Interstitial high-dose-rate brachytherapy after breast conserving surgery

ANTONIO RULLI[1,3], FRANCESCO BARBERINI[3], MICHELE SCIALPI[4], LUCIANO IZZO[7], ILARIA D'ANGELI[8], STEFANIA GORI[1,2], ANGELO SIDONI[1,5], FABIO RONDELLI[3], GIUSEPPE NOYA[3] and CINZIA ARISTEI[1,6]

[1]Breast Unit, [2]Medical Oncology, Perugia General Hospital, Perugia; [3]Department of Surgery, Institutes of [4]Radiology, [5]Pathologic Anatomy and Histology, [6]Radiation Oncology, University of Perugia, Perugia; [7]General Surgery Unit, [8]Department of Heart and Great Vessels 'A. Reale', University of Rome 'La Sapienza' Rome 00161, Italy

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Abstract. We evaluated local recurrence, toxicity rate and cosmetic outcome in 72 patients treated with high-dose-rate (HDR) brachytherapy after breast conserving surgery. HDR brachytherapy was administered: i) as partial breast irradiation (PBI) in 64 patients with low-risk early stage breast cancer, enrolled in a phase II prospective study; ii) as PBI after a second conservative surgery as treatment of local relapse in 3 patients; iii) for delivering a boost after whole breast external beam radiotherapy in 5 patients. Implantation was done during surgery (breast conserving or re-excision to achieve adequate surgical margins), with the wound open, or postoperatively. The implant was well tolerated in all patients, so no premature catheter removal was required. At a median follow-up of 32 months (range 5-52) no local recurrence has been observed. Toxicity was very low. Cosmetic outcome was excellent/good in a high percentage of patients. Our results suggest that PBI administered with HDR brachytherapy is feasible in selected patients with low risk early stage breast carcinoma. PBI seems feasible to repeat radiotherapy after a salvage breast conserving surgery for local relapse in a second attempt to preserve the breast.

Introduction

Treatment of choice for early-stage breast cancer is breast conserving surgery followed by whole breast external bream radiotherapy (RT) which provides similar results to mastectomy (1-6). As external beam RT takes 5-6 weeks and 80-90% of local recurrences after breast conserving treatment are in the tumour bed, whole breast RT could be over-treatment in a high percentage of patients (7). Consequently, trials were designed for partial breast irradiation (PBI), that is the irradiation of the excisional cavity plus a 1-2-cm margin.

PBI is administered using interstitial brachytherapy at low, pulsed or high dose rate (HDR), endocavitary HDR brachytherapy with MammoSite (Proxima Therapeutics, Alpharetta, GA), three dimensional external beam RT in the supine or prone position, intensity modulated RT and intraoperative RT (IORT) with electrons or photons (8-26). Interstitial brachytherapy, the most common modality with the largest series of patients, delivers high doses to small volumes in the tumour bed and spares surrounding tissues. Its main indication in breast cancer is for delivering a boost after whole breast external beam RT. Although the boost is generally administered with external beam radiotherapy, using electrons or photons, brachytherapy distributes the dose better in voluminous breasts and deep located tumours (27).

Brachytherapy is becoming more widespread in PBI after conservative surgery, in patients at low-risk early-stage breast cancer and there are even some reports of using brachytherapy for PBI in patients with isolated breast relapse (28-30).

This study reports results of HDR brachytherapy: i) as PBI after conservative surgery; ii) as PBI after a second conservative surgery as treatment of local relapse; iii) for delivering a boost after whole breast external beam RT.

Materials and methods

From August 2003 to July 2007, 72 patients, who had received breast conserving surgery for breast carcinoma at Breast Unit, Perugia General Hospital, were treated with HDR interstitial brachytherapy.

The phase II experimental PBI protocol was proposed by radiation oncologists and surgeons in the Breast Unit multidisciplinary team, and approved by radiologists, pathologists and medical oncologists. Inclusion criteria were: i) written informed consent; ii) age over 40 years; iii) diagnosis of breast carcinoma ≤ 2.5 cm; iv) no plurifocal lesions; v) suitable breast for brachyterapy; vi) negative lymph nodes; vii) negative

Correspondence to: Dr Ilaria D'Angeli, Policlinico Umberto I, Sapienza University of Rome, Viale del Policlinico 155, Rome 00161, Italy
E-mail: ilaria.d@libero.it

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Table I. Characteristics of patient and histological findings.

Treatment modality	PBI as sole radiation therapy	PBI for local relapses	Boost performed with interstitial brachytherapy
No. of patients	64	3	5
Median age (range) (years)	66 (49-84)	57 (44-64)	65 (56-66)
Histology			
Infiltrating ductal	51 (21 G1, 26 G2, 4 G3)	3 (3 G2)	3 (2 G2, 1 G3)
Infiltrating tubular	1	0	1
Infiltrating papillary	1	0	1
DCIS	11	0	0
Median tumor size (range) (mm)	9 (2-28)	8 (8-11)	6 (3-20)
Estrogen receptors			
Positive	54	2	3
Negative	6	1	1
Not determined	4	0	1
Progesterone receptors			
Positive	43	1	3
Negative	18	2	1
Not determined	3	0	1
Ki-67			
Positive (>25%)	5	1	1
Negative	54	2	3
Not determined	5	0	1
p53			
Positive (>20%)	5	0	0
Negative	49	3	3
Not determined	10	0	2
c-erbB-2			
Positive	3 (2 IHC3$^+$, 1 FISH)	0	0
Negative	54	2	4
nd	7 (1 IHC 2+)	1 (1 IHC 2$^+$)	1

IHC, immunohistochemistry; FISH, fluorescent *in situ* hybridization.

resected margins; viii) absence of the extensive intraductal component; ix) no infiltrated lobular carcinoma or lobular carcinoma *in situ*; x) no Paget disease of the nipple; and xi) no cutaneous infiltration.

All patients underwent breast conserving surgery; 4 or 6 surgical titanium clips were positioned by the surgeon at the boundaries of the excision cavity (superior, inferior, medial, lateral, plus/minus anterior and posterior). Axillary surgery (sentinel lymph node biopsy or axillary dissection) was performed in 64 patients. It was not done in patients in relapse and in 5 of those with ductal carcinoma *in situ*.

HDR brachytherapy was used to administered PBI in 67 patients (64 with stage I/II disease; 3 with a single local relapse after a conservative surgery followed by whole breast RT), and to administer a boost in 5 patients, 3 of whom did not satisfy histological inclusion criteria in experimental PBI trial. Table I describes patient characteristics and histological findings reported according to the aim of treatment.

Implantation was done during surgery (breast conserving or re-excision to achieve adequate surgical margins), when the wound was open, or at a median of 8 weeks post-operatively for patients enrolled in the PBI trial and those treated with PBI for local relapse. In patients who received a boost, implantation was performed during surgery or after whole breast RT. Table II reports surgical details and implantation timing according to the aim of treatment.

When implantation was done intraoperatively, before starting the procedure, the radiation oncologist evaluated the geometry and dimensions of the excisional cavity and the breast size and decided the number of plans and catheters

Table II. Surgical details and implantation timing.

Treatment modality	PBI as sole radiation therapy	PBI for local relapses	Boost performed with interstitial brachytherapy
Axillary surgery			
Sentinel node biopsy	47	0	3
Axillary dissection	12	0	2
No treatment	5	3	0
Implantation timing			
During surgery	14	1	3
After surgery	50	2	2

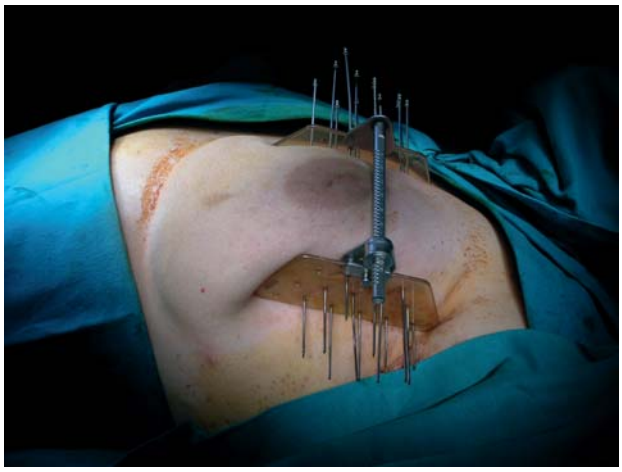

Figure 1. Needle implantation. A triangular plastic template and a metal template holder are used.

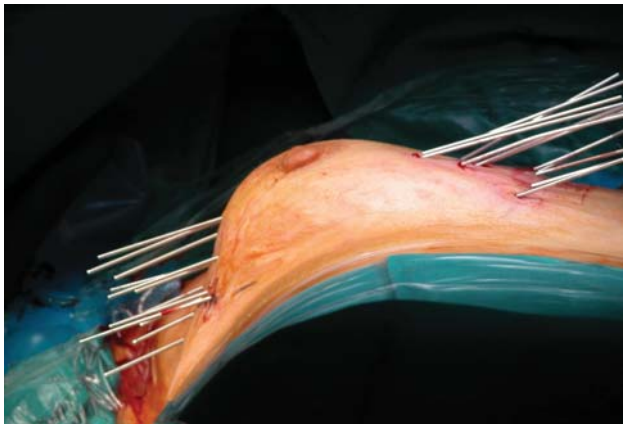

Figure 2. All needles are implanted.

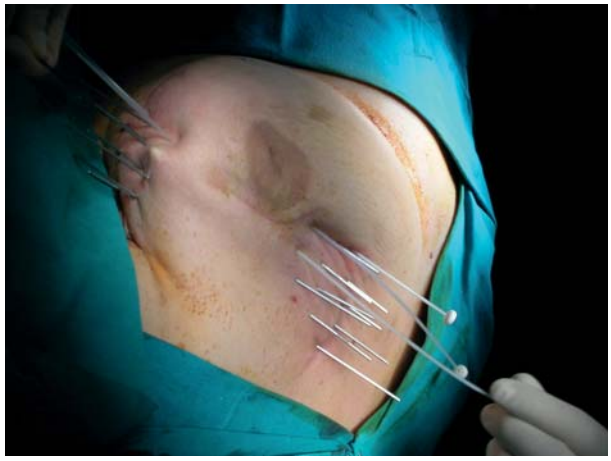

Figure 3. Needels are replaced with plastic catheter.

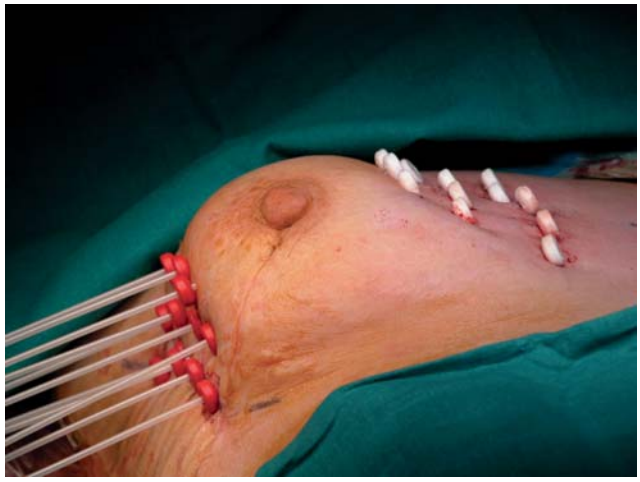

Figure 4. All catheters are implanted; the cavity is closed.

needed for good coverage of target volume. Needles were implanted using a triangular plastic template and a metal template holder. After needle placement the template and the holder were removed and the needles were replaced with flexible catheters. Positioning the implant required about 20 min beyond standard operating times. The wound was closed after implantation.

Before post-operative implants patients underwent a breast computed tomography (CT) scan to define implant geometry (31). The implantation procedure followed the same steps previously described. In Figs. 1-7 different implantation steps are indicated. Only in 2 of the 5 patients treated with brachytherapy to received the boost, needles were not replaced with catheters.

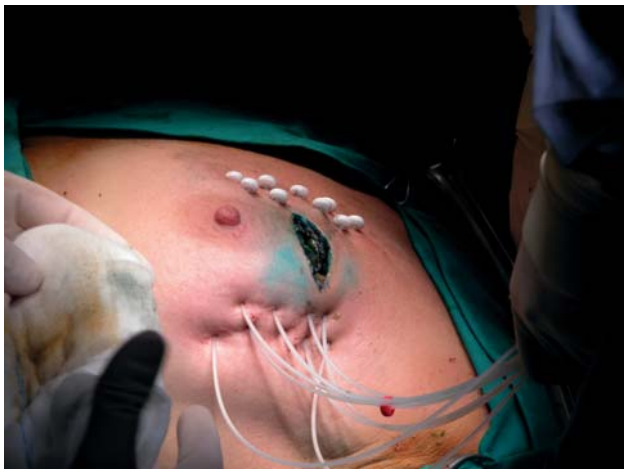

Figure 5. Implantation done during surgery, with an open wound.

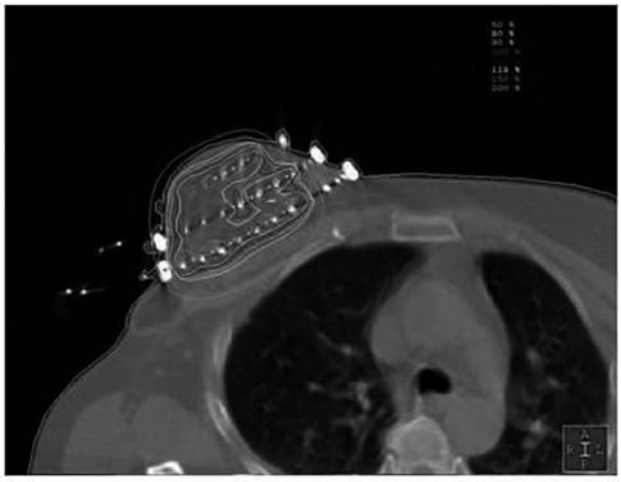

Figure 7. A 3-plane implant and dose distribution in planning target volume.

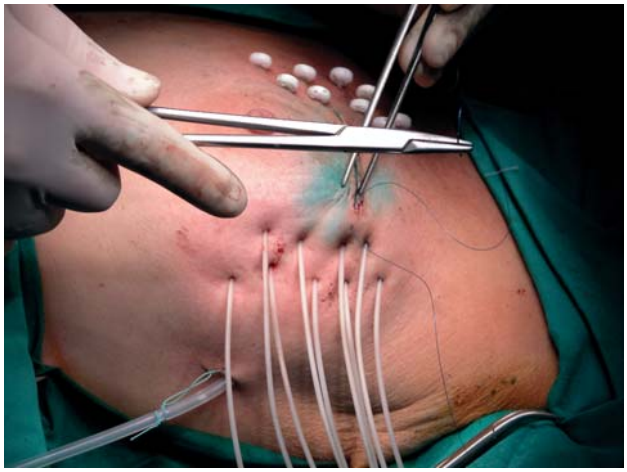

Figure 6. Wound closure after implantation.

After implantation, a breast CT served to evaluate implant placement and perform dosimetry. Doses varied with treatment. Patients enrolled in the PBI phase II study received a total dose of 32 Gy in 8 fractions (4 Gy twice a day, separated by at least 6 h), over 4 consecutive days. One patient treated with PBI for local relapse received a total dose of 24 Gy (3 Gy twice a day, separated by at least 6 h, for 4 consecutive days), while in the other 2 the same schedule adopted in the phase II trial was employed (4 Gy twice a day, separated by at least 6 h, for 4 consecutive days, up to 32 Gy). The boost dose was 9 Gy, administered in a single fraction, in 2 patients and 4 Gy up to a total dose of 12 Gy in the other 3.

Treatment was performed by a Nucletron microSelectron HDR^{192} Ir remote afterloading system (Nucletron, B.V., Neenendaal, The Netherlands).

Adjuvant chemotherapy and/or hormonal therapy were prescribed after discussion of each case by multidisciplinary breast-cancer group.

Patients were followed up for 2-3 weeks after implant removal for medication and control of any perioperative complications related to brachytherapy and/or surgery.

Check-ups were performed every 3 months for the first two years and then every 6 months. Mammography was done 6 months after brachytherapy and then yearly.

At each check-up treatment-related toxicity and cosmetic results were assessed. Cosmesis was evaluated on the Harvard criteria (32) as follows: excellent, perfect symmetry, no skin alterations, no visible catheter entry/exit sequelae; good, slight skin distortion, retraction or edema, any visible teleangectasia, any visible catheter entry/exit scar, or mild hyperpigmentation; fair-moderation distortion of the nipple or breast symmetry, moderate hyperpigmentation, or prominent skin retraction, edema or telangiectasia; poor, marked distortion, edema, fibrosis, or severe hyperpigmentation.

Results

The implant was well tolerated in all patients, so no premature catheter removal was required. At a median follow-up of 32 months (range 5-52), no local recurrence has been observed. Transient erythema and hyperpigmentation around catheter entrance and exit points, were observed. Eight patients (11%) developed teleangectasia and 1 fat necrosis, which manifested as a palpable mass. The cosmetic outcome was excellent, good, and fair/poor in 74, 23 and 3% of patients respectively.

Discussion

The results of our study confirm that PBI administered with high-dose-rate brachytherapy is feasible in selected patients with early stage breast carcinoma. At a median follow-up of 32 months no local recurrence has been observed, toxicity was low and cosmetic outcome excellent or good in a high percentage of patients. However, as we are still awaiting the results of ongoing phase III randomized trials, PBI must be considered an experimental treatment that can be administered only under protocols approved by the Ethics Committee after the patient has provided specific informed consent. Participation in this PBI trial necessarily modified some surgical approaches. First, instead of quadrantectomy, the surgical breast conserving procedure which is widespread

in Italy, we made a wide excision. Secondly, titanium clips were placed at the cavity border so that the surgical cavity could be located precisely on post-implant CT. Data from literature report that, unfortunately, clips are not always left. For this reason, techniques to localize the surgical cavity on pre-implant CT have been described (32). Instead clips have to be placed on the excision cavity borders when they are re-approximate or when implant is performed during surgery; this is in fact the only way to localize the target volume on CT slices. When implantation was done intraoperatively, the pathologist had to provide some histological data, such as histological type, margin status and information on the sentinel lymph node involvement before implantation. However, the pathologist could not give results of the microscopic margin and extensive intraductal component status or perform a full sentinel node analysis. Therefore, therapy was started in patients implanted during surgery only after the definitive histological diagnosis had been received.

One of the main advantages of PBI is the lack of delay in administering RT after surgery. As treatment is completed before initiating adjuvant chemotherapy, the timing of administration of the different therapeutic modalities can be optimized. Another advantage is that PBI provides a better quality of the life because RT can be completed while the patient is in hospital for surgery (33).

In 3 selected patients PBI was administered to repeat RT after a salvage breast conserving surgery for local relapse in a second attempt to preserve the breast. Even though mastectomy is standard treatment of local breast carcinoma recurrence after conservative therapy, there are some encouraging preliminary reports of a conservative approach followed by PBI administered with brachytherapy which offers a second chance. In our patients the approach was well-tolerated and results indicated it seemed feasible, even though, due to the very low number of treated patients, definitive conclusions can not be drawn.

Finally, in 5 patients brachytherapy was employed to administered a boost. Although brachytherapy is one modality for delivering the boost after external bream whole breast RT, its use is not widespread since brachytherapy facilities are not available in all centres. In our limited series 3 patients had been implanted during surgery to receive PBI, but histological findings precluded it. In 2 patients, with very large breasts and a deep localized tumour, treatment was given in a single dose of 9 Gy after whole breast RT. In these case catheters were not implanted and needles were used.

In conclusion, we would like to underline the importance of interdisciplinary discussion of therapeutic approaches to patients with breast carcinoma. Our Breast Unit gives the professional involved in diagnosis and treatment of breast cancer the opportunity to choose the best treatment for each patient, including PBI.

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