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Research Article

Investigation of Optimal Strategy of Internal Target Volume Generation for Liver Stereotactic Body Radiotherapy (SBRT)

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Abstract

Objective: To investigate if limited number of respiratory phases can be used to accurately generate Internal Target Volume (ITV) for liver Stereotactic Body Radiotherapy (SBRT).

Materials and Methods: Free Breathing (FB) and four Dimensional Computerized Tomography (4DCT) scans of 10 patients who underwent liver radiation were included. Gross Tumor Volumes (GTV) was contoured in 10 respiratory phases to generate GTV ITV_4D. Different GTV ITVs were derived from selected phase contouring (GTV $ITV_{2phases}$ (Phase 0 and 50), GTV $ITV_{3phases}$ (Phase 30, 60 and 90), GTV $ITV_{5phases}$ (Phase 0, 20, 40, 60 and 80)) and their volumes and spatial concordance with GTV ITV_4D was investigated. The position of centre of mass (COM) of individual GTVs were measured and systematic and random errors were calculated. Population internal margin (PM) was generated using van Herk's formula and applied to FB volume to obtain GTV population margin (GTV_PM).

Results: GTV $ITV_{5phases}$ encompassed 90% (range 82.4-94.8%) of the GTV ITV_4D. The mean volume (in percentage) of GTV $ITV_{2phases}$ and GTV $ITV_{3phases}$ overlapping with GTV ITV_4D was 79.8% (range 69.4-84.4%) and 80.6% (range 71.1-89.1%) respectively. The directional population margins in antero-posterior (AP), Medio-Lateral (ML) and Supero-Inferior (SI) directions were 2.46mm, 1.75mm, 3.45mm respectively. GTV ITV_PM encompassed 99.4% GTV ITV_4D, but with highest spatial mismatch.

Conclusion: Contouring in alternate respiratory phases may safely be used for generation ITV. Adding population based margin to FB volume lead to high spatial mismatch when compared to GTV ITV_4D.

Keywords: 4DCT; Liver; SBRT

Introduction

The success of liver Stereotactic Body Radiation Therapy (SBRT) programmed depends on high precision delivery of hypo fractionated radiation and accurate sparing of adjacent Organs at Risk (OARs). While proximity to OARs is well addressed with the use of highly conformal treatment planning techniques [1,2] the intra-fraction target displacement poses challenge in accurate delivery of planned hypo fractionated treatment to the target. While the average liver motion varies from 3-50mm [1], the Centre Of Mass (COM) of the tumor (or target) moves about 9.7mm±5mm [2]. Often anisotropic margin of 1-2cm is added to the Gross Tumor Volume (GTV) to account for the target motion without actual knowledge of patient specific motion [3,4] which may not be representative of anisotropic tumor trajectory. This may lead to under dosing of target volume or overdosing the OARs. Different strategies have been adopted to estimate the target motion like ultrasonography/x-ray cine fluoroscopy [5,6]. In recent years, four dimensional CT (4DCT) has been widely used to generate Internal Target Volume (ITV) for hepatic and pulmonary tumors [7,8]. ITV generation using 4DCT involves contouring of target volume in each of the respiratory phases, which may possibly be an accurate method of ITV generation. Various commercial systems are presently available to bin the respiration correlated CT into number of respiratory phases. Binning the 4DCT data set into 10 respiratory phases is considered optimum. However, target delineation in all the phases is time consuming and labor intensive. Ability to accurately characterize respiratory phase movement in limited phase datasets or maximum/minimum intensity projection images (MIP/MinIP) may provide a time efficient method of encompassing internal target motion [9] Unlike lung tumors, limited information on accuracy of MIP/MinIP is available for liver tumors. Furthermore contouring on MIP/MinIP may not be applicable [6] to all intrahepatic tumors due to variability in enhancement patterns and occasionally presence of I^{131} Lipidiol and other artifacts after Trans Arterial Chemo Embolization (TACE) Or Radiofrequency Ablation (RFA).

The present study was designed with a primary aim to determine the minimum optimal number of respiratory phases that can be used to encompass 90% of ITV generated using all 10 respiratory phases .The secondary aim of the study was to characterize 3 dimensional liver tumor displacement as a function of respiration such that ITV could be generated even if 4DCT platform is not available.

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Table 1: Patient and Tumour Characteristics.

Patient	Age (years)	Sex	Diagnosis	Maximum Tumour size at Radiotherapy planning in (cm)	Previous treatment Received
1	66	Male	Intrahepatic Cholangiocarcinoma	8.2	None
2	64	Male	Hepatocellular Carcinoma	6.8	Sorafenib+ TACE twice
3	46	Male	Carcinoma Gall Bladder	6.7	None
4	44	Female	Cholangiocarcinoma	4.6	Chemo 8# (GEMOX)
5	57	Male	Carcinoma Gall Bladder	3.4	Chemo 2# (GEMOX)
6	53	Male	Carcinoma Gall Bladder	5.5	Chemo 8# (GEMOX)
7	39	Male	Metastatic Carcinoma	4.5	8# FOLFOX+ RFA+ 3#FOLFIRI
8	59	Female	Cholangiocarcinoma	5.5	4# Gemcitabine+Cisplatin
9	49	Male	Hepatocellular carcinoma	10.1	None
10	46	Male	Cholangiocarcinoma	2.1	None

TACE: Transarterial Chemo-Embolisation; GEMOX: Gemcitabine + Oxaliplatin; FOLFOX: 5-FU, Leucovorin, oxaliplatin; FOLFIRI: 5-FU, Leucovorin, irinitecan, RFA: Radiofrequency ablation.

Materials and Methods

From September 2013 to April 2014, all patients (n=10) who underwent 4DCT for planning SBRT/high dose chemo-radiation for primary or metastatic hepatobiliary tumor were included.

Simulation and 4DCT data acquisition

Varian Real Time Positioning Management System (RPM) (Version 1.7.5, Palo Alto CA USA) was used for 4DCT data acquisition [10]. Calibration of RPM infrared camera was performed at a pre-adjusted patient height prior to 4DCT simulation. Patients were subsequently positioned supine with arms placed overhead. All data acquisition was during un coached free breathing. A marker block with 6 reflective infrared markers was placed midway between xiphisternum and umbilicus. Motion of marker block represented the respiratory motion which was captured by the infrared camera and respiratory signal was recorded in synchronization with the X-ray "ON" signal from the GE CT scanner (Light speed 16, Version, Waukesha, WI). The periodicity meter helped in establishing periodic breathing (a regular breathing period and a periodic sinusoidal wave pattern). Contrast enhanced free breathing scan (2.5mm slice thickness) was performed and this was immediately followed by 4DCT scan. In two patients due to non-rhythmic breathing, 4DCT data acquisition was done on a different time point than the free breathing scan. The 4DCT images were acquired in axial cine mode; continuous scans were performed at each couch position till the entire region of interest was scanned. The CT acquisition parameters were as follows: 120 kV, 300-400 mA and slice thickness of 2.5 mm. The scanning time was 90-120 seconds. A total of 1200-1500 axial images were obtained for each patient. Position of infrared marker block was marked on the patient surface for future reference to reproduce on treatment couch.

After 4DCT data acquisition, the 4D software (Advantage 4D, GE Medical Systems, Fairfield, Waukesha, WI USA, version 4.4) binned the images into 10 phases based on the temporal correlation between surface motion and data acquisition and were evenly distributed over the respiratory cycle. The phases were labeled as CT0% to CT90%. CT0% corresponds to end inhalation, CT20% mid exhalation, CT50% end exhalation and CT80% to mid-inhalation. Each percentage was therefore a target phase that could be represented by a set of images that have been acquired at that phase of respiratory cycle. Phase error was then determined for each of the reconstructed data sets. Maximum phase error for each data set represented proportion of images within the target data set that are farthest from target phase. Phase error of ≤10% was taken as cut off for each phase to be considered for target delineation. All the images were exported into treatment planning system (Eclipse Varian V8.9, Palo Alto CA, USA) for target delineation.

Assessment of adequate number of GTV phases for target delineation

Gross Tumor Volume (GTV) was delineated in contrast enhanced free breathing (FB) scan (GTV FB) and in all the 10 respiratory phase data sets by a single radiation oncologist (MS). GTV represented the lesion visualized in the planning CT or diagnostic positron emission tomography (PET CT) or magnetic resonance imaging (MRI) scan as contrast enhanced rim. All the 10 phase contours were then projected onto the FB scan. The GTV of all 10 phases were combined using Boolean operation to obtain the internal target volume (GTV ITV_4D). To identify minimal number of datasets that would be required encompass the target motion we generated different GTV ITV's using a) end inhalation-end exhalation dataset (GTV_ITV_{2phase} i.e. GTV 0 and GTV 50), b) 3respiratory phases (GTV_ITV_{3phase} i.e. GTV30, GTV60 and GTV90) c) 5 respiratory phases (GTV_ITV_{5phase} i.e. GTV0, GTV20, GTV40, GTV60, GTV80). GTV ITV_4Drepresented the reference volume against which all other ITVs were compared.

The volume of different ITV types was derived from Eclipse workstation and percentage of GTV ITV_4D encompassed by each of the ITV types was determined. In addition to percentage of GTV_ ITV 4D encompassed, the distance of ITV missed in each of the directions (superior, inferior, anterior, posterior, right and left) with limited datasets was determined.

Generation of internal margin

GTV's in all respiratory phases were projected on free breathing CT scan and GTV displacement as a function of respiratory motion was assessed by measuring the deviation of centre of mass (COM) of individual GTVs from the reference scan, i.e. the free breathing scan. The COM displacement during respiratory cycle of each of the patient

Table 2: Absolute and Percentage of mean GTV Volume variation over 10 respiratory phases in all patients.

Patients	GTV_0 Vol in cc (%)	GTV_10 Vol in cc (%)	GTV_20 Vol in cc (%)	GTV_30 Vol in cc (%)	GTV_40 Vol in cc (%)	GTV_50 Vol in cc (%)	GTV_60 Vol in cc (%)	GTV_70 Vol in cc (%)	GTV_80 Vol in cc (%)	GTV_90 Vol in cc (%)	Mean GTV Averaged over all phases (cc)
1	251.3 -98.9	252.7 -99.6	255.4 -100.6	266.2 -104.9	244.7 -96.4	258 -101.7	255.7 -100.8	256.5 -101.1	252.1 -99.3	245.2 -96.6	253.8
2	161.5 -97.1	159.7 -96	173.9 -104.5	161.3 -97	171.4 -103.1	165.1 -99.3	168.2 -101.2	167.5 -100.8	161 -96.8	173.5 -104.3	166.3
3	84.4 -96.5	91.2 -104.4	84.4 -96.6	85.2 -97.5	86.6 -99	85.8 -98.2	83.1 -95.1	91.3 -104.4	91.6 -104.8	90.6 -103.7	87.4
4	21.4 -105.8	19.6 -96.7	19.9 -98.4	19.5 -96.2	19.8 -97.9	21.2 -104.6	19.6 -96.7	20.3 -100.3	20.2 -99.8	20.9 -103.5	20.2
5	35.7 -104.2	32.5 -95	34.5 -100.7	34.9 -102	33.6 -98.1	35.4 -103.4	34.6 -101	33.8 -98.8	32.8 -95.8	34.7 -101.3	34.3
6	98.22 -101.4	99 -102.2	92.7 -95.8	95.4 -98.6	98.6 -101.8	100.4 -103.7	93.6 -96.6	94 -97.1	98.7 -102	97.6 -100.8	96.8
7	20 -98.4	20.6 -101.3	20.8 -102.5	20.4 -100.4	19.8 -97.4	19.5 -95.8	21.4 -105.2	20 -98.4	20.4 -100.5	20.3 -100	20.3
8	30.1 -94.7	32.2 -101.3	31.6 -99.4	32.9 -103.5	32 -100.6	30.5 -95.9	31.9 -100.3	32.7 -102.8	31.2 -98.1	32.5 -102.2	31.8
9	434.5 -101.3	436.5 -101.7	435.7 -101.5	429.2 -100	439.3 -102.4	417.9 -97.4	434.4 -101.2	418.6 -97.6	419.4 -97.7	425.5 -99.2	429.1
10	26.5 -101.9	25.8 -99.2	25.9 -99.5	25.1 -96.6	26.3 -101.2	25.5 -98	25.2 -96.9	27.1 -104.1	26 -100.1	26.7 -102.7	26
Range	96.2- 105.8%	96.0- 104.4%	95.8- 104.5%	96.2- 104.9%	96.4- 103.1%	95.8- 103.7%	95.1- 105.2%	97.6- 104.1%	95.8- 104.8%	96.6- 104.3%	-

Table 3: Table depicting percentage of volume of GTV ITV_4D encompassed while using limited datasets for ITV generation.

Patients	GTV ITV_4D (in cc)	GTV_FB (%)	GTV ITV_{2ph} (%)	GTV ITV_{3ph} (%)	GTV ITV_{5ph} (%)	GTV_PM (%)
1	428.9	58.8	78.5	80.7	93	84.9
2	233.1	70.3	84.3	89.1	92.5	100.4
3	129.8	63.3	82.2	88.9	90.8	103.9
4	41.6	-	83.3	75.8	91.5	100.4
5	66	59.5	69.4	71.1	82.4	97.7
6	192.3	50.8	80	78.4	85.2	75.4
7	45.2	47.5	71.8	76.2	89.6	97.4
8	52.0	55.6	80.9	86.9	94.8	115.1
9	594.8	74	84.4	88	93.3	105.9
10	54.5	53.2	83.5	71.1	91.9	113.3
Range (in %)		47.5-74	69.4-84.4	71.1-89.1	82.4-94.8	75.4-115.1

GTV ITV_4D: GTV generated using all phases; GTV_FB: GTV free breathing; GTV ITV_{2ph}: GTV 0+GTV50; GTV ITV_{3ph}: GTV30+GTV60+GTV90; GTV_{5ph}: GTV 0+GTV20+GTV40+GTV60+GTV80; GTV_PM: GTV population margin.

was used to calculate population systematic (predictable displacement due to breathing) and random (unpredictable displacement due to breathing) tumor displacement

Systematic (Σ) and random (σ) breath cycle displacement was calculated in Antero-Posterior (AP), Medio-Lateral (ML) and Supero-Inferior (SI) direction. The systematic component represents the displacements of respiratory origin present during the entire course of normal respiratory cycle. Individual systematic displacement was calculated from mean values of all displacements and population systematic error was calculated from the standard deviation (SD) of mean displacement for all individual patients. The random error represents the random respiratory movements which may unexpectedly displace the tumor. The individual random error was measured from the SD of mean displacement for each patient and population random error was calculated from the mean of the SD of all patients. The internal margin (IM) due to internal target motion was calculated by using van Herk's method [11]. The internal margin derived from van Herk's formula was applied to the free breathing GTV to obtain the GTV ITV population margin (GTV ITV_PM). This volume was also compared with the GTV ITV_4D obtained from combining all phases of respiratory cycle to assess if the variations in breath cycle in a patient population could be used to derive internal target volume and applied to clinical situations wherein 4DCT is not available.

Results

The median age of the study population (n=10) was 51 years (range 39-69 years). Of these 80% were males. None of the patients had history of any pre-existing respiratory morbidity or history of smoking which could adversely affect their respiratory wave form. The patient and tumor characteristics have been described in the Table 1.

In all the 4D data sets the phase error was less than 10% (mean 6.5%, range 3%-12%). Only one patient had 12% phase error in one of the data sets. The intra-observer variation in GTV delineation was ≤5% (0.5-8%; Table 2).

Table 4: Spatial mismatch from GTV ITV_4D (mean (± S.D) in mm) while using limited datasets or population based margins for ITV generation.

GTV ITV	Superior in mm	Inferior in mm	Anterior in mm	Posterior in mm	Right in mm	Left in mm
GTV ITV_{2ph}	0.7 (1.6)	2.6 (3)	3.4 (2.4)	3.4 (1.2)	2.6 (1.4)	2.8 (1.7)
GTV ITV_{3ph}	2.8 (3.2)	3.7 (3.7)	2.2 (0.8)	2.7 (0.9)	2 (0.8)	1.5 (1.2)
GTV ITV_{5ph}	1.7 (2.3)	1.3 (1.3)	1.5 (2.4)	1 (0.9)	1.2 (1)	1.2 (0.8)
GTV_PM	7.4 (4.3)	8.1 (4.6)	4.1 (2.8)	3.2 (1.1)	3.2 (0.9)	3.6 (1.1)

Table 5: Mean Centre of Mass (COM) displacement and S.D. (standard deviation) over respiratory cycle.

Patients	Mean COM (mm)			Mean S.D.		
	X (ML)	**Y (AP)**	**Z (SI)**	**X (ML)**	**Y (AP)**	**Z (SI)**
1	1.1	2.1	4.3	0.7	1.7	1.6
2	0.8	1.2	2.2	0.5	0.7	1.4
3	0.5	0.9	2.3	0.4	0.8	1.4
4	0.4	1.4	3.2	1.2	1.3	1.5
5	0.8	1.4	3.4	0.8	0.7	2.3
6	1.9	2.6	4.6	1.3	1.4	3.6
7	1.2	2.6	2.8	1.2	1.5	1
8	0.4	0.9	2.2	0.2	0.9	1.3
9	1.3	0.8	2	0.7	0.5	1
10	1.2	0.9	2.5	1.2	0.5	1.7
	0.5	0.7	0.9	0.8	1	1.7
S.D of Mean (∑)				**Mean of S.D (σ)**		

ML: Medio-lateral; AP: Antero-posterior; SI: Supero-inferior; S.D: Standard deviation.

Volumes of GTV ITV_4D, GTV $ITV_{2phases,}$ GTV $ITV_{3phases}$ and GTV $ITV_{5phases}$ are depicted in Table 3. The mean volume (in percentage) of different GTV ITVs overlapping the GTV ITV_4D was as follows: 79.8% (range 69.4-84.4%) for GTV $ITV_{2phases}$, 80.6% (71.1 to 89.1%) for GTV $ITV_{3phases}$, 90.5% (range 82.4 to 94.8%) for GTV $ITV_{5phases}$.

It was observed that GTV ITV computed from limited phases were smaller than the volume using all 10 phases (GTV ITV_4D). The mean surface distance (in mm) between GTV ITV_4D and the test ITV's is depicted in the Table 4. GTV_{5phase} had the least mean surface distances among all GTV ITV's. From the Table 3, it is seen when 5 data sets (alternate phases of respiration) were used for contouring, the mean variation in volume from GTV ITV_4D was within 10%. The variation was higher in patients 5 and 6 (Table 3). This variation could be attributed to the difference in respiratory wave form at the time of baseline recording and actual scan acquisition. From the above, it can be inferred that at least 5 datasets are needed for reliable generation of GTV ITV that would encompass at least 90% of the target displacement as a function of respiration.

Generation of population margin for respiratory displacement

The mean displacement of COM during respiratory cycle and SD is given in Table 5. The margin for target displacement was generated by using van Herk's formula [11]. The proposed margins in AP, ML and SI directions are 2.46mm, 1.75mm, 3.45mm respectively. This directional population margin was added to GTV_FB to obtain the population margin based ITV (GTV ITV_PM). GTV ITV_ PM constituted 99.4% of GTV ITV_4D on an average (Range 75.4%-115.1%). However as seen in Figure 1, there was spatial mismatch between GTV_ITV 4D generated using 4DCT scan and GTV ITV_PM generated using population margins. The mean surface distance between GTV_ITV 4D and GTV ITV_PM is depicted in Table 4. As seen the greatest mismatch was in supero-inferior direction. Though on volume to volume comparison GTVITV_PM was closest to GTV ITV_4D the spatial deviation from surface of GTV_ITV 4D was greatest while using this margin expansion technique.

Discussion

The present study was designed to investigate if lesser number of respiratory phases could be used for generating ITV for liver SBRT. Previous studies using 4DCT in lung and liver cancer have demonstrated the adequacy of target contouring in 2 extreme phases of respiration (end inspiration-end expiration CT 0%, 50%) [12,13]. Mian Xi et al using contrast enhanced 4DCT demonstrated that extreme phases of respiration can be used to encompass 94% of ITV [13]. However we did not find 2 phase contouring to be sufficient in encompassing GTV ITV_4D.The difference in the results observed in our study could be attributed to the differences in contouring methodology. While Xi et al edited ITV to the liver surface; we did not edit the ITV to the liver surface. The resultant difference in ITV volumes could thereby impact percentage coverage. While Xi et al used contrast enhanced 4DCT scans, we acquired 4DCT immediately after contrast enhanced free breathing scan. The diagnostic PET CT scan and MRI scan aided target delineation. However, as both our reference and test scans (GTV $ITV_{2phases}$) were derived from the same data set it is unlikely to impact proportional assessment of volumes. While we did not find any incremental improvement after adding a mid inhalation dataset (CT 30%), the volume of ITV encompassed increased to 90% (82%-94%) by including 5 respiratory or every alternate phase. In two patients less than 85% of the ITV was encompassed. Excluding these 2 patients the coverage of $GTV_{5phases}$ marginally increased to 92% suggesting that the average is not substantially affected by these 2 patients.

To further evaluate areas of spatiotemporal miss, while using limited respiratory phases, we evaluated the surface distance between limited phase ITV's and GTV ITV_4D. As seen in the Table 4, the mean surface distance between the two volumes is less than 1.5 mm in all directions while using 5 respiratory phases and less than 3.5mm while using 2 respiratory phases. Xi et al observed 1.1-1.7 mm surface distance variation while using 2 extreme respiratory phases. While the 90% ITV coverage achieved by use of 5 respiratory phases may be considered clinically acceptable an extra directional margin may be added as suggested in Table 3 if considered appropriate by the treating physician.

In this study we also investigated if the centre of mass displacement data generated out of 4DCT could be used for generating ITV on GTV contoured on free breathing scans. As respiratory displacement may have both systematic (arising out of registration of free breathing and 4DCT data sets) and random component (change in respiratory wave form during wave form and actual scan acquisition), we used Van Herk Formula to generate margin[11]. Using AP, ML and SI expansion of 2.5mm, 1.8mm and 3.5mm on GTV delineated on free breathing scan GTV ITV_4D could be encompassed 97% of the

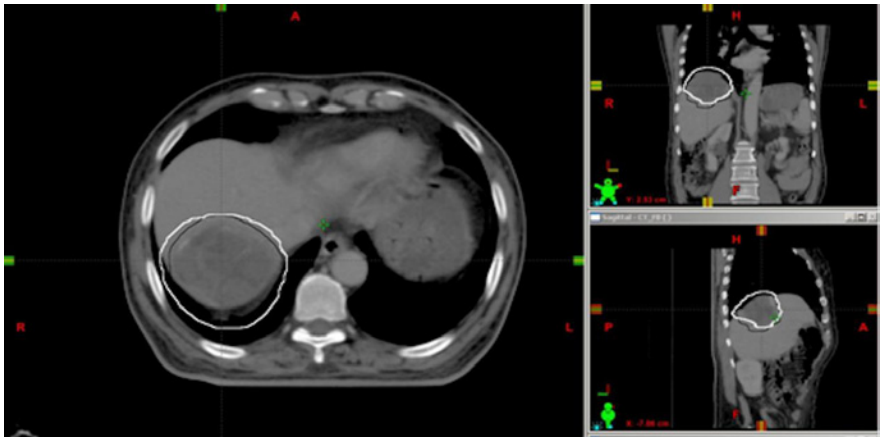

Figure 1: GTV ITV_4D and GTV_PM: Figure showing GTV_PM (black) encompassing major volume of GTV ITV_4D (white), but with spatial mismatch while maintaining the contour shape.

times. However, we observed spatial mismatch in 8/10 patients using this method of ITV generation. The surface distance of GTV ITV_PM from reference ITV is depicted in Table 4. While there was only minimal variation in the volume of GTV ITV_4D and that generated using directional marginal expansion (GTV ITV_PM). However, when spatial concordance was investigated, clinically significant mismatch was observed (Figure 1). On an average 39.8% (range 15.5%-68.6%) volume generated by giving directional margin was outside the GTV ITV_4D. This suggests that the common volume between GTV ITV_4D and GTV_PM was in the range of 60% on an average. This could possibly be attributed to difference between the captured respiratory signal related sorting and actual tumor displacement and differences in baseline liver position between 4DCT and free breathing scan. Also, the three dimensional displacement calculated do not account for rotations and deformations in liver surface which may possibly be automatically accounted while taking 4D CT scan.

While the results of our study demonstrate feasibility of using alternate respiratory phases for ITV generation it is of particular note that this is applicable only to patients with rhythmic breathing. The present study methodology also has certain limitations. Firstly, we have included only patients with predictable wave form with <10% of phase error. Secondly, the 4D margin proposed can only be used in patients who have predictable breathing. The spatial mismatch demonstrated between GTV ITV _PM may also be a result of extrapolating 3D margins on a free breathing scan. As we did not acquire breathe hold scan we are unable to determine if extrapolation of these 4D margins on breath hold scan would have led to lesser spatial mismatch. However, in the study by Kou et al, they analyzed 3 different margin recipes (full amplitude motion margin, 70% of the full amplitude motion margin and no margin for motion) based on tumor motion and their biological impact. They observed no difference in biological impact between full motion margin and 70% motion margin suggesting that 70% motion margin is also sufficient to avoid dosimetric errors [14].

Finally, one must remember that respiratory wave form captured during limited part of respiratory cycle as in 4DCT may or may not be representative of the entire breathing pattern. In the study by Ge et al, it is shown that even planning on 4DCT may not account for daily intrafraction motion of intraabdominal tumors. It may underestimate or overestimate the intrafraction motion [15]. Studies comparing 4DCT with Cine MRI demonstrate that Cine MRI detects larger difference in intra-fraction motion for hepatic tumors especially in supero-inferior direction. This indicates a need for larger margin than the ITV defined by 4DCT to encompass the motion detected by Cine MR [16]. However as we did not perform cine MRI in this population any inference regarding the same is beyond the scope of present study.

Conclusion

From the present study, it can be concluded that at least 5 respiratory phases are required for >90% characterization of respiratory ITV for liver SBRT. 3D margin expansions lead to similar volumes, but with spatial mismatch. Whether 3D expansion strategy fits on breath hold data sets needs further investigations.

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