Interfractional and intrafractional setup errors in radiotherapy for tumors analyzed by cone-beam computed tomography

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Key words: radiotherapy, cone-beam computed tomography (CBCT), setup errors

Background and Objective: Both interfractional and intrafractional setup errors may affect the precision of radiotherapy. This study was to analyze the interfractional and intrafractional setup errors in radiotherapy for tumors using cone-beam computed tomography (CBCT). Methods: Of the 51 patients received radiotherapy, 19 had head and neck tumors, 25 had thoracic tumors, and seven had abdominal-pelvic tumors. Patients received CBCT scans after initial setup, after re-positioning and after radiation delivery. The CBCT images were registered to the planning CT images, and setup errors on X, Y, Z axes were analyzed. Results: A total of 1 934 CBCT scans were performed on 51 patients, of which 955 were performed after initial setup, 525 after re-positioning and 454 after radiation delivery. The interfractional setup errors on X, Y and Z axes were (1.2 ± 0.9) mm, (1.2 ± 1.1) mm and (1.0 ± 0.8) mm, respectively, for head and neck tumors; (2.3 ± 1.9) mm, (4.2 ± 3.7) mm and (2.4 ± 2.1) mm, respectively, for thoracic tumors; (1.7 ± 1.5) mm, (4.7 ± 3.6) mm and (2.1 ± 1.6) mm, respectively, for abdominal-pelvic tumors. Comparing with the post-correction position, the post-treatment setup errors in head and neck tumors increased significantly on all three axes (p < 0.05), whereas the difference was not significant in trunk tumors (p > 0.05). Conclusions: Measurement and correction of interfractional setup errors before each fraction using CBCT could help to improve the precision of radiotherapy. The interfractional setup error variations are obvious in head and neck tumors and should be taken into account during treatment planning. The intrafractional setup errors in trunk tumors need further study.

Image-guided radiotherapy (IGRT) as a precision radiotherapy technique has been rapidly developed and used in clinic in recent years. Among different techniques used in IGRT, the cone-beam computed tomography (CBCT) image guidance has the advantage of providing the 3-dimensional (3D) information of both target and normal tissue position at treatment which can be used for setup correction and improving the accuracy of radiotherapy delivery. The technique is based on the x-ray volumetric imaging (XVI), of which consecutive images are acquired at one gantry rotation and reconstructed into 3D volumetric images. The images presented as CBCT sections are registered to the input planning CT. By comparing the CBCT images acquired before each treatment with the planning CT image, the positional errors of tumor in three dimensions can be determined.1-5

The Elekta Synergy is an integrated IGRT system which consists of a digital linear accelerator and an XVI system. Since April, 2006, the West China Hospital of Sichuan University has started to use this system in online setup correction for radiotherapy of cancer. The preliminary results are reported in this paper.

Materials and Methods

Patient data. From April 2006 to July 2006, 51 tumor patients were treated in the West China Hospital, including 38 men and 13 women, aged 29-78 years (median, 57 years). Of the 51 patients, 19 had head and neck (HN) tumors, including 14 had nasopharyngeal carcinoma (NPC), three had brain tumor (one received radiation at three target sites), one had laryngeal cancer, and one had cervical vertebral metastatic cancer; 25 had thoracic tumors, including 23 had lung cancer or lung metastatic cancer (four received radiation at two target sites in the lungs), and two had esophageal cancer; seven had abdominal-pelvic tumors.

Patient immobilization. Patients were all set up in the supine position. HN or HN-shoulder carbon fiber base-plate and customized thermal plastic facial masks (Med-Tec, USA) were used for head and neck tumors. Carbon fiber base-plate and customized thermal plastic body masks were used for tumors of the trunk. The stereotactic body frames (SBF, Elekta, Crawley, UK) were used for five cases of lung cancer. Customized thermoplastic body frame and active breathing control (ABC) were used for six cases of lung cancer.

Parameters to acquire XVI. The parameters to acquire XVI for head and neck are as follows: 100 kV, S20 collimator with small field of view (FOV, 27.7 cm), gantry rotation from 255 to 260 to100 degrees, with nominal scan dose of 0.9 mGy to the tissues within the

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field, reconstruction with medium resolution algorithm. The parameters to acquire XVI for tumors of the trunk were as follow: 100-120 kV, FOV 42.6cm (M20 collimator), gantry rotation starts from 182 to 160 degrees, with a nominal scan dose of 10–16 mGy.

Pre-correction CBCT (CBCT at initial setup) for each fraction should be acquired and automatically matched with the planning CT to obtain the shifts of initial tumor position in the left-right (X), superior-inferior (Y) and anterior-posterior (Z) directions. According to literature review and equipment precision, setup errors exceeding 2 mm should be corrected by shifting the treatment couch in the direction based on the digital readouts of the couch position. Post-correction CBCT was acquired for verification. If setup errors were ≤ 2 mm in all three directions, the patient received treatment immediately. If the setup errors still exceeded 2 mm on the second CBCT, corrections should be applied until the errors fulfill the action limit. Post-treatment CBCT was acquired after completion of radiation delivery to detect the motion during treatment.

**Analysis of setup errors and online correction.** The setup errors were analyzed with the Elekta XVI software. The planning CT images with the planning data sets were transferred to the XVI system. The region of interest (ROI) was defined on the CBCT images with the registration clip box (a tool provided in the XVI software) and matched with the planning CT images to obtain the 3D deviations between CBCT and the planning CT. The planning isocenter was defined as the registration reference point, which is always the center of the planning target volume (PTV). The setup errors were corrected with this reference point. Automatic bone match was applied for head and neck tumors, with the registration clip box confined to the tumor and surrounding bony structures and excluding the lower neck. Automatic soft tissue match was used for thoracic tumors, with the clip box enclosing the tumor only and excluding moving organs such as the heart. Automatic grey scale or bone scale match was used for abdominal-pelvic tumors based on different tumor types, with the clip box either confined to the tumor or with the surrounding bones. For the cases with two or more targets, separate match and treatment were applied for each target. For tumors with significant deformation in volumes and contours during the course of radiotherapy, re-planning was performed with updated simulation CT to avoid significant systematic errors in image registration.

Interfractonal error was defined as the deviation of anatomic structures between the pre-treatment position and planning CT, intrafractonal error was defined as the errors caused by organ motion or patient position change during treatment. As CBCT of each fraction was compared with the same planning CT, the shifts between pre-correction CBCT and planning CT could be regarded as interfractional errors, and the differences between post-correction CBCT and post-treatment CBCT could be regarded as intrafractalional errors.

**Statistical analysis.** The overall setup errors were calculated based on the CBCT-measured 3D setup errors for individual patients. The mean errors represented the systematic errors, and the standard deviation of the mean was considered as the random setup errors. In order to illustrate the magnitude of setup error values, absolute values of position errors were used for calculation. The 95% probability distribution of setup errors was represented by Mean ± 1.96×SD. In this study, only translational errors were corrected. SPSS 13.0 statistics software package was used for statistical analysis. The F-test was used to test the difference between setup errors before correction, after correction and after treatment. A p value of < 0.05 was considered significant.

**Results**

**CBCT imaging.** A total of 1934 CBCT scans were performed on 51 patients, including 955 pre-correction CBCT scans. In 312 (32.7%) pre-correction CBCT scans, the setup errors were ≤ 2 mm on all axes and no correction was performed, including 281 (64.3%) head and neck scans, 12 (3.4%) thoracic scans and 20 (12.1%) abdominal-pelvic scans. A total of 525 post-correction CBCT scans were performed, and 454 post-treatment CBCT scans were performed (Table 1).

**Setup errors for head and neck tumors.** The setup errors for the head and neck on 727 CBCT scans are showed in Table 2. The setup errors after initial setup were (1.2 ± 0.9) mm on X axis, (1.2 ± 1.1) mm on Y axis, and (1.0 ± 0.8) mm on Z axis. The frequencies of setup errors > 2 mm were 18.3% on X axis, 16.4% on Y axis, and 8.2% on Z axis. After online setup correction, the setup errors were reduced. The differences between pre- and post-correction setup errors on the X, Y and Z axes were significant (p < 0.001). Only 2.7% of the errors on X and Y axes were > 2mm. The differences between pre-correction and post-treatment setup errors were also significant (all p < 0.05). The post-treatment setup errors on all three axes were significantly increased as compared with post-correction setup errors (p < 0.05). To compensate for 95% probability distribution of the setup errors, the isotropic margin was extended by 4 mm for pre-correction position, 2 mm for post-correction position, and 3 mm for post-treatment position. The increment of 1 mm margin was needed for intrafractonal setup errors.

**Setup errors for thoracic tumors.** A total of 828 CBCT scans were acquired for thoracic tumors. The setup errors are showed in Table 3. The upper limits for 95% probability distribution of pre-correction setup errors were 7.1 mm on X axis, 11.5 mm on Y axis, and 6.5 mm on Z axis. The greatest pre-correction setup errors occurred on Y axis, with 32.9% ≤ 2 mm, 48.7% ≤ 3 mm and 70.5% ≤ 5 mm. After online correction, the setup errors were reduced significantly on all X, Y and Z axes (p < 0.001). On Y axis, 9.8% of the post-correction errors were still > 2 mm while 98.3% of them were ≤ 3 mm. The differences between pre-correction and post-treatment setup errors were significant (P < 0.05). After treatment, 17.6% of the post-correction errors on Y axis were still ≥ 2 mm, while 95.2% of them were ≤ 3 mm. There was no significant difference between post-correction and post-treatment errors on X, Y and Z axes (p > 0.05), with the intrafractonal errors of < 1 mm.

There was no significant difference in setup errors among different fixation procedures for thoracic tumor patients immobilized.
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Setup errors for abdominal-pelvic tumors. The setup errors on 379 CBCT scans of abdominal-pelvic tumors were similar to those of thoracic tumors (Table 4). The greatest pre-correction setup error occurred on Y axis, with 33.3% ≤ 2 mm, 40% ≤ 3 mm, and 61.2% ≤ 5 mm. The upper limits for 95% probability distribution of pre-correction setup errors were 4.6 mm on X axis, 11.8 mm on Y axis, and 5.4 mm on Z axis. After online correction, the setup errors were significantly reduced on X, Y and Z axes (p < 0.001). The frequencies of errors ≤ 2 mm and ≤ 3 mm were 86.6% and 96.9% respectively, on Y axis. The upper limits for the 95% probability distribution of post-correction setup errors were 2.8 mm on X axis, 2.8 mm on Y axis, and 2.2 mm on Z axis. As compared with pre-correction setup errors, post-treatment setup errors were significantly increased on all three axes (p < 0.001), with 80.5% ≤ 2 mm and 93.1% ≤ 3 mm. The upper limits for 95% probability distribution of post-correction setup errors were 3.2 mm on Z axis. The post-treatment setup errors increased by 1.0–1.5 mm as compared with post-correction errors, but the difference was not significant on all axes (p > 0.05).

Discussion

The patient setup at each fraction of radiotherapy is affected by many factors. The reproducibility of patient positioning is the major barrier for improvement of radiotherapy precision. Based on literature report, the interfractional errors ranged 2–10 mm for head and neck,7-9 and 5–40 mm for the trunk.10-12 In conventional radiotherapy planning, this setup uncertainty are handled by adding a PTV to clinical target volume (CTV) margin, which would increase the irradiated volume, result in increased probability of complications and limit the dose escalation for tumor, and eventually reduce tumor control and patient survival. On the other hand, as the patient position may vary during each fraction of radiation, the intrafractional error may also affect the precision of treatment. Therefore, to quantify the 3D position variation of tumor during treatment and ensure the precise implementation of radiotherapy is also important.13-15

In this study, a total of 955 pre-correction CBCT scans were performed on 51 patients. The frequency of pre-correction errors ≤ 2 mm on all three axes was 64.3% for head and neck tumors, 3.4% for thoracic tumors, and 12.1% for abdominal-pelvic tumors. In head and neck tumors, the mean pre-correction setup error was about two mm on all three axes. After online correction, the setup errors were significantly reduced on all three axes (p < 0.001), with 80.5% ≤ 2 mm and 93.1% ≤ 3 mm. The upper limits for 95% probability distribution of post-correction setup errors were 1.0 mm on X axis, 1.1 mm on Y axis, and 1.1 mm on Z axis. The post-treatment setup errors increased by 1.0 mm as compared with post-correction errors, but the difference was not significant on all axes (p > 0.05).

Table 2  Setup errors of 727 head and neck CBCT scans

<table>
<thead>
<tr>
<th>Axis</th>
<th>Setup errors (mm)</th>
<th>Frequency of setup errors ≤ 2 mm (%)</th>
<th>Frequency of setup errors ≤ 3 mm (%)</th>
<th>Frequency of setup errors ≤ 5 mm (%)</th>
</tr>
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<tr>
<td></td>
<td>First scan</td>
<td>Second scan</td>
<td>Third scan</td>
<td>First scan</td>
</tr>
<tr>
<td>X</td>
<td>1.2±0.9</td>
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<td>0.9±0.8</td>
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<td>Y</td>
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<td>0.6±0.5</td>
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<tr>
<td>Z</td>
<td>1.0±0.8</td>
<td>0.6±0.5</td>
<td>0.9±0.7</td>
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Table 3  Setup errors of 828 thoracic CBCT scans

<table>
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<th>Axis</th>
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<th>Frequency of setup errors ≤ 3 mm (%)</th>
<th>Frequency of setup errors ≤ 5 mm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First scan</td>
<td>Second scan</td>
<td>Third scan</td>
<td>First scan</td>
</tr>
<tr>
<td>X</td>
<td>2.3±1.9</td>
<td>0.8±0.7</td>
<td>0.9±0.8</td>
<td>53.5</td>
</tr>
<tr>
<td>Y</td>
<td>4.2±3.7</td>
<td>0.9±0.8</td>
<td>1.1±1.0</td>
<td>32.9</td>
</tr>
<tr>
<td>Z</td>
<td>2.4±2.1</td>
<td>0.8±0.7</td>
<td>1.0±0.8</td>
<td>53.5</td>
</tr>
</tbody>
</table>

Footnotes as in Table 2.

Table 4  Setup errors of 379 abdominal-pelvic CBCT sessions

<table>
<thead>
<tr>
<th>Axis</th>
<th>Setup errors (mm)</th>
<th>Frequency of setup errors ≤ 2 mm (%)</th>
<th>Frequency of setup errors ≤ 3 mm (%)</th>
<th>Frequency of setup errors ≤ 5 mm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First scan</td>
<td>Second scan</td>
<td>Third scan</td>
<td>First scan</td>
</tr>
<tr>
<td>X</td>
<td>1.7±1.5</td>
<td>0.8±1.0</td>
<td>1.2±1.6</td>
<td>68.5</td>
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<tr>
<td>Y</td>
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<td>1.3±1.1</td>
<td>33.3</td>
</tr>
<tr>
<td>Z</td>
<td>2.1±1.6</td>
<td>0.7±0.6</td>
<td>1.0±1.1</td>
<td>56.4</td>
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Footnotes as in Table 2.
post-correction and post-treatment CBCT. Significant intrafractional motion was observed in some patients with a maximum of five mm. This may due to longer treatment time of intensity-modulated radiotherapy (IMRT) applied for these patients. In addition, the significant mucosa radiation reaction may induce swallowing and coughing which may also contribute to the motion during treatment. For head and neck tumors, with online correction, the margin to cover 95% probability of interfractional and intrafractional errors would be 3 mm and, if the mechanical accuracy of treatment was considered, a five mm margin would suffice the planned PTV. In contrast, if no online correction was applied, the interfractional error alone would need a four mm margin, and a total margin of seven mm was needed. These results suggest that with a two mm action limit, CBCT-guided online correction is beneficial for reducing PTV margin in radiotherapy of head and neck cancer.

In thoracic tumors, the frequency of pre-correction setup errors ≤ 2 mm was 53.5% on X axis, 32.9% on Y axis, and 53.5% on Z axis; the frequency of pre-correction setup errors ≤ 3 mm was 73.7% on X axis, 48.7% on Y axis, and 72.0% on Z axis. The interfractional errors were significant in thoracic tumors, with the greatest error of 20 mm on Y axis. The errors on Z axis were also significant, with the greatest error of 15 mm. However, after online correction and after treatment, the errors were both significantly reduced (p < 0.001). After correction, 98.3% of the errors were ≤ 3 mm. Compared with post-correction errors, the post-treatment errors in thoracic tumors were somewhat increased, with 95.2% of them ≤ 3 mm, but the difference between post-correction and post-treatment errors was not significant. Our results indicate that for thoracic tumors, CBCT-guided online detection and correction of setup errors was beneficial for reducing PTV margin, which would potentially protect normal tissues. The patient position was stable during treatment, with a small intrafractional positional variability (Table 3). It should be pointed out that only setup errors were considered for this study. To design PTV for thoracic tumors, the respiration motion should be taken into account.

The setup errors for abdominal-pelvic tumors were similar to those of thoracic tumors in this study. Great setup errors were detected at initial setup, with the greatest error of 17 mm on Y axis. The frequency of great errors was higher on Y axis than on X and Z axes. If CBCT-guided online correction was not performed, the upper limits for the 95% distribution of interfractional errors were 4.6 mm on X axis, 11.8 mm on Y axis, and 5.2 mm on Z axis. Comparing with pre-correction setup errors, post-correction and post-treatment setup errors were significantly reduced on all three axes (p < 0.001). After correction, 96.9% of the setup errors were within 3 mm. There was no significant difference between post-correction and post-treatment errors. In our study, one patient with pancreas metastatic cancer suffered from discomfort during radiation, with the post-treatment setup error on Y axis significantly increased up to seven mm due to significant patient motion during treatment. The results suggest that the interfractional setup errors for abdominal-pelvic tumors are considerably large, especially on Y axis. However, the setup errors were reduced after online correction. As the position remained stable during treatment, the intrafractional positional variability was small. Similar to the results in thoracic tumors, 13.4% of the residual errors in abdominal-pelvic tumors were still > 2 mm and 96.7% were ≤ 3 mm after correction. The post-correction residual errors and intrafractional errors in abdominal-pelvic tumors were greater than those in head and neck tumors and thoracic tumors. With online correction, the total margin to cover 95% of the residual errors and intrafractional motion was 3.2–4.3 mm, while the PTV extension should be 5.2–6.3 mm if no correction was applied.

Both interfractional and intrafractional errors exist in the process of radiotherapy and affect the accuracy of treatment, while accurate detection and quantification of interfractional and intrafractional errors using CBCT may help to improve the precision of radiotherapy.6,16,17 Similarly, our study showed that detection and correction of interfractional errors before each treatment fraction using CBCT is beneficial for improving treatment precision. Intrafractional errors are obvious in radiotherapy of head and neck cancer and should be accounted for during radiotherapy planning. For the intrafractional errors of thoracic tumors and abdominal-pelvic tumors, more studies are needed.

It has been considered that using different immobilization techniques can influence the setup precision.6 In radiotherapy for head and neck tumors, the HN-shoulder fixation frame is considered to have higher repositioning precision than the HN frame. However, in this study the differences in setup errors using these two fixation devices were not significant. This may due to the small scale of cases in this study as well as a small region of interest chosen for image registration, which only includes the tumor and surrounding tissues. In this study, three immobilization devices (SBF alone, thermoplastic frame alone, thermoplastic frame plus ABC) were used for thoracic tumors, with no significant difference in positioning reproducibility among them, which may also due to the small scale of cases. Further study is needed to determine the role of fixation technique in patient setup accuracy.

In conclusion, using CBCT imaging provided by the Synergy system, the 3D structure of tumor targets and surrounding normal tissues can be obtained for each patient before radiation and therefore useful for evaluation of setup errors in radiotherapy. However, the planning CT only represents a snap-shot of tumor during simulation, while CBCT requires 30–60 s for reconstruction. Therefore, CBCT may be similar to a slow CT which has a blurred image on the trajectory of motion, and may result in a systematic error during image registration with planning CT. In addition, different registration methods (for example, with different regions of interest) may also produce errors which may affect the accuracy of measurement. These limitations need to be overcome in further studies.

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References
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