Radiotherapy for lung cancer
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Kilo-voltage cone beam CT setup measurements for lung cancer patients; first clinical results and comparison with electronic portal-imaging device

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Abstract

Purpose: Kilovoltage cone-beam computed tomography (CBCT) has been developed to provide accurate soft-tissue and bony setup information. We evaluated clinical CBCT setup data and compared CBCT measurements with electronic portal imaging device (EPID) images.

Material and Methods: The setup error for CBCT scans at the treatment unit relative to the planning CT was measured for 62 patients (524 scans). For 19 of these patients (172 scans) also portal images were made. The mean, systematic setup error (\( \Sigma \)) and random setup error (\( \sigma \)) were calculated for the CBCT and the EPID. Also the differences between CBCT and EPID and the rotational setup error derived from the CBCT were evaluated.

An offline SAL correction protocol, based on the CBCT measurements, was used to reduce systematic setup errors and the impact of this protocol was evaluated.

Results: The CBCT setup errors were significantly larger than the EPID setup errors for the CC and AP directions (\( p < 0.05 \)) due to discrepancy of the setup errors by the EPID relative to CBCT. The mean overall setup errors after correction measured with the CBCT were 0.2 mm (\( \Sigma = 1.6 \) mm, \( \sigma = 2.9 \) mm) in the left-right, -0.8 mm (\( \Sigma = 1.7 \) mm, \( \sigma = 4.0 \) mm) in cranial-caudal and 0.0 mm (\( \Sigma = 1.5 \) mm, \( \sigma = 2.0 \) mm) in the anterior-posterior direction. Using our correction protocol only two patients had mean setup errors larger than 5 mm, without this correction protocol more than 51\% of the patients would have had a setup error larger than 5 mm.

Conclusion: Three-dimensional kilovoltage CBCT scans provided more accurate information concerning the setup of lung cancer patients than was available with prior techniques.
Introduction
Correct target positioning is of major concern in the delivery of radiotherapy. However, the position of the target is subject to geometric uncertainties due to variability in patient positioning and internal organ motion [1]. Awareness of these uncertainties in the planning of radiotherapy is essential. Appropriate margins for an adequate coverage of the target volume have to be taken into account. 3D conformal planning techniques improve dose distributions by sharpening dose gradients between target volume and surrounding tissue. Consequently, increased prescription doses and improved sparing of normal tissue can be achieved. However, the steep dose gradient between tumor and critical structures makes 3D conformal techniques more sensitive to geometric uncertainties [2]. Consequently, accurate setup verification over the course of treatment is very important for an adequate treatment.

Erridge et al. [3] evaluated setup errors during treatment for lung cancer patients by electronic portal image device (EPID) measurements using an off-line correction protocol. Systematic setup errors ($\Sigma$) of 1.4, 1.5 and 1.3 mm were observed in the left-right, cranial-caudal and anterior-posterior directions, respectively. Similar data were found by de Boer et al. and Van Sornsen de Koste et al. [4,5]. The accuracy of the measurements of setup errors itself, could however not be evaluated, because a reference procedure (i.e. golden standard) was lacking.

Recently, kilovoltage (kV) conebeam CT scanners (CBCT) integrated with a linear accelerator (linac) became available in many institutions. The scanner is mounted on the gantry of a linac and provides detailed high resolution 3D information of the patient internal anatomy just prior to the treatment [6]. Consequently, the data from the kV CBCT allows accurate measurements of the systematic and random setup errors.

The introduction of the kV CBCT in our department has enabled acquisition of clinical data concerning the setup of lung cancer patients during treatment. First, we measured setup errors with both an electronic portal image device and a kV CBCT scanner during the treatment of 19 patients. Thereafter, the setup errors of subsequently treated patients were measured with the CBCT scanner only. The purpose of this study is to investigate and compare the setup measured with the EPID and with the CBCT. In addition, we will evaluate the clinical setup data using kV CBCT of lung cancer patients during the treatment and the impact of the setup correction protocol.

Material and Methods

Patients and measurements
Both cone beam CT (CBCT) scans and images from the electronic portal-imaging
device (EPID) were acquired for lung cancer patients to compare the setup error as measured by these two techniques. Patients were positioned in an arm support without a body frame. First a CBCT scan was performed immediately followed by the portal images (generally within a time period of less than 5 minutes). For 19 patients, treated between July 2003 and July 2004, a total of 172 scans were made (Table 1). For the first 4 patients the setup verification/correction protocol [7] was based on the EPID images, after March 2004 this protocol was based on the CBCT scans. After the first 19 patients (with both EPID images and CBCT scans), EPID images were only made at the first fraction for quality control purposes. From August 2004 to May 2005 for a total of 43 patients CBCT setup measurements (352 scans) were made for lung cancer patients.

| Table 1 |
|-----------------|-----------------|-----------------|
|                | **EPID and CBCT** | **Only CBCT**   | **Total** |
| EPID correction protocol | 4 (31)           |                  | 4 (31)    |
| CBCT correction protocol   | 15 (141)         | 43 (352)         | 58 (493)  |
| Total                     | 19 (172)         | 43 (352)         | 62 (524)  |

The number of patients, type of imaging modality and used correction protocol. Number of scans is indicated between brackets. EPID: Electronic Portal Imaging Device. CBCT: Cone Beam Computed Tomography.

**EPID images**

During radiotherapy, two orthogonal EPID images (anterior-posterior and lateral) were acquired using an a-Si flat panel detector (Elekta iViewGT) using 5 Monitor Units each. These images were acquired using in-house developed software at a resolution of 1 x 1 mm² pixel size at the iso-center plane.

Digital reconstructed radiographs (DRRs) were made from the planning CT using in-house developed software. The planning CT was performed on a single slice CT scanner. The slice distance was set on 5 mm due to the limitation of the planning system (U-Mplan, University of Michigan). A bone template was defined on the DRR (using a simulator film as visual guide). The DRR was matched automatically on the portal field edge, followed by automatic registration and in almost all cases a manual adaptation of the bony anatomy. The vertebra, clavicles and ribs were used for the image registration (Figure 1). Two orthogonal EPID images were used for setup measurements, the registrations of which were subsequently combined to a 3D setup error.

**CBCT scanner**

The CBCT scanner (Elekta Synergy, Elekta Oncology Systems Ltd., Crawley, West Sussex, UK) consisted of a conventional x-ray tube (kV source) and an a-Si flat panel detector, both mounted on the gantry of the linear accelerator (linac).
The linac (MV source) was an Elekta SL20i medical accelerator. The lung cancer patients were scanned with a short scan protocol acquiring about 330 or 670 projections (depending of the frame rate of the imager) over an arc of 200° yielding an imaging dose of about 2 cGy at the iso-center. An in-house developed implementation of the filtered back projection algorithm [8] provided a reconstruction of 330 images into a 256³ volume (1 mm cubic voxel size) in about 21 s on a 2.8 GHz PC. More details were previously described [9]. An object can be relocated within less than 1 mm of the prescribed location using the CBCT scanner, whereby the delivery precision is constant over a duration of at least 3 months [10].

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**Figure 1.** Match of the Electronic Portal Image (EPI) and the Digital Reconstructed Radiograph (DRR). The green dots are the contour tracing dots from the DRR, the green line representing the anatomy structure outline.

**Figure 2.** Match of the planning CT and the Cone-Beam CT (CBCT) whereby a user-defined 3-D region of interest (blue dashed line) was positioned around the vertebra. The inner and outer red line represents the gross target volume and clinical target volume, respectively.
Chapter 7

Setup measurements based on CBCT

The planning CT scan and the iso-center position, to be used as reference, was imported from the planning system. The bony anatomy in the CBCT scans was automatically registered to the planning scan using chamfer matching or grey value (cross correlation ratio) matching. The match procedure included a user-defined 3-D rectangular shaped region of interest that was positioned around the vertebrae in the planning CT (Figure 2). The registration was based on a rigid body assumption providing 3 translations and 3 rotations.

Patient setup correction

Setup measurements were performed after completion of the daily treatment to drive an off-line 3D shrinking action level (SAL) protocol [11]. Required corrections had to be applied in the remaining treatments fractions to reduce systematic setup errors. This protocol tests the length of the setup error vector against a shrinking action level: \( \alpha/\sqrt{N} \), with \( N \) the number of consecutive measurements and an initial action level \( \alpha = 9 \) mm. For the first three consecutive fractions setup measurements were performed (i.e. \( N_{\text{max}} = 3 \)). If the mean of vector length (average of the consecutive measurements) was smaller than \( \alpha/\sqrt{N} \), no correction was applied. Subsequently, once a week setup measurements were made. For this weekly check, the average of the last three measurements was tested against an action level of \( \alpha = 9/\sqrt{3} = 5.2 \) mm. The protocol was restarted (i.e. again 3 consecutive measurements) after a correction was applied. Only setup corrections of 3 mm or larger were applied for the (left-right (LR), cranial-caudal (CC) and anterior-posterior (AP) directions to limit workload.

Differences between EPID and CBCT and statistics

As previously described [12] the setup errors are separated into systematic- and random errors. The random error (\( \sigma \)) is the deviation that occurs between different fractions (i.e. inter-fraction setup variation), while the systematic error (\( \Sigma \)) is the deviation between the simulation patient position and the average patient position (i.e. inter-patient setup variation). The random error for the entire population is the root mean square (RMS) of the individual random errors. The systematic error is the standard deviation of the individual patient errors. The mean, systematic error and the random setup error were calculated for the EPID setup error and CBCT setup error. We evaluated the impact of the corrections if the corrections were derived from the EPID measurements (i.e. theoretical analysis because the clinically used corrections were based on the CBCT). In other words, the corrections based on EPID measurements on the setup accuracy as measured by the CBCT were evaluated. Therefore we first removed the actually performed corrections from the EPID and CBCT data sets (i.e. uncorrected EPID and CBCT dataset). Subsequently, we applied the correction protocol on the uncorrected EPID and
CBCT setup data: first clinical results and comparison with EPID

Table 2

<table>
<thead>
<tr>
<th>Translations (N = 19, n = 170)</th>
<th>Axis</th>
<th>Mean (mm)</th>
<th>S(1 SD, mm)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference EPID – CBCT</td>
<td>LR</td>
<td>0.1</td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>0.7</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>0.3</td>
<td>2.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

The mean setup error, standard deviation of the translational systematic errors (δ) and random errors (σ) measured with the EPID and the CBCT, respectively. N and n are the number of patients and the number of measurements, respectively.

CBCT data sets, retrospectively, by calculating couch corrections prescribed by the EPID data (EPID correction) and by the CBCT data (CBCT correction). Hereafter, the EPID correction was added on the uncorrected CBCT data set. Linear regression analysis of the EPID setup data as a function of the CBCT data was performed. The paired T-test was used to evaluate whether the EPID setup data were significant different from the CBCT setup data. Correlations between the translational setup differences (i.e. difference between EPID and CBCT) and the rotations measured with the CBCT were tested with the Pearson correlation coefficient. Retrospectively, the corrections applied according to the SAL protocol were removed. The setup errors (vector length) of both uncorrected data and the corrected data (i.e. clinically used data) were analyzed to evaluate the impact of the SAL procedure.

Results

I Setup measurements of EPID and CBCT

Translations: Differences between EPID and CBCT

Setup errors measured with the EPID were plotted against the setup errors of the CBCT (Figure 3). In general the setup errors measured with the CBCT were larger than the EPID setup errors. The regression coefficient (β) for the LR, CC and AP directions were 0.86 (95% confidence interval (CI) = 0.76 – 0.96), 0.67 (95% CI = 0.60 – 0.74) and 0.47 (95% CI = 0.35 – 0.58), respectively.

We calculated the mean of the difference between each pair of measurements (Table 2), i.e. difference between what was measured with the EPID and CBCT for each fraction. For the LR direction the mean difference was 0.1 mm (p = 0.5). For the CC and AP directions the mean differences were significantly different from zero (0.7 mm, p < 0.001 and 0.3 mm, p = 0.04, respectively). If the EPID data were used to determine the required corrections (see material and methods), a mean setup error of 1.8 mm would have been observed in the CC direction (Table 3). However, when evaluating these EPID corrections with the CBCT measurements, an actual mean setup error resulted of −4.5 mm, with a large Σ of 3.8 mm. If the CBCT measurements themselves were used in the correction protocol, a significant smaller
Rotational errors (especially out of plane) are difficult to measure using 2D portal image analysis. We therefore evaluated the impact of these rotational setup errors measured with CBCT on the differences observed between EPID and CBCT measured in the translational directions. The correlation coefficient of the rotational setup errors and the vector length in the plane where the largest difference might be expected were calculated (i.e. vector length in the plane perpendicular to the rotation axis). The correlation coefficient of the vector length in the plane perpendicular to the LR axis and the rotations around the LR axis was 0.2 (p = 0.01). Similarly, the correlation coefficients of the vector length in the plane perpendicular to the CC and AP axes and the rotations around the CC and AP axis, respectively, were both 0.17 (p = 0.03).

Translations; Setup error of CBCT
Four hundred ninety-three CBCT setup measurements were performed for 58 patients (corrections were based on CBCT). There was quite a variation in the number of corrections applied per patient with a maximum (35%) at 1 correction, for 29% of the patients no correction was applied and for only 2% of the patients 5
CBCT setup data: first clinical results and comparison with EPID

Table 3

<table>
<thead>
<tr>
<th>A. corrections based on EPID (N = 19, n = 170)</th>
<th>Axis</th>
<th>Mean (mm)</th>
<th>± (1 SD, mm)</th>
<th>(1 SD, mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPID</td>
<td>LR</td>
<td>0.0</td>
<td>2.2</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>CC</td>
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<td>5.2</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>0.2</td>
<td>0.9</td>
<td>2.1</td>
</tr>
<tr>
<td>CBCT</td>
<td>LR</td>
<td>0.2</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>-4.5</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>-0.2</td>
<td>1.6</td>
<td>2.5</td>
</tr>
<tr>
<td>B. corrections based on CBCT (N = 19, n = 170)</td>
<td>Axis</td>
<td>Mean (mm)</td>
<td>± (1 SD, mm)</td>
<td>(1 SD, mm)</td>
</tr>
<tr>
<td>CBCT</td>
<td>LR</td>
<td>0.0</td>
<td>1.7</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>-1.3</td>
<td>1.9</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>AP</td>
<td>0.3</td>
<td>1.2</td>
<td>2.6</td>
</tr>
</tbody>
</table>

A. The mean setup error, standard deviation of the systematic errors (±) and random errors (σ) using the EPID and CBCT measurements with the corrections based on the EPID data.
B. The mean setup error, standard deviation of the systematic errors (±) and random errors (σ) using the CBCT measurements with the corrections based on the CBCT data. N and n are the number of patients and the number of measurements, respectively. EPID: Electronic Portal Imaging Device. CBCT: Cone beam Computed Tomography.

corrections were needed according to the SAL correction protocol (Figure 4). During the treatment of all 58 patients 76 corrections were applied (i.e. 1.3 correction per patient). The total number of corrections (in any direction) was 134. The deviations in the setup were largest in the CC direction for the mean, systematic error as well as the random error (Table 4).

Table 4

<table>
<thead>
<tr>
<th>A. CBCT (N = 58, n = 491)</th>
<th>Axis</th>
<th>Mean (mm)</th>
<th>± (1 SD, mm)</th>
<th>(1 SD, mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>0.2</td>
<td>1.6</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>-0.8</td>
<td>1.7</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>AP</td>
<td>0.0</td>
<td>1.5</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

B. CBCT corrections removed

| Axis | Mean (mm) | ± (1 SD, mm) | (1 SD, mm) |
| LR | 0.7 | 3.1 | 2.5 |
| CC | -2.3 | 4.0 | 3.4 |
| AP | -0.1 | 2.0 | 2.0 |

A. The mean and standard deviation of the translational systematic errors (±) and random errors (σ) if no setup corrections were made. B. The mean, ± and σ if no setup corrections were made.

Setup error of CBCT without corrections

If no corrections were applied to the setup of the patients, the mean of the setup errors in the CC direction was more than 2.0 mm (Table 4). The systematic errors (±) without corrections were 3.1 mm, 4.0 mm and 2.0 mm for the LR, CC and AP direction, respectively. The random error was 0.6 mm smaller without setup correction in the CC directions, for the LR and AP direction the difference was
smaller (Table 4). Applying the SAL correction protocol, only 2% of the patients had a mean setup error (vector length) larger than 5 mm. Without this protocol, more than 51% of the patients would have had a mean set up error larger than 5 mm (Figure 5).

Rotations; Distribution of rotations
The mean rotational setup errors around the LR, CC and AP axis were small (0.1°). For all axes, the standard deviations of both systematic and random errors were of the order of 1 degree.

Discussion
Set up differences of EPID and CBCT
For 19 lung cancer patients, we performed 172 setup measurements with both portal images and CBCT scans. Setup errors measured with CBCT were generally larger than those measured with EPID. The largest difference between the EPID and CBCT measurements were observed in the CC and AP direction whereas the differences in the LR direction were not significant. Assuming that the CBCT system is more accurate [10], one might expect the setup error determined with CBCT to be smaller, since there is less measurement inaccuracy. On the other hand, because portal images were assumed to be less accurate, larger measurement errors might be the result. This study showed that EPID analysis resulted in a smaller estimated setup error in our group of lung cancer patients, and that the discrepancy was statistically significant. If the EPID were used to determine required corrections, a large under-estimation of the setup error would have been made. (Table 2 and 3, Figure 3).

There are several potential sources for the discrepancies observed between the EPID and CBCT. First, although the time interval between the CBCT and EPID
measurements was small, the observed setup differences between CBCT scans and EPID images might be due to patient and/or respiratory motion. Van Herk et al. [13] investigated this possible explanation of the observed differences. Digital reconstructed radiographs (DRR) were calculated from the CBCT scans and compared with the corresponding EPID images for 4 patients (32 CBCT scans). The difference between the DRR of CBCT data and the EPID image from the same day was generally small (< 1 mm). Consequently, the patient motion between image acquisitions and respiration motion hardly contributed to the observed differences.

Secondly, EPID images measures only the setup errors in the LR, CC, and AP directions. Three-dimensional (3D) CBCT scans provide, in a significant way, accurate information concerning rotations [14]. If rotations were responsible for the observed differences between CBCT and EPID, they were most likely to cause differences in the plane perpendicular to the rotation axis. We did observe a correlation between the rotations and the differences between CBCT and EPID in these planes. Although the correlation was significant, only 20% or less (correlation coefficient ≤ 0.2) of the observed differences could be explained by rotations. Consequently, the (out-of-plane) rotations, detected by the CBCT, were only partly responsible for the observed differences between CBCT and EPID.

Thirdly, match procedures using CBCT and EPID images do have different regions of interest. The vertebra, clavicles and ribs were used for the EPID image registration whereas the match procedure of the CBCT included only the vertebrae. However, clavicles and ribs are more subject to (respiratory) motion, which should have been resulted in larger setup errors for the EPID (i.e. the opposite of what we observed).

A fourth reason might be the poor visibility of anatomical structures in the DRRs (calculated from the planning CT scan) and portal images might be the most important source of setup error differences. Because of this poor visibility it is more difficult to manually shift the portal image to the DRR, which may result in less corrections. CT slice spacing used for treatment planning, which is 5 mm in our study causes most details of the vertebrae to be lost (Fig. 1A).

Setup errors consist of day-to-day variation in patients positioning (i.e. random setup errors) and discrepancies induced during the preparation of the treatments (i.e. systematic errors). In particular, the impact of these systematic setup errors on the dose to the clinical target volume (CTV) was considerably [15]. Previously, Erridge et al. observed similar setup errors as measured in the current study with EPID analysis for 97 lung cancer patients treated in our department. In addition, Van Sornsen de Koste et al. and de Boer et al. observed similar setup errors in 20 and 40 lung cancer patients, respectively. These studies probably have had an underestimation of the setup error of lung cancer patients, which may have resulted in an under-dosage to the CTV.
Chapter 7

Setup verification and correction based on CBCT

From the time when the kilo-voltage (kV) CBCT was in clinical use in our department, target positioning was based on the planning CT and 3D kV CBCT images. Consequently, for 58 lung cancer patients accurate setup information was documented during their treatment course.

The setup error measured with the CBCT scan was used to drive a 3D shrinking action-level (SAL) protocol. The goal of the protocol is to reduce the systematic error during the remaining treatment. Our protocol was based on previous results from our institute [16,17] whereby 41% of the patients had a set-up error with a vector length larger than 5 mm based on portal images. After correction, only 1% of the patients had a set-up error larger than 5 mm. In our study these numbers were 51% without correction and 2% after correction, respectively.

Optimization of the SAL protocol is important to reduce systematic errors with acceptable random errors. A high initial action level ($\alpha$) might result in fewer corrections but also with larger systematic errors, whereas a low $\alpha$ might result in more corrections with an increase in random errors. We used an $\alpha$ of 9 mm and three subsequent measurements ($N_{\text{max}} = 3$) in the first stage (and after a correction was applied). Using this protocol, 1.3 corrections per patients were needed. Before the use of the CBCT, in our institution 0.9 corrections (data not presented) per patient were applied using the EPID images (using the identical SAL protocol). Van Sornsen de Koste et al. [18] applied 0.8 corrections per patient using a comparable SAL protocol ($\alpha = 8$ mm, $N_{\text{max}} = 3$), and the systematic errors in this study were in the range of our results (1.5 for the LR and CC direction and 1.3 for the AP direction).

The estimated setup error equals true setup error plus measurement error. The registration accuracy of the CBCT will reduce the measurement error. Consequently, the measured setup error of the CBCT will be closer to the true setup error. Because the EPID data might have underestimated the errors, fewer corrections were applied during treatment.

Guckenberger et al. [19] evaluated the setup error of the bony anatomy in the stereotactic body frame for 21 patients registered with CBCT. Larger systematic errors (3.2 mm CC, 2.6 mm AP and 1.8 mm LR) were observed whereas the random errors were smaller (2.1 mm CC, 1.1 mm AP and 2.0 mm LR), which is not surprisingly because of the smaller number of scans (fractions). The systematic positioning error of the patients in the stereotactic body frame contributed substantially to the group mean error of the tumor position. Nevertheless, a poor correlation was observed between the position errors of the patients (bony anatomy) and the tumor (soft tissue), which was emphasized for tumors with increased range of breathing motion (which was also observed previously by Wülfl et al [20]). This emphasizes the importance of appropriate setup measurements (bony anatomy) and tumor position localization (soft tissue). Respiratory motion (i.e. tumor motion,
the so called fourth-dimension (4D) in imaging) can be incorporated both in the planning phase (4D-CT)[21,22] and during irradiation (4D-CBCT)[19,23,24]. These image strategies will ensure higher levels of accuracy in treatment delivery. In other words, image guided radiotherapy (IGRT) is the corner stone for current and future irradiation techniques as hypofractionation, dose escalation radiotherapy and gated radiotherapy.

Accurate setup of the patient and corrections for rotational errors will improve the accuracy of the treatment. Optimization of normal tissue complications and tumour control with respect to innovative delivery techniques require accurate imaging techniques. Therefore, the current focus on fractionation schemes and dose adaptation must be accompanied by accurate imaging techniques.

In our study we illustrated, with clinical data, that kV CBCT provides accurate target positioning data for lung cancer patients.
References

CBCT setup data: first clinical results and comparison with EPID
