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ORIGINAL ARTICLE

The Influence of Treatment Position (Prone vs. Supine) on Clip Displacement, Seroma, Tumor Bed and Partial Breast Target Volumes: Comparative Study

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Abstract To analyse the displacement of surgical clips in prone (*Pr*) position and assess the consequences on target volumes and integral dose of partial breast irradiation (PBI). 30 post-lumpectomy breast cancer patients underwent CT imaging in supine (*Su)* and *Pr*. Clip displacements were measured by the distances from the clips to a common fix bony reference point. On each dataset, the tumour bed (TB = clips ± seroma), clinical target volume (CTV = TB + 1.5 cm) and planning target volumes (PTV = CTV + 1 cm) for PBI were determined and the volume pairs were compared. Furthermore estimation of integral dose ratio (IDR) within the breast from tangential treatment was performed as the ratio of the irradiated breast volume and the volume encompassing all clips. Clips close to the chest wall (CW) in *Su* showed significantly less displacement in *Pr*. The mean volumes of seroma, CTV and PTV were significantly higher in *Pr* than in *Su*. The PTV volume difference (*Pr*-*Su*) was significantly higher in patients with presence of seroma, deep clips and TB location in the superior-internal-quadrant (SIQ) and at the junction of superior quadrants (jSQ). In a multivariate analysis two factors remained significant: seroma and TB localization in SIQ-jSQ. The IDR was significantly larger in *Su* than in *Pr* (7.6 vs. 4.1 $p<0.01$). Clip displacements varied considerably with respect to their relative position to the CW. In selected patients *Pr* position potentially leads to a significant increase in target volumes of PBI. Tangential beam arrangement for PBI should be avoided, not only in *Su* but in *Pr* as well in case of clip-based target volume definition.

Keywords Breast cancer · Prone breast radiotherapy · Partial breast irradiation · Target volume

Introduction

Supine (*Su*) whole breast irradiation (WBI) is considered as the standard treatment for early breast cancer (BC) after breast conserving surgery improving local tumor control and overall

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survival [1, 2]. Over the past several years, there has been growing interest in the use of partial-breast irradiation (PBI) as an alternative to WBI [3–6]. PBI offers decreased overall treatment time and reduced dose delivery to uninvolved portion of the breast and adjacent organs at risk [3–6]. PBI has been already introduced in prone (*Pr)* position [7, 8]. Formenti et al. have reported comparable 5-year efficacy, cosmetics, and toxicity of prone three-dimensional conformal external beam radiation therapy to other forms of PBI [7].

So far, there is no consensus concerning the way to define the tumor bed (TB). Some have advocated the use of surgical clips with or without seroma, others have used only seroma cavity [3, 4] . In Europe, CT and clip-based TB delineation is considered as the gold standard [9]. However, by placing the patient in *Pr,* the size and shape of the breast and TB are significantly modified. These changes are essentially characterised by deformation and elongation. Furthermore, variability in individual clips and/or seroma displacements may have potential impact on target volumes for PBI. To the best of our knowledge, this issue has not been investigated before. Moreover there are no comparative data exists between clip-based target volumes for PBI in *Pr* and *Su* positions.

The present work purposed 1) to focus on the clips displacements related to *Pr* position, 2) to analyse their consequences on target volumes, 3) to identify potential predictive factors and predict the integral dose consequences of such displacements.

Table 1 Patient and tumor characteristics

Variable	Mean (range) or Number (%)
No. of patients	30
Age, years, mean (range)	62 (38–79)
Weight, kg, mean (range)	71 (51–100)
T stage (%)	
Tis	4 (14)
T1b	6 (20)
T1c	13 (43)
T2	7 (23)
Breast side (%)	
Right	12 (40)
Left	18 (60)
Localization of tumor bed (%)	
SIQ	4 (13)
jSQs	8 (27)
SEQ	9 (30)
jQEs	2 (6.5)
jIQs	2 (6.5)
IEQ	5 (17)
No. of surgical clips, mean (range)	5 (1–15)
Presence of seroma (%)	9 (30)
Cup size (%)	
A	2 (6.5)
B	9 (30)
C	9 (30)
D	8 (27)
E	2 (6.5)

Abbreviations: *SIQ* superior-internal-quadrant, *jSQs* junction of superior quadrants, *SEQ* superior-external-quadrant, *jEQs* junction of external quadrants, *jIQs* junction of inferior quadrants, *IEQ* inferior-external-quadrant

Materials and Methods

Patient Population

Thirty post-lumpectomy BC patients with T1-2 invasive ductal carcinoma or ductal-carcinoma-in situ were included in this study regardless of breast size. The protocol was approved by the ethics committee of the CHU de Liege. Patient and tumor characteristics are presented in Table 1.

Patient Positioning and Image Acquisition

Non-contrast computed tomography (CT) imaging (Philips Medical Systems, UK, 85 cm bore and slice-thickness 3 mm) was performed in *Su* and *Pr* positions. Copper wires were taped around the edges of the palpable breast-tissue. For *Pr* positioning, the preliminary model of Sagittilt® (Orfit Industries, Wijnegem, Belgium) system was used.

Analysis of Clip Displacement

To assess clip displacement in *Pr* position, we measured the 3D vector (3Dv) between each clip and a common bony reference point. Here, the 3D alignment toolbar of the treatment planning system (Pinnacle, Philips Medical Systems) was used. A vertebral point easily recognized in the same patient was used to align the centre of the coordinate system. Then, measures of the perpendicular distances among the clips and the coordinate system in *x, y* and *z* directions were performed in both positions, and 3Dv differences (Δ3Dv) were calculated. The shortest distances between the individual clips and the chest wall (CW) in *Su* position were also registered.

Target Volume Definition

Target volumes were defined by the same radiation oncologist. Throughout the study, the same contouring guidelines were followed in order to minimize intra-observer variability of the TB and achieve the most precise and objective comparison. First, each clip was defined individually in both positions, followed by the delineation of the seroma in case of presence. Only the clearly circumscribed seromas were considered as TB to minimize contouring variability. The clinical target volume (CTV) was defined as a uniform 3D 1.5 cm expansion around the TB to encompass microscopic disease. This volume was limited circumferentially at 5 mm from skin and by the CW. The planning target volume (PTV) was generated by the addition of uniform 1 cm margin to CTV in all directions, limited by 5 mm from skin. For patients possessing both clips and seromas, target volumes were also defined without the seroma. The volumes for the two positions were paired and compared.

To predict the dosimetric consequence of the clip displacement, theoretical beam directions of ±60° and ±240° gantry angles were used for the approximation. For determining the smallest cuboid volume encompassing all clips ("minimal boost") the axial (±330° plane) and cranio-caudal field sizes were combined with the axial path-length (Fig. 1). Furthermore average path-lengths of the breast were measured on the central plan at the central distance between the field border and the nipple, and were used to calculate the minimal irradiated breast volume. The ratio of the minimal irradiated breast volume and the minimal boost were used to estimate the integral dose contribution to the normal breast tissue.

Statistical Analysis

Results were expressed as mean and standard deviation (SD) for quantitative variables and as numbers and percentages for categorical findings. Correlations were calculated to measure the relations between the extent of clip displacement (Δ3Dv) and the distance from the CW in *Su*. Volumes in *Su* and *Pr* positions were compared by Wilcoxon signed-rank test, while the Kruskal-Wallis test was applied to compare patients with or without seroma. Univariate and multiple regression analysis were used to assess the relationship between volume differences and a set of covariates: age, body weight, left/right side, cup size, localization of TB, number of clips, presence of seroma and deep clips (defined as located < 1 cm from CW). Two tailed t-test were using to compare integral dose ratios (IDR) for *Su* and *Pr* datasets. Results were considered to be significant at the 5 % level ($p < 0.05$). Calculations were made using SAS version 9.2 (SAS Institute, Cary, NC, USA) statistical package.

Results

Clip Displacement in Function of the Distance from the Chest Wall in Su

A total of 147 clips were available and their displacements were analyzed. Significant positive correlations were found between the extent of clip displacement and the distance from the CW in *Su* ($r = 0.64$, $p < 0.0001$) (Fig. 2). The smallest displacement was observed for clips situated close to the CW ($p < 0.0001$).

Comparison of Seroma, CTV, PTV Between Pr and Su

In 9 patients the seroma was defined together with the clips as a part of the TB. As seen in Table 2, the volume of seroma and each target volume, including CTV and PTV, were significantly higher in *Pr* than in *Su*. The volume of PTV increased in 24 (80.0 %) patients, reaching more than 30 cm^3 in 10 (30 %) cases.

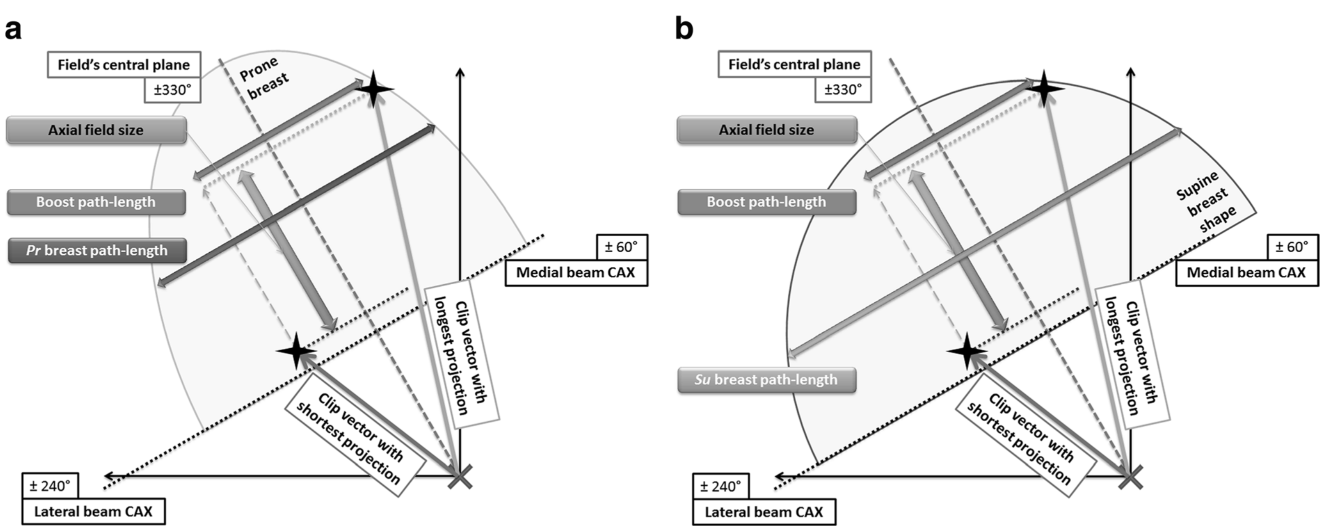
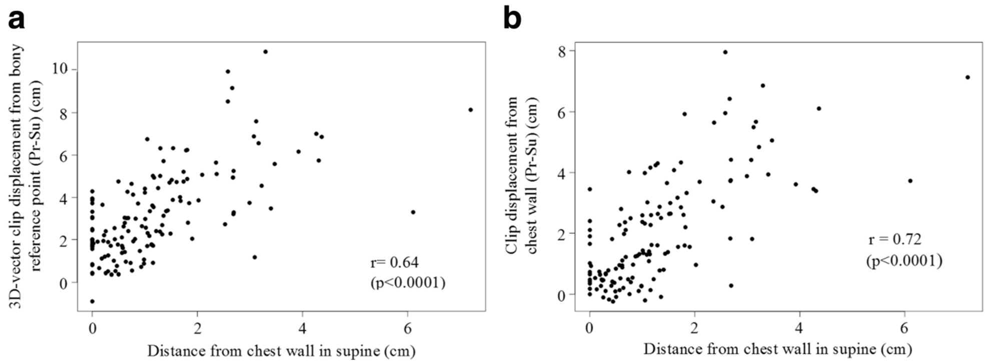


Fig. 1 Schematic geometrical presentation of the integral dose determination using standard and symmetric setup (CAX = central axis). **a** prone, **b** supine)

Fig. 2 3D vectorial clip displacement in *Pr* position in function of the distance from the chest wall in *Su*



Comparison of Volumes Between Pr and Su Positions and Between Patients with or Without Seroma

The volumes of CTV and PTV were not significantly different between patients with and without seroma in *Pr* and in *Su* (Table 2). However, the difference between *Pr* and *Su* for each target volume was significantly larger for patients with seroma than for patients without seroma: CTV ($p=0.0047$), and PTV1 ($p=0.0047$) (Table 2).

Factors Related to Volume Changes

In univariate analysis, PTV volume differences (*Pr-Su*) were significantly higher in patients with presence of seroma, TB localization in the superior-internal-quadrant (SIQ) and at the junction of superior quadrants (jSQ) and in case of deep clips (Table 3). In these patients the average absolute volume increase ranged between 30 and 40 cm^3.

In multivariate analysis two variables remained significant: presence of seroma and localization in SIQ-jSQ (Table 3*)*. It should be mentioned that a volume increase of more than 30 cm^3 for PTV was observed in only one single patient with TB not localized in SIQ-jSQ. Such an increase in volume was not observed in patients not harboring a deep-seated clip.

Integral Dose Estimation

Based on the theoretical beam directions non-significant differences were found in the minimal boost (27 cm^3 vs. 22.6 cm^3, $p=0.74$) and minimal irradiated breast (83.3 cm^3 vs. 68.2 cm^3, $p=0.34$) volume between *Su* and *Pr*. The IDR resulted in statistically significant differences ($p<0.01$) between 7.6 for *Su* and 4.1 for *Pr* (Table 4*)*.

Discussion

The present study aimed to analyse the clip displacements in *Pr* position and their volumetric consequences as compared to *Su* in the frame of PBI. As far as we know, there are no data reported in the literature on this topic. We found that clip displacements illustrative of conformal changes of the breast varied considerably with respect to their relative position to the CW. The smallest displacements were observed for clips situated close to the CW. This finding can be explained easily since the extent of breast tissue elongation is more limited close to the insertional/adhesional surface at the pectoral fascia. The second important finding of this study concerned the significant increase of CTV, PTV in *Pr* position: the greater the margin around the TB, the larger the difference in volume between *Pr* and *Su*, ranging on average from 13 cm^3 (CTV) to

Table 2 Comparison of volumes between *Pr* and *Su* positions and between patients with or without seroma

Volume (cm^3)	Prone	p-value	Supine	p-value	Pr-Sup	p-value
Seroma*	8.6 ± 8.6		7.7 ± 7.5			*0.004*†
CTV	88.5 ± 37.0		75.0 ± 32.3			*<0.0001*†
seroma	108 ± 42.6	0.081††	80.9 ± 34	0.54††	26.9 ± 16.5	*0.0047*††
no seroma**	80.2 ± 32		72.5 ± 32.1		7.7 ± 10.7	
PTV	233 ± 76.4		211 ± 70.1			*0.0004*†
seroma	268 ± 90.9	0.13††	220 ± 83.1	0.98††	48.0 ± 33.2	*0.0047*††
no seroma	218 ± 66		207 ± 65.7		10.8 ± 24.8	

Abbreviations: mean ± SD, * 9 patients, **21 patients, † Wilcoxon sign-rank test, †† Kruskal-Wallis test

Table 3 Univariate- and multivariate regression analysis for PTV volume difference (*Pr-Su*)

Variables	Univariate analysis					Multivariate analysis	
	Category	n	Mean ± SD	r†	p-value††	Coefficient (SE)	p-value
Age, years		30		−0.16	0.40	−1.01 (0.39)	0.019
No. of clips		30		−0.032	0.87	1.19 (1.33)	0.38
WB volume, cm^3		30		−0.004	0.98	−0.02 (0.01)	0.21
Weight, kg		30		0.31	0.10	0.57 (0.35)	0.11
Cup size, A-E		30		0.085	0.65		
Breast	Right	12	30.2 ± 42.9		0.26	−9.24 (7.38)	0.22
	Left	18	16.5 ± 22.1				
Seroma	Present	9	48.1 ± 33.2		*0.002*	29.4 (9.00)	*0.0037*
	Absent	21	10.8 ± 24.8				
Localization	SIQ-jSQs	12	46.4 ± 31.2		*0.002*	6.45 (10.0)	0.53
	Others	18	5.72 ± 20.64				
Deep clip	Present	21	31.2 ± 32.8		*0.013*	32.8 (8.16)	*0.0006*
	Absent	9	0.47 ± 17.2				

Abbreviations: † regression coefficient, †† t-Student test, *WB* whole breast volume, *SIQ* superior-internal-quadrant, *jSQs* junction of superior quadrants

22 (PTV) cm^3. The seroma volume was also significantly higher in *Pr* than in *Su*. However, the absolute mean difference was less than 1 cm^3. It seemed that there was a tendency to delineate a larger volume for the seromas in *Pr* than in *Su.* This difference may come from the collapsed TB in *Su* which could open up in *Pr* leading to a better visibility of the seroma.

Both univariate and multivariate analyses confirmed that patients with seroma and TB locations in the SIQ-jSQ developed a highly significant volume increase in *Pr*. In these cases the mean absolute volume increase of PTV was approximately 40 cm^3 reaching an absolute maximum of 100 cm^3. The presence of deep clips was significant only in the univariate analysis, indicating that this variable in itself was not enough to predict volume increase. Notably, only 33 % (10/30) of the patients developed > 30 cm^3 volume increase despite the fact that 70 % (21/30) of the cases had deep-seated clips.

Volume increase in *Pr* was mainly linked to the differential clip/seroma displacement but also to the way of CTV, PTV definition. For TB in the SIQ, this enlargement could be explained mostly by the anatomical change of the breast. In *Pr* this quadrant could open up filled with breast tissue above the TB, providing an extra space for the expansion of CTV and PTV margin principally into the anterior direction (Fig. 3a). In the upper central region (jSQ) deep clips remained relatively stable while the superficial ones displaced more, making areas available for the 1.5 cm CTV volume expansion, which was previously limited by the pectoral muscle (Fig. 3b). Furthermore, the lateral margin expansion was not limited by the skin. This phenomenon was observed in patients with seroma based TB also. In contrast, for patients with TB in the external quadrants this volume increase was not present as the clips were located close to the skin surface (Fig. 4a), preventing further volume expansion. Superficial TBs had a tendency to move together with the breast without any volumetric consequences (Fig. 4b).

How can one overcome this apparent increase in target volume? The first solution would be the reduction of CTV margin by using asymmetrical margins (2 cm - free resection margin) [10]. However, as *Pr* positioning causes significant clip displacements and tissue deformations, a direct translation

Table 4 Summary table of the axial and cranio-caudal dimension for the clip and breast and the corresponding integral dose ratio

	Clip Axial extent (cm)		Clip CC extent (cm)		Clip axial-length (cm)		Breast axial-length (cm)		Integral dose ratio	
	Su	Pr	Su	Pr	Su	Pr	Su	Pr	Su	Pr
Mean	1.75	3.13	2.42	2.16	3.52	2.58	16.50	9.18	7.64	4.10
SD	1.35	1.87	1.21	1.22	2.79	0.90	1.94	2.01	8.46	3.13
CI (95 %)	0.52	0.73	0.47	0.47	1.08	0.35	0.78	0.81	3.28	1.21
p-value†		*<0.01*		0.04		0.07		*<0.01*		*<0.01*

Abbreviations: CC cranio-caudal, *Su* supine, *Pr* Prone, *SD* standard deviation, *CI* confidence interval, † two-tailed T-test

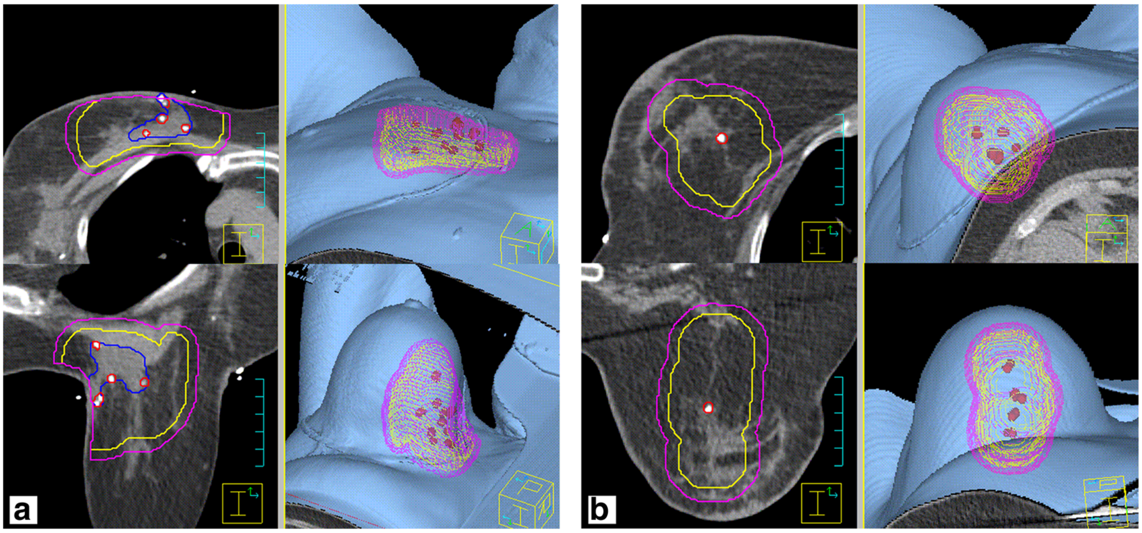


Fig. 3 Representative cases for PBI volume increase in *Pr*. Corresponding axial slices (*left*) and 3D reconstructions (*right*) in supine (*top*) and prone (*bottom*). Clips (*red*), PTV0.5 (*CTV+ 0.5*, *yellow*), PTV (*pink*), seroma (*blue*) are presented. **a** TB in superior-internal-quadrant. **b** TB in the upper central region with simultaneously presented deep clips

from pathologic results is not feasible, warranting symmetrical margins. The second solution would be the decrease of PTV margins [11]. Based on recently published reports, a 1–1.4 cm margin is recommended to compensate set-up errors in *Pr* [11–14]. Ahunbay et al. [11] highlighted that PTV margin could be drastically decreased (from 1.39 to 0.27 cm) if more sophisticated repositioning alignment strategies were used during daily CBCT imaging.

Balance between the adequate target coverage and the OAR dose might eventually limit the beam arrangements to the classical tangential directions for PBI. This may contribute to a larger irradiated volume of the treated breast outside the PTV-PBI, leading into no or limited dosimetrical and therefore clinical differences between PBI and WBI for the axial extent. Internal dose within the treated breast should be monitored closely as the incidence of moderate to severe late toxicity are associated with several dose-volume parameters of the relative volume of ipsilateral breast tissue [15, 16]. Knowing that many different techniques could be used to treat the entire or partial breast volume both in *Su* and *Pr* [17–19] position, a comprehensive and adequate dosimetric comparison is clearly not feasible without any bias due to differences in the target definition and planning. By using the minimal boost and irradiated breast volume as surrogate we simplified this challenge and focused on the consequences of tangential beam arrangements for PBI. Based on our approximation we found that in *Su* 7.6× larger breast volume might be irradiated relative to the boost volume if only tangents would be used, while this ratio would be only 4.1× for *Pr*. Our estimation clearly indicates the need for pursuit a different beam arrangement in both

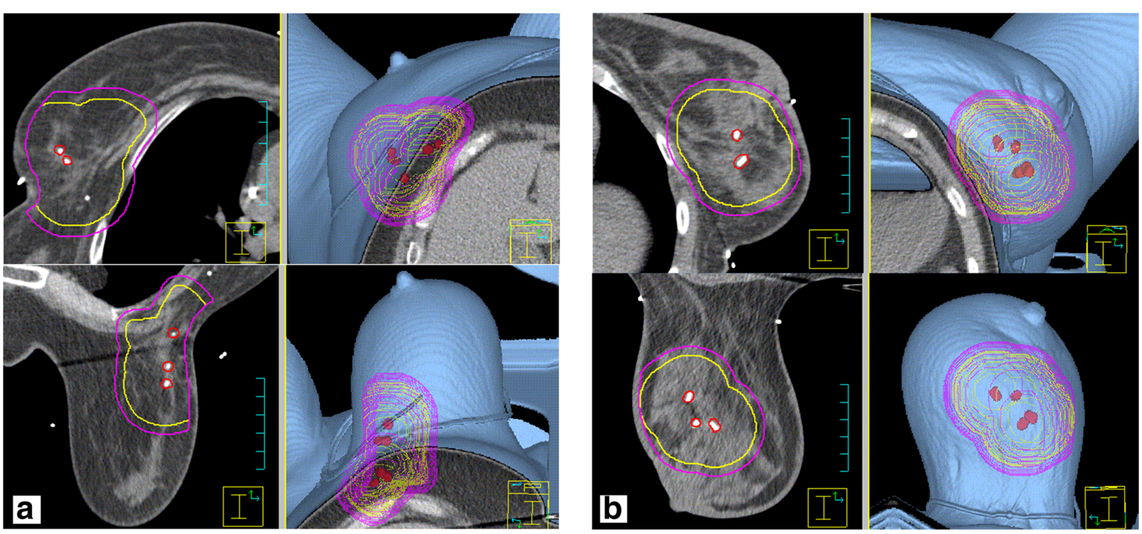


Fig. 4 Representative cases for unchanged PBI volume in *Pr*. **a** TB in the external quadrant. **b** Superficial TB

positions. To overcome the integral dose problem large variety of techniques using multiple directions with non-coplanar beams exist as well [17–20]. To date only the NYU group treated large cohort of PBI patients with mini-tangents [7]. However they use seroma based target volume definition and reduced CTV-PTV margin that required by the supine RTOG trial 0413 [21]. Followed the warning signals of the relative large integral dose estimated in our cohort, we feel obligatory to investigate various class solutions to propose more conformal irradiation of the PBI volume and exploit the maximum therapeutic ratio in *Pr*.

One main limitation of this study is the low number of cases. Nevertheless, the trends are highlighted. One can also argue that patients with pT2 (>3 cm), DCIS or younger than 50 years are not candidates for PBI [3, 4]. These factors however do not correlate with the volume differences observed in our study (Table 3). Our target volume definition could be also criticized. However, this method allows us to reduce intra- and interobserver variability while keeping the philosophy of PBI target volume definition. Furthermore there are no intra- and inter-observer variability results as well as published consensus guidelines for target volume definition in *Pr* neither for PBI nor for whole breast irradiation as compared to supine.

This analysis should not be considered as a report against prone PBI. However, our data indicates that there may be pitfalls when selecting patients for PBI in *Pr* and do emphasize the necessity of an individualized approach instead of a systematic replacement of *Su* by *Pr* if clip-based target volume definition is used. Furthermore to reduce the higher integral dose within the treated breast, other than the simple tangential beam arrangement should be also used in *Pr* similarly to *Su*.

Conclusion

Clip displacements varied considerably with respect to their relative position to the CW. In selected patients Pr position potentially leads to a significant increase in target volumes of PBI. Tangential beam arrangement for PBI should be avoided, not only in Su but in Pr as well in case of clip-based target volume definition.

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