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FULL PAPER

Displacement of the lumpectomy cavity defined by surgical clips and seroma based on 4D-CT scan for external-beam partial breast irradiation after breast-conserving surgery: a comparative study

¹Y DING, MD, ¹J LI, MD, ¹W WANG, MD, ¹S WANG, MD, ¹T FAN, MD, ¹M XU, MD, ¹Q SHAO, MD and ²Z MA, MD

¹Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan, China

²Department of Gynecological Oncology, Shandong Cancer Hospital and Institute, Jinan, China

Address correspondence to: Mr Jian Bin Li

E-mail: lijianbin@msn.com

Objective: To compare the displacements of the lumpectomy cavity delineated by the surgical clips and the seroma based on four-dimensional CT (4D-CT) for external-beam partial breast irradiation (EB-PBI) after breast-conserving surgery (BCS).

Methods: 14 breast cancer patients after BCS were recruited for EB-PBI and undertook 4D-CT simulation. On the 10 sets of the 4D-CT images, all the surgical clips in the cavity were delineated. The gross tumour volume (GTV) formed by the clips, the seroma, and both the clips and the seroma were defined as GTV_c, GTV_s and GTV_{c+s}, respectively. The displacements of the centre of mass (COM) of the clips, GTV_c, GTV_s, GTV_{c+s} and the selected clips in the three-dimensional (3D) directions were recorded and compared.

Results: In the left-right, anterior-posterior and superior-inferior directions, the displacements were 2.20, 1.80 and

2.70 mm for the clip COM; 0.90, 1.05 and 1.20 mm for GTV_c; 0.80, 1.05 and 0.80 mm for GTV_s; and 0.90, 1.20 and 1.40 mm for GTV_{c+s}, respectively. In the 3D directions, the displacements of the clip COM were greater than the GTV_c, GTV_s, GTV_{c+s}, and the displacements of the clip COM, GTV_{c+s}, GTV_c and GTV_s were significantly greater than the displacements of the selected clips ($p < 0.05$).

Conclusion: The displacements of the clip COM were greater than that of the GTV_c, GTV_s, GTV_{c+s} and the four selected clips. The optimal internal target volume should be defined based on the boundary displacements.

Advances in knowledge: When the GTV was delineated using the clips and/or the seroma, there was displacement difference between the lumpectomy cavity centre and the boundary for the EB-PBI. The optimal internal target volume should be defined based on the boundary displacements of the lumpectomy cavity.

Previous studies have reported that approximately 70–80% of the in-breast tumour recurrences occurred in the vicinity of the tumour bed (TB) and that the absolute risk of ipsilateral breast recurrence away from the primary tumour site is approximately 1.5–3.5% [1–4]. Thus, for early-stage breast cancer patients after breast-conserving surgery (BCS), partial breast irradiation (PBI), treating only the lumpectomy cavity with a suitable margin, may achieve a similar local control rate and an overall survival rate to whole-breast irradiation treating the whole breast. External-beam partial breast irradiation (EB-PBI) is an important approach in PBI, and clinical research has demonstrated that EB-PBI can achieve excellent results after strict patient selection and accurate target volume delineation [5,6].

Accurate delineation of the TB is essential for EB-PBI [7]. Surgical clips and seroma were important surrogates in

location and displacement measurement of the TB [8–10]. The optimal number of surgical clips, seroma clarity score (SCS), the delineation experience and contouring guidelines were important factors for TB delineation on CT images [10–14]. The target volume was typically defined using surgical clips, the seroma and any post-operative tissue changes when available [9]. The respiratory-induced displacements and set-up error were important components in EB-PBI planning, and the residual error was not > 5 mm after online error correction based on cone-beam CT [15]. Therefore, respiratory-induced TB motion is the major component of the planning target volume for EB-PBI [8]. Four-dimensional CT (4D-CT) simulation has enabled CT data acquisition to be correlated with the respiratory cycle. Therefore, 4D-CT was pervasively used in delineating the target volume and forming the internal target volume (ITV) for EB-PBI [16,17].

Although the displacements of the target volume delineated based on clips and seroma have been obtained using 4D-CT in prior studies [16,17], the displacement differences among target volumes have not been fully illustrated. In order to investigate the displacement differences among the target volumes delineated based on clips and/or seroma, we measured and compared the three-dimensional (3D) displacements among three target volumes, the centre of mass (COM) of all the surgical clips and four selected boundary clips during free-breathing (FB).

MATERIALS AND METHODS

Patients

Institutional review board approval and informed consent were obtained for the present study. The study population consisted of 14 consecutive breast cancer patients (6 left-sided and 8 right-sided lesions) with early-stage breast cancer referred to post-operative radiotherapy (RT) after BCS. For every patient, more than four surgical clips were used to mark the boundaries of the lumpectomy cavity. In order to improve the delineation accuracy, in this study, all the patients recruited were with SCS 3–5 [10] in the lumpectomy cavity. All the patients were free from chronic lung diseases, their ventilation functions were normal and they accepted FB training. The patients enrolled were counselled and signed consent protocol.

Four-dimensional CT simulation and image acquisition

All the 14 patients underwent a standard FB virtual CT breast simulation with both arms outreached and raised in a supine position on a breast board. The 4D-CT images recording the respiratory signal were acquired with a thickness of 3 mm at the conclusion of the standard CT simulation using a 16-slice Brilliance Big Bore CT scanner (Philips Medical Systems, Cleveland, OH). The signals were sent to the scanner to label a time tag on each CT image. GE Advantage 4D software (GE Healthcare, Waukesha, WI) sorted the reconstructed 4D-CT images into 10 respiratory phases on the basis of these tags, with 0% corresponding to end inhalation (CT₀) and 50% corresponding to end-exhalation (CT₅₀). Then the constructed 4D-CT image sets were transferred to the Eclipse treatment planning system (Eclipse™ 8.6; Varian Medical Systems, Palo Alto, CA) for structure delineation.

Gross tumour volume delineation

The 10–90% phases of 4D-CT images were registered on the 0% phase images, which served as the basic phase image. All the

surgical clips were delineated on the 10 sets of the registered images by the same radiation oncologist. The surgical clips representing the superior, inferior, posterior and lateral boundary of lumpectomy cavity were selected and marked as the upper, lower, inner and outer clips, respectively. All the surgical clips was described as a group, which was named as the mass of the clips. All the surgical clips in the cavity were delineated on the 10 phases of the 4D-CT images by a radiation oncologist. The gross tumour volume (GTV) formed by the clips, the seroma, and both the clips and the seroma were defined as GTV_c, GTV_s and GTV_{c+s}, respectively.

Three-dimensional co-ordinates measurement

The planning system automatically outputs the 3D co-ordinate parameters of the 10 sets of the registered images in the left–right (LR), anterior–posterior (AP) and superior–inferior (SI) directions for GTV_c, GTV_s, GTV_{c+s}, the selected boundary clips and the COM of the clips. The 3D co-ordinate parameters of the clip COM, GTV_c, GTV_s, GTV_{c+s} and the selected boundary clips on the 10 phase of images were recorded. The peak-to-peak displacements (the maximum value of the co-ordinate minus the minimum value of the co-ordinate) of the clip COM, GTV_c, GTV_s, GTV_{c+s} and the selected boundary clips in the 3D directions throughout 10 phases of 4D-CT were obtained.

Statistical analyses

SPSS® v.17.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis. The Mann–Whitney test was used to compare the displacements among the clip COM, GTV_c, GTV_s, GTV_{c+s} and the selected clips in the 3D directions. The one-way analysis of variance test and Wilcoxon signed-rank test were used to compare the displacements among different directions for the clip COM, GTV_c, GTV_s, GTV_{c+s} and the selected clips. Values of $p < 0.05$ were regarded as significant.

RESULTS

The 3D displacements of the clip COM, GTV_c, GTV_s and GTV_{c+s} are listed in Table 1. The ranges of displacement in the LR, AP and SI directions were 0.90–6.60, 0.70–4.20 and 1.30–4.50 mm for the clip COM; 0.50–2.40, 0.60–1.90 and 0.40–3.00 mm for GTV_{c+s}; 0.50–1.80, 0.40–1.80 and 0.50–2.80 mm for GTV_c; and 0.40–2.10, 0.70–1.80 and 0.40–1.80 mm for GTV_s, respectively. There were no significant displacement differences among the 3D directions for clip COM, GTV_c, GTV_s and GTV_{c+s}, respectively ($p > 0.05$). The displacements of the clip COM were significantly greater

Table 1. The displacements of the clip COM, GTV_{c+s}, GTV_c and GTV_s in the three-dimensional directions (median)

Target volume	LR (mm)	AP (mm)	SI (mm)	χ^2	p
The clip COM	2.200	1.800	2.700	3.84	0.147
GTV _{c+s}	0.900	1.200	1.400	2.86	0.239
GTV _c	0.900	1.050	1.200	2.05	0.359
GTV _s	0.800	1.050	1.100	3.65	0.161
χ^2	20.780	15.380	21.020		
p	0.000	0.002	0.000		

AP, anterior–posterior; COM, centre of mass; GTV_c, gross tumour volume formed by the clips; GTV_s, gross tumour volume formed by the seroma; GTV_{c+s}, gross tumour volume formed by both the clips and the seroma; LR, left–right; SI, superior–inferior.

Table 2. Displacement comparison among the clip COM, GTV_{c+s}, GTV_c and GTV_s in the same direction

Paired comparison	LR		AP		SI	
	Z	p	Z	p	Z	p
The clip COM vs GTV _{c+s}	-3.235	0.001	-2.098	0.036	-3.108	0.002
The clip COM vs GTV _c	-3.181	0.001	-2.294	0.022	-2.952	0.003
The clip COM vs GTV _s	-3.300	0.001	-2.489	0.013	-3.299	0.001
GTV _{c+s} vs GTV _c	-1.415	0.157	-1.790	0.073	-1.294	0.196
GTV _{c+s} vs GTV _s	-1.141	0.254	-0.347	0.729	-2.138	0.700
GTV _c vs GTV _s	-0.356	0.722	-0.035	0.972	-1.896	0.055

AP, anterior-posterior; COM, centre of mass; GTV_c, gross tumour volume formed by the clips; GTV_s, gross tumour volume formed by the seroma; GTV_{c+s}, gross tumour volume formed by both the clips and the seroma; LR, left-right; SI, superior-inferior.

than those of the GTV_{c+s}, GTV_c and GTV_s in the 3D directions ($p < 0.05$) (Table 2).

The displacements of different clips in the same direction were similar (Table 3). The paired displacement comparison between the COM, GTV_{c+s}, GTV_c, GTV_s and the selected boundary clips in the 3D directions are listed in Table 4. In the 3D directions, the displacements of the clip COM, GTV_{c+s}, GTV_c and GTV_s were greater than those of all the selected clips ($p < 0.05$).

DISCUSSION

The seroma and surgical clips were important surrogates in GTV delineation and displacement measurement for EB-PBI. The majority of similar studies have measured the respiratory-induced displacement of GTV delineation based on the surgical clips [11,17,18]. How to outline the GTV based on the scattered clips in the lumpectomy cavity remains to be established, and the volumetric nature of the cavity may not be accurately reflected. The delineation accuracy was significantly influenced by the number of clips, the delineation experience and the contouring guidelines [11–13,19,20]. The seroma clarity and volume in the lumpectomy cavity decreased as a function of time from surgery to the planning CT scan. Using the CT-based seroma to guide the PBI target volume definition can be challenging, primarily because of the lack of clarity in certain situations [21]. Kader et al [10] reported that the seroma volume and clarity score was changing as a function of the interval between surgery and the planning CT scan. Given the magnitude and time trends in seroma volume and clarity loss, the optimal time to obtain the planning CT scan for PBI is within 8 weeks after surgery [10].

It is important to take into account the displacement difference among the 3D directions in forming the ITV for EB-PBI. We found that the primary displacements of the lumpectomy cavity were in the AP and SI directions. During the simulation, the patients lifted and outreached the bilateral hands and lay in a supine position on the breast brackets, which may account for the displacement trends. But there were no significant differences among the 3D directions for the clip COM, GTV_c, GTV_s and GTV_{c+s}. Based on the information, we hypothesised that it was feasible to calculate the ITV from the lumpectomy cavity using uniform 3D expansions.

The displacement magnitude of the clip COM in this study was similar to the results acquired by Wang et al [17], who applied 4D-CT to explore the displacement for EB-PBI and reported that the displacements of the geometric (consisting of all the surgical clips) centre in the LR, AP and SI directions were 1.4 ± 0.4 , 2.0 ± 1.0 and 1.9 ± 1.0 mm, respectively. We found that in the 3D directions, the similar displacements of the clip COM were significantly larger than those of the GTV_c, GTV_s, GTV_{c+s}. This might be explained by the fact that the displacements of the clip COM were influenced by the displacement of all the clips, and the lumpectomy cavity deformation induced by respiration during intrafraction irradiation. The GTV_c was delineated based on the boundary clips, which only appeared in one layer or a few layers of CT images. The delineation experience, contouring guidelines and the number of clips in the lumpectomy cavity were associated with the delineation accuracy and repeatability [11–13,19]. When delineating the GTV based on the seroma, both the variations in seroma volume and clarity as a function of time from surgery and the seroma deformation

Table 3. The displacements of the selected boundary clips in the LR, AP and SI directions (median)

Selected boundary clips	LR (mm)	AP (mm)	SI (mm)
Upper clip	0.40	0.70	0.45
Lower clip	0.60	0.75	0.75
Outer clip	0.45	0.90	0.40
Inner clip	0.40	0.75	0.75

AP, anterior-posterior; LR, left-right; SI, superior-inferior.

Table 4. Displacement comparison among the clip COM, GTV_{c+s}, GTV_c, GTV_s and the selected clips in the same direction

Selected clip	The clip COM				GTV _{c+s}			GTV _c			GTV _s		
	LR	AP	SI		LR	AP	SI	LR	AP	SI	LR	AP	SI
Upper clip	Z	-4.513	-3.807	-4.165	-3.929	-3.373	-2.509	-3.740	-2.817	-2.234	-3.162	-3.294	-1.233
	p	0.000	0.000	0.000	0.000	0.000	0.011	0.000	0.004	0.024	0.001	0.001	0.227
Lower clip	Z	-4.327	-3.133	-4.418	-2.540	-1.822	-1.036	-2.306	-1.313	-2.144	-1.642	-1.499	-0.533
	p	0.000	0.001	0.000	0.011	0.069	0.306	0.021	0.194	0.031	0.104	0.137	0.603
Outer clip	Z	-4.051	-3.021	-3.751	-2.843	-1.753	-2.577	-2.676	-1.154	-2.578	-2.179	-0.972	-1.733
	p	0.000	0.002	0.000	0.004	0.085	0.009	0.007	0.265	0.009	0.031	0.352	0.085
Inner clip	Z	-4.425	-3.367	-4.094	-3.485	-2.489	-2.026	-3.328	-1.871	-1.936	-2.668	-2.111	-0.300
	p	0.000	0.000	0.000	0.000	0.012	0.044	0.001	0.062	0.056	0.007	0.035	0.769

AP, anterior-posterior; COM, centre of mass; GTV_c, gross tumour volume formed by the clips; GTV_s, gross tumour volume formed by the seroma; GTV_{c+s}, gross tumour volume formed by both the clips and the seroma; LR, left-right; SI, superior-inferior.

induced by respiration would influence the location and size of the GTV_s significantly. The displacements of the clip COM were not in accordance with those of GTV_c and GTV_s during the respiratory cycle. Park et al [9] obtained similar results by 4D-CT; they reported the average position of the geometric seroma relative to the clip COM of the fiducial pre treatment compared with post treatment as 1 ± 1 mm. In the current study, there was no significant displacement difference among the target volumes formed by the seroma, the clips, and both the clips and the seroma in the 3D directions. These results indicated that the displacements of the GTV defined using the clips and/or the seroma in the lumpectomy cavity were more accurate in reflecting the displacements of the lumpectomy cavity for EB-PBI.

The clips implanted in the boundaries of the lumpectomy cavity were prevalently used in guiding target volume delineation and displacement measurement for EB-PBI [8,15,22]. Kim et al [18] analysed 19 studies of respiratory motion in patients treated with accelerated partial breast irradiation. Of the 19 studies, surgical clips and gold fiducial markers were used as references in measuring the displacements in 11 studies. In this study, the 3D displacements of selected clips were similar to those in previous studies [17,23]. Based on 4D-CT, Wang et al [17] reported that the intrafraction displacements in the LR, AP and SI directions were 0.4 ± 0.2 , 0.9 ± 0.4 and 0.9 ± 0.6 mm for the upper clip; 0.6 ± 0.3 , 0.9 ± 0.4 and 1.4 ± 0.9 mm for the lower clip; 0.4 ± 0.2 , 0.9 ± 0.4 and 0.7 ± 0.5 mm for the outer clip; and 0.4 ± 0.3 , 0.7 ± 0.4 and 0.9 ± 0.6 mm for the inner clip, respectively. Harris et al [23] applied 4D-CT to track gold fiducial markers in the surgical cavity and found that the average fiducial motion resulted from respiration was 0.8 mm. These results showed that the mean intrafraction motion of the surgical clips measured by 4D-CT was about 1.0 mm in the 3D directions. The displacements obtained by other conventional imaging methods were larger than those obtained by 4D-CT. Yamashita et al [16] used daily pre- and post-RT KV imaging to track TB clips and found that the respiratory-induced displacements were 0.9 ± 0.2 , 1.7 ± 0.5 and 1.1 ± 0.3 mm in the LR, AP and SI directions, respectively. Yue et al [24] reported that the intrafraction motion of fiducial markers obtained by kilovoltage (KV) imaging were 1.5 ± 1.9 , 2.9 ± 1.9 and 1.6 ± 1.7 mm in the LR, AP and SI directions, respectively. Gagel et al [25] reported that the average displacement of the chest wall was 0.24 mm during moderate deep-inspiration breath-hold. The results of these studies showed that the intrafraction motion of the surgical clips measured by 4D-CT was smaller than that based on KV imaging, and that breathing control could reduce the intrafraction motion.

In the current study, the displacements of the clip COM, GTV_{c+s}, GTV_c and GTV_s were larger than those of the selected clips in the 3D directions. The possible reasons included (1) that the displacements of the clip COM were the composite results of all the clips and influenced by the lumpectomy cavity deformation induced by respiration; (2) as mentioned above, lumpectomy cavity delineation based on clips or seroma might result in variation in the target volume and 3D displacements [21,26]; (3) the delineation accuracy and conformity were associated with the clip number, SCS, and can be improved by training staff participating in PBI trials and refining contouring

guidelines [13,21,26,27]. Current evidence illustrated that the displacements of the lumpectomy cavity centre were not consistent with those of the boundary clips. The displacements of the lumpectomy cavity were important references in defining the ITV. When the ITV was expanded based on the centre displacements, there was more normal tissue being unnecessarily irradiated, and retracted modification based on the boundary displacements was needed in order to get the optimal ITV. Therefore, the optimal ITV should be defined by expanding the lumpectomy cavity based on the displacements of the boundary.

CONCLUSION

The results of our study have shown that in the 3D directions, the displacements of the clip COM consisting of all the

clips were larger than those of the GTV_c , GTV_s , GTV_{c+s} and the four selected clips, but there was no displacement difference between the GTV_c , GTV_s and GTV_{c+s} in the same direction. Meanwhile, there were no significant differences between the different directions for the clip COM, GTV_c , GTV_s and GTV_{c+s} . The results of this study indicated that the optimal ITV should be defined by expanding the lumpectomy cavity based on the boundary displacement uniformly.

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