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3-D Conformal Photon Boost in the Treatment of Early Stage Breast Cancer: Four Year Follow Up Results

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Abstract In the treatment of early stage breast cancer, breast conserving surgery (BCS) followed by whole breast irradiation (WBI) is the standard treatment. The impact of the tumor bed boost following WBI is well-defined, but there are various delivery methods. In this study we demonstrate our 4 year experience with the 3-D conformal boost technique. Between January 2004 and June 2005, 77 early stage (Stage I–II) breast cancer patients were treated in our institute with whole breast irradiation (WBI, 50.4 Gy in 28 fractions) after breast conserving surgery. Following WBI, 3-D conformal photon boost was delivered (10–16 Gy in five to eight fractions) for all patients. The clinical outcome was retrospectively recorded in terms of survival and local control. The side effect profile (fibrosis, fat necrosis and cosmetic outcome) was also recorded and studied. In our patient group the mean follow up time was 46.8 months (median: 52, range: 17–71, SD: 14.4) The 4-year probability of local tumor control was 96% (crude rate: 74/77–96.1%), the 4-year probability of overall survival was 96% (crude rate: 74/77–96.1%) in this patient group. In case of the distant metastasis free survival the probability was 89, 5% (crude rate: 70/77–90, 1%). Probability of disease specific survival was 98% (crude rate: 76/77–98. 7%). Local relapse occurred in three cases (3.9%). In ten cases (12.9%) asymptomatic grade I–II breast fibrosis, in eight cases (10.4%) asymptomatic breast fat necrosis were registered. For 14 patients (18.2%) asymptomatic lung fibrosis was recorded on the control CT scans. In term of the relapse free survival, the close resection margin and the nodal positivity resulted in significant difference in favor of the clear resection margin group and the node negative group. In this study the 3-D conformal photon boost resulted in good local control and side effect profile. The presence of tumor bed clips resulted in significantly lower boost PTV volumes, but no correlation was found between the irradiated boost volume and the breast fibrosis. In the relapse free survival analysis, nodal negativity and clear margin status resulted in significantly better RFS.

Keywords Breast cancer · Radiotherapy · 3-D conformal photon boost

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Introduction

Breast conserving surgery followed by whole breast irradiation (WBI) is standard in the treatment of early stage breast cancer. There are several randomized, controlled trial data to demonstrate the local control and survival benefit of this treatment modality [6, 7, 24]. The EORTC 'boost versus no boost' randomized trial clearly demonstrated a significantly better local control rate with the higher radiotherapy dose, especially in women younger than 50 years of age [17].

The standard WBI therapy typically includes two tangential fields with a total dose of 50 Gy during a 5 week to 6 week treatment time, followed by a boost dose to the tumor bed. Usually five to eight fractions are given after the WBI. There are several different delivery methods of the tumor bed boost. Direct field electron, 3-D conformal photon, intensity modulated radiotherapy (IMRT), interstitial high dose rate afterloading (HDR-AL) are the most commonly used techniques [9].

In our institute the CT based 3D conformal photon boost method has been used since 2003. The purpose of this study was to analyze the survival-, recurrence- and side effect profile of the 3-D conformal photon boost technique.

Material and Methods

Patient Characteristics

Between January 2004 and June 2005, 77 early stage (Stage I–II) breast cancer patients were enrolled in this study. All of these patients were treated with WBI followed by 3D based photon boost after breast conserving surgery. The mean age was 58 year (range: 37–79). Altogether 53 node negative (N0), 24 node positive (N1) cases were registered. Detailed patient characteristics are shown in Table 1.

Following detailed patient information of the nature of the procedure, all patients provided written informed consent under an institutionally approved subjects research protocol.

Contouring-Treatment Planning

All patients underwent 3D CT based WBI planning, using Theraplan@ Plus Software (MDS Nordion, 2001). Planning target volumes (PTV) were contoured on axial CT slices, (8 mm slice thickness, 5 mm spacing), used routinely in our institute. Anatomic information from the CT scan was used to define target volumes and normal structures. The breast volume was initially delineated using the clinical radiopaque markers and breast CT appearance.

For WBI planning, two tangential beams were used with the respect of the normal structures (lung, heart, head of humerus contralateral breast). Tangential fields were designed using the clinical parameters, the target breast volume was then defined more precisely as the tissue encompassed by these tangential fields minus a 1-cm margin from the posterior beam edge and 0.5-cm margin from the skin edge. The total dose of 50.4 Gy in 1.8 Gy fractions was prescribed to a normalization point on the central CT slice 2 cm from the posterior border of the tangent fields, according to the ICRU recommendations [12]. In cases when the defined point was within the lung parenchyma, it was moved anteriorly towards the chest-wall interface.

The excision cavity (boost GTV) was contoured on the planning CT scans. In ideal cases titanium tumor bed clips defined the extension of the tumor bed. When surgical clips

Table 1 Patient characteristics

Characteristics	
Patients	n=77
- Age (mean-range)	58 (37–79)
- ≤40	n=19
- ≥ 40	n=58
Stage (AJCC classification)	
- Stage I (T1, N0)	n=53
- Stage II (T1-N1;T2-N0-N1)	n=24
Nodal status	
- Node negative	n=54
- Node positive	n=23
Tumor Grade(histological)	
Grade I	n=14
Grade II	n=39
Grade III	n=24
Surgery	
- excision with SLNB[a] or ABD[b]	n=77
- reexcision	n=3
Surgical margin	
- close (<10 mm)	n=53
- clear (≥10 mm)	n=16
- unknown	n=8
Tumor bed clips	
- no clip	n=18
- single clip	n=39
- multiple clips (range: 2–7, mean=4,2)	n=20
Adjuvant radiotherapy	
- WBI[c] dose	50.4 Gy
3D photon boost	n=77 (100%)
- 10 Gy	n=69
- 16 Gy	n=8
Chemotherapy/hormonal therapy	
- chemotherapy	n=46
- hormonal therapy	n=72
Tumor bed volume (cm^3)	
- mean	60.2
- median	56
- range	10–148
- SD	33.5

[a] Sentinel node biopsy

[b] Axillary block dissection

[c] Whole breast irradiation

were not present (or in cases with limited number of the clips) preoperative mammography- and ultrasound data, surgical description and postoperative contrast enhanced CT scan information were used for tumor bed definition. In all cases tumor bed was defined by a team of three physicians (two independent radiologists and a radiation oncologist). In case of a clear surgical margin (>10 mm), 1 cm margin was added to the tumor bed with respect of the anatomical structures (to avoid ribs, heart, lung tissue). In case of close surgical margins, an additional planning margin was added depending on the pathological findings (1 cm minus the pathological margin distance in cm). This volume was defined as the clinical target volume (CTV). Tumor beds with unknown margin data were contoured as close margin cases. For the planning target volume definition (PTV) 3 mm to 4 mm margin was added to CTV for the compensation of the set up errors and breathing motions.

Two oblique, wedged fields were applied individually for the 3D based photon boost plans. A boost dose of 10–16 Gy was prescribed to the tumor bed providing a minimal 90% coverage of the target.

Patient Follow Up

The patient follow-up schedule was the following:

- The first follow-up visit occurred 6 weeks after the end of the radiotherapy (physical examination)
- Visits scheduled every 3 months for the first 2 years consisted of a physical examination on every visit, two mammography, one chest CT scan, one bone scan yearly)
- Examinations were scheduled every 6 months during years three to five consisting of a physical examination on every visit, two mammography, one chest CT scan, one bone scan yearly.

Clinical follow-up data were recorded, collected, archived and analyzed using Microsoft Excel Software@. For side effect analysis the RTOG/EORTC system was used [29] When reporting fat necrosis the scoring system published by Lovey et al. [28] was used. Cosmetic results were assessed using the Harvard criteria [30].

Statistical Analysis

Survival data was defined as the time from the end of the radiotherapy treatment to the date of the event (disease specific death, distant metastasis, local relapse). Data were updated on 30th of May, 2009. Probality of survival was estimated using the Kaplan-Meier method. Single variable survival analyses were assessed using the Wilcoxon and log-rank tests, while the multivariate regression was assessed with the Chi square and Cox model. The p level <0.05 was considered as significant.

Results

The mean follow up time was 46.8 months (median: 52, range:17–71, SD: 14.4). Local relapse was registered in three cases (3.9%). Altogether two lung-, three liver-, and additionally two bone metastases were recorded. In the follow up period, three deaths were registered (one disease specific, two cardiovascular- Table 2). The 4-year probability of local tumor control was 96% (crude rate: 74/77–96.1%), the 4-year probability of overall survival was 96% (crude rate: 74/77–96.1%) in this patient group. In case of the distant metastases free survival the probability was 89.5% (crude rate:70/77–90.1%). Probability of disease specific overall survival was 98% (crude rate: 76/77–98.7%)

The recorded mean tumor bed volume was 60.2 cm^3 (median: 56, range: 10–148, SD: 33.5) In ten cases, (12.9%) grade I–II breast fibrosis and in eight cases (10.4%) asymptomatic (no clinical sign present) breast fat necrosis (Grade I) were found. Asymptomatic lung fibrosis was found in 14 cases (18.2%). Good or excellent cosmetic results were registered in 68 patients (88.3%), while fare cosmetic outcome was registered in nine cases (11.7%) (Table 3).

In term of the local relapse free survival the close resection and the nodal positivity resulted in a significant difference in favor of the clear resection group (4-year probability of local tumor control-crude rate 95% vs. 100%

Table 2 Survival functions. Probability rates based on Kaplan-Meier analysis

Results-survival functions	
4-year probability of local tumor control	96% (crude rate: 74/77–96.1%)
4-year probability of overall survival	96% (crude rate: 74/77–96.1%)
4-year probability of distant metastasis free survival	89.5% (crude rate: 70/77–90.1%)
4-year probability of disease specific survival	98% (crude rate: 76/77–98.7%)
Time to local progression (mean-months)	38.7
Local relapse	***n*=3 (3.9%)**
Distant metastasis	***n*=7 (9%)**
- lung	*n*=2
- liver	*n*=3
- bone	*n*=2
Deaths	***n***=3
- disease specific	*n*=1
- cardiovascular	*n*=2

Table 3 Late side effects and cosmetic results

Results-side effects	
Breast fibrosis(RTOG/EORTC-29)	***n*=10 (12.9%)**
- grade I	*n*=2
- grade II	*n*=8
- grade III	*n*=0
Fat necrosis (28.)	***n*=8 (10.4%)**
- grade 0–II	*n*=8
- grade II–III	*n*=0
- asymptomatic	*n*=8
- symptomatic	*n*=0
Lung fibrosis	***n*=14 (18.2%)**
- asymptomatic	*n*=14
- symptomatic	*n*=0
Telangiectasia[a]	
- *unknown*	*n*=28 (36%)
- *grade I*	*n*=5 (7%)
- *grade II*	*n*=2 (2.5%)
- *grade III*	*n*=0
Cosmetic outcome	
- *excellent*	*n*=29
- *good*	*n*=40
- *fair*	*n*=8
- poor	*n*=0

[a] Data on skin side effects were available for 49 out of 77 patients (63.6%)

Table 4) and the node negative group (4-year probability of local tumor control-crude rate 87% vs. 100% Table 4). No correlation was found between the presence of breast fibrosis, fat necrosis and the tumor bed volume. The close resection status resulted in higher mean tumor bed volume, but the difference showed to be insignificant (Fig. 2, Table 4). Both the presence and number of clips were significantly associated with the boost PTV volume (101.7 vs. 51.2 $cm^3$and 40.9 cm^3, p=0.0001; Fig. 2, Table 4).

Discussion

The role of the tumor bed boost is well defined in the postoperative treatment of early stage breast cancer patients. Randomized and controlled studies have shown the impact that the boost has on local tumor control [1, 20]. Various boost studies have reported 20–50% relative reduction in local failure. During patient selection, females below the age of 50 are routinely recommended to receive tumor bed boost. Additional risk factors for local recurrence can be big tumor size, close surgical margins, high grade invasive ductal or in situ ductal tumors, high mitotic index, hormone receptor negative tumors (contraindication for hormonal therapy), and presence of extensive intraductal component [9]. In our group of patients, nodal positivity and close resection margins resulted in a significantly higher local relapse rate (Table 4, Fig. 1). The influence of the nodal status on local tumor control should be special characteristics of our patient group.

Various delivery methods of tumor bed boost can be applied: the main possible techniques used are the photon, the electron and the high dose rate after loading brachytherapy (HDR-AL) boost, administered either intraoperatively or following the WBI. In focus of local control and side effects, when comparing the interstitial brachytherapy (BT) to external beam techniques, BT seems to be equal or even better in case of deep situated tumors [16, 23]. There are many institutes where direct electron field is used by focusing on the skin scar for boost irradiation of the tumor bed. Multiple studies have shown the high likelihood of missing the true peri-lumpectomy target volume when clinical localization focusing on the scar is used [3, 4, 15]. In our previous planning study [13] we demonstrated that 3D CT based photon boost technique gives better coverage to the tumor bed and higher conformality compared to electron boost and for the superficial targets (tumor bed-skin distance 1 cm to 2 cm) photon boost seems to be the better choice.

In case of tumor bed boost irradiation, an important issue to address is the tumor bed definition. CT scans are useful for localizing the postlumpectomy cavity [2, 8, 22], while

Table 4 Results for the variable analysis. Statistically significant values marked as bold

Variable-dependent factor	Values-mean (median; SD)	P
Tumor bed clip- boost volume		
- no clip	101.7 cm^3 (101.5; 24.7)	**0.0001**
- single clip	51.2 cm^3 (51; 26.5)	
- multiple clip	40.9 cm^3 (36; 19.1)	
Resection status- boost volume		
- close	60.6 cm^3 (56; 31.1)	0.45
- clear	51.2 cm^3 (51; 26.5)	
Breast fibrosis- boost volume		
- Grade 0 fibrosis	58.6 cm^3 (54.5; 34,61)	0.9821
- Grade I–II fibrosis	57.5 cm^3 (54; 26.9)	
Fat necrosis- boost volume		
- Grade 0 fat necrosis	61.7 cm^3 (53; 35.8)	0.401
- Grade I fat necrosis	54.6 cm^3 (56.5; 18.6)	
4-year probability of local tumor control—*Resection status*		
- close	58/61–95%	**0.0403**
- clear	16/16–100%	
4-year probability of local tumor control—*Nodal status*		
- N0	54/54–100%	**0.00075**
- N1	20/23–87%	

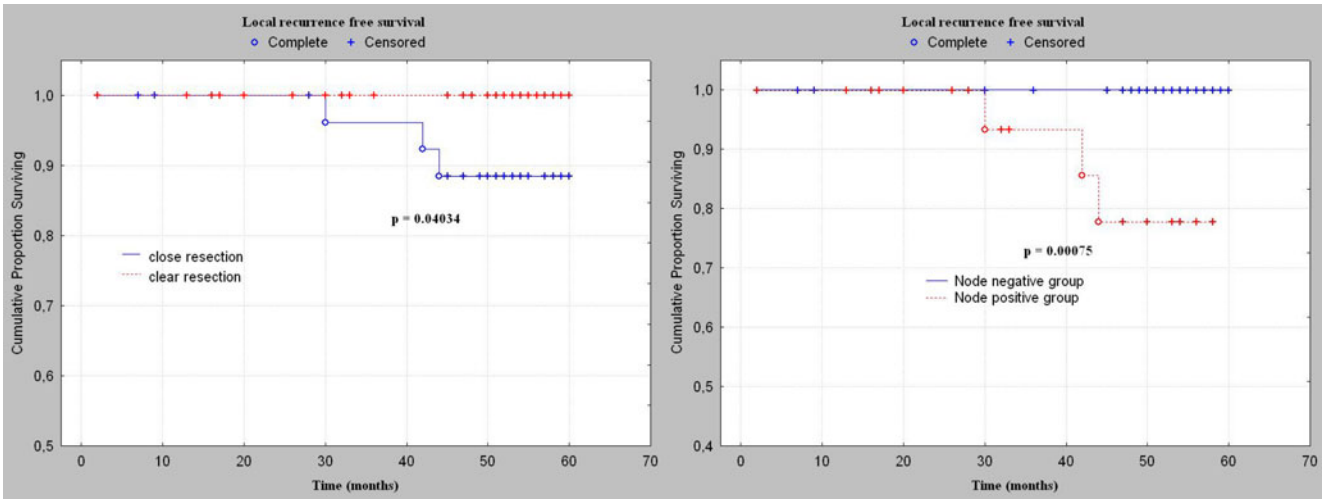

Fig. 1 In the local relapse free survival the close resection and the nodal positivity resulted significant difference in favor of the safe resection group (*left* side, *red line*) and the node negative group (*right* side *blue line*)

ultrasonography has also been demonstrated to be an acceptable imaging modality [19]. Placement of surgical clips at the lumpectomy cavity seems to be the most optimal way to assist tumor bed localization [8, 27]. To date there have been several studies comparing the accuracy of clinical localization to the use of surgical clips. No clear definition was given for adequacy of target coverage in several earlier studies. In more recent studies, 'adequate' coverage has been variously defined, ranging from surgical clips being within the treatment fields, to requiring inclusion of a margin of up to 2 cm around all clips. Depending on these definitions and the precise method of clinical localization, the accuracy of clinical localization ranged from 26% to 83%. Clinical set up covering the surgical scar with a minimum 1 cm margin in each direction resulted in a 39% rate of adequate coverage, defined as inclusion of all surgical clips with at least a 1 cm margin. Higher rates of adequacy were found when larger clinical margins of up to 4 cm were used, however, for many patients this would approximate whole breast irradiation [3–5, 10, 11, 14, 15, 18]. A study designed by Smitt et al. found that both the ability to visualize the excision cavity and the cavity size declined over time; results were similar with CT and ultrasound, highlighting the potential for treating excess normal tissues if boosts were planned based on CT scans in the early post-operative period (30 days) [22]. Regine et al. compared both clinical set up and CT planning to surgical clips and found that CT planned boosts are adequate in 17/17 cases, as compared to 5/17 for clinical set-up [18].

In our study 59/77 patients (76%) had surgical clips in the tumor bed, but only 20 (26%) of them had multiple clips. In these cases the number of implanted clips ranged from 2 to 7, with a mean number of 4. Ideally for tumor bed marking, six clips should be used marking the tumor bed borders in all directions. In our study the mean tumor bed volume was measured as 60.3 cm^3 for this patient group,

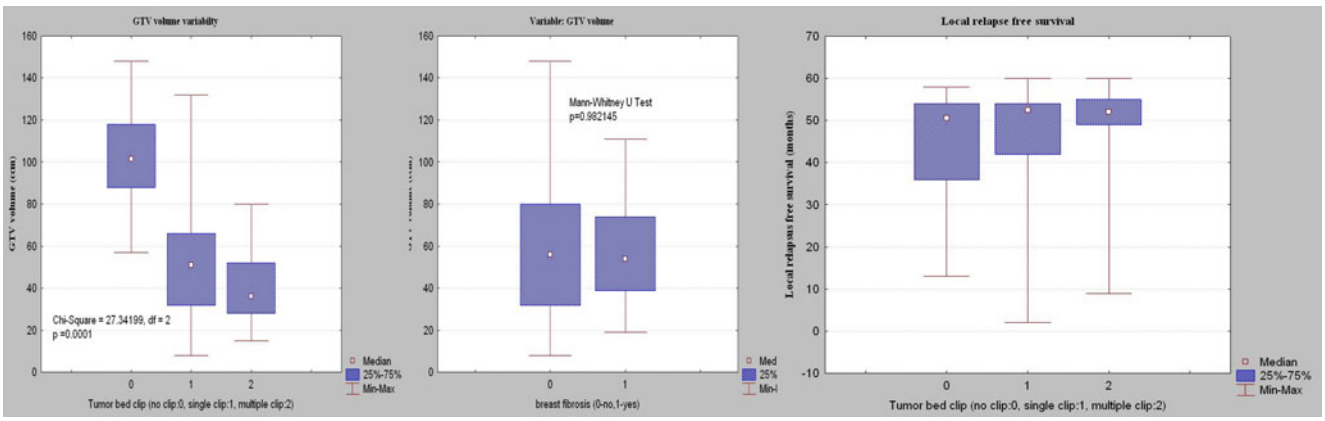

Fig. 2 The presence of tumor bed clips resulted in a significantly lower tumor bed volume (*left* side column 0). No correlation was found between the breast fibrosis and the tumor bed volume (*middle* image/graph). The presence of tumor bed clips didn't result in better local relapsus free survival (*right* side)

(Table 3). This volume was significantly lower compared to EORTC "boost-versus-no boost" trial's photon boost volume (288 cm^3), and on the same level with interstitial HDR-AL boost volume (60 cm^3) [17]. The CT based 3D planning allowed us to use well defined and smaller PTV volumes. In his study Shafak Al Uwini et al. (EORTC boost versus no boost trial compared to Young Boost trial) concluded that the introduction of CT-based volume delineation and treatment planning for the delivery with external beam radiotherapy of a boost in the framework of breast conserving therapy resulted in a significant increase of the irradiated boost volume, independent of the boost technique [21]. The reported median tumor bed volume from the Young trial was 127.1 cm^3, however, there is no information about the tumor bed clip status. In our study, the boost volumes in patients without tumor bed clips presented as being nearly equal to this value (101.8 cm^3–127.1 cm^3). Our results suggest that the presence of the clips result in a significantly lower tumor bed volume (Fig. 2, Table 4).

In the radiotherapy of breast cancer patients the cosmetic outcome is also a very important issue to be considered. Beside the boost method other important factors influencing the cosmetic outcome include tumor location, size of excision, breast size and operative complications [9]. Another influencing factor is the subjectivity: in our study the cosmetic outcome scoring was based on the patients and the examiners decision (four independent institutes). The reported 89.6% (69/77 cases) of good and excellent results seems to be similar compared to the data found in the literature [25, 26]. In the EORTC study for the boost group the best cosmetic results were presented in case of HDR-AL boost, using the smallest PTV volumes, suggesting a possible relation between the boost volume and good cosmetic outcome. Our side effect profile seems to be better compared with the reported EORTC values. In our experience the following factors may have positively influenced the side effect profile: lower tumor bed volumes, lower boost doses (only eight patients received 16 Gy), fibrosis and fat necrosis scoring based on new diagnostic mammography findings, only 4 year mean follow up time.

Conclusion

3D conformal photon boost is a feasible treatment modality for breast cancer patients. Our results are comparable with other boost studies in respect to the local control and side effect profile. The presence of tumor bed clips resulted in a significantly lower boost PTV volumes, however, no correlation was found between the boost volume and breast fibrosis. In the local relapse free survival analysis, nodal negativity and safe resection resulted in significantly higher RFS.

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