

# Reexcision and perioperative high-dose-rate brachytherapy in the treatment of local relapse after breast conservation: an alternative to salvage mastectomy

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## Abstract

**Purpose:** To evaluate the feasibility and efficacy of second breast-conserving surgery with reirradiation using perioperative high-dose-rate interstitial brachytherapy for the treatment of local recurrence developing after previous breast-conserving therapy.

**Material and methods:** Between 1999 and 2007, twelve patients with isolated local recurrence initially treated for breast carcinoma with the use of conservative surgery and radiation therapy, underwent a repeat breast-conserving surgery and perioperative high-dose-rate multicatheter brachytherapy. Breast cancer related events, late side effects, and cosmetic results were assessed retrospectively.

**Results:** At a median follow-up of 56 months (range: 8-112) second local recurrence has not occurred, yielding a 100% mastectomy-free survival. Four patients (33.3%) developed subsequent distant metastasis and died of breast cancer. The 5-year actuarial rate of disease-free, cancer-specific, and overall survival was 65.6%, 78.6%, and 78.6%, respectively. Cosmetic results were rated good, fair, poor and unknown in 6 (50%), 2 (17%), 1 (8%) and 3 (25%) patients, respectively. Grade 2 skin toxicity and fibrosis occurred in 1 (8%) and 2 (17%) patients. Asymptomatic fat necrosis was detected in 6 (50%) women. No patient developed grade 3-4 late side effects.

**Conclusions:** Second breast-conserving surgery followed by partial breast reirradiation is a safe and effective option for the management of selected patients developing local recurrence after previous breast-conserving therapy. Perioperative high-dose-rate brachytherapy with adequate fractionation may decrease the risk of second local relapse with acceptable cosmetic results and low rate of late side effects.

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**Key words:** breast cancer, local recurrence, reirradiation, HDR brachytherapy.

## Purpose

Breast-conserving surgery (BCS) and postoperative radiotherapy (RT) became widely accepted for the treatment of early-stage invasive breast cancer in the last four decades [1, 2]. In spite of adequate BCS and RT, the rate of ipsilateral breast tumour recurrence (IBTR) is approximately 10% [2-4]. In such cases salvage mastectomy is the standard treatment, however wide reexcision of the recurrent tumour is also a reasonable option for selected patients [4-16]. The incidence of second local recurrence (LR) after repeat conservative surgery has been reported in the range from 7 to 50% [5-7, 9-13, 15, 16].

Theoretically, reirradiation after second BCS may decrease the chance of second LR [4, 17]. However, reirradiation of the whole breast with a significant dose is considered inappropriate because of the high risk of serious late side effects. Interstitial multicatheter brachytherapy (BT) was successfully used to deliver an additional (boost) dose limited to the vicinity of the tumour bed following whole breast irradiation (WBI), or as the sole radiation treatment after BCS [18-24]. Due to the ability of focusing radiation dose by BT to a limited volume (while sparing surrounding normal tissues), intraoperative implantation and perioperative BT is a promising method to retreat the tumour

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bed with an effective dose after previous BCS and WBI [25-33].

Therefore, the aim of this study was to evaluate the feasibility and efficacy of second breast-conserving operation with reirradiation using perioperative high-dose-rate (HDR) interstitial BT for the treatment of IBTR developed after previous breast-conserving therapy.

## Material and methods

### Treatment of initial breast cancer

Between March 1999 and June 2007, twelve patients initially treated for breast carcinoma by conservative surgery and RT who had isolated IBTR underwent repeated BCS and perioperative HDR multicatheter BT. Patient, tumour, and treatment characteristics for the initial breast cancer are summarized in Table 1. Initially all patients underwent a wide excision and level I-II axillary dissection. Postoperative RT consisted of 46 to 50 Gy WBI administered by two tangential 6-9 MV photon beams with conventional fractionation (2 Gy/day, 5 fractions/week). Seven patients (58%) received a tumour bed boost of 8 to 16 Gy using 6-15 MeV direct electron fields. 46 to 50 Gy regional nodal RT was given to 3 patients (25%).

### Treatment of ipsilateral breast tumour recurrence

Patient, tumour, and treatment characteristics for LR are summarized in Table 2. Wide reexcision of the re-

current tumours were performed under general anesthesia. During reoperation the walls of the excision cavity were marked with 4 to 6 surgical clips. Afterwards, with the surgical wound open, 4 to 10 guide needles in 1 to 3 planes were placed in the tumour bed, spaced 15-20 mm apart (Fig. 1A). The guide needles were replaced with plastic catheters and secured with fixation buttons. After implantation the wound was closed with sutures (Fig. 1B). On the second postoperative day isocentric X-ray films were taken of the implanted breast and a computerized treatment planning was performed. The active source positions in each catheter and the reference dose points were defined to deliver 100% of the prescribed dose to the clipped area with 1 cm margin in each direction excluding the pectoral muscle and 5-mm

**Table 2.** Patient, tumour, and treatment characteristics for local recurrence

| Characteristic   | Study population (n = 12)              |
|--|--|
| Mean age (years)<br>range                                  | 58<br>37-78                            |
| Premenopausal  | 4 (33%)                                |
| Mean time to LR (months)<br>range                          | 78.5<br>37-136                         |
| Type of LR<br>tumour bed recurrence<br>elsewhere failure   | 8 (67%)<br>4 (33%)                     |
| Histologic type<br>ductal<br>lobular                       | 11 (92%)<br>1 (8%)                     |
| Mean tumour size (mm)<br>range                             | 16.2<br>8-40                           |
| Margin status<br>close ( $\leq 2$ mm)<br>clear ( $> 2$ mm) | 5 (42%)<br>7 (58%)                     |
| HG<br>1<br>2<br>3  | 3 (25%)<br>5 (42%)<br>4 (33%)          |
| Hormonal status<br>ER+ PR+<br>ER+ PR-<br>ER- PR-<br>UK     | 8 (67%)<br>1 (8%)<br>2 (17%)<br>1 (8%) |
| RT dose (dose [Gy] $\times$ fraction no.)                  | 4.4 $\times$ 5                         |
| Implant planes<br>single<br>double<br>triple               | 8 (67%)<br>3 (25%)<br>1 (8%)           |
| Median catheter no.<br>range                               | 5<br>4-10                              |
| Systemic therapy<br>CHT<br>HT<br>none                      | 3 (25%)<br>8 (67%)<br>1 (8%)           |

LR – local recurrence, HG – histological grade, ER – estrogen receptor, PR – progesterone receptor, RT – radiotherapy, UK – unknown, CHT – chemotherapy, HT – hormonal therapy

**Table 1.** Patient, tumour, and treatment characteristics for initial breast cancer

| Characteristic  | Study population (n = 12)                |
|---|--|
| Mean age (years)<br>range                               | 52<br>34-71                              |
| Premenopausal   | 5 (42%)                                  |
| Histologic type<br>ductal<br>ductal + lobular           | 11 (92%)<br>1 (8%)                       |
| TNM stage<br>pT1 pN0<br>pT2 pN0<br>pT1 pN1a<br>pT2 pN1a | 7 (58%)<br>2 (17%)<br>2 (17%)<br>1 (8%)  |
| HG<br>1<br>2<br>3<br>UK                                 | 2 (17%)<br>5 (42%)<br>3 (25%)<br>2 (17%) |
| Mean RT dose (Gy)<br>range                              | 55.8<br>48-66                            |
| Systemic therapy<br>CHT<br>HT<br>none                   | 5 (42%)<br>2 (16%)<br>5 (42%)            |

HG – histologic grade, RT – radiotherapy, UK – unknown, CHT – chemotherapy, HT – hormonal therapy

rim of subcutaneous tissue beneath the skin. The distances of reference dose points from the catheters were 7 to 11 mm. Patients were treated with a HDR afterloading equipment using the iridium-192 isotope. The irradiation commenced 48 hours after salvage surgery. The prescribed total dose of 22 Gy consisted of 5 fractions of 4.4 Gy, each given at least 6 hours apart and with a twice-a-day fractionation over 3 days. After the last fraction, the catheters were removed and the patients were discharged on the following day.

#### *Follow-up and statistical analysis*

Patients were seen every 3 months in the first 2 years after salvage treatment and every 6 months thereafter. Mammography, breast and abdominal ultrasound examinations, chest X-ray, and blood tests were performed annually. In case of uncertain mammography and ultrasound findings, breast MRI and/or aspiration cytology of suspicious lesions were performed to differentiate between second LR and localized fibrosis or fat necrosis. The cosmetic results were assessed using the Harvard criteria [34]. Skin side effects and fibrosis were scored by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scoring scheme [35]. All available mammography films were carefully reviewed for asymptomatic fat necrosis (i.e. oil-cysts and/or coarse calcifications).

All time intervals were calculated from the date of salvage surgery. The actuarial rates of specific events and survivals were calculated using the Kaplan-Meier method [36]. The SOLO software (Department of Biometrics, University of California, Los Angeles, CA, USA) was used for statistical analyses.

## Results

#### *Treatment outcome*

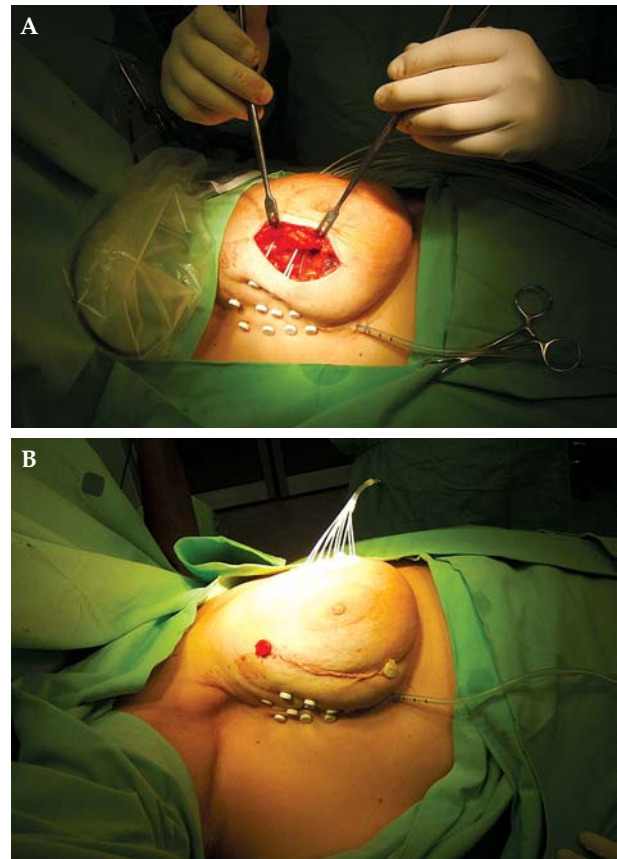
At a median follow-up of 56 months (range: 8 to 112 months) after IBTR second LR has not occurred, yielding a 100% mastectomy-free survival. Overall, 4 patients (33.3%) developed subsequent distant metastases 3 to 33 months after IBTR and died of breast cancer within 8 to 84 months after salvage treatment. Thus, at the end of follow-up period 8 patients (66.7%) were alive with no evidence of disease. The 5-year actuarial rate of disease-free, cancer-specific, and overall survival was 65.6%, 78.6%, and 78.6%, respectively. Two patients (17%) developed second primary malignancies including one hypernephroma and one colon cancer diagnosed in 41 and 53 month after breast LR. No regional nodal failure or contralateral breast cancer occurred during the follow-up period.

#### *Cosmetic results and side effects*

The cosmetic results and late radiation side effects are listed in Table 3. Among the patients for whom cosmetic results data were available, the rate of good cosmetic results was 66.7% (6 out of 9 patients) (Fig. 2). No patient developed grade 3-4 late side effects. All fat necroses were asymptomatic and required no surgical intervention.

## Discussion

Mastectomy has been considered the standard treatment for IBTR after previous breast-conserving therapy [5-8, 14, 15]. However, second BCS was also reported by several authors as a viable alternative in selected cases (Table 4) [5-7, 9-13, 15, 16]. The largest study



**Fig. 1.** (A) Reexcision and intraoperative implantation with 10 flexible afterloading catheters for perioperative interstitial HDR brachytherapy of the tumour bed. (B) The wound is closed by sutures, the ends of each catheter are secured with plastic buttons



**Fig. 2.** Good cosmetic result with slight hyperpigmentation and minimal fibrosis 43 months after reexcision and perioperative HDR brachytherapy

comparing salvage mastectomy to second conservative surgery was reported by Salvadori *et al.* [15]. Fifty-seven out of 190 (30%) intramammary recurrences were reoperated with further local resection. The incidence of second IBTR at 5 years was higher in the reexcision group (19%), compared to the mastectomy group (4%), however, there was no significant difference in survival between the two groups. Kurtz *et al.* [12] reported 62%

5-year local control and 67% overall survival after conservative reoperation. Both authors concluded that reexcision is a particularly satisfactory alternative to salvage mastectomy for selected cases and further studies are required in order to refine the indications. In our previous study, the rate of second LR following salvage excision or mastectomy was 28% (9 of 32) and 16% (5 of 32), respectively ( $p = 0.2265$ ) [9]. Furthermore, the type of salvage surgery (mastectomy vs. repeat wide tumour excision) was not a significant predictor of postrecurrence survival, and for patients with  $\leq 2$  cm in-breast recurrence 10-year survival was 81% after both salvage modalities. Others reported an incidence of second LR after repeat conservative surgery in the range of 7 to 50% [5-7, 10, 16].

Reirradiation after second BCS may decrease the chance of second LR [4, 17]. However, reirradiation of the whole breast with significant dose is considered inappropriate because of the high risk of serious late side effects. In the study of Deutsch *et al.* [17], 39 women with an IBTR after lumpectomy and breast irradiation were treated with excision of the IBTR and 50 Gy RT to the operative area using electrons. The repeat course of RT to the new operative area was well tolerated, and no late sequel occurred other than skin pigmentation changes. After a median follow-up of 51.5 months, 8 patients (21%) developed another IBTR.

As interstitial BT was successfully used for partial breast irradiation, several groups suggested partial breast BT as a possible treatment option to decrease the chance of second LR after repeat BCS (Table 5) [4, 25-33].

Maulard *et al.* [29] treated 15 patients by limited tumourectomy plus 30 Gy perioperative low-dose-rate (LDR) BT for a 2.4 cm mean diameter isolated LR. With a median follow-up of 40 months, four patients (26.7%) experienced second LR.

**Table 3.** Cosmetic results and late radiation side effects

| Variable          | Study population<br>(n = 12) |
|-------------------|------------------------------|
| Cosmetic results  |                              |
| excellent         | 0 (0%)                       |
| good              | 6 (50%)                      |
| fair              | 2 (17%)                      |
| poor              | 1 (8%)                       |
| UK                | 3 (25%)                      |
| Skin side effects |                              |
| grade 0           | 3 (25%)                      |
| grade 1           | 5 (42%)                      |
| grade 2           | 1 (8%)                       |
| grade 3           | 0 (0%)                       |
| UK                | 3 (25%)                      |
| Fibrosis          |                              |
| grade 0           | 5 (41%)                      |
| grade 1           | 2 (17%)                      |
| grade 2           | 2 (17%)                      |
| grade 3           | 0 (0%)                       |
| UK                | 3 (25%)                      |
| Fat necrosis      |                              |
| asymptomatic      | 6 (50%)                      |
| symptomatic       | 0 (0%)                       |

UK – unknown

**Table 4.** Results of second conservative surgery (without radiotherapy) versus salvage mastectomy

| Institution                 | Median FUP<br>(years) | No. of patients |        | Crude 2 <sup>nd</sup> LR% (n) |          | 5-y 2 <sup>nd</sup> LR% |        | 5-y OS% |        |
|-----------------------------|-----------------------|-----------------|--------|-------------------------------|----------|-------------------------|--------|---------|--------|
|                             |                       | CS              | vs. MT | CS                            | vs. MT   | CS                      | vs. MT | CS      | vs. MT |
| EIO, Milan [15]             | 6.1                   | 57              | 133    | 14% (8)                       | 3% (4)   | 19%                     | 4%     | 85%     | 70%    |
| HNIO, Budapest [9]          | 13.8                  | 32              | 32     | 28% (9)                       | 16% (5)  | NR                      | NR     | 77%*    | 55%*   |
| Karolinska Hosp. [7]        | 6                     | 14              | 65     | 50% (7)                       | 18% (12) | 33%                     | 12%    | NR      | NR     |
| Dutch Study Group [16]      | 4.3                   | 20              | 229    | 40% (8)                       | 22% (51) | NR                      | NR     | NR      | NR     |
| Yale-New Haven Hosp. [6]    | 13.8                  | 30              | 116    | 7% (2)                        | 7% (8)   | NR                      | NR     | 66%†    | 58%†   |
| Osaka Medical Center [10]   | 3.6                   | 30              | 11     | 30% (9)                       | 0% (0)   | 37%‡                    | 0%     | 90%     | 91%    |
| JCRT, Boston [5]            | 3.25                  | 16              | 123    | 31% (5)                       | 6% (7)   | NR                      | NR     | NR      | 79%    |
| Marseille Cancer Inst. [13] | 2.9                   | 34              | 36     | 9% (3)                        | 3% (1)   | 22%                     | 4%     | NR      | NR     |
| Marseille Cancer Inst. [11] | 6                     | 52              | –      | 23% (12)                      | –        | 21%                     | –      | 79%     | –      |
| Marseille Cancer Inst. [12] | 4.25                  | 50              | –      | 32% (16)                      | –        | 38%                     | –      | 67%     | –      |
| University Pennsylvania [8] | 3.7                   | –               | 112    | –                             | 3% (3)   | –                       | NR     | –       | 86%    |
| All patients                | 2.9-13.8              | 335             | 857    | 24% (79)                      | 11% (91) | 19-38%                  | 0-12%  | 66-85%  | 55-91% |

FUP – follow-up period, 2<sup>nd</sup> LR – second local recurrence, OS – overall survival, CS – conservative surgery, MT – mastectomy,

EIO – European Institute of Oncology, HNIO – Hungarian National Institute of Oncology, NS – not stated, JCRT – Joint Cancer for Radiation Therapy

\* 10-year actuarial rate for cancer-specific survival

† 10-year actuarial rate

‡ 3-year actuarial rate

In the combined series from Marseille and Nice, 69 patients with LR received a second lumpectomy followed by interstitial LDR BT [25, 28]. The dose of salvage BT was 30 Gy ( $n = 24$ ) in Nice and 45-50 Gy ( $n = 45$ ) in Marseille. Eleven patients developed a second in-breast recurrence, yielding a 5-year actuarial LR rate of 22.6%. Grade 3 late complications occurred in 8.7% of patients. A significantly higher rate of grade 2-3 side effects was associated with a total dose (initial RT plus salvage BT) above 100 Gy (30% vs. 4%;  $p = 0.008$ ). The authors recommended the delivery of LDR BT dose of at least 46 Gy using double-plane implants after initial WBI of 50 Gy.

Authors from the Beth Israel Medical Center, New York have reported the initial experience of a phase I-II study evaluating the feasibility of a second lumpectomy and breast BT for localized LR previously treated with BCS and RT [26]. The first 6 patients received an LDR BT dose of 30 Gy, while BT dose was increased to 45 Gy for the remaining 9 women. At a median follow-up of 36 months, only one patient (6.7%) developed a second LR. The 3-year rate of LR was 11% without a negative impact of BT on the eventual cosmetic results.

Till date, only one series used interstitial HDR BT after repeat BCS to treat locally recurrent breast cancer [27]. Overall 41 patients with breast-only recurrences after conservative treatment were treated with second lumpectomy followed by HDR BT of 30 Gy in 12 fractions over 5 days. The actuarial 12-year second LR rate was only 14.8%, and cosmetic results were satisfactory in 90%.

Another series used PDR BT after repeat BCS to treat locally recurrent breast cancer [32]. Eight patients underwent combination of PDR BT (12.5-28 Gy) and external beam RT (12-30 Gy), while nine patients were treated with PDR BT (40-50 Gy) alone. At a median follow-up of 5 years, none out of nine patients treated with PDR BT had a second LR.

Recently, investigators from the Allegheny General Hospital, Pittsburgh reported their experience in relation

to 26 patients treated with lumpectomy and LDR interstitial BT ( $n = 22$ ) or HDR intracavitary BT ( $n = 4$ ) using the MammoSite® and Contura® applicators [33]. Twenty-five out of 26 patients (96%) remained free of second LR with a median follow-up of 38 months.

In the present study, all patients were controlled locally with the use of second conservative surgery and perioperative HDR multicatheter BT. Reirradiation with HDR BT did not compromise cosmetic results and did not cause severe (grade 3-4) late side effects.

Based on the promising results of single-institution studies, both European and American experts proposed multicentric phase II-III clinical trials to test the safety and efficacy of repeat BCS and partial breast BT for the management of in-breast LRs [4, 25, 28, 30, 31]. An optimal patient selection for such studies would include women with unicentric IBTRs measuring < 2 cm without concurrent regional and distant recurrence diagnosed at least 3 years after the initial treatment of breast cancer [4].

## Conclusions

In conclusion, reexcision is a practicable alternative to mastectomy for the treatment of isolated, solitary, parenchymal IBTR after previous breast-conserving therapy. Perioperative HDR BT with adequate fractionation may decrease the risk of second relapse without significant increase of the risk of radiation side effects. Further prospective studies are required to define the value of second BCS plus reirradiation in comparison with salvage mastectomy, as well as with tumour reexcision without RT.

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**Table 5.** Results of brachytherapy as reirradiation after repeat breast-conserving surgery

| Institution                  | Technique | RT scheme<br>(dose [Gy] × fraction no.) | Median FUP<br>(years) | Second LR<br>% (n) | Annual LR<br>% | Exc./good<br>cosmesis % |
|------------------------------|-----------|---|-----------------------|--------------------|----------------|-------------------------|
| Nice & Marseilles [25, 28]   | LDR       | 30 × 1; 45-50 × 1                       | 4.2                   | 15.9 (11 of 69)    | 3.8            | NR                      |
| Beth Israel Med. Center [26] | LDR       | 30 × 1; 45 × 1                          | 3                     | 6.7 (1 of 15)      | 2.2            | 100*                    |
| University Paris [29]        | LDR       | 30 × 1                                  | 3.3                   | 26.7 (4 of 15)     | 8.1            | 16                      |
| University Wien [32]         | PDR       | 40-50/0.5-1†                            | 5                     | 0 (0 of 9)         | 0              | 29                      |
| Barcelona [27]               | HDR       | 2.5 × 12                                | NR‡                   | 7.3 (3 of 41)      | NR             | 90                      |
| Pittsburgh [33]              | LDR/HDR§  | 45-50 × 1/3.4 × 10                      | 3.2                   | 3.8 (1 of 26)      | 1.2            | 92                      |
| Present study                | HDR       | 4.4 × 5                                 | 4.7                   | 0 (0 of 12)        | 0              | 67                      |
| All patients                 |           |   | 3-5                   | 10.7 (20 of 187)   | 0-8.1          | 16-100                  |

RT – radiotherapy, FUP – follow-up period, LR – local recurrence, LDR – low-dose-rate, PDR – pulsed-dose-rate, HDR – high-dose-rate, NR – not reported  
\* cosmetic results compared to baseline after second breast-conserving surgery

† total dose/pulse dose

‡ follow-up was reported in the range of 1 to 12 years

§ four out of 26 patients were treated with intracavitary HDR brachytherapy using the MammoSite® ( $n = 3$ ) or the Contura® ( $n = 1$ ) balloon applicators

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