided the type of external radiotherapy treatment scheme based on the possibility of accomplishing the dose constraints to the heart, lung and contralateral breast. The median delivered dose for the WBI was 45 Gy (range 39.6–50).

### Follow-up and toxicity

Follow up visits were done after surgery and before WBI by both the gynecologist and the radiation oncologist. The evaluation by the radiation oncologist was performed 4–6 weeks after WBI. Toxicity was assessed with the Common Terminology Criteria for Adverse Events (CTCAE version 4.0) (grades 1–5) after surgery and after external radiation therapy. Toxicities were recorded in the breast, except for seroma and hematoma, which were reported in the volume of the boost. The next follow-ups were performed every 3–4 months with clinical examinations and yearly mammograms.

### Statistical analysis

The study endpoints of local recurrence (LR), regional recurrence (RR), distant recurrence (DR) and overall survival (OS) were evaluated. LR was calculated from the date of IOERT to the date of the first in-IOERT field recurrence, RR was measured from the date of IOERT to the date of first outside-IOERT field recurrence within the anatomical site, DR was measured from the date of IOERT to the date of the first recurrence at distance. OS was calculated from the date of IOERT to the date of death or last contact.

The mean, standard deviation, median, range and frequencies of the prognostic variables were analyzed. The differences in toxicity between the groups were evaluated with the Chi-square test and Odds Ratio with a confidence interval of 95%. The overall survival was analyzed with the Kaplan–Meier method and the Log-Rank test was used for contrasting results, considering the *p* value of <0.05 bilaterally significant. The statistical analysis was carried out through the IBM SPSS version 25.0 program for Windows.

### Results

A total of 46 patients were treated with IOERT boost during BCS. The median age of the population was 64.5 years (range 40–90) and the median follow-up was 62 months (range 4–86).

At the time of diagnosis, 84.8% (39) of the patients were diagnosed with invasive ductal carcinoma, the 4.3% (2) were diagnosed with invasive lobular carcinoma and the remaining 10.8% (5) were diagnosed with other histological subtypes such as invasive papillary carcinoma, medullary carcinoma and tubular carcinoma. The preoperative histological Grade was grade II for 52.2% (24) of the patients. Grade I for 26.1% (12) and Grade III for 21.7% (10).

Lumpectomy was performed for all patients and presented free surgical margins (defined as no ink contact) for all of them. During surgery sentinel lymph node dissection was performed for 39 patients (84.8%) while axillary lymph node dissection was performed for 7 patients (15.2%). Sentinel lymph node dissection was not performed for one patient because the axillary ultrasound and the biopsy were negative and the patient's age was 80 years. All patients received IOERT boost. 39 patients received a total dose of 10–12 Gy, prescribed to the 90% isodose while 4 patients were converted from IOERT exclusive (20 Gy) to IOERT boost due to histopathological characteristics.

The post-surgical median pathological tumor size was 16 mm (range 6–52). The pathological T stage was pT1c for 43.5% (20) of the patients, pT2 for 28.3% (13), pT1b for 26.1% (12), and pT3 for 2.2 (1) of the patients. Regarding the pathological N stage, 67.4% (31) of the patients were pN0, 17.4% (8) were pN1, 10.9% (5) were pNmic, 4.3% (2) were pN2. Finally, the observed immunophenotypes for 52.2% (24) of the patients were Luminal A-like, for 21.7% (10) Luminal B-like, for 13% (6) HER2 positive and the remaining 13% (6) triple negative. Complete tumor characteristics are displayed in Table 1.

### Treatment characteristics

For 11 of the patients (23.9%) neoadjuvant chemotherapy was performed, 1 patient (2.2%) received neoadjuvant

**Table 1** Tumor characteristics

	<i>n</i>	%
Pathological T stage		
T1a	0	0
T1b	12	26.1
T1c	20	43.5
T2	13	28.3
T3	1	2.2
Pathological N stage		
N0	31	67.4
Nmic	5	10.9
N1	8	17.4
N2	2	4.3
Histological Subtype		
Invasive ductal carcinoma	39	84.8
Invasive lobular carcinoma	2	4.3
Others		
Medullar carcinoma	1	2.2
Papillar carcinoma	2	4.3
Tubular carcinoma	2	4.3
Histological Grade		
G1	12	26.1
G2	24	52.2
G3	10	21.7
Immunophenotype		
Luminal A like	24	52.2
Luminal B like	10	21.7
HER2 positive	6	13
Triple negative	6	13

hormonal therapy. The rest of the patients (34 patients) did not undergo neoadjuvant systemic treatment. After surgery 10 patients (21.7%) received adjuvant chemotherapy, 33 patients (71.7%) received adjuvant hormonal therapy and 3 patients (6.5%) did not receive systemic adjuvant treatment.

The median interval between the IOERT and the start of the WBI was 53.5 days (range 18–230). 25 patients took less than 60 days to start WBI (14 patients were Luminal A like, 6 luminal B like, 4 triple negative, 1 HER2 positive) and 21 patients took more than 60 days (10 patients were Luminal A like, 4 luminal B like, 2 triple negative, 5 HER2 positive). We found no significant differences between the time interval to start WBI according to the immunophenotype of the patients. WBI was applied either after adjuvant chemotherapy or concomitantly with systemic hormonal therapy. WBI was performed by 3D conformal radiotherapy in tangential technique, using 6/18 MV photons in supine position. 18 patients (39.1%) were treated under an hypofractionated scheme with a total dose of 40.05 Gy in 15 fractions, dose constraints were defined by Ipsilateral lung: V20 Gy < 20%, Dose mean (Dmean) < 15 Gy, Heart (Left

**Table 2** Treatment characteristics

	<i>n</i>	%
Sentinel lymph node dissection	39	84.8
Axillary lymph node dissection	7	15.2
Neoadjuvant chemotherapy	11	23.9
Neoadjuvant hormonal therapy	1	2.2
Adjuvant chemotherapy	10	21.7
Adjuvant hormonal therapy	39	84.8
IOERT (total dose)		
10 Gy	38	82.6
12 Gy	4	8.7
20 Gy	4	8.7
WBI (total dose)		
40.05 Gy/15 fractions	18	39.1
45 Gy/25 fractions	25	54.3
50 Gy/25 fractions	3	6.5

Breast): V20Gy < 10%, Dmax 40 Gy, Dmean < 5 Gy, Contralateral breast: V10gy < 10%. D1cc < 15gy. Dmean < 5 Gy, Contralateral lung: V10Gy < 10%. Dmax < 5 Gy, Liver (Right Breast): V30 < 30%. And the remaining 28 patients (60.9%) were treated under a normofractionated scheme with a total dose of 45–50 Gy in 25 fractions (fraction size of 1.8 or 2 Gy), dose constraints were defined by Ipsilateral lung: V20 Gy < 30%, Dmean < 15 Gy, Heart (Left Breast): V25Gy < 10%, Dmean < 5 Gy, Contralateral breast: V10gy < 10%. D1cc < 15gy, Dmean < 5 Gy, Contralateral lung: V10Gy < 10%. Dmean < 5 Gy, Liver (Right Breast): V30 < 30%. A summary of the treatment characteristics is shown in Table 2.

## Toxicity

Acute adverse events were assessed with the CTCAE v. 4.0. No patients developed a wound infection after surgery. Wound suture dehiscence was not documented. 2 patients (4.3%) presented Grade 1 hematoma in the mammary region. Three patients (6.5%) had Grade 1 seroma in the lumpectomy bed and Grade 2 seroma was observed for one patient (2.2%). At the end of the WBI and after one month of follow-up Grade 1 radiodermatitis in the breast was observed for 30 patients (65.2%), Grade 2 for 15 patients (32.6%) and Grade 3 for one patient. On the other hand, Grade 1 breast edema was documented for 10 patients (21.7%) and Grade 2 for 5 patients (10.9%) (5); Grade 1 breast pain was observed for 10 patients (21.7%). Finally, Grade 1 and 2 fibrosis in the breast were observed for 4 patients (8.7%) and 1 patient, respectively. No Grade 4 toxicity was reported.

Chronic adverse events were recorded after 6 and 12 months of follow-up and were assessed with the CTCAE v. 4.0. The following toxicities were observed: Grade 1

**Table 3** Acute toxicity according to CTCAE v. 4.0

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Fibrosis	4(8.7)	1(2.2)	0	0	0
Seroma	3(6.5)	1(2.2)	0	0	0
Hematoma	2(4.3)	0	0	0	0
Pain	10(21.7)	0	0	0	0
Edema	10(21.7)	5(10.9)	0	0	0
Radiodermatitis	30(65.2)	15(32.6)	1(2.2)	0	0
Fat necrosis	0	0	0	0	0

**Table 4** Chronic toxicity according to CTCAE v. 4.0

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Fibrosis	3(6.5)	3(6.5)	0	0	0
Seroma	2(4.3)	1(2.2)	0	0	0
Hematoma	1(2.2)	0	0	0	0
Pain	2(4.3)	0	0	0	0
Edema	1(2.2)	0	0	0	0
Fat necrosis	2(4.3)	0	0	0	0

fibrosis for 3 patients (6.5%) and Grade 2 fibrosis for 3 patients (6.5%), Grade 1 seroma for 2 patients (4.3%) and Grade 2 seroma was reported for 1 patient (2.2%), Grade 1 hematoma for 1 patient (2.2%). Grade 1 breast pain was present for 2 patients (4.3%), Grade 1 edema for 1 patient (2.2%) and Grade 1 localized fat necrosis was observed for

2 patients (4.3%). Grade 3–4 fibrosis was not observed as chronic toxicity. No significant differences were found for chronic toxicity between patients who underwent external radiotherapy with hypofractionated schemes and patients treated with the normofractionated scheme ( $p$ : 0.513 with 95% CI: 0.392–0.723). Information about acute and chronic toxicity is reported in Tables 3 and 4, respectively.

**Oncological outcome/recurrence patterns**

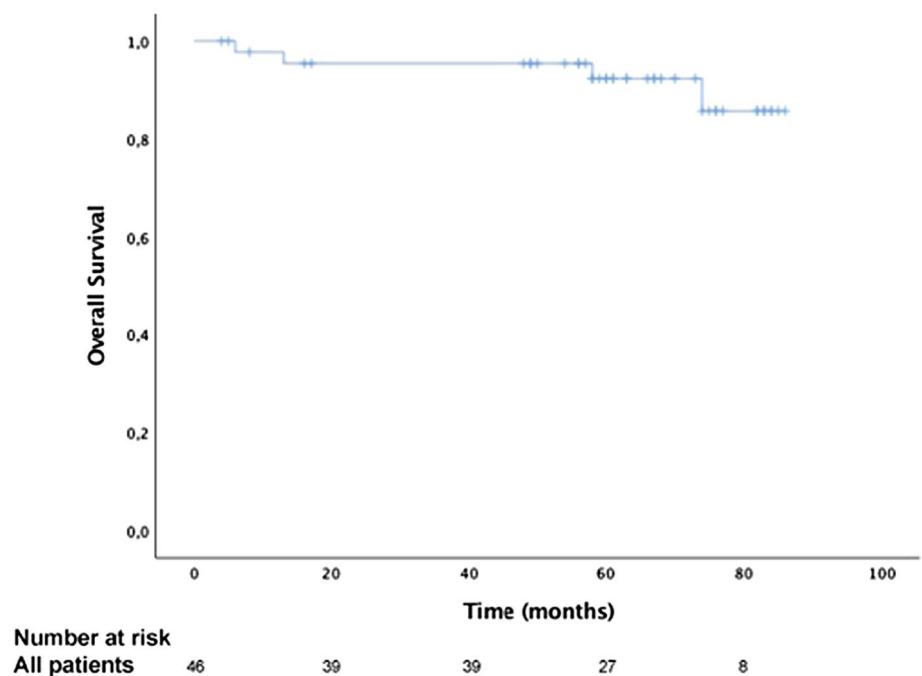
Two patients (4.3%) presented distant metastatic progression. Of these two patients, one had positive HER2 phenotype and the time of to progression at the end of WBI was 9 months. And the other patient triple-negative phenotype and pathological axillary lymph nodes at diagnosis, the time to progression at the end of WBI was 3 months.

At the end of the study, 4 patients (8.7%) had died, 2 from breast carcinoma and the other 2 patients due to non-related causes. 42 (91.3%) patients were alive at the end of the study. Median overall survival was not reached. Corresponding Kaplan–Meier chart are displayed in Fig. 2.

**Discussion**

Several clinical trials have demonstrated that up to a 75% of LR are located in or near the primary tumor bed [2] and that the addition of an additional dose to the tumor bed significantly reduces IBRs [3]. IORT boost has several advantages in terms of accuracy, dose delivery and homogeneity in comparison with external or interstitial boost techniques

**Fig. 2** Kaplan–Meier of overall survival after IOERT boost





[8, 16]. We reported breast toxicities after IORT-boost with a median follow-up of 62 months (range 4–86). Only 6 patients developed chronic fibrosis (13%), 3 Grade 1 and 3 Grade 2. No Grades  $\geq 3$  were observed. In another study, we retrospectively analyzed skin toxicity comparing the hypofractionated scheme versus normofractionated scheme for the boost irradiation. 96 breast cancer (pT1pN0/mic and pT2pN0/mic) patients were included. 49 patients were treated with normofractionated boost delivering 16 Gy in 8 fractions (2 Gy/fraction) and 47 patients were treated with the hypofractionated boost delivering 13.35 Gy in 5 fractions (2.67 Gy/fraction). The median follow-up was 21.3 months (range 5–41). Fibrosis grades 1–2 was observed only for four patients treated with normofractionated boost and for one patient of the hypofractionated boost group. We observed no differences for late skin toxicities between the two groups ( $p$ : 0.16) [26].

In the present study, 39% of the patients were treated using the hypofractionated scheme for the WBI since this regimen was adopted as our standard clinical practice based on the results of the START trial [22]. Hypofractionation for WBI has proven to be isoeffective when compared with conventional fractionation in terms of local control and late toxicity [22, 23]. Consequently, it has been argued that breast cancer cells have a low  $\alpha/\beta$ , around 4. Using the linear-quadratic model, with and  $\alpha/\beta = 4$ , a 10 Gy single dose IOERT boost is equivalent to 23 Gy delivered in a normofractionated 2 Gy scheme. With this in mind, it seemed reasonable to evaluate the combination of an IOERT boost and hypofractionated WBI. Consequently, in 2008, Ivaldi et al. published the results of a phase 2 trial evaluating the combination of IOERT and hypofractionated WBI in which they analyzed 204 women diagnosed with early-stage breast cancer treated with breast-conserving surgery. During surgery, a 12 Gy IOERT boost was delivered to the tumor bed. Adjuvant local treatment was completed with WBI, which consisted of a cycle of 13 fractions of 2.85 Gy throughout the whole breast up to a total dose of 37.05 Gy delivered once a day. Peak acute skin toxicity was observed at the end of WBI (182 evaluable patients) with 7 (3.8%) patients presenting Grade 3, 52 (28.6%) Grade 2, 123 (67.6%) Grade 1. Finally, a total of 108 patients were evaluated for late toxicity. The late skin toxicity recorded was Grade 4 in 1 patient (0.9%), Grade 3 in 1 patient, and Grade 2 or less in 106 patients (98.2%) [24].

It is also noticeable the prospective multicenter trial (HIOB) on IOERT followed by hypofractionated WBI. They observed acute effects with CTCAE-score 0/1 for 91% of the patients at the end of treatment and 92% of the patients 4 weeks later. Late toxicity Grading 0/1 (mean values, ranges) by LENT-SOMA criteria were observed in (92.7%, 89–97.3) at 4/5 months, rising to (96.5%, 91–100) at 6 years post WBI [20]. Grade 3 reactions were observed as

follows: Pain for 0.2% of the patients (0–0.5), 0.07% (0–0.3) presented breast edema, Fibrosis was observed for a 0.7% (0–1), telangiectasia for a 0.4% (0–3) and 1.4% (0.4–3) of the patients presented shrinkage or retraction of the affected breast. In our series chronic toxicities were found for 15 patients, 11 patients with Grade 1 and only 4 patients with Grade 2. We assessed the following risk factors: age at diagnosis, tumor size, fibrosis grade. No differences were found in terms of the analyzed risk factors for chronic toxicity.

Kaiser et al. reported 770 cases treated with IOERT with normofractionated WBI with a 10-year median follow-up, 38 patients (4.9%) presented wound complications. A second surgery was necessary for 28 patients (3.6%) due to either postoperative bleeding at the resection site of the breast or the SLN area, or due to wound infection. In our series, no patients presented surgical wound infections, suture dehiscence, or bleeding. Kaiser et al. also reported late cosmesis outcome assessment in 261 patients after a median follow-up of 56 months. 91% of patients rated their breast cosmesis as satisfactory (excellent/good) and 95% as acceptable (excellent/good/moderate), whereas physician ratings turned out to be a bit more critical, with 64% as satisfactory and 95% as acceptable [15].

Köning L. et al. retrospectively analyzed the acute toxicity and early oncological results for 157 patients irradiated with IOERT with a single 10 Gy dose followed by either normofractionated WBI (88%) or hypofractionated WBI (9%). In their study, the post-operative adverse events were mild: with Grade 1–2 seroma and hematoma for 26% of the patients and Grade 3 for 0.6% of the patients. Grade 2–3 wound infections occurred for 2.2% of the patients and Grade 1–2 wound dehiscence for 1.9% of the patients. 90.9% of the patients presented Grade 1–2 acute dermatitis at 6–8 weeks after WBI. These findings are well in line with the present study. In our series, we have reported less toxicity after surgery. In terms of acute dermatitis 4–8 weeks after WBI, 97% of the patients from Köning et al. presented acute Grade 1–2 radiodermatitis, 2.2% presented Grade 3, and no Grade 4 was reported. We also found similar results in our previous series, treated with Hypofractionated external boost [26].

### Long term outcomes

In 2013 the long-term results of a pooled analysis of 6 institutions by the International Society of Intraoperative Radiation Therapy (ISIRT) were published. With 1,109 patients this study represents the largest published group of patients with an IOERT boost in combination with WBI. With a median follow up of 72.4 months (0.8–239), only 16 in-breast recurrences were observed, yielding a local tumor control rate of 99.2%. Relapses occurred 12.5–151 months after the primary treatment.

Taking into account patient age, annual in-breast recurrence rates amounted to 0.64, 0.34, 0.21, and 0.16% for patients < 40 years; 40–49 years; 50–59 years and  $\geq 60$  years, respectively. This trend of decreasing LR rates with rising patient age was recorded for both: in-quadrant and out-quadrant relapses, however, in multivariate analysis only the ones corresponding to Grade 3 reached statistical significance ( $p = 0.031$ ) as a predictive factor for local recurrence development. No statistically significant differences were found in the remaining risk factors [14].

Kaiser et al. reported 770 cases treated with IOERT. With a median follow up of 10-years the rates for local control, locoregional control and OS were 97.2% (95% CI 95.5–98.2), 96.5% (95% CI 94.7–97.7) and 85.7% (95% CI, 82.8–88.1), respectively. By Cox proportional hazards regression, HER2 positive and triple negative were independent prognostic factors for developing a LR compared with luminal A subtypes (hazard ratio [HR], 15.02 [95% CI 2.9–77.78] and 12.87 [95% CI 3.37–49], respectively;  $p < 0.05$ ). This fact was not evidenced for grade 3 tumors or for a positive nodal status as reported previously by Fastner G et al. [14]. Other potential parameters, like age, tumor size and multifocality, tube size, systemic treatment (chemotherapeutic or antihormonal), or the time gap between IOERT and WBI were not statistically assessable by a complete Cox regression analysis because of the low number of events in these groups [15].

Köning L. et al. found that 2 and 3-year OS were 97.5 and 93.6% respectively, whereas they reported a 0.7 and 2.8% distant progression-free survival at 2 and 3 years. In breast recurrence and contralateral breast cancer rates after 3 years were 1.9 and 2.8%, respectively. All the patients with a local in-breast recurrence had a TN subtype and also suffered from distant disease progression with the development of metastasis shortly after the initial diagnosis (median 9 months) [25].

In the HIOB trial, with a median follow up of 45 months (0–74), reported no in-breast recurrence. 11 patients died (four due to breast cancer), 11 metastasized, and one developed a regional supraclavicular relapse. The 3-year disease-free survival rate was 97.8% (95% CI 96.6–99.1). However, the data on this trial was too immature to report statistically significant results regarding oncological outcome. [20].

In our series, with a median follow up of 62 months, no patients suffered from an in-breast LR event or contralateral breast recurrence. Yielding to a local tumor control rate of 100%. Two patients (4.3%) presented distant metastatic progression. Of these two patients, one had a positive HER2 phenotype and the other patient a triple-negative phenotype and pathological axillary lymph nodes at diagnosis. At the end of the study, 4 patients (8.7%) had died, 2 from breast carcinoma and the other 2 patients due to causes different to

their cancer diagnosis. 91.3% of the patients were alive at the end of the study.

## Limitations of this study

Due to the low numbers of patients analyzed, our clinical interpretation of statistical results should be approached with caution. The selection criteria for study eligibility was heterogeneous, making it difficult to draw any definite clinical conclusions. Moreover, our study was not a randomized trial comparing IOERT as a boost versus external standard techniques (electrons, photons) or interstitial brachytherapy.

## Conclusion

IOERT boost in breast cancer treatment during BCS is a safe option with low chronic toxicity. And provides high local control rates for breast-cancer patients with tumor stages I to III and for all risk settings.

**Funding** Not applicable.

## Compliance with ethical standards

**Conflicts of interest** All the authors not have any conflicts of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** All the patients signed informed consent.

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