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Original paper

Ultrasound-based repositioning and real-time monitoring for abdominal SBRT in DIBH

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ABSTRACT

Aim: Ultrasound-based repositioning and real-time-monitoring aim at the improvement of the precision of SBRT in deep inspiration breath-hold (DIBH). Accuracy of ultrasound-based daily repositioning was estimated by comparison with DIBH-cone-beam-CT. Intrafraction motion during beam-delivery was assessed by ultrasound-real-time-monitoring.

Patients/methods: Residual error after ultrasound-based interfractional repositioning (85 fractions, 16 SBRT-series; 14 patients) was assessed by marker-based (7 series) or liver-contour-based (9 series) matching in DIBH-CBCT. During beam-delivery, the percentage of 3D misalignment vector below 2 mm, between 2 and 5 mm, 5–7 mm and over 7 mm was estimated. Percentage of relevant target-displacements was analyzed as a function of DIBH-duration.

Results: Residual error after ultrasound-based positioning was 0.4 ± 3.3 mm in LR (left-right), 0.2 ± 4.3 mm in CC (cranio-caudal) and 1.0 ± 3.0 mm in AP (anterior-posterior) directions (vector magnitude 5.4 ± 3.3 mm, MV ± SD). Over 544 DIBHs, target displacement was 1.3 ± 0.5 mm, 0.7 ± 0.3 mm, 1.6 ± 0.6 mm for CC, LR and AP directions, respectively (3D-vector 2.5 ± 0.7 mm). 3D misalignment vector length was below 2 mm in 49.8%, between 2 and 7 mm in 46.3%, and over 7 mm in 3.9% of the beam-delivery-time. During the first 5 s of the DIBH, 3D-misalignment vector length was always below 10 mm. Percentage of target displacements over 10 mm was 0.2%, 0.5% and 0.8% for 10 s, 15 s and 20 s DIBH-duration.

Conclusions: Ultrasound-based interfractional repositioning is an accurate method for daily localization of abdominal DIBH-SBRT targets. Residual motion is < 7 mm in 96% of the beam-delivery-time. Deviations > 10 mm occur rarely and can be avoided by gating the beam at a predefined threshold. Ideal DIBH-duration should not exceed 15 s.

1. Introduction

Stereotactic Body Radiotherapy (SBRT) results in excellent local control rates and low toxicity for hepatocellular carcinoma [1] and liver oligometastases [2–7]. However, local control rates after SBRT of hepatic lesions are still lower than those of lung lesions [8] and large tumors near central hepatobiliary structures or intestine are still challenging to treat. Local control rates may be further improved by the use of advanced motion management techniques such as tracking or gating in deep inspiration breath-hold (DIBH), as this efficiently reduces safety margins, and thus normal tissue exposure [9–11]. Repeated DIBH can be established with various approaches such as voluntary breath-hold, surface tracking or computer-based air (flow) volumetry devices such as ABC (Active Breathing Coordinator, Elekta AB, Sweden) [12–16]. Despite high clinical/in vivo accuracy results [17], inter- and especially intrafractional variability of breath-hold [18,19] remains an issue and resulting errors should be detected and corrected/compensated based on online motion monitoring. To establish such a paradigm, SBRT in

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DIBH can be combined with 4D-ultrasound [20–22] to additionally monitor target and/or surrogate position during DIBH. Ultrasound is a markerless, non-invasive, cost-effective way to localize target structures and monitor target motion without additional radiation [20,21]. Daily ultrasound-based repositioning has been established with previous ultrasound systems, which, however, are not able to perform intrafractional tracking/monitoring [23]. Target localization and motion surveillance of the prostate by transperineal imaging before each fraction was already demonstrated to be feasible [20,24]. Potential of ultrasound for daily repositioning of abdominal sites and real-time tracking is under investigation but currently there are no commercially available systems for these target regions.

In a framework of a prospective study, we assessed the interfractional positioning accuracy achievable with an experimental ultrasound system [20,25] for abdominal targets by comparing ultrasound readings with marker-based matching and matching based on liver contour in DIBH CBCT. In addition, we assessed the residual motion during beam-delivery for DIBH-SBRT based on real-time ultrasound (US) monitoring data acquired by an experimental version "Anticosti" of the Clarity Autoscan 3D ultrasound-tracking system provided by Elekta AB [20,25].

2. Patients and methods

2.1. Patients, treatment and ultrasound workflow

A total of 14 patients with 16 abdominal targets were included sequentially in this analysis after informed consent and IRB approval (2014-413 M-MA, amendment 2017). There were no exclusion/inclusion criteria regarding age, height, weight or other anatomical features. Patients (11 male, 3 female, 69 ± 13 years old) had a median Body Mass Index (BMI) of 26 kg/m^2 (MV ± SD; 26.9 ± 4.4 kg/m^2). 15 lesions were liver metastases of various primaries (10 colorectal cancer, 1 SCLC, 1 melanoma, 2 pancreatic carcinoma, 1 hepatocellular carcinoma) and one lesion was a lymph node metastasis of SCLC located near the pancreatic head. All patients were treated with image-guided SBRT in moderate DIBH up to a total dose of 60 Gy in 5–12 fractions, depending on tumor size, central or peripheral localization, residual liver capacity and proximity to serial organs at risk. Treatment delivery was performed with a linear accelerator (Versa HD, Elekta AB, Sweden) with flattening-filter-free (FFF) VMAT plans (Monaco, Elekta AB) as published previously [26]. Briefly, CT datasets with a slice thickness of 3 mm (Brilliance Big Bore Oncology Configuration, Philips, Netherlands) were acquired after patient training in computer-controlled DIBH with ABC (Elekta AB) after i.v. contrast administration. Immediately after the treatment planning CT, an ultrasound reference dataset was acquired with the research version "Anticosti" of the Clarity Autoscan (Elekta AB) in ABC-based DIBH. The ultrasound probe was placed with a multi-joint fixation arm along the right mid-axillary line [20]. A suitable acoustic window was chosen by an experienced radiation oncologist in an intercostal space to ensure minimal probe pressure. The probe was never positioned transabdominally to avoid pressure-induced deformations. To acquire volumetric images, a standard convex abdominal US-probe with a central frequency of 5 MHz is equipped with a motor to perform a sweeping motion with a 2D frame rate of 45 Hz in a range of 25°–35° [20]. A fiducial tree attached to the probe in a fixed geometrical relationship allowed the detection of the probe and the target structure localisation by infrared optical tracking. Isocenter coordinates were matched online and automatically transferred to the Clarity system. After planning, structures and final isocenter were imported to Anticosti and an echo-contrast-rich ultrasound-tracking structure (the GTV itself or as a surrogate, a portal/liver vein branch) in the center of the scanning area was contoured in proximity of the GTV (Fig. 1). Quality assurance was carried out daily by using an ultrasound phantom (Clarity calibration/QA phantom, CIRS Inc., Norfolk, USA) with a tolerance of 1 mm in each direction (containing pins equally spaced by 1 mm). Under controlled conditions, the system has an accuracy of 1.4 ± 1.6 mm for a scanning range of 30° measured in a 4D-phantom [20].

For the daily treatment sessions, patients were initially repositioned based on the skin marks in DIBH. Afterwards, a daily 3D ultrasound image was acquired in DIBH and the position of the surrogate structure was corrected based on the Clarity shift [24,27]. After an ultrasound-data based table move, a DIBH-cone-beam CT image was acquired and used for final repositioning. Matching was performed manually in the XVI (Elekta AB, Sweden) software based on existing metal markers/calcifications in 7 series (1 patient, for example, with a marker due to previous microwave ablation of the metastasis, 4 series with previous liver surgery and surgical clips (Fig. 1), 2 series with calcifications within the GTV due to previous chemotherapy or the liver/soft tissue contour (9 patients without marker). The pre-existing hepatic metal markers/fiducials could be used as a surrogate structure to reduce user-dependent repositioning accuracy, however, still manual matching has been used. Daily US-based positioning in DIBH was performed by 6 well-trained users, however, with different experience levels with ultrasound (4 RTTs and 2 radiation oncologists; all with user training for Clarity Autoscan and DIBH). The Anticosti-positioning relied on the visualization of soft tissue anatomy in ultrasound images. The left-right, craniocaudal and antero-posterior components of translation corrections were documented and 3D translation vector was calculated. Additional time needed for the daily ultrasound setup was documented. A CBCT dataset was acquired in DIBH following ultrasound-based positioning to determine the residual error after ultrasound shift in this 3D volume data set and, if necessary, to correct the final treatment position. Initial errors after skin-mark based repositioning were calculated as the sums of the US-based correction and residual errors.

2.2. Interfractional repositioning protocol, image analysis

We performed the following imaging protocol/analyses sequentially for each patient (Fig. 2):

1. Skin mark-based positioning during ABC-based DIBH
2. Anticosti-alignment and ultrasound-based position correction based on surrogate structure (GTV or portal vein branch) position
3. Online CBCT matching based on metal fiducials (if present) or on liver contour, if fiducials not present – this forms the basis for estimating residual errors after positioning based on soft tissue anatomy with Anticosti.

2.3. Intrafractional residual motion measured by ultrasound tracking during beam delivery

Motion data of each DIBH during beam delivery was documented and analyzed for left–right (LR), craniocaudal (CC) and antero-posterior (AP) components. 3D error vector length was calculated. Influence of breath-hold duration on the residual error was evaluated. The percentage of target displacements < 2 mm, 2–7 mm, 7–10 mm and > 10 mm was analyzed in relation to beam-delivery-time and DIBH duration.

2.4. Data processing

Overall mean value (MV) and standard deviation (SD), group systematic error (M; measurements in one patient over all fractions), standard deviation of the systematic error (Σ) and standard deviation of the random error (σ) of all translational errors in each direction were calculated following the methodology outlined by van Herk et al. [23,28,29]).

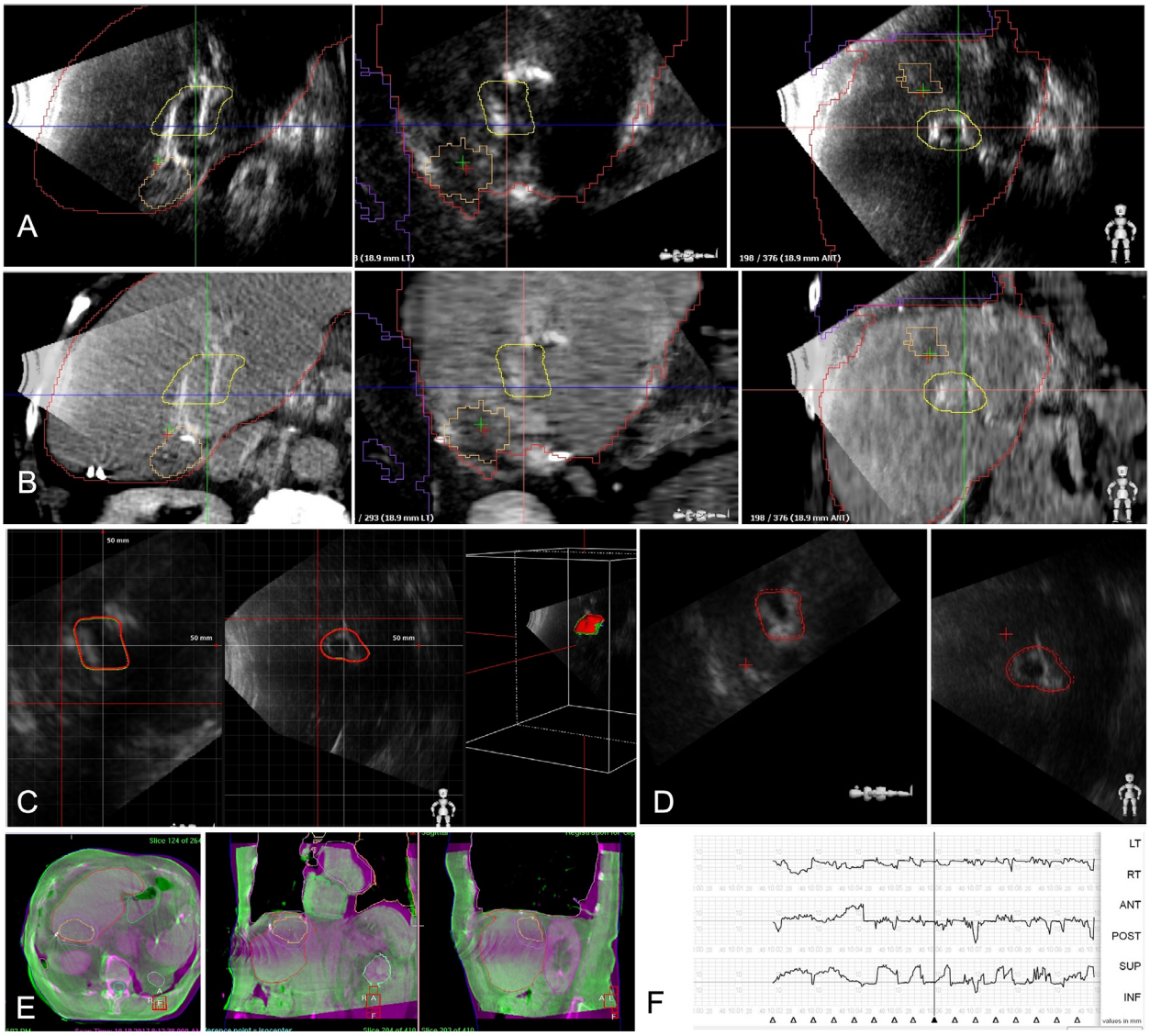

Fig. 1. US setup, positioning reference and repositioning workflow. A) US reference in transversal, coronal and sagittal reconstruction (portal vein branch in yellow in the vicinity of the target volume, marked orange) acquired directly after the planning CT, B) US reference matched to the planning CT, C) US-based table position correction before CBCT imaging, D), tracking of the surrogate structure during DIBH-CBCT, E) marker-based matching in the CBCT after ultrasound-based positioning, F) tracking during repeated DIBH. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. Patient characteristics and ultrasound-based workflow

Sonographic quality was sufficient to localize and track structures in the liver for all 14 patients. In 7 series, internal fiducials could be used to reduce the user-dependence in the manual matching of the CBCT: these were implanted markers placed during previous surgery (n = 4) or invasive microwave ablation (n = 1) or calcifications of the GTV due to chemotherapy (n = 3). For the other 9 series, liver contour has been used as a matching surrogate.

The mean additional time needed for the ultrasound setup was 9 ± 3 min (median 10 min) in 85 fractions for an experienced and well-trained team. Of a total of 544 observed DIBHs, 94% were tracked correctly by the ultrasound system based on online visual control (ultrasound monitoring was online controlled visually – assuring correct correspondence of the tracking contour with the tracked structure – by a physicist and a radiation oncologist throughout beam delivery).

3.2. Ultrasound-based table shifts

After skin-mark based daily repositioning in DIBH, ultrasound-based estimation of surrogate structure position was performed and the table position was corrected with a magnitude of 1.3 ± 5.7 mm in LR, 1.3 ± 7.5 mm in CC, and −0.2 ± 7.2 mm in AP direction. 3D vector length of the daily ultrasound-based shift was 10.6 ± 5.6 mm (MV ± SD, Table 1). After ultrasound-based shift, a DIBH-CBCT was performed to correct residual errors after US and to define final target position for beam delivery.

3.3. Residual error after ultrasound-based patient shift

The residual error after ultrasound-based repositioning measured by DIBH-only CBCT based on matching on fiducials (n = 7) or liver contour (n = 9) was 0.4 ± 3.3 mm (MV ± SD) in LR (M = −0.5 mm, Σ = 1.9 mm, σ = 2.8 mm), −0.2 ± 4.3 mm in CC (M = −0.3 mm, Σ = 2.9 mm, σ = 3.4 mm), and 1.0 ± 3.0 mm in AP (M = 1.2 mm, Σ = 1.8 mm, σ = 2.7 mm) direction. Residual error vector length after ultrasound-based repositioning was 5.4 ± 3.3 mm (median 5.1 mm,

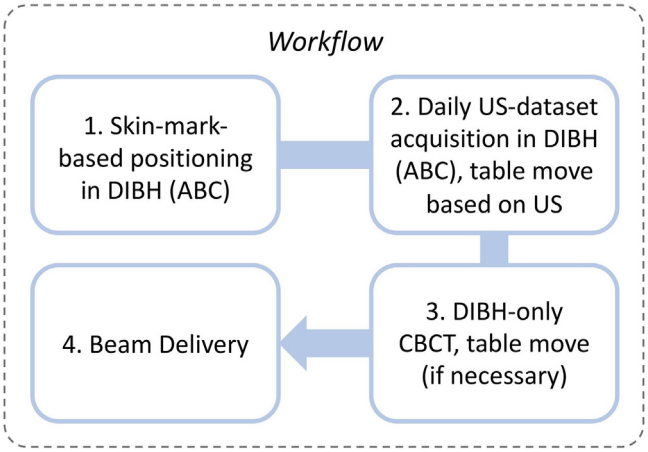

Fig. 2. Daily repositioning workflow. First, patients have been positioned based on skin marks. Afterwards, US-based alignment and ultrasound-based table shift based on surrogate structure (GTV or portal vein branch) position. Finally, online CBCT matching based on metal fiducials (if present) or on liver contour, if fiducials not present – this forms the basis for estimating residual errors after positioning based on soft tissue anatomy with Anticosti. Beam delivery after residual error correction.

Table 1, Fig. 3).

No difference was observed in residual error after ultrasound-based repositioning measured by CBCT if comparing patients with marker in the anatomic proximity to the GTV (0.3 ± 3.7 mm in LR, 0.7 ± 4.5 mm in CC and 1.4 ± 3.2 mm in AP direction, 3D vector 5.8 ± 3.6 mm, median 5.3 mm) versus patients with matching on liver contour only (1.0 ± 2.7 mm in LR, −1.1 ± 3.4 mm in CC and 1.0 ± 2.9 mm in AP direction, 3D vector 4.9 ± 2.5 mm, median 5.0 mm). No individual differences could be observed regarding age, BMI or gender, however, no statistical analysis was possible as a consequence of low patient number and homogeneous BMI/age distribution.

3.4. Overall error after skin-marked based repositioning in DIBH

Error (MV ± SD) after skin-mark based positioning only was 0.9 ± 7.4 mm in LR (M = 0.8 mm, Σ = 4.1 mm, σ = 4.6 mm), −1.5 ± 10.1 mm in CC (−M = 1.5 mm, Σ = 7.1 mm, σ = 7.7 mm) and 0.8 ± 7.8 mm in AP (M = 0.7 mm, Σ = 4.4 mm, σ = 7.2 mm) direction. Overall error vector length was 13.3 ± 6.5 mm (MV ± SD; median: 12.3 mm, Table 1).

3.5. Intrafractional motion during beam delivery

After repositioning based on ultrasound and CBCT, 61 treatment fractions with 544 DIBHs of 9 patients were analyzed (for the remaining patients the ultrasound probe was removed after the DIBH-CBCT and before dose delivery to allow for an optimal treatment sequence arrangement). 94% of the DIBHs were tracked correctly by the system based on online visual control online. Summing up all measurement points over all patients, US-tracking-detected target displacement (MV ± SD) during beam delivery in DIBH was 1.3 ± 0.5 mm, 0.7 ± 0.3 mm, 1.6 ± 0.6 mm for CC, LR and AP directions, respectively (3D vector 2.5 ± 0.7 mm). 3D target misalignment vector length (mainly AP and CC motion) was below 2 mm in 49.8%, between 2 and 5 mm in 38.2%, between 5 and 7 mm in 8.0%, between 7 and 10 mm in 3.1% and over 10 mm in 0.8% of the delivery time (Fig. 4A). During the first 5 s of the DIBH, no 3D vector lengths of target displacement larger than 10 mm was observed. Percentage of target displacements larger than 10 mm were 0.2%, 0.5% and 0.8% for 10 s, 15 s and 20 s DIBH duration, respectively (Fig. 4B). Target displacement in LR direction has the lowest component compared to AP and CC along DIBH. Percentage of relevant target displacements below 2 mm in LR direction were 99.2%, 96.6%, 94.8% and 92.9% for 5 s, 10 s, 15 s and 20 s DIBH duration, respectively (Fig. 4C).

4. Discussion

Liver SBRT is challenging due to respiration-dependent organ motion, organ deformations and low intrahepatic contrast in kV imaging [30–33]. Minimizing PTV margins is advantageous in cases of unfavorable tumor-to-liver volume or vicinity of the PTV to serial OARs (central hepatobiliary structures, stomach, small bowel [34,35]) is encountered. However, this can lead to marginal misses if no active motion management techniques are used. Due to its optimal sonographic accessibility and high echo-contrast differences, the liver is an optimal organ for ultrasound-based imaging for both daily repositioning and intrafractional motion monitoring of residual motion in a DIBH-setup [16,26,36].

Our data have shown that the sonographic quality was sufficient for daily repositioning. Reasons for the infrequently observed tracking failure (6%) are most likely software-related, as the experimental system works with a software developed for low-frequency and low-amplitude motion pattern of the prostate. No displacement of the US-probe during CBCT was observed. An adaptation of the software to the motion pattern studied here would therefore likely further reduce tracking failure.

Table 1
Residual error after skin-mark based positioning and ultrasound-based positioning. Abbreviations: Overall mean value (MV), standard deviation (SD), group systematic error (M), standard deviation of the systematic error (Σ), standard deviation of the random error (σ).

Translation (mm)					
n = 85		LR	CC	AP	Vector
Clarity shift (mm)	MV ± SD	1.3 ± 5.7	−1.3 ± 7.5	−0.2 ± 7.2	10.6 ± 5.6
	median	1.0	−1.3	−0.3	9.9
Skin set-up marks-error (mm)	MV ± SD	0.9 ± 7.4	−1.5 ± 10.1	0.8 ± 7.8	13.3 ± 6.5
	median	1.0	−2.2	1.2	12.3
	(min, max)	(−14.1, 18.2)	(−25.9, 28)	(−26.1, 18.8)	(0.8, 30.4)
	M	1.8	−1.5	0.7	13.5
	Σ	4.1	7.1	4.4	3.9
	σ	6.4	7.7	7.2	5.6
Ultrasound Anticosti residual error (measured by XVI, mm)	MV ± SD	−0.4 ± 3.3	−0.02 ± 0.43	1.0 ± 3.0	5.4 ± 3.3
	median	0.00	0.00	1.0	5.1
	(min, max)	(−8.0, 8.9)	(−1.20, 1.40)	(−5.0, 11)	(0.0, 14.2)
	M	−0.5	−0.03	1.2	5.6
	Σ	1.9	0.29	1.8	2.1
	σ	2.8	0.34	2.7	2.6

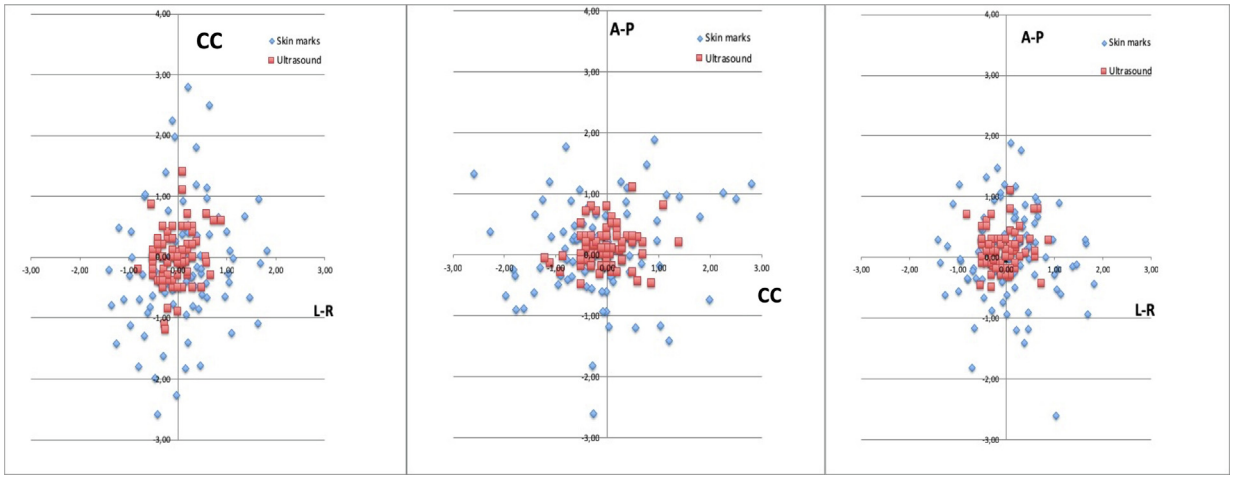

Fig. 3. Residual error (all values in cm) after positioning on skin marks (blue) vs. ultrasound-based repositioning (red), left-right vs. antero-posterior. Craniocaudal vs. left-right, craniocaudal vs. antero-posterior. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The daily additional time, which is required for US system setup is in an acceptable range of < 10 min needing no more than 2 treatment slots if using FFF and DIBH and may eventually be further reduced in an experienced team. In comparison to previous publications, however, we could observe a learning curve regarding setup-time and frequency of tracking failure pointing to the importance of the ultrasound education and training of the staff. Skin-mark based repositioning is certainly not recommended for any SBRT treatment. After ultrasound-based repositioning, there were only small systematic errors, in the left-right and craniocaudal directions (< 0.5 mm) and 1.2 mm in the anterior-posterior direction. Ultrasound-based repositioning has been discussed negatively in the literature due to user-dependence and possible image quality issues. In this series, however, in all patients, daily repositioning error after skin marks could be substantially reduced and the US based positioning resulted in a precision very similar to marker-based matching in DIBH-CBCT.

Due to the fact that ultrasound-based imaging only depicts a small part of the liver while the relevant organs at risk (e.g. stomach, intestine) are not/partly visible, we still recommend the combined use with breath-hold CBCT for daily repositioning, which has been shown to be very robust with minimal changes in liver motion amplitude over the treatment course [31], though US data are essential to track intrafractional (inter- and intra-breath-hold) uncertainties. Residual motion during DIBH-SBRT beam-delivery was < 5 mm in 88% and < 7 mm in 96% of the delivery time, corresponding to previous results of residual motion data obtained during interfractional imaging by DIBH-CBCT in the same setup [26]. Main residual motion components are in CC and AP directions while almost no LR motion can be observed. Larger deviations which could probably have dosimetric consequences occur rarely (< 4%) and could be avoided by stopping the beam by a predefined threshold if ultrasound-based tracking becomes commercially available also for the abdominal region or in a similar setting with DIBH implemented on an MRI-linac [37]. Ideal DIBH duration for SBRT should not exceed 15 s as larger errors occur more frequently if the DIBH duration increases probably due to compensatory motion or diaphragm relaxation and exhaustion of the patient and lung volume changes due to oxygen depletion at the end of longer breath hold.

If using US during delivery, the error between the breath holds can be kept in this range and the beam may be stopped if the motion exceeds a pre-estimated threshold. A methodical limitation is introduced by the fact that the ultrasound reference and planning CT and daily ultrasound imaging are all acquired during single DIBHs, contrary to the CBCT which is a summed image of projections acquired during 6 breath-holds [26]. This issue is being evaluated in ongoing work with reconstruction of projections acquired during a single breath-hold and faster gantry imaging making a CBCT possible in 1 DIBH [38]. There are certainly still several further issues to be solved, if US-based repositioning and tracking is being used. The ultrasound probe has to be considered (spared from the primary beam) during treatment planning. Experience and training of the user probably plays a larger role in the acceptance of the US-based workflow than for other approaches. An automated matching algorithm with increased user-independence may reduce these issues. Remaining minor planning issues have to be resolved and compound dosimetric consequences of the observed residual motion and gating threshold during various image guided DIBH treatment approaches will have to be evaluated. For the estimation of an optimal GTV-PTV margin certainly all error sources during the delivery chain have to be considered including intrinsic mechanical accuracy of the used systems, contouring uncertainities, residual interfractional and intrafractional variations.

For an optimal tracking system in all treatment situations, further vendor-driven modifications (higher frame rate, faster tracking algorithm, user-independent robotic ultrasound probe positioning) would be desirable and would result in its applicability to a broad range of users.

5. Conclusions

Ultrasound-based interfractional repositioning is an accurate method for daily targeting of abdominal lesions with DIBH-SBRT, making markerless, soft-tissue based positioning a clinically viable IGRT-option. Residual motion during DIBH-SBRT beam delivery is < 5 mm in 88% and < 7 mm in 96% of the delivery time. Main residual motion components are in CC and AP directions while almost no LR motion can be observed. Ideal DIBH duration should not exceed 15 s as larger errors occur more frequently if the DIBH duration increases.

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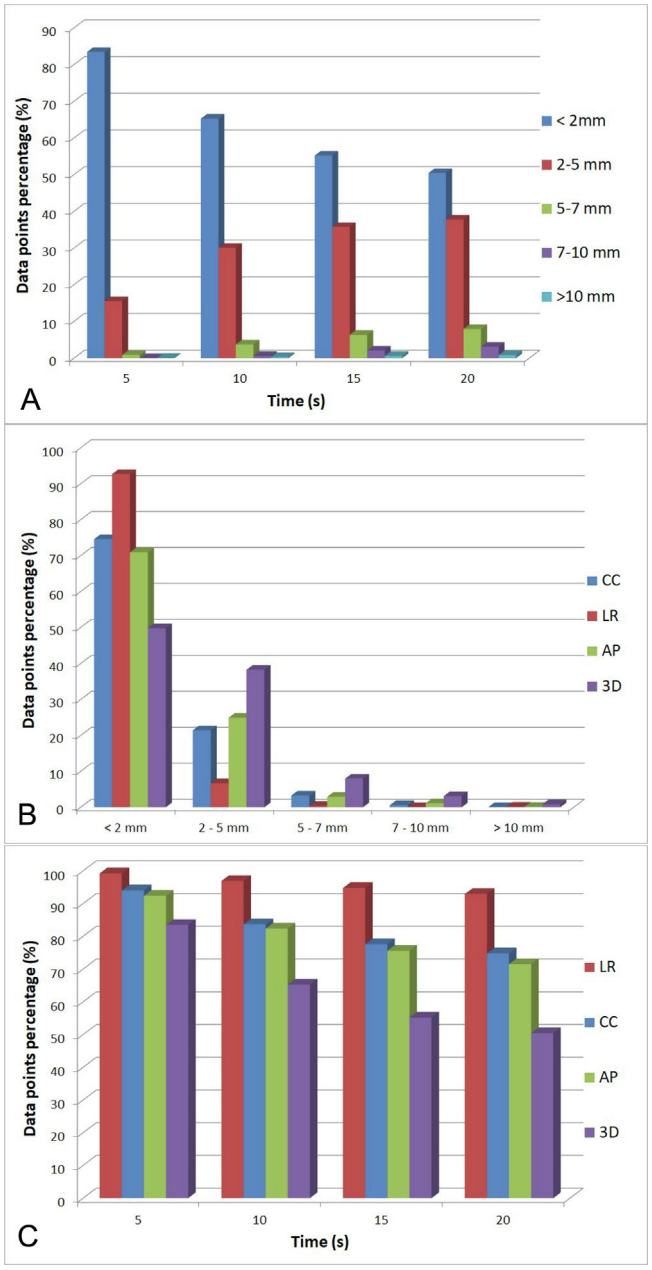

Fig. 4. A) Probability distribution of the maximum ultrasound-tracking based target displacement in CC, LR, AP directions and 3D vector-length (in percent of all data) during beam delivery. B) Probability distribution of the 3D vector-length after a certain DIBH duration (in percent). C) Percentage of target displacement below 2 mm depending on DIBH duration (in %) in LR, CC, AP directions and 3D vector.

Declaration of Competing Interest

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