Original paper

Pulsed-dose-rate peri-operative brachytherapy as an interstitial boost in organ-sparing treatment of breast cancer

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Abstract

Purpose: To evaluate peri-operative multicatheter interstitial pulsed-dose-rate brachytherapy (PDR-BT) with an intra-operative catheter placement to boost the tumor excision site in breast cancer patients treated conservatively.

Material and methods: Between May 2002 and October 2008, 96 consecutive T1-3N0-2M0 breast cancer patients underwent breast-conserving therapy (BCT) including peri-operative PDR-BT boost, followed by whole breast external beam radiotherapy (WBRT). The BT dose of 15 Gy (1 Gy/pulse/h) was given on the following day after surgery.

Results: No increased bleeding or delayed wound healing related to the implants were observed. The only side effects included one case of temporary peri-operative breast infection and 3 cases of fat necrosis, both early and late. In 11 patients (11.4%), subsequent WBRT was omitted owing to the final pathology findings. These included eight patients who underwent mastectomy due to multiple adverse prognostic pathological features, one case of lobular carcinoma *in situ*, and two cases with no malignant tumor. With a median follow-up of 12 years (range: 7-14 years), among 85 patients who completed BCT, there was one ipsilateral breast tumor and one locoregional nodal recurrence. Six patients developed distant metastases and one was diagnosed with angiosarcoma within irradiated breast. The actuarial 5- and 10-year disease free survival was 90% (95% CI: 84-96%) and 87% (95% CI: 80-94%), respectively, for the patients with invasive breast cancer, and 91% (95% CI: 84-97%) and 89% (95% CI: 82-96%), respectively, for patients who completed BCT. Good cosmetic outcome by self-assessment was achieved in 58 out of 64 (91%) evaluable patients.

Conclusions: Peri-operative PDR-BT boost with intra-operative tube placement followed by EBRT is feasible and devoid of considerable toxicity, and provides excellent long-term local control. However, this strategy necessitates careful patient selection and histological confirmation of primary diagnosis.

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Key words: brachytherapy, breast cancer, breast conserving therapy, PDR.

Purpose

Breast conserving therapy (BCT) is currently considered as the standard management of early breast cancer. Reduced risk of local recurrence in patients administered a boost dose of 16 Gy to the tumor bed in addition to 50 Gy delivered to the whole breast, was confirmed in a large randomized trial [1,2]. This effect was particularly apparent in a subset of patients younger than 50 years. Locoregional recurrence is associated with distant metastases and increased mortality. Boost options include interstitial brachytherapy (BT), electron or photon therapy, all following or preceding whole breast radiotherapy (WBRT) using external beam [1,3,4,5,6,7]. In all above approaches, the extent of boost tumor volume may be incorrect if the tumor bed is determined using clinical parameters (e.g., palpation, pre-operative mammography, scar position, operative and pathology reports, or surgical clips placed at the excision site boundaries) [8,9,10]. The direct visualization of the operative site during surgery allows for decreasing the risk of "geographical miss" in determining the target volume.

Pulsed-dose-rate (PDR) treatment is a BT modality combining the physical advantages of high-dose-rate (HDR) technology (isodose optimization, radiation safety) with radiobiological advantages of conventional low-dose-rate (LDR) BT. Despite its favorable radiobiological features, PDR-BT has rarely been used as a component of BCT. Here, we present our experience with this method used as an interstitial boost.

Material and methods

Study group included 96 consecutive patients with microscopically confirmed early breast cancer, 17 of whom,

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with initial T1-3 or N1-2 tumor, received induction chemotherapy. All patients underwent BCT between May 2002 and October 2008, including peri-operative PDR-BT boost following intra-operative BT tube placement to the primary tumor excision site (Table 1) and were technically suitable for BT. Breast carcinoma was primarily diagnosed using excisional or tru-cut biopsy in 59 women (61.5%) and by fine needle aspiration biopsy in the remaining 37 patients (38.5%). Flexible tubes were implanted during breast conserving surgery (BCS) including primary tumor excision or re-excision, with immediate tumor cavity reconstruction using surrounding breast tissue in all but one case. Axillary lymph node management included either sentinel node biopsy or nodal dissection. The BT implant covered the tumor excision site and the 1-2 cm margin of normal breast whenever possible. The number of tubes ranged between 4 and 17 (median: 9). In most of patients, in order to guide needles, the standardized templates for a triangular array with a space of 10-14 mm were used. On the following day, 2D radiographic verifications of tube placement with the skin markers were taken, digitized, and entered into a BT planning system (PLATO, version 13.7 or 14.1, Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). The target volume was calculated based on the actual position of catheters. The skin dose was reduced by keeping a distance of at least 10 mm from the first dwell position of the stepping source. The dosimetry was calculated using volume optimization technique. A total dose of 15 Gy (1 Gy per pulse repeated every hour) was delivered. Brachytherapy was followed by external beam radiotherapy (EBRT) to the entire breast after the final histology of the excised tissue had been obtained.

Follow-up data including cosmetic outcome assessed by a patient were obtained through personal contact or phone interview. Classification of side effects was performed using the Common Terminology Criteria for Adverse Events version 4.0, and late toxicity was reported if it occurred at least 6 months after BT.

Statistical analysis was performed with SPSS software (version 13.0, IBM, USA). Time to event endpoints was estimated using Kaplan-Meier method from the date of brachytherapy to the date of any local, regional or distant relapse, or death from breast cancer, whichever occurred first, or to the date of last visit in case of no events.

Results

On the average, tube implantation prolonged time of surgery by no more than 20 minutes. In three cases with deep located tumor, to construct the deep plane close to or upon the pectoralis minor muscle, tubes were implanted before excision cavity closing. Detailed BT implant and some dosimetric parameters were reported elsewhere [11]. The average volume for the prescribed dose (V_{100}) was 34.1 cc (range: 10.8-95.6 cc), and the median V_{100} for 93 patients with invasive tumor was 31.2 cc. At the time of the analysis, data regarding another dose-volume parameters were available in 36 patients (38.7% of all patients with invasive breast cancer). In this subgroup, the median volume of tissue receiving 150% (V_{150}) of the prescribed dose was 10.7 cc (range:

Table 1. Patient and treatment characteristics (n = 96)

Variable	n (%)
Age (years)	
Range	27-72
Median	51
≤ 40	9 (9.4)
41-50	34 (35.4)
TNM stage at presentation	
T1 N0-2	78 (81)
T2 N0-2	16 (17)
T3 N0	2 (2)
Prior chemotherapy	17 (17.7)
Histology	
Invasive ductal	71 (74)
Invasive lobular	11 (11)
Other	14 (15)
Final margin status (n = 94)	
Negative	80 (85.1)
Positive[a, b]	5 (5.3)
Close[a] (≤ 5 mm)	9 (9.6)
Surgery	
Primary	68 (70.8)
Re-excision after excisional biopsy	28 (29.1)
Sentinel node biopsy	16 (16.6)
Axillary excision and sampling	80 (83.3)
Brachytherapy implant	
One-plane	7 (7)
Two-plane	81 (84)
Three-plane	8 (8)
Number of tubes	
Range	4-17
Median	9
Volume at the prescribed isodose (V_{100}) (cc)	
Range	10.8-95.5
Mean	34.1
Whole breast radiotherapy (n = 85)	
50 Gy/25 fractions	67 (78.8)
42.5 Gy/17 fractions or 40.05 Gy/15 fractions	18 (21.2)
Adjuvant therapy (n = 93)	
Chemotherapy	30 (32.2)
Hormonal therapy	58 (62.4)

[a] – invasive and/or in situ ductal carcinoma present at an linked margin, [b] – including three patients with invasive ductal carcinoma; an adequate margins in two of them was unachievable due to tumor adjunction to the chest wall, the third one underwent subsequent mastectomy, V_{100} – the percent volume of the post-implant receiving 100% of the prescribed dose, cc – cm^3

2.87-33.44 cc), and the median dose homogeneity index [DHI], defined as 1-(V_{150}/V_{100}), was 0.72 (range: 0.53-0.78). In 91 patients, BT has started the day after the implant placement, and in five patients BT was delayed by 1-2 days. Subsequent WBRT was abandoned in 11 patients (11.4%). These included eight cases with multiple adverse prognostic pathological factors diagnosed postoperatively, implying the superiority of mastectomy, one with the final diagnosis of lobular carcinoma *in situ*, and two with no malignant tumor; all originally were diagnosed with fine needle aspiration as carcinoma. The remaining 85 patients received WBRT, including one with massive axillary lymph node involvement, in whom breast irradiation was preceded by chemotherapy. Except this case, the break between BT and WBRT ranged from 8 to 31 days (median: 12 days).

No intense bleeding during surgery or at tube removal was observed and neither there were wound healing problems or significant skin reactions related to the implant. One patient with re-excision experienced temporary peri-operative breast infection requiring antibiotic administration. No routine analgesics during therapy or at tube removal were administered. One patient with large-sized breast underwent subsequent surgical intervention due to grade 3 fat necrosis. In this case, WBRT was delayed up to 31 days after BT. Late grade 3 fat necrosis occurred in another two patients. Overall, four patients (4.3%) experienced serious side effects.

After median follow-up of 12 years (range: 7-14), one case of "true" local recurrence and one regional nodal recurrence were observed (1.2% each). Four patients (4.7%) developed contralateral breast carcinoma (of another histology in two patients or another histological grade in two patients). Six years after BCT, one patient presented with angiosarcoma within the irradiated breast outside of the primary breast cancer. Another seven patients (8.2%) developed second cancer including lung, ovarian, colon, skin cancer, and lymphoma. Apart from a case with angiosarcoma and a case with disseminated ovarian cancer, six relapsed breast cancer patients died due to cancer dissemination.

The actuarial 5- and 10-year disease-free survival was 90% (95% CI: 84-96%), and 87% (95% CI: 80-94%), respectively, for the whole cohort of 93 invasive breast cancer patients, and 91% (95% CI: 84-97%) and 89% (95% CI: 82-96%), respectively, for patients who completed BCT.

In 58 out of 64 (91%) assessable patients, a good or excellent self-assessed cosmetic result was obtained. The remaining four patients scored cosmetic effect as fair and two patients as poor. One patient with fair cosmetic effect had no tumor excision site reconstruction during BCS, and another one, due to centrally located tumor, required the nipple-areolar complex excision.

Discussion

Intra-operative irradiation using electron beams, photon beams, or BT tube implantation provides a high precision boost, thus minimizing the risk of a "geographical miss" [12,13,14,15]. We demonstrated the feasibility, good tolerance, and efficacy of the peri-operative BT using PDR. The only severe toxicity included three cases of fat necrosis. Interstitial PDR-BT boost seems to be particularly suitable component of BCT, owing to its hypothetical favorable cosmetic outcomes. High local control and satisfactory cosmesis with PDR boost following the whole breast EBRT in breast cancer was reported by other authors [4,5].

The rationale for a BT boost is the delivery of a high dose to the tumor bed with reduced exposure of the skin, lung, and subcutaneous tissue. The important advantages of intra-operative implant include reduced risk of "geographical miss", shortening the treatment time, and avoidance of another anesthesia. An apparent limitation of this approach is the lack of the full pathology assessment, especially regarding the margin status at the time of BT.

In this series, 28 patients (29%) underwent a re-excision, and in the breast cancer group the tumor resection margins were tumor-free in 85% of patients. Among cases with positive or close margin, none developed local recurrence. Positive pathologic margin has been considered a major risk factor for ipsilateral breast tumor recurrence (IBTR), although the use of higher boost dose in these cases is debatable [16,17]. A substantial risk of residual disease was reported for breast cancer patients with < 2 mm margin of excision [18]. In the large retrospective study of 8485 early breast cancer patients with 5% IBTR incidence at 10-years, the invasive carcinoma margin status did not influence the risk of local relapse [19]. In this cohort, 9% of patients underwent a re-excision, and IBTR-free interval was longer for patients who received a RT boost or systemic therapy. A multidisciplinary consensus from 2014 defined an adequate breast cancer margin as no ink on tumor [20]. The role of surgical resection margins after breast-conserving surgery is summarized in recently published Senonetwork recommendations [21]. This document proposes standards for investigating resection margins and recommends in patients with positive margins re-excision or mastectomy, or increasing the boost dose during radiotherapy. In case of negative margins, boost administration and its dose depend on the estimated risk of local recurrence, which is linked to demographic and pathological tumor features as well as the width of surgical margin.

In this series, diagnosis was established using excisional or tru-cut biopsy in the majority of patients; nevertheless, in 11.4% of patients subsequent WBRT was omitted due to the postoperative pathology findings. All these patients were primarily diagnosed by fine needle aspiration cytology used in the first period of this study. Thus, obtaining the definite diagnosis by a tru-cut biopsy seems to be essential in all patients considered for this strategy.

The optimal total and boost doses as well as BT dose rate, have not yet been determined in BCT. In this series, 15 Gy boost dose and 1 Gy/pulse/h, followed by 50 Gy or 40.05 Gy and 42.5 Gy (2 Gy or 2.67 and 2.5 Gy daily dose, respectively) to the whole breast were used. Others administered 20-25 Gy as the PDR boost following breast 50 Gy EBRT [4,5]. Harms *et al*. [5] tailored the PDR boost dose according to pathologic tumor characteristics. These authors found that the 25 Gy boost dose is associated with a significantly higher rate of late toxicity compared to 20 Gy. Others reported poorer cosmetic outcome in patients boosted with dose rates above 1 Gy/h [22]. Until recently, in patients managed with BCT, the standard WBRT dose was 50 Gy. Recently, mildly hypofractionated

schedules of radiotherapy are commonly used. Indications and modalities of radiotherapy boost in hypofractionated schedules have not been fully determined. The boost dose was used in 43-75% of patients enrolled in three out of four randomized trials of hypofractionated radiotherapy as a part of BCT in early breast cancer patients [23].

Immediate tumor bed reconstruction used in this series is not routinely used for BCT. This approach allows for good cosmetics even in cases with large excision volume. Immediate catheter placement reduces the target volume; however, its determination remains subjective. In our series, the mean target volume was relatively small (34 cc). This may allow for better cosmetic outcome but at the expense of potentially increased risk of local recurrence. Harms *et al*. [5], in a series of patients with high risk of recurrence, reported the mean PDR boost volume of 57 cc. In the study by Resch *et al*. [24], in which 60% of patients underwent quadrantectomy, 18% wide excision and 22% tumorectomy, the average volume for the "prescribed dose" was 83 cc. Of note, in that study, the type of surgery did not impact the local control. Notably, excellent local control (1.6% "true local recurrence" at 10 years for patients after quadrantectomy, 0% for wide excision, and 2.2% for tumorectomy) was accompanied by a fair cosmetic effect (excellent or good cosmetic effect in only 38% of patients).

In this series, three patients underwent surgical intervention for fat necrosis. In one of them, the treated volume was relatively high (V_{100} of 56.4 cc). The DHI was available for two patients, and in both cases, it was 0.68 (V_{150} of 10.7 cc and 17.8 cc). The reported incidence of fat necrosis including symptomatic/clinically overt cases varies considerably in particular studies, and is influenced by differences in patient characteristics, treatment, duration of follow-up, and diagnostic criteria for a diagnosis of fat necrosis. No late fat necrosis was reported in the two above mentioned studies applying PDR BT boost at a dose of 15-25 Gy following whole breast irradiation [4,5]. The median follow-up in these series was 30 months and 60.9 months. In another small series with patients boosted with PDR BT with the median dose of 12.3 Gy (range: 12.0-20.3 Gy) (median V_{100} of 55.2 cc, median DHI: 0.82), in addition to 50.4 Gy WBRT, the incidence of mammographically evident signs of fat necrosis was 9.0% at the median follow-up of 37.5 months, but no patient needed surgical intervention [25]. After a median follow-up of 46 months, fat necrosis in one case (1.3%) was observed in a series with HDR-BT (median V_{100} of 94.49 cc) performed immediately after completing WBRT [26]. The late toxicity data in patients treated with multicatheter interstitial HDR-BT as a form of accelerated partial breast irradiation (APBI), suggest that V_{150} and V_{200}, as well as anthracycline-based chemotherapy administered after APBI may be associated with an increased risk of fat necrosis [27]. In another APBI study, acute breast infection and anthracycline-based chemotherapy, number of catheters, V_{100}, V_{150}, V_{200}, and integrated reference air-kerma were associated with fat necrosis [28]. Of these, V_{150} was independent treatment-related parameter. In these studies, the mean V_{100} was 176 cc and 239 cc, respectively.

Our series includes 17 breast cancer patients (17.7%) who were administered preoperative chemotherapy, an increasingly used strategy [29]. In this group, one patient developed angiosarcoma of the irradiated breast six years after BCT. Secondary angiosarcoma may develop in a lymphedematous arm, in the irradiated chest wall after radical mastectomy, and following BCT. This event is rare but associated with poor prognosis. In a large retrospective series of 18,115 breast cancers treated with BCT, including 50 Gy whole breast irradiation and a boost dose of 15-25 Gy, post-irradiation angiosarcoma was diagnosed in only nine cases, after the median latency period of approximately 74 months [30]. Adjuvant radiotherapy, an indispensable part of BCT, is associated with the risk of second malignancy including all sarcomas and angiosarcoma [31]. Beside radiotherapy, partial mastectomies and lymph node dissections were found to be independent risk factors for the development of angiosarcoma in breast cancer patients [32]. Post-irradiation breast angiosarcoma, the most frequent second type of sarcoma after primary breast cancer, has been paradoxically increasingly reported since currently most women with breast cancer have long-term survival. In addition, the increasing use of intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), might be associated with a higher risk of mutagenesis. Due to the higher number of fields and monitor units, these newer techniques have been shown to have greater out-of-beam doses including higher low dose exposure of the normal structures. Whether angiosarcoma is induced by radiation or persistent edema, or has a multifactorial origin is not clear. Our patient with ypT2N1 breast cancer underwent axillary dissection and received irradiation at a standard dose of 50 Gy in 25 fractions with tangential fields to the breast and the supraclavicular region. Thus, despite the lack of clinical lymphedema, she might have had some minimal subclinical lymph stasis involving the breast. The addition of neoadjuvant chemotherapy consisting of 6 cycles of doxorubicin and docetaxel, might have also contributed to secondary malignancy in this patient.

Conclusions

Peri-operative PDR-BT with tube implantation at the time of surgery seems to be a safe and convenient boost method allowing for good local control and satisfactory cosmetic effect. The direct visualization of the operative site during surgery allows for precise defining of the tumor bed and decreases the risk of "geographical miss" in determining the target volume. However, in a proportion of patients, the treatment plan should be verified after the final histology is obtained. Therefore, this strategy necessitates careful patient selection and primary histological diagnosis.

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Disclosure

Authors report no conflict of interest.

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