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Original paper

Breast deformation during the course of radiotherapy: The need for an additional outer margin

J. Seppälä[a,*], K. Vuolukka[a], T. Virén[a], J. Heikkilä[a], J.T.J. Honkanen[a], A. Pandey[b], A. Al-Gburi[b], M. Shah[b], S. Sefa[b], T. Koivumäki[c]

[a] Center of Oncology, Kuopio University Hospital, Kuopio, Finland
[b] Department of Applied Physics, University of Eastern Finland, Kuopio, Finland
[c] Department of Medical Physics, Central Finland Central Hospital, Jyväskylä, Finland

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ABSTRACT

Purpose: The aim of this retrospective study was to investigate and quantify the extent of breast deformation during the course of breast cancer (BC) radiotherapy (RT). The magnitude of breast deformation determines the additional outer margin needed for treatment planning to deliver a full dose to the target volume. This is especially important when using inverse planning techniques.

Methods: A total of 93 BC patients treated with RT and with daily CBCT image guidance were selected for this study. Patients underwent either only breast-conserving surgery (BCS) ($n = 5$), BCS with sentinel node biopsy ($n = 57$) or BCS with radical axillary node dissection ($n = 31$). The treatment area included the whole breast and chest wall (54%) or also the axillary lymph nodes (46%). 3D-registration was conducted between 1731 CBCT images and the respective planning CT images to assess the difference in breast surface.

Results: The largest maximum breast surface expansion (MBSE) was 15 mm; the average was 2.4 ± 2.1 mm. In 294 fractions (17%), the MBSE was ≥ 5 mm. An outer margin of 8 mm would have been required to cover the whole breast in 95% of the treated fractions. There was a statistically significant correlation between the MBSE and body mass index ($r = 0.38$, $p = 0.001$).

Conclusions: Significant changes in the breast surface occur during the course of BC RT which should be considered in treatment planning. An additional margin outside the breast surface of at least 8 mm is required to take into account the anatomical changes occurring during BC RT.

1. Introduction

Whole-breast external beam radiotherapy (RT) after breast-conserving surgery (BCS) is the golden standard in breast cancer (BC) treatment since it substantially reduces the risk of local recurrence [1]. Unfortunately, RT can also cause acute or late toxicities such as erythema, edema, pneumonitis, fibrosis, breast shrinkage and cardiotoxicity [2–5]. The incidences of acute and late toxicities of RT have been reported to correlate significantly with poor dose distributions [6,7]. In recent years, the application of volumetric modulated arc therapy (VMAT) techniques has increased in modern RT. In BC RT, the use of VMAT techniques can decrease the radiation doses delivered to critical structures, such as lungs and heart, and simultaneously increase the homogeneity in the treated area reducing the probability of toxicities [8–10].

In BC RT, the clinical target volume (CTV) includes the mammary gland adjoined to the skin. To ensure a full dose coverage of the CTV, an expansion is added to create a planning target volume (PTV), intended to take account of all the treatment related inter- and intra-fractional uncertainties. Breast edema, one of the anatomical uncertainties, is a well-recognized morbidity reported to occur in anything from 15 up to 90% of the women treated with BCS [11–13]. In order to cover the whole breast and to take account of these anatomical changes, an outer margin is needed for treatment planning to deliver a full dose to the target volume.

With conventional tangential RT techniques, the field size can readily be adjusted outside the skin with a proper margin without increasing the dose to the healthy structures. Moreover, with most of the intensity modulated RT (IMRT) planning techniques, the dose can be expanded outside the skin by manual fluence extension to ensure adequate target dose coverage even in cases with breast deformations. However, with modern VMAT techniques, the expansion of the dose

* Corresponding author at: Kuopio University Hospital, Centre of Oncology/Radiotherapy dept. (4251), Kelkkailijantie 7, rak. 7, 3.krs, 70210 Kuopio, Finland.
E-mail address: jan.seppala@kuh.fi (J. Seppälä).

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outside the skin surface is more problematic. Some optimization algorithms have the possibility to add a so-called autoflash or skin flash to the treated volume in which the dose is expanded outside the skin [10]. In optimization systems where it is not possible to expand the dose outside the skin automatically, one solution is to use “optimization” or “pretend” or “virtual” bolus in plan creation and to expand the PTV outside the original body contour. After the plan optimization, the bolus is removed in the final dose calculation [14–16]. The removal of the optimization bolus will, however, exert an effect on the dose distribution and this makes the planning task challenging and more laborious and furthermore, the effect increases with a thicker bolus. Naturally the bolus and the PTV expansion added should encompass all the uncertainties that occur outside of the skin contour defined in the planning CT image.

The extent of the outer PTV margin required to expand the dose outside the skin is currently unknown. The swelling and positional changes of the breast during the course of RT treatment can exert a major effect on the dose coverage of the target volume [17]. This study was designed to investigate the amount of breast deformations by analyzing daily variations from the cone beam CT (CBCT) images in the treatment position. As far as we are aware, this is the first systematic study which has investigated the changes occurring in the breast surface during BC RT. The data presented in this study can be used in defining the extent of the external outer margin needed in BC RT, especially with inverse planned treatment techniques such as VMAT and IMRT.

2. Methods

2.1. Patient population

A total of 93 BC patients (48 left and 45 right sided), were retrospectively selected for the study. The patients were randomly selected from two different time periods (October 2013 - September 2014 and November 2016 - September 2017) since we wanted to include patients for the analysis who had been treated either with or without deep inspiration breath hold (DIBH) technique (the former patient group without DIBH and the latter with DIBH).

Patients underwent either only BCS (lumpectomy) ($n = 5$), BCS with sentinel node biopsy (SNB) ($n = 57$) or BCS with radical axillary node dissection ($n = 31$). A slight majority i.e. 54%, of the patients included in this study received neoadjuvant chemotherapy and 10% were HER2-positive. The detailed patient characteristics are presented in Table 1.

All the patients were imaged for treatment planning in the supine position on a breast board (C-Qual™ Breastboard, Civco Radiotherapy, USA) with arms above the head in a Toshiba (Aquillion LB, Toshiba Medical Systems Corporation, Japan) or a Siemens (Somatom Definition AS, Siemens Healthcare GmbH, Germany) CT (Fig. 1A). Twenty left sided patients were imaged in DIBH with the guidance of an optical system (Sentinel, C-RAD AB, Sweden) while the remainder of left as well as all right sided patients were imaged with free breathing.

The delineated CTV included the whole breast and chest wall in 54% of the patients whereas the axillary lymph nodes were included in the remaining 46% of cases. A margin of 5 mm was added to the CTV to generate a PTV. Hypofractionation (15 × 2.67 Gy ad 40.05 Gy) was mainly used in the breast only treatments while the patients in whom the axillary lymph nodes had been delineated were treated with conventional fractionation of 25 × 2 Gy ad 50 Gy.

All the patients were treated with a VMAT technique using 6 MV photon energy either with two opposing tangential VMAT fields [10] or two continuous clockwise and counterclockwise VMAT fields of approximately 240°. Each treatment field was set to have an autoflash of 2 cm (extension of the dose into the air) for the PTV in the Monaco treatment planning system (Monaco v3.3 and v5.11, Elekta AB, Stockholm, Sweden).

Table 1
Characteristics of the patients.

Characteristic	Classification	Number of patients (%)
Side	Left	48 (52%)
	Right	45 (48%)
DIBH	Yes	20 (22%)
	No	73 (78%)
Fractionation	Hypo (15 fr)	49 (53%)
	Conventional (25 fr)	44 (47%)
Extent of surgery	BCS only	5 (5%)
	BCS and SNB	57 (61%)
	BCS and radical axillary node dissection	31 (33%)
Number of dissected axillary nodes	0–2	35 (38%)
	3–10	33 (35%)
	greater than 10	25 (27%)
Chemotherapy	Yes	50 (54%)
	No	44 (46%)
Time between surgery and CT simulation	< 1 month	21 (23%)
	1–4 months	28 (30%)
	greater than 4 months	44 (47%)
BMI *	< 25 (normal weight)	18 (25%)
	25–30 (overweight)	35 (49%)
	greater than30 (obese)	19 (26%)

BCS = Breast-conserving surgery
BMI = Body mass index
DIBH = Deep inspiration breath hold
SNB = Sentinel node biopsy
* = data available from 72 patients

Patients were treated with an Elekta Infinity linear accelerator with Agility MLC. Before every treatment fraction, the patients were aligned using the skin marks and room lasers. Daily low dose CBCT images (imaging protocol 100 kV, 20 mA/frame, 10 ms/frame, 174 frames, S20 collimator, rotation of 190°, approximated duration of 32 s, the average dose from one CBCT scan about 0.1 cGy) were acquired after patient setup (Fig. 1B) and the treatment isocenter was positioned based on the 3D image registration.

The acquired daily CBCT images were analyzed retrospectively with the automated tools in the Mosaiq patient verification system (v2.62, Elekta AB). Maximum mutual information (MMI) registration was performed in 6D with a box shaped region of interest between 1731 CBCT and the respective planning CT images. First, the automated registration was performed based on the chest wall and the respective shifts and rotations were recorded (Fig. 2A). Second, the registration was limited to the surface areas of the breast tissue only and the difference between the two registrations was again recorded (Fig. 2B). The subtraction of the two different registrations allowed the calculation of the average change in breast surface contour which was independent of any errors in patient positioning. A 2-dimensional vector magnitude was calculated from the right/left and anterior/posterior shifts for each fraction to represent the maximum breast surface expansion (MBSE). By using the values of MBSEs we defined the outer margin needed to account the anatomical changes during BC RT.

Statistical analysis was conducted with Microsoft Excel using two-sided Students *t*-test and Pearson correlation analysis. A p value of < 0.05 was considered to be statistically significant. The study was approved by the institutional scientific and ethics committee.

3. Results

This study included 93 BC patients and a total of 1835 treatment fractions. Of these, 104 of the CBCT images were excluded, mainly because of artefacts on the edge of the CBCT image and poor image quality which prevented the automated registration. Thus, a total of 1731 daily CBCT images were analyzed. Patient age was on average 64 years (range 42-89y) and the mean volume of the PTV was 1471 cm^3 (range 311–2394 cm^3). This volume included also the lymph node areas

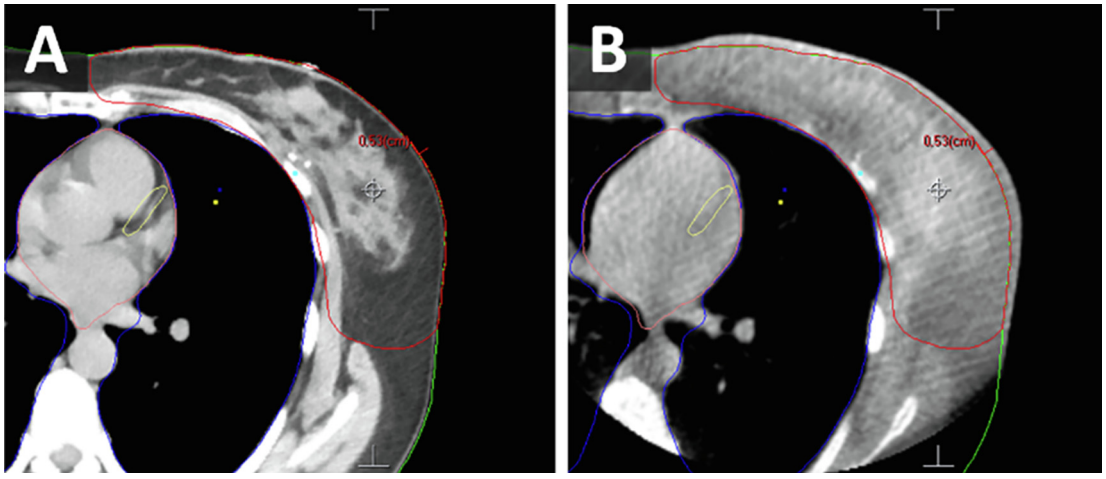

Fig. 1. (A) Planning CT and (B) corresponding CBCT of one fraction in one left sided patient.

if treated. The average time interval between the surgery and the CT simulation was 101 ± 66 days whereas it was only 8 ± 3 days between CT simulation and the first fraction. The mean overall treatment time was 27 days.

On average, the MBSE was 2.4 ± 2.1 mm during the treatment course of the whole population. With 35 patients (38%), the MBSE was always ≤ 3 mm. However, in 32 (34%) patients, there was an MBSE of 5 mm or more, and furthermore in 12 (13%) patients, an MBSE ≥ 8 mm was detected. The largest MBSE recorded was 15 mm while in 294 fractions (17%) the MBSE was ≥5 mm. An outer margin of 8 mm would have been sufficient to cover the whole breast surface in 95% of the treated fractions. The recorded MBSE values are presented in Fig. 3.

On average, the absolute rotational differences between CBCT and planning CT in the breast area were 1.9°, 1.7° and 2.0° in coronal, sagittal and transversal directions, respectively. In 21% of fractions, the breast had a rotational error larger than 4°.

Body mass index (BMI) displayed a significant positive correlation with the recorded MBSE ($r = 0.38$, $n = 72$, $p = 0.001$). The MBSEs were slightly but significantly larger in left sided patients (left 2.6 ± 2.3 mm, right 2.1 ± 1.9 mm, $r = 0.32$, $p = 0.002$). The difference between left and right side was also statistically significant in the coronal (left 0.6 ± 2.7°, −0.1 ± 2.3°, $p < 0.001$) and transversal (left −0.8 ± 2.8°, right 0.2 ± 2.6°, $p < 0.001$) rotations. No correlation was found between the MBSE and the patient's age ($r = 0.13$, $p = 0.21$) or the extent of surgery ($r = 0.01$, $p = 0.89$). Furthermore, the time between surgery and radiotherapy ($r = 0.15$, $p = 0.16$) or the number of nodes removed ($r = 0.03$, $p = 0.80$) did not correlate with the MBSE. Instead, a weak correlation was observed with the PTV size ($r = 0.20$, $p = 0.06$).

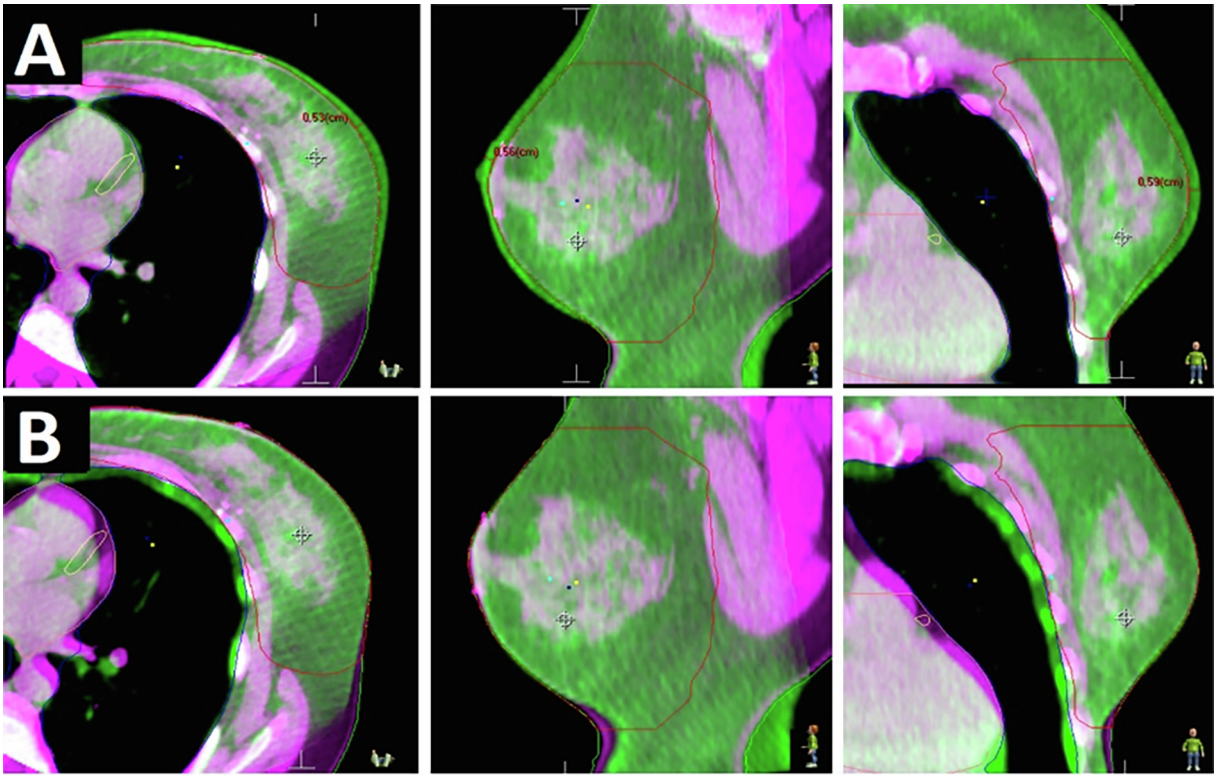

Fig. 2. Planning CT (magenta) and CBCT (green) image registrations were performed (A) first based on the mutual information of the chest wall and (B) second only on the surface areas.

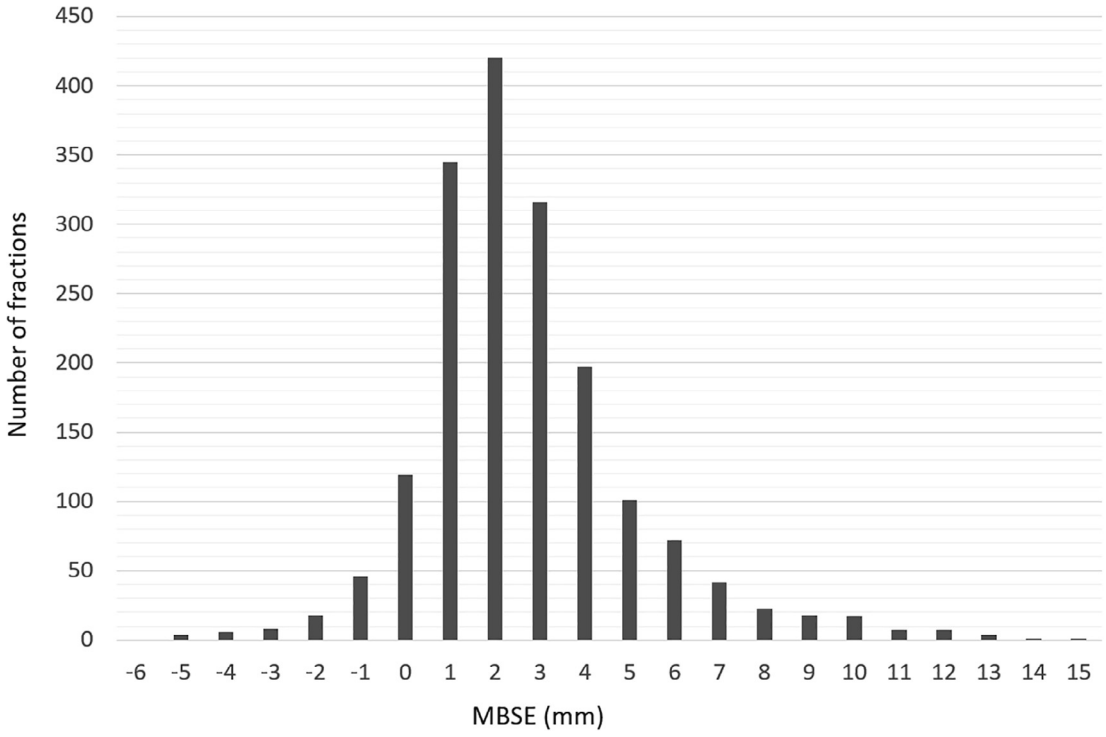

Fig. 3. Histogram of the daily maximum breast surface expansions (MBSE) in all of the investigated setup images. A positive MBSE value refers to the expansion of the breast contour.

4. Discussion

In this retrospective study, we investigated 1731 CBCT images to quantify the extent of breast deformation occurring during BC RT. We observed that the MBSE was 5 mm or larger in 17% of the treated fractions. This highlights the need for the use of an additional outer margin when using inverse optimization with VMAT or IMRT techniques in order to avoid underdosing the breast tissue.

Breast edema, seroma and hematoma have been reported to occur during the course of BC RT [18,19]. Gonzales et al. reported breast edema rates of 15.8% with patients undergoing modified radical mastectomy or BCS [20]. The occurrence of the reported edema was unpredictable [19]. Back et al. found that breast edema was associated with surgical factors and was evident in 20.5% of their patients [12]. These observed swelling rates are in line with our results which showed that with more than 34% of our BC patients, at least once during the course of their RT treatment, displayed a breast swelling larger than 5 mm. Breast edema has also been reported to correlate with the extent of surgery and a larger breast size [21,22]. Here, the breast swelling was found to correlate with BMI. In addition, there was a borderline correlation between PTV volume and MBSE. Even though increased age has also been reported to be a risk factor for breast edema [22], it was not a significant variable in our study.

We calculated the difference in breast surface as the difference between the outer contour of planning CT and the daily CBCT images. We acknowledge that some of the deformations of the breast reported in this study are not solely attributable to the swelling of the soft tissue but could be related to positioning errors. Even though a breast board with arm fixation was used, the patient's arms may be in a slightly different position in each CBCT. This can cause the breast to be in a slightly different position. However, all the breast surface changes, either resulting from positional changes or swelling, will result in a degradation of the planned dose distribution.

In current practise, an electronic portal imaging device capable of MV-imaging or 2D-imaging with kV energies is typically used in confirmation of the patient's position. In 2D-imaging protocols, the patient's position is verified by using bony anatomy, such as the sternum, vertebrae and ribs, as a surrogate for the soft tissue [23,24]. It has been reported that if one applies 2D kV-imaging, then the intrafraction movement may be underestimated [25]. In our study, daily CBCT set-up images were used to quantify the extent of the breast surface changes. As far as we are aware, this is the first time that the daily variations in breast deformations have been systematically investigated.

Previously, few studies have evaluated the effect of simulated breast swelling on the quality of the VMAT treatment plans. If there is no expansion of the dose into the air, the under-dosage can be severe in a case of breast edema or patient displacement; 5 and 10 mm discrepancies leading to 5% and 25% reduction in V95%, respectively [14]. Further, the use of 7 mm PTV expansion with 10 mm optimization bolus have been reported to produce acceptable PTV coverage even in case of 10 mm breast expansion [14]. Rossi et al. concluded that optimization to PTV with 5 mm in-air expansion and using 8 mm optimization bolus might be sufficient for most of the breast cancer patients [26]. In case of large (10 mm) deformations, larger PTV extension or replanning was recommended. However, performance of autoflash tool, where the collimator leaves are opened when the beam direction and leaf motion intersect with the PTV and air interface, is not well known. Based on the results presented in this study, treatment planning techniques that are robust in case of up to 8 mm breast expansion should be used in the BC RT.

The MBSE values presented in this study considered also the rotational errors in the position of the breast. The average rotational errors were approximately two degrees in all three directions. In 21% of the fractions, at least one rotational error was larger than four degrees. However, if the rotational errors are not corrected before the treatment, for example with a 6D-couch, a four-degree rotation would represent an additional translational error of 4 mm for a point of interest located 6 cm from the treatment isocenter. In addition, we did not investigate the largest surface shape change of a single point but rather took an average of the whole skin area. As a result, the maximum surface expansions in a single point will be larger than the reported average MBSE

values.

With 3D-image guidance, the set-up uncertainties can be minimized, although not totally eliminated. As discussed above, the rotational errors of the patient or the breast itself can introduce a considerable uncertainty at the distal borders of the PTV. The anatomical changes in the shape of the breast investigated in this study, contributes to these total uncertainties. In addition, possible patient movement during the treatment and breathing motion need to be considered when determining the treatment margins for BC RT [27]. If the patients are treated with free breathing, then the motion amplitude also increases the amount of surface expansion needed. The breathing related amplitude has been approximated to be 1.5 to 2 mm [28]. In our study, the CBCT acquisition time was 35 s. The slow CBCT imaging might have caused a slight blurring of the reconstructed images but this does not explain the deformations since the blurring also occurred at the chest wall, which was used as a reference. Moreover, we did not observe any difference in the MBSEs between the patients imaged in DIBH or in free breathing.

One key limitation of this study is that it was performed in a single institute. The patients underwent the surgical procedures by a single team following the national guidelines but we acknowledge that practice protocols might vary between different operating centers around the world. In addition, all of the studied patients were treated with the same fixation system. Nonetheless, the arms above the head positioning of the patients is most commonly used in RT departments and the systematic effects of various fixations systems on the position of the arms have been reported to be a mere few millimeters at most [29,30].

An outer margin of 8 mm would have been required to cover the whole breast surface in 95% of the treated fractions. However, it should be noted that this assumption is based on the total number of fractions e.g. in those patients with extensive deformations, this would be an underestimate of the outer margin needed. The BMI and the side of the treatment were found to correlate with the breast surface expansion. However, the nature of breast deformation is not predictable and might also depend on patient specific issues such as treatment-related lymphedema and changes in the lymphatic circulation [31]. Because of the unpredicted breast tissue deformations, we recommend that daily or at least weekly 3D-imaging should be used to identify patients with large breast surface expansions. Large deformations might require individual replanning in some patients because of the increased tissue and the resulting non-even dose distributions [17]. In addition, large surface expansions might result some underdosing of the target volume with VMAT dose delivery because of the limited in-air outmargins.

5. Conclusions

In this study, significant changes were detected in the breast surface during the course of BC RT. In addition to the conventional PTV margin for set-up errors, an additional margin outside the breast surface is required to take account of changes in the breast's surface in whole breast irradiation. The amount of expansion outside the body needs to be at least 8 mm to compensate for the deformation of the breast during the course of treatment. The anatomical deformations occurring in the breast were not fully predictable, although a moderate correlation was found with BMI and with the side of the treatment.

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