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Title

A novel internal target volume definition based on velocity and time of respiratory target motion for external beam radiotherapy

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Abstract

This study aimed to develop a novel internal target volume (ITV) definition for respiratory motion targets, considering target motion velocity and time. The proposed ITV was evaluated in respiratory-gated radiotherapy. An ITV modified with target motion velocity and time (ITVvt) was defined as an ITV that includes a target motion based on target motion velocity and time. The target motion velocity was calculated using four-dimensional computed tomography (4DCT) images. The ITVvts were created from phantom and clinical 4DCT images. The phantom 4DCT images were acquired using a solid phantom that moved with a sinusoidal waveform (peak-to-peak amplitudes of 10 and 20 mm and cycles of 2–6 s). The clinical 4DCT images were obtained from eight lung cancer cases. In respiratory-gated radiotherapy, the ITVvt was compared with conventional ITVs for beam times of 0.5–2 s within the gating window. The conventional ITV was created by adding a uniform margin as the maximum motion within the gating window. In the phantom images, the maximum volume difference between the ITVvt and conventional ITV was –81.9%. In the clinical images, the maximum volume difference was –53.6%. Shorter respiratory cycles and longer BTs resulted in smaller ITVvt compared with the conventional ITV. Therefore, the proposed ITVvt plan could be used to reduce treatment volumes and doses to normal tissues.

Keywords: internal target volume, 4DCT, target motion velocity, time

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2. Introduction

Radiotherapy is performed with motion management for respiratory motion targets such as lung, liver, and pancreatic cancers. These techniques include breath-hold [1] and respiratory gating.[2,3] During the breath-hold technique, patients hold their breath while radiation isadministered. Devices monitor respiration by tracking either surface motion or fiducial markers on the patient.[4,5] Respiratory-gated radiotherapy synchronizes the delivery of radiation beams with respiratory motions, typically detected through abdominal wall movements or pressure changes. The radiation beam is delivered within a selected gate window on the respiratory waveform. Another method involves the use of fiducial markers as internal surrogates for the tumor.[6] These methods can reduce the treated volumes and normal tissue doses compared to radiotherapy with free breathing.[7–10]

In respiratory-gated radiotherapy, the target with respiratory motion moves within a gating window**.**[11–13] Therefore, the internal target volume (ITV) should include target motions within this window. The direction and amplitude of target motion vary depending on the tumor's location in respiratory motion targets, such as in lung cancer.[14] Therefore, a three-dimensional margin is required to account for target motion for each patient. ITVs are created using numerous methods. One approach adds a large margin covering all target motions to a clinical target volume (CTV).[15] There is a method that adds a uniform margin to the end-expiration phase CT images.[16,17] Another approach uses maximum intensity projection (MIP), derived from four-dimensional computed tomography (4DCT), to contour the ITV.[18,19] This method is useful when there are significant density differences between the target and surrounding tissues, such as in lung cancer. Alternatively, ITVs can be created by summing contoured targets, such as the gross tumor volume (GTV) or CTV, on 4DCT images within the gating

window.[15,20,21] All these conventional methods utilize 4DCT images. However, these approaches do not consider the continuous motion and temporal variations across each phase of the 4DCT; instead, they create an ITV based on static representations derived from 4DCT images.

Although 4DCT images are treated as static representations, in reality, target motion velocity varies with the respiratory phase. This motion velocity can lead to blurring artifacts into the CT images, following target motion[22,23], which introduces uncertainty regarding the target position on each CT slice. The target position uncertainty depends on the target motion velocity and the CT scan time. Additionally, an ITV margin must include motion during beam delivery time in respiratory-gated radiotherapy. The faster the target moves, the larger is the target motion amplitude of the tumor.[24] When the beam delivery time within the gating window is the same, the motion area of a rapidly moving target is larger than that of a slowly moving target. Thus, a larger ITV margin is required for rapidly moving targets. Conversely, when the target moves slowly, a smaller ITV margin is sufficient. Furthermore, using a respiratory motion monitoring device introduces latency in both the beam-on and beam-off states[25,26] in respiratory-gated radiotherapy. The latency from the gate-on/off to the beam-on/off state can result in the beam being delivered to a location where the target is not present, due to target motion during the latency. The target motion during the beam delivery depends on the target motion velocity. However, the current ITV methods cannot estimate the target motion based on the target motion velocity and time (such as CT scan time or beam delivery time). Consequently, they cannot set an ITV margin that appropriately accounts for this motion. Therefore, developing an ITV method based on target motion velocity and time is crucial for enhancing the accuracy of respiratory-gated radiotherapy.

This study aimed to develop a novel ITV definition that considers target motion velocity and time. The developed ITV was evaluated under varying target motion velocities and times, and compared with conventional ITV (conv ITV) in respiratory-gated radiotherapy. The feasibility of the proposed ITV was evaluated using phantom and clinical 4DCT images.

3. Materials and Methods

3.1. ITV modified with target motion velocity and time

The ITV modified with target motion velocity and time (ITVvt) includes an area where the target is present based on its motion velocity and time. Fig. 1 shows a simplified diagram of the ITVvt creation process. The target moved sequentially through time points T_{i-1}, T_i, and T_{i+1} with centroid positions P_{i-1}, P_i, and P_{i+1}, where $i-1$, i, and $i+1$ denote the phase numbers (Fig. 1 (a)). The target motion velocity was defined for any given time because it varies throughout the phases.[24,27] The target motion velocities, V_{i-1} (from P_{i-1} to P_i) and V_i (from P_i to P_{i+1}) were calculated as follows:

$$V_{i-1} = \frac{P_i - P_{i-1}}{T_i - T_{i-1}} \quad (1)$$

$$V_i = \frac{P_{i+1} - P_i}{T_{i+1} - T_i} \quad (2)$$

Fig. 1 (b) shows the ITVvt when the target moves from $T_i - TPU_{i-1}$ to $T_i + TPU_i$. TPU_{i-1} and TPU_i are the time causing position uncertainty (TPU) of the target from P_{i-1} to P_i and P_i to P_{i+1}, respectively. TPU is a time that causes uncertainty in the target position because of its motion, which can include beam delivery time, latency of gate-on and -off, or 4DCT scan time. Estimated motion distance is defined as the distance the target may move during TPU. The estimated motion distances D_{i-1} (from $T_i - TPU_{i-1}$ to T_i) and D_i (from T_i to

$T_i + TPU_i$) were calculated as follows:

$$D_{i-1} = V_{i-1} \times TPU_{i-1} \quad (3)$$

$$D_i = V_i \times TPU_i \quad (4)$$

Finally, ITVvt was defined as the area in which the target at P_i moved along D_{i-1} and D_i. Fig. 1 (b) shows a conv ITV for reference. The conv ITV uniformly adds a margin to the target at P_i to include all target motions.

In respiratory-gated radiotherapy, the ITVvt should include the target motion according to the respiratory phase within the gating window. Since the target motion within the gating window is the same as the target motion during beam irradiation, ITVvt is determined based on the target motion during the beam time (BT). The 4DCT images were used to create the ITVvt in respiratory-gated radiotherapy. Fig. 2 (a) shows the respiratory waveform with a gating window. The gating window includes respiratory phases $i-1$, i, and $i+1$ with time points T_{i-1}, T_i, and T_{i+1}, respectively. BT denotes the time at which the radiation beams are delivered within the gating window. Fig. 2 (b) shows the target motion from T_{i-2} to T_{i+2} in 4DCT images alongside the beam-on and -off states. The target motion velocity (black arrow) and position varied across the phases. Because the beams are delivered within the gating window that includes respiratory phases $i-1$, i, and $i+1$, a TPU is set for T_{i-1}, T_i, and T_{i+1}. Subsequently, the $ITVvt_{i-1}$, $ITVvt_i$, and $ITVvt_{i+1}$ were created for the 4DCT images of respiratory phase $i-1$, i, and $i+1$, respectively, by using the TPU and target motion velocity. For example, at respiratory phase i, the estimated motion distance from T_i to $T_i + TPU_i$ was calculated from V_i and TPU_i, and the estimated motion distance from T_i to $T_i - TPU_i'$ was calculated from V_{i-1} and TPU_i'. The $ITVvt_i$ was created by moving the target at respiratory phase i along both the estimated motion distances. Fig. 2 (c) shows the ITVvt of respiratory-

gated radiotherapy in the 4DCT image of respiratory phase i. The ITVvt was created by summing the $ITVvt_{i-1}$, $ITVvt_i$, and $ITVvt_{i+1}$. As shown in Fig. 2 (c), the ITVvt includes the target motion within the BT.

The ITVvt definition requires the target motion velocity between the phase of the 4DCT images. Calculating the target motion velocity requires determining the centroid position of the target at each respiratory phase and the time between these phases of the 4DCT images. Therefore, an ITVvt can be generated with the 4DCT images sorted either by amplitude or phase bins.[28] For the 4DCT images sorted by phase bins, the times between each phase are determined by the respiratory cycle because the times between each phase are consistent. When the 4DCT images are sorted into phase bins, the target motion velocity can be calculated utilizing the respiratory cycle.

3.2. Acquisition of 4DCT images

3.2.1. Phantom images

The 4DCT images were acquired using water-equivalent solid phantoms and a motion phantom. The water equivalent solid phantom was a 30×30×20 cm^3 RW3 slab phantom (PTW, Freiburg, Germany). The motion phantom was a CIRS Dynamic Thorax phantom (Computerized Imaging Reference Systems, Inc., Norfolk, VA, USA). To simulate the target centroid, positioned 12 cm below the top of the phantom surface, a 1.5 mm Disposable Gold Marker (Olympus Medical Systems, Tokyo, Japan) was inserted into the solid phantom. The solid phantom was attached to a motion phantom, and 4DCT images were acquired with different amplitudes and cycles of the dynamic phantom (Fig. 3). The dynamic conditions were six sinusoidal patterns with peak-to-peak (PtoP) amplitudes of 10 and 20 mm in the superior-inferior (SI) direction and cycles of 2, 4, and 6 s. The CT scanner was a SOMATOM Confidence CT scanner (Siemens Healthcare, Erlangen, Germany) with a respiratory motion

monitor, AZ-733VI (Anzai Medical Co., Tokyo, Japan), which recorded the CIRS surrogate. The scan parameters were 120 kV, 50 mA/rotation, a gantry rotation time of 0.5 s, and a slice thickness of 2 mm. The 4DCT images were reconstructed by sorting into 10 breathing phases (0–90%, with a 10% phase step). Phases 0% and 50% corresponded to inspiration and exhalation, respectively.

The tumors in the 4DCT images of the solid phantom were delineated using MIM software version 7.2.8 (MIM Software Inc., Cleveland, OH, USA). For all 4DCT images, the inserted gold marker was contoured, and spheres with a 3, 6, and 9 cm diameter were created at the centroid of the gold marker as the CTV.

3.2.2. Clinical images

We selected 4DCT images of lung cancer to evaluate the ITVvts in clinical images. Eight cases with different tumor sizes and locations were selected from the 4DCT images and structure sets of lung cancer provided by The Cancer Imaging Archive (TCIA).[29] The 4DCT images were sorted into 10 breathing phases using phase-based binning.[30]

A tumor contour obtained from the structure sets of TCIA was defined as a GTV, and the CTV was defined to be the same as the GTV. The ITVvt was created from the CTV. Table 1 lists the CTV location, size, and maximum motion amplitudes based on target locations in the 50% phase.

Generation of the ITVvt from the 4DCT images required the times between each phase of the 4DCT images. However, TCIA does not provide information about respiratory motion and cycles. The 4DCT images of TCIA were sorted into phase bins, and the times were equally divided. The time between the phases (TP) of the 4DCT images, sorted by number of phase bins, can be calculated from the respiratory cycle as follows:

$$TP = \frac{\text{respiratory cycle}}{\text{number of phase bins}} \quad (5)$$

ITVvts were created with respiratory cycles of 2, 4, and 6 s in TCIA images.

3.3. ITVvt creation

The ITVvts were created from CTVs with BTs of 0.5, 1.0, and 2.0 s in respiratory-gated radiotherapy using phantom and clinical 4DCT images. The gating window was set at the center of the 50% phase. ITVvt creation requires the target motion velocities and TPUs of each phase within the gating window. The target motion velocities were calculated using the target positions and the times between each phase of the 4DCT images. These velocities were calculated based on the centroid positions of the CTV. Both the clinical and phantom images had a respiratory cycle of 2, 4, and 6 s. Using equation 5, the time between each phase of the 4DCT images was calculated by dividing the respiratory cycle by 10 phases. Table 2 lists the respiratory phases included in the BTs. Considering that the ITVvt for respiratory-gated radiotherapy is created using 4DCT images of the phases within the BT, the TPUs were set for the phases within the gating window. TPUs were assigned based on the divided time of the BT. Each TPU was set individually for each respiratory phase, ensuring no overlap with TPUs from other phases. The total TPU for the phases was equal to the BT. Therefore, the ITVvt includes the target motion during the BT. In this ITVvt creation, TPU does not include the latency of gate-on and -off and CT scan time.

The procedure for creating ITVvts involves the following steps. First, contours within the RTSTRUCT files in DICOM format are converted into a proprietary binary format, specific to NumPy library [31] of Python programming language, using in-house software. Second, the binary files of the contours are input into the in-house ITVvt creation software, generating contours for the ITVvt in binary format at each phase. Third, the

contours for the ITVvt are converted from binary to DICOM format. Finally, the ITVvt in each phase within the gating window is summed at the MIM workstation.

3.4. Evaluation

We evaluated ITVvts with varying target motion velocities and BTs. This study evaluated volume differences compared to the CTV of 50% phase and ITVvt. Subsequently, we compared the volumes of the ITVvts and conv ITVs. The conv ITV was defined as an ITV with a uniform internal margin (IM) added to the CTV. The IMs of the conv ITVs represented the maximum target motion within the gating window.

4. Results

The motion amplitudes of the targets are shown in Fig. 4 (a) and 5 (a) for the phantom and clinical images, respectively. Their three-dimensional amplitudes were determined relative to the 50% phase. For the phantom images, the maximum amplitude was 20 mm at the 0% phase under dynamic conditions of a 20 mm PtoP amplitude and a 4 s cycle. For the clinical images, the maximum amplitude was 11.3 mm at the 90% phase for patient P114. The variations in target motion velocity between the phases for the phantom and clinical images are shown in Fig. 4 (b) and 5 (b), respectively. The velocity in the clinical images is shown for a 4 s respiratory cycle. The velocity in the phantom images varied depending on the dynamic conditions, while in the clinical images, it varied across patients and phases. Table 3 and 4 list the maximum velocities in the phantom and clinical images, respectively. For the phantom images, the maximum velocity was 28.5 mm/s during the 20–30% phase with a PtoP amplitude of 20 mm and 2 s cycle. For the clinical images, the maximum velocity was 27.9 mm/s during the 80–90% phase for patient P106 with a respiratory cycle of 2 s. In all cases, the target motion velocities were higher for shorter

196 respiratory cycles.

197 Fig. 6 shows the sagittal images of the ITVvts and conv ITVs on the 4DCT images at the 50% phase. The
198 dynamic condition of the phantom was a 20 mm PtoP amplitude, and the clinical images correspond to patient
199 P114. The ITVvt includes only the area where the target moves. The ITVvts in the phantom images increased in
200 the SI direction because the dynamic phantom moved consistently in that direction. Shorter cycles and longer BTs
201 resulted in larger ITVvts and conv ITVs in both the phantom and clinical images.

202 Fig. 7 shows the volume differences between CTV and ITVvt at the 50% phase in the phantom images. The
203 maximum volume difference was 99.2% under the conditions of 3 cm target diameter, 20 mm PtoP amplitude, 2 s
204 cycle, and 2 s BT . The minimum volume difference in the phantom images was 0.8% under the conditions of 9
205 cm target diameter, 10 mm PtoP amplitude, 6 s cycle, and 0.5 s BT. The ITVvt tended to increase with larger PtoP
206 amplitudes, shorter cycles, longer BTs, and smaller target sizes.

207 Fig. 8 shows the volume differences between CTV and ITVvt at the 50% phase in the clinical images. The
208 maximum volume difference in the clinical images was 82.5% under the conditions of 2 s respiratory cycle and 2
209 s BT for patient P106. The minimum volume difference in the clinical images was –0.03% under the conditions of
210 0.5 BT at 4 s cycle and 0.5 and 1 s BT at 6 s for patient P103. Similar to the phantom images, the ITVvt in the
211 clinical images tended to increase with shorter cycles and longer BTs.

212 Fig. 9 shows the volume differences between ITVvt and conv ITV in the phantom and clinical images. In the
213 phantom images, the maximum volume difference was –81.9% under the conditions with a target size of 3 cm, a
214 PtoP amplitude of 20 mm, a cycle of 2 s, and BT of 2 s. In the clinical images, the maximum volume difference

was –53.6% when the respiratory cycle was 2 s and the BT was 2 s for patient P101. In the phantom images, the volume difference for a PtoP amplitude of 20 mm was generally larger than for a PtoP amplitude of 10 mm. In both the phantom and clinical images, the ITVvt was smaller than the conv ITV when the cycle was shorter and the BT was longer.

5. Discussion

We developed a novel definition of ITV, namely ITVvt, that includes the target motion based on the target motion velocity and time. In this study, we evaluated the volume differences between the ITVvt and conv ITV. The results demonstrated that the ITVvt was smaller than the conv ITV, with up to –53.6% difference in the clinical images.

The target motion velocity exhibited variations among the patients and phases as shown in Fig. 4 (b) and 5 (b) for the phantom and clinical images, respectively. Similar to the findings in a previous study, the target motion velocity was high when the target motion range was large.[24] In the phantom images, the target motion velocity was slow around the 50% phase and fast around the 30% and 70% phases. However, this trend was not observed in the clinical images because the target motion in clinical cases does not follow a sinusoidal pattern, unlike the controlled motion of the dynamic phantom. If a patient's breathing is unstable, the beam may not be irradiated accurately in respiratory-gated radiotherapy.[32] It is important to use respiratory coaching with audio prompting or visual feedback to improve respiratory reproducibility for patients who are not breathing steadily. [33,34]

The target motion velocity was calculated for each respiratory cycle in clinical images. Table 4 shows that the target motion velocity changes significantly with changes in the respiratory cycle. The respiratory cycle is a

crucial factor in creating the ITVvt. Additionally, Table 4 indicates that the target motion velocity increases with decreasing respiratory cycles owing to the shorter time between phases. Because the target motion velocity may be affected by lung function, it is important to create individualized ITVvts for each patient. If the respiratory cycle changes during a treatment period, the ITVvt may have to be modified to account for changes in the target motion velocity.

Fig. 7 and 8 show that the ITVvt is dependent on the cycle and BT. In particular, ITVvt was larger than CTV at the 50% phase when the cycle was shorter and the BT was longer. When the respiratory cycle was long and the BT was short, the ITVvt was not substantially larger than the CTV at the 50% phase. The target motion velocity was high for short cycles. Therefore, the ITVvt was large because the estimated motion distance is longer with high motion velocity and longer BT.

ITVvt was generally smaller than conv ITV in both the phantom and clinical images. The difference was notable in the phantom images when the PtoP amplitude was 20 mm compared with 10 mm. This is because ITVvt includes only the area of the target motion, whereas the conv ITV adds a uniform margin which accounts for the maximum motion of the CTV within the gating window. Therefore, a treatment plan using ITVvt could reduce treatment volumes, particularly for patients with significant target motions.

The ITVvt is recommended for all cases with respiratory motion. This is because ITVvt can include only the target motion area, resulting in a smaller volume than conv ITV. Particularly, when the target has a high motion velocity, the ITVvt results in an even smaller compared to conv ITV. Therefore, it is especially recommended to use ITVvt when the target has a high motion velocity.

ITVvt can consider various time factors in respiratory-gated radiotherapy. First, the ITVvt can include the scan time of the 4DCT images. Because the target moves during the 4DCT scan, the target position involves uncertainty in the 4DCT images. By including the scan time in the TPU, ITVvt can estimate the uncertainty of the target motion during the 4DCT scan. Second, the ITVvt can incorporate the time factor of the gating window in respiratory-gated radiotherapy. The gating window causes latency between the gate-on/off and beam-on/off states. The beam is not delivered during the time from the gate-on to beam-on, and the beam continues to be delivered during the time from the gate-off to beam-off. By adjusting the BT to account for these latencies, the ITVvt can effectively represent the motion during actual beam delivery. Therefore, ITVvt can adequately include the target motion in respiratory-gated radiotherapy.

An ITVvt plan introduces some clinical implications because it is smaller than a conv ITV. First, the ITVvt plan needs a precision radiotherapy technique to deliver the beam accurately. Because ITVvt provides only the minimum margin to cover the target motion, delivery errors could result in an insufficient target dose. Therefore, a high-precision delivery technique is necessary to use the ITVvt plan. Second, it has the potential for hypofractionated radiotherapy. Because an ITVvt is smaller than a conv ITV, the ITVvt plan can reduce the dose to surrounding normal tissues while allowing higher doses to the tumor. This could enable the implementation of hypofractionated treatment.

For a target that moves rapidly, the ITVvt may be larger than the conv ITV with a narrow gating window in respiratory-gated radiotherapy. When the target moves rapidly, the uncertainty of the target motion is large during the gantry rotation in the 4DCT scan. Therefore, the uncertainty of the target motion may be larger than the target

motion within the narrow gating window. When TPU includes the CT scan time, the ITVvt can include the uncertainty of the target motion during the 4DCT scan. Because conv ITV cannot consider the uncertainty of the target motion during the 4DCT scan, a conv ITV plan may deliver an underdose. Therefore, although the ITVvt may be larger than the conv ITV, an ITVvt plan can ensure sufficient target coverage.

Some techniques use MIPs or averaged images to create ITVs. Techniques such as the internal GTV (iGTV) and internal CTV (iCTV) delineated from 4DCT tend to underestimate the target volume,[21,35] thereby increasing the potential for reduced target coverage.[36] Additionally, iGTV and iCTV do not include continuous motion between each phase of the 4DCT images. In particular, when the target motion velocity is high, the target motion between each phase cannot be incorporated into the ITV. In contrast, the ITVvt, although it may increase the ITV, can consider the continuous motion between phases. Therefore, compared with MIP or iGTV, the ITVvt can appropriately incorporate target motion.

An ITVvt margin depends on the target motion velocity and time. On the other hand, a PTV margin, such as a setup margin, is not influenced by these factors. The ITVvt margin and the PTV margin are independent of each other. Therefore, when creating the PTV from the ITVvt, the PTV margin is uniformly added to the ITVvt.

This study focused on three important considerations. First was the accuracy of the target position in 4DCT images. The target position was obtained from 4DCT images. However, when the target motion velocity is high, the impact of partial projection artifacts[22,37,38] in 4DCT can cause uncertainty in target delineation.[39] Therefore, the rotation speed of the gantry should be as high as possible to mitigate this effect. The clinical images used in this study have sorting artifacts.[30] The artifact can cause uncertainty in the target motion velocity because

of its effect on target delineation. Therefore, the ITVvt could also have uncertainty. Second, the trajectory of the tumor motion and respiratory cycle may change daily.[14] In this study, ITVvt was created from one 4DCT per patient. If the respiratory cycle or trajectory changes, the ITVvt may not have sufficient margin. Therefore, it may be better to create ITVvt by combining multiple 4DCT images. Last, this study is a simulation study. The ITVvt concept was proposed in this study. Although the ITVvts were created from 4DCT images of lung cancer in the TCIA database, the clinical impact on the dose distribution is unknown. Future studies should evaluate the dose distribution of the ITVvt plan.

To further this research and use ITVvts optimally, two additional studies are proposed. First, dose distribution should be measured to ensure that an ITVvt plan delivers adequate doses coverage to a target. Second, the dose to normal tissues in an ITVvt plan should be evaluated compared with a conv ITV plan. ITVvt could reduce the treatment volumes, thereby decreasing the doses to normal tissues. Additionally, respiratory-gated radiotherapy is performed using both photon and proton therapy. An ITVvt plan for proton therapy could potentially reduce doses to normal tissues more effectively than photon therapy. Therefore, the effectiveness of ITVvt in treatment planning should be validated for both photon and proton therapy.

6. Conclusion

In this study, we developed a novel ITV definition, referred to as the ITVvt, based on the target motion velocity and time. The ITVvt can include the target motion within the gating window in respiratory-gated radiotherapy. In particular, the ITVvts were larger for shorter cycles and longer BTs. The ITVvts were smaller than conv ITVs because ITVvts only include the target motion, whereas conv ITVs have uniform margins. An ITVvt

plan could reduce treatment volumes, thereby decreasing the doses to normal tissues. When the target motion velocity is high within the narrow gating window, a conv ITV may lead to inadequate target coverage, whereas the ITVvt plan can ensure adequate target coverage.

Declarations

Conflict of interest The authors have no conflict to disclose.

Ethics approval All procedures involving human participants were performed in accordance with the ethical standards of the Institutional Review Board and the 1964 Helsinki Declaration and its later amendments. Ethical approval was not required for this study as we used the clinical 4DCT images from an open database.

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Data availability statements

The data that support the findings of this study are not openly available due to reasons of sensitivity.

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Figure/Table Legends

Fig. 1. Schematic of the ITVvt creation process. (a) A target motion. The targe moves sequentially through respiratory phases $i-1$, i, and $i+1$. The orange, blue, and green spheres are the targets at P_{i-1}, P_i, and P_{i+1}, respectively. (b) The ITVvt created from the target at P_i. D_{i-1} and D_i are the estimated motion distances from $T_i - TPU_{i-1}$ to T_i and T_i to $T_i + TPU_{i+1}$, respectively. The left and right translucent blue spheres are the targets at $T_i - TPU_{i-1}$ and $T_i + TPU_{i+1}$, respectively. A conv ITV is also shown for reference

Fig. 2. Schematic of the process of generating ITVvt in respiratory-gated radiotherapy. (a) A respiratory waveform with a gating window (GW). The horizontal axis represents time. (b) A target in 4DCT images at respiratory phase $i-2$ to $i+2$, and $ITVvt_{i-1}$, $ITVvt_i$, and $ITVvt_{i+1}$ at respiratory phases $i-1$, i, and $i+1$, respectively. The black arrow indicates the target motion velocity. (c) ITVvt in respiratory-gated radiotherapy in the 4DCT image at respiratory phase i

Fig. 3. Setup of phantom imaging with a motion phantom

Fig. 4 . (a) Motion amplitudes of the targets relative to the 50% phase and (b) target motion velocities between the phases in the phantom images. The motion amplitudes and target motion velocities in the phantom images are shown for each dynamic condition of the PtoP amplitudes and cycles (C).

Fig. 5. (a) Motion amplitudes of the targets relative to the 50% phase and (b) target motion velocities between the phases in the clinical images. The target motion velocities of the clinical images were calculated for the respiratory cycle of 4 s

Fig. 6 . Sagittal images of ITVvt and conv ITV on the 4DCT images of the 50% phase for various BTs and cycles.

449 The blue area represents CTV, the red line represents ITVvt, and the green line represents conv ITV. In the phantom

450 images, the pink line represents the gold marker

451 Fig. 7 . Volume differences between CTV and ITVvt at the 50% phase in the phantom images with respect to

452 cycles for various BTs

453 Fig. 8 . Volume differences between CTV and ITVvt at the 50% phase in the clinical images with respect to cycles

454 for various BTs

455 Fig. 9 . Volume differences between ITVvt and conv ITV with respect to cycles for various BTs: (a) in the phantom

456 images for different PtoP amplitudes and (b) in the clinical images

457 Table 1 Patient characteristics

458 Table 2 Phase within the gating window corresponding to cycle and BT

459 Table 3 Maximum velocities in 3 dimensions and corresponding phases in the phantom images

460 Table 4 Maximum velocities in 3 dimensions and corresponding phases in the clinical images