A Study on the Displacements of the Clips in Surgical Cavity for External-beam Partial Breast Irradiation after Breast-conserving Surgery Based on 4DCT

Suzhen WANG¹, Jianbin LI¹*, Wei WANG¹, Yingjie ZHANG¹, Fengxing LI¹, Tingyong FAN¹ and Dongping SHANG²

Breast neoplasm/Breast-conserving treatment/External-beam partial breast irradiation/Four-dimensional computed tomography/Displacement.

To explore the clip and the geometrical center displacements based on the four-dimensional computed tomography (4DCT) for external-beam partial breast irradiation (EB-PBI), fourteen breast cancer patients treated with breast-conserving surgery were recruited for EB-PBI and undertook 4DCT simulation during free breathing. The displacements of the selected clips and the geometrical center at left-right (LR), anterior-posterior (AP) and superior-inferior (SI) directions were measured. The comparison and the correlation of the displacement between the selected clips and the geometric center were analyzed. The displacements in AP and SI were greater than that in LR for the same selected clip (P < 0.05). Almost all the displacements of the geometrical center were greater than that of the selected clips in the same direction, (P < 0.05), except the displacements of lower clip in SI direction. The displacement of the geometric center showed a statistical correlation with the upper clip and lower clip in SI direction (both P < 0.05). Therefore, the internal margin in AP and SI directions should be greater than LR direction for the purpose of adequate target coverage and sparing more normal tissue. This study also indicates that the displacement of a single clip was not qualified to substitute for the displacement of the target based on all clips of the surgical cavity.

INTRODUCTION

Over the last three decades, breast cancer has been the second most common cancer in women. Breast-conserving surgery (BCS) followed by radiotherapy (RT) became the standard for early-stage breast carcinoma. This strategy is a safe procedure with acceptable side effects and cosmesis, and the local recurrence rate is significantly lowered due to adjuvant radiotherapy to the mammary gland.¹,² Consensus of experts is that the tumor recurrence mostly appears at the primary tumor and its adjacent area after breast conserving therapy,³,⁴ thus partial breast irradiation (PBI) which only irradiates to the tumor bed has become the hot topic of breast cancer radiotherapy. PBI includes interstitial brachytherapy (IBT), balloon intra-cavity brachytherapy (BIBT), intraoperative radiotherapy (IORT), and three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT).⁵⁻¹⁰ Compared with IBT, BIBT, and IORT, external-beam partial breast irradiation (EB-PBI) is featured with easy implement, controllable dose distribution, and no infection risk.

By using hyperfractionated accelerated radiation therapy in 1 to 10 fractions delivered in up to 5 days, EB-PBI irradiates the surgical cavity and the surrounding breast tissue. Therefore, the definition of target volumes, correction of setup errors, and limitation of respiration-induced target movements are critical processes of EB-PBI.¹¹ In EB-PBI, intrafractional target motion caused by respiratory is the main component of planning target volume (PTV).¹² Many studies have demonstrated that surgical clips could serve well as surrogates of the lumpectomy cavity. Meanwhile, the clip in the surgical cavity is more applicable to the target motion measurement and setup error correction than skin surface markers, chest wall or bone anatomy.¹³,¹⁴

Four-dimensional CT (4DCT) has been considered as a reliable and effective tool for assessing tumor and organ motion. 4DCT images can eliminate the motion artifacts of clips caused by respiratory motion, therefore they can accurately reflect clip motion throughout the respiratory cycle.¹⁵
The use of 4DCT can lead to improvements in target definition and decreases in normal tissues irradiation. Therefore, this study investigated the clip displacement of surgical cavity based on the 4DCT for patients of EB-PBI after breast-conserving surgery. This study also investigated the displacement of the geometric center consisting of all the clips in the surgical cavity and its association with the displacement of the selected clips to define the internal target volume (ITV) for EB-PBI.

METHODS AND MATERIALS

Patient characteristics

Fourteen breast cancer patients with BCS, who were enrolled for EB-PBI, undertook 4DCT simulation scanning with a median age of 41.5 years (range 34–54). There were five cases with the left side breast lesion and nine cases with right side lesions. Among of them, ten lesions located in the outer quadrant and four in inner quadrant of the breast. Five to seven roundish silver clips with 2 mm-aperture were implanted. The silver clips were fixed to the superior, inferior, medial, lateral, and posterior walls of the surgical cavity, respectively. All patients were free of chronic lung diseases and their ventilation function was normal with brachial lift and outreach freely. The patient’s arms and head were immobilized with a breast tray. Informed consent was obtained from all the patients prior to the treatment.

CT simulation and image acquisition

During the simulation, all patients took a supine position in a breast tray with the bilateral upper limbs outreached and lifted on arm brackets, followed by laser alignment. Metal marks were applied to the laser cross-marked points in the bilateral axial midline and the anterior midline. At free respiratory status, a 4DCT chest scan was acquired on a 16-slice CT scanner (Philips Brilliance Bores CT, Netherlands). During the 4DCT scanning, the respiratory signal was recorded with the Varian Real-time Positioning Management (RPM) gating system (Varian Medical Systems, Palo Alto, CA, USA) by tracking the trajectory of the infrared markers placed on the patient’s abdomen. The signal was sent to the scanner to label a time tag on each CT image. GE Advantage 4D software (GE Healthcare, Waukesha, WI, USA) sorts the reconstructed 4DCT images into ten respiratory phases on the basis of these tags, with 0% corresponding to end-inhalation (EI) and 50% corresponding to end-exhalation (EE). The 4DCT images were reconstructed using a thickness of 2 mm and then transferred to the Eclipse treatment planning system (TPS) (Eclipse 8.6, Varian Medical Systems) for structure delineation and treatment plan generation.

Selected clips and geometry motion

In the planning treatment system, the 4DCT image of the 0% phase served as a background (referred as benchmark) and the other nine phases were registered. Using the same window width (600 HU) and window level (160HU) settings, clips were manually delineated on the 10 phases of the 4DCT images by a radiation oncologist. Then the planning system automatically outputted the geometric center that consisted of all the clips in each wall of the CT images. Each clip in the surgical cavity represented different border of the tumor bed, to simplify the descriptions, the upper clip, lower clip, inner clip and outer clip were used to denote the selected silver clip of the superior, inferior, posterior and lateral walls of the surgical cavity, respectively. The 0%-phase of 4DCT images served as a background to establish the coordinate system, and it also served as the reference template upon which the other phases of the CT images were registered. The planning system automatically outputted the coordinate parameters of the 10 sets of the registered images in the left-right (LR), anterior-posterior (AP) and superior-inferior (SI) directions for both the selected clips and the geometric center. Then the coordinate parameters of the clip and the geometrical center were recorded of the ten phases in breathing respectively for the same direction. Then, the peak-to-peak displacements (the maximum value of the coordinate minus the minimum value of the coordinate) of the selected clips and geometric center in the LR, AP and SI directions throughout 10 phases of 4DCT were obtained.

Statistical analysis

The SPSS 17.0 software was used for statistical analysis. A normal distribution test and a test for homogeneity of variance were performed. The independent sample t-test was used for comparison of displacements in different directions for the same clip; displacements in the same direction of different clips and displacements between the selected clip and the geometric center in the same direction. The correlation between displacements of the selected clip and the geometric center has been calculated by the Pearson correlation analysis. Values of $P < 0.05$ were regarded as significant.

RESULTS

The data of displacement in LR, AP, and SI directions for the selected clips are listed in Table 1. Displacement of the

<table>
<thead>
<tr>
<th>Selected clips</th>
<th>LR (mm)</th>
<th>AP (mm)</th>
<th>SI (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper clip</td>
<td>0.4 ± 0.2</td>
<td>0.9 ± 0.4</td>
<td>0.9 ± 0.6</td>
</tr>
<tr>
<td>Inner clip</td>
<td>0.4 ± 0.3</td>
<td>0.7 ± 0.4</td>
<td>0.9 ± 0.6</td>
</tr>
<tr>
<td>Outer clip</td>
<td>0.4 ± 0.2</td>
<td>0.9 ± 0.4</td>
<td>0.7 ± 0.5</td>
</tr>
<tr>
<td>Lower clip</td>
<td>0.6 ± 0.3</td>
<td>0.9 ± 0.4</td>
<td>1.4 ± 0.9</td>
</tr>
</tbody>
</table>

Abbreviations: LR = left-right, AP = anterior-posterior, SI = superior-inferior.
95% confidence interval (95% CI) of the selected clips in the LR, AP and SI directions were 0.3–0.6 mm, 0.7–1.1 mm, 0.6–1.2 mm for the upper clip, 0.3–0.6 mm, 0.5–0.9 mm, 0.6–1.3 mm for the inner clip, 0.3–0.5 mm, 0.5–1.0 mm, 0.5–1.2 mm for the outer clip, and 0.4–0.7 mm, 0.7–1.2 mm, 0.9–1.9 mm for the lower clip.

Displacements of the same clip in the different directions were different; the displacement in the LR direction was smaller than that in the AP and SI directions, and the differences were statistically significant ($P < 0.05$), but there was no statistically significant difference between the displacements in the AP and SI directions ($P > 0.05$). The displacement comparison between the different directions for the same clip were included in Table 2.

Table 2. Displacement comparison between the different directions of the same clip.

<table>
<thead>
<tr>
<th>Selected clip</th>
<th>LR vs. AP</th>
<th>LR vs. SI</th>
<th>AP vs. SI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t$ value</td>
<td>$P$ value</td>
<td>$t$ value</td>
</tr>
<tr>
<td>Upper clip</td>
<td>–4.145</td>
<td>0.000</td>
<td>–2.971</td>
</tr>
<tr>
<td>Inner clip</td>
<td>–2.138</td>
<td>0.042</td>
<td>–2.980</td>
</tr>
<tr>
<td>Outer clip</td>
<td>–3.059</td>
<td>0.007</td>
<td>–2.516</td>
</tr>
<tr>
<td>Lower clip</td>
<td>–2.680</td>
<td>0.013</td>
<td>–3.239</td>
</tr>
</tbody>
</table>

Table 3 showed the displacement comparison of the different clips in the same direction. The displacement of the lower clip was greater than that of the outer clip in the SI direction and the difference was statistically significant ($t = −2.353, P = 0.026$), but there was no statistically significant difference between the lower and outer clips in the LR and AP directions and the differences between the other selected clips in the same direction were not statistically significant ($P > 0.05$).

The displacements of the geometric center in the LR, AP and SI directions were $1.4 ± 0.4$ mm (95% CI, 1.1–1.6 mm), $2.0 ± 1.0$ mm (95% CI, 1.4–2.6 mm) and $1.9 ± 1.0$ mm (95% CI, 1.3–2.5 mm), respectively. The displacement in the LR direction was significantly less than that in the AP ($t = −2.295, P = 0.035$) and SI direction ($t = −2.138, P = 0.042$) direction, and AP displacement was similar to SI displacement ($t = 0.313, P = 0.757$).

In the same direction of LR and AP, the displacement of the geometric center was always greater than that of the selected clips. The differences in the displacement of the selected clip and the geometric center, except the geometric center and the lower clip ($t = 1.404, P = 0.172$), were also statistically significant in the SI direction ($P < 0.05$). Table 4 shows the displacement comparisons of the geometric center and the selected clips in the same direction.

The association between the displacement of the geometric center and selected clip was negative correlation both in

Table 3. Displacement comparison of the different clips in the same direction.

<table>
<thead>
<tr>
<th>Paired comparison</th>
<th>LR</th>
<th>AP</th>
<th>SI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t$ value</td>
<td>$P$ value</td>
<td>$t$ value</td>
</tr>
<tr>
<td>Upper clip vs. inner clip</td>
<td>–0.151</td>
<td>0.881</td>
<td>1.463</td>
</tr>
<tr>
<td>Upper clip vs. outer clip</td>
<td>–0.094</td>
<td>0.926</td>
<td>0.768</td>
</tr>
<tr>
<td>Upper clip vs. lower clip</td>
<td>–1.598</td>
<td>0.122</td>
<td>–0.142</td>
</tr>
<tr>
<td>Inner clip vs. outer clip</td>
<td>0.087</td>
<td>0.931</td>
<td>–0.616</td>
</tr>
<tr>
<td>Inner clip vs. lower clip</td>
<td>–1.373</td>
<td>0.181</td>
<td>–1.499</td>
</tr>
<tr>
<td>Outer clip vs. lower clip</td>
<td>–1.766</td>
<td>0.092</td>
<td>–0.852</td>
</tr>
</tbody>
</table>

Table 4. Displacement comparisons of the geometric center and the selected clips in the same direction.

<table>
<thead>
<tr>
<th>Paired comparison</th>
<th>LR</th>
<th>AP</th>
<th>SI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t$ value</td>
<td>$P$ value</td>
<td>$t$ value</td>
</tr>
<tr>
<td>geometric center vs. upper clip</td>
<td>7.622</td>
<td>0.000</td>
<td>3.833</td>
</tr>
<tr>
<td>geometric center vs. inner clip</td>
<td>7.274</td>
<td>0.000</td>
<td>4.530</td>
</tr>
<tr>
<td>geometric center vs. outer clip</td>
<td>8.216</td>
<td>0.000</td>
<td>4.160</td>
</tr>
<tr>
<td>geometric center vs. lower clip</td>
<td>6.226</td>
<td>0.000</td>
<td>3.690</td>
</tr>
</tbody>
</table>

Abbreviations: LR = left-right, AP = anterior-posterior, SI = superior-inferior.
LR direction and in AP direction. But neither showed statistical significance. (LR direction: \( r = -0.256, P = 0.378 \) for the upper clip; \( r = -0.108, P = 0.714 \) for the lower clip; \( r = -0.083, P = 0.778 \) for the inner clip; \( r = -0.446, P = 0.11 \) for the outer clip, respectively. AP direction: \( r = -0.185, P = 0.526 \) for the upper clip; \( r = -0.281, P = 0.33 \) for the lower clip; \( r = -0.027, P = 0.926 \) for the inner clip; \( r = -0.18, P = 0.535 \) for the outer clip, respectively).

The association between the displacement of the geometric center and the inner clip was a positive correlation in the SI direction not statistically significant \( (r = 0.271, P = 0.348) \). Similarly, there was a positive correlation and not statistically significant between the displacement of the geometric center and the outer clip \( (r = 0.304, P = 0.291) \). The displacement of the geometric center was positively correlated with the upper clip \( (r = 0.891, P = 0.000) \) and the lower clip \( (r = 0.646, P = 0.013) \).

**DISCUSSION**

Off-line or on-line verification of image-guided radiotherapy (IGRT) is the key method to reduce the effect of setup error towards target motion.\(^{13,18}\) After off-line or on-line error correction by cone-beam CT (CBCT), KV or MV-level X-ray, ITV caused by respiratory movement becomes the main basis for determining PTV of EB-PBI. Metal clips (silver clip or titanium clip) implanted in the surgical cavity are important reference for measuring and determining EB-PBI target motion.\(^{19-21}\) In this study, the 4DCT based results showed that the displacements in the LR, AP and SI directions were \( 0.4 \pm 0.2 \) mm, \( 0.9 \pm 0.4 \) mm and \( 0.9 \pm 0.6 \) mm for the upper clip in the surgical cavity, \( 0.4 \pm 0.3 \) mm, \( 0.7 \pm 0.4 \) mm and \( 0.9 \pm 0.6 \) mm for the inner clip, \( 0.4 \pm 0.2 \) mm, \( 0.8 \pm 0.4 \) mm and \( 0.7 \pm 0.5 \) mm for the outer clip and \( 0.6 \pm 0.3 \) mm, \( 0.9 \pm 0.4 \) mm and \( 1.4 \pm 0.9 \) mm for the lower clip, respectively. Ahn \( et \ al.\)\(^{22}\) applied 4DCT to twenty one patients after breast-conserving surgery and found that the displacements in the LR, AP and SI directions for the clips in the surgical cavity ranged from \( 0.2 \pm 0.1 \) mm, \( 1.1 \pm 0.6 \) mm and \( 0.5 \pm 0.4 \) mm, respectively. These results show that clip motion in the AP and SI directions were larger than that in the LR direction. However, no significant differences were noticed between the AP and SI direction. The motion range for different clips in the same direction was similar. The possible reasons included (1) thorax expansion with breathing, which resulted in varied clip displacement in different directions; (2) breast size and shape; (3) location of the surgical cavity; (4) fixed position, such as the patient in a horizontal or supine position on a tilt breast bracket. In this study, the patients lifted and outrretched the bilateral hands and lay in a supine position on the 15° tilt breast brackets, which may be one of the reasons for the similar displacement between the AP and SI directions.

Tumor bed motion caused by respiration is the composi-
senting the displacements of the center of the EB-PBI target volume determined by all the clips in the surgical cavity.

In addition, we investigated the association of three-dimensional displacements between geometric center and the selected clips individually. It was found that the displacements of geometric center were associated with the upper and the lower clips in the SI direction. This result demonstrated that the movement of the surgical cavity in the breast during the breathing cycle was a non-rigid motion. Displacements of geometric center that consisted of all the clips, together with the moving range and the direction of all clips, represented more target volume information. We considered it was unreasonable to represent the overall EB-PBI target volume using a single clip displacement. In addition, the geometry consisting of all the clips in the surgical cavity can more accurately reflect the displacements of the EB-PBI target volume at free respiratory status. When delineate the gross target volume (GTV) in the CT simulation images, clips in each boundary of the surgical cavity only appeared in one layer or a few layers of CT images, which no clip could be provide mark for other layers on CT simulation images. All of these would affect the outlined GTV location and size, thereby affecting both the location and displacement of the target volume center.

This is a preliminary observation for the clip displacement of lumpectomy cavity based on 4DCT technique in our radiation center. Though a small sample size, our study showed that the 4DCT should be an effective method to determine the displacement of the selected clips or the geometry consisting of all the clips in the surgical cavity for EB-PBI. For adequate target coverage and sparing more normal tissue, the internal margin in AP and SI direction should be greater than LR direction in free breathing. The study also indicates that the displacement of a single selected clip of the surgical cavity was not qualified to substitute for the displacement of the whole target. Further studies should be necessary to validate our results.

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