Published in final edited form as:

Pract Radiat Oncol. 2014 ; 4(3): 160–166. doi:10.1016/j.prro.2013.07.001.

Simplified Strategies to Determine the Mean Respiratory Position for Liver Radiotherapy Planning

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Abstract

Purpose—Establishing the time-weighted mean respiratory position in the liver is challenging due to poor tumor contrast on 4D imaging. The purpose of this study is to validate simplified strategies in determining the mean position of liver tumors for radiotherapy planning, and quantify the potential for planning target volume (PTV) reduction.

Methods—Full, ten-phase 4D CT datasets from ten liver radiotherapy patients were analyzed to compare two techniques. First, a mid-ventilation CT was chosen from the initial reconstruction of the 4D CT. This was based on the minimum displacement of the diaphragm at each phase relative to its mean respiratory position, calculated using rigid registration over all 4D CT phases. Second, the exhale 4D CT was deformed to the inhale 4D CT using biomechanical-based deformable registration. The diaphragm's mean cranio-caudal position in the respiratory cycle (normalized as a percentage relative to exhale) was applied to the exhale-to-inhale deformation map assuming a linear trajectory to reconstruct a mid-position CT. These strategies were compared to the time-weighted mean respiratory position, calculated with deformable registration over all ten 4D CT phases. PTVs incorporating respiratory motion were then compared for two planning strategies: exhale 4D CT using the internal target volume (ITV), or mid-position CT using dose-probability margins.

Results—Compared to the mean respiratory tumor position, the mid-ventilation CT and mid-position CT had mean (maximum) tumor vector errors of 1.0 ± 0.5 (2.1) mm and 0.6 ± 0.3 (1.4) mm respectively, within the image resolution. Compared to ITV-based PTV, dose-probability PTV reduced the irradiated volume by $34 \pm 7\%$ on average, up to 43%.

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Conflict of Interest Notification: K.K. Brock has financial interest in the technology reported in this manuscript through a licensing agreement with RaySearch Laboratories.

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Conclusion—Simplified strategies to select a mid-ventilation CT or reconstruct a mid-position CT for the liver were validated with respect to the mean respiratory position. These datasets require significantly smaller PTVs, potentially allowing for dose-escalated liver SBRT to improve local control.

Introduction

Stereotactic-body radiotherapy (SBRT) for liver cancer patients results in better clinical outcomes with higher doses (1, 2). SBRT doses up to 60 Gy in 6 fractions have been delivered without serious liver toxicity using individualized dose-allocation(3), however, this dose is often not achievable due to overlap of the planning target volume (PTV) with the neighboring luminal gastrointestinal structures. The volume of normal tissue irradiation, and thus dose-allocation, is governed largely by the technical details in the planning of SBRT.

On average, the liver moves 11 to 25 mm during normal respiration(4). A common way to incorporate the patient's specific breathing motion into the PTV is to create an internal target volume (ITV), a composite volume of the tumor on each phase of planning 4D CT. Unless automated intravenous contrast is synchronized with 4D CT acquisition liver tumors are not well visualized(5), requiring the use of surrogates (e.g. liver, diaphragm, etc.) to measure motion. Because the tumor spends only a fraction of time at each position of the breathing cycle, the ITV can be considered unnecessarily large. If the planning CT represents the patient's geometry in its time-averaged respiratory position, smaller dose-probability PTV margins can be used to achieve a specific clinical goal (e.g. 95% of prescribed dose is received by 90% of patients(6)). ITV-based PTV for lung radiotherapy has been shown to be 33% larger on average than dose-probability margins(7). Similar gains may be possible in the liver provided the mean position can be established, currently a challenging task.

Wolthaus *et al.* developed the mid-ventilation CT for lung radiotherapy by reconstructing a single 4D CT phase around the time-percentage closest to the tumor's time-averaged position(8). This time-percentage is derived from the tumor or diaphragm motion, itself requiring an initial 10-phase 4DCT reconstruction, or directly using the external respiratory signal from image acquisition(9). If hysteresis is present however, the mid-ventilation CT will not represent the time-averaged position accurately. A mid-position CT accounting for hysteresis can be reconstructed however by means of deformable image registration and an average 4D deformation map(10). A full 4D deformation map from nine deformable registrations is needed making this approach potentially computationally expensive.

These findings have not yet been confirmed for liver radiotherapy. Unlike the lung, liver tumors are not well visualized on 4D CT making the time-averaged position difficult to validate. The aim of this study was to evaluate simple and accurate methods to select a mid-ventilation CT, or create a mid-position CT for liver SBRT planning. The potential impact on PTV reduction was also quantified as this may facilitate substantial normal tissue sparing and dose-escalated liver SBRT.

Methods and Materials

Patient and imaging data

Data from ten patients treated on clinical trials of liver SBRT were used (Table 1). 4D CT was acquired under normal breathing, using a multi-slice scanner coupled to a respiratory signal (abdominal bellows device or infrared chest marker). Ten phases were reconstructed using phase-based sorting, with each phase representing one tenth of the breathing period. Typically, 50% represents the end-exhale and 0% the end-inhale phases. Contouring and SBRT planning was generally done on the exhale 4D CT, with tumor delineation based on fused contrast-enhanced CT or MR, both acquired under voluntary normal exhale breath-hold.

For this study, the liver was contoured on all 4D CT phases by a single observer. The GTV contour on exhale 4D CT was unaltered from the clinical plan. In three cases where the planning dataset was the contrast-enhanced breath-hold CT, the GTV contour was transferred to the non-contrast exhale 4D CT. The 4D CT was acquired immediately after the breath-hold CT and therefore did not requiring any further registration. The accuracy of liver alignment was visually inspected on the fused images, and quantified using the Dice similarity coefficient between the liver contours on the exhale 4D CT and breath-hold CT. The mean Dice coefficient was 0.96, thus differences in liver position were negligible. It was not possible to accurately contour the GTV on all 4D CT phases due to contrast wash out during image acquisition.

Deformable image registration

The exhale 4D CT was registered to the remaining 4D CT phases using Morfeus, a biomechanical model-based deformable image registration algorithm. Briefly, the primary liver contour on the exhale 4D CT is converted into a 3D surface mesh which establishes a correspondence with the secondary liver surfaces, created from liver contours on the other phases, by means of guided surface projections (HyperMorph; Altair Engineering, Troy MI). The internal liver and GTV deform according to assigned tissue biomechanics. Because this algorithm is independent of the image intensity, the accuracy of the GTV registration is independent of the contrast of the GTV in each image. The accuracy (absolute mean $\pm$ standard deviation) of Morfeus has been previously shown to be 1.2 ± 0.7 , 1.7 ± 1.4 and 1.4 ± 1.0 mm in the left-right, anterior-posterior and cranio-caudal directions respectively(11).

Strategies to estimate the mean respiratory position

The true time-weighted mean respiratory GTV position, hereafter referred to as the time-averaged position, was calculated as the average GTV position determined using deformable registration over all ten 4D CT phases. Two simplified strategies were investigated to select or reconstruct a CT that estimates the time-averaged position (concept shown in Fig. 1). The accuracy of both is reported as the GTV's center-of-mass position relative to the time-averaged position.

The first strategy selects one of the initial ten 4D CT phases (10% bins) as the mid-ventilation CT. Assuming a scenario where the 4D CT lacks GTV-contrast and deformable registration is not available to track the GTV, the cranio-caudal diaphragm motion was measured using a local rigid registration on each 4D CT (Fig. 2). The mean diaphragm position was calculated over all ten phases, and the phase with the smallest diaphragm displacement relative to the mean diaphragm position was chosen as the mid-ventilation CT. This assumes that the diaphragm and GTV motion correlate well with no phase shifts.

The second strategy reconstructs the mid-position CT using a single deformable registration between the exhale and inhale 4D CT to capture the maximum GTV motion. Each patient's cranio-caudal diaphragm motion, from above, was normalized (exhale=0, inhale=1) and the mean position was calculated to estimate the mid-position of the GTV. This assumes the diaphragm and the GTV mean position occur at the same relative position between exhale and inhale. This percentage was then applied to the linear trajectory of the exhale-to-inhale deformation map to deform the exhale 4D CT into the mid-position CT assuming no hysteresis. Both the patient-specific diaphragm position and the population diaphragm position (averaged over all ten patients) were tested. The proposed workflows are compared in Fig. 3.

PTV margin calculations

The required GTV to PTV margins were quantified for two planning strategies. The first uses the exhale position as the planning dataset while incorporating the ITV into the PTV. The second uses the mean position as the planning dataset and applies a true dose-probability PTV that does not encompass the full motion extent. The margin recipe proposed by van Herk(12) was applied to ensure 95% of the prescribed dose is received by 90% of the population. Both include the population inter- and intra-fraction liver SBRT setup errors and the deformable registration accuracy, all previously quantified to be < 2 mm individually. This results in a baseline margin of 3.7 (left-right), 4.5 (anterior-posterior) and 5.4 (cranio-caudal) mm, excluding a component for respiration. For the ITV-based PTV, this margin was *added linearly* to the maximum GTV respiratory motion. For the dose-probability PTV, the systematic errors (i.e. GTV on the mid-position CT versus the time-averaged mean) and random errors (i.e. one third the GTV amplitude(6)) for respiration were incorporated directly into the margin as shown in Table 2, with no further linear expansion. The GTV to PTV volume was compared for both strategies.

Results

Respiratory motion quantification

Accurate quantification of respiratory motion is required for both ITV-based and dose-probability PTV approaches. On average, the maximum cranio-caudal diaphragm motion calculated with rigid registration was 2.1 mm larger ($p<0.02$) than the GTV motion calculated with deformable registration (Table 3). Although the GTV and diaphragm motion correlated well ($R^2=0.77$), the diaphragm had at least 3 mm greater motion in 30% of patients (range: 4.0 to 5.5 mm). Respiration-induced deformation caused multi-focal GTVs within the liver to have differences in amplitude up to 6 mm (Fig. 4). The maximum motion

for both structures occurred between the same 4D CT phase pairs in 9 of 10 patients. One patient had a slight phase shift where the maximum motion was between 50% and 0% for the GTV and 50% and 0% for the diaphragm, however the difference in diaphragm motion between these phase pairs was only 0.7 mm.

4D GTV position versus mean position

The GTV was mapped from end-exhale to the remaining 4D CT phases using deformable registration. The GTV position at each of the 10 phases was then compared to its time-averaged position to quantify the inherent GTV error at each of the initial 4D CT phases reconstructed with 10%-bins. Using Figure 1 to illustrate, the distance between the time-averaged position (black circle) and each 4D CT phases (white circles) was calculated.

Across all patients, the mean GTV errors were smallest at the 20% (exhalation) followed by the 80% (inhalation) phases. Three patients had GTV errors greater than 2 mm on the 20% phase (range: 2.3 – 3.2 mm, all in the cranio-caudal direction). Individually however, the phase with the smallest GTV error was patient specific and was most commonly the 20% phase (5 patients), followed by the 80% phase (2 patients), then the 10%, 30% and 70% phases (1 patient each).

Mid-ventilation CT and mid-position CT accuracy

Since the 4D GTV position would not be known without deformable registration, mid-ventilation CT selection was based solely on the 4D diaphragm position. Using Figure 1 to illustrate, the phase (white box) with the diaphragm closest to the mean diaphragm position (grey box) would be selected. Ideally, this phase would also have the GTV error relative to the time-averaged GTV position (white versus black circles). Selection of the mid-ventilation CT in this manner coincided with the phase having the smallest GTV error relative to the time-averaged position in 50% of patients, and the second smallest error in the other 50%. One patient had a GTV error of 2.1 mm in the cranio-caudal direction while all others were 1.1 mm.

The mid-position CT was reconstructed by applying the patient's mean normalized diaphragm position (average: 0.43 ± 0.08 , range: 0.35 to 0.61) as a percentage to the single exhale-to-inhale deformation map. This was within 0.01 ± 0.06 (range: -0.05 to 0.13) of the normalized mean cranio-caudal position of the GTV determined using deformable-registration on all 4D phases. For the mid-position CT reconstructed with the patient's mean normalized diaphragm position, two patients had cranio-caudal GTV errors of 1.0 and 1.1 mm relative to the time-averaged position while all other errors were < 1 mm. In Figure 1, this error is the difference between the grey and black circles. Applying the population's mean normalized diaphragm position of 43% to each patient's deformation map resulted in similar average GTV errors on the mid-position CT created with the patient-specific diaphragm position ($p > 0.27$). Two patients had cranio-caudal errors of 1.4 and 1.3 mm, while all other errors were < 1 mm.

Table 4 compares the mean GTV errors relative to the time-averaged position for the various possible planning datasets.

Impact of mean position on the required PTV

Compared to planning at exhale with ITV-based PTV, planning on the mid-position CT with dose-probability PTV resulted in a GTV to PTV volume reduction (mean±standard deviation) of 34±7% up to a maximum of 43%. This translates into 66±38 cc (maximum 126 cc) of surrounding normal tissue that could be potentially spared full dose.

Discussion

To the authors' knowledge no studies have quantified the accuracy of the mid-ventilation or mid-position CT for liver radiotherapy planning. Selecting a single 4D CT phase as the mid-ventilation CT using only rigid registration to quantify diaphragm motion in a commercial treatment planning system resulted in tumor errors relative to the time-averaged position of approximately 2 mm in all patients. Reconstructing a mid-position CT using a single deformation map (exhale to inhale) resulted in tumor errors of approximately 1 mm in all patients. Liver SBRT planning on these datasets with dose-probability PTV would encompass an average of 34% less normal tissue volume inside the PTV compared to planning at exhale with ITV-based PTV.

The mid-ventilation CT was simply selected from the initial ten 4D CT datasets (10% bins), avoiding the reconstruction of an extra CT around the exact time-percentage where the tumor is closest to the mean position. The latter requires either the raw data from the scanner, or the external respiratory signal which may be prone to errors caused by phase shifts(9). The mean error on the mid-ventilation CT was small (1.0 ± 0.5 mm) and likely a combination of the 4D CT binning, and tumor hysteresis including only considering cranio-caudal motion for mid-ventilation CT selection. GTV position errors versus the time-averaged position were smallest at the 20% and 80% phases, similar to the exact time-percentages reported previously in the lung ($20.7\pm2.2\%$ for exhalation and $78.8\pm2.9\%$ for inhalation(8)). Hysteresis has been previously shown to be greater than 1 mm in only 20% of liver patients(13). Because the tumor is moving relatively fast near the mid-ventilation phase it may be prone to imaging artifacts. One patient with a mid-ventilation CT error of 2 mm had 4D sorting artifacts near the liver on the intermediate phases but not on exhale or inhale, likely contributing to this error. This patient's GTV also had 14.9 mm of motion, though no strong correlations were seen between patients' residual GTV errors and GTV amplitude (data not shown).

The mid-position CT previously proposed for lung requires deformable registration of each 4D CT phase to establish the time-averaged position(10). Because all phases are used, delineation accuracy can be improved due the averaging out of phases with artifacts and reduced image noise(10). At the authors' institution however, liver GTVs are delineated directly on the planning exhale 4D CT but are based on the fused contrast enhanced tri-phasic CT and/or MR images after performing a rigid liver-to-liver registration. In instances where substantial liver deformation is observed, the registration is focused to the region of the liver surrounding the GTV.

Although the mid-ventilation CT selection requires a smaller workload, the simplified mid-position CT reconstruction in this study uses only one deformable registration on the

extreme phases and it avoids planning on the artifact-prone intermediate phases. In the absence of intravenous contrast synchronized with 4D CT acquisition, the use of deformable registration may be advantageous for quantifying GTV motion for PTV determination because of the diaphragms' overestimation and by accounting for differences in GTV motion due to respiration-induced liver deformation (Fig 4.). The deformation map was combined with either the patient's or the population mean normalized diaphragm position resulting in mean vector errors of 0.6 ± 0.3 and 0.8 ± 0.4 mm respectively. The latter strategy is further simplified by avoiding the diaphragm motion analysis for each patient without sacrificing accuracy. Note that this study deformed only the liver for simplicity. To reconstruct the entire mid-position CT in clinical practice the liver, spleen, and external body would require contouring on the exhale and inhale 4D CT to obtain a multi-organ deformation map(11).

Validation of the mean respiratory position would ideally compare the GTV position on mid-ventilation or mid-position CT to the average of the actual GTV position identified on all 4D CT phases. This was impossible to do on the majority of patients due to the poor tumor contrast. The errors reported above are therefore relative to the GTV's time-averaged position predicted by deformable registration. Morfeus was previously shown to be accurate inside the liver to within 2 mm. For only three patients in this study additional validation was possible by identifying an anatomic landmark visible on all 4D CT phases. For two patients, residual intravenous contrast allowed the exhale GTV contour to be copied and rigidly fit to subsequent phases. In the third, residual Lipiodol from previous therapy was contoured using an auto-threshold segmentation tool on each 4D CT phase image. Comparing the true image-based time-averaged position of the landmarks' centroid to that predicted by Morfeus resulted in an average registration error of 1.0 ± 1.4 mm. Comparing the true image-based time-averaged position of the landmarks' centroid to that predicted via the mid-ventilation or mid-position CT workflows resulted in errors of 1.1 ± 0.3 and 0.8 ± 0.7 mm respectively, on the order of deformable registration accuracy and within the image resolution.

The importance of this work is supported by the increasing adoption of liver SBRT and the added commercially available cone-beam CT capability for daily 4D image-guidance to the mean position. Planning and delivery at the mean position with dose-probability based margins requires 34% less volume of normal tissue irradiation on average, compared to the commonly used ITV-based margins. These strategies may facilitate liver SBRT dose-escalation, which observed dose-response relationships suggest could improve local control.

Conclusion

Simplified methods to select or reconstruct the mid-ventilation CT and mid-position CT were validated for liver radiotherapy planning with respect to the time-weighted mean respiratory position. It was shown that establishing the mean position at planning could be presently implemented with a reasonable 2 mm accuracy using simple, clinically and widely available tools (i.e. even without deformable image registration).

Acknowledgments

The authors thank Laura Dawson for her collaboration and for providing the patient data, acquired during clinical trials supported by the National Cancer Institute of Canada grant 18207 and the Canadian Institutes for Health Research (CIHR) grant 202477. This research is supported by the U.S. National Institutes of Health, 5RO1CA124714-02. K.K. Brock is supported through a Cancer Care Ontario Research Chair, and M. Velec through a CIHR Fellowship.

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Fig. 1.

Left: Schema showing the 4D CT tumor motion (solid line, white circles); the possible mid-ventilation CT, the mid-position CT (grey circle) along the linear exhale-to-inhale trajectory (dashed line), versus the time-averaged position (black circle). Note that it is possible for multiple phases (e.g. 20% and 80%) to be selected as the mid-ventilation CT if they are equally close to the time-averaged position. Right: the cranio-caudal diaphragm (white boxes) position on 4D CT. Mid-ventilation CT was selected as the phase with the diaphragm closest to the mean diaphragm position (grey box). The relative cranio-caudal mean diaphragm position was also applied to the exhale-to-inhale 4D CT deformation map to generate the mid-position CT.

Fig. 2.

The local rigid registration volume is around the left diaphragm, and excludes the chest wall and heart. A mutual information algorithm was used, only considering translations.

Fig. 3.
Workflows to select a mid-ventilation CT or reconstruct a mid-position CT.

Fig. 4.

Diaphragm and GTV motion over all 4D CT phases for one patient (GTV location shown on the inset figure).

Table 1

Patient and imaging details.

Variable	Description (number of patients)
Breathing motion management	Free-breathing (6) Abdominal compression plate (4)
4D CT image resolution	1.0×1.0×2.0 mm (6) 1.0×1.0×2.5 mm (4)
Clinical planning dataset	End-exhale 4D CT (7) Voluntary exhale breath-hold CT (3)
Dataset(s) used for tumor delineation	Contrast-enhanced CT (6) MRI (8)
Gross tumor volume (GTV)	Range 11 – 532 cm ³

Table 2

Example calculation of the inferior PTV margin applied to the GTV on the exhale 4D CT where the breathing amplitude is fully encompassed (ITV-based PTV), or on the mid-position CT where the amplitude is incorporated into the PTV as a random error.

	ITV-based PTV applied to the GTV on exhale 4D CT	Dose-probability PTV applied to the GTV on mid-position CT
Inter-fraction setup errors (inter)	$\Sigma_{\text{inter}}, \sigma_{\text{inter}}$	$\Sigma_{\text{inter}}, \sigma_{\text{inter}}$
Intra-fraction setup errors (intra)	$\Sigma_{\text{intra}}, \sigma_{\text{intra}}$	$\Sigma_{\text{intra}}, \sigma_{\text{intra}}$
Deformable image registration accuracy (dir)	$\Sigma_{\text{dir}}, \sigma_{\text{dir}}$	$\Sigma_{\text{dir}}, \sigma_{\text{dir}}$
Error in mean respiratory position (mid-position CT error)	n/a	$\Sigma_{\text{mid-position CT error}}$
Patient-specific GTV amplitude (A) *	A	$\sigma_{\text{amplitude}} \approx A/3$
Required margin [†]	$2.5\Sigma_{\text{total}} + 0.7\sigma_{\text{total}} + A$	$2.5\Sigma_{\text{total}} + 0.7\sigma_{\text{total}}$

Abbreviations: Σ =standard deviation of systematic error; σ =standard deviation of random errors.

* modelled with deformable registration between exhale and inhale 4D CT

[†] All Σ and all σ from each column are added in quadrature to determine the Σ_{total} , and σ_{total} respectively.

Table 3

Maximum amplitude on 4D CT (in mm).

	GTV motion			Diaphragm motion	
	Left-right	Anterior-posterior	Cranio-caudal	Vector magnitude	Cranio-caudal
Mean±standard deviation	-1.9±1.5	2.9±1.9	10.3±3.8	11.1±3.9	12.4±4.3
Range	-4.1, 0.9	-0.6, 5.7	6.0, 17.3	6.4, 18.6	5.8, 19.4

Table 4

Errors in liver tumor position for different planning CT datasets relative to the time-averaged position, in mm.

Dataset	GTV error, mean $\pm$ standard deviation (max)			
	Left-right	Anterior-posterior	Cranio-caudal	Vector magnitude
20% 4D CT phase	0.1 $\pm$ 0.5 (0.8)	0.2 $\pm$ 0.8 (1.8)	0.7 $\pm$ 1.6 (3.2)	1.7 $\pm$ 1.6 (3.7)
80% 4D CT phase	-0.5 $\pm$ 0.6 (1.9)	0.5 $\pm$ 0.8 (2.9)	1.0 $\pm$ 2.4 (4.8)	1.8 $\pm$ 1.6 (6.0)
Mid-ventilation CT	-0.1 $\pm$ 0.4 (0.8)	0.1 $\pm$ 0.6 (1.1)	0.2 $\pm$ 0.8 (2.0)	1.0 $\pm$ 0.5 (2.0)
Mid-position CT (using patient-specific diaphragm position)	0.1 $\pm$ 0.3 (0.4)	-0.1 $\pm$ 0.4 (0.8)	0.0 $\pm$ 0.6 (1.1)	0.6 $\pm$ 0.3 (1.4)
Mid-position CT (using population diaphragm position)	0.1 $\pm$ 0.3 (0.6)	-0.1 $\pm$ 0.3 (0.6)	0.0 $\pm$ 0.8 (1.4)	0.8 $\pm$ 0.4 (1.5)