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RESEARCH

Respiratory Motion, Anterior Heart Displacement and Heart Dosimetry: Comparison Between Prone (*Pr*) and Supine (*Su*) Whole Breast Irradiation

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Abstract To analyze respiratory motion of surgical clips, chest wall (CW) and the anterior displacement of the heart and its impact on heart dosimetry between prone (*Pr*) and supine (*Su*) positions during whole breast radiotherapy after breast conserving surgery. Sixteen patients underwent 4D-CT for radiotherapy planning in *Pr* and *Su* positions. Maximum inhale and maximum exhale phases were analyzed. Mean 3D vectorial displacements±standard deviations (SD) of the surgical clips were measured. Volumetric changes of the CW were recorded and compared. Cardiac displacement was assessed by a volume between the inner surface of CW and the myocardium of the heart (CW/H-V). For left-sided cases, comparative dosimetry was performed in each position simulating no- (*Pr*-noC, *Su*-noC) versus daily correction protocols (*Pr*-C, *Su*-C). The movements of 81 surgical clips were analyzed. Prone positioning significantly reduced both the mean 3D vectorial displacements (1.1±0.6 (*Pr*) vs. 2.0±0.9 mm (*Su*), $p<0.01$) and their variability (0.3±0.2 vs. 0.5±0.3 mm, $p=0.01$). Respiration-induced volumetric changes of CW were also significantly lower in *Pr* (2.3±4.9 vs. 9.6±7.1 cm^3, $p<0.01$). The CW/H-V was significantly smaller in *Pr* than in *Su* (39.9±14.6 vs. 64.3±28.2 cm^3, $p<0.01$). Besides identical target coverage heart, left-anterior-descending coronary artery (LADCA) and ipsilateral lung dose parameters were lowered with *Pr*-C compared to *Pr*-noC, *Su*-C and *Su*-noC. Prone position significantly reduced respiration-related surgical clip movements, their variability as well as CW movements. Significant anterior heart displacement was observed in *Pr*. Prone position with daily online correction could maximize the heart and LADCA protection.

Keywords Breast cancer · Prone breast radiotherapy · 4D-computed tomography · Respiratory motion · Left-anterior-descending coronary artery

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Introduction

Radiotherapy (RT) in supine (*Su*) position is the standard treatment for early breast cancer (BC) after breast conserving surgery (BCS) improving local tumor control and overall survival [1–3]. Recent evidence supports the use of hypofractionated whole breast (WBI) and accelerated partial breast (PBI) irradiation for selected patients with similar outcomes compared to conventionally fractionated WBI [4–7]. Use of a simultaneously integrated boost is also a promising method of maintaining a shorter radiation schedule [8]. For these investigational techniques a higher fractionation dose is used, which may be close to the limits of normal tissue tolerance. Therefore any achievable reduction in irradiated non-target volume without compromising target coverage is a meaningful step towards better treatment. Within this context, an important goal is to reduce the margin between the clinical (CTV) and planning target volume (PTV), as the PTV is accounting for setup inaccuracies as well as movement-related uncertainties. However, before any reduction of safety margins, a better understanding of some factors beyond our control is required, such as respiratory motion.

Recent investigations in *Su* position revealed not only a wide range of target motion but also a different magnitude of respiratory motion for the different parts of the tumor bed (TB) [9].

Reducing respiratory related target movement could be achieved by different methods: either with a breath-hold techniques or simply positioning the patient in Prone (*Pr*) [10–18]. So far three small studies using magnetic sensors or four dimensional (4D)-CT compared the respiratory motion between *Pr* and *Su* and confirmed that both surgical clip- and chest wall (CW) movements are significantly reduced in *Pr* position [11, 15, 18]. Besides improved target dose homogeneity, *Pr* potentially decreases the radiation burden to lungs [10–18], while for heart the advantages are not obvious in all cases. Recent evidence showed an increased risk of major coronary events of 7.4 % per 1 Gy increase in mean heart dose [19]. The heart protection in *Pr*, especially with small breast size is a debated issue [10, 13, 16, 20, 21], due to anterior movement of the heart and the left-anterior-descending coronary artery (LADCA).

Beyond the respiratory related movements, the patient set-up accuracy is a cornerstone of safety margin reductions. The required CTV-PTV margins heavily depend on set-up accuracy and the applied verification protocol, thus having a high impact on dose delivery to the surrounding organs at risks (OARs). Since set-up errors seem to be inferior in *Pr* as compared to *Su* [11, 14, 15, 18, 22], we wanted to investigate whether dosimetric advantages of *Pr* could be maintained if a different treatment verification strategy is used.

In our study we aimed to analyze the respiratory motion differences between *Pr* and *Su* position and to investigate whether *Pr* position could reduce the variability of individual clip movement. We also compared the anterior heart displacements in both positions and its consequences on heart dosimetry, simulating no- versus daily online correction protocol for the left-sided breast cancer patients within this cohort.

Methods Materials

This study was approved by the Ethics Committee of the Centre Hospitalier Universitaire de Liège (CHU). Sixteen women underwent BCS for T1-2 invasive ductal-lobular carcinoma or high-grade ductal-carcinoma-in situ and were included independently of the breast size. The patient and tumor characteristics are presented in Table 1. All patients were eventually treated in *Su* position.

Respiratory Motion Analysis

Patient Positioning and Image Acquisition

For all patients a non-contrast 4D-CT CT-scan (Philips Medical Systems, UK, 85 cm bore, slice-thickness of 3 mm, C6 to below diaphragm) was performed under free-breathing conditions in both positions. The 4D-CT was performed in combination with a coiled belt (Philips) placed under tension around

Table 1 Patient and tumor characteristics

Variables	Values
No. of patients	16
Age, years, mean (range)	62 (38–79)
Weight, kg, mean (range)	71 (51–100)
T stage (%)	
Tis	1 (6)
T1b-c	12 (75)
T2	3 (19)
Breast side (%)	
Right	7 (44)
Left	9 (56)
Localization of tumor bed (%)	
IQs	4 (25)
Central	4 (25)
EQs	8 (50)
No. of surgical clips, mean (range)	5 (1–15)
Cup size (%)	
A–B	6 (38)
C–D	8 (50)
≥E	2 (12)
Whole breast volume, cm^3, mean (range)	780 (160–1873)

IQs internal-quadrants, *EQs* external quadrants lower ribs and epigastrium to record respiratory phases. The 4D-CT data were reconstructed in 10 phases, from 0 % to 90 % in steps of 10 % of the respiratory phase.

Analysis and Statistics

For analyzing the respiratory motion, datasets of the maximum inhale (50 %) and maximum exhale (0 %) phases were selected. In order to assess and compare the respiratory motion of clips, the mean and maximum 3D vectorial displacements (v3D)±standard deviations (SD) were measured. The clips were numbered consecutively from cranial to caudal. The CT coordinates (x, y, z) of each individual clip were recorded in the abovementioned two phases. The v3Ds were calculated and compared in both positions (Fig. 1). Results were compared using Wilcoxon sign-rank test.

Respiratory motion of the CW was assessed by an indirect approach. For each patient an anterior lung segment (ALS) was defined at the level of the clips, first on the maximum exhale dataset (Fig. 1). We defined its posterior border by drawing a straight line between the midpoint of the sternum and the midpoint of the lateral CW and then we closed the contour anteriorly by following the inner surface of the thoracic cage. We repeated the delineation in the maximal inhale phase while keeping the posterior border fixed. The volume differences of ALS (ΔALS) in both positions were recorded and compared using Wilcoxon sign-rank test.

Comparisons of means between different classes of variables were made using an ANOVA and a Kruskal-Wallis test. Correlations (Pearson and Spearman) were calculated between continuous variables. Statistical analysis was done using SAS version 9.2 (SAS Institute, Cary, NC, USA). Results were considered to be significant at the 5 % level (α= 0.05).

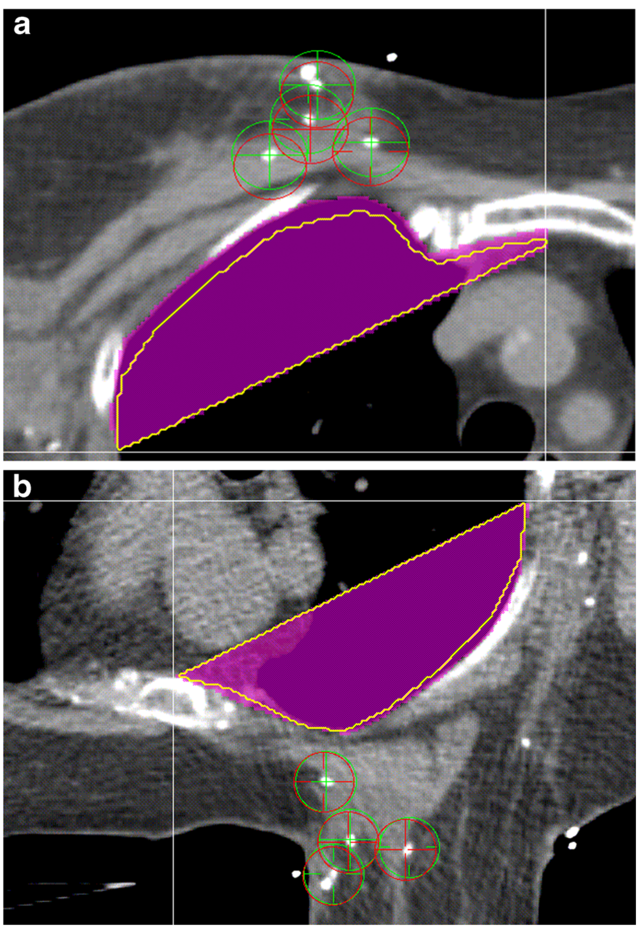

Fig. 1 Clip and thoracic wall movement analysis. Corresponding axial slices in *Su* (**a**) and *Pr* (**b**) in normal breathing condition. Surgical clips and anterior lung segment volumes are shown in maximal inhale (*green circles*, *purple contour*) and maximal exhale positions (*red circles*, *yellow contour*)

Set- Up Accuracy

All patients were treated in *Su* position using daily online cone-beam CT verification (Elekta XVI, version 4.2, Elekta ltd, Crawley, UK). Since *Pr* setup data from the analyzed cohort is not available, for dosimetric purposes we used the set-up data of 16 patients treated in *Pr* position. The two cohorts were matched on the breast cup size. Retrospective margin validation was performed in both positions by selecting the smallest margin for each direction which is covering 95 % of the set-up errors, mimicking the proposed coverage from the classical margin formula of van Herk [23].

Anterior Heart Displacement, Target and Non-Target Tissue Delineation, Radiotherapy Planning and Analysis

For this analysis all left sided breast cancer patients were selected (n=9). Six patients had a UK Cup size of A–B with a median CTV volume≤410 cc.

Cardiac displacement was assessed by defining a volume between the inner surface of the CW and the myocardium. The medial border of the contour was the sternum while laterally a vertical line perpendicular to the most lateral extent of the heart was respected. This pre-cardiac volume in *Su* was then compared with the corresponding measurement in *Pr* in each case individually. Results were compared using a Wilcoxon sign-rank test.

Heart and LADCA were defined according published criteria [24]. Whole-breast (WB) clinical-target-volume (CTV) was defined using wire plus any additional breast-tissue visualized on CT, limited by 5 mm from skin and chest-wall/lung interfaces. Since the dosimetric results strongly depend on the applied margin and indirectly on the treatment verification policy, we created two PTVs in each position:

- First we generated a PTV taking into account both setup- and respiratory errors. As a setup error we applied the above calculated prone -and supine related margins. This PTV represents the offline verification strategy.
- Afterwards, a PTV was created using only the respiratory error supposing that daily online treatment verification was used.

Thus, four plans were created for each patient: Prone corrected (*Pr*-C), Prone non-corrected (*Pr*-noC), Supine corrected (*Su*-C) and Supine non-corrected (*Su*-noC).

For each position, two 6 MV tangential field-in-field approach were used with a total of six segments [25]. A median dose of 40.5 Gy was prescribed to the WB in 15 fractions of 2.67 Gy. A total of 36 plans (four per left-sided patient) were generated using the same optimization objectives. Dosimetric evaluation for heart, LADCA and ipsilateral lung was performed using the following dose parameters: Dmean and D2 (the dose exceeding 2 % of the dose-volume histogram (DVH) points) and the proportion of the volume receiving at least 10 and 18 Gy (V10, V18). The treatment planning system was Pinnacle V9.6 (Philips Inc., Eindhoven, The Netherlands). ANOVA test was used for comparison of dose-volume parameters between the different planning strategies.

Results

Comparison of Respiration Induced 3D Vectorial Clip Displacements Between Pr and Su

Eighty-one surgical clip movements were analyzed. Patients had on average 5.1±3.1 clips. *Pr* positioning significantly reduced not only the mean 3D vectorial clip displacements (1.1±0.6 mm (*Pr*) vs. 2.0±0.9 mm (*Su*), p=0.001), but also their movement variability (0.3±0.2 mm vs. 0.5±0.3 mm, p= 0.011) (Fig. 2). Focusing only on the clips having the largest v3D in *Su* or the largest Δv3D between the two positions, the difference became more obvious (0.9±0.6 mm vs. 2.4± 1.3 mm, p=0.0004 and 1.09±0.66 mm vs. 2.55±1.22 mm).

No correlation was observed between mean Δv3D and the following patient-related parameters: breast side (left vs. right), T stage, TB localization (quadrants), cup size, number of clips (Wilcoxon test, <0.05), age and weight (Pearson test, <0.05).

Chest Wall Movement

The ΔALS was significantly higher in *Su* position than in *Pr* position (9.6±7.1 cm^3 vs. 2.3±4.9 cm^3) (p<0.01), suggesting that CW movements are considerably reduced in *Pr* position. We did not find any correlation between respiration-induced CW movements and the following patient related parameters: breast side, T stage, TB localization, cup size, number of clips (Wilcoxon test, <0.05), age and weight (Pearson test, <0.05).

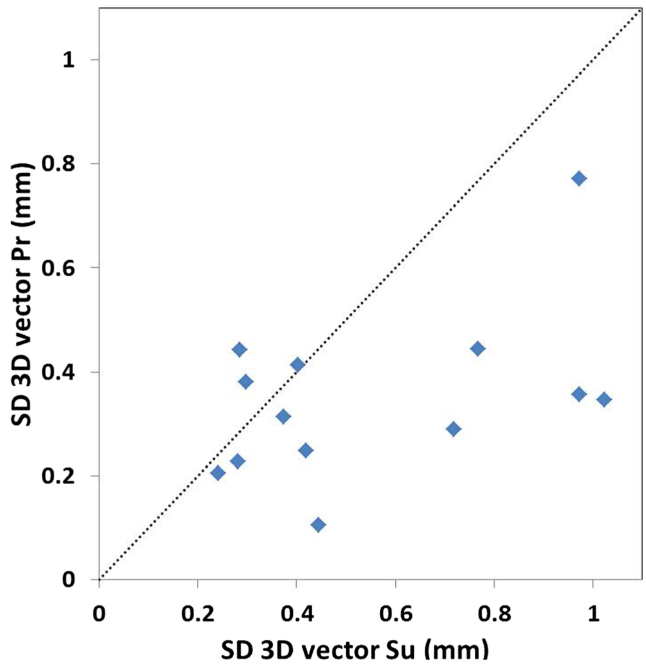

Fig. 2 Variability of individual clip movement per patients: Prone vs. Supine

There was no significant association between mean Δv3D and ΔALS (Pearson test, p=0.39), nor between maximum Δv3D and ΔALS (p=0.11).

Anterior Heart Displacement

The mean volume of the pre-cardiac space was significantly smaller in *Pr* position than (39.9±14.6 cm^3 vs. 64.3± 28.2 cm^3) in *Su* position (p<0.01), reflecting an anterior movement of the heart in *Pr*.

Set-Up Accuracy

Figure 3 shows the cumulative probability of the setup errors for each direction in both *Pr* and *Su* positions. The smallest margins which cover 95 % of the setup errors were consistently larger for prone position, especially in the lateral direction: longitudinal: 5.6 (Su) vs. 8.7 mm (Pr), vertical: 5.9 vs. 6.5 mm, lateral: 10.2 vs. 4.8 mm.

Planning Parameters

There were no significant differences between the volumes in *Su* and *Pr*. Identical CTV coverage were obtained for each individual plan, thus comparison of the DVH related OAR

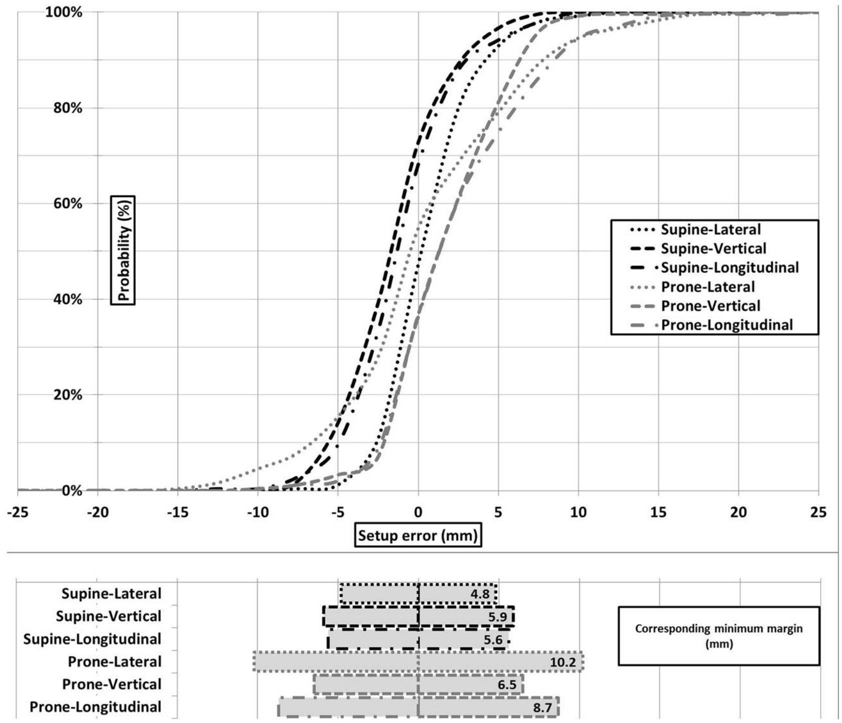

Fig. 3 Cumulative probability of setup errors in *Su* and *Pr* position and the corresponding values to cover 95 % of the setup errors (in mm)

parameters were not influenced by individual adaptation of the treatment fields.

Dosimetric parameters for left-sided breast cancer patients are presented in Table 2.

Heart and LAD dose parameters were lower for Pr-C compared to the other three situations (*Pr*-noC, *Su*-C, *Su*-noC). Statistically significant differences ($p<0.05$) were reached for the heart Dmean, V10, V18 and for the V18 of the LADCA. As the SDs of the observed values were also lowest for Pr-C this might suggest that the achieved results are more consistent compared to *Pr*-noC, *Su*-C or *Su*-noC.

Prone position significantly decreased lung dose as compared to *Su* plans ($p<0.05$). All lung parameters were at least three times lower in *Pr*-C than in *Su*-C.

Table 2 Dosimetric parameters for left-sided breast cancer patients

Mean (SD)		Prone corrected	Prone non corrected	Supine corrected	Supine non corrected	*p*-value
CTV	Volume (cc)	394 (252)		409 (233)		NS
	Dmean (Gy)	39.8 (0.2)	39.9 (0.2)	40.1 (0.1)	40.1 (0)	NS
Heart	Volume (cc)	610 (92)		604 (68)		NS
	Dmean (Gy)	1.5 (0.4)	2 (0.6)	1.9 (0.6)	2.4 (0.9)	$p<0.05$
	V10Gy (%)	0.5 (0.5)	2.4 (2)	1.5 (1.4)	3.3 (2.9)	$p<0.05$
	V18Gy (%)	0.1 (0.2)	1 (1)	0.8 (0.8)	1.9 (1.8)	$p<0.05$
	D2 (Gy)	4 (1.7)	11.1 (6.6)	8.7 (6.3)	14.6 (10)	NS
LADCA	Volume (cc)	4 (1)		5 (1)		NS
	Dmean (Gy)	4.9 (2.7)	8.9 (5)	7 (3.8)	10.9 (5.7)	NS
	V10Gy (%)	13.6 (15.9)	33.2 (23.9)	25.2 (19.9)	33.2 (23.9)	NS
	V18Gy (%)	5.4 (7.9)	22.3 (19.4)	13 (11.3)	29.6 (22.8)	
	D2 (Gy)	14 (9.8)	23.7 (10.8)	16.2 (13)	22.1 (15.1)	NS
Lung_IL	Volume (cc)	1639 (494)		1576 (505)		NS
	Dmean (Gy)	1 (0.3)	1.3 (0.5)	3.5 (1.2)	4.3 (1.5)	$p<0.05$
	V10Gy (%)	0.9 (0.9)	1.7 (1.5)	9.8 (1.3)	13 (1.4)	$p<0.05$
	V18Gy (%)	0.5 (0.5)	1 (0.9)	6.9 (1.3)	9.5 (1.5)	$p<0.05$
	D2 (Gy)	5.2 (3.5)	9.7 (7.5)	32.9 (2.1)	35 (1.8)	$p<0.05$

NS not significant

Table 3 Comparative studies on respiratory motion (*Su* vs. *Pr*)

Author	pts	Modality	Structure	Motion magnitude (*Su* vs. *Pr*) (mm)	Max or SD (mm)
Morrow [14]	3/3 *	4D-CT	CW	2.3 vs. 0.1	0.9 vs. 0.4
Kirby [10]	26	4D-CT	CW	3 vs. 1	7 vs. 2
			Clips	RL: 1 v.s 0	RL: 3 vs. 1
				SI: 1 vs 0	SI: 3 vs.1
				AP: 3 vs 0.5	AP: 6 vs.2
Veldeman [17]	10	Magnetic sensor	Breast	0.5 vs .32	0.28 vs. 0.12
				1.27 vs. 0.92	0.6 vs. 0.38
Lakosi et al.	16	4D-CT	Clips	2 vs 1.1	0.6 vs 0.9
			Clips †	2.4 vs. 0.9	1.3 vs. 0.6
			CW **	9.6 vs. 2.3 cm^3	7.1 vs 4.9 cm^3

pts patients, *CW* chest wall, *RL* right-left, *SI* supero-inferior, *AP* antero-posterior, *SD* standard deviation, *not the same pts, ** volumetric comparison, † most mobile clips

Discussion

The primary objective of the study was to compare the respiratory motion of surgical clips and CW between *Pr* and *Su* position using 4D-CT data in normal breathing condition.

One possible way to reduce and harmonize respiration induced CW and TB motion would be the *Pr* position [11, 14, 15, 18]. This can be explained by thoracic- and abdominal wall compression and the fact that clips move away from the CW by gravity. Our results correspond well with the published data as we found a significantly reduced respiration-related clip and CW movement in *Pr* position (Table 3.) If we consider all clips, an average of 1 mm absolute reduction of 3D vectors was achieved in *Pr* (1.1±0.6 mm (Pr) vs. 2.0±0.9 mm (Su)), while for the most mobile clips the reduction was more than 2.5 times higher (0.9±0.6 mm vs. 2.4±1.3 mm).

Several authors described that different parts of the (clip-based) target can move differently in *Su* [15, 26, 27]. Price et al. and Morrow et al. observed that the lateral and, in some cases, superior parts of the breast surface moved more than the medial one [15, 28]. In contrast, other authors found that the most superior located markers move the least [27]. In our analysis we did not find any association between respiration-related clip motion and TB localization. However, the difference in individual clip movement is clearly observed in both positions (Fig. 2). This raises the question whether *Pr* position could not only limit but also synchronize the individual clip movement within the TB. More interestingly, we found that 3D vector' SDs per patients were on average more significantly reduced in *Pr* than in *Su* (see Fig. 2) supporting our hypothesis.

Prone position predictably and significantly reduced respiration-induced CW movements as well. We did not find any correlation between the magnitude of the CW motion and the clip displacements between the two positions (*Pr*-*Su*). This means that relatively large respiratory movements could be effectively reduced by *Pr*, but on the other hand, non-expected clip movements may also occur despite small CW movement differences. The latter could be explained by the changed motion patterns of the CW in *Pr*: in *Pr* the anterior chest wall movement is reduced, and as a compensation, the

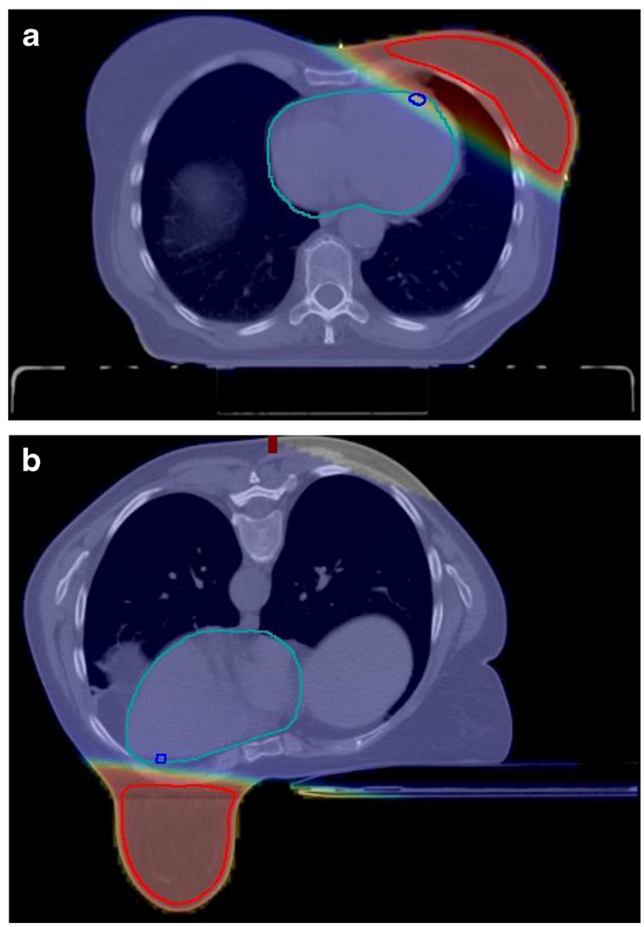

Fig. 4 Isodose distribution for Patient 6 in transverse plane. Good example for heart sparing. Note the anterior displacement of heart and LADCA in *Pr* position. LADCA (*blue*), heart (*green*), CTV (*red*)

back moves more. This could translate into a “paradox” motion, where the clips during inspiration show rather a posterolateral movement than an anterior displacement. Another reason could be the changed spatial distribution of the clips, since in *Pr* the relative position of the clips both relative to each other and to the CW are changed.

The potential advantages of *Pr* would be the lung and heart protection and a better homogeneity with accordingly reduced acute- and probably long term side effects [10, 12, 13, 16]. The reduced and synchronized TB motion may also represent a benefit since it allows decreasing CTV-PTV margin and as a consequence the volume of normal breast tissue irradiated. As there is a risk of higher treatment set-up errors in *Pr*, the beneficial effect of reduced respiratory motion can only be maintained if adequate daily image guidance is asssured [11, 14, 15, 18]. Our preliminary clinical results with prone breast WBI showed comparable set-up accuracy with the published data [29]. However the set-up accuracy of *Pr* could not be the part of this publication since our patients were treated in *Su*. In order to compensate the lack of *Pr* set-up data, we selected a matched cohort treated in *Pr* position. To simulate the effect of treatment position and verification protocols we performed a retrospective margin validation, which underlined the necessity of using larger CTV-PTV margins in *Pr* position if no daily correction protocol is applied.

The second objective of our study was to examine the anterior displacement of the heart and its impact on heart dosimetry, simulating different treatment verification methods. We found a significant anterior displacement of the heart in *Pr* position. This finding corresponds well with the results of Chino et al. notwithstanding a different methodology [30]. Recent publications already recommend *Pr* position for all left-sided breast cancer with large breasts achieving at least the same or even better heart protection than in *Su* [10, 13, 16]. However, for small breast sizes individual comparative planning studies or the use of predictive models are warranted [10, 13, 16, 22]. It should be mentioned that these studies focused on heart dose parameters. Only two publication evaluated radiation dose to the LADCA in *Pr* and *Su* WBI. Both used similar CTV-PTV margins for planning comparison. In the German study, the heart dose was not different between the two positions [20]. They reported a significantly higher dose exposure to the LADCA in *Pr* [20] which was whereas Kirby et al. had previously found lower LADCA and heart doses [11]. The difference might be related to the different contouring and treatment techniques. Furthermore, the applied margin and verification methods could potentially influence the dosimetric outcome as well. If the set-up precision is different between *Pr* and *Su* position (as it was shown in our data, Fig. 3), for comparative purposes one cannot apply the same CTV-PTV margin if no daily treatment verification available. Accordingly, the amount of incidentally included heart and LADCA volume would be different between the two groups. Thus we aimed to explore how the verification protocol can influence the dosimetric parameters between *Pr* and *Su* if treatment position-related CTV-PTV margins were applied. We demonstrated that *Pr* position with daily correction protocol could achieve the best protection of the heart and LADCA (Table 2, Fig. 4). However this advantage might disappear without daily corrections and became comparable with *Su* with proper daily CBCT. As it was expected the ipsilateral lung dose delivery was significantly better in *Pr* position. To reduce the risk of low dose radiation exposure [31], well established CBCT acquisition parameters are needed. We applied the parameters suggested by De Puysseleyr et al. [32], which correspond to a total of 81 mGy imaging dose for the entire treatment.

One main limitation of this study is the low number of cases. Nevertheless, in terms of respiratory motion analysis it represents the second largest series and even if the number of cases is limited the trends are indicated. One can also argue that the direction of the clip movement was not presented and analyzed separately. The magnitude of respiration-related motion in *Pr* is however very small—even for the most mobile clips - which may reduce the clinical relevance of this kind of analysis.

Conclusion

Pr position significantly reduced both respiration-related chest wall- and surgical clip motion. *Pr* position also decreased the individual clip movement variability. We recommend daily set-up verification to maximize the heart protection effect in *Pr* position.

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