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Original article

Intraoperative partial irradiation for highly selected patients with breast cancer: Results of the INTRAOBS prospective study

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ABSTRACT

Purpose. – To evaluate our long-term experience on one-day breast intraoperative radiotherapy (IORT) given as sole radiation treatment to selected patients with breast cancer.
Methods and materials. – Inclusion criteria of INTRAOBS study (prospective observational study) were: ER+ T1N0 unifocal ductal carcinoma; absence of lymphovascular invasion or of extensive intraductal component (Scarff-Bloom-Richardson grade III and HER2+++ excluded). Two different linacs were used (20 Gy/1 fraction): one dedicated electron linac (< October 2011), and afterwards a mobile linac (50 kV photons). The primary endpoint was the local recurrence rate (=ipsilateral breast cancer recurrences number). Secondary endpoints were recurrence-free survival (RFS), overall and specific survival, cosmetic results, and patient satisfaction.
Results. – Of the present pre-planned analysis for the first 200 patients (median age: 68 years; range, 59–87 years) who received IORT between January 2010 and October 2014 (median follow-up of 53.4 months). A total of 193 patients were still alive. The local recurrence rate was 2.5% ($n = 5$). The 1- and 5-year local RFS rates were 100% and 95.2%, respectively. At 12 months post-surgery, satisfaction about IORT was excellent for 86.9% of patients. Cosmetic results were considered by patients and physicians as good or very good in 89.4% and 97.3% of cases, respectively.
Conclusions. – IORT for selected patients with breast cancer shows low recurrence rates, good cosmetic outcomes and excellent satisfaction.

Mots clés :
Cancer du sein
Radiothérapie intra-opératoire
Récidive
Satisfaction des patientes
Résultats esthétiques

RÉSUMÉ

Objectif de l'étude. – Évaluation au long terme de notre expérience de radiothérapie peropératoire comme traitement local adjuvant exclusif de cancers du sein sélectionnés.
Matériel et méthodes. – Les critères d'inclusion d'INTRAOBS (étude prospective observationnelle) étaient: carcinome canalaire infiltrant unifocal; stafe T1N0, expression des récepturs hormonaux+; absence d'invasion lympho-vasculaire ou de composante intracanalaire extensive (grade III Scarff-Bloom-Richardson et HER2+++ exclus). Deux types d'accélérateur linéaite ont été utilisés pour délivrer 20 Gy/une séance: l'un spécifique (électrons, avant octobre 2011); l'autre, mobile (photons de 50 kV, après octobre 2011). Le taux de rechute locale était le critère principal (=nombre de récidives intra-mammaire homolatérales). Les critères secondaires étaient les survies sans récidive (SSR), globale et spécifique, les résultats esthétiques et la satisfaction du traitement par les patientes.

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Résultats. – De l'analyse pré-planifiée des 200 premières patientes (âge médian: 68 ans; min-max: 59-87 ans) traitées par orrafiayion peropératoire entre janvier 2010 et octobre 2014 (suivi médian = 53,4 mois). Au total, 193 patientes étaient en vie. Le taux de rechute locale était de 2,5 % ($n = 5$), le taux de s sans récidive locale à 1 et 5 ans de respectivement 100 % et de 95,2 %. Au total, 86,9 % des patientes étaient satisfaites du traitement par irradiation peropératoire un an après la chirurgie, avec des résultats esthétiques bons ou excellents pour 89,4 % des patientes (contre 97,3 % après évaluation médicale).

Conclusions. – Peu de récidives locales surviennent après radiothérapie peropératoire lorsqu'elle est délivrée chez des patientes atteintes d'un cancer du sein sélectionnées, avec des résultats esthétiques satisfaisant et un taux de satisfaction excellent.

1. Introduction

Breast conserving surgery followed by whole breast external beam radiotherapy (WBRT) is the standard of care for women with early-localized breast cancer (BC). WBRT reduces by 2/3 the risk of recurrences, but its potential side effects can affect the quality of life and psychological outcome [1]. Moreover, patients must undergo daily radiotherapy sessions in hospital for 3 to 6 weeks.

Two randomized trials (CALGB 9343 and PRIME II) compared loco-regional recurrence and overall survival (OS) in ≥ 65-year-old patients with early stage BC at low risk of recurrence who received adjuvant endocrine therapy alone or combined with WBRT [2,3]. In both trials, OS was comparable in the two treatment arms; however, loco-regional recurrences progressively increased in the group without WBRT over time.

In this context, intraoperative radiotherapy (IORT) represents a feasible strategy to reduce the irradiated volume and the treatment time. Based on our previous results [4,5], we modified our clinical practice and we propose exclusive IORT to all patients with low-risk BC because we think that it represents a safe compromise between WBRT and omission of any radiotherapy. We report here results from a prospective observational study (INTRAOBS study), which assessed the risk of ipsilateral breast recurrence (IBRT) after IORT, among BC patients who have similar inclusion criteria of the randomized trials (CALGB 9343 and PRIME II).

2. Materials and methods

2.1. Study design and patients

From January 2010 to October 2018, this monocentric prospective observational (INTRAOBS) study included patients aged 60 and more with invasive BC considered at low risk of recurrence: unifocal ductal carcinoma or histological favorable subtypes (invasive lobular carcinoma were excluded), tumor diameter ≤ 2 cm, clinical negative node status, estrogen receptor (ER) positive, absence of lymphovascular invasion or of extensive intraductal component. From 2014, patients with Scarff-Bloom-Richardson (SBR) grade III ($n = 8$) and HER2 overexpressing ($n = 1$) BC were excluded. No neoadjuvant treatment was allowed. Breast volumes were considered large for cup sizes higher than C.

2.2. Patient information and inclusion procedure

Informed consent was collected before surgery by radiation oncologists for final inclusion.

2.3. Surgical and Intra-Operative Radiation Therapy (IORT) procedures

Conserving BC surgery and IORT were carried out as previously reported [4,5]. Briefly, lumpectomy was performed with a centered incision adapted to the tumor size. Frozen tumor sections were analyzed by a pathologist to check the tumor-free margins (≤ 2 mm), and axillary lymph node dissection was performed using a sentinel lymph node procedure.

The tissue surrounding the excision cavity received a single fraction of 20 Gy. The collimator was adjusted according to the IORT technique. Until October 2011, the tissue around the excision cavity was mobilized and temporarily approximated with sutures to bring it into the radiation planning target volume. As described in our first phase II trial [4], electrons (6 or 9 MeV) were delivered using a dedicated linear accelerator installed in the surgical theatre. After that date, a one-day BC treatment procedure was introduced and consisted in an ambulatory surgery including IORT (using a mobile linear accelerator to deliver low energy (50 kV) photons [6]). As described by Vaidya et al. [7], the appropriately sized (30–50 mm diameter) spherical applicator was placed in the tumor bed and the gland fixed to the applicator with temporary purse-strings. Radiation was delivered to the tumor bed over 17–30 min and the tumor bed surface receives 20 Gy, attenuated to 5–7 Gy at 1 cm of depth.

At the end of the procedure, the tumor cavity was remodeled and the incision was closed according to standard procedures.

2.4. Additional treatments and postoperative evaluation

In patients with local recurrence risk factors described on the definitive pathology report (extensive in situ ductal carcinoma, multifocality, pN+, lobular subtype, SBR grade III, lymphovascular invasion, pT2) or after a second conservative surgery required to obtain adequate margins, an additional external beam radiotherapy was performed 46–50 Gy to mammary gland in pN0/pN+ patients; and to mammary gland and nodes area in pN+ patients. Adjuvant systemic therapy was prescribed according to international and local guidelines.

2.5. Endpoints

The primary endpoint was the local recurrence rate, defined as the number of ipsilateral BC recurrences. Secondary endpoints were progression-free survival (PFS), overall survival (OS) and specific survival, cosmetic results, impact of IORT on the patients' autonomy and satisfaction.

Table 1
Patients' characteristics at baseline.

	$n = 200$
Age (years), median (range)	68 (60–87)
WHO Performance Status, *n* (%)	
0	197 (98.5)
1	3 (1.5)
BMI (kg/m^2), median (range)	25.9 (18.4–39.1)
BMI ≤ 30, *n* (%)	157 (78.9)
BMI > 30, *n* (%)	42 (21.1)
Missing, *n* (%)	1
Breast size, *n* (%)	
Small	53 (29.8)
Large	125 (70.2)
Missing	22

Abbreviations: BMI: body mass index; WHO: World Health Organization.

2.6. Toxicities, cosmetic results and satisfaction index

Toxicities (according to the Common Toxicity Criteria Adverse Events, CTCAE version 4.0) and cosmetic results were evaluated by the patients and the medical staff at week 3 (acute), and at month 6 and 12 (late) after surgery/IORT. For the cosmetic evaluation (breast symmetry, consistency, nipple symmetry and global evaluation) scores ranged from 1 to 4 (1: "very good", 2: "good", 3: "poor", 4: "very poor"). Breast photographs (frontal and profile views) were also taken. A patient satisfaction index was developed using a visual analog scale (VAS) going from 1 (poor satisfaction) to 10 (excellent satisfaction).

2.7. Statistical analyses

Continuous variables were described as number of observations (*n*), medians and ranges. For categorical variables, frequencies and percentages were calculated relative to the total population without missing data. The missing categories were added to refer to all the data. All survival events were measured from the day of surgery to the event: loco-regional/distant recurrence (assessed by clinical examination, mammography or breast ultrasound) or death for RFS, and death for OS. RFS and OS rates were estimated using the Kaplan–Meier method. Statistical analyses were performed using the STATA 13.0 software (StataCorp, College Station, TX, USA).

3. Results

3.1. Patients' characteristics at baseline

Between January 2010 and October 2018, 637 patients were included in the prospective INTRAOBS study and signed the informed consent before surgery. Among them, 611 received IORT. The present study will report data for the first 200 patients treated with IORT between January 2010 and October 2014. According to the French health Ministry recommendations, the publication of the pre-planned analysis of the first 200 patients was mandatory.

The median age was 68 years (range, 59–87 years). Moreover, 98.5% (*n* = 197) of them had an excellent performance status (grade 0), 21.1% (*n* = 42) had a BMI > 30, and 70.2% (*n* = 125) had large breast size (Table 1).

Invasive ductal carcinoma or a favorable BC subtype (tubular, mucinous) was diagnosed in 195 patients (96.5%), with a final pathological tumor size equal or lower than 2 cm in 197 patients (98.5%). Axillary sentinel nodes were negative in 191 patients (95.5%). The SBR grade was I in 36.5% and II in 59.1% of patients. Unfavorable pathology subtype was established on the final pathological report for 4,4% (1 patient with cerb2 +++) and 4,4% with grade III tumors. All patients had ER-positive tumors (median expression value of 95%; range, 40–100%) (Table 2).

Table 2
Breast cancer pathology analysis summary.

Tumor feature	Number of patients (%)
pT	200
T0	1 (0.5)
Tis	2 (1.0)
T1a	18 (9.0)
T1b	89 (44.7)
T1c	87 (43.7)
T2	2 (1.0)
Missing	1
pN	200
N0	191 (95.5)
N1mi	3 (1.5)
N1a	6 (3.0)
Tumor subtype	200
Invasive ductal carcinoma	186 (93)
Tubular carcinoma	3 (1.5)
Mucinous carcinoma	4 (2.0)
Lobular carcinoma	3 (1.5)
Others	4 (2.0)
SBR Grade	200
I	73 (36.5)
II	117 (59.1)
III	8 (4.0)
Missing	2
Lymphovascular invasion	7 (3.5)
Extensive DCIS	4 (1)
ER expression	
Yes	200

Abbreviations: SBR: Scarff-Bloom-Richardson; ER: estrogen receptor; DCIS: ductal carcinoma in situ; pN1mi: micrometastasis.

3.2. Treatments

IORT was delivered using our dedicated electron beam linear accelerator electron IORT; (*n* = 30 patients; 15%) or an Intrabeam device (photon IORT; *n* = 170 patients; 85%).

Postoperative WBRT was proposed to 20 patients and delivered to 16 patients (due to 3 patients withdrawal, 1 medical omission) and reasons were detailed in Table 3. Most patients (98.3%) received adjuvant endocrine therapy (tamoxifen or aromatase inhibitors). Three patients (1.5%) received also adjuvant chemotherapy according to our guideline policies for patients with unfavorable definitive pathology report (Table 3).

3.3. Treatment tolerance

Acute and late toxicities were reported by 100% and 89% of patients, respectively (Table 4). At week 3 post-surgery/IORT, the main grade 1–2 toxicities were erythema (*n* = 12, 6%), palpable hematoma (*n* = 19, 9.5%) and pain (NRS higher than 4; *n* = 10, 5%). One grade 3 hematoma that required a second surgery was observed 10 days after surgery. Within the 12 months of follow-up, only grade 1–2 toxicities were reported, mainly fibrosis (*n* = 36, 20.2%) and hyperpigmentation (*n* = 13, 6.5%).

No difference was observed between patients treated by electron or photon IORT.

3.4. Cosmetic evaluation and patient satisfaction

Cosmetic outcome was evaluated in 167 patients at 6 months and in 165 patients at 12 months after IORT (Table 5). Overall, cosmetic results at 12 months were considered by patients and by physicians as good or very good in 89.4% and 97.3% of cases, respectively.

Table 3
Breast cancer management.

Surgery	
Surgery, *n* (%)	200 (100)
Axillary node dissection	10 (5)
Sentinel lymph node dissection	196 (98)
Size of surgical sample (cm^3), median (range)	72.0 (0.1–396)
Resection margins (mm), median (range)	10.0 (0–30)
Number of resected lymph nodes, median (range)	2.0 (0–9)
Intraoperative radiotherapy, *n* (%)	
Electron IORT	30 (15%)
Photon IORT	170 (85%)
Whole breast external beam radiotherapy	
Indication for WBRT, *n* (%)	20 (10.0)
Positive margins, second conservative surgery	2 (10.5)
Positive lymph nodes	3 (15.8)
Tumor multifocality	4 (21.1)
Lobular carcinoma	3 (15.8)
Extensive DCIS	5 (25)
Tumor size	1 (5.3)
Unfavorable histologic type (SBR grade III, LVI)	3 (15.8)
Patients who received postoperative WBRT, *n* (%)	16 (84.2)
Dose per fraction (Gy), median (range)	2.1 (2–6)
Number of fractions (Gy), median (range)	23 (5–25)
Systemic treatment, *n* (%)	
Chemotherapy	3 (1.5)
Endocrine therapy	173 (98.3)
No treatment	27 (13.5)

Abbreviations: WBRT: whole breast external beam radiotherapy; DCIS: ductal carcinoma in situ; IORT: intraoperative radiotherapy; SBR: Scarff-Bloom-Richardson; LVI: lymphovascular invasion.

Table 4
Treatment tolerance.

	Acute toxicity 3 weeks post-surgery	Toxicity within 12 months
Grade 1–2 toxicities, *n* (%)		
Erythema	12 (6)	NA
Hematoma	19 (9.5)	NA
Breast pain (NRS for pain > 4)	10 (5)	NA
Telangiectasia	NA	3 (1.6)
Atrophy	NA	1 (0.5)
Fibrosis	NA	36 (20.2)
Hyperpigmentation	NA	13 (6.5)
Grade 3-4 toxicities, *n* (%)	1 (0.6)[a]	0
Missing	0	22 (11)

Abbreviation: NA: not applicable; VAS: visual analog scale.
[a] Grade 3 toxicity: hematoma at day 10 post-surgery that required surgery.

Data on the patient satisfaction about IORT at 6 months and 12 months post-IORT were available for 197 and 158 patients, respectively. Satisfaction was excellent (VAS scores 9 and 10) for 86% and 86.9% of patients at 6 and 12 months, respectively.

No difference was observed between patients treated by electron or photon IORT.

3.5. Cancer outcome

After a median follow-up of 53.4 months (95% CI 49.2–54.7), 193 patients were still alive. Seven patients died (3.5%) from non-BC related diseases. The median OS was not reached. The 1-year and 5-year OS rates were 99.5% (95% CI 96–100) and 95.8% (95% CI 91–98), respectively.

The median local RFS was not reached (Fig. 1). The local recurrence rate (primary endpoint) was 2.5% ($n = 5$, 95% CI 0.8–5.7). The 1-year and 5-year local RFS rates were 100% and 95.2% (95% CI 88–98), respectively.

Five patients presented a local recurrence after a median interval of 47.5 months post-surgery (range, 22.0–59.5 months). Details were listed in Table 6.

4. Discussion

This prospective observational study reports the outcome for the first 200 patients with early stage low-risk BC who received IORT. Our findings indicate that this therapeutic strategy is a reliable alternative to conventional postoperative WBRT in this selected population. Both cancer and cosmetic outcomes are promising for this personalized approach supported by the patients and encouraged by clinical-economic constraints.

WBRT remains the gold standard for patients undergoing conservative surgery for BC. While meta-analyses have extensively reported WBRT positive impact in terms of IBTR rate improvement in all women, irrespective of their age [8], WBRT omission has been assessed in low risk breast cancers patients (older than 65-70 years, ER-positive BC) in two randomized clinical trials (CALGB 9343 and PRIME II) [2,3]. Adjuvant breast radiotherapy significantly decreased local relapse even among old patients with pT1N0 ER-positive BC (5-years IBRT rates = 1.3% in WBRT arm versus 4.1% in no-WBRT arm, PRIME II study) [3]. Similar results were observed in CALGB 9343 study with a longer median follow-up (at 12.6 years, 2% versus 10%, respectively) [2]. Among the 32 patients who presented a loco-regional recurrence, 27 (84.4%) had IBTR. In this patients' population, personalized radiotherapy approaches (shorter duration treatment, equal tumor control with lower risk of toxicities), as single-fraction IORT or other partial breast irradiation strategies, will be justified.

A recent meta-analysis ($n = 5415$) summarized the available evidence on IORT efficacy and safety compared with WBRT using data from two randomized controlled trials (ELIOT and TARGIT-A) and two non-randomized trials patients [9]: IORT should be used only in patients with low-risk BC. As ELIOT trial enrolled "high risk" patients (large tumor size for 14% of patients; pN+ for 26% of patients; grade 3 for 20% of patients) [10], this possibly explaining a higher IBTR rate in IORT-arm (4.4% at 5 years) [11]. A strict selection is required for IORT indication. This is in line with our previous phase II trial [5] and the present results (2.5% recurrence rate at 53.4 months). When patients were highly selected for IORT, as well as patient selection criteria used in The TARGIT-A study (non-inferiority trial) [7], "pre-pathology" group (randomization before surgery), the 5-years IBTR rates were 2.1% in the IORT and 1.1% in the WBRT arm, without significant difference. Furthermore, only 10% of patients in our study required post-surgery WBRT, against 19% in "pre-pathology" TARGIT-A patients. That demonstrates that a very strict patients' selection allow a tailored strategy which will avoid 90% of over treatments without any consequence on OS.

To our knowledge, patients' satisfaction index is reported for the first time. At 12 months, cosmetic outcome was considered "very good" or "good" by 89.4% patients while 70.2% of patients had large breast volumes at inclusion. In such patients' population, WBRT is known to procure pejorative outcome. Similarly, analysis of the cosmetic results in a subgroup of patients in the TARGIT-A study at 1 and 2 years post-treatment [12] indicated better outcome in patients in the IORT arm compared with those in the WBRT arm. Moreover, patient satisfaction of the global therapeutic strategy and care was very good or excellent. In the Australian group of the TARGIT-A trial (209 women), 60% of patients in the IORT group were willing to choose IORT despite the higher risk of local recurrence (4–6%), valuing the convenience of IORT much more than the 12% of patients in the WBRT group who would have accepted the increased risk of IORT [13,14].

Table 5
Cosmetic evaluation and patient satisfaction.

	6 months		12 months	
	Physician evaluation	Patient evaluation	Physician evaluation	Patient evaluation
Cosmetic assessment, *n* (%)		167 (83.5)		165 (82.5)
NA, *n* (%)		1 (0.5)		1 (0.5)
Missing, *n* (%)		32 (16)		34 (17)
Breast symmetry, *n* (%)	145 (100.0)	163 (100.0)	144 (100.0)	159 (100.0)
Very good	80 (55.2)	64 (39.3)	91 (63.2)	57 (35.8)
Good	58 (40.0)	78 (47.9)	49 (34.0)	89 (56.0)
Poor	7 (4.8)	20 (12.3)	4 (2.8)	12 (7.5)
Fair	–	1 (0.6)	–	1 (0.6)
Missing	55	37	56	41
Breast sensibility, *n* (%)	NA	164 (100.0)	NA	163 (100.0)
Very good		60 (36.6)		75 (46.3)
Good		73 (44.5)		61 (37.7)
Poor		29 (17.7)		24 (14.8)
Fair		2 (1.2)		2 (1.2)
Missing		36		38
Breast consistency, *n* (%)	148 (100.0)	165 (100.0)	147 (100.0)	161 (100.0)
Very good	74 (50.0)	65 (39.4)	121 (82.3)	80 (49.7)
Good	60 (40.5)	82 (49.7)	25 (17.0)	67 (41.6)
Poor	13 (8.8)	17 (10.3)	1 (0.7)	14 (8.7)
Fair	1 (0.7)	1 (0.6)	–	–
Missing	52	35	53	39
Nipple symmetry, *n* (%)	144 (100.0)	156 (100.0)	144 (100.0)	157 (100.0)
Very good	81 (56.3)	75 (48.1)	108 (75.0)	74 (47.1)
Good	55 (38.2)	67 (42.9)	33 (22.9)	66 (42.0)
Poor	8 (5.6)	13 (8.3)	3 (2.1)	16 (10.2)
Fair	–	1 (0.6)	–	1 (0.6)
Missing	56	44	56	43
Global, *n* (%)	147 (100.0)	164 (100.0)	146 (100.0)	161 (100.0)
Very good	77 (52.4)	68 (41.5)	102 (69.9)	73 (45.3)
Good	63 (42.9)	86 (52.4)	40 (27.4)	71 (44.1)
Poor	7 (4.8)	9 (5.5)	4 (2.7)	16 (9.9)
Fair	–	1 (0.6)	–	1 (0.6)
Missing	53	36	54	39
Patient satisfaction, *n* (%) NA 163 (%) NA 160 (%)				
Poor (< 5)		0		1 (0.6)
Fair (5–6/10)		4 (2.5)		0
Good (7–8/10)		18 (11.0)		20 (12.5)
Excellent (9–10/10)		141(86.5)		139 (86.9)
Missing		37		40

Abbreviation: NA: not applicable

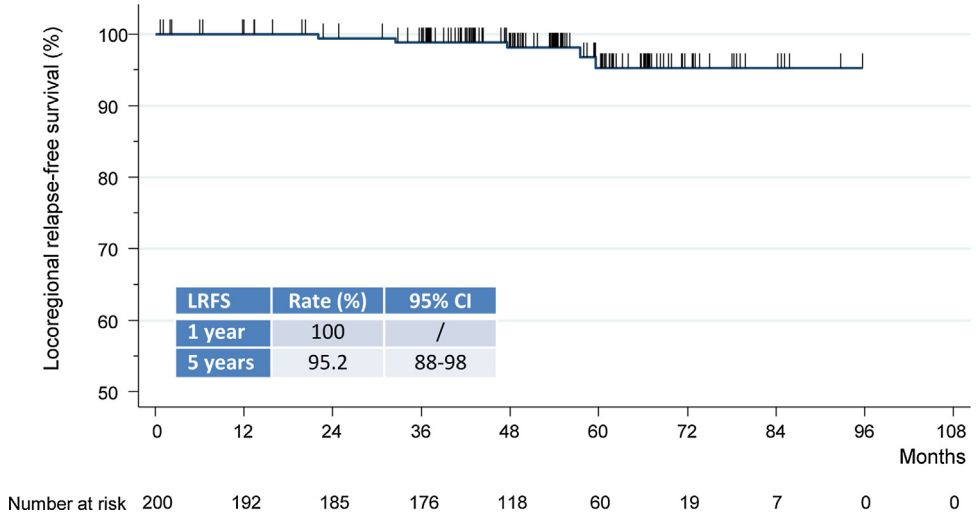

Fig. 1. Locoregional relapse-free survival (LRFS).

Considering the life-expectancy improvement, more women will be eligible for IORT in the next decades. The few cost-effectiveness studies and reviews have all concluded that targeted IORT is more cost-effective that standard WBRT [15–17]. The economic analysis extrapolated from the TARGIT-A trial, over a 10-year time horizon, showed that IORT has a higher mean health gain (quality-adjusted life years, non-inferiority in terms of cancer recurrence, high likelihood for IORT to be superior in terms of non-breast-cancer mortality) at a lower cost [18].

Table 6
Description of local recurrences.

Patients	Time to recurrence (month)	Histologic subtype of primary tumor	Adjuvant WBRT for primary cancer	histologic subtype of local recurrence	Salvage treatment
1	63	SBR II, ER+ 7 mm No LVI nor IEC Margin > 15 mm	0	SBR I, ER + 8 mm close to the primary tumor bed	Salvage mastectomy Axillary curage
2	54	SBRI ER+ No residual disease post biopsy	0	SBRI, ER+ 9 mm Close to the primary tumor bed	Conservative surgery Adjuvant WBRT
3	34	SBR II, ER+ 5 mm IEC +(low interm grade for 80%)	0	Micro-invasive In situ carcinoma - 4 mm	Salvage mastectomy
4	49	SBR II, ER+ HER2neg 15 mm In situ 20% Margins> 8 mm	0	Ductal SBR III, ER 0, HER +++ Ductal 11 + 7 mm Distant from primary	Salvage Mastectomy
5	22	SBR III, ER+ HER2neg 18 mm Margins > 10 mm IEC (40%) high grade	0 declined	Ductal SBR III ER0 PR0 HER 0 (basal) Distant from primary	No local treatment

5. Conclusion

The results of our trial performed in an institution with a long IORT experience, confirm that IORT as sole radiation treatment during breast conservative surgery is a reliable alternative to conventional WBRT for carefully selected patients with very low risk of local recurrence. This one-day cost-effective approach also shows good cosmetic outcomes and high patient satisfaction.

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Disclosure of interest

The authors declare that they have no competing interest.

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