Image acquisition optimization of a limited-angle intrafraction verification (LIVE) system for lung radiotherapy

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Purpose: Limited-angle intrafraction verification (LIVE) has been previously developed for four-dimensional (4D) intrafraction target verification either during arc delivery or between three-dimensional (3D)/IMRT beams. Preliminary studies showed that LIVE can accurately estimate the target volume using kV/MV projections acquired over orthogonal view 30° scan angles. Currently, the LIVE imaging acquisition requires slow gantry rotation and is not clinically optimized. The goal of this study is to optimize the image acquisition parameters of LIVE for different patient respiratory periods and gantry rotation speeds for the effective clinical implementation of the system.

Method: Limited-angle intrafraction verification imaging acquisition was optimized using a digital anthropomorphic phantom (XCAT) with simulated respiratory periods varying from 3 s to 6 s and gantry rotation speeds varying from 1°/s to 6°/s. LIVE scanning time was optimized by minimizing the number of respiratory cycles needed for the four-dimensional scan, and imaging dose was optimized by minimizing the number of kV and MV projections needed for four-dimensional estimation. The estimation accuracy was evaluated by calculating both the center-of-mass-shift (COMS) and three-dimensional volume-percentage-difference (VPD) between the tumor in estimated images and the ground truth images. The robustness of LIVE was evaluated with varied respiratory patterns, tumor sizes, and tumor locations in XCAT simulation. A dynamic thoracic phantom (CIRS) was used to further validate the optimized imaging schemes from XCAT study with changes of respiratory patterns, tumor sizes, and imaging scanning directions.

Results: Respiratory periods, gantry rotation speeds, number of respiratory cycles scanned and number of kV/MV projections acquired were all positively correlated with the estimation accuracy of LIVE. Faster gantry rotation speed or longer respiratory period allowed less respiratory cycles to be scanned and less kV/MV projections to be acquired to estimate the target volume accurately. Regarding the scanning time minimization, for patient respiratory periods of 3–4 s, gantry rotation speeds of 1°/s, 2°/s, 3–6°/s required scanning of five, four, and three respiratory cycles, respectively. For patient respiratory periods of 5–6 s, the corresponding respiratory cycles required in the scan changed to four, three, and two cycles, respectively. Regarding the imaging dose minimization, for patient respiratory periods of 3–4 s, gantry rotation speeds of 1°/s, 2–4°/s, 5–6°/s required acquiring of 7, 5, 4 kV and MV projections, respectively. For patient respiratory periods of 5–6 s, 5 kV and 5 MV projections are sufficient for all gantry rotation speeds. The optimized LIVE system was robust against breathing pattern, tumor size and tumor location changes. In the CIRS study, the optimized LIVE system achieved the average center-of-mass-shift (COMS)/volume-percentage-difference (VPD) of 0.3 ± 0.1 mm/ $7.7 \pm 2.0\%$ for the scanning time priority case, 0.2 ± 0.1 mm/ $6.1 \pm 1.2\%$ for the imaging dose priority case, respectively, among all gantry rotation speeds tested. LIVE was robust against different scanning directions investigated.

Conclusion: The LIVE system has been preliminarily optimized for different patient respiratory periods and treatment gantry rotation speeds using digital and physical phantoms. The optimized imaging parameters, including number of respiratory cycles scanned and kV/MV projection numbers acquired, provide guidelines for optimizing the scanning time and imaging dose of the LIVE system

for its future evaluations and clinical implementations through patient studies. © 2017 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.12647]

Key words: 4D-CBCT, free-form deformation, intrafraction verification, limited angle, motion modeling

1. INTRODUCTION

In addition to pretreatment localization and verification, monitoring intrafraction motion in a clinical workflow of moving targets is critical in target localization, as intrafraction motion can potentially leads to under coverage of the tumor and overdose to healthy tissues.^{1,2} This is especially critical for lung stereotactic body radiation therapy (SBRT) due to its tight PTV margin, high fractional dose, and long treatment time.³ Although FFF beams have been introduced to shorten the treatment time, studies showed that FFF beams may lead to severe interplay effects for IMRT/VMAT treatments due to its high dose rate and higher whole body integral dose due to its softer energy spectrum.^{4–6}

Four-dimensional cone-beam CT (4D-CBCT)^{7–9} and four-dimensional digital tomosynthesis (4D-DTS)^{10–12} have been developed previously to provide on-board four-dimensional localization of moving targets. However, conventional 4D-CBCT reconstructed by the Feldkamp–Davis–Kress (FDK) algorithm¹³ requires the acquisition of four-dimensional projections over a full rotation angle. This leads to long acquisition time (~ a few minutes), high imaging dose (~2 cGy at isocenter),⁷ and limited mechanical clearance. Reducing the projection number will violate the Nyquist–Shannon sampling theorem leading to serious streak artifacts, while reducing the exposure will reduce the number of photons detected leading to increased noise level in the reconstructed images. There are many algorithms for reconstruction using undersampled data, such as PICCS^{14,15} and ASD-POCS.¹⁶ However, each algorithm has its own disadvantage. The PICCS algorithms sacrifice temporal resolution to some degree and its image quality may be affected by the prior images quality. The ASD-POCS is a very computationally expensive iterative algorithm.

Compare with 4D-CBCT, 4D-DTS acquires only limited-angle projections for reconstruction, it requires much less scan time and has lower imaging dose, but it suffers from degraded resolution along the plane-to-plane direction without full volumetric information.¹⁷ These drawbacks limit the applications of 4D-CBCT and 4D-DTS for intrafraction verification.

The LIVE system has been recently developed to address the limitations of 4D-CBCT and 4D-DTS.¹⁸ It acquires only limited-angle orthogonal kV and beam's eye view (BEV) MV projections either during arc delivery or in-between 3D/IMRT beams to estimate high-quality 4D-CBCT images based on prior knowledge and a motion modeling and free-form deformation (MM-FD) technique.^{19,20} Preliminary studies demonstrated that LIVE can estimate the target volume for each respiratory phase accurately using kV/MV projections acquired at 1°/projection over orthogonal-view 30° scan

angles. However, such acquisition requires slow gantry rotation, which is not clinically optimized. Therefore, it is important to study and optimize the image acquisition of LIVE so that an imaging protocol can be developed to implement it effectively for different patient scenarios and gantry rotation speeds in various treatments.

In this study, we aim to optimize the LIVE system for various patient and treatment scenarios. Specifically, the patient respiratory period and the gantry rotation speed determined by the specific treatment plan were used as the input parameters for the optimization. The number of respiratory cycles need to be scanned (related to scanning time) and the minimum kV and MV projections need to be acquired (related to imaging dose) to estimate the four-dimensional volume were optimized for the LIVE system. The optimization was first performed using a digital anthropomorphic phantom (XCAT) for various respiratory pattern changes and tumor size changes from planning 4D-CT to on-board volume. Various tumor sizes and locations were simulated in XCAT as well to study the robustness of the optimized LIVE system. A dynamic thoracic phantom was used afterward to further validate the optimized imaging schemes from XCAT study with changes of respiratory patterns, tumor sizes, and imaging scanning directions.

2. MATERIALS AND METHODS

2.A. LIVE estimation algorithm

Limited-angle intrafraction verification uses planning 4D-CT images as prior knowledge, and considers the on-board volumetric images to be estimated as a deformation of the prior images. Specifically, one selected phase of the 4D-CT images is used as the prior CT volume (CT_{prior}). Each phase of the on-board 4D-CBCT ($CBCT_{new}$ at any phase n) is represented as a deformation of the CT_{prior} based on a deformation field map D :

$$CBCT_{new(n)}(i, j, k) = CT_{prior}(i + D_x(i, j, k), j + D_y(i, j, k), k + D_z(i, j, k)) \quad (1)$$

Where D_x , D_y , and D_z represent the deformation fields along the three canonical directions of the Cartesian coordinate system. The CBCT estimation problem is now converted to a problem of solving the deformation field map D . The data fidelity constraint, as shown in the following equation, is used to solve D :

$$P(CBCT_{new(n)}) = OBI(n) \quad (2)$$

Where P represents the projection matrices that project the three-dimensional volume $CBCT_{new(n)}$ to digitally

reconstructed radiographs (DRRs) according to the cone-beam geometry, $OBI(n)$ is the on-board kV/MV image acquired at phase n . Equation (2) requires the simulated cone-beam projections of $CBCT_{new(n)}$ estimated at one phase to match with the actual projection data acquired at the corresponding phase. The LIVE system uses orthogonal kV and MV projections acquired only over a limited scan angle for 4D-CBCT image estimation. Therefore, the equations in Eq. (2) are not enough to solve all the variables in the deformation field map $\mathbf{D}$. To address this issue, structural-based motion modeling (SMM) and weighted free-form deformation (WFD) models have been employed in LIVE to reduce or regulate the variables in $\mathbf{D}$,²¹ as shown in Fig. 1.

Limited-angle intrafraction verification uses the SMM to obtain a coarse estimation of the deformation field map (DFM). First, the end-expiration phase of a 4D-CT previously acquired for planning is selected as CT_{prior} in this study due to its relative stability. The CT_{prior} is then registered to all the other phases of the 4D-CT using deformable image registration to obtain a series of deformation field maps. The deformation field maps are divided into two structures: tumor and body excluding tumor. Then, principal component analysis (PCA) is used to extract motion modes $\{\tilde{\mathbf{D}}_{0,tumor}^j\}$ and $\{\tilde{\mathbf{D}}_{0,body}^j\}$ from the deformation field maps for the two structures. The deformation field map $\mathbf{D}$ to be solved in Eq. (1) is represented by a weighted linear combination of the first three principal motion modes for each structure, as shown in the following equation:

$$\mathbf{D}_{coarse} = \mathbf{D}_{0,ave} + \sum_{j=1}^3 w_{j,tumor} \tilde{\mathbf{D}}_{0,tumor}^j + \sum_{j=1}^3 w_{j,body} \tilde{\mathbf{D}}_{0,body}^j \quad (3)$$

Where $\mathbf{D}_{0,ave}$ is the average of DFMs obtained from 4D-CT, $w_{j,tumor}$ and $w_{j,body}$ are the structure-specific coefficients to be solved, subject to the data fidelity constraint in Eq. (2). Through PCA motion modeling, the problem of solving the deformation field map $\mathbf{D}$ is converted into solving coefficients of the deformation modes, which substantially reduces the degree of freedom to find $\mathbf{D}$. A gradient descent method is used as the optimizer to solve the coefficients, as was used in our previous studies.^{21, 22}

Although PCA-based SMM is efficient in solving the deformation field, its accuracy is dependent on the accuracy of the motion model extracted from 4D-CT. Patient anatomical and breathing pattern changes from 4D-CT simulation to treatment will reduce the accuracy of the estimation. To address this issue, LIVE uses the WFD-based model with energy constraints to further fine-tune $\mathbf{D}$ voxel by voxel after SMM. The WFD model allows each voxel to move freely without assumption of motion modes. The deformation energy constraint is used to minimize the deformation energy E of the field to preserve its smoothness,²³ and the normalized cross correlation (NCC) metric is used for the data fidelity constraint. The data fidelity function is defined as following:

$$f(\mathbf{D}) = \| -[(1-w)NCC_{global} + wNCC_{ROI}] \|_2 \leq \varepsilon \quad (4)$$

where w is the weighting coefficient, which ranges from 0 to 1. ε here accounts for the fact that DRRs cannot be exactly matched to on-board projections even when the DFMs are perfect. The data fidelity constraint increases the deformation energy E while reducing the data fidelity error. During the optimization process, the deformation energy minimization and data fidelity constraint are enforced consecutively through gradient descent optimization with adaptive control of the step size of the deformation energy minimization to reach final convergence. Details about solving $\mathbf{D}$ based on the data fidelity and energy constraints using the WFD model can be found in Refs. [21,22]. In brief, the WFD method is used to correct for any errors caused by the assumptions of motion modes in the SMM model. After the deformation field map $\mathbf{D}$ is solved, the on-board volume is obtained by deforming the prior volumes based on the final $\mathbf{D}$ according to Eq. (1).

2.B. Imaging acquisition scheme

In this study, we focused on evaluating and optimizing the LIVE system using digital XCAT and physical CIRS phantoms. The XCAT study was carried out solely based on simulation, while the CIRS phantom study was carried out through experiments. In the CIRS phantom study, a GE LightSpeed RT scanner (GE Healthcare, Waukesha, WI,

FIG. 1. Flowchart of the estimation algorithm of the LIVE system. [Color figure can be viewed at wileyonlinelibrary.com]

USA) was used to acquire 4D-CT of the CIRS phantom and the Varian TrueBeam research mode was used to acquire the kV&MV projections.

In the design of this LIVE imaging protocol, our objectives are to obtain intrafractional 4D localization with minimal scanning time or minimal extra imaging dose to the patient. Figure 2 shows the kV-MV acquisition scheme of the LIVE system.

As shown in Fig. 2, kV and MV projections are acquired concurrently during the gantry rotation of patient treatment. The kV and MV projections are sorted into individual phases to estimate each phase images in LIVE. Figure 2 shows the kV/MV projections acquired for phase 1 estimation as an example. The number of projections N_s acquired for one phase over a single respiratory cycle depends on the imaging frame rate f , patient respiratory period t , and number of phases p in each respiratory cycle. The relationship is as follows:

$$N_s = \frac{f \cdot t}{p} \quad (5)$$

In this study, p was set to 10 phases for 4D-CBCT estimation. The scan angle θ_s for each phase over a single respiratory cycle can be obtained by:

$$\theta_s = \frac{\omega \cdot t}{p} \quad (6)$$

where ω is the gantry rotation speed. In LIVE acquisition, multiple respiratory cycles may need to be scanned to acquire enough kV/MV projections for estimation, as shown in Fig. 2. The total number of projections N_t and total scanning angle θ_t , over a number of respiratory cycles scanned m , for a single phase, can be calculated by the following equations:

$$N_t = N_s \cdot m = \frac{f \cdot t \cdot m}{p} \quad (7)$$

FIG. 2. kV-MV acquisition scheme of LIVE. [Color figure can be viewed at wileyonlinelibrary.com]

$$\theta_t = \theta_s \cdot m = \frac{\omega \cdot t \cdot m}{p} \quad (8)$$

Note that θ_t is composed of multiple limited scan angles θ_s separated by a separation angle of $(p-1) \cdot \theta_s$, as shown in Fig. 2.

2.C. Acquisition optimization strategies

Respiratory period t and gantry rotation speed ω are patient and treatment dependent, and therefore they were used as the input parameters for the optimization study. The scanning time T required for each verification is proportional to the number of respiratory cycles m scanned:

$$T = m \cdot t \quad (9)$$

Shorter scanning time for each verification means that intrafraction verification can be performed at shorter time intervals or higher frequencies. kV/MV imaging dose is proportional to the number of kV/MV projections N_t acquired in the scanning time T . Less projections acquired for each estimation means less imaging dose introduced to patient. In this study, respiratory cycle number m and projection number N_t were optimized accordingly based on the input parameters t and ω . We optimized the acquisition in two different approaches:

- Minimal scanning time (scanning time priority): minimizing number of respiratory cycles needed by LIVE without restraining the number of projections.
- Minimal imaging dose (imaging dose priority): minimizing number of projections needed by LIVE without restraining the scanning time.

To summarize, the goal of this study is to optimize the number of respiratory cycles m and kV/MV projection numbers N_t needed for LIVE estimation based on the patient respiratory period t and gantry rotation speed ω . Specifically, the optimization was performed for respiratory periods varied from 3 s to 6 s, and gantry rotation speeds varied from 1°/s to 6°/s to cover the typical patient and treatment scenarios.

2.D. Digital anthropomorphic phantom study

2.D.1. Generation of prior images

The four-dimensional extended Cardiac-Torso (XCAT) phantom was used in this study to simulate the prior 4D-CT and on-board 4D-CBCTs. XCAT uses nonuniform rational B-spline surfaces to model detailed human anatomy based on databases from the National Library of Medicine and patient datasets,²⁴ it generates four-dimensional images based on anatomical and respiratory parameters input by the user. The respiratory motion of both the body and tumor of the 4D-XCAT images can be controlled separately by two respiratory curves: the diaphragm curve and the chest wall curve. The

diaphragm curve mainly determines the motion in the superior-inferior (SI) direction, and the chest wall curve mainly controls the motion in the anterior-posterior (AP) direction.

In our study, XCAT was first used to simulate patient 4D-CT images with a spherical tumor of 3 cm diameter inserted into middle of the lung. The peak-to-peak respiratory motion amplitudes for body were 3 cm along SI direction and 2 cm in AP direction. Both the body volume and tumor volume were simulated to move according to the same diaphragm and chest wall curves. The end-expiration phase of the 4D-CT was used as the prior image volume.

2.D.2. Effects of anatomical and breathing pattern changes

Patient anatomical and breathing pattern changes were then simulated in the on-board image volume by XCAT for the following eight scenarios:

1. Body and tumor move according to the same diaphragm curve and chest wall curve, but peak to peak amplitude of diaphragm curve changes to 2 cm and that of the chest wall curve changes to 1.2 cm.
2. Based on scenario 1, also with tumor diameter shrinking by 5 mm.
3. Based on scenario 1, also with tumor diameter expanding by 5 mm.
4. Based on scenario 1, also with tumor's average position shifted in SI direction by 8 mm.
5. Based on scenario 1, also with tumor's average position shifted in AP direction by 8 mm.
6. Based on scenario 1, also with tumor's average position shifted in SI, AP, and lateral directions by 5 mm each.
7. Based on scenario 1, but with tumor having 20% phases shift relative to the body volume respiratory cycle.
8. Body volume and tumor move according to different diaphragm and chest wall curves: the peak-to-peak amplitudes of the diaphragm curve for body and tumor are 2 and 4 cm, respectively; and those of chest wall curve for body and tumor are 1.2 and 3 cm, respectively.

In order to simulate the on-board kV and portal MV projections, two monochromatic energies were used to generate on-board image volumes: 40 keV to simulate on-board kV imaging and 1 MeV (the highest beam energy XCAT can achieve) to simulate on-board MV imaging. Full fan on-board kV projections were simulated using ray-tracing method based on the kV imaging volume, and BEV-MV projections were simulated based on the MV imaging volume. The new on-board volume was estimated by the LIVE system using the prior 4D-CT images and simulated on-board kV-MV projections with the imaging acquisition schemes specified in Sections 2.B and 2.C. The simulated on-board kV imaging volume was used as the ground truth to evaluate the accuracy of the LIVE estimation.

2.D.3. Effects of tumor size change

Tumor sizes of 2 cm, 3 cm, and 4 cm in diameter were simulated for all scenarios listed in Section 2.D.2 to investigate the robustness of LIVE against different tumor sizes after imaging acquisition optimization. The tumor location was set in the middle of lung.

2.D.4. Effects of tumor location change

With a 3 cm diameter tumor, three different tumor locations in the lung were simulated using the XCAT phantom: one with the tumor in the middle of the lung, one with the tumor near the chest wall, and one with the tumor near the mediastinum. For the middle of lung case, the tumor was in the middle of the lung without any adjacent critical structures. For the chest wall case, the tumor was attached to the chest wall and close to the spinal cord. For the mediastinum case, the tumor was in the right lung and close to the mediastinum.

2.E. Physical dynamic thoracic phantom study

Experiments were performed using a dynamic computerized imaging reference system (CIRS) phantom to further assess the LIVE with optimized imaging scheme from XCAT study. The CIRS phantom is a precision instrument that provides known, accurate and reproducible target motion inside a tissue-equivalent phantom for investigating the impact of tumor motion inside the lung.

In our experiments, a GE CT was used to acquire 4D-CT scans in cine mode using 120 kVp, 192 mAs per rotation. The image size was $512 \times 512 \times 120$ for each phase and the resolution was $1 \times 1 \times 1.25 \text{ mm}^3$. A 3 cm diameter and soft tissue-equivalent (density: 1.06 g/cc) spherical insert was placed inside the phantom to simulate a tumor and was programmed to move based on a $\cos^4(x)$ curve in SI direction with 4 s/cycle and 2 cm peak-to-peak amplitude.

After the 4D-CT scan, internal target volume (ITV) was contoured based on the maximum intensity projection (MIP) images of the 4D-CT, and PTV was generated by expanding the ITV by 5 mm on lateral direction and 7 mm on longitudinal direction. Six dynamic conformal arc plans were made in Eclipse using 6 MV beam to deliver $12.5 \text{ Gy} \times 4$ to the PTV with gantry rotation speeds varied from $1^\circ/\text{s}$ to $6^\circ/\text{s}$. The MLC aperture in the plans was generated by adding a 5 mm margin to the PTV in all directions. True beam (Varian Medical Systems, Palo Alto, CA, USA) research mode was used for treatment delivery and simultaneous kV-MV acquisition. The MLC positions were exported from the plans made in Eclipse and used for specifying the MLC locations in the xml file used for research mode delivery. The BEV-MV and kV projections were alternately acquired in LIVE system using Truebeam develop mode to avoid cross scattering. The MV projections were acquired by enabling MV cine ("Continuous" mode) acquisition during treatment. The kV projections were acquired by enabling intermittent kV projection

("DynamicGain" mode) acquisition. To simulate anatomical variation and motion pattern change from 4D-CT to 4D-CBCT acquisition, the 3 cm insert was replaced by a 2 cm insert, and its motion amplitude was increased from 2 cm to 3 cm. The end expiration phase of the 4D-CT was used as the prior image, and the end-inspiration phase of the on-board images were estimated by LIVE.

2.F. Evaluation metrics

The images estimated from the LIVE system were evaluated by comparison to the ground truth images in the phantom studies. In XCAT, the ground truth images were generated using the diaphragm curve and the chest wall curve input with different tumor location as listed in Section 2.D.2. In the CIRS study, the ground truth images were acquired by the CT scanner with a 2 cm tumor inserted in the phantom and moves in 3 cm amplitude. To quantitatively evaluate the accuracy of LIVE, tumors were automatically contoured based on HU threshold in both estimated images and ground truth CBCT images for comparison. Two metrics were defined to calculate the accuracy of the estimated tumor volume: center-of-mass-shift (COMS) and volume-percentage-difference (VPD). COMS is defined by the following formula:

$$\text{COMS} = \sqrt{\Delta x^2 + \Delta y^2 + \Delta z^2} \quad (10)$$

Where Δx , Δy , Δz are the center-of-mass distances from V to V_0 . VPD is defined by the following formula:

$$\text{VPD} = \frac{|V \cup V_0 - V \cap V_0|}{V_0} * 100\% \quad (11)$$

Where V is the tumor volume contoured in the estimated image and V_0 is that contoured in the ground truth image. COMS indicates the tumor location difference and VPD indicates the tumor shape difference between the estimated images from LIVE and the ground truth images. A perfect estimation expects COMS value of 0 mm and VPD value of 0%. The COMS threshold used in this study was 1 mm for all the eight scenarios described in Section 2.D.2. For 1 mm COMS shift, the corresponding VPDs can be calculated from Eq. (11) are 12%, 10%, and 8.5% for tumor size of 2.5 cm, 3 cm, and 3.5 cm, respectively. Based on these estimations, the VPD thresholds used in this study were 12% for scenario 2, 8.5% for scenario 3, and 10% for the other scenarios.

3. RESULTS

The simulation results from XCAT phantom and experimental results from CIRS phantom will be presented in this section. Following the imaging acquisition optimization and evaluation steps described in the methods and materials section, we first present the effects of gantry rotation speed and respiratory period on the estimation accuracy of LIVE in Section 3.A.1. The optimization results for scanning time priority (minimizing scan time) and imaging dose priority (minimizing dose) cases are then provided in Sections 3.A.2 and 3.A.3. The results of the robustness of LIVE against different

tumor sizes and tumor locations are presented in Sections 3.A.4 and 3.A.5. Finally, the CIRS motion phantom results for different gantry rotation speeds and scanning directions are presented in Section 3.B to further validate the optimized imaging scheme from XCAT study.

3.A. Digital XCAT phantom results

3.A.1. Effects of gantry rotation speed and respiratory period

As explained previously, the patient respiratory period and the gantry rotation speed are determined by the specific patient and treatment plan, and they were used as the input parameters for the optimization. This section studies the effects of the two input parameters on the LIVE verification. The tumors were automatically contoured based on HU threshold in both estimated images from LIVE and ground truth CBCT images generated from XCAT for comparison. The COMS and VPD were extracted to quantify the accuracy of the estimated tumor position and volume. Figure 3 shows the COMS and VPD of the images estimated from LIVE for various gantry rotation speeds when using 4 kV and 4 portal MV projections acquired over four respiratory cycles. The respiratory period was set to be 4 s. A total number of 40 kV and 40 MV projections were acquired within 4 respiratory cycles in this case with 4 kV and 4 MV projections for each phase. It can be observed that faster gantry rotation speed achieved better estimation accuracy while using same number of kV and MV projections and respiratory cycles.

Figure 4 shows the COMS and VPD of the images estimated from LIVE for various respiratory periods when using 5 kV and 5 portal MV projections acquired over five

FIG. 3. COMS and VPD of the CBCT estimated from LIVE for different gantry rotation speeds. The estimation used 4 kV and 4 portal MV projections acquired in four respiratory cycles. The respiratory period was 4 s. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 4. COMS and VPD of the CBCT estimated from LIVE for different respiratory periods. The estimation used 5 kV and 5 portal MV projections acquired in five respiratory cycles. Gantry rotation speed was set to be $1^\circ/\text{s}$. [Color figure can be viewed at wileyonlinelibrary.com]

respiratory cycles. The gantry rotation speed was set to be $1^\circ/\text{s}$. It can be observed that longer respiratory period yielded better estimation accuracy while using same number of kV and MV projections and respiratory cycles.

3.A.2. Minimum respiratory cycles required for LIVE image estimation (scanning time priority)

This section aims to study the minimal respiratory cycles that need to be scanned for LIVE verification when the kV and MV projections are sufficiently sampled. The minimal number of respiratory cycles corresponds to the minimal scanning time needed for LIVE. Figure 5 shows the COMS and VPD for all eight XCAT scenarios with CBCT estimation from LIVE using kV and MV projections acquired from different numbers of respiratory cycles. Respiratory period was 4 s and gantry rotation speed was set to be $6^\circ/\text{s}$. Both kV and MV frame rates were 10 frames/s. It can be observed that with 3 respiratory cycles, the COMS and VPD are under the threshold defined in Section 2.F. The estimated images are shown in Fig. 6 for tumor shrinkage case (scenario 2).

Similar to Figs. 5 and 6, the COMS and VPD were calculated from the images estimated from LIVE with gantry rotation speeds varying from $1^\circ/\text{s}$ to $6^\circ/\text{s}$ and respiratory times varying from 3 s to 6 s. The minimum respiratory cycles required for different gantry rotation speeds and different respiratory periods were determined using the thresholds described in Section 2.F. The results are shown in Table I.

3.A.3. Minimum projections required for LIVE image estimation (imaging dose priority)

Section 3.A.2 studied the minimal scanning time achievable by LIVE without restraining the number of projections

FIG. 5. COMS and VPD for XCAT scenarios with CBCT estimation from LIVE using kV and portal MV projections acquired from different numbers of respiratory cycles. Respiratory period was 4 s and gantry rotation speed was set to be $6^\circ/\text{s}$. Both kV and MV frame rates were 10 frames/s. [Color figure can be viewed at wileyonlinelibrary.com]

acquired. This section will study the minimal projection numbers needed by LIVE without restraining the scanning time.

Figure 7 shows the COMS and VPD of the images estimated from LIVE using different number of kV and portal MV projections when respiratory period was 4 s and gantry rotation speed was $6^\circ/\text{s}$. kV and MV projection numbers were set to be the same in this study.

Table II lists the minimum kV/MV projections required for LIVE image estimation for different gantry rotation speeds and respiratory periods. The imaging frequency was set to be 1 projection/phase/cycle.

3.A.4. Effects of tumor size

Table III shows the estimation results for all 8 XCAT scenarios for 2 cm tumor, 3 cm tumor, and 4 cm tumor using the imaging acquisition optimized LIVE. It can be observed that the COMS results are consistent for different sizes of tumor, and the VPDs from 2 cm tumor is larger than those from 3 cm tumor and 4 cm tumor because of the sensitivity of VPD to the actual tumor size.

3.A.5. Effects of tumor location

Table IV lists the imaging estimation accuracy of the optimized LIVE system for all eight XCAT scenarios for different tumor locations.

3.B. Physical dynamic CIRS phantom results

Figure 8 shows an example of (a) raw kV image at 0° and (b) raw MV portal image at 90° acquired concurrently during the arc treatment delivery, while (c) and (d) are the

FIG. 6. Comparison of prior CT at end-expiration phase, estimated on-board CBCT at end-inspiration phase by LIVE using 12 kV and 12 portal MV projections acquired in three respiratory cycles for 4 s respiratory period and 6°/s gantry rotation speed, and ground truth CBCT at end-inspiration phase for XCAT scenario 2. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE I. The minimum respiratory cycles required for different gantry rotation speeds and respiratory periods. Both kV and MV frame rates were 10 frames/s.

Min. respiratory cycles		Gantry speed (°/s)					
		1	2	3	4	5	6
Resp. period (s)	3	5	4	3	3	3	3
	4	5	3	3	3	3	3
	5	4	3	3	3	2	2
	6	4	3	3	2	2	2

FIG. 7. COMS and VPD for XCAT scenarios with CBCT estimation from LIVE using different number of kV and portal MV projections. Respiratory period was 4 s and gantry rotation speed was set to be 6°/s. The imaging frequency was set to be 1 projection/phase/cycle. [Color figure can be viewed at wileyonlinelibrary.com]

projections after blank scan normalization and $-\log$ transformation.

3.B.1. Estimation accuracy from LIVE

Figure 9 shows the image estimation results from the optimized LIVE system using 4 kV and 4 portal MV projections acquired in four respiratory cycles in the CIRS phantom study. The respiratory period was 4 s and the gantry rotation speed was 6°/s. Table V shows the COMS and VPD results for different gantry rotation speeds in CIRS phantom study for 4 s respiratory period. The number of respiratory cycles scanned in the scanning time priority case and the number of kV/MV projections in the imaging dose priority case were determined based on the optimization in Section 3.A. It can be seen that the optimized LIVE system achieved accurate estimation of the CBCT images. The mean COMS and VPD among all gantry rotation speeds were 0.3 ± 0.1 mm and $7.7 \pm 2.0\%$ in scanning time priority case, 0.2 ± 0.1 mm and $6.1 \pm 1.2\%$ in imaging dose priority case, respectively.

3.B.2. Effects of scanning directions

Table VI shows the image estimation accuracy of the optimized LIVE system for different scanning directions. It can be clearly seen that the estimation accuracy is robust against the variations of scan directions. The mean COMS and VPD among all scanning direction was 0.3 ± 0.1 mm and $7.4 \pm 1.4\%$.

4. DISCUSSIONS

This study optimized the imaging acquisition schemes of the LIVE system with respect to minimizing its scanning time

TABLE II. kV/MV projection numbers required for LIVE image estimation for different gantry rotation speeds and respiratory periods. Both kV and portal MV imaging frequencies were 1 projection/phase/cycle.

Min. kV/MV projections	Gantry speed (°/s)					
	1	2	3	4	5	6
Resp. period (s)	3	7	5	5	5	4
	4	6	5	5	5	4
	5	5	5	5	4	5
	6	5	5	4	4	5

TABLE III. COMS and VPD for XCAT scenarios with CBCT estimation from LIVE for different tumor sizes. Respiratory period was 4 s and gantry rotation speed was set to be 6°/s. The estimation used 4 kV projections and 4 portal MV projections acquired in four respiratory cycles.

Scenarios		1	2	3	4	5	6	7	8
COMS (mm)	2 cm	0.1	0.3	0.1	0.1	0.1	0.3	0.1	0.3
	3 cm	0.1	0.5	0.1	0.2	0.2	0.1	0.1	0.2
	4 cm	0.1	0.4	0.2	0.3	0.1	0.4	0.2	0.2
VPD (%)	2 cm	3.3	9.8	4.8	6.9	3.3	6.3	5.2	4.5
	3 cm	2.8	8.8	4.9	4.6	3.1	3.6	3.6	5.5
	4 cm	2.4	5.3	4.7	4.1	2.3	5.3	3.5	3.5

TABLE IV. COMS and VPD for XCAT scenarios with CBCT estimation from LIVE for different tumor location. Respiratory period was 4 s and gantry rotation speed was set to be 6°/s. The estimation used 4 kV projections and 4 portal MV projections acquired in four respiratory cycles.

Scenarios		1	2	3	4	5	6	7	8
COMS (mm)	Middle of lung	0.1	0.5	0.1	0.2	0.2	0.1	0.1	0.2
	Chest wall	0.1	0.5	0.3	0.5	0.6	0.5	0.2	0.5
	Mediastinum	0.2	0.2	0.4	0.3	0.6	0.6	0.5	0.4
VPD (%)	Middle of lung	2.8	8.8	4.9	4.6	3.1	3.6	3.6	5.5
	Chest wall	5.7	9.5	6.4	7.1	9.6	8.2	7.2	7.4
	Mediastinum	7.3	7.8	8.3	8.9	8.1	4.5	3.8	9.9

and imaging dose for 4D intrafraction verification for lung radiotherapy. XCAT simulation and CIRS phantom studies demonstrated the feasibility of optimizing the LIVE imaging parameters to balance between efficiency, accuracy, and

imaging dose for different patient and treatment scenarios during implementation.

4.A. Imaging acquisition optimization

In the scanning time priority mode, results in Table I showed that for patient respiratory periods of 3–4 s, gantry rotation speeds of 1°/s, 2°/s, 3–6°/s, required scanning of five, four, and three respiratory cycles, respectively. For patient respiratory periods of 5–6 s, the corresponding respiratory cycles required in the scan changed to four, three, and two cycles, respectively. In the imaging dose priority mode, results in Table II showed that for patient respiratory periods of 3–4 s, gantry rotation speeds of 1°/s, 2–4°/s, 5–6°/s required acquiring of 7, 5, 4 kV and MV projections, respectively. For patient respiratory periods of 5–6 s, 5 kV and 5 MV projections are sufficient for all gantry rotation speeds.

The accuracy of estimated images from LIVE was positively correlated with the gantry rotation speed (Fig. 3), patient respiratory period (Fig. 4), the number of respiratory cycles (Fig. 5), and the number of kV/MV projections (Fig. 7). This is because the LIVE estimation accuracy is dependent on total number of projections and total scanning angle. Higher number of projections or larger scanning angles leads to better accuracy for the LIVE estimation. Based on Eqs. (7) and (8), the total number of projections is determined by kV/MV projections per cycle and the number of respiratory cycles, while the total scanning angle is determined by the number of respiratory cycles, respiratory period and gantry rotation speed. Therefore, faster gantry rotation speed, longer patient respiratory period, more number of respiratory cycles or number of kV/MV projections led to improvement of the accuracy of LIVE.

Due to this reason, faster gantry rotation speed and longer respiratory period allowed less respiratory cycles to be scanned and less kV/MV projections to be acquired, as shown in Tables I and II. However, there are two exceptions in Table II, for the gantry rotation speed of 6°/s, respiratory period of 5 s, and gantry rotation speed of 5°/s, respiratory period of 6 s, the LIVE estimation needed more projections compared to the scenarios with slower gantry rotation speeds or shorter respiratory periods. This is because the kV and MV scanning angles were overlapped with redundant

FIG. 8. An example of kV and portal MV images acquired concurrently during the arc treatment. (a) raw kV image at 0°. (b) raw MV portal image at 90°. (c) kV image at 0° after blank scan normalization and $-\log$ transformation. (d) MV portal image at 90° after blank scan normalization and $-\log$ transformation.

FIG. 9. Comparison of prior CT, estimated CBCT by the LIVE system, and the ground truth CT. Respiratory cycle time was 4 s and gantry rotation was 6°/s. The LIVE estimation used 4 kV and 4 portal MV projections acquired in 4 breathing. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE V. Accuracy of LIVE estimation using the optimized imaging parameters for respiratory cycle of 4 s and different gantry rotation speeds in the CIRS phantom study. In the scanning time priority case, the respiratory cycles used for estimation were 5, 3 for gantry rotation speed of 1°/s, 2–6°/s, respectively, kV and MV frame rates were both set to be six frame/s; In the imaging dose priority case, kV and MV projection numbers used for estimation were 6, 5, 4 each for gantry rotation speed of 1°/s, 2–4°/s, and 5–6°/s, respectively.

		Gantry speed (°/s)						
		1	2	3	4	5	6	
Scanning time priority	COMS (mm)	0.2	0.5	0.4	0.3	0.4	0.2	
	VPD (%)	5.1	9.9	9.4	7.6	8.3	5.6	
Imaging dose priority	COMS (mm)	0.2	0.3	0.2	0.2	0.3	0.2	
	VPD (%)	5.7	7.7	6.6	5.3	6.9	4.5	

information for these two scenarios. As shown in Table VII, the 4th and 5th sets of kV scan angle were overlapped with the 1st and 2nd sets of MV scan angle. These overlapping kV and MV image acquisitions contained redundant projections with less amount of useful information for LIVE image estimation. As a result, more projections were needed in these two scenarios.

4.B. Effects of tumor size, location, and imaging scanning direction

Table III showed that the imaging acquisition optimized LIVE system was robust against different tumor sizes. The COMS from 2 cm tumor and 4 cm tumor were consistent with the results from 3 cm tumor for all eight XCAT scenarios. The VPDs from 2 cm tumor were consistently large than those from 3 cm and 4 cm tumors, as the VPD is inversely proportional to the tumor volume V_0 as showed in Eq. (11).

The XCAT results in Table IV demonstrated that the image estimation accuracy of the acquisition optimized LIVE system was robust against different tumor locations. CIRS phantom results from Table VI demonstrated the robustness of the LIVE system against scanning directions.

4.C. Clinical implementation

In clinical practice, the optimized LIVE system can be implemented through different acquisition schemes for different patient respiratory periods and types of treatments. In conformal arc treatments, LIVE uses the limited-angle treatment MV images and orthogonal kV images acquired during arc delivery for estimation. As a result, the image acquisition gantry rotation speed of LIVE is determined by the arc delivery rotation speed defined in the treatment plan, which varies from 1°/s to 6°/s. After certain gantry rotation angle, the LIVE system can generate volumetric images based on the most recent limited-angle kV and portal MV projections to verify target position. If the target is within the PTV, the arc treatment continues. Otherwise, the treatment can be stopped to correct the target misalignment. Note that the limited-angle BEV-MV projections are acquired from the exit fluence of the treatment beam with no extra MV imaging dose introduced, but concurrent kV projections introduce extra imaging dose to the patient in this case. In rapid arc treatments, since the treatment field is partially blocked by the MLC during delivery, the BEV-MV projections may not provide sufficient information for LIVE image estimation. In addition, the gantry rotation speed varies during VMAT delivery. As an alternative, orthogonal kV and MV projections can be acquired between adjacent arc deliveries for intrafraction verification. The MV projections will still be confined to the BEV of the target region without blocking the target. Unlike the

TABLE VI. COMS and VPD results of the CBCT images estimated with the optimized LIVE system using projections acquired along different scanning directions in the CIRS phantom study. Respiratory period was 4 s and gantry rotation speed was set to be 3°/s. The LIVE estimation used 5 kV and 5 portal MV projections acquired in five breathing cycles.

Scanning directions	kV: 90°–150° MV: 180°–240°	kV: 150°–210° MV: 240°–300°	kV: 210°–270° MV: 300°–0°	kV: 270°–330° MV: 0°–60°	kV: 330°–30° MV: 60°–120°
COMS (mm)	0.2	0.4	0.3	0.2	0.4
VPD (%)	6.6	9.1	7.3	5.6	8.3

TABLE VII. The first five imaging angle sets for gantry rotation speed of 6°/s and respiratory period of 5 s, or gantry rotation speed of 5°/s and respiratory period of 6 s.

Acquisition set	1	2	3	4	5
kV scan angle	90°–93°	120°–123°	150°–153°	180°–183°	210°–213°
MV scan angle	180°–183°	210°–213°	240°–243°	270°–273°	300°–303°

conformal arc treatments, the gantry rotation speed is controllable in this scenario, and can be maximized to 6°/s to minimize the scanning time and imaging dose of LIVE. In 3D/IMRT treatments, LIVE can acquire orthogonal kV and MV projections as the gantry rotates from one beam to the next for verification in-between beams. Similar to rapid arc treatments, the MV projections will be confined to BEV of the target region, and the gantry rotation speed can be maximized to 6°/s. Note that the BEV-MV imaging dose from LIVE verification in rapid arc and 3D/IMRT treatments is extra dose to the target, and can be accounted for in the planning process by incorporating the imaging dose in the plan.²⁵

Limited-angle intrafraction verification requires scanning of a few breathing cycles to estimate 4D images of the patient. Therefore, for irregular respirations, LIVE captures the average tumor motion over a few breathing cycles (two to five cycles as listed in Tables I and II). As a result, the temporal resolution of intrafraction verification based on LIVE will be the two to five respiratory cycles. Although less ideal than verification after each respiratory cycle, the verification frequency of two to five respiratory cycles based on LIVE allows us to at most miss the target for two to five respiratory cycles, which is a major improvement over current practice where no intrafraction four-dimensional verification technique is available to verify the tumor position during the actual treatment. In addition, considering that two to five respiratory cycles are much shorter than a SBRT treatment time, we expect the dosimetric consequence of missing the target in such a short period to be clinically insignificant. Further patient studies are warranted to evaluate the performance of LIVE under irregular breathing patterns.

This study marks the first step to develop and optimize an imaging protocol for the LIVE system for different patient and treatment scenarios. The establishment of such imaging protocol builds the foundation for future clinical implementation and evaluation of the system. The optimized image acquisition also enhances the efficiency or reduces imaging dose of the LIVE system so that intrafraction verification can be performed effectively for different types of treatments to

minimize the localization errors in SBRT, which paves the road to further margin reduction and dose escalation in the future.

4.D. Limitation of this study

The current studies have optimized LIVE system using the XCAT simulation and the CIRS phantom. Another motion thoracic phantom available on the market is RSD Dynamic Breathing Phantom (RSD Radiology Support Device). The RSD phantom fills and empties of air to replicate humanoid lung motion, and contains a movable tumor which moves independently within one of the lung volumes. However, its geometry is as simple as the CIRS phantom and may not be sophisticated to fully test the performance of LIVE tracking as well.

Simulation and phantom studies provide us the unique opportunities to simulate different patient and image acquisition scenarios to evaluate the accuracy and robustness of the system against each scenario. Besides, ground truth images are always available in these studies to evaluate the accuracy of the system. However, the real patient anatomy is more complicate than the anatomical structures in XCAT and CIRS phantom, in order to accurately estimate the target volume, LIVE may need more respiratory cycles and kV/MV projections. Further patient studies are warranted to further evaluate the optimized imaging acquisition schemes of LIVE from this study. The COMS in patient studies is expected to be larger than the sub-mm accuracy achieved in the phantom studies. Our previous studies using orthogonal limited-angle kV projections achieved accuracy less than 2 mm in the patient study, so we expect the results using kV/MV in LIVE to be comparable.²⁰ One challenge with the patient study is to obtain the ground truth images for evaluating the accuracy of the method. On-board 4D-CBCT estimated from fully sampled four-dimensional cone-beam projections can be used as the ground truth, but it is not presently available on Varian LINACS. The other challenge is that concurrent kV and portal MV imaging is only available in Varian development

mode and not available in the clinical mode for real patient imaging. One possible option is to use the Monte Carlo simulation to simulate the kV and portal MV images from 4D-CBCT²⁶ for patient studies. Future patient studies will be carried out to fully evaluate the efficacy of the optimized LIVE system once 4D-CBCT and kV/MV acquisitions become available.

5. CONCLUSION

The pilot study has been performed to optimize image acquisition for the LIVE system to estimate 4D volumetric images using kV and portal MV projections acquired in limited angles either during arc treatment or in-between static 3D/IMRT beams. The preliminary results from simulation and phantom studies gave us valuable insights about the optimization of the LIVE system for different treatment techniques and patient scenarios, and built the foundation for future clinical implementation of the LIVE system for four-dimensional intrafraction verification of lung SBRT.

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REFERENCES

- Li W, Purdie TG, Taremi M, et al. Effect of immobilization and performance status on intrafraction motion for stereotactic lung radiotherapy: analysis of 133 patients. *Int J Radiat Oncol Biol Phys.* 2011;81:1568–1575.
- Zhao B, Yang Y, Li T, Li X, Heron DE, Huq MS. Dosimetric effect of intrafraction tumor motion in phase gated lung stereotactic body radiotherapy. *Med Phys.* 2012;39:6629–6637.
- Purdie TG, Bissonnette JP, Franks K, et al. Cone-beam computed tomography for on-line image guidance of lung stereotactic radiotherapy: localization, verification, and intrafraction tumor position. *Int J Radiat Oncol Biol Phys.* 2007;68:243–252.
- Liu C, Snyder MG, Orton CG. Point/counterpoint. The future of IMRT/SBRT lies in the use of unflattened x-ray beams. *Med Phys.* 2013;40:060601.
- Verbakel W, Ong C, Senan S, Cuijpers JP, Slotman BJ, Dahele M. Flattening filter-free beams for SBRT: advantages and risks. *Int J Radiat Oncol.* 2012;84:S826–S827.
- Georg D, Knoos T, McClean B. Current status and future perspective of flattening filter free photon beams. *Med Phys.* 2011;38:1280–1293.
- Sonke JJ, Zijp L, Remeijer P, van Herk M. Respiratory correlated cone beam CT. *Med Phys.* 2005;32:1176–1186.
- Dietrich L, Jetter S, Tucking T, Nill S, Oelfke U. Linac-integrated 4D cone beam CT: first experimental results. *Phys Med Biol.* 2006;51:2939–2952.
- Lu J, Guerrero TM, Munro P, et al. Four-dimensional cone beam CT with adaptive gantry rotation and adaptive data sampling. *Med Phys.* 2007;34:3520–3529.
- Maurer J, Godfrey D, Wang Z, Yin FF. On-board four-dimensional digital tomosynthesis: first experimental results. *Med Phys.* 2008;35:3574–3583.
- Maurer J, Pan T, Yin FF. Slow gantry rotation acquisition technique for on-board four-dimensional digital tomosynthesis. *Med Phys.* 2010;37:921–933.
- Ren L, Godfrey DJ, Yan H, Wu QJ, Yin FF. Automatic registration between reference and on-board digital tomosynthesis images for positioning verification. *Med Phys.* 2008;35:664–672.
- Feldkamp LA, Davis LC, Kress JW. Practical cone-beam algorithm. *J Opt Soc Am A.* 1984;1:612–619.
- Chen GH, Tang J, Leng S. Prior image constrained compressed sensing (PICCS): a method to accurately reconstruct dynamic CT images from highly undersampled projection data sets. *Med Phys.* 2008;35:660–663.
- Lauzier PT, Tang J, Chen GH. Prior image constrained compressed sensing: implementation and performance evaluation. *Med Phys.* 2012;39:66–80.
- Sidky EY, Pan X. Image reconstruction in circular cone-beam computed tomography by constrained, total-variation minimization. *Phys Med Biol.* 2008;53:4777–4807.
- Ren L, Zhang J, Thongphiew D, et al. A novel digital tomosynthesis (DTS) reconstruction method using a deformation field map. *Med Phys.* 2008;35:3110–3115.
- Ren L, Zhang Y, Yin FF. A limited-angle intrafraction verification (LIVE) system for radiation therapy. *Med Phys.* 2014;41:020701.
- Zhang Y, Yin FF, Segars WP, Ren L. A technique for estimating 4D-CBCT using prior knowledge and limited-angle projections. *Med Phys.* 2013;40:121701.
- Zhang Y, Yin FF, Pan TS, Vergalasova I, Ren L. Preliminary clinical evaluation of a 4D-CBCT estimation technique using prior information and limited-angle projections. *Radiother Oncol.* 2015;115:22–29.
- Harris W, Zhang Y, Yin FF, Ren L. Estimating 4D CBCT from prior information and extremely limited angle projections using structural PCA and weighted free-form deformation for lung radiotherapy. *Med Phys.* 2017;44:1089–1104.
- Zhang Y, Yin FF, Zhang Y, Ren L. Reducing scan angle using adaptive prior knowledge for a limited-angle intrafraction verification (LIVE) system for conformal arc radiotherapy. *Phys Med Biol.* 2017;62:3859–3882.
- Lu WG, Chen ML, Olivera GH, Ruchala KJ, Mackie TR. Fast free-form deformable registration via calculus of variations. *Phys Med Biol.* 2004;49:3067–3087.
- Segars WP, Sturgeon G, Mendonca S, Grimes J, Tsui BMW. 4D XCAT phantom for multimodality imaging research. *Med Phys.* 2010;37:4902–4915.
- Alaei P, Ding G, Guan H. Inclusion of the dose from kilovoltage cone beam CT in the radiation therapy treatment plans. *Med Phys.* 2010;37:244–248.
- Jia X, Yan H, Cervino L, Folkerts M, Jiang SB. A GPU tool for efficient, accurate, and realistic simulation of cone beam CT projections. *Med Phys.* 2012;39:7368–7378.