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Accelerated partial breast irradiation using 3D conformal radiotherapy: Toxicity and cosmetic outcome

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ABSTRACT

Purpose: The aim of this paper is to analyze the incidence of acute and late toxicity and cosmetic outcome in breast cancer patients submitted to breast conserving surgery and three-dimensional conformal radiotherapy (3D-CRT) to deliver accelerated partial breast irradiation (APBI).
Methods and materials: 84 patients were treated with 3D-CRT for APBI. This technique was assessed in patients with low risk stage I breast cancer enrolled from September 2005 to July 2011. The prescribed dose was 34/38.5 Gy delivered in 10 fractions twice daily over 5 consecutive days. Four to five non-coplanar 6 MV beams were used. In all CT scans Gross Tumor Volume (GTV) was defined around the surgical clips. A 1.5 cm margin was added by defining a Clinical Target Volume (CTV). A margin of 1 cm was added to CTV to define the planning target volume (PTV). The dose–volume constraints were followed in accordance with the NSABP/RTOG protocol. Late toxicity was evaluated according to the RTOG grading schema. The cosmetic assessment was performed using the Harvard scale.
Results: Median patient age was 66 years (range 51–87). Median follow-up was 36.5 months (range 13–83). The overall incidence of acute skin toxicities was 46.4% for grade 1 and 1% for grade 2. The incidence of late toxicity was 16.7% for grade 1, 2.4% for grade 2 and 3.6% for grade 3. No grade 4 toxicity was observed. The most pronounced grade 2 late toxicity was telangiectasia, developed in three patients. Cosmetics results were excellent for 52%, good for 42%, fair for 5% and poor for 1% of the patients. There was no statistical correlation between toxicity rates and prescribed doses ($p = 0.33$) or irradiated volume ($p = 0.45$).
Conclusions: APBI using 3D-CRT is technically feasible with very low acute and late toxicity. Long-term results are needed to assess its efficacy in reducing the incidence of breast relapse.

Introduction

Whole breast irradiation (WBI) is the standard of care for early breast cancer patients who receive breast conserving therapy (BCT). With classic WBI schedules, a dose of 50 gray (Gy) in 25 fractions, 5 days per week, for 5 weeks is delivered to the mammary gland. An additional boost of 10–16 Gy to the tumor bed is often prescribed and loco-regional lymph nodes can also be irradiated in selected patients. This approach minimizes the risk of local failure and improves disease-specific survival with acceptable heart, lung and skin toxicity. Its safety has been demonstrated by several meta-analyses, with local failure rates of 0.5–1% per year of follow-up [1].

It has been reported that only the minority of North-American patients who were potential candidates for BCT actually received it [2], although this trend is changing [3]. Many factors contributed to the underutilization of BCT; however, the logistic problem of undergoing 5–7 weeks of daily radiation certainly played a major role, particularly for elderly patients and for those who live at long distances from radiation facilities [4]. Over a 5-year period spanning from 2000 to 2004, patients from Northern Italy faced a reduced probability of receiving a mastectomy [odds ratio (OR)

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0.70; confidence interval (CI) 0.56–0.88]; nevertheless, radiotherapy was not administered in 20.3% of those submitted to breast conserving surgery, with distance from radiotherapy facilities being the most important factor for radiotherapy omission (OR: 1.75; CI: 1.39–2.20 for those at a travel distance of >45 min) [5]. An epidemiological study from our region confirmed these results in 2007 [6].

The possibility to deliver adjuvant radiotherapy either intra-operatively or as a shorter course post-operatively has certainly the potential to increase the acceptance of BCT. Furthermore, the majority of ipsi-lateral breast relapses after BCT occur in close proximity to the lumpectomy cavity. Given these considerations, many clinicians started to question the opportunity of WBI and accelerated partial breast irradiation (APBI) was developed as a possible alternative for patients with early-stage breast cancer.

Several single-institution experiences, phase I/II trials, and, more recently, prospective randomized studies have been conducted to determine the safety and efficacy of APBI [7]. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B39/Radiation Therapy Oncology Group (RTOG) 0432 trial, a three-dimensional (3D) conformal APBI arm has been used to deliver a total dose of 38.5 Gy in 10 fractions, twice daily, over 1 week [8]. This dose has been determined by mathematical and biological modeling [9]. In the present study, the preliminary results of a mono-institutional series of early breast cancer patients treated with a similar conformal ABPI will be reported.

Methods

A phase II trial of APBI was approved by one internal and one external Ethical Committee in 2005. Primary objective of this study was to determine the feasibility, reproducibility, side effects and cosmetics results of the technique. The study population consisted of 84 patients recruited between September 2005 and July 2011 (Table 1). Eligibility criteria were similar to those of the protocol by Vicini et al. [10] and included post-menopausal women (defined as follows: prior bilateral oophorectomy, more than 12 months since last menstrual period with no prior hysterectomy, at least 55 years of age with prior hysterectomy, under 55 years of age with a prior hysterectomy without oophorectomy and with estradiol and follicle-stimulating hormone levels consistent with menopause), with a ≤3 cm invasive ductal carcinoma, absence of an extensive intraductal component (EIC), no skin involvement, and no Paget's disease of the nipple, surgery consisting of a wide local excision with negative surgical margins by at least 2 mm, negative sentinel node biopsy and/or axillary dissection. These clinical and pathologic features where chosen to select patients at low risk of local relapse and are also suggested by the American Society for Therapeutic Radiology and Oncology (ASTRO) [9]. The placement of radiopaque surgical clips delineating the extent of the lumpectomy cavity was mandatory for study entry. A total of 6 clips were positioned after tumor removal delineating the planes of an ideal cube representing the surgical cavity.

3D-conformal radiotherapy (3D-CRT) was performed in accordance with the technique and dose–volume constraints specified in the NSABP/RTOG protocol. Computed tomography-based 3D planning was performed for all patients. CT images were then acquired at 3 mm thick intervals from the level of the mandible through the lung bases. The following structures were outlined: tumor bed, clinical target volume (CTV), planning target volume (PTV), and PTV for evaluation (PTV_Eval). The tumor bed was contoured by means of computed tomography, taking into account postoperative changes and location of surgical clips. The clinical target volume (CTV) was defined as the tumor bed with a 1.5 cm margin, while the minimum distance from skin and chest wall was set at 0.5 cm. The planning target volume (PTV) was defined as the clinical target volume with a 1.0 cm margin. The copied contouring of the PTV was modified to create PTV_eval, which included the PTV but excluded the first 5 mm below the skin surface. The PTV-Eval was used to evaluate the appropriate target coverage.

Table 1
Baseline patient characteristics ($n = 84$).

Variable	Number (%)
Age (years)	
Median	66
Range	51–87
Follow-up (months)	
Median	36.5
Range	13–83
Breast side	
Left	37 (44)
Right	46 (55)
Bilateral	1 (1)
pT Stage	
pT1mi	4 (4.8)
pT1a	9 (11)
pT1b	32 (38.1)
pT1c	38 (45.2)
pT2	1 (1.2)
Histology	
Ductal N.O.S.[a]	72 (85.7)
Mucinous	7 (8.3)
Tubular	3 (3.6)
Intracystic papillary	2 (2.4)
Grading	
1	30 (35.7)
2	34 (40.5)
3	18 (21.4)
n.e.[b]	2 (2.4)
Tumor estrogen receptor status	
Negative[c]	0
Positive[c]	84 (100)
Radiation dose	
34 Gy	60 (71.4)
38.5 Gy	24 (28.6)
Endocrine therapy[d]	83(98.8)
Chemotherapy	0

[a] N.O.S.: Not otherwise specified.
[b] n.e.: Not evaluated.
[c] Negative: <1%, positive ≥1%.
[d] Tamoxifen (3.7%) or aromatase inhibitor (96.4%).

Four to five no-coplanar 6 MV beams arranged tangentially to the breast were used, five fields for the left and four for right breasts respectively. Field arrangements generally approximated breast tangents with a 10°–20° steeper gantry angle for the medial beams to spare breast tissue maximally and couch angles of 15°–70°. The irradiation was performed by Linac Clinac 600 (Varian@), that is equipped with 6 mm micro-multileaf, which provides excellent conformation to the target.

The initial prescription dose was 3.4 Gy twice daily, to reach a total dose of 34 Gy delivered within 1 week. Once acquired sufficient expertise with the technique, after the first 60 patients, we escalated the total dose to 38.5 Gy, at 3.85 Gy per fraction. The fractions were separated by 6 h interval. Plans were evaluated both quantitatively (dose–volume histograms) and qualitatively (isodose curves). Plans were checked for radiation conformity and dose homogeneity indices. The dose–volume constraints were followed in accordance with the specifications dictated in the NSABP/RTOG protocol. In brief, <50% of the whole breast reference volume should receive ≥50% of the prescribed dose and <25% of the whole breast reference volume should receive the prescribed dose. The contralateral breast reference volume should receive <3% of the prescribed dose to any point. Less than 10% of the ipsilateral lung should receive 30% of the prescribed dose and <10% of the contralateral lung should receive 5% of the prescribed dose. For right-sided lesions, <5% of the heart should receive 5% of the

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prescribed dose, while for left-sided lesions the volume of the heart receiving 5% of the prescribed dose (V5) should fall below that for whole-breast radiation with tangential fields.

The whole breast volume (BV) was defined as all tissue delimited by standard whole breast tangent fields, excluding tissues deep to the chest wall such as the lung, heart, pericardial fat, and liver. The volume of breast tissue receiving 5%, 20%, 50%, 80%, and 100% of the prescription dose (V5, V20, V50, V80, and V100, respectively) was recorded.

Adjuvant systemic therapy was prescribed after multidisciplinary evaluation and was mostly based on the most recent San Gallen Expert Meeting Consensus [11].

After treatment, patients underwent clinical evaluation every 3–6 months and screening mammography yearly. Any suspicious abnormalities underwent diagnostic imaging and biopsy, as indicated. Late effects and cosmetic outcome were evaluated at each clinical visit. Late skin and subcutaneous toxicity were evaluated in accordance with the RTOG grading schema. The cosmetic assessment was performed by the physician using the contralateral, untreated breast as the reference. The cosmetic outcome was scored using the Harvard scale [12]. An excellent cosmetic result score was assigned when the treated breast looked like essentially the same as the contralateral one (as it relates to radiation effects). A good cosmetic score was assigned for minimal but identifiable radiation effects of the treated breast. A fair score meant that significant radiation effects were readily observable. A poor score was used for severe sequelae of breast tissue secondary to radiation effects. A patient-based cosmetic evaluation was done by a structured telephone interview. Patients were instructed to assess their outcome according to the standard European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Rating System for Cosmetic Results of Breast Conserving Treatment [13]. In brief, they were asked to compare their treated breast with the untreated breast and grade the following items: breast size and shape, location and shape of areola/nipple, skin color, breast edema, appearance of surgical scar, telangiectasia, and global cosmetic result. Items were graded on the following four-point scale: no difference or excellent, small difference or good; moderate difference or fair, and large difference or poor.

All available follow-up mammograms were retrospectively reviewed by one expert radiologist searching for any visible sign of fat necrosis. Several other parameters such as the time elapsed to the occurrence of fat necrosis, the coexistence of related symptoms as well as the prescription of additional diagnostic procedures to rule out a local relapse, were documented. Any possible relationship between the radiologic diagnosis of fat necrosis and either the dose delivered, the PTV or the cosmetic outcome was also examined.

Statistical analysis was performed using MedCalc Software to evaluate the correlation between PTV volume, fractionation dose, acute/late toxicity, fat necrosis. A *t*-test was performed to evaluate the statistical correlation between PTV, fractionation dose, acute/late toxicity, cosmetic outcome and fat necrosis.

Results

Eighty-four patients were enrolled and available to assess efficacy, cosmesis, and toxicity associated with the procedure. Median age was 66 years (range: 51–87) and median follow-up was 36.5 months (range: 13–83). The most common pathologic finding was invasive ductal carcinoma and mean tumor size was 11 (1–25) mm. Tumor size was <10 mm in 33 patients (53%) and >20 mm in 4 (6%) (Table 1).

Early side effects

Skin acute toxicity of grade 0, 1 and 2 was detected in respectively in 52%, 46.4% and 1% of the patients. No Grade 3 or 4 toxicity was observed. Eight patients reported mild (6 patients) to moderate (2 patients) pain; however, none required medication. No severe acute skin reaction with moist desquamation was observed at 1 and 3 months after completion of APBI (Table 2).

Late side effects

Skin late toxicity of grade 0, 1, 2, 3 was detected in respectively 78.6%, 16.7%, 2.4% and 3.6% of the patients. No Grade 4 toxicity was observed (Table 2). In particular, mild hyperpigmentation was observed at 12 months in 10 patients (11.9%). Two patients had a 4 cm^2 telangiectasia, and 1 patient had a larger than 10 cm^2 telangiectasia (Fig. 1). In this case, the PTV_EVAL/whole-breast volume ratio was larger than 20%. Moreover, the region of teleangiectasia can be seen around a skin fold, which is predictive for the development of this complication.

Twenty patients had grade 1 fibrosis, and 4 patients had a moderate field contracture (grade 2). Sixteen (19.1%) patients had grade 1–2 breast pain at the site of irradiation at a median of 6 months after the end of irradiation (range: 1–28). Among these, 11 patients had occasional breast pain, while 5 patients had pain decreasing with time, but none required any medication.

We retrospectively reviewed the mammograms of 64 patients performed after radiotherapy at our Radiology Department to evaluate the occurrence fat necrosis. In 45 (70.3%) cases we found radiological evidence of fat necrosis in the absence of any clinical symptom. The median time to detection of fat necrosis was 11 months (range: 4–24 months). We did not observe any correlation among fat necrosis and D_{max} ($p = 2.09$), PTV ($p = 1.9$), and breast pain ($p = 3.4$).

In one patient we observed a rib fracture near the tumor cavity one year after the end of radiotherapy in the absence of any reported traumatic event. The CT images and isodose distribution are shown in Fig. 2. The PTV volume/breast ratio was 30% and the treatment was completed in 1 week (July 2011) for a total dose of 3850 cGy and was not prescribed aromatase inhibitors. She had a negative first follow-up visit at 3 months after completion of APBI. In January 2012, six months after the completion of therapy, the patient returned complaining of left chest wall pain. A chest targeted radiograph showed a fracture of the seventh rib. A month later, another X-ray showed a complete healing of the fracture, but with poor calcification of the bone in spite of a normal bone densitometry. Since a subsequent FDG-PET showed a suspicious uptake of the tracer in the region of the seventh rib, the patient was referred to biopsy whose result was negative for breast cancer cells. To date, X-ray shows a complete radiological resolution of the fracture.

Cosmetic outcome and patients' satisfaction

The overall cosmetic outcome with regards to radiation effects was scored in all patients by a single radiotherapist (M.G.) at approximately 6 months of follow up. It was rated as excellent, good, fair and poor in respectively 52%, 42%, 5% and 1% of the patients. At a mean follow up of 49.3 months, patients' assessment of

Table 2
Acute and late toxicity.

Variable	Grade	Number (%)
Acute		
Erythema	G1	39 (46.4)
Late		
Erythema	G1	13 (16.7)
Fibrosis	G2	4 (4.8)
Hyperpigmentation	G1	10 (11.9)
Telangiectasia	G3	3 (3.6)

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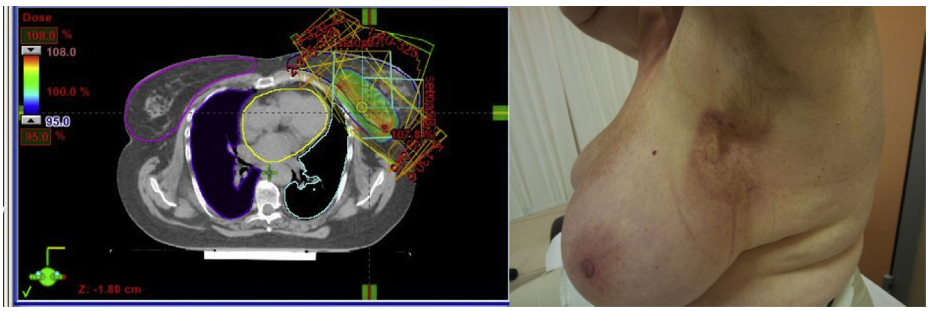

Fig. 1. Treatment plan with axial dose distribution and follow-up picture of the patient with important telangiectasia.

their own overall cosmetic outcome was similarly good (Table 3). Only a minority of the patients judged that the treated breast was "moderately different" when compared with the contralateral breast as far as breast size (7.2%), breast shape and location (6.1%) and shape of the areola/nipple (3.6%) were concerned. Poor results were most frequently attributed to the occurrence of an unpleasant surgical scar (2.4%), displacement of the areola/nipple (1.2%), and telengectasia (1.2%).

Delivery of the planned dose

The PTV/WB ratio was highly correlated with the ability to respect the dose–volume constraints adopted in other protocols of partial breast irradiation. Nevertheless, we treated also patients with large PTV volume as compared to breast volume (50% patients had a ratio of volumes PTV(cc)/WB(cc) $>$ 20%) and, with respect to DVH constraints, we did not observe any correlation between PTV/WB ratio and late toxicity ($p = 0.45$). Furthermore, the comparison between the two groups of patients that received 34 and 38.5 Gy did not reveal any difference in late and acute toxicity ($p = 0.33$).

Local control

No local relapse has been observed to date, whereas one patient developed an axillary lymph-node metastasis, confirmed by biopsy, two years after the end of radiotherapy. Another patient had a distant bone metastasis, sixteen months after the end of radiotherapy.

Discussion

The majority of ipsilateral breast recurrences after BCT occur in close proximity to the lumpectomy cavity [14]. Indeed, multiple randomized trials [15] and retrospective studies [16] comparing lumpectomy alone vs lumpectomy followed by WBI showed no difference in the rate of relapses elsewhere in the breast. On the other hand, numerous attempts to identify a patient population at very low risk for local recurrence after lumpectomy alone have been unsuccessful [17]. This would suggest that the main effect of post-lumpectomy RT is actually a reduction of the recurrence rate in the index quadrant. Therefore, confining RT to the tissues surrounding the tumor bed could be appropriate in selected patients and certainly safer as compared to lumpectomy alone. Specific patient and tumor characteristics best suitable for identifying a subset of patients at low risk of recurrence elsewhere in the breast have been described previously. They include patient age $<$40 years, invasive ductal histology, negative surgical margins by at least 2 mm, and no EIC.

By confining treatment to a limited volume of breast tissue adjacent to the lumpectomy cavity, it is possible to deliver a larger dose per fraction, thereby reducing overall treatment time to approximately 1 week, while maintaining good tumor control and cosmetic results. Multiple APBI modalities have been described and could be divided into two groups: invasive [18] and non-invasive techniques [19]. However, several questions concerning APBI are still unresolved, such as the definition of optimal total dose, dose per fraction and number of fractions, as well as the selection of the best modality to deliver the dose: external vs brachytherapy, IMRT vs 3D-CRT, with the patient in prone vs supine position.

The present study confirms that the 3D-CRT APBI treatment protocol described by Vicini et al. [10] is simple, reproducible and safe. While achieving appropriate PTV coverage, APBI offers significant dosimetric sparing of normal tissues and acceptable late toxicities. Although APBI has recently been recommended by European and American radiation oncology societies, several unanswered questions remain, such as optimal patient eligibility criteria, CTV, PTV and breast definition, technique of dose delivery, dose fractionation, total dose, and dosimetric constraints associated with fewer late side effects.

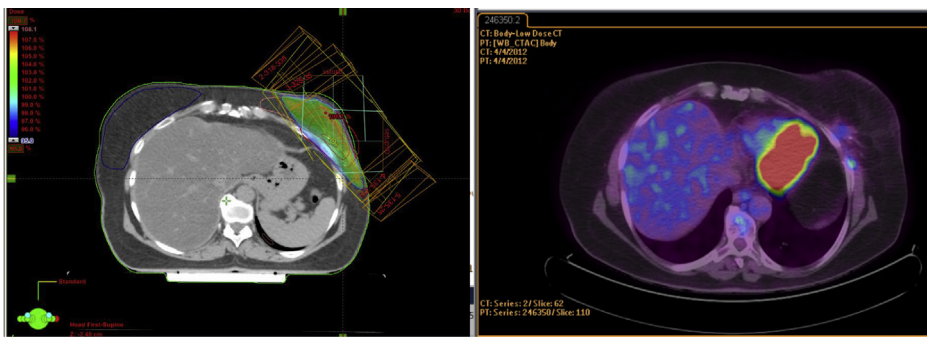

Fig. 2. Treatment plan with dose distribution of the patient with rib fracture. The fractured rib is covered by 100% of isodose.

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Table 3
Patients' assessment of cosmetic outcome of the treated vs the untreated breast.

Parameter	No difference or excellent *n* (%)	Small difference or good *n* (%)	Moderate difference or fair *n* (%)	Large difference or poor *n* (%)
Breast size	42 (50%)	36 (42.8%)	6 (7.2%)	0 (0%)
Breast shape	44 (52.3%)	35 (41.6%)	5 (6.1%)	0 (0%)
Location and shape of areola/nipple	65 (77.4%)	15 (17.8%)	3 (3.6%)	1 (1.2%)
Skin color	62 (73.8%)	20 (23.8%)	2 (2.4%)	0 (0%)
Breast edema	75 (89.3%)	8 (9.5%)	1 (1.2%)	0 (0%)
Appearance of surgical scar	64 (76.2%)	16 (19%)	2 (2.4%)	2 (2.4%)
Teleangectasia	79 (94%)	2 (2.4%)	2 (2.4%)	1 (1.2%)
Global cosmetic assessment	37 (44%)	38 (45.2%)	8 (9.6%)	1 (1.2%)

Our acute and late toxicity results are similar to those of other APBI protocols, even if a proper comparison among studies is hampered by the use of both different acute toxicity (RTOG/EORTC and CTC) and late toxicity (SOMA-LENT and RTOG/EORTC) scales and variable time intervals of follow up assessment. Indeed, in our series the physician's assessment at mean follow up of 6 months revealed 3 cases of G3 teleangectasia, while further 2 cases of respectively mild and moderate teleangectasia were reported by the patients at a mean follow up of almost 50 months (Tables 2 and 3).

In our experience, compliance with treatment was excellent thanks to short treatment duration and lack of associated tiredness, with a reported satisfaction rate of 97.6%. The cosmetic surgical outcome was generally good, likely thanks to the small mean tumor diameter (less than 2 cm in 93% of the cases) and to the frequent adoption of oncoplastic techniques for breast remodeling after tumor removal (Fig. 3). Radiotherapy appeared to slightly worsen the cosmetic results only in a minority of the cases, mainly due to the occurrence of significant fibrosis (4.8%) and teleangectasia (3.6%). Our assessment of cosmetic outcomes was quite favorable, whereas literature data on invasive APBI treatments (brachytherapy, Mammosite), show that cosmetic outcome is rated as fair to poor in nearly 20% of patients [20]. A thorough patients' judgment of their own cosmetic outcomes revealed similar findings, and a very low rate of results rated as "poor". This was expected as it has been already reported that patients tend to evaluate the esthetic outcomes more positively than health care providers [21].

Although 3D-conformal APBI has been described as having better homogeneity of PTV coverage than invasive techniques, some unacceptable toxicities have been recently reported [22,23]. The most frequent moderate complications (grade III) are fibrosis, skin pigmentation changes, pain and telangiectasia, although their overall incidence is below 4%.

In our experience only three patients presented skin telangiectasia in the irradiated area; in one case the breast volume was greater then 1700 cc and in another patient the skin surface was irregular due to a poor cosmetic result after surgery. Some authors emphasize that patients with PTV/WB volume ratios $\geq$0.2 cannot meet the necessary dose–volume constraints, while according to others the limiting CTV/WB volume ratios is $\geq$0.3 (IRMA Italian Trial). In our experience, this parameter had no significant influence on the cosmetic result, even if the only patient with grade 3 telangiectasia had a PTV/WB volume ratio larger than 0.2.

As suggested by Lövey et al. [24], RTOG/EORTC and LENT-SOMA classifications of fat necrosis have limited clinical applicability. We then decided to classify fat necrosis essentially on the basis of its radiological visibility (any sign/no sign) and clinical relevance (symptomatic/non symptomatic). A very sensitive interpretation of signs attributable to fat necrosis by our radiologist may account for its higher occurrence in our series (70.5%) as compared to others (13–36.8%) [24,25]. Nevertheless, in our experience fat necrosis was not correlated with a deterioration of the cosmetic outcome or with the onset of clinical symptoms. This finding is in line with that of a randomized trial that compared the 4-year actuarial rate of fat necrosis after whole breast irradiation, interstitial high-dose-rate brachytherapy and partial-breast electron irradiation (respectively 28.7, 36.8 and 17.5%, respectively) and found that only symptomatic fat necrosis (8.5%, 11.4% and 7.5%, respectively) was significantly associated with a worse cosmetic outcome [24].

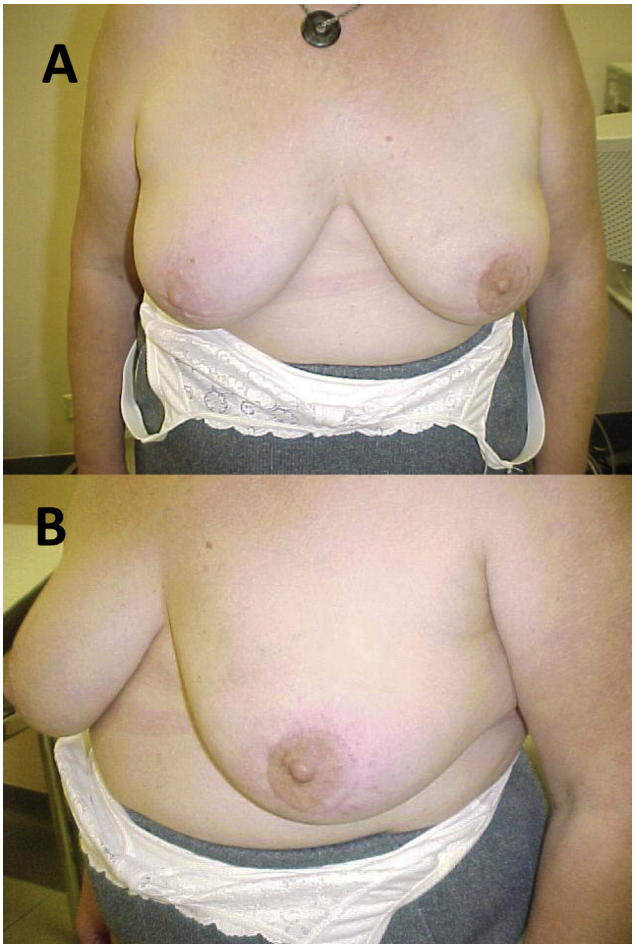

Fig. 3. Cosmetic result at 5 years follow up after a wide local excision with "round block" oncoplastic technique and accelerated partial irradiation for a T1 N0 M0 tumor in the inner quadrants of the left breast. A: frontal view; B: oblique view.

Transient chest wall/rib pain was reported by 19% of our patients of at any point during follow-up. This finding is comparable with that observed in another study of PBI-brachytherapy, in which 19 patients (21.3%) complained of the same symptom.

Conversely, to our knowledge, there is only another paper reporting the occurrence of rib fracture after APBI. Although we believe that a direct causal link cannot be fully demonstrated in our case of rib fracture, skeletal complications of radiation therapy have been well described. In particular, pathologic rib fractures have been reported as a consequence of external beam radiation therapy for breast carcinoma at a dose of 45 Gy. Previous studies have indicated that permanent osseous damage is rare at external beam doses lower than 30 Gy. Nevertheless, in the mature skeleton normal bone reparative processes may be hindered by radiation-induced vascular damage, thus reducing local bone matrix formation and increasing osteopenia with its related risk of fracture.

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In conclusion, we found that 3D-CRT APBI can be safely and effectively delivered in breast cancer patients at low risk of relapse submitted to breast conserving surgery, with excellent patient compliance and low toxicity. Although the occurrence of chest wall pain and rib fractures is quite rare, attempts should be made to keep the volume of rib irradiated at a minimum. Mammary fat necrosis following lumpectomy and post-operative breast irradiation is a common side effect. Management is generally expectant as most patients are asymptomatic and cosmesis is rarely affected, but clinicians should be aware of its occurrence as it may raise the suspect of local relapse at follow up examinations. Although no local recurrence was observed at a median follow up of 36.5 months, the number of expected events is so low that no firm conclusion can be drawn from our data regarding the oncological safety of the procedure.

Conflict of interest statement

All authors must have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work do disclose.

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