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Cine CT without a respiratory surrogate in planning of stereotactic radiotherapy for non-small cell lung cancer

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Abstract

Purpose—To determine whether cine computed tomography (CT) can serve as an alternative to four-dimensional (4D)-CT by providing tumor motion information and producing equivalent target volumes when contoured upon for radiation treatment planning without a respiratory surrogate.

Methods and Materials—Cine CT images from a commercial CT scanner were used to form maximum intensity projection (MIP) and respiratory-averaged CT (RACT) image sets. These image sets then were used together to define targets for radiotherapy. Phantoms oscillating under irregular motion were used to assess differences between contouring on cine CT and 4D-CT. We also retrospectively reviewed image sets for 27 patients at our institution who received stereotactic radiotherapy for stage I non-small cell lung cancer. Patients were included if tumor motion was greater than 1 cm. Lesions were first contoured using MIP and RACT image sets processed from cine CT, then with 4D-CT MIP and 10-phase image sets. Mean ratios of volume magnitude were compared with intraobserver variation, mean centroid shifts were calculated, and volume overlap was assessed with the normalized Dice similarity coefficient index.

Results—The phantom studies demonstrated that cine CT captured a greater extent of irregular tumor motion than 4D-CT, producing a larger tumor volume. The patient studies demonstrated that gross tumor defined on cine imaging was similar to or slightly larger than that defined on 4D-CT.

Conclusions—Cine CT is a promising alternative to 4D-CT for stereotactic radiation treatment planning.

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Conflict of Interest Notification

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Keywords

4D-CT; cine CT; contouring

II. INTRODUCTION

Respiratory motion remains a large source of uncertainty in planning radiotherapy for non-small cell lung cancer (NSCLC) and standard helical computed tomography (CT) can induce artifacts when imaging thoracic lesions under the influence of respiratory motion [1]. Managing respiratory motion, however, can be a complicated and expensive endeavor [2, 3]. AAPM Task Group 76 [2] provides several alternatives for “motion encompassing” methods of CT scanning, including breath-hold CT (which often differs from the natural inspiration and expiration of normal breathing [4]) and slow-CT scanning [5] (which produces reconstruction artifact [6]).

Four-dimensional CT (4D-CT) overcomes these issues by collecting multiple images at a single couch position, thereby capturing different phases of the respiratory cycle [7–10]. Normally, ten 3-D image sets representing 10 phases in the respiratory cycle are formed. Several studies have shown that 4D-CT is useful in implementing 4-D treatment planning [11–14]. Recently, 4D-CT was demonstrated to be effective in target definition for stereotactic radiotherapy (SRT) for NSCLC [14, 15], and 4D-CT is currently used at our institution for this purpose.

Though 4D-CT is useful, implementation may be costly for some clinics. Setup cost for GE 4D-CT includes a respiratory surrogate, commercial software, and proprietary workstation, in addition to the scanner itself. The cost of this additional hardware and software can be as high as the cost of a CT scanner without 4D-CT.

In this paper, we investigate the potential of making 4D-CT-caliber imaging more accessible by offering an alternative approach to obtaining tumor motion information that does not use 4D-CT and yet accomplishes most of the functions of 4D-CT imaging. We propose the use of maximum intensity projection (MIP) and respiratory-averaged CT (RACT) images directly obtained from cine CT data, the *unsorted* images from which 4D-CT phase images are selected [16, 17], together for radiation treatment planning. Our approach does not rely on any respiratory surrogate measurement device and thus would be applicable to all clinics with a GE LightSpeed multi-slice CT (MSCT) scanner (GE Health Care, Waukesha, WI). Because cine CT is a standard feature on all GE LightSpeed MSCT scanners and approximately several thousand of these scanners are available in clinics around the world, our approach, if validated, could potentially be implemented on a widespread basis with dedicated additional software and no additional hardware. Previously, we qualitatively explored the use of MIP and RACT together for contouring small lesions [17]. The purpose of the current study was to quantitatively compare contour delineation using standard 4D-CT imaging (including MIP) versus our proposed cine CT method (contouring with cine MIP and cine RACT together), and demonstrate their potential equivalence for a population of NSCLC patients who received SRT.

This task was undertaken in two steps: First, phantom scans were used to explore the differences between cine CT and 4D-CT imaging. Second, stage I NSCLC lesions in patients who received SRT were contoured on cine CT and 4D-CT image sets to determine if the resulting target volumes were equivalent.

III. METHODS AND MATERIALS

III.1. Cine acquisition and image processing

Acquisition of 4D-CT images by GE scanners operating in cine mode has been described previously [7, 10]. Briefly, cine mode scanning utilizes a stationary couch while the x-ray beam is on. The gantry goes through multiple revolutions at each couch position for the duration of 1 breath cycle plus 1 second, continuously collecting projections of the subject. The stream of data is retrospectively reconstructed into 20 to 50 images at each couch position called “cine CT” images.

To create 4D-CT images, the cine CT images are correlated with the patient’s respiratory cycle, which is indicated by the trace of a respiratory surrogate, such as a spirometer [8], an abdominal pressure belt [18], or an external fiducial marker tracking system, such as the RPM system (Varian, Palo Alto, CA), which was used in this study. Ten images are selected to represent the 10 phases of the respiratory waveform at each couch position. This process, called “phase binning,” culminates in 10 3-D image sets that represent 10 specific phases of the respiratory cycle, which are collectively referred to as the 4D-CT image set.

The maximum intensity projection (MIP) of a 4D-CT image set finds the largest CT value across the 10 phases of the respiratory cycle for every voxel and displays it in a single 3-D image set [7]. Simply stated, if a lung tumor is present at a certain location in any of the 10 phases, it will show up in the MIP. Studies have demonstrated the similarity of volumes contoured on 4D-CT MIP and 4D-CT phase images [19, 20].

The same process can be used to form a MIP from cine CT except *all* the cine images at each slice location are used, not only images that have been sorted into the 10 phases. Thus, cine MIP is produced from many more images (between 20 and 50) than 4D-CT MIP (10 images, one per phase). As in 4D-CT, if the tumor is present in any of these images, it will appear on the MIP.

Gross tumor contouring on the MIP essentially includes delineation of the tumor’s physiological motion during respiration. This new gross tumor volume, which we call the internal gross tumor volume (IGTV), includes *patient-specific* motion information derived from CT imaging. In this manuscript, the source of an image set or target volume will be denoted in a subscript after the volume or image set name, such as MIP_{4D-CT} to denote MIP processed from 4D-CT, or $IGTV_{cine}$ to denote IGTV contoured on cine CT image sets.

One drawback of contouring on the MIP is that surrounding structures can “overwrite” the CT value recorded by a moving tumor. For example, the motion paths of the liver and a tumor in the lower lobe of the lung may overlap, and since the tumor and liver are of similar density, there is a loss of contrast between them in the resulting images. This problem has

been noted by several authors, who recommend caution when using MIP in these circumstances [19–21].

Respiratory-averaged CT (RACT) was originally intended for attenuation correction of positron emission tomography (PET) in thoracic PET/CT imaging [4, 16, 22]. In 4D-CT, RACT is a temporal arithmetic average of the 10 phase image sets at each slice location, which results in a blurred appearance. In the case of a solitary lung lesion, CT numbers are roughly proportional to the amount of time the voxel is occupied by tumor [23]. Once again, the same process can be applied to cine CT, except using all the cine images at a slice location. This technique has been successfully applied to attenuation correction CT for cardiac PET/CT [16]. A diagram comparing RACT_{4D-CT} and RACT_{cine} generation is shown in Figure 1.

Cover *et al.* used RACT_{4D-CT} to assess tumor motion [23]. We recently investigated the use of RACT_{cine} to provide contrast in situations where motion extent on the MIP is obscured by surrounding tissue and had promising qualitative results [17]. In the current study, we will show quantitatively that using MIP_{cine} and RACT_{cine} together provides sufficient data for radiotherapy target definition even in cases where the lesion is adjacent to tissue of equal or greater density.

III.2. Phantom study

The objective of the phantom study was to show that MIP_{cine} captured the full extent of irregular motion more precisely than MIP_{4D-CT} (i.e. show that volumes segmented on MIP_{4D-CT} are smaller than those from MIP_{cine}).

We scanned a NEMA IEC 2001 phantom (Data Spectrum, Chapel Hill, NC) that contained 6 water-filled spheres using a GE Discovery ST PET/CT scanner, the CT portion of which is a LightSpeed 8-slice scanner. The phantom was placed on a platform driven by a single-axis stepper motor (Velmex Inc., Bloomfield, NY) for one-dimensional motion. The irregular motion (previously described in [24]) was nearly sinusoidal with amplitude and frequency respectively varying from 0.7 to 1.10 cm and 15 to 20 cycles per minute. Ten cine scans were acquired with the following cine scan protocol: 120 kV, 50 mA, 2.5 mm slice thickness, gantry rotation of 0.5 s, cine interval of 0.2 s, cine duration of 7.5 s (twice the average breathing cycle of the irregular pattern plus one gantry rotation). MIP_{cine} and MIP_{4D-CT} were reconstructed.

A threshold of -700 HU was used to segment the IGTV on both MIP_{cine} and MIP_{4D-CT}. Volume measurements were taken for each of the 6 spheres on the 10 scans, and means of the IGTVs on MIP_{4D-CT} and MIP_{cine} were compared for statistically significant differences using a paired *t*-test.

III.3. Tumor contouring on patient image sets

We retrospectively reviewed the patient database in radiation oncology at our institution to identify patients with stage I NSCLC who received 4D-CT simulation, had been treated with SRT, and who had tumor motion greater than 1 cm. Between January of 2005 and April of 2007, 26 patients (27 tumors) fit our criteria. The study protocol was DR07-0809, approved

by the institutional review board. We determined the extent of tumor motion by visually assessing the displacement between extreme phases of the 4DCT (usually 0% and 50%). Motion extent greater than 1 cm was included because this feature represents the “worst case” scenario for motion artifact and, if successful, the method demonstrated in this study could easily be applied to scenarios where motion is less severe.

Patients were divided into two groups: 12 patients were in the “high contrast” group (13 tumors), with lesions in the midst of the lung parenchyma, and 14 were in the “low contrast” group, with lesions adjacent to structures of equal or higher density. Patients were separated in this fashion to reflect the concerns of previous studies that the MIP will not have enough contrast to determine the tumor edges when the target is adjacent to dense structures [19, 20].

Each patient had one cine CT scan during which the patient’s respiratory signal was acquired. Two sets of images were reconstructed: 4D-CT images including 10 phase images, MIP_{4D-CT} and RAC_{4D-CT} derived from the 10 phase images and produced by the GE Advantage 4D-CT software, and MIP_{cine} and RAC_{cine} directly from the raw cine CT images on a PC by our software [17]. All cine scans were performed at 120 kV and 100 mA, with the exception of two patients, whose scans were performed at 150 mA and 80 mA. Gantry rotation was set to 0.5 s.

First, to investigate patient contouring while minimizing the influence of a human observer, IGTV was auto-segmented on MIP_{cine} and MIP_{4D-CT} for 11 high-contrast lesions that were conducive to auto-segmentation (i.e. not adjacent to dense structures) and compared with a paired *t*-test.

One radiation oncologist (JYC) well-versed in thoracic SRT then contoured the tumors in all patients using Pinnacle³ version 7.6 treatment planning software (Philips Medical Systems, Madison, WI). The radiation oncologist first contoured the $IGTV_{cine}$ in all patients from high- and low-contrast tumor groups using MIP_{cine} and RAC_{cine} concurrently. Then, the radiation oncologist contoured the $IGTV_{4D-CT}$ according to the current clinical protocol at our institution: the MIP_{4D-CT} was first used to outline an IGTV and this volume was then adjusted based on the 4D-CT 10-phase images. Note that contours were not delineated on individual phase images because our clinical protocol utilizes the MIP and phase data together to form a contour. All delineation was performed using the “lung” window/level in the treatment planning software.

III.4. Analysis

$IGTV_{4D-CT}$ and $IGTV_{cine}$ volume magnitudes were compared statistically by taking the ratio of the volume magnitudes, determining the mean, and constructing 95% confidence intervals. Lesions of 3 patients per group were re-contoured on 4D-CT phase imaging by JYC at least 2 months after initial contouring. Resulting volumes were compared with initial 4D-CT results and the average percent differences represented the intraobserver variation for each group. Confidence intervals were compared with measured intraobserver variation. Centroid shift between $IGTV_{4D-CT}$ and $IGTV_{cine}$ was compared statistically using a log-normal distribution. 95% confidence intervals were constructed around the mean centroid

shift (geometric mean was used with the logarithmic transformation) to assess the variability of centroid shift.

Overlap between the two volumes was assessed with the Dice Similarity Coefficient index (DSC), which is a measure of the degree of overlap between two areas or volumes [25, 26]. For A (a “reference” volume) and B (a delineated volume) to be compared to the reference,

$$DSC(A, B) = \frac{2 \times |A \cap B|}{|A| + |B|} \quad (1)$$

The DSC is similar to the concordance index in that it is very sensitive to small changes in volume when the volumes being compared are small. However, the DSC is normalized to the sum of the two volumes rather than the union [27], and as with any manual segmentation, some uncertainty exists in the tumor delineation. The *normalized* DSC (NDSC) takes both these issues into account by dividing the DSC in equation 1 by an “uncertainty index,” which was defined as the DSC of the reference volume with the reference volume contracted by 1 mm (A_{-1}), or the width of one CT pixel in the transverse plane using a 50 cm field-of-view and 512 by 512 image matrix. The NDSC, therefore, was given by

$$NDSC(A, B) = \frac{DSC(A, B)}{UI(A)} = \frac{\frac{2 \times |A \cap B|}{|A| + |B|}}{\frac{2 \times |A \cap A_{-1}|}{|A| + |A_{-1}|}} \quad (2)$$

If the NDSC was greater than 1, the DSC of the experimental volumes would be greater than the uncertainty index, implying that the volumes agreed to less than 1 mm uncertainty. In this study, the reference volume was IGTV_{4D-CT} and the comparison volume was IGTV_{cine}.

IV. RESULTS

IV.1. Phantom study

Volumes drawn on 10 MIP_{cine} and MIP_{4D-CT} image sets at a -700 HU threshold were compared with a paired t -test. The mean volume magnitudes of the MIP_{cine} volumes were significantly larger than the mean MIP_{4D-CT} volumes for all 6 spheres in the phantom (Table 1). By examining the images, it was determined that most differences occurred in the most superior and inferior slices of the motion path and were not caused by in-slice motion artifact, which implies that the larger volume on MIP_{cine} better captured the full extent of motion through better sampling of the irregular motion.

IV.2. Tumor contouring on patient image sets

For the auto-segmented volumes of 11 high-contrast lesions, the IGTV_{cine} was significantly larger than IGTV_{4D-CT} ($p=0.02$), analogous to the phantom results.

Volume measurements and ratios of manually segmented IGTV_{cine} and IGTV_{4D-CT} for the 27 lesions are shown in Table 2. Paired t -tests found no significant difference between the

mean $IGTV_{\text{cine}}$ and $IGTV_{4D-CT}$ volumes in patients with high-contrast tumors ($p=0.32$) or patients with low-contrast tumors ($p=0.29$). The mean volume ratios of groups 1 and 2 were 1.05 and 0.97 respectively, with 95% confidence intervals of (0.96, 1.13) and (0.90, 1.05) respectively. Intraobserver variation was 8.8% in patients with high-contrast tumors and 10.9% in patients with low-contrast tumors. The 95% confidence intervals indicate the contouring variation in the low-contrast group was within the measured intraobserver variation ($p < 0.05$) [28]. This was not the case for the high-contrast group: The distribution was shifted slightly higher, implying $IGTV_{\text{cine}}$ was slightly larger than $IGTV_{4D-CT}$ (Figure 2).

Mean centroid shift was 0.9 mm and 1.4 mm for the high- and low-contrast groups respectively. The upper 95% confidence interval was 1.5 mm for high-contrast lesions and 2.0 mm for low-contrast lesions, indicating that cine CT produces volumes positioned similarly to those drawn on 4D-CT, even for cases where the tumor is adjacent to surrounding tissue.

The results of the DSC analyses are shown in Table 2. DSCs for both the high- and low-contrast groups were well over 0.7, which is considered good overlap [26, 29]. The mean NDSC values were 0.99 for patients with high-contrast tumors and 0.97 for those with low-contrast tumors, which implies that the volumes were slightly below the threshold for agreement within 1 mm uncertainty.

Images from 2 patients with low-contrast tumors are shown in figures 3 and 4. In Figure 3, the edges of the tumor that border the lung are clearly defined on the MIP, but the edges adjacent to higher density tissue are difficult to discern. By applying the RACT, however, the edges become much more apparent; the degraded density of the RACT provides contrast to define these borders. In Figure 4, the liver obscures the lesion on the MIP, but the RACT reveals the transverse extent of the tumor.

V. DISCUSSION

Our results indicate that it is possible to reconstruct MIP and RACT directly from cine CT images obtained from GE LightSpeed MSCT scanners already in use and the contours drawn with these images sets for target volumes in SRT are similar to those drawn by full 10-phase 4D-CT image sets.

One advantage that derives from our findings is the potential that cine CT can be used for treatment planning without many additional costs of 4D-CT. Cine CT is easy to implement when using the GE LightSpeed MSCT scanner because it is a currently available standard scanning mode for that unit. Other manufacturers use a low-pitch helical acquisition mode for 4D-CT acquisition, which requires a respiratory trace to reconstruct images [9, 30]. In theory, low-pitch helical data could be subjected to a sort of “cine type” processing; however, data that are not included in 4D-CT reconstruction cannot be accessed easily after reconstruction is completed. In the future, it may be possible to implement a similar reconstruction process to low-pitch helical data, but no such method has been developed yet.

Cine CT scans were also attempted on the CT scanners of other manufacturers [8, 31], but the ability to scan a large area seems to be limited by protocol setup.

Bradley *et al.* [21] compared volumes contoured on helical CT, MIP_{4D-CT} and RACT_{4D-CT} images to determine which was largest and thus would presumably be less prone to geometric miss. They found that contours based on MIP_{4D-CT} were significantly larger than those based on the other image types. A recent study by Cai *et al.* [32] used dynamic MRI to show that MIP_{4D-CT} underestimates the true extent of tumor motion for lesions moving irregularly and that the underestimation is proportional to the variability of the respiratory pattern. The authors identified limited temporal resolution and “incomplete sampling strategy” as causes for the underestimation. Processing the MIP from cine CT improves the limited sampling of the MIP_{4D-CT} image set because it includes the complete set of cine images at each couch position, not just a 10-phase subset.

When 4D-CT is formed by phase binning and more than one breathing cycle of a naturally varying respiratory waveform is imaged, it is possible that the end inspiration (0%) and end expiration (50%) phases will not include the images which represent the largest motion extent of a tumor. Including more samples in the MIP process will increase the chances that the largest motion extent is imaged. This effect is demonstrated diagrammatically in figure 5, and most likely explains the results of the phantom and patient auto-segmentation studies, where IGTV_{cine} was significantly larger than IGTV_{4D-CT}.

Sampling can be further improved by increasing the cine duration. We previously found that 90% of patients have average breathing cycle periods of less than 6 s [16]; thus, we recommended that cine durations of 6 s be chosen for cine CT acquisition [33]. Increasing the cine duration beyond one average breathing cycle, however, will provide better sampling of the varying respiratory waveform and therefore a more encompassing MIP_{cine} image set.

One limitation of our method is that processing directly from cine CT will include rare respiratory irregularities such as coughing in the image sets. This is undesirable because such aberrations represent relatively unique events and should not be included in treatment planning. It may be possible, however, to isolate this effect by manually removing images affected by such an event [17].

In the manual segmentation study, cine-CT-based radiation treatment planning performed as well as 4D-CT. The results of our study show that including RACT_{cine} in the delineation process with MIP_{cine} is sufficient in producing IGTVs similar (within intraobserver variability) to those formed with full 4D-CT for lesions adjacent to tissue of equal or greater density. Several authors have cautioned against using MIP in these cases [19–21], and one group has recommended that RACT not be used for contouring because the edges of the tumor are blurred by motion [21]. Figures 3 and 4, though, clearly show the benefit of using MIP and RACT together in these instances.

It is of interest that IGTV_{4D-CT} and IGTV_{cine} were not equivalent in the high-contrast group of tumors, where the lesions were *not* adjacent to dense structures. Mean IGTV_{cine} was larger, though not significantly, than IGTV_{4D-CT}. This result can most likely be attributed to two factors: First, the average volume of high-contrast tumors was approximately two-thirds

the average volume of low-contrast tumors, so an identical volume difference between $IGTV_{cine}$ and $IGTV_{4D-CT}$ in both groups would be a larger *percentage* difference in the first group than in the second, which would affect the volume ratio. Second, as described before, MIP_{cine} uses the entire set of cine CT images for processing (between 20 – 50 images per slice location), which is a much larger sample than MIP_{4D-CT} processing (10 images per slice location). The slightly larger $IGTV_{cine}$ in the manually-contoured high-contrast tumors is consistent with the results of the patient and phantom auto-segmentation studies.

This effect was apparent in the case of patient 1, whose volume ratio was the second largest of all 27 patients. Figure 6 displays the MIP_{4D-CT} and MIP_{cine} images for patient 1, highlighting the region of increased density at the inferior region of the tumor in the MIP_{cine} which is not present in the MIP_{4D-CT} .

Though cine- and 4D-CT-defined tumor contours for treatment planning showed good agreement on the whole, individual cases still demonstrated the pitfalls of using MIP for contouring. Three patients with the lowest NDSC values (patients 18, 22, 26) all had lesions near the diaphragm where it was difficult to determine inferior extent because of overlap with the liver, even with RACT. We have developed a method to improve MIP_{cine} by removing cine CT images from the MIP process that cause this overlap, potentially eliminating the problem altogether, but this method has not yet been validated.

V.1. Application to larger tumors

We believe that the use of cine CT in treatment planning will be limited in larger tumors and later-stage lung cancer because of more complicated involvement with surrounding tissue. Incorporating positron emission tomography (PET) into the cine CT treatment planning process may provide additional contrast for target definition in these cases. Several studies have analyzed the impact of including PET data in GTV delineation for NSCLC and have yielded noteworthy results, mostly due to the inclusion of lymph nodes and exclusion of atelectasis [34–36]. Those studies suggest that metabolic information from PET helps physicians discriminate between normal and malignant tissue that is indistinguishable on CT alone, which can sometimes occur when using MIP.

V.2. Dose Calculation

Treatment planning with cine CT also requires an appropriate image set for dose calculation. Currently, $RACT_{4D-CT}$ is used to calculate dose in thoracic treatment plans at our institution because it more accurately represents structures in motion over one fraction of radiation therapy than helical CT. A validation of this technique compared with 4D dose calculation was recently published by Admiraal *et al* [37]. The intuitive replacement for $RACT_{4D-CT}$ in cine-based radiation treatment planning is $RACT_{cine}$. Since $RACT_{cine}$ is formed by averaging *all* the images in the cine acquisition, however, different parts of the respiratory cycle could be under- or overemphasized in patients if the cine acquisition was one and a half respiratory cycles [33]. This under- or overemphasis could cause fluctuations in calculated dose distributions.

In addition to better sampling a varying respiratory cycle, increasing the cine duration will produce better averaging in the RAC_{cine} which could alleviate bias toward the inhalation or exhalation phase for dose calculation purposes [16]. We believe that increasing the cine duration to 2 breathing cycles will provide a stable RAC_{cine} data set for dose calculation. We are currently investigating this hypothesis. If additional dose due to lengthening the cine duration is a concern, our experience has shown that good quality MIP and RACT images could still be produced from tube currents at 40 mA [17] and 0.5 s gantry rotation.

VI. CONCLUSIONS

Though it represents great step forward in accounting for tumor motion in CT simulation, 4D-CT is complex and is costly for many cancer centers. This study has presented an alternative to 4D-CT for treatment planning that does not require additional hardware or commercial software beyond that already available on scanners already in use. Processing MIP and RACT directly from the cine CT images and using these images sets together to define targets for SRT produces volumes that are similar to those drawn by full 10-phase 4D-CT.

We recommend that treatment centers without access to 4D-CT consider using cine CT in addition to helical CT to incorporate motion of small mobile lung lesions into CT simulation of NSCLC. For centers with 4D-CT facilities, we encourage use of the MIP_{cine} image set over the MIP_{4D-CT} image set, which has been shown to underestimate the extent of tumor motion. Because MIP_{cine} can be produced from the same raw data as 4D-CT, supplemental information could be gathered without placing patients at any additional risk.

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REFERENCES

1. Chen GT, Kung JH, Beaudette KP. Artifacts in computed tomography scanning of moving objects. *Semin Radiat Oncol*. 2004; 14:19–26. [PubMed: 14752730]
2. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. *Med Phys*. 2006; 33:3874–3900. [PubMed: 17089851]
3. Langen KM, Jones DT. Organ motion and its management. *Int J Radiat Oncol Biol Phys*. 2001; 50:265–278. [PubMed: 11316572]
4. Pan T, Mawlawi O, Nehmeh SA, et al. Attenuation correction of PET images with respiration-averaged CT images in PET/CT. *J Nucl Med*. 2005; 46:1481–1487. [PubMed: 16157531]
5. Lagerwaard FJ, Van Sornsen de Koste JR, Nijssen-Visser MR, et al. Multiple "slow" CT scans for incorporating lung tumor mobility in radiotherapy planning. *Int J Radiat Oncol Biol Phys*. 2001; 51:932–937. [PubMed: 11704313]
6. Bacharach SL. PET/CT attenuation correction: breathing lessons. *J Nucl Med*. 2007; 48:677–679. [PubMed: 17475952]
7. Pan T, Lee TY, Rietzel E, et al. 4D-CT imaging of a volume influenced by respiratory motion on multi-slice CT. *Med Phys*. 2004; 31:333–340. [PubMed: 15000619]
8. Low DA, Nystrom M, Kalinin E, et al. A method for the reconstruction of four-dimensional synchronized CT scans acquired during free breathing. *Med Phys*. 2003; 30:1254–1263. [PubMed: 12852551]

9. Keall PJ, Starkschall G, Shukla H, et al. Acquiring 4D thoracic CT scans using a multislice helical method. *Phys Med Biol*. 2004; 49:2053–2067. [PubMed: 15214541]
10. Rietzel E, Pan T, Chen GT. Four-dimensional computed tomography: image formation and clinical protocol. *Med Phys*. 2005; 32:874–889. [PubMed: 15895570]
11. D'Souza WD, Nazareth DP, Zhang B, et al. The use of gated and 4D CT imaging in planning for stereotactic body radiation therapy. *Med Dosim*. 2007; 32:92–101. [PubMed: 17472888]
12. Alasti H, Cho YB, Vandermeer AD, et al. A novel four-dimensional radiotherapy method for lung cancer: imaging, treatment planning and delivery. *Phys Med Biol*. 2006; 51:3251–3267. [PubMed: 16757875]
13. Rietzel E, Liu AK, Doppke KP, et al. Design of 4D treatment planning target volumes. *Int J Radiat Oncol Biol Phys*. 2006; 66:287–295. [PubMed: 16904528]
14. Underberg RW, Lagerwaard FJ, Cuijpers JP, et al. Four-dimensional CT scans for treatment planning in stereotactic radiotherapy for stage I lung cancer. *Int J Radiat Oncol Biol Phys*. 2004; 60:1283–1290. [PubMed: 15519801]
15. Guckenberger M, Wilbert J, Meyer J, et al. Is a single respiratory correlated 4DCT study sufficient for evaluation of breathing motion? *Int J Radiat Oncol Biol Phys*. 2007; 67:1352–1359. [PubMed: 17394941]
16. Pan T, Mawlawi O, Luo D, et al. Attenuation correction of PET cardiac data with low-dose average CT in PET/CT. *Med Phys*. 2006; 33:3931–3938. [PubMed: 17089855]
17. Pan T, Sun X, Luo D. Improvement of the cine-CT based 4D-CT imaging. *Med Phys*. 2007; 34:4499–4503. [PubMed: 18072515]
18. Wink N, Panknin C, Solberg TD. Phase versus amplitude sorting of 4D-CT data. *J Appl Clin Med Phys*. 2006; 7:77–85. [PubMed: 16518319]
19. Underberg RW, Lagerwaard FJ, Slotman BJ, et al. Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer. *Int J Radiat Oncol Biol Phys*. 2005; 63:253–260. [PubMed: 16111596]
20. Rietzel E, Chen GT, Choi NC, et al. Four-dimensional image-based treatment planning: Target volume segmentation and dose calculation in the presence of respiratory motion. *Int J Radiat Oncol Biol Phys*. 2005; 61:1535–1550. [PubMed: 15817360]
21. Bradley JD, Nofal AN, El Naqa IM, et al. Comparison of helical, maximum intensity projection (MIP), and averaged intensity (AI) 4D CT imaging for stereotactic body radiation therapy (SBRT) planning in lung cancer. *Radiother Oncol*. 2006; 81:264–268. [PubMed: 17113668]
22. Gould KL, Pan T, Loghin C, et al. Frequent diagnostic errors in cardiac PET/CT due to misregistration of CT attenuation and emission PET images: a definitive analysis of causes, consequences, and corrections. *J Nucl Med*. 2007; 48:1112–1121. [PubMed: 17574974]
23. Cover KS, Lagerwaard FJ, Senan S. Color intensity projections: a rapid approach for evaluating four-dimensional CT scans in treatment planning. *Int J Radiat Oncol Biol Phys*. 2006; 64:954–961. [PubMed: 16458780]
24. Starkschall G, Desai N, Balter P, et al. Quantitative assessment of four-dimensional computed tomography image acquisition quality. *J Appl Clin Med Phys*. 2007; 8:2362. [PubMed: 17712299]
25. Dice LR. Measures of the amount of ecologic association between species. *Ecology*. 1945; 26:297–302.
26. Zou KH, Warfield SK, Bharatha A, et al. Statistical validation of image segmentation quality based on a spatial overlap index. *Acad Radiol*. 2004; 11:178–189. [PubMed: 14974593]
27. Giraud P, Elles S, Helfre S, et al. Conformal radiotherapy for lung cancer: different delineation of the gross tumor volume (GTV) by radiologists and radiation oncologists. *Radiother Oncol*. 2002; 62:27–36. [PubMed: 11830310]
28. Feng S, Liang Q, Kinser RD, et al. Testing equivalence between two laboratories or two methods using paired-sample analysis and interval hypothesis testing. *Anal Bioanal Chem*. 2006; 385:975–981. [PubMed: 16791581]
29. Bartko JJ. Measurement and reliability: statistical thinking considerations. *Schizophr Bull*. 1991; 17:483–489. [PubMed: 1947873]
30. Pan T. Comparison of helical and cine acquisitions for 4D-CT imaging with multislice CT. *Med Phys*. 2005; 32:627–634. [PubMed: 15789609]

31. McClelland JR, Blackall JM, Tarte S, et al. A continuous 4D motion model from multiple respiratory cycles for use in lung radiotherapy. *Med Phys.* 2006; 33:3348–3358. [PubMed: 17022231]
32. Cai J, Read PW, Baisden JM, et al. Estimation of error in maximal intensity projection-based internal target volume of lung tumors: a simulation and comparison study using dynamic magnetic resonance imaging. *Int J Radiat Oncol Biol Phys.* 2007; 69:895–902. [PubMed: 17889270]
33. Chi PC, Mawlawi O, Nehmeh SA, et al. Design of respiration averaged CT for attenuation correction of the PET data from PET/CT. *Med Phys.* 2007; 34:2039–2047. [PubMed: 17654907]
34. van Baardwijk A, Baumert BG, Bosmans G, et al. The current status of FDG-PET in tumour volume definition in radiotherapy treatment planning. *Cancer Treat Rev.* 2006; 32:245–260. [PubMed: 16563636]
35. Nestle U, Walter K, Schmidt S, et al. 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: high impact in patients with atelectasis. *Int J Radiat Oncol Biol Phys.* 1999; 44:593–597. [PubMed: 10348289]
36. Bradley J, Thorstad WL, Mutic S, et al. Impact of FDG-PET on radiation therapy volume delineation in non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2004; 59:78–86. [PubMed: 15093902]
37. Admiraal MA, Schuring D, Hurkmans CW. Dose calculations accounting for breathing motion in stereotactic lung radiotherapy based on 4D-CT and the internal target volume. *Radiother Oncol.* 2007

Figure 1.

Comparison of respiration-averaged (RA)CT creation process from 4D-CT and cine CT. Cine CT images are acquired on a multi-slice scanner (in this case, 8 slices) at certain intervals during the respiratory cycle. Images are correlated with a respiratory waveform to create 4D-CT. RACT can be formed by either averaging the 10-phase 4DCT images or averaging the cine images directly without waveform correlation. Maximum intensity projection is processed in the same way. (EE = end expiration, EI = end inspiration., $RACT_{cine}$ = RACT processed from cine CT, $RACT_{4D-CT}$ = RACT processed from 4D-CT)

Figure 2.

Mean ratios of volume magnitudes for the high-contrast lesions (top) and low contrast-lesions (bottom). 90% confidence intervals are shown in gray. Intraobserver variation measured from 3 patients re-contoured in each group is shown in black, centered at 1. The 90% confidence intervals lie entirely within the intraobserver variation for the low-contrast lesions, but the mean and confidence limits are higher for the high-contrast lesions, slightly outside the intraobserver variation interval. CI = confidence interval.

Figure 3.

Sagittal slices showing (left) cine maximum intensity projection and (right) cine respiratory-averaged CT. The lesion near the chest wall is easy to delineate with MIP along the lung, but the similar CT numbers in the chest wall reduce contrast. The blurred RACT restores this contrast and facilitates contouring along the chest wall.

Figure 4.

Transverse slices showing (left) cine maximum intensity projection and (right) cine respiratory-averaged CT. The lesion near the diaphragm is difficult to distinguish on the MIP alone, but the RACT does a better job providing contrast.

Figure 5.

Observed motion extent in 4D-CT (top) and MIP processed from cine CT (bottom). When the cine CT images are correlated with the respiratory waveform and images representing the 10 phases are selected, the 0% and 50% phases do not represent the largest motion extent of the tumor at this couch position because the lower amplitude images happen to match the phase more closely. Note that the image selected for 90% is at a larger amplitude than the 0% image, which will most likely cause an artifact in the 90% image set. Even with the 90% image, a MIP generated from this 4D-CT image set will still underestimate the extent of tumor motion. MIP generated from cine CT, however (shown below) includes all images along the respiratory waveform and therefore captures the extent of motion correctly.

Figure 6. (top row) 4D-CT maximum intensity projections, transverse, sagittal, coronal slices, (bottom row) cine maximum intensity projections, transverse, sagittal, coronal slices. Red contours are manually segmented IGTV_{cine} and green contours are manually segmented IGTV_{4D-CT}. The red contours are larger because MIP_{cine} captures more of the irregular respiratory motion, producing higher density regions near the inferior part of the tumor.

Table 1

Significance values for phantom study

Sphere Diameter [cm]	MIP4D-CT		MIPcine		P value
	Mean Volume [cm ³]	Standard Deviation [cm ³]	Mean Volume [cm ³]	Standard Deviation [cm ³]	
3.7	49.8	0.8	51.0	1.1	<0.01
2.8	24.9	0.5	25.7	0.8	<0.01
2.2	13.7	0.3	14.1	0.4	0.02
1.7	7.9	0.2	8.2	0.3	<0.01
1.3	4.4	0.2	4.6	0.2	0.04
1.0	2.5	0.1	2.7	0.1	0.01

Abbreviations: MIP4D-CT = Maximum intensity projection reconstructed from four-dimensional computed tomography; MIP_{cine} = Maximum intensity projection reconstructed directly from cine CT

Table 2

Internal gross tumor volume measurements

Patient #	High-contrast Patients				Patient #	Low-contrast Patients			
	IGTV _{cine} [cm ³]	IGTV _{4D-CT} [cm ³]	Ratio	DSC		IGTV _{cine} [cm ³]	IGTV _{4D-CT} [cm ³]	Ratio	DSC
1	12.6	9.8	1.28	0.83	14	5.0	5.8	0.86	0.99
2	11.0	12.6	0.87	0.84	15	12.1	11.7	1.04	0.99
3	4.8	3.9	1.26	0.78	16	21.6	20.2	1.07	0.95
4	6.6	6.7	1.00	0.90	17	4.1	4.1	0.99	0.97
5	15.2	13.8	1.10	0.90	18	5.8	6.8	0.84	0.93
6	4.3	3.6	1.20	0.81	19	8.1	7.9	1.03	0.98
7	2.9	2.8	1.04	0.78	20	3.0	3.3	0.90	0.96
8	11.5	11.2	1.02	0.88	21	2.4	2.5	0.97	1.08
9*	2.0	2.1	0.94	0.75	22	22.4	27.1	0.83	0.92
10*	15.1	13.8	1.09	0.86	23	14.0	15.4	0.91	1.01
11	2.9	2.9	0.99	0.81	24	14.8	15.8	0.93	0.95
12	6.1	7.3	0.83	0.84	25	38.1	37.5	1.02	0.97
13	18.6	18.8	0.99	0.87	26	22.1	24.2	0.91	0.91
					27	8.5	6.4	1.33	0.97
Average	8.7	8.4	1.05	0.84		13.1	13.5	0.97	0.97
SD	5.5	5.4	0.14	0.05		10.1	10.5	0.13	0.04
CI95			±0.08					±0.07	
CI90			±0.07					±0.06	

Abbreviations: CI90 = 90% confidence interval. SD = standard deviation. 4D-CT = four-dimensional computed tomography. IGTV_{cine} = internal gross tumor volume based on cine imaging. IGTV_{4D-CT} = internal gross tumor volume based on 4D-CT imaging. DSC = Dice similarity coefficient index; NDSC = normalized Dice similarity coefficient index.

* Bisynchronous lesions