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Five-year results of accelerated partial breast irradiation: A single-institution retrospective review of 289 cases

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ABSTRACT

PURPOSE: The purpose of the study was to describe our institutional experience with accelerated partial breast irradiation (APBI) using multicatheter brachytherapy with high-dose-rate. We report 5-year survival outcomes, cosmesis, and treatment-related toxicity.

METHODS AND MATERIALS: This included a retrospective review of patients who underwent breast-conserving surgery followed by APBI at our institution from 2004 to 2017.

RESULTS: A total of 289 patients were evaluated. Median followup was 72 months. Median age was 70 years. APBI was the only primary treatment in 86.2% of cases with early-stage breast cancer and a second conservative treatment in 13.8%. The implant was performed postoperatively in 213 patients (73.7%) and intraoperatively in 76 (26.3%). The most common radiation schemes were 10 fractions of 3.4 Gy and eight fractions of 4 Gy. Elderly or frail patients (10%) received a single 16 Gy dose. Of the 289 patients, 215 met Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology criteria for APBI; in this group, late side effects included Grade 2 (G2) fibrosis (14.8%), skin discoloration at the catheter points (8.8%), and telangiectasia (0.5%). The cosmetic result was considered excellent or good in 88.3% of cases. Five-year local control, disease-free, cancer-specific, and overall survival rates were 98.9%, 96.7%, 99.1%, and 95.6%, respectively.

CONCLUSIONS: Local control and survival outcomes at 5 years of followup in this group of well-selected patients were excellent, with low rates of treatment-related toxicity. These findings confirm the safety and effectiveness of APBI, even in elderly and frail patients. These results provide further support for the clinical use of APBI in suitable patients. © 2021 Published by Elsevier Inc. on behalf of American Brachytherapy Society.

Keywords: Accelerated partial breast irradiation; Brachytherapy; Breast cancer; Interstitial multicatheter; Breast-conserving therapy

Background

Standard treatment for early-stage breast cancer (ESBC) consists of breast-conserving surgery (BCS) followed by whole-breast irradiation (WBI) (1−4), an approach known as breast-conserving therapy. However, in the last decade, accelerated partial breast irradiation (APBI) has emerged as a promising alternative to WBI for selected patients. APBI has an important advantage over WBI in that the radiation is delivered directly to the target area, thus avoiding unnecessary toxicity to nearby organs (heart, lungs, and ribs) and healthy tissues (5−7). Several randomized controlled trials (RCTs) have compared APBI with standard WBI, demonstrating that, in well-selected patients, APBI is at least equivalent to WBI for numerous outcome measures, including local control (LC), disease-free survival (DFS), overall survival (OS), and cosmesis (8,9).

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Numerous approaches to APBI are available, including intracavitary (10) and interstitial brachytherapy, intraoperative radiation therapy (IORT) (x-rays or electrons) (11,12), external beam radiotherapy (EBRT) (three-dimensional radiation therapy [3D-CRT] (13−15), intensity-modulated radiotherapy) (16), and proton therapy (17). However, the most widely used technique, with the largest evidence base, is interstitial multicatheter brachytherapy (MC-BT), delivered intraoperatively or postoperatively (18). Although there is a growing body of evidence from RCTs, as well as prospective and retrospective studies, to support APBI after BCS (19,20), a growing number of studies support the viability and safety of MC-BT APBI as salvage therapy in patients with recurrent ipsilateral breast cancer. The second breast-conserving therapy could be considered an alternative to mastectomy in selected patients (21,22). Although MC-BT APBI has been explored as a primary tumor treatment, the evidence base to support this indication is limited, mainly consisting of small retrospective studies and only three RCTs (13,23,24).

In this context, we retrospectively reviewed our institutional experience with APBI in a large series of patients who underwent APBI for ESBC as either exclusive primary treatment or second conservative salvage treatment. Here, we describe treatment survival outcomes and treatment-related toxicity separately for each group.

Methods and materials

Patient data

To date, we have performed more than 500 MC-BT APBI procedures, both as a primary cancer treatment and salvage therapy in patients with ipsilateral breast cancer recurrence. In this study, we retrospectively reviewed 289 patients who underwent MC-BT APBI at our institution (Catalan Institute of Oncology, Barcelona, Spain) between February 2004 and June 2017. We included those patients with a diagnosis of ESBC (the primary tumor) and ≥24 months of followup after APBI. Although most patients (n = 219; 76%) were treated in the context of routine clinical care, 70 cases were involved in an RCT. To be deemed eligible for APBI, the patients were required to meet the ‘‘appropriate group’’ criteria recommended by the Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) (25). All results were updated as of January 2021.

Procedure

All patients underwent BCS followed by surgical axillary staging by sentinel lymph node biopsy, except for the following: women ≥ 75 years old (26), patients with histological Grade 1, cN0 (axillary ultrasound and magnetic resonance imaging), and hormone receptor-positive patients receiving endocrine therapy given that the surgical procedure does not compromise breast cancer mortality, DFS, or OS (27).

The APBI implant was performed intraoperatively in 76 patients (26.3%) and postoperatively (≤12 weeks after surgery) in the other 213 patients (73.7%). The intraoperative procedure allowed us to precisely locate the tumor bed and surrounding tissues to insert the catheters immediately after lumpectomy (Fig. 1) (18). In the postoperative group, catheter insertion was guided by ultrasound. In this case, APBI was administered after the definitive pathological findings were known, using the MC-BT approach with the longest followup and best survival results reported to date (20,24). The specific method varied in accordance with the individual characteristics of the patient and the tumor, as well as on the availability of our medical team to travel to the hospital where the patient underwent surgery (our institution is a monographic cancer center).

Following the guidelines for MC-BT APBI detailed in the GEC-ESTRO consensus statement (28−30), we contoured the volume and developed the treatment plan. We identified the surgical bed with an expanded safety margin that varied in accordance with the size of the free resection

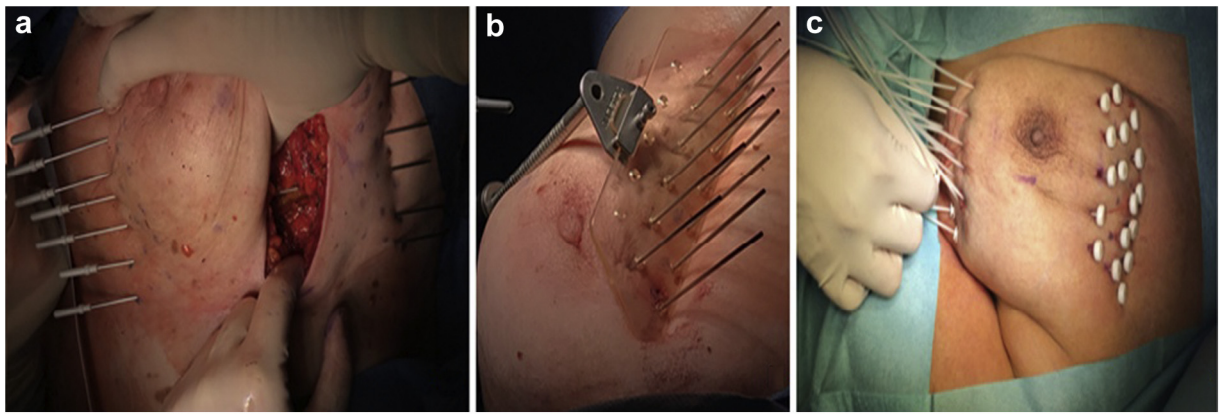

Fig. 1. (a, b) The images on the left show an intraoperative procedure with needles inserted during the lumpectomy. (c) The image on the right depicts postoperative multicatheter ultrasound-guided interstitial brachytherapy.

margin. In this way, we generated the planning target volume and established the dose as described in ICRU report 58 (31).

In accordance with our institutional protocol, the initial followup visit, which includes mammography, is performed 6−8 months after treatment. Subsequent followup visits are performed every 6 months during the first 2 years and annually thereafter. Mammography is performed yearly afterward.

Fractionation schedules

Several different fractionation schedules were used in this series. Seventy patients participated in two different RCTs; of these, 43 participated in a single-center Phase II RCT on APBI conducted at our institution in the years 2004−2005 (data not published). In that RCT, participants received high-dose-rate interstitial MC-BT APBI delivered in 10 fractions of 3.4 Gy, based on the scheme proposed by Vicini *et al.* (13). The other 27 patients were included in the MC-BT APBI arm (second arm) of the Phase III GEC-ESTRO European trial (24), with a fractionation schedule of eight fractions of 4 Gy targeted to the original tumor bed. The fractionation schemes used in the remaining 219 patients were either the same as those used in the two RCTs or seven fractions of 4.3 Gy, except for elderly or frail patients, who received a single fraction of 16 Gy based on the approach described by Hannoun-Levi *et al.* (32). Table 1 shows the percentage of patients who received each fractionation schedule.

Fractionation was twice per day because most patients were admitted to the treatment unit for the duration of the entire treatment course to ensure at least 6 h between fractions (in many cases $>$ 8 h), which allowed patients to complete treatment in 3−5 days.

Toxicity and cosmesis

Toxicity was assessed in accordance with the Radiation Therapy Oncology Group and the European Organization for Cancer Research and Treatment (RTOG-EORTC) scale (33). The acute morbidity criteria of the RTOG are used to grade the relevant toxicity of radiation therapy from day 1 (start of therapy) to day 90. Subsequently, we used the RTOG-EORTC criteria to assess late side effects.

Cosmetic outcomes were assessed during followup visits using the Harvard/NSABP/RTOG breast cosmesis scale (excellent, good, fair, or poor) (34). The criteria for these scores were obtained from our internal scale to quantify coloration, fibrosis, and symmetry in accordance with the degrees described by the RTOG-EORTC.

Statistical analysis

Statistical analysis was performed with SPSS statistical software program, v23.0 (IBM-SPSS Inc.; Chicago, IL; USA). Survival outcomes, including LC, DFS, OS, and cancer-specific survival (CSS), were evaluated with the Kaplan−Meier method.

Results

Patient, tumor, and treatment characteristics

A total of 289 patients were included in this study. For the analysis, we evaluated two distinct groups: those who received APBI as primary treatment (n = 249), but 215 have met the criteria of ESTRO low risk, and those who received APBI as a second conservative treatment (n = 40). Of the last patients, they had previously received EBRT to the involved breast as part of the first conservative treatment.

The main patient demographics, tumor-related characteristics, and dosimetric parameters are given in Table 1. Median followup was 72 months (range, 27−216). Median age was 70 years (range, 35−92). Note that one young patient (age = 35) received APBI because of her high body mass index (BMI = 65), which precluded the use of EBRT.

We treated 29 frail elderly patients (10%), identified as presenting a medical complexity and reduced tolerance to medical and surgical interventions; for this reason, we opted for single-dose APBI, altering their vulnerability as little as possible.

Given the relatively limited number of cases per group, we could not perform a multivariate analysis to check for differences between the different fractionation schemes.

At least 90% of the defined planning target volume received 100% of the prescribed dose, and in only one case, dose nonuniformity ratio was over 0.35 (median nonuniformity ratio = 0.34).

Treatment-related toxicity and cosmetic outcomes

Fibrosis was the most common side effect observed in our series, with an incidence of moderate (G2) induration in the primary and salvage groups of 14.8% (32/215) and 47.5% (19/40), respectively. Only one case of G2 telangiectasia was observed in the patients who received APBI alone. No G3 or G4 cases were observed in the primary therapy group. However, in the salvage APBI group (n = 40), 27.5% (n = 11) and 7.5% (n = 3) of the patients developed late G3 and G4 fibrosis, respectively. This outcome is mostly due to treatment for recurrent disease, which means they had already undergone at least two surgeries plus previous adjuvant external WBI.

Overall, the implant was well tolerated, with only 2 patients (one of whom also had fibromyalgia) reporting G2 breast pain. Acute infection and hematoma were the most common perioperative complications.

In accordance with the four-point Harvard/NSABP/RTOG scale (34), 86.2% of evaluable patients had excellent (n = 86) or good (n = 137) cosmesis. However, in the patients who received APBI for the primary tumor, 88.3% had

Table 1
Patient demographics and tumor and implant treatment characteristics

Characteristics		N	%
Age	Median	70	
	Range	35[a]–92	
T stage	pTis	4	1.4%
	pT1a	5	1.7%
	pT1b	56	19.4%
	pT1c	177	61.2%
	pT2 (≤3 cm)	47	16.3%
N stage	cN0[b]	66	22.8%
	pN0	215	74.4%
	pN1mi	6	2.1%
	pN1	2	0.7%
Stage	0	1	0.4%
	I	256	88.8%
	IIA	31	10.4%
	IIB	1	0.4%
Histology type	Invasive ductal carcinoma	262	90.7%
	Ductal carcinoma *in situ*	4	1.4%
	Invasive lobular carcinoma	3	1%
	Mucinous carcinoma	12	4.2%
	Invasive papillary carcinoma	8	2.7%
Histological grade	1	75	26%
	2	144	49.8%
	3	21	7.3%
	Unknown	49	16.9%
Molecular classification	Luminal A-like	129	79.2%
	Luminal B-like	19	11.6%
	Her-2 overexpressed	8	5%
	Basal Like	7	4.2%
	Unknown	126	43.6%
APBI indication	Primary tumor	249	82.6%
	Salvage treatment	40	13.8%
APBI technique	Intraoperative	76	26.3%
	Postoperative	213	73.7%
Fractionation schedule	32 Gy (4 Gy × 8)	158	55%
	34 Gy (3.4 Gy × 10)	68	23%
	30.10 Gy (4.3 Gy × 7)	34	12%
	16 Gy (16 Gy × 1)	29	10%
V100 (cc)	Median	156.3	
	Range	52.6–300	
V150 (cc)	Median	34.4	
	Range	9–59.3	
DNR < 0.35	Median	0.34	
	Range	0.26–0.41	
CI > 0.9	Median	0.93	
	Range	0.82–99	
Number of catheters	Median	15	
	Range	5–24	
Number of planes	Median	3	
	Range	1–4	

APBI = accelerated partial breast irradiation; N = nodal; T = tumor; DNR = dose nonhomogeneity ratio; CI = coverage index.
[a] Includes 1 patient (age 35) who was not suitable for EBRT because of an extremely high body mass index (BMI = 65).
[b] Without surgical axillary staging.

excellent/good cosmesis. Of the 86 cases with excellent cosmesis, 12 received a single 16 Gy dose. By contrast, 11 (27.5%) of the patients who underwent salvage APBI, which involved reirradiation of the ipsilateral breast, presented poor cosmetic results.

A detailed toxicity profile and summary of cosmetic outcomes in the primary and salvage treatment subgroups are given in Tables 2 and 3, respectively. Harvard score data were not available in 3.7% of the exclusive APBI group ($n = 8$) and 10% of the second conservative treatment group ($n = 4$).

Late treatment-related toxicity in the frail/elderly group ($n = 29$) was mainly G1 and G2 fibrosis (50% [$n = 8$] and 12.5% [$n = 2$], respectively), with 75% ($n = 12$) achieving excellent cosmesis. We did not find any significant between-group differences in toxicity or cosmetic results between the different fractionation schemes.

Survival analysis

A total of 249 patients were initially included in the primary APBI treatment group. However, for the survival analysis, we excluded the following cases: pN1mi, pN1 (by sentinel lymph node biopsy), and cN0. Thus, 215 patients were considered evaluable and included in the analysis.

At five years, LC was 98.9% (Fig. 2). Five-year OS, DFS, and CSS rates were, respectively, 95.6%, 96.7%, and 99.1%. During the followup period, 30 deaths (14%) occurred, but only five of these were breast cancer related. Two deaths were due to SARS-CoV-2. Overall, local recurrence was observed in 2 patients (0.9%). In addition, 1 patient (0.5%) experienced an axillary recurrence and 4

Table 2
Toxicity profile and cosmetic outcome: patients treated for a primary breast tumor and well-selected patients in accordance with the ESTRO low group (215 patients)

Toxicity	N	%
Acute toxicity		
Infectious mastitis	5	2.3%
Hematoma	9	4.2%
Late toxicity		
Fibrosis G0–G1	183	85.1%
Fibrosis G2	32	14.8%
Fibrosis G3	0	0%
Fibrosis G4	0	0%
Mastitis	2	0.9%
Telangiectasia G1	3	1.4%
Telangiectasia G2	1	0.5%
Hypochromic skin spots	11	5.1%
Skin hyperpigmentation	8	3.7%
Fat necrosis	2	0.9%
Breast pain G1	5	2.3%
Breast pain G2	1	0.5%
Cosmetic score	**N**	**%**
Excellent	76	35.3%
Good	114	53%
Fair	7	3.3%
Poor	0	0%
No data available	8	3.7%

G = grade; ESTRO = European Society for Radiotherapy and Oncology.

Table 3
Toxicity profile and cosmetic outcome: patients treated for breast local recurrence (40 patients)

Toxicity	N	%
Acute toxicity		
Infectious mastitis	7	17.5%
Hematoma	1	2.5%
Late toxicity		
Fibrosis G0−G1	7	17.5%
Fibrosis G2	19	47.5%
Fibrosis G3	11	27.5%
Fibrosis G4	3	7.5%
Mastitis	6	15%
Telangiectasia G1	1	2.5%
Telangiectasia G2	3	7.5%
Hypochromic skin spots	8	20%
Skin hyperpigmentation	5	12.5%
Fat necrosis	1	2.5%
Breast pain G1	1	2.5%
Breast pain G2	1	2.5%
Cosmetic score	**N**	**%**
Excellent	0	0%
Good	23	57.5%
Fair	6	15%
Poor	7	17.5%
No data available	4	10%

G = grade.

patients (1.8%) developed systemic relapse (mainly bone and brain metastases).

In the salvage APBI group, an ipsilateral breast tumor relapse (IBTR) in a different quadrant occurred in 2 patients, at 3 and 5 years after treatment, respectively. One of these patients underwent salvage mastectomy, and the other developed distant metastasis, but both were alive at the last followup. Five-year LC and survival rates (Fig. 2) were, respectively, as follows: LC, OS, DFS, and CSS, 96.6%, 85.3%, 95.7%, and 97.5%. Apart from the case described previously, 3 other patients (7.5%) developed distant recurrence (mainly bone, brain, and liver metastases).

Discussion

To our knowledge, the present study includes one of the largest single-institution patient cohorts in Europe treated with MC-BT APBI with extended followup. Moreover, we report the lowest local recurrence rates of studies reported to date. Table 4 summarizes the IBTR data from the most relevant published randomized and nonrandomized clinical studies of MC-BT with at least 5 years of followup.

In the present study, we retrospectively reviewed survival, toxicity, and cosmesis results in 289 patients who underwent BCS followed by APBI with MC-BT. The main focus of the present analysis was on the outcomes in the 215 patients who underwent APBI as primary treatment. Although APBI is only appropriate for a well-selected population, it represents an important advance in treatment de-escalation and a step forward in personalized medicine, reducing treatment time and the volume of healthy tissue that received radiation. Table 5 compares the suitability criteria established by the main medical societies for patient selection.

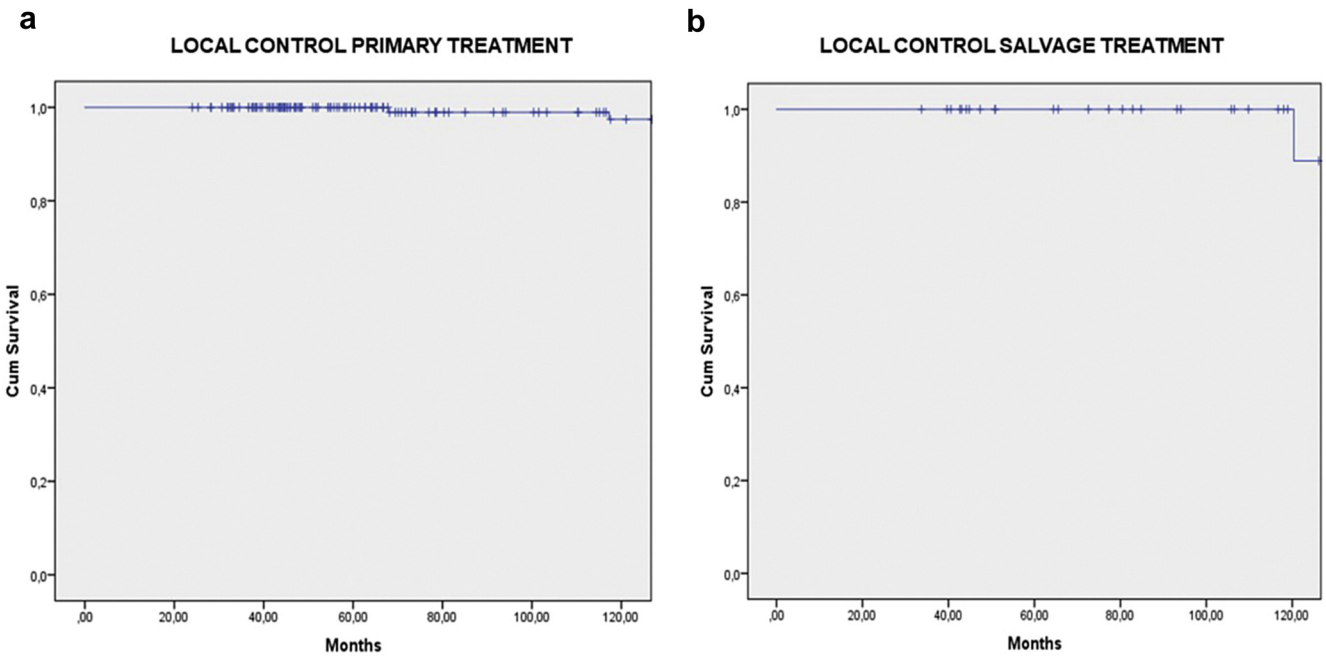

Fig. 2. The Kaplan−Meier survival curve depicting 5-year local control rates in (a) the primary treatment group (98.9%) and in (b) the salvage treatment group (96.6%).

Table 4
Comparison of studies that have evaluated APBI with interstitial brachytherapy with more than 5 years of followup (FU)

Study	Author	Center	Trial design	Enrollment	*N*	FU (years)	Technique	Dose/fractionation	Total dose	5-Y IBTR	Cosmesis outcome
Single-institution, randomized											
NIO-Hungary	Polgár *et al.* (23,35,36)	S−I	Phase III	1998−2004	88	18.2	HDR	5.2 Gy × 7	36.4 Gy	9.6% (20 y)	Good/excellent: 77%
Single-institution, nonrandomized											
Ochsner Clinic	King *et al.* (37)	S−I	Phase I/II	1992−1993	51	6.25	LDR HDR	LDR = 4 d HDR = 4 Gy × 8	LDR = 45 Gy HDR = 32 Gy	3.9%	Good/excellent: 75%
Ontario	Perera *et al.* (38)	S−I	Pilot study	1992−1996	39	7.58	HDR	3.72 Gy × 10	37.2 Gy	16.1%	Median overall cosmetic score: 89 (0−100)
WBH	Shah *et al.* (39,40)	S−I	Matched-pair analysis	1993−2001	199	12	LDR HDR	LDR = 0.52 Gy/h × 96 h HDR = 4 Gy × 8; 3.4 Gy × 10	LDR = 50 Gy HDR = 32 Gy; 34 Gy	5%	Good/excellent: 99%
Sweden	Johansson *et al.* (41)	S−I	Retrospective	1993−2003	50	7.2	PDR	5 d	50 Gy	4%	Good/excellent: 56%
WBH	Jawad *et al.* (42)	S−I	Retrospective	1993−2012	195	6.7	LDR HDR	LDR = 0.52 Gy/h × 96 h HDR = 4 Gy × 8; 3.4 Gy × 10	LDR = 50 Gy HDR = 32 Gy; 34 Gy	2.2% (suitable group)	NR
NIO-Hungary	Polgár *et al.* (43)	S−I	Phase II	1996−1998	45	11.1	HDR	4.33 Gy × 7 5.2 Gy × 7	30.3 Gy 36.4 Gy	4.4%	Good/excellent: 78%
Boston	Hattangadi *et al.* (44)	S−I	Phase I−II	1997−2001	50	11.2	LDR	0.5 Gy/h	50 Gy 55 Gy 60 Gy	15% (12 y)	Good/excellent: 67%
Boston	Kaufman *et al.* (45)	S−I	Phase I−II	1997−2001	33	5.88	HDR	3.4 Gy × 10	34 Gy	6.1%	Good/excellent: 88.9%
ICO-Barcelona	Laplana *et al.* (present study)	S−I	Retrospective	2004−2017	215	6	HDR	3.4 Gy × 10 8 Gy × 4 4.3 Gy × 7 16 Gy × 1	34 Gy 32 Gy 30.1 Gy 16 Gy	0.9%	Good/excellent: 88.3%
Multicentric, randomized											
NCT00402519	GEC-ESTRO (24,46)	MC	Phase III	2004−2009	633	6.6	PDR HDR	PDR = 50 Gy HDR = 4 Gy × 8; 4.3 Gy × 7	PDR = 50 Gy HDR = 32 Gy; 30.1 Gy	1.4%	Good/excellent: 81%
NSABP B-39/ RTOG 0413	Vicini *et al.* (13)	MC	Phase III	2005−2013	120	10.2	HDR	3.4 Gy × 10	34 Gy	4% (10 y)	PBI = WBI (patients) PBI worse (physician)
Multicentric, nonrandomized											
RTOG 95-17	Rabinovitch *et al.* (47,48)	MC	Phase II	1997−2000	98	11.3	LDR HDR	LDR = 3.5−5 d HDR = 3.4 Gy × 10	LDR = 45 Gy HDR = 34 Gy	4%	Good/excellent: 68%
German-Austrian	Strnad *et al.* (49,50)	MC	Phase II	2000−2005	274	5.33	PDR HDR	PDR = 0.6 Gy/h HDR = 4 Gy × 8	PDR = 50 Gy HDR = 32 Gy	2.2%	Good/excellent: 90%

APBI = accelerated partial breast irradiation; IBTR = ipsilateral breast tumor relapse; HDR = high-dose-rate; ICO = Institut Català d'Oncologia; LDR = low-dose-rate; MC = Multicentric; NIO = National Institute of Oncology; NR = not reported; PDR = pulsed dose rate; RTOG = Radiation Therapy Oncology Group; S−I = single institution; WBH = William Beaumont Hospital; WBI = whole-breast irradiation.

Table 5
Patient suitability criteria for APBI as per the various consensus guidelines

Features	GEC-ESTRO (2016) (24,25)	ASTRO (2018) (51−53)	ABS (2018) (54)	ASBS (2011) (55)
Age	≥50 years old	≥50 years old	≥45 years old	≥45 years old (IDC) ≥50 years old (DCIS)
Size	≤3 cm	≤3 cm IDC ≤2.5 cm DCIS	≤3 cm	≤3 cm
Nodal status	Negative	Negative	Negative	Negative
Histology	IDC	IDC and DCIS	All invasive subtypes and DCIS	IDC and DCIS
Centricity	Unicentric and unifocal	Unicentric, clinically unifocal	Unifocal	Unifocal
Estrogen receptor	Any	Positive	Any	-
Surgical margins	Negative (≥2 mm)	Negative (≥2 mm) IDC Negative (≥2 mm) DCIS	Negative microscopic	Negative microscopic
Lymphovascular space invasion	Not present	Not present	Not present	Not present
Chemotherapy	No neoadjuvant	No neoadjuvant	-	-

APBI = accelerated partial breast irradiation; GEC-ESTRO = Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology; ASTRO = American Society for Radiation Oncology; ABS = American Brachytherapy Society; ASBS = American Society of Breast Surgeons; IDC = invasive ductal carcinoma; DCIS = ductal carcinoma *in situ*.

Our long-term followup data demonstrate excellent results for APBI MC-BT on all survival measures (LC, OS, DFS, and CSS)—with rates > 95% in all cases—findings that confirm both the safety and value of this technique, thus supporting its use as an alternative to WBI in properly selected patients. Compared with the recurrence rates reported in the two published RCTs (23,24), the rates in our cohort were low, with a local recurrence rate of less than 1%, axillary recurrence of 0.5%, and systemic recurrence (mainly bone and brain metastases) of 1.8%. In the first RCT conducted to compare APBI with WBI (23,35), Polgár *et al.* reported 5-, 10-, and 20-year actuarial LR rates of 4.7%, 5.9%, and 9.6%, respectively, at a median followup of 17 years (36); OS was 93.7%, 77.2%, and 59.5%, DFS was 88.8%, 86.2%, and 79.7%, and CSS was 98.4%, 94.9%, and 92.6%, respectively. Those findings were further supported by the outcomes of the GEC-ESTRO noninferiority trial conducted by Strand *et al.* and published in 2016 (24), which is the only RCT that applied MC-BT alone. The IBTR rate in that trial was approximately 1%, in line with our results. Taken together, both trials provide clear evidence for the effectiveness of APBI with MC-BT in terms of survival outcomes and toxicity rates (46). Vicini *et al.* (13) performed a Phase III trial to evaluate different types of APBI in a large, heterogeneous group of patients (n = 2093); however, only 120 of those patients were treated with MC-BT, and no subgroup analyses were performed to compare the various techniques. Those authors found that the prespecified study criteria for APBI equivalence and complete breast irradiation were not met, findings that contradict those reported in the aforementioned trials.

The technique with the strongest evidence base is interstitial MC-BT. Nonetheless, there are many possible approaches to APBI, including the intracavitary approach and EBRT. Two prospective Phase III RCTs evaluated the equivalence of intraoperative APBI (IORT) to WBI. Those studies delivered a single fraction using a mobile linear accelerator that generates low energy X-rays (TARGIT) (11) or electrons (ELIOT) (12). In the TARGIT trial, Vaidya *et al.* reported a higher rate of recurrence after IORT than conventional treatment (2.11% vs. 0.95%), with no significant differences in treatment outcomes at 8.5 years; importantly, the patients who received intraoperative APBI had better cosmetic outcomes than those who received WBI. The IBTR rate at five years in the electron arm of the ELIOT trial was significantly greater than the rate for WBI (2.5% vs. 0.4%). However, 10-year OS and DFS rates were very good, close to 90% and 95%, respectively. It is important to emphasize that these two RCTs did not apply the strict selection criteria agreed on by the societies like GEC-ESTRO, American Society for Radiation Oncology, American Brachytherapy Society, and American Society of Breast Surgeons (Table 5), which would have allowed the IORT to be used as a boost followed by WBI in patients who present risk factors in the definitive pathological examination.

In our study, the most common treatment-related toxicities were breast fibrosis (G2 = 14.8%), skin discoloration (G2 = 8.8%), and telangiectasia (G2 = 0.5%). However, most patients (88.3%) had good or excellent cosmesis. These results are consistent with other published reports on the interstitial modality, such as in the prospective study in Hungary, which reported good or excellent cosmesis in 78% of patients at the 11-year followup (23) and in the other multicenter prospective Phase II study by Ott *et al.*, who reported good/excellent cosmesis in 90% of patients (49). Considered together, these findings provide further support for the routine use of APBI in well-selected patients. Importantly, in the primary treatment group in our study, no G3 or G4 late side effects were observed, a finding that stands in contrast to other studies, such as the NRG Oncology/RTOG 9517 study, in which 13% of patients developed G3 skin toxicity (13). Moreover, our good results also contrast with those obtained in the RAPID RCT (APBI delivered with 3D-CRT), which confirmed the noninferiority of that APBI technique versus WBI in terms of

LC, but with increased late tissue toxicity and adverse cosmesis associated with EBRT (14), probably due to the twice daily treatment regimen and some inconsistencies in target volume definition. Irradiation volumes smaller than 160 cc and a sufficient time interval between fractions to ensure complete recovery of normal tissue play a crucial role in determining the development of late side effects. Indeed, this may at least partially explain the good cosmetic results in the GEC-ESTRO interstitial APBI series (46). Our data regarding good cosmesis and low rates of fibrosis are probably due to the relatively small size of the implant volumes (mean $<$ 160 cc) and because the use of multiple catheters allows for a more homogeneous dose distribution, permitting us to maintain the proper time interval ($\geq$6 h) between fractions to ensure the optimal recovery of normal tissue. In fact, in many cases, this interval was $>$8 h because many patients were admitted to the treatment unit for the duration of the entire treatment course.

The recently updated results of the Florence Phase III 10-year followup trial (16), in which fractions were delivered once daily, showed that toxicity and cosmetic results were significantly better in the APBI group. In addition, the positive (but not significant) trend in favor of the partial breast irradiation arm versus WBI in terms of the rate of contralateral breast cancer opens an interesting door for future research.

APBI greatly reduces the risks that radiation poses to healthy organs and tissues, particularly the lung, as evidenced by the findings reported by Hoekstra *et al.* (56), who demonstrated a 2- to 4-fold risk reduction for secondary cancers with APBI versus WBI. In addition to the many clinical advantages of APBI, this technique also has logistical benefits related to the shorter duration of MC-BT treatment, which implies a significant time saving in the use of linear accelerators, thus increasing the availability of these machines for patients who require EBRT. In turn, this could reduce treatment delays and improve quality of life (57).

APBI treatment

Two schemes for MC-BT–based APBI have been validated in RCTs: eight fractions $\times$ 4 Gy per fraction used in the European Phase III study in which our center participated and seven sessions $\times$ 4.3 Gy per session (24). In both schemes, fractions are administered twice daily with an interval of at least 6 h between fractions. In a Phase II trial carried out at our institution (data not published), we administered 10 fractions of 3.4 Gy based on the scheme developed by Vicini *et al.* (13). In frail and elderly patients, we usually administer a single dose of 16 Gy following the technique described by Hannoun-Lévi (32). The 5-year interim results in terms of survival, toxicity, and cosmesis are encouraging. This scheme allows patients to receive complete treatment after BCS, considering the impact of treatment on the patients' functional status (as defined in the GERICO-O3 Phase II trial) (58). In addition, this single treatment approach greatly reduces the need for travel to the center. In our cohort of elderly patients, 29 patients (median age = 83 years) were treated with this fractionation schedule; however, only 16 of them met the inclusion criteria (pN0). Late treatment-related toxicity was mainly G1 and G2 fibrosis in 50% and 12.5% of cases, respectively, a finding that is consistent with the 5-year outcomes in the French study (32) (31.3% and 12.5%, respectively). In the study by Hannoun-Lévi *et al.*, 76.4% of patients had excellent cosmesis, which is in line with our results (75%), despite the small sample size in our series (n = 16). We did not separately analyze survival outcomes in this subgroup.

All the treatment regimens applied in our study were well tolerated by patients. The optimal fractionation scheme for APBI using MC-BT has not yet been determined, and several different schemes have been described. For example, Polgár *et al.* (23) used a fractionation scheme of 5.2 Gy per fraction for 7 days, achieving significantly better cosmetic results with the high-dose-rate MC-BT implants versus WBI. Other recently published fractionation schedules have also proven to be feasible and safe, such as those described in the Phase I–II multicenter trial by Guinot et al. (59), who applied either four fractions of 6.25 Gy or three fractions of 7.45 Gy in 2 or 3 days, an approach they called "very APBI". Those authors did not observe any differences in acute effects for very APBI compared with those obtained in the GEC-ESTRO Phase III APBI trial (24,46). As described in the ESTRO-ACROP guidelines, different fractionations can be considered, provided that they correspond to a biologically equivalent total dose EQD2 (α/β = 4–5 Gy) ranging from 42 to 45 Gy (28).

Study strengths and limitations

The main limitation of this study is the retrospective design. A second limitation is the use of various fractionation schemes, although this was attributable to three factors: (*1*) the participation of some of our patients in clinical trials, (*2*) changes in approach over the 13-year study period, and (*3*) adjustments to the scheme to suit patient-specific characteristics. Nonetheless, the EQD2 was equivalent in all cases.

By contrast, the main strength of this study is the large number of patients, which is among the five largest single-center studies conducted to date to assess the effectiveness of interstitial MC-BT APBI in patients with ESBC and as a salvage treatment for ipsilateral breast recurrence. Given that MC-BT requires significant experience and surgical skills, another strength of our study is that the technique was performed by only three different brachytherapists over the 13-year study period. This consistency over time may also, at least partially, explain our excellent results.

Conclusions

The findings of the present study support the safety and efficacy of APBI in well-selected patients. Our results confirm previous reports showing low rates of treatment-related toxicity, with excellent LC and survival outcomes at the 5-year followup. Despite the limited number of elderly and frail patients in our cohort, the outcomes obtained in this subgroup suggest that single-dose APBI may be especially appropriate in this subset of patients, although more data are needed to confirm these findings.

Although APBI appears to be well on its way to becoming a standard treatment in ESBC, the optimal technique remains unclear. At present, the choice of technique mainly depends on the experience of the treating center, although the multicatheter technique is the most widely used approach with the longest followup. The long-term outcomes of ongoing clinical trials will help to identify the optimal candidates for ABPI.

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