

Comparison of two techniques of interstitial pulsed dose rate boost brachytherapy in conservative treatment of breast cancer

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Abstract

Purpose: The aim of this work is to compare selected parameters of implants and natural dose volume histograms for two techniques of interstitial pulsed dose rate brachytherapy (PDR BT) as a boost to the tumour bed in breast-conserving therapy (BCT).

Material and methods: Data of T₁₋₃N₀₋₂M₀ breast cancer patients who underwent BCT with BT boost between 05.2002 and 12.2008 were analysed. Ninety two patients were implanted with rigid tubes after breast irradiation (group A) and 96 had a peri-operative BT with an intra-operative flexible tube placement and subsequent whole breast radiotherapy (group B). In both groups PDR BT of 15 Gy (1 Gy/pulse/h) was administered based on Paris system rules, and volume optimization using BT planning system PLATO.

Results: Three-plane implant was used in 62% and 8% of patients in group A and B, respectively, and two-plane implant in 38% of group A and in 84% of group B, with a median of 11 and 9 tubes respectively. The average volume for the prescribed dose (V₁₀₀) was 42.0 ± 25.4 cc (group A) and 34.1 ± 19.7 cc (group B), respectively (p = 0.017). The individual V₅₀ and V₂₀₀ were similar. Quality index (QI) was not impacted by the technique of BT (mean QI was 1.80 ± 0.10 and 1.75 ± 0.46 for the groups A and B, respectively). Uniformity index (UI) in respective groups was 1.60 ± 0.10 and 1.52 ± 0.21 (p = 0.001).

Conclusions: Implant volume encompassed by prescribed dose was significantly lower with intra-operative plastic tubes placement. In respect to the QI, these two BT techniques were comparable. The target volume coverage by the dose distribution as defined by UI was better for rigid tubes.

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Key words: breast cancer, brachytherapy, pulsed dose rate.

Purpose

Breast conserving therapy (BCT) is currently considered the standard management of early breast cancer. It offers equal local control and survival, as well as superior psychosocial outcomes compared to modified radical mastectomy. A highly significant reduction in the local recurrence rate at 5 years (4.3% vs. 6.8%) in patients that were administered a boost dose of 16 Gy to the tumour bed in addition of 50 Gy whole breast irradiation in BCT, especially in women younger than 50 years, was confirmed in a large randomized trial [1]. BCT is now performed also in some patients with larger tumours following their shrinkage with induction of chemotherapy. Boost options

include electron or photon beam therapy or, less frequently, interstitial brachytherapy (BT), all following or preceding external beam radiotherapy (EBRT) to the entire breast. BT may employ rigid or plastic tubes.

Currently used clinical parameters (e.g. palpation, pre-operative mammography, scar position, operative and pathology reports, surgical clips placed at the excision site boundaries) to determine the extent of boost volume may be imprecise [2]. Traditionally BT is applied following completion of breast EBRT. BT may also precede EBRT, preferably as an intra-operative procedure (during primary tumour excision or re-excision), as well as a peri-operative therapy with intra-operative implantation of BT catheters. The direct visualization of the operative site during surgery

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allows to decrease the risk of ‘geographical miss’ in determining the boost target volume.

Pulsed dose rate (PDR) BT is believed to combine the physical advantages of high dose rate (HDR) technology (isodose optimization, radiation safety) with radiobiological advantages of conventional low dose rate (LDR) BT. Notably, this method provides satisfactory concordance between measured and calculated doses of PDR stepping source technology, and the associated optimisation algorithm [3].

Dose-volume histograms (DVHs) describe the dose distribution in and around an implant; they provide the dosimetric parameters that determine the degree of coverage of the target volume, dose homogeneity within the target volume, and irradiation of tissues outside the target volume. The implant uniformity is expressed quantitatively by several parameters including the dose homogeneity index and uniformity index (UI). Thus, UI quantifies how well a target volume is covered by the dose distribution. The quality index (QI) resembles the UI, but is independent of the prescription dose.

We compared selected parameters of implants and DVHs for two techniques of PDR BT employed as an interstitial boost in BCT: BT applied after breast EBRT or as a procedure preceding EBRT to the whole breast.

Material and methods

Study group included 188 T₁₋₃N₀₋₂M₀ female breast cancer patients who between 5.2002 and 12.2008 underwent interstitial PDR boost BT to the primary tumour

excision site (Table 1). Ten percent of patients received preoperative chemotherapy and all patients were technically suitable for BT. In all cases the implantation was performed using general anaesthesia. Ninety two patients underwent implantation with rigid tubes after whole breast EBRT (group A) and 96 had an intra-operative flexible tube placement, followed by external beam whole breast irradiation (group B). Flexible tubes were implanted during primary tumour excision or re-excision (in all but one case with immediate tumour cavity reconstruction using surrounding breast tissue). In three cases with deep located tumour, in order to construct the deep plane close to or upon the pectoralis minor muscle, the tubes were implanted before excision cavity closing. Axillary lymph node management in both groups included either sentinel lymph node biopsy or nodal dissection. The BT implant covered the tumour excision site and the margin of normal breast. The standardized templates for a triangular array with a space of 10 or 16 mm were used in all cases in group A and in selected cases in group B. In group A BT started on the same day, and in group B – on the following day (or within a couple of days in few cases). In the latter group prior to isotope insertion radiographic verifications of tube placement with the skin markers were taken, digitised and entered into PLATO BPS (version 13.7 and 14) planning system. The target volume was defined as the volume encompassing the tumour bed with approximately 1-2 cm margin whenever possible. This volume was specified by the physician participating in tube placement – as determined intra-operatively (group B) or based on available clinical parameters (group A). 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 according to the Paris system rules. Within almost all group B, in order to improve dose homogeneity and to compensate underdosage at the margins of the implant, geometrical volume optimization (GVO) was used. The optimized treatment plans were analyzed with cumulative and Anderson’s “natural” DVH. The reference dose was defined as 85% of the Paris system, corrected by a factor of 0.85. In all patients a dose of 15 Gy (1 Gy per pulse repeated every hour) was delivered with the use of Microselectron PDR unit (Nucletron®, Netherlands). In both groups the delivery of EBRT to the entire breast consisted of 50 Gy/25 fractions or 42.5 Gy/17 fractions.

Statistical comparisons were made with the Student test and χ^2 test. Statistical significance was assumed at $p < 0.05$.

Results

Sixty two percent of group A patients received a three-plane implant and 38% – two-plane (Table 2). In group B 84% of patients received two-plane implant ($p < 0.01$), 8% – three-plane and seven patients (7%) – one-plane. The median of 11 and 9 tubes were implanted in group A and B, respectively. The average volume for the prescribed dose (V_{100}) was 42.0 ± 25.4 cc (group A)

Table 1. Patient characteristics

Variable	Group A (n = 92)	Group B (n = 96)
Age (years)		
range	37-76	27-72
mean	59	51
TNM stage at presentation		
T1 N0-2	84 (91%)	78 (81%)*
T2 N0-2	7 (8%)	16 (17%)
T3 N0	1 (1%)	2 (2%)
Prior chemotherapy**		
yes	16 (17%)	17 (18%)
no	76 (83%)	79 (82%)
Histology		
invasive ductal	75 (81%)	71 (74%)
invasive lobular	9 (10%)	11 (11%)
other	8 (9%)	14 (15%)*
Final margin status		
negative	89 (97%)	82 (86%)
positive	–	5 (5%)
close (≤ 5 mm)	3 (3%)	9 (9%)
Surgery		
primary	87 (95%)	61 (64%)
reexcision after excisional biopsy	5 (5%)	35 (36%)
sentinel node biopsy	9 (10%)	15 (16%)
axillary excision and sampling	83 (90%)	81 (84%)

* including one patient with lobular carcinoma in situ and two with benign (fibrous cystic) breast lesions

** either in neoadjuvant setting or after surgical procedure before breast irradiation

Table 2. Implant and dosimetric parameters

Variable	Group A (n = 92)	Group B (n = 96)	p value
Brachytherapy implant			
one-plane	–	7 (7%)	< 0.01
two-plane	35 (38%)	81 (84%)	
three-plane	57 (62%)	8 (8%)	
Number of tubes			
range	7-18	4-17	
median	11	9	
Volume (cc) at the prescribed isodose (V_{100})			
mean \pm SD	42.0 \pm 25.4	34.1 \pm 19.7	0.017
Volume (cc) at the 50% isodose (V_{50})			
mean \pm SD	90.3 \pm 64.9	90.6 \pm 49.9	0.97
Volume (cc) at the 200% isodose (V_{200})			
mean \pm SD	4.8 \pm 2.5	4.5 \pm 3.5	0.50
Uniformity index (UI)			
range	1.34-2.10	0.87-1.88	0.001
mean	1.60 \pm 0.10	1.52 \pm 0.21	
Quality index (QI)			
range	1.37-2.00	1.27-2.49	0.31
mean	1.80 \pm 0.10	1.75 \pm 0.46	

and 34.1 ± 19.7 cc (group B), ($p = 0.017$). The respective V_{50} and volume at high doses (V_{200}) were similar. Quality index (QI) was not impacted by the BT technique (mean QI of 1.80 and 1.75 for the groups A and B, respectively). Uniformity index (UI) in respective groups was 1.60 and 1.52 ($p = 0.001$).

In a subgroup of T1 breast tumour patients the mean V_{100} was 40.0 ± 23.3 cc and 34.39 ± 21.14 cc for group A and B, respectively ($p = 0.11$). There was no difference between the mean V_{100} in group B patients implanted during primary tumour excision and those who were re-excised (was 33.07 ± 18.85 and 36.18 ± 21.76 cc in either group, respectively; $p = 0.46$).

In average, the plastic tube implantation prolonged the time of surgery by no more than 25 minutes. Due to multiple adverse prognostic pathological factors implying the superiority of mastectomy subsequent breast EBRT was abandoned in eight (8%) group B patients. In one patient with massive axillary lymph node involvement breast irradiation was preceded by chemotherapy.

Discussion

The success of BCT in terms of both local control and cosmetic outcome depends on several treatment factors including those related to surgery (the resection volume, the width of the resection margins) or radiotherapy (the radiation technique, dose/dose rate and volume). Of the latter, particular importance is given to the radiation boost. In general, the higher total radiation dose and the larger treatment volume, the lower risk for local recurrence. Tumour foci at a distance of more than 2 cm from the clinically apparent reference tumour were reported in 41% of mastectomy specimen [4]. Several authors demonstrated the impact of the implant volume on local control in BCT [5-7]. A trend to improved local control with a treated boost volume above 65 cc was

reported by Perez *et al.* [6]. In another study [8] in 6 out of 10 breast failures at the periphery of the treated volume, the mean total excision volume (80 cc) was almost twice the mean of implant volume (44 cc).

On the other hand, cosmetic outcome is inversely related to increasing radiation dose and volume of irradiated breast tissue [5, 9].

We demonstrated significantly lower implant volume encompassed by prescribed dose with intra-operative plastic tubes placement. Nevertheless, the mean target volumes in both groups were relatively small (42.0 cc and 34.1 cc) compared to other series. This feature may be associated with better cosmetic result, but at the expense of potentially increased risk of local recurrence. In Harms *et al.* [10] series of patients with high risk of recurrence (incomplete resection, vascular invasion, close resection margin, and T2G3 > 3 cm tumours) the mean boost volume of PDR BT (20 or 25 Gy, 1 Gy per pulse/hour) was 57 cc in the entire series, 53 cc in T1, 58 cc in T2, and 73 cc in T3 tumours. They applied two-plane implant in 91% of patients, with the median of 9 (range 5-12) flexible catheters, and a geometrical optimization algorithm. The boost volume comprised of the tumour bed and a surrounding, individually modified margin of 2-3 cm. The dose was specified in a simulation of the Paris system by choosing a reference isodose which adequately covered the clinical target volume and represented approximately 85% of the dose to the basal points. The actuarial 8-year local control rate of 93% and cosmetic outcome rated by 90% of the patients as excellent or good were achieved. In the large series of LDR and HDR BT boost [7] in which 60% patients underwent a quadrantectomy (18% wide excision, 22% tumourectomy), the average volume covered by the reference isodose of the Paris System (85% of the mean central dose (MCD) was 73 cc for LDR and 52 cc for HDR

BR. The majority of patients (83%) received a two-plane implant with 5-9 needles (most often 7). In this series excellent local control (1.6% "true local recurrence" at 10 years for patients after quadrantectomy, 0% for wide excision and 2.2% for tumourectomy) was associated with a fair cosmetic effect (excellent or good cosmetic result in only 38% of patients). Noteworthy, no significant impact of surgical approach on local recurrence rate was noted. In the EORTC "boost versus no boost" trial in the BT (dose rate of 10 Gy in 24 hours) group including 240 patients, the median boost target volume was 60 cc (compared to the median of 144 and 288 cc in more numerous fast electrons and photon beam groups), and the mean V_{100} was 50 cc [11]. The target area for the additional dose was the site of the primary tumour with a margin of 1.5 cm after microscopically complete excision and 3 cm after incomplete excision or in case of invasive cancer with extensive ductal carcinoma in situ. Of note, despite the lower treatment volume, comparative analysis of the three boost techniques revealed similar results in terms of fibrosis and local control. Overall, a 5-year actuarial local recurrence rate was 4.3%, 48% of which occurred in the primary tumour bed, 9% in the scar, 28% outside the original tumour area, and 14% were diffused. In another LDR-series, the mean treated volume was 48 cc (dose homogeneity index 0.73) [8] or 65 cc [12], and in HDR-series [13] the volume for the reference isodose (85% of the MCD) was 39 cc.

Dosimetric quality of the implant is another factor that may influence cosmetic result. Currently, the dose distribution patterns from interstitial implants are being performed with the use of computer planning systems allowing calculation of the doses in a large number of volume elements. This quantitative assessment often results in a large variation of dose delivered both within and outside the target volume. The clinical importance of interstitial implant dosimetric characteristics has not yet been clearly defined. We selected UI and QI as the quantitative parameters to compare the two boost BT techniques in BCT. A mean UI of 1.60 and 1.52, and QI of 1.80 and 1.75 were satisfactory. Based upon the QI, these two interstitial BT methods are comparable. However, the target volume coverage by the dose distribution as defined by UI is better for rigid tubes. In the Fritz *et al.* [14] study of 35 flexible PDR breast implants, in which GVO was used, QI was 1.76 ± 0.16 , and UI 1.62 ± 0.11 .

The underlying principle of a BT boost is to deliver a high dose to the tumour bed while reducing exposure of the skin, lung, and subcutaneous tissue. Intra-operative implant may additionally reduce the risk of 'geographical miss', shorten the treatment time and avoid another anaesthesia. The immediate catheter placement may reduce target volume in a number of cases, however, the determination of implant volume remains subjective. Moreover, the immediate tumour bed reconstruction used in the B group (not typical for BCT) allows for a good cosmetic result even in the cases with large excision volume. The lack of the final histology at the time of BT, especially regarding the margin status, remains an important limitation of this approach.

Conclusions

In conclusion, upon analysed parameters there is some difference between the peri-operative PDR BT with the intra-operative tube implantation and traditional BT boost performed after the whole breast irradiation. Implant volume encompassed by the prescribed dose was significantly lower with intra-operative plastic tubes placement. In respect to the QI, these two BT techniques were comparable. The target volume coverage by the dose distribution as defined by UI was better for rigid tubes. More patients and longer follow-up are needed to assess the local control and cosmetic outcome obtained with these two boost BT techniques.

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