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Short communication

Accelerated partial breast irradiation with interstitial multicatheter brachytherapy after breast-conserving surgery for low-risk early breast cancer

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ABSTRACT

Patients with low-risk invasive ductal carcinoma treated with breast-conserving surgery (BCS) were included in a multicatheter brachytherapy APBI protocol. The primary endpoint was ipsilateral breast recurrence. Between December 2008–December 2017, 186 low-risk breast cancer patients were treated with APBI using interstitial multicatheter brachytherapy and followed prospectively. At 5-years of follow-up, cumulative local recurrence (LR) and cause-specific survival was 1.1% (95% CI 0.3–1.9) and 98.3% (95% CI 97.3–99.3%) respectively. No grade 3 adverse effects were observed. Postoperative APBI using multicatheter brachytherapy after BCS in early breast cancer patients have excellent rates of local control and survival, without significant toxicity.

1. Introduction

Breast cancer is the most common cancer diagnosed among women in Europe [1]. Currently, postoperative whole breast radiation therapy (WBRT) is considered the standard treatment after BCS [2,3], using hypofractionated schedules [4,5].

Results from the EORTC trial [3] highlights the role of tumour bed treatment in postoperative radiation therapy. Guidelines from GEC-ESTRO [6,7], ASTRO [8–10] and ABS [11,12] defined patients to whom the following could be safely reduced: a) the breast volume irradiated, b) the treatment time, and c) the unneeded radiation exposure to the health tissues. For these reasons, the concept of accelerated partial irradiation (APBI) in early breast cancer after BCS, has gained acceptance.

Multicatheter brachytherapy is a widely accepted APBI technique after several phase II trials [13–15] and an important phase III trial driven by the GEC-ESTRO [16]. These trials, have shown non-inferior APBI local control results compared to WBRT [16], better toxicity profile [17]and quality of life [18].

The aim of the present study was to assess the results on ipsilateral breast recurrence and long term toxicity, in patients with low-risk invasive carcinoma and low-risk ductal carcinoma in situ (DCIS) of the female breast after breast-conserving treatment.

2. Patients and methods

2.1. Eligibility

Eligible for this study were women with early breast cancer who had undergone BCS, axillary dissection or sentinel node biopsy,

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with microscopically clear resection margins and who met the following criteria: age ≥50 years, tumour size ≤3 cm, and pN0 and M0 breast cancer. Patients with lymphovascular invasion and pure DCIS lesions were also considered eligible.

Patients with the following criteria were excluded: age <50 years, multicentricity/multifocality, extensive intraductal component, Paget's disease, pathological skin involvement, synchronous or previous breast cancer, positive lymph nodes, history of other malignant disease, or pregnant or lactating patients.

Patients were followed prospectively under the Spanish RD1566/1998 regulation for Radiation therapy Quality Assurance. The study was approved by the ethics committee and informed consent was obtained from all patients.

2.2. Procedures

Pre-planning computed tomography (CT) and planning CT scans (for treatment planning and documentation of multicatheter brachytherapy) were performed for all patients. Interstitial multiplananr (2–3 planes) implants were placed using a free-hand technique encompassing the surgical cavity with a safety margin. Intraplane and interplane catheter spacing used was 1.5 cm. Dose-volume histogram analysis was performed to evaluate dose coverage, homogeneity, and normal tissue limits.

APBI was delivered with a Microselectron-HDR® unit at a total dose of 32 Gy in eight fractions (8 × 4 Gy) in five days, with a 6 h' minimum interval between fractions. After completing treatment, patients were followed every 3 months for 2 years, every 6 months for the next 3 years, and annually thereafter. Clinical examination included documentation of late adverse effects using the CTCAE 4.0 scale. Follow-up mammography was scheduled annually.

Patients with risk factors for systemic disease received postoperative systemic treatment according to local treatment protocol following multidisciplinary team recommendations.

2.3. Outcomes

The primary endpoint of this study was ipsilateral LR. The secondary endpoints were the incidence and severity of early and late adverse effects, cumulative incidence of regional recurrence and distant metastasis, survival (overall survival, cause-specific survival). Survival curves were generated using the Kaplan–Meier method and compared using the two-sided log-rank test. A probability level of 0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

4. Results

Between December 1st, 2008 and December 11th, 2017, 182 women with early-stage breast cancer after BCS with clear resection margins were included and fully completed the protocol for APBI using multicatheter brachytherapy.

Only 13 cases were pure DCIS. Only 15 infiltrating tumours showed lymphovascular invasion. The most common molecular subtype was luminal (95.6%). Follow-up was closed on February 1st, 2019. The mean follow-up was 69 months (range, 12–124) and the mean age at treatment was 67 years (range 50–92) (Table 1).

At a median follow up of 68 months, only 2 cases have developed local recurrence (LR). The cumulative incidence of LR at 5 years was 1.1% (95% CI, 0.3–1.9) (Fig. 1). One patient relapsed in the tumour bed at 23 months and the other elsewhere in the ipsilateral breast at 14 months. Both recurrences occurred during the prescribed endocrine treatment (ET). One case of regional recurrence was reported (5-year cumulative incidence rate, 99.4 ± 0.06%). The cumulative incidence of distant metastases at 5 years was 1.7% (95% CI, 0.7–2.7) and the 5-year disease-free survival was 97.2% (95% CI, 96–98.4). From the 119 patients with follow-up longer than 60 months, 112 patients (94.1%) were prescribed ET. None of the 103 patients (92%) that completed 5 years of ET and none of the 9 patients (8%) that didn't complete it have developed any recurrence. All recurrences (local, nodal and sistemic) developed during the first 5-year follow-up and all these patients complied with the ET.

The 5-year cumulative cause-specific survival and overall survival rates were 98.3% (95% CI, 97.3–99.3) and 93.2% (95% CI, 91.2–95.2), respectively (Figs. 2 and 3). One out of 15 patients with lymphovascular invasion experienced disease relapsed compared with 1 out of 152 cases with infiltrating tumours without lymphovascular invasion (p = 0.032). One patient developed contralateral breast cancer (0.6%). Nine patients developed second primary cancer (4.8%).

Acute toxicity was mild as radiodermitis (grade 2 in 1 patient), hyperpigmentation (grade 2 in 1 patient) or acute induration (grade 2 in 3 patients) and no grade 3 toxicity was reported. No grade 3–4 late adverse effects were recorded. Grade 2 breast

Table 1
Patient, tumour and postoperative treatment characteristics.

	n = 182
Age (years)	
Median (IQR)	67 (50–92)
>50–60	42 (23%)
>60–70	68 (38%)
>70–80	44 (24%)
>80	28 (15%)
Menopausal status	
Premenopausal	11 (6%)
Postmenopausal	171 (94%)
Histological type	
Ductal	153 (84,1%)
Ductal in situ	13 (7,1%)
Others	16 (8.8%)
Tumour status	
pTis	13 (7.1%)
pT1mi	2 (1.1%)
pT1a	13 (7.1%)
pT1b	65 (35.8%)
pT1c	81 (44.5%)
pT2	8 (4.4%)
Tumour grade	
1	112 (61.5%)
2	58 (31.9%)
3	12 (6.6%)
ER status	
Positive	172 (94.5%)
Negative	10 (5.5%)
PR status	
Positive	157 (86.3%)
Negative	25 (13.7%)
Her2 status	
Positive	6 (3.3%)
Negative	157 (86.3%)
Unknown	19 (10.4%)
Molecular subtype	
Luminal	174 (95.6%)
No luminal subtypes	8 (4.4%)
Chemotherapy	
No	176 (96.7%)
Yes	6 (3.3%)
Endocrine treatment	
Yes	169 (92.9%)
No	13 (7.1%)
Endocrine treatment compliance ≥ 60 months	
Yes	103 (92%)
No	9 (8%)

Data are presented as the number (%) or median (IQR). ER, oestrogen receptor; PR, progesterone receptor.

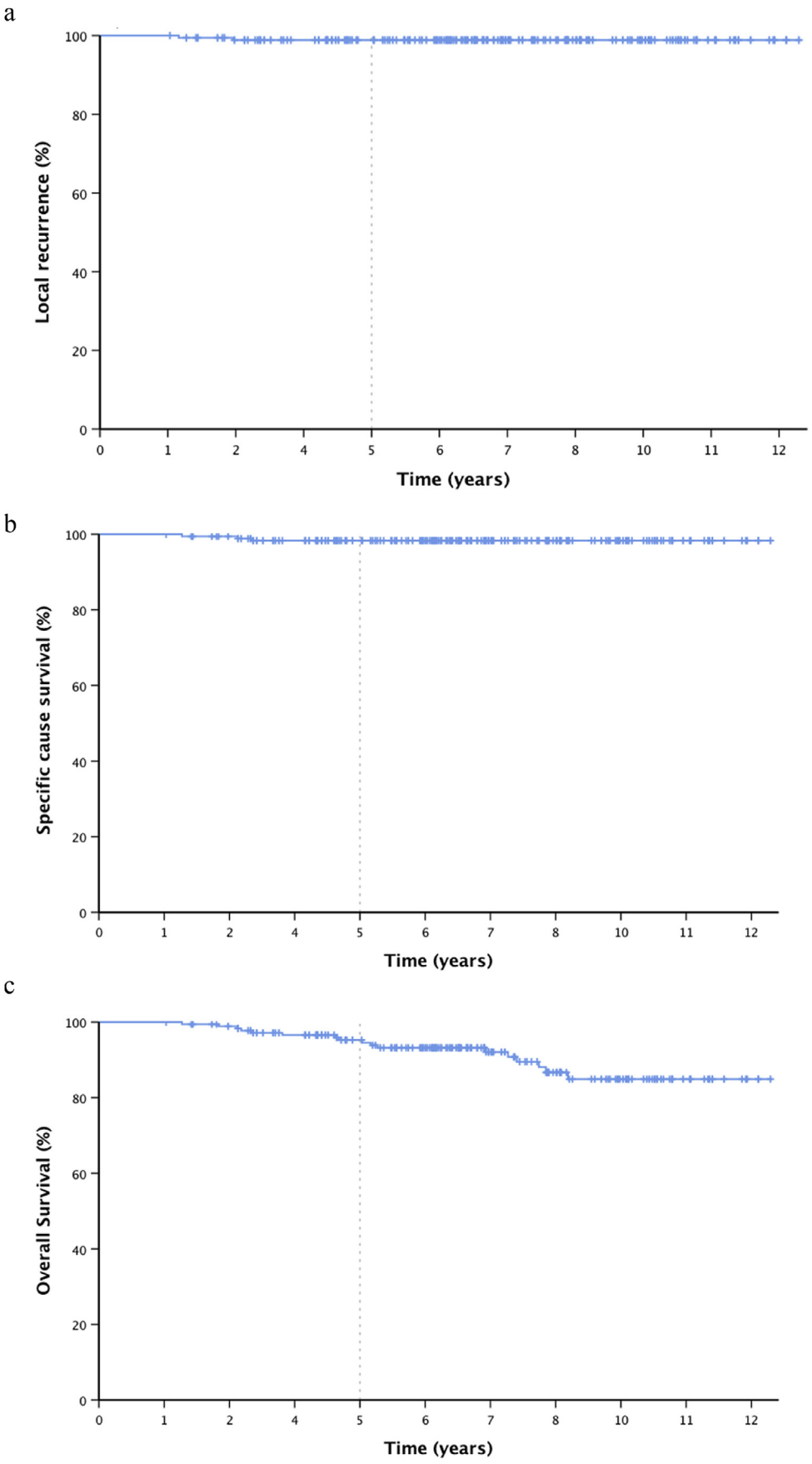

Fig. 1. Kaplan–Meier curve of local recurrence.Fig. 1b Kaplan–Meier curve of cause-specific survival.Fig. 1b Kaplan–Meier curve of overall survival.

induration was observed in 9 patients (5.5%), chronic hyperpigmentation in 1 patient (0.6%), and telangiectasia in 4 patients (2.4%).

5. Discussion

Postoperative radiation therapy after BCS reduce the risk of ipsilateral breast recurrence by about 70% [1,16,19]. A meta-analysis conducted by the EBCTCG showed a reduction in the 10 year first recurrence rate from 35% to 19.3%, and a breast cancer survival gain of 3.8% at 15 years when postoperative radiation therapy was delivered [19]. Several approaches of postoperative radiation therapy have been developed to reduce normal tissue dose [20], including: prone-position technique, IMRT, breathing-adapted IGRT and APBI. APBI offers the largest reduction in radiation dose to surrounding healthy tissues [15,17]. Multicatheter interstitial brachytherapy for APBI has been assessed, in several phase II trials [13–15] and one international phase 3 randomized trial [16,] and shown excellent long-term local tumour control, survival, and cosmetic results with a low-rate of late adverse effects [16,21].

Omission of postoperative whole-breast irradiation for low-risk tumours has been investigated. Pötter [22] reported a higher proportion of local recurrence with no radiation therapy (5.1% vs 0.4%; $p = 0.0001$) and lower 5-year disease-free survival (6.1% vs 2.1%; $p = 0.002$) without significant differences in 5-year overall survival (96.2% vs 97.9%).

Our results demonstrate excellent clinical outcomes following APBI. The 5-year actuarial recurrence rate of 1.1% obtained was comparable to that obtained in previous series that analysed clinical outcomes following APBI. Polgar and colleagues [16] reported a 5-year LR rate of 4.4% and 9.3% at 10 and 12 years respectively. Strnad et al. reported a 5-year LR rate of 1.44%[16]. Mild late adverse effects have been described in our series, similar to those published by the GEC-ESTRO group [16]: grade 2 fibrosis (5.5% vs 7%), grade 2 telangiectasia (2.4% vs 3%) and grade 2 hyperpigmentation (0.6% vs <1%).

In conclusion, our results confirm that postoperative APBI using multicatheter brachytherapy after BCS, is not only as effective as postoperative WBRT for selected patients with early-stage breast cancer, but also provides significantly fewer late adverse skin effects. Moreover, these findings provide clinical evidence to support the use of interstitial multicatheter brachytherapy-based APBI in the treatment of patients with low-risk breast cancer treated with breast-conserving surgery, providing another step in the generalization of this approach. A longer follow-up would be needed to confirm this excellent local relapse rate in this low-risk group of patients.

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Declaration of competing interest

The authors declare no conflict of interest.

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