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FULL PAPER

Intrafractional fiducial marker position variations in stereotactic liver radiotherapy during voluntary deep inspiration breath-hold

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Objectives: To evaluate intrafractional fiducial marker position variations during stereotactic body radiotherapy (SBRT) in patients treated for liver metastases in visually guided, voluntary deep inspiration breath-hold (DIBH).

Methods: 10 patients with implanted fiducial markers were studied. Respiratory coaching with visual guidance was used to ensure comfortable voluntary breath-holds for SBRT imaging and delivery. Three DIBH CTs were acquired for treatment planning. Pre- and post-treatment CBCTs were acquired for each of the three treatment fractions. Per-fraction marker position was evaluated on planar 2D kV images acquired during treatment fractions for 4 of the 10 patients.

Results: The median difference in marker position was 0.3 cm (range, 0.0–0.9 cm) between the three DIBH CTs and 0.3 cm (range, 0.1 to 1.4 cm) between pre- and

post-treatment CBCTs. The maximum intrafractional variation in marker position in craniocaudal (CC) direction on planar kV images was 0.7 to 1.3 cm and up to 1.0 cm during a single DIBH.

Conclusion: Difference in marker position of up to 1.0 cm was observed during a single DIBH despite use of narrow external gating window and visual feedback. Stability examination on pre-treatment DIBH CTs was not sufficient to guarantee per-fraction stability. Evaluation of differences in marker position on pre- and post-treatment CBCT did not always reveal the full magnitude of the intrafractional variation.

Advances in knowledge To increase treatment accuracy, it is necessary to apply real-time monitoring of the tumour or a reliable internal surrogate when delivering liver SBRT in voluntary DIBH.

INTRODUCTION

High radiation doses are delivered in few treatment fractions in stereotactic body radiotherapy (SBRT) for liver metastases. Accuracy is therefore crucial to achieve tumour control while avoiding unnecessary dose to surrounding normal tissue. But accuracy can be compromised by intrafractional variations such as respiratory motion^{1–3} and internal drift.^{4–6} Several respiratory motion management methods to reduce intrafractional variations have been proposed: Abdominal compression, respiratory gating, real-time tumour tracking and breath-hold.^{7–9} Such techniques have the potential to reduce planning target volume (PTV) margins and radiation-induced toxicities and can allow extensive dose escalation to the tumour.¹⁰

Liver SBRT in breath-hold using computer-controlled, spirometry-based devices has been investigated^{11–16}

whereas, to the best of our knowledge, no studies examined voluntary breath-hold using external optical tracking. In this study we investigate variations in fiducial marker position during liver SBRT using voluntary deep inspiration breath-hold under optical tracking.

METHODS AND MATERIALS

Patients

Intrafractional marker position variations were studied in 10 patients with implanted fiducial markers receiving liver SBRT in DIBH. The patients were selected from a prospective study, investigating SBRT in patients with liver metastases at Rigshospitalet, University of Copenhagen, between March 2018 and September 2019 (Figure 1). The prospective study was approved by the regional committee on health research ethics (approval number: H-17033786).

Figure 1. Flowchart of patient selection. Five patients were not eligible to participate in the prospective study due to lack of MR compatibility (four patients) or blindness (one patient). In this study, we focus on the 10 patients with implanted markers treated in DIBH (bold square). kV images were not acquired for the first five patients with markers treated in DIBH, since it was not technically and logistically available from the start of the study. DIBH, deep inspiration breath-hold.

Fiducial markers

Three fiducial markers were percutaneously implanted in the tumour vicinity using ultrasound guidance within 1 week prior to the imaging for treatment planning. The implanted markers were either Goldlock (cylinder with star-shaped cross-section, 1 × 3 mm, Beampoint AB, Sweden) or Gold Anchor (cylinder with multiple cut-outs, 0.4 × 10 mm, Naslund Medical AB, Sweden). Within this study, we denoted the marker placed most cranially Marker 1 and the marker placed most caudally Marker 3.

Respiratory coaching

Patients attended a respiratory coaching session before CT imaging to train comfortable voluntary breath-holds for CT imaging and treatment delivery. Patients were instructed to hold their breath for 20 s in deep inspiration breath-hold (DIBH) with visual guidance using Real-Time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA). A reflective

Figure 2. Panel A: Planning CT performed in DIBH with delineated GTV (red contour) and PTV (green contour). Panel B: Treatment plan in three fractions with dose colour wash ranging from 22.2% (15 Gy) to 103.3% (maximum dose). Dose prescription is described in detail in the Methods and Materials section. Panel C: Pre-treatment CBCT performed in DIBH. Panel D: Posterior planar kV image acquired per-fraction showing three fiducial markers.

marker box was placed at the level of xiphoid process, the level of breath-hold was set individually for each patient, with a narrow gating window of maximum 3.0 mm. The chosen level was used for imaging and treatment delivery.

Image acquisition for treatment planning

One 4DCT with i.v. contrast and three consecutive DIBH CTs were acquired on a Somatom Definition AS scanner (Siemens Healthineers, Germany). All CT images were reconstructed with a 2 mm slice separation. One of the three DIBH CTs with median position of markers was used for treatment planning. MR scans (10–12 different sequences) were performed in DIBH without visual guidance on 1.5 T Siemens Magnetom Avanto scanner (Siemens Healthineers, Germany).

Delineation

The planning CT was individually registered rigidly in 6D with an MR scan in Eclipse (Varian Medical Systems, Palo Alto, CA) focusing on the area of the tumour to guide delineation of the gross tumour volume (GTV). The GTV was delineated on the planning CT (Figure 2A) by a senior radiologist and approved by a senior oncologist. GTV to PTV margins were 10 mm in cranio-caudal (CC) direction and 5 mm in anteroposterior (AP) and left-right (LR).¹⁷ Fiducial markers were delineated individually by applying a threshold of 500 Hounsfield units in the area of the marker. The centre of mass of each fiducial marker was identified and used to define the marker position.

Treatment planning

All patients were treated with volumetric modulated arc radiotherapy (VMAT): one to three partial arcs, 180–200 degrees, 10 MV flattening filter free (FFF) with dose rate of 2400 monitor

units (MU) per minute.¹⁸ Treatment plans were performed in Eclipse (Varian Medical Systems, Palo Alto, CA) using AcurosXB 15.5.11 and a calculation grid size of 1 mm.

Patients were treated according to the national DLGCG (Danish Liver Cancer and Biliary Cancer Group) guidelines.¹⁹ All patients were treated in three fractions with prescription dose of 67.5 Gy: 99% of GTV should be covered by at least 95% of prescription dose, and 99% of PTV should be covered by at least 67%. The plan was normalised to the mean GTV dose (Figure 2B).

Treatment and image guidance

Patients were treated in DIBH on a linear accelerator (True-Beam, Varian Medical Systems, Palo Alto, CA) with one to three rest days between each treatment fraction. Full fan CBCTs were performed in DIBH before and after each treatment fraction (Figure 2C). Daily patient position correction was performed online before each treatment fraction using rigid registration (x, y, z and yaw) on fiducial markers. For offline evaluation of difference in marker position on pre- and post-treatment CBCT, the marker position was manually identified as the centre of the marker due to marker artefacts on CBCT. The marker position was identified two times for all patients, and the average was used.

Per-fraction kV imaging

Per-fraction planar 2D kV images were acquired for every 10 degrees of the gantry rotation (Figure 2D) for five of out of ten patients (it was not technically and logistically available from the start of the study). Only the CC marker position was evaluated on the planar kV images due to 2D geometry. Due to lack of image contrast in one patient, it was only possible to evaluate marker position in four out of five patients. These four patients had Gold Anchor fiducial markers implanted and were treated with one partial arc of 180 degrees. The position of the markers was defined manually as the most cranial part of each marker since it was difficult to identify the centre of the marker consistently throughout all images due to the rotation.

RESULTS

All patients had one liver metastasis treated with SBRT. The primary cancer was colorectal cancer for eight patients, lung cancer for one patient and oesophageal cancer for one patient. Median age for the ten patients was 70 years (range, 51 to 81 years). Images of the tumour location for each patient can be seen in Figure A1 in [Supplementary Material 1](#).

Median distance from each fiducial marker to the centre of the GTV on the planning CT was 3.1 cm (range, 0.4 to 5.0 cm), see [Table 1](#). Marker to marker distances remained stable in most cases on three repeat DIBH CT and on the pre- and post-treatment CBCT, both with a distance variation of 0.0 to 0.4 cm (median, 0.1 cm). The median marker motion in CC direction in free breathing estimated on the four-dimensional CT was 0.9 cm (range, 0.4 to 2.4 cm). In one patient, two fiducial markers were placed close together and appeared as one on CTs and CBCTs. In another patient, one marker was split in two parts during implantation and appeared as two markers on CTs and CBCTs.

The three pre-treatment DIBH CTs were acquired with a median time of 37 s (range, 25–110 s) between each CT. The median difference in marker position was 0.3 cm (range, 0.0–0.9 cm) between the three DIBH CTs (Figure 3). Reporting of breath-hold compliance at imaging can be found in Appendix B in [Supplementary Material 1](#).

Turning to the treatment imaging, the CBCTs were all acquired in three to five breath-holds. The median difference in marker position was 0.3 cm (range, 0.1–1.4 cm) between the pre-treatment CBCT and the post-treatment CBCT (Figure 4). Treatment delivery was performed in four to seven DIBHs. The median time of treatment delivery was 3 min (range, 2–5 min). The median time between the start of pre-treatment CBCT and the end of post-treatment CBCT was 13 min (range, 8–20 min). Difference in marker position between the pre- and the post-treatment CBCT did not correlate significantly with time between pre- and the post-treatment CBCT (Pearson's correlation coefficient $r = 0.13$, $p = 0.23$), see Figure A2 in [Supplementary Material 1](#).

For the four patients with evaluable per-fraction kV images, the maximum difference in marker position (CC direction) on planar kV images during a single fraction was between 0.7 and 1.3 cm, and maximum difference was 0.3 to 1.0 cm within a single DIBH, despite narrow gating windows of 2.2 to 3.0 mm on the external optical surrogate. Marker position on the planar kV images and external respiratory signal as function of time can be seen for each of the four patients in Figure 5 and Figures A3–A5 in [Supplementary Material 1](#). Cranial marker drift was observed during each breath-hold for patients 8 (Figure A4) and 9 (Figure 5), while no such pattern was observed for patients 7 (Figure A3) and 10 (Figure A5).

DISCUSSION

We evaluated marker position variations in liver SBRT in voluntary, visually guided DIBH. The marker position between the three consecutive DIBH CTs was in most cases reproducible (median difference in marker position of 0.3 cm), but reproducible inter-DIBH marker position did not guarantee per-fraction stability. For instance, differences in marker position in CC direction between the DIBH CTs were less than 0.5 cm for patient 9 (Figure 3), but intrafractional variations of up to 1.3 cm in CC direction were observed (Figure 5). On the individual fraction days, evaluation of intrafractional variation using marker position on pre- and post-treatment CBCT did not always reveal the full magnitude of the variation during a treatment fraction. For example, the maximum difference in marker position in CC direction between the two DIBH CBCTs for patient 9 in first treatment fraction was 0.2 cm (Figure 4), whereas the maximum difference in marker position in CC direction evaluated on the per-fraction was 1.3 cm (Figure 5).

Treatment delivery accuracy can also be compromised by residual set-up errors in the image guidance.^{20,21} While the image quality of CBCT is improved in DIBH compared to free breathing,²² the image guidance accuracy is furthermore challenged by a very limited visualisation of the liver tumour on the CBCT. Seppenwoolde et al have reported that implanted fiducial

Table 1. Target and liver volumes, marker distance to GTV and marker motion in free breathing for the 10 patients

	Patients	1	2	3	4	5	6	7	8	9	10
Volumes [cc]	GTV	18.2	32.5	13.0	7.1	3.4	2.3	3.5	10.1	50.7	3.5
	PTV	62.0	80.9	45.9	27.5	22.1	15.9	21.1	9.9	137	21.9
	Liver	2324	1350	1429	1466	851	2224	1780	1341	1472	1553
Distance to GTV [cm]	Marker 1	4.1	2.3	2.5	2.1	2.9	1.6	1.8	1.8	3.2	2.8
	Marker 2	3.2	3.0	4.0	2.3	3.4	3.7	4.0	0.4	3.5	3.3
	Marker 3	4.6	2.6	4.2	3.0	2.2	3.3	5.0	-	3.9	4.6
	Marker 4	-	-	-	-	-	2.0	-	-	-	-
Marker motion in free breathing [cm]	Marker COM	3.7	2.3	3.2	2.2	2.7	2.3	3.5	0.9	2.8	3.4
	LR	0.1	0.4	0.3	0.2	0.3	0.2	0.1	0.2	0.1	0.1
	AP	0.1	0.3	0.1	0.8	0.3	0.2	0.2	0.4	0.3	0.5
	CC	0.8	1.1	0.6	1.7	1.3	0.4	0.8	2.4*	0.8	1.1
	r	0.8	1.2	0.6	1.9	1.4	0.5	0.9	2.5	0.9	1.2

CBCT, cone beam CT; COM, centre of mass; 4DCT, four-dimensional CT; GTV, gross tumour volume; PTV, planning target volume.

*Marker motion was difficult to evaluate due to substantial artefacts from irregular breathing on the 4DCT.

Marker motion in free breathing was measured on the 4DCT and calculated as COM of all markers. One marker was split in two parts during implantation (Patient 6) and appeared as two markers on CTs and CBCTs. Two markers were placed close together (Patient 8) and appeared as one on CTs and CBCTs.

Figure 3. Difference in marker position between the planning CT and the two other CTs for the ten patients. The four panels show the difference in marker position in LR direction, AP direction, CC direction and absolute 3D displacement (r), respectively. A positive difference in marker position means that the marker shifted in right direction, posterior direction or caudal direction compared to the planning CT. 3D, three-dimensional; AP, anteroposterior; CC, craniocaudal; LR, left-right.

markers were a favourable surrogate for the tumour compared to diaphragm or bony anatomy, as long as they were implanted in the tumour vicinity.²³ In the same study, the marker-based set-up accuracy decreased with increasing distance between marker and tumour.²³ Other studies on marker to marker stability indicated the importance of fiducial markers being implanted in

Figure 4. Difference in marker position between the pre-treatment CBCT and the post-treatment CBCT. The four panels show the difference in marker position in LR direction, AP direction, CC direction and absolute 3D displacement (r), respectively. A positive difference in marker position means that the marker shifted in right direction, posterior direction or caudal direction on the post-treatment CBCT compared to the pre-treatment CBCT. 3D, three-dimensional; AP, anteroposterior; CBCT, cone beam CT; CC, craniocaudal; LR, left-right.

Figure 5. Intrafractional variation of the marker position for patient 9, as observed on planar kV images (blue squares, triangles and circles, representing each of the three markers) and external respiratory signal (red curve, representing the chest motion of the patient) during treatment in DIBH. The grey areas illustrate time intervals with beam on. Difference in marker position was measured relative to the marker position on the first kV image in each fraction. A positive difference in marker position means a shift in cranial direction. For this patient, the markers were moving cranially during each DIBH. Motion of 1 cm during a single DIBH and 1.3 cm during a single treatment fraction was seen for Marker 1. The external respiratory signal was measured in AP direction (right y-axis). A gating window of 2.9 mm was used for this patient. DIBH, deep inspiration breath-hold.

the tumour vicinity mainly due to liver deformations^{24,25} while migration of the fiducial markers has been shown to be negligible.²⁶ In our study, all markers were implanted within 5.0 cm from the centre of the GTV, and marker to marker distances were stable for the three consecutive DIBH CTs and for pre- and post-treatment CBCTs.

External respiratory signal has previously been reported to correlate with internal fiducial motion in the liver in free breathing,^{27,28} however, correlation in free breathing does not necessarily imply correlation in breath-hold. A study from our department has previously reported small intra- and inter-DIBH uncertainties for non-small cell lung cancer patients using the RPM system, with standard deviations for intra-DIBH ranging from 0.0 to 1.3 mm and inter-DIBH up

to 4.5 mm.²⁹ High intra- and inter-DIBH reproducibility had been observed with computer-controlled spirometry-based DIBH for abdominal tumours using active breathing control and additional ultrasound real-time monitoring; Vogel et al found residual motion of less than 5 mm in 95% of the cases between DIBHs and intra-DIBH residual motion of less than 5 mm in 99% of the cases,¹¹ and Boda-Heggemann et al report residual motion less than 5 mm in 88% of the delivery time.¹² In contrast, we observed the large intrafractional variations of the internal fiducial markers in voluntary DIBH treatments on the per-treatment kV images, while these variations were not observed on the external respiratory signal. We can conclude that a stable respiratory signal within a narrow gating window from an external optical gating marker is not a suitable surrogate for stability of internal fiducial markers, and hence tumours, in liver SBRT.

For liver SBRT in expiration breath-hold using active breathing control, the average intrafraction CC reproducibility of diaphragm relative to vertebral bodies evaluated on positioning radiographs was estimated to 1.5 mm (range, 0.6–3.9 mm) by Eccles et al³⁰ and 2.5 mm (range, 1.8–3.7 mm) by Dawson et al.³¹ The exhale phase had been shown to be more stable than the inhale phase in free breathing.⁶ Our results

highlighted that, in order to ensure accurate delivery of liver SBRT in voluntary DIBH, it is necessary to apply real-time monitoring during treatment delivery, e.g. MR-guided radiotherapy^{32,33} or internal electromagnetic transponders.⁶ In our department, these findings led to a clinical decision to treat liver SBRT on MR-guided linear accelerator which enables real-time monitoring of the treated anatomy during treatment.

CONCLUSION

Stability examination of the position of the implanted fiducial markers on pre-treatment consecutive DIBH CTs did not guarantee per-fraction marker stability in liver SBRT. Similarly, evaluation of intrafractional variation of the marker position based on the pre- and post-treatment CBCT did not always reveal the full magnitude of the variation. In order to increase treatment accuracy, it is necessary to apply real-time monitoring of the tumour or a reliable internal surrogate when delivering liver SBRT in visually guided, voluntary DIBH.

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