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Validation of Geometric and Dosimetric Accuracy of Edge Accelerator Gating With Electromagnetic Tracking: A Phantom Study

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ABSTRACT This work was to devise a comprehensive testing scheme to evaluate the geometric and dosimetric accuracy of the Edge accelerator gating with electromagnetic tracking (EMT) for its safety in clinical application. A CIRS thorax phantom was scanned with four-dimensional cone-beam CT (4D-CBCT) on an Edge accelerator while the simulated tumor was simultaneously tracked with an EMT system using Calypso. The geometric accuracy was validated by comparing the motion trajectories derived from Calypso and 4D-CBCT with the ground truth from motion control software. The two-dimensional and three-dimensional dynamic doses were measured with the Matrixx and ArcCHECK installed on a motion platform, both with and without EMT. For tumor motion with 5, 7.5 mm amplitudes, the average absolute differences of sample position between Calypso and the ground truth were 0.286±0.234 mm, 0.407±0.331 mm respectively. Dosimetric accuracy was validated with 3 mm/3% gamma criterion. The average gamma pass rates of 2D dynamic dose validation based on Matrixx were less than 46% without EMT, 97.3% using 2 mm gating limit, 96% using 3 mm gating limit and 93.4% using 5mm gating limit respectively. The mean 3D dynamic dose validation pass rates based on ArcCHECK were 65.9% without EMT, 96.2% using 3 mm gating limit, and 92.5% using 5 mm gating limit with EMT respectively. The geometric accuracy of the Calypso system in tracking the moving target area was stable at the submillimeter level. The dosimetric accuracy could be improved significantly with EMT using an appropriate gating limit.

INDEX TERMS Radiotherapy, accuracy, electromagnetic tracking.

I. INTRODUCTION

In radiation therapy, intra-fractional tumor motions significantly limit the accuracy of radiation delivery and bring potential harm to organs at risk (OAR) around the tumor during treatment [1]. The goal of radiotherapy is to maximize the absorbed dose to the target volume while minimizing the dose to the surrounding healthy tissue. However, the position of thoracic organs and tissues is constantly changing during the treatment due to respiratory motion, which is likely to cause the edge of tumor to move outside the irradiation field, while healthy tissue may also enter the irradiation field of the plan, which will limit the total dose the patient can safely receive [2]. More seriously, it may cause complications in patients. Therefore, accurate tumor tracking is important to reduce the adverse factors of respiratory motion. To deliver high-dose radiation adapting to the intra-fractional tumor motion, real-time imaging and tracking of the tumor motion during the treatment had become a critical task in radiation therapy research [3].

Current real-time tumor tracking technologies rely on the implantation of radiopaque fiducial markers [4]. Poulsen *et al.* [5] developed a probability-based method for tumor trajectory abstraction from CBCT projections with markers. However, fiducial marker implantation is an invasive and costly procedure that is not widely available.

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Shieh *et al.* [6] proposed a Bayesian approach which uses the framework of the extended Kalman filter combining a prediction and measurement methods for markerless tumor tracking for the first time. Santanam *et al.* [7] compared the static and dynamic tracking accuracy of the Calypso system to that of an on-board imaging kilovoltage X-ray system for simultaneous use of the two systems. Two kV portal images were obtained at each phantom location using the OBI system. In this manner, three-dimensional deviations from the isocenter position were measured. Rau *et al.* [8] proposed the assessment of intrafractional organ motion as the integration of a continuous measurement of target position using electromagnetic tracking system and sporadic x-ray imaging of the treatment field. The successive measurement should be based on inner fiducial markers rather than rely on a correlative model between external and internal marker movement [9]. The method of tumor tracking is suitable for tumors that show significant intrafractional movement such as lung tumors.

The Calypso electromagnetic tracking (EMT) system (Varian Medical Systems, Palo Alto, CA) has been proved to be an accurate tool to localize and track during radiation therapy [10]. The system uses three wireless transponders which are currently implanted into the tumor using a needle in a procedure similar to gold fiducial implants currently in use clinically. During treatment planning, the transponder positions, as indicated in CT imaging, are recorded with respect to the isocenter. It has been researched by several groups for lung and pancreatic cancer treatments, where respiratory movement is more challenging in the context of treatment planning [11], [12]. Calypso has been recently declared by the FDA for soft-tissue application including liver, allowing for gated treatment of the liver based on the movement of the target volume itself. Delta4 phantom with HexaMotion platform was used to perform end-to-end validations to evaluate the dosimetric accuracy of gated beam delivery for liver SABR [13]. Balter *et al.* [14] have reported the localization of transponders with respect to the array, addressing the accuracy of the position readouts during tracking. An additional study by Santanam *et al.* [15] described the quality assurance commissioning procedures to assure accurate operation of the system. The translational localization accuracies were detected to be within 0.01 cm. Rune Hansen *et al.* [16] provided the first performance tests of the TrueBeam accelerator system for Calypso-guided couch and MLC tracking containing the first direct comparison of tracking for volumetric arc therapy. In a clinical prostate cancer treatment research, Willoughby *et al.* [17] have involved the first human application of the system, to evaluate the localization accuracy of EMT compared with radiographic localization and to assess its performance to obtain real-time prostate-motion information. The electromagnetic tracking system can track the tumor motion during the treatment, but the tracking accuracy is uncertain in treatment. This study provided the first characterization and performance tests of the geometric and dosimetric accuracy of the Edge system with Calypso using CIRS thorax phantom and dynamic dosimeter. Several validation methods were developed to ensure safety in the clinical application of Calypso.

II. MATERIALS AND METHODS

A. THE CALYPSO 4D ELECTROMAGNETIC TRACKING SYSTEM

The Calypso System is a tumor localization system designed for use during radiation therapy. It has 5 main components: Beacon transponders; Console; Electromagnetic array; Optical system; Tracking station [18]. The use of the Calypso System for target localization is based on the system's detection of electromagnetic signals generated by markers called Beacon transponders. These transponders could be implanted in or near the treatment target, or placed on the patient's skin surface. When used with the Calypso System, the Beacon transponder signals enable objective measurement of the location of the treatment target in 3 dimensions. The Calypso can automatically turn the treatment beam on and off based on the target position relative to the gating limits. Target position information is presented to the radiation therapist using simple and objective on-screen graphics, numerical data, and auditory indicators when the target moves outside of the predefined gating limits for target motion [19]. The update rate of Calypso System is 10Hz.

B. GEOMETRIC ACCURACY OF EMT

CBCT image-guided is the standard in radiotherapy position. The motion trajectory of the tumor for patient was abstracted based on the projection of 4D-CBCT because the ground truth of tumor position was uncertain [20]. The validation method of geometric accuracy consisted of the combination of EMT and 4D-CBCT using the CIRS thorax phantom in this study. The ground truth for tumor position was generated from the motion control software of CIRS. The CIRS dynamic thorax phantom model (Computerized Image Reference System Inc, 2428 Almeda Avenue Suite 316, Norfolk, VA 23513, USA) was used to represent respiratory motion with the 3cm spherical imaging insert [21]. Three transponders were fixed to the surface of the simulative tumor in a triangular pattern. Then, the simulative tumor was inserted into the CIRS phantom. Transponders moved with the tumor in the superior-inferior (SI) direction. FIGURE 1 shows the CIRS phantom used for simulating tumor motion. The motion trajectory of the tumor was abstracted based on the projection of 4D-CBCT while the EMT system reported the trajectory of the tumor simultaneously. We compared the motion trajectory from EMT and 4D-CBCT with the ground truth to validate the geometric accuracy.

1) SIMULTANEOUS TUMOR TRACKING

We proposed simultaneous tumor tracking using the EMT system and x-ray imaging of a mobile target inside CIRS phantom. The in-built sinusoidal breathing traces were used with 10, 15 mm peak-to-peak motion (5, 7.5 mm amplitude)

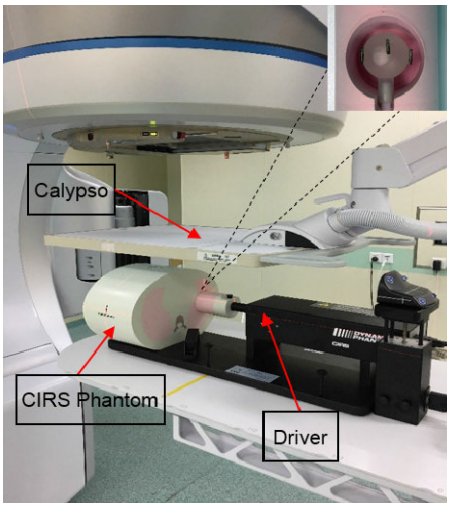

FIGURE 1. CIRS phantom.

in the SI direction and respiratory periods of 3 and 6s respectively. The respiratory signal was detected by the real-time position management (RPM) system (Respiratory Gating System v1.7, Varian Medical Systems, Inc). A CIRS thorax phantom with three Calypso Beacons was imaged by 4D-CBCT at a series of gantry angles on an Edge accelerator while the Beacon positions were simultaneously tracked using the EMT system [22].

2) 4D-CBCT ACQUISITION

4D-CT images were acquired on a 16-slice helical CT simulator (Sensation Open, Siemens Healthineers, Berlin, Germany) as respiration-correlated CT. The waveform was obtained during the first 4D-CT acquisition with RPM and used as the reference waveform for guidance during all subsequent imaging sessions. 4D-CBCT images were acquired on a commercial CBCT scanner (On-Board Imager v1.3, Varian Medical Systems, Inc). The external breathing surrogate during 4D-CT scanning was used in the CBCT acquisition system to fuse each CBCT projection with the surrogate respiratory signal through in-house software and hardware tools. Approximately 1800 projections were acquired within 2 minutes with half-fan mode. The scanning parameter was 125 kVp, 20 mA, and 20 ms in a single 360° gantry rotation. The CBCT projections were divided into 10 phases (0 to 90%, phase-based binning) with the respiratory signal from the external surrogate. As with 4DCT, the 0% phase corresponded with the end of inhalation. 4D-CBCT was reconstructed using an in-house Feldkamp Davis-Kress (FDK) reconstruction algorithm, with minimal preprocessing [23]. FIGURE 2 shows several phase images from 4D-CBCT images.

3) TRAJECTORY OF TRACKING BASED ON 4D-CBCT

A 4D-CT was performed as part of the standard radiotherapy treatment planning process with thorax phantom. First, the contour of the tumor on the average CT for planning was used to generate digitally reconstructed radiographs (DRRs) at every projection angle. The anatomy-without-tumor dataset was created by subtracting the tumor-only dataset from the average CT and adding the simulative lung dataset so that the tumor voxels were replaced by simulative lung tissue. For every CBCT projection position, two sets of DRRs were created: one showing only the tumor, and another with the anatomy without the tumor based on average images. Second, DRRs of anatomy without tumor were rigidly registered to CBCT projections to obtain the fused DRR. The projections were subtracted from the DRRs, resulting in a projection dataset containing primarily tumor. Finally, the tumor on the projection image was located. A second registration was performed between the subtracted projection and DRR of the tumor. The trajectory of tracking was generated by the localization of tumor on every projection [24]. The largest respiratory motion was in the superior-inferior (SI) direction, the SI direction also corresponded to the axis of rotation of the gantry. Only the SI direction tumor positions and motions were discussed in this article.

4) EVALUATION

In order to evaluate the geometric accuracy of EMT and compare it with other methods, several evaluation indexes were introduced. The geometric accuracy of EMT and tracking with 4D-CBCT can be evaluated using the following metrics.

We define the deviation as a_i:

$$a_i = b_i - b_i^* \tag{1}$$

where b_i is the measurement value derived from Calypso or 4D-CBCT, b_i^* is the ground truth. The mean absolute

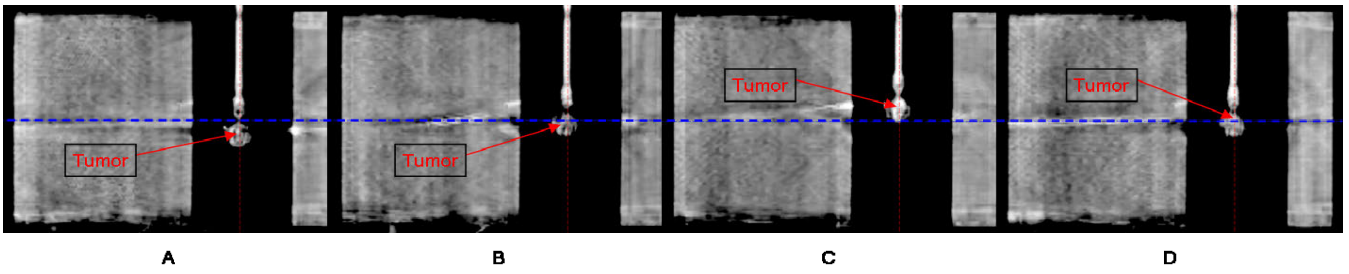

FIGURE 2. A: Peak Exhale, B: Mid Inhale, C: Peak Inhale, D: Mid Exhale phase of the 4D-CBCT scan. The blue dashed line was drawn to aid the visualization of the motion.

deviation (MAD) is the absolute value of the deviation from the arithmetic mean of all individual observations. MAD is defined as [25]:

$$MAD = \frac{1}{N}\sum_{i=1}^{N}|a_i| \tag{2}$$

where N is the number of sample points. MAD is an average of the absolute deviation $|a_i|$.

Standard Deviation (SD) describes the average distance from the mean of each data. SD is the square root of the average of squared errors. SD can reflect the dispersion of a data set, the smaller the standard deviation, the less these values deviate from the average. SD is sensitive to outliers [26]. SD is defined as:

$$SD = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(|a_i| - MAD)^2} \tag{3}$$

C. DOSIMETRIC VERIFICATION OF EMT

A numerical control respiratory motion platform which can simulate SI direction of the tumor motion while carrying Matrixx or Arccheck was designed and made in our department. IMRT and VMAT plan about lung tumor were carried out 2D or 3D dynamic dose verification with EMT in different gating thresholds, comparing dose by measurement with dose from planning system in 3 mm/3% gamma criterion to evaluate the contribution of dose accuracy with Calypso [27]. The optional Dynamic Edge Gating feature provided an output signal to hold the beam of Varian linear accelerators when the treatment target moved outside of the gating limits. The gating limits were researched to find how large limits can be still maintaining dosimetric accuracy.

1) 2D DYNAMIC DOSE VERIFICATION

The I'mRT MatriXX (IBA Dosimetry GmbH, Germany) device consists of a two-dimensional (2D) array of ionization chambers. There are 1,020 vented parallel plate ion chambers on the array detector, arranged in 32 × 32 grid. MatriXX has been validated for 2D dose measurements, and was increasingly used in photon beam dosimetry and patient-specific quality assurance [28]. Two surface transponders were fixed to the surface of the MatriXX and aligned with the crosshair. The dose distribution was measured with the MatriXX 2D ionization chamber array and compared with Dose Cube Data, calculated by treatment planning systems. FIGURE 3 shows the Matrixx on the motion platform. To evaluate the dosimetric accuracy of EMT delivery, Matrixx was irradiated on the motion platform with and without EMT compensation. 10 cases of lung tumor IMRT plan were carried out 2D dynamic dose verification with EMT using 2, 3, and 5 mm gating limits, contrasting dose by measurement with dose from the planning system in 3 mm/3% gamma criterion to evaluate the contribution of dose accuracy with Calypso EMT system. The information about IMRT plans is shown in Table 1. The amplitude in SI direction of the motion platform was 10 mm and the period was 3s.

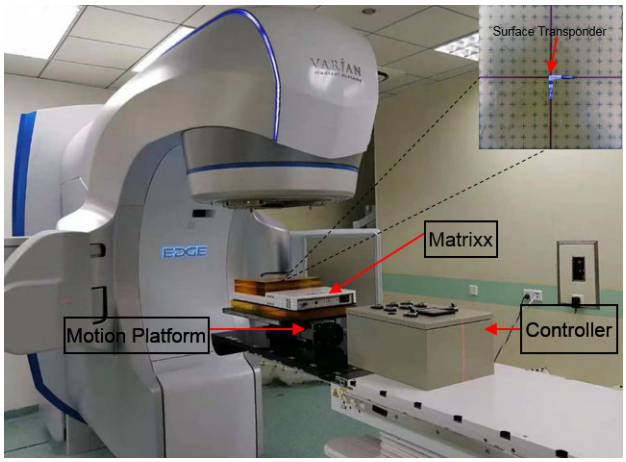

FIGURE 3. Matrixx on the motion platform.

TABLE 1. Parameters of IMRT plan.

Plan No.	Energy /MV	Field No.	Beam Type	Dose Rate	Monitor Units
1	6	7	Step and Shoot	600	710
2	6	7	Step and Shoot	600	742
3	6	7	Step and Shoot	600	495
4	6	5	Step and Shoot	600	636
5	6	7	Step and Shoot	600	542
6	6	5	Step and Shoot	600	576
7	6	7	Step and Shoot	600	645
8	6	5	Step and Shoot	600	621
9	6	7	Step and Shoot	600	685
10	6	7	Step and Shoot	600	578

2) 3D DYNAMIC DOSE VERIFICATION

The 3D dynamic dose was measured with the ArcCHECK dosimeter. The ArcCHECK, (Model 1220, Sun Nuclear, Melbourne, FL) is a 3-dimensional dosimetry QA system intended for the measurement of radiotherapy dose distributions that were delivered, and compared to the dose distribution calculated by the planning system. It is a cylindrical water-equivalent phantom with a three-dimensional array of 1386 diode detectors, arranged in a spiral pattern, with 10 mm sensor spacing. Dose measurements from each sensor were updated every 50ms [29]. FIGURE 4 shows ArcCHECK on the motion platform. Three transponders were fixed to the surface of ArcCHECK in a triangular pattern and placed at the IEC coordinates relative to the isocenter: A: (−6, −1.5, and 5 cm), B: (−6, 1.5, and 5 cm), and C: (6, 0, and 5.5 cm).

The motion platform was programmed to provide realistic Lung respiratory motion to the ArcCHECK phantom. The motion waveform had an amplitude of 10 mm in the

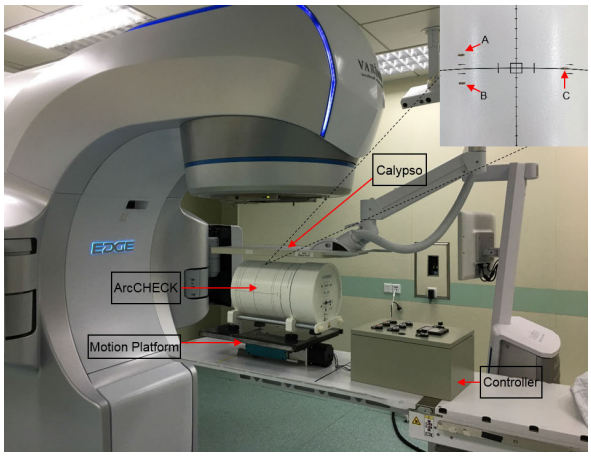

FIGURE 4. ArcCHECK on the motion platform, A, B, C: Transponder.

TABLE 2. Parameters of VMAT plan.

Plan No.	Energy /MV	Gantry Start/°	Gantry Stop/°	Beam Type	Dose Rate	Monitor Units
1	6	240	110	Arc	600	368
2	6	235	115	Arc	600	396
3	6	245	105	Arc	600	347
4	6	240	110	Arc	600	473
5	6	235	115	Arc	600	421
6	6	235	115	Arc	600	388
7	6	240	110	Arc	600	435
8	6	245	105	Arc	600	424
9	6	245	105	Arc	600	399
10	6	235	115	Arc	600	416

SI direction and a period of 3s. Calypso was then used to track the ArcCHECK phantom in real-time. Our objective was to measure the relative dynamic tracking accuracy in order to identify any additional errors introduced by tracking fast continuous 2D motion. A test was performed using the motion platform and ArcCHECK phantom to verify the dosimetric accuracy and establish the clinical workflow of gated SBRT treatment of the Lung using Calypso. The end-of expiration phase was used for contouring, volume modulated arc therapy (VMAT) optimization, and transponder coordinate determination. For treatment, the moving phantom was set up on a Varian Edge by aligning the end-of-expiration phase to the expected position using Calypso. 10 cases of lung tumor VMAT plan were carried out to verify the 3D dynamic dose. First, the treatment beam was delivered without EMT while the phantom was moving. Second, the treatment beam was gated with EMT using 3 and 5 mm gating limit. The information about VMAT plans is shown in Table 2. The dose from the planning system was compared to the delivered dose using gamma analysis within the ArcCHECK software [30].

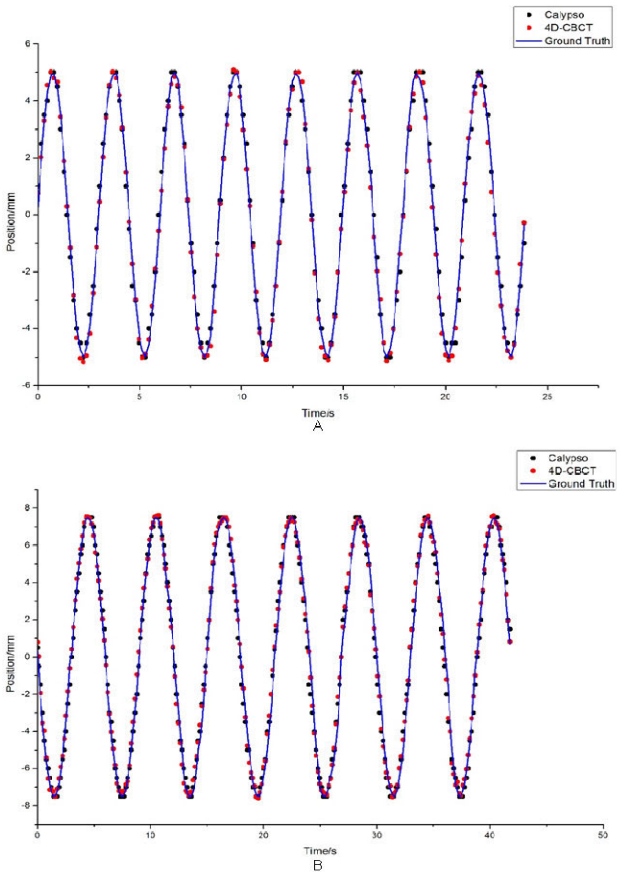

FIGURE 5. A, B are showing trajectory from Calypso, 4D-CBCT and motion control software with 5, 7.5 mm amplitudes respectively, the black dot corresponding to the trajectory from Calypso, the red dot corresponding to the trajectory from 4D-CBCT, the blue line corresponding to the ground truth of the trajectory.

III. RESULTS

A. GEOMETRIC ACCURACY OF EMT

shows the result of synchronizing the 4D-CBCT system with Calypso and the signals used to synchronize. The trajectory of tumor motion in the SI direction was a function of time. The ground truth position of tumor was obtained from motion control software. For tumor motion with 5, 7.5 mm amplitudes, the errors of tracking accuracy were 0.286±0.234, 0.407±0.331 mm (MAD±SD) based on Calypso and 0.213±0.154, 0.297±0.246 mm (MAD±SD) based on 4D-CBCT, respectively. The tracking error at the end of inhalation and exhalation was larger. The black dots on behalf of the tumor position from Calypso at the peak were away from the blue line. Most of the black and red dots were in accordance with the blue line, as shown in FIGURE 5. The tumor position from the two tracking systems was matching with the ground truth, overall.

B. DOSIMETRIC VERIFICATION OF EMT

1) 2D DYNAMIC DOSE VERIFICATION

The dose distribution was evaluated by the gamma method with parameters of 3 mm/3%. The gamma pass rate was

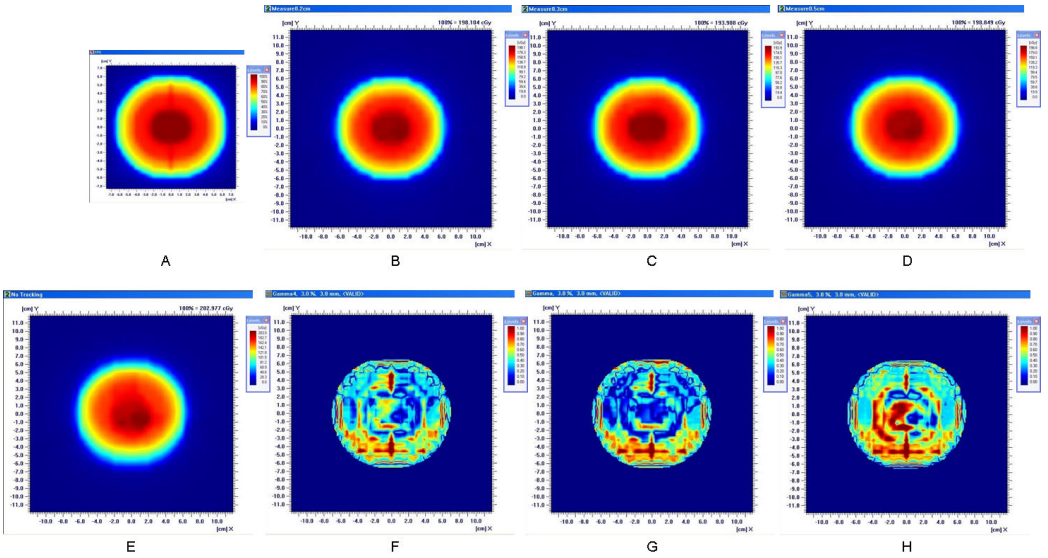

FIGURE 6. A: Planned dose distribution, B: Measured dose distribution using 2 mm gating limit, C: Measured dose distribution using 3 mm gating limit, D: Measured dose distribution using 5 mm gating limit, E: Measured dose distribution without EMT F: Gamma comparison with EMT using 2 mm gating limit, G: Gamma comparison with EMT using 3 mm gating limit, H: Gamma comparison with EMT using 5 mm gating limit.

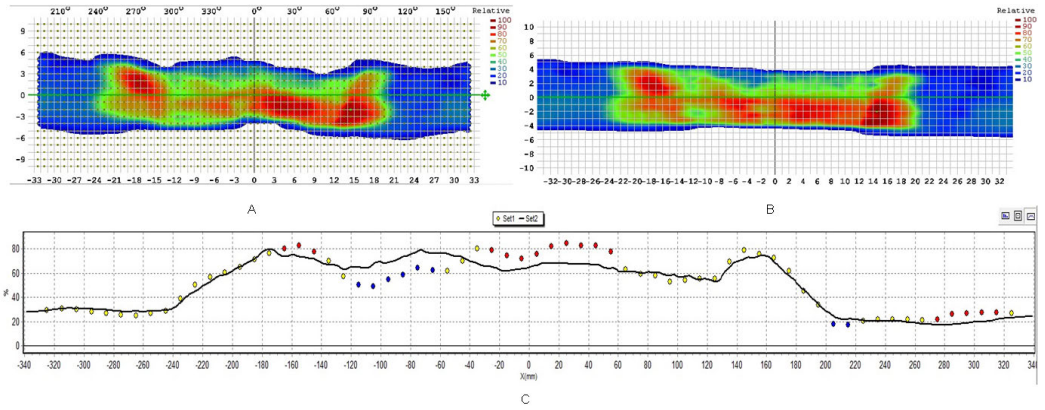

FIGURE 7. Comparison between calculated and measured doses without EMT.

less than 46% when Matrixx was irradiated on the motion platform without EMT. When increasing the gating limits beyond the known extent of planned motion, the gamma pass rates decreased as expected. The average gamma pass rates for the gated treatment delivery using 2, 3, and 5 mm gating limits were 97.3%, 96%, and 93.4%, respectively. Gating tracking with EMT significantly improved plan pass rate from below 50% to above 90%. The gamma pass rate using 5 mm gating limits decreased about 3% relative to using 3 mm gating limits and less than 95%. The dose distributions of the plan and measured are shown in FIGURE 6.

2) 3D DYNAMIC DOSE VERIFICATION

The mean 3D dynamic dose validation pass rates of VMAT plans were 65.9% without EMT, 96.2% with EMT using 3 mm gating limit, and 92.5% with EMT using 5 mm gating limit respectively. The comparison between measured and calculated doses and dose profiles are shown in FIGURE 7-9. When increasing the gating limits beyond the known extent of planned motion, the gamma pass rates decreased as expected. The result of verification showed good agreement between the measured and calculated doses (>95% gamma pass rate) when using the gating limit about a quarter of the range of motion from the phases used for planning. The gamma pass rate was less than 95% with EMT using 5 mm gating limit. The profile showed poor agreement between the measured and calculated doses using 5 mm gating limit. Therefore, we recommend determining baseline gating limits by measuring the extent of target motion during the respiratory phases used for planning, and then adding 1 mm to those baseline gating limits to make the treatment more efficient.

IV. DISCUSSION

4D-CBCT facilitated verification of lung tumor motion before each treatment fraction and enabled accurate patient setup in lung stereotactic ablative body radiation

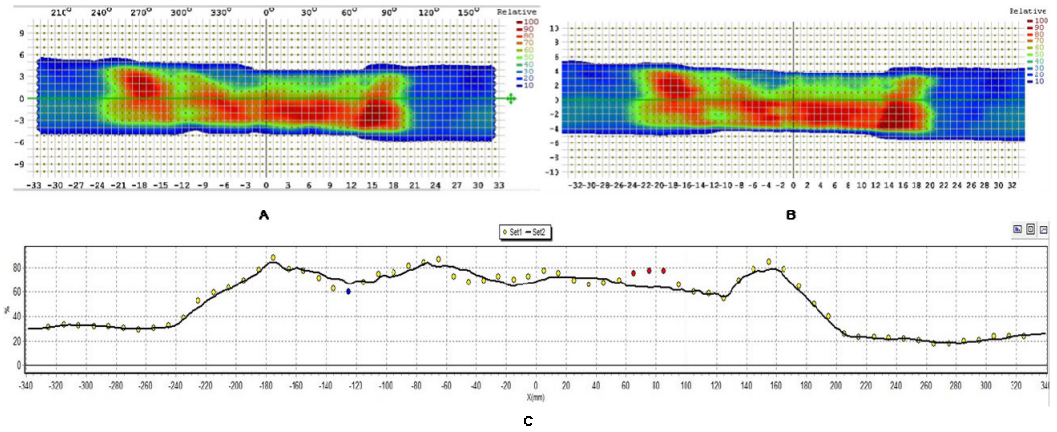

FIGURE 8. Comparison between calculated and measured doses with EMT using 3 mm gating limit.

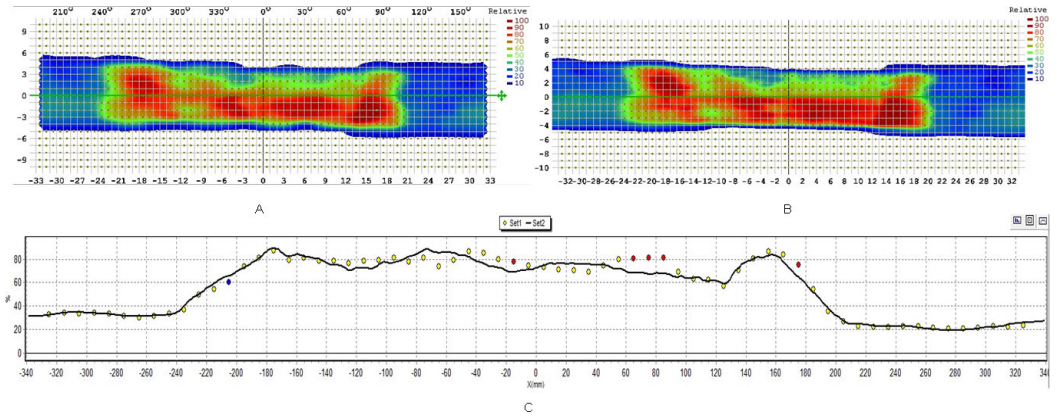

FIGURE 9. Comparison between calculated and measured doses with EMT using 5 mm gating limit. A: Measured dose distribution, B: Planned dose distribution, C: Dose profile.

therapy (SABR). Direct tumor tracking methods primarily tracked internally implanted fiducial markers or use fluoroscopic imaging. Fiducial markers were easier to monitor, but any method using implanted fiducial markers in lung increased extra risks [31]. The method of markerless tumor tracking based on 4D-CBCT raw projection data had been developed in our study. We had integrated EMT using Calypso with the 4D-CBCT imaging system of a radiotherapy Linac. The ground truth position of the simulative tumor was exported from the motion control software of CIRS. The motion trajectories of the tumor both from Calypso and 4D-CBCT were in accordance with the ground truth. The absolute error of tracking accuracy based on 4D-CBCT was smaller than based on Calypso. The motion trajectory of the tumor for patient with lung cancer can be abstracted based on the projection of 4D-CBCT although the real-time tumor motion was not absolutely represented in 4D-CBCT scans. The main difference was at the end of the inhale and exhale because Calypso system occurred latency when the direction of the tumor motion was changed. Yuasa *et al.* [32] investigated the accuracy of motion trajectory measurement depending on the gantry speed during CBCT acquisition in a phantom study and observed a loss of accuracy for high gantry speeds of 4-6°/s. Image acquisition at slower gantry speeds and a larger number of projections could potentially improve the accuracy of the motion representation in 4D-CBCT scans. Calypso could accurately report the location of the tumor by comparison with the ground truth position. The results indicate that the manufacturer specified tracking accuracy of below 1 mm was maintained. The SI motion is always in the same orientation on all projection images regardless of gantry angle. Any movement perpendicular to the SI direction would be projected along the orthogonal orientation, which changes with gantry angle. Our motion tracking algorithm based on the projection of 4D-CBCT is effective if motion irregularity and daily anatomy variation happen in the SI direction. Calypso can show the position of the tumor with respect to isocenter in 3D direction. The EMT gating system can handle irregular tumor motion and anatomy variation. However, a re-localization is to be performed if the transponder centroid drifts more than 5 mm due to anatomy variation.

Smith *et al.* [33] developed an interface between Calypso and a Varian Trilogy linear accelerator. A film phantom was

mounted on a motion platform programmed with lung motion trajectories. The dosimetric advantages of beam gating and the system latencies were quantified, while dosimetry with film required calibration and dose analysis was complex. Lung tumor plans including IMRT and VMAT were carried out in Matrixx and ArcCHECK on the motion platform without EMT and with EMT for dynamic 2D and 3D dose verification in this study. An obvious reduction of the high dose regions and a widening of the low dose regions were observed without EMT, in comparison with the dose from the plan. Gating tracking with EMT can significantly improve plan pass rate. Gating limits should initially be set by the extent of tumor motion on the phase for planning. The gamma pass rates decreased by about 3% with a 2 mm increase in the gating limit. Target movement had more influence on VMAT plan than IMRT plan. Using 3 mm tracking limit could guarantee plan pass rate above 95% for tumor motion with 10 mm amplitude while treatment efficiency would be guaranteed. Increasing the limits beyond this amount would improve the treatment efficiency at the cost of dosimetric accuracy. Lung tumor plans were performed using the motion platform and dosimeter to verify the dosimetric accuracy and establish the clinical workflow of gated SBRT treatment of the lung using Calypso. Additionally, the implanted beacon transponders had been shown to be stable in the CIRS phantom, while lung tumor tracking might be more challenging because the transponders would not likely have a fixed relationship to the lung tumor. The incorporation of the uncertainty would affect the size of the gating limit. High-dose gradients were necessary for dose escalation to the tumor while ensuring that the surrounding organ at risks received a lower dose. The dose gradients achieved with EMT were larger than those achieved without intervention in the presence of motion.

V. CONCLUSION

The dynamic tracking accuracy of the Calypso system met the manufacturer's specification, even for continuous large amplitude motion that can be encountered when tracking simulated lung tumor. The trajectory of the tumor from Calypso was in good agreement with the ground truth. The geometric accuracy of the Calypso system in tracking the moving target area was stable at the submillimeter level. The dosimetric accuracy could be improved significantly with EMT using an appropriate gating limit. We developed effective validation methods for clinical application of Calypso successfully. For the next work, we plan to use in patients with lung cancer and test the performance of Calypso on different datasets.

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(Zhenhui Dai and Hua Zhang contributed equally to this work.)

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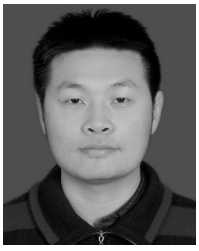

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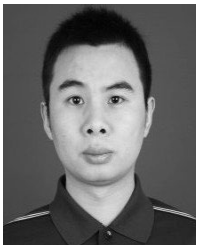

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