

ORIGINAL ARTICLE



Precision of T2 TSE MRI-CT-image fusions based on gold fiducials and repetitive T2 TSE MRI-MRI-fusions for adaptive IGRT of prostate cancer by using phantom and patient data

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ABSTRACT

Introduction: To increase precision of radiation treatment (RT) delivery in prostate cancer, MRI-based RT as well as the use of fiducials like gold markers (GMs) have shown promising results. Their combined use is currently under investigation in clinical trials. Here, we aimed to evaluate a workflow of image registration based on GMs between CT and MRI as well as weekly MRI-MRI adaption based on T2 TSE sequence.

Material and methods: A gel-phantom with two inserted GMs was scanned with CT and three different MR-scanners of 1.5 and 3 T (T2 TSE and T1 VIBE-Dixon, isotropic, voxel size $2 \times 2 \times 2$ mm). After image fusion, deviations for fiducial and gel match were measured and artifacts were evaluated. Additionally, CT-MRI-match deviations and MRI-MRI-match deviations of 10 Patients from the M-basePro study using GMs were assessed.

Results: GMs were visible in all imaging modalities. The outer gel contours were matched with <1 mm deviation, contour volumes varied between 0 and 1%. The deviations of the GMs were less than 2 mm in any direction of MRI/CT. Shifts of peripherally or centrally located GMs were randomly distributed. The average MRI-CT-match precision of 10 patients with GMs was 1.9 mm (range 1.1–3.1 mm).

Conclusions: Match inaccuracies for GMs between reference CT and voxel-isotropic T2-TSE sequences are small. Spatial deviations of CT- and MR-contoured fiducials were less than 2 mm, i.e., below SLT of the applied modalities. In patients, the average CT-MRI-match precision for GMs was 1.9 mm supporting their use in MR-guided high precision RT.

ARTICLE HISTORY

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Introduction

Current state-of-the-art of external beam radiotherapy (EBRT) for prostate cancer includes image-guided radiotherapy (IGRT) based on planning computed tomography (CT). According to national guidelines, cross-sectional imaging including magnetic resonance imaging (MRI) is recommended for high-risk patients [1,2]. Due to the higher spatial accuracy, a more precise delineation could be achieved using MRI [3–5]. The tumor(s) in the prostate can be visualized and specifically targeted [6]. And MR-biomonitoring and adaptive treatment are currently evolving in prostate cancer and other tumor entities [7]. Reduction of the planning target volume (PTV) margins due to improved definition of the prostate including dominant lesions, i.e., the intraprostatic tumor by MRI or PET [8], is impeded by inter- and intrafractional organ movements of prostate and surrounding organs at risk (OAR) like bowel and bladder volume changes [9,10].

Daily cone-beam CT (CBCT) for IGRT compensates for interfractional changes of prostatic movement mainly caused by different OAR volumes. The additional application of fiducials like gold markers (GMs) is one approach to further increase accuracy by a GM-based daily match of the prostate to the initial planning CT (reference image). The use of different fiducials with portal imaging or CBCT is well established in clinical routine [1,11]. However, the combination of MRI planning and the use of GMs in regard to visibility on MRI [12,13], distortion of MRI data by artifacts [14] and anisotropic deformation of MRI-sequences [15] with underestimated prostatic volumes (target miss) are currently under investigation.

Here, we aimed to evaluate the accuracy of image registration based on GMs between CT and MRI in a phantom using three different MR scanners with 1.5 and 3.0 T. In addition, we used clinical data of a current clinical trial including

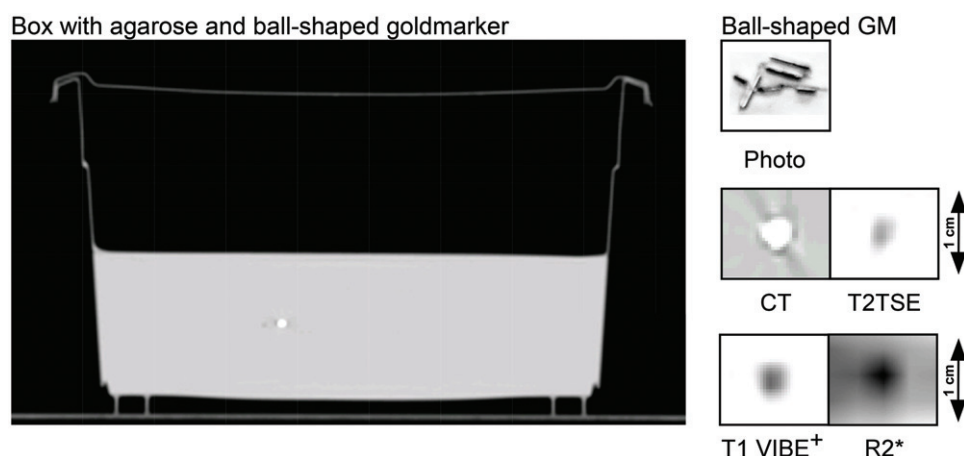


Figure 1. CT-image of Phantom for CT and MRI. The phantom consists of a plastic box filled with agarose gel and two fiducials. The appearance of the fiducials (Gold Anchor[®]) is shown as photo, on MRI (T2 TSE, T1 VIBE *Dixon and R2*) and on CT.

multiple MRI data sets of 10 patients (M-base Pro 1.0 study, ClinicalTrials.gov Identifier: NCT02724670) to validate its feasibility and the workflow regarding image fusion of additional weekly MRIs during EBRT.

Material and methods

Phantom specifications and measurements

To evaluate the accuracy of image fusion with different MRI-scanners a phantom containing fiducials was established using a rectangular plastic box (of $22.5 \times 12.76 \times 13.66 \text{ cm}^3$) filled to a height of 6.7 cm with a 1.5% agarose gel (Agar, Sigma-Aldrich, St. Louis, USA). Two GMs ($0.28 \text{ mm} \times 10 \text{ mm}$, Gold AnchorTM) were centrally and peripherally inserted into the gel structure. Assuming a cylindrical shape with several 'cave-ins' (Figure 1), their volume can be estimated to be around 0.3 mm^3 . Permanent markers for laser coordinate systems were added to achieve positioning reliability. To visualize the coordinates in CT and MRI Gelomyrtol-capsules (G. Pohl-Boskamp GmbH & Co. KG, Hohenlockstedt, Germany) were fixed at these positions. The CT-image of the phantom and the GMs on CT and MRI are shown in Figure 1.

The 'planning' CT (Philips Brilliance Big Bore CT, Philips Medical Systems, Cleveland, Ohio, US) of the phantom was performed as a reference for image fusion of MRIs. MRIs of the phantom were performed with three clinical MR-scanners: (a) 1.5 T MRI (MAGNETOM[®] Symphony, Siemens Healthcare GmbH, Erlangen, Germany; 'Symphony'), (b) 1.5 T MRI (MAGNETOM[®] Aera, Siemens Healthcare GmbH, Erlangen, Germany; Aera) and (c) 3 T (MAGNETOM[®] Skyra, Siemens Healthcare GmbH, Erlangen, Germany; Skyra). Sequence specifications are given in Table 1. Voxel size was $2 \times 2 \times 2 \text{ mm}$ in all imaging modalities but on the Symphony tomograph, which allows only for a near-isotropic voxel of $2 \times 2.1 \times 2.1 \text{ mm}$. The T2 TSE sequence was used for all inter-scanner comparisons. T1 VIBE Dixon and R2* sequences were used to test visualization of fiducials. For the R2* sequence, a T2* sequence was used without computing of the relaxivity.

MRIs were performed with abdominal coils. The region of interest included always the entire phantom. To exclude

geometric errors of the phantom due to decay, the CT was performed as reference and after retrieval of all MRIs an additional CT was taken, demonstrating robustness of the agar phantom. All sequences were rigidly matched to the reference CT using Oncentra MasterPlan (Nucletron, Columbia, MD, US) using an implemented mutual information algorithm. The registration of the CT with the T2 TSE sequences (colored contours) is shown in the supplement material. The quality of image registration by mutual information was verified by measuring the alignment of the outer gel structure. The geometrical midpoint in the axial plane was defined for each image data set. The deviation of midpoints of MRI-sequences from the CT-reference point and related volumes were measured using tools from Oncentra MasterPlan software (i.e., the definition of reference point, vector deviation). The GMs volumes were contoured for all image modalities and the volume was calculated by the radiotherapy planning program (Oncentra MasterPlan). Two observers (DW, ACM) compared visibility of the artifacts in all image modalities for validity of treatment planning. The estimated center of mass (CMCT) of each GM-contour was defined as the reference point in the CT. Then, the distance of the CM of each GM-contour in each MRI to the CMCT was determined as visualized in Figure 2. The deviations were further measured as x-, y- and z-coordinates by the same method and the resulting vector length was calculated.

Clinical data evaluation

To study robustness of consecutive image fusion in a threshold-based adaptive protocol we evaluated 10 patient samples of the 'prospective MR-based adaptive IGRT of prostate cancer' study (Mbase Pro 1.0 study, ClinicalTrials.gov Identifier: NCT02724670). In this study patients, each received a planning CT followed by GM-based image registration using an R2*-sequence from 3 T MRI (3 mm SLT, Repetition Time 328 ms, Echo Time 4.1 ms, Number of Averages 1, Spacing between slices 3, Number of Phase encoding steps 144, phase-encoding direction left to right). R2*-sequence was matched by landmark using the GMs in CT and R2* for anatomical registration. The co-registration of T2 TSE was

Table 1. Specifications of used MRI-sequences.

Modality	Slice thickness	Isotropy	Sequence	TR	TE	NA	PES	SBS
1.5T-MRT (Symphony ^a)	2 mm	Almost isotropic	T2w TSE	8060	121	1	399	2.4
1.5T-MRT (Aera ^a)	2 mm	Isotropic (2 × 2 × 2 mm)	T2w TSE	7500	118	2	161	2.5
			T1 VIBE Dixon	6.57	2.39	1	162	
3T-MRT (Skyra ^a)	2 mm	Isotropic (2 × 2 × 2 mm)	T2w TSE	4330	89	1	191	4.6
			T1 TSE	450	18	1	148	4.6
			T1 VIBE Dixon	3.94	2.46	1	161	
	3 mm		R2 ^a	328	4.1	1	144	3

w: weighted imaging; TSE: turbo spin-echo; TR: repetition time in milliseconds (ms); TE: echo time (ms); NA: number of averages; PES: number of phase encoding steps; IF: Image frequency; SBS: Spacing between slices.

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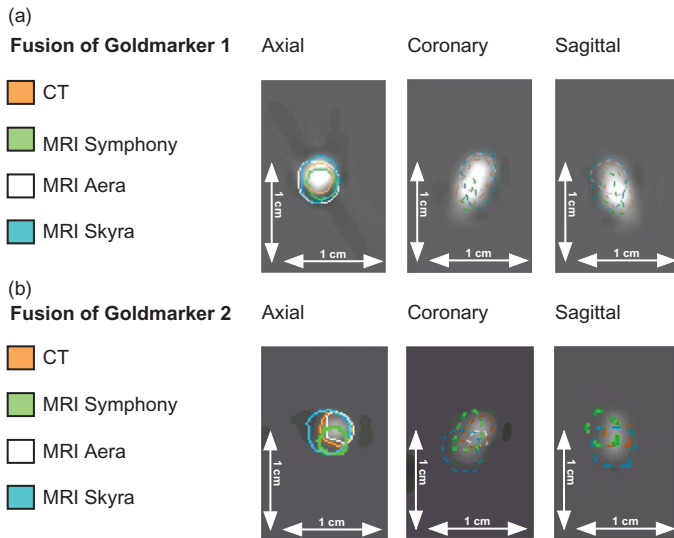


Figure 2. Match of a centrally and a peripherally inserted fiducial. The CT-image (3 dimensions) of (a) a centrally and (b) a peripherally inserted gold-marker are given with the colored contours of the matched T2 TSE sequences of three different MR-scanners (Symphony, Aera, Skyra)*. The scale of 10mm indicates the magnification. *Siemens Healthcare GmbH, Erlangen, Germany.

performed automatically in Oncentra MasterPlan. This sequence served as basis for consecutive matches of weekly T2 TSE sequences using intraprostatic landmarks and was used for delineation of the dominant lesion as shown in Figure 3(a–b). The match correctness was visually checked by the overlap of MR 1 and the consecutive MRs in regard to the position of chosen intraprostatic landmarks and after contouring of the prostate (visual check of contour deviations/midpoint of contour). Match precision of the CT-MRI-image-fusion was measured by two observers (ACM, DW) using the average squared errors (ASE) of 5–10 chosen anatomical points per match.

In the clinical study, significant prostatic volume reductions (caused by concomitant androgen deprivation) are investigated by weekly MRIs and in case of relevant reductions the treatment plan is adapted. Therefore, we additionally evaluated landmark-based match precision of 10 patient samples using a weekly MRI based on 5–10 anatomical identical intraprostatic points (MRI-MRI-match), Figure 3(c). Relevant intraprostatic points comprised upper and lower position of urethra, and at least at two central slices anatomical characteristics like benign prostatic lesions, dominant lesion or others. Within the slice containing the intraprostatic landmarks we added bilateral landmarks of prostate to

ensure correct orientation of the match. Match precision of the MRI-MRI-matches (8 MRI per patient, $n = 80$) was measured by two different observers (ACM, DW) by the ASE of each MRI-MRI-match. The landmark based matching was performed by two radiation oncologists (ACM, DW) to account for interobserver variability.

Results

Phantom data

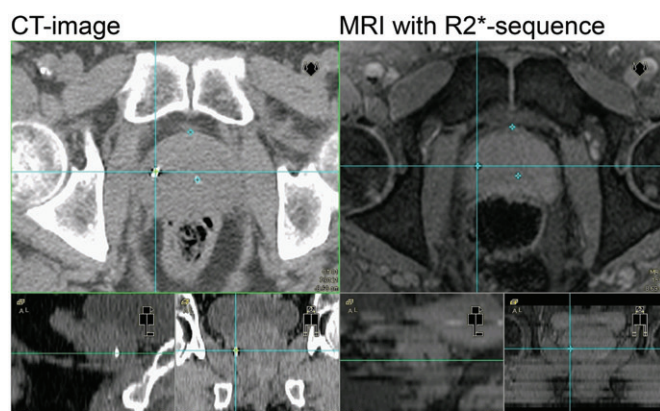
The registration of MRIs by mutual information (reference = CT) was excellent. Our self-made phantom was capable of visualizing GMs in CT and MRI as demonstrated in Figure 1. A deviation between the outer contours of the agarose gel volumes was visually almost undetectable and the measurement of midpoint-deviations supported that finding with variations of less than 1 mm in x- and y-axis (Table 2). This is confirmed by the small difference ($\leq 1\%$) between the agarose gel volumes (Table 2, Supplement Figure 1).

The subjective visibility of GMs (2 observers) did not vary between the 1.5 T MRI data but was best in the 3 T sequences (Figure 1) also indicated by small GM volume differences favoring 3 T sequences with slightly larger volumes, Table 2. The images of the fiducials in phantom and prostate (Figures 1–3) indicate that artifacts are small but present in CT images. The CT-artifacts did not impair contouring on CT. Artifacts around the GMs were detected in the MRI-sequences (T2 TSE, T1-VIBE Dixon, R2*) but appear to be small (Figures 1 and 3). The largest deviation of the MRIs from the CT was observed for the 3 T MRI match (Table 3 and Figure 2). However, all deviations were below 2 mm with only one vector length above 2 mm.

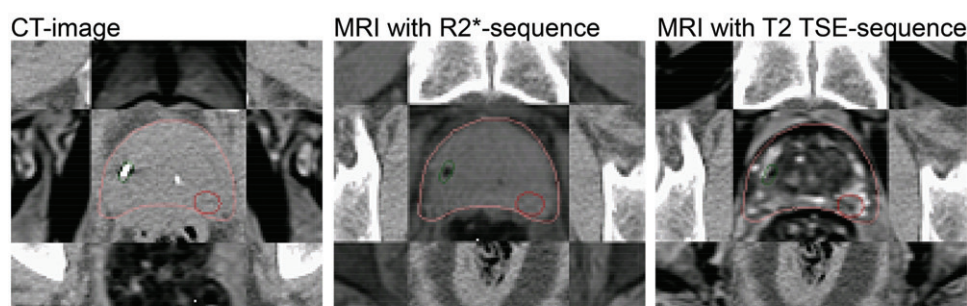
Patient data – fiducial-based match as baseline

The clinical datasets of 10 landmark based CT-MRI-matches showed an average deviation of 1.9 mm (range 1.2–2.9 mm, Table 4). The example in Figure 3(a) shows matching deviations of CT and R2* below 1 mm (ASE 0.5 mm). Co-registration of the T2 TSE sequence leads to a very precise match as indicated by the contour around the prostate in the CT-, R2*- and T2 TSE images (Figure 3(b)).

(a) **Image registration of CT and MRI by fiducial**



(b) **Image registration for consecutive matched diagnostic MRI sequence**



(c) **Image fusion based on pre-existing registration**

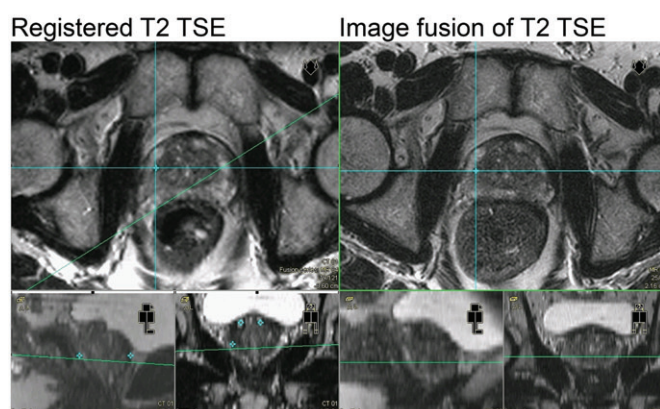


Figure 3. MR-image fusion workflow in a clinical study. (a) Image registration by GM using R2*-sequence from 3 T MRI (Skyra)*. (b) Consecutive match of T2 TSE sequence for tumor delineation. (c) Match of a weekly derived T2 TSE sequences using the marker-matched T2 TSE sequence (b) for registration on anatomical identical intraprostatic points (MRI-MRI-match). For details, see the method section. *Siemens Healthcare GmbH, Erlangen, Germany.

T2 TSE-co-registration used as baseline for consecutive matches

The accuracy of weekly MRIs (T2 TSE) for volume measurement of 10 patient data sets (8 MRI per patient, $n = 80$) were evaluated by calculating the average of the ASE per patient and giving the average of that: 1.6 mm (range 1.0–2.4 mm, Table 4). The landmark-based approach was visually accurate and replicable in all cases (Figure 3(c)).

Discussion

Here, we report the feasibility of a novel clinical workflow for adaptive RT using the co-registered T2 TSE sequence as

baseline enabling consecutive landmark-based T2 TSE matches with acceptable deviations of 1.9 mm in average i.e., below slice thickness. This finding appears to be relevant because the T2 TSE sequence is used for contouring of the dominant lesion but the small GMs are invisible (i.e., no artifacts) in this sequence. Therefore, registration on CT in a clinical setting (GMs in prostate) is performed indirectly using a R2* or gradient echo (GE) sequence and in a second step the T2 TSE is co-registered for contouring. In this study, we could demonstrate the robustness of MR-CT registration with GMs based on the clinically applied T2 TSE sequence in a phantom with three MR-scanner generations.

The pre-condition for the phantom study was the correct registration of all modalities by the planning software OTP.

Table 2. Volumes of the gel-contour and the goldmarker-contours. Additionally the deviations of the midpoint of the gel contours in the MRI sequences compared to CT.

	Volume [ml]			Deviations [mm] of geometric midpoint of the gel contour (axial view) from midpoint of CT (reference point)	
	Gel-contour	Goldmarker 1	Goldmarker 2	x	y
CT	1912.14	0.03	0.03	0	0
Symphony	1912.14	0.02	0.02	0.6	0.6
Aera	1917.47	0.03	0.02	0.1	0.5
Skyra	1892.77	0.06	0.04	0.4	0.9

Table 3. Spatial deviations of two fiducials in all dimensions.

Parameter	Goldmarker 1				Goldmarker 2			
	Deviation from CT reference [mm]				Deviation from CT reference [mm]			
Axis	x	y	z	Length of vector	x	y	z	Length of vector
Symphony	1.0	0.7	1.4	1.9	0.6	0.0	1.4	1.5
Aera	0.0	1.1	1.7	2.0	0.1	0.9	0.2	0.9
Skyra	0.3	0.0	1.3	1.4	1.8	1.9	0.4	2.6

The reference point was the midpoint of each goldmarker on CT-image. 3D-Deviations of both goldmarker in T2 TSE-sequence from reference (CT) were measured for each MR-scanner (Symphony, Aera, Skyra). In addition, the resulting vector of deviation was calculated.

Table 4. Results of CT-MRI registration and T2 TSE-based MRI-MRI registration of 10 patient samples each.

Patients	Average Squared Error (ASE)	
	Initial CT-MRI match [mm]	Average of the eight weekly MRI matches [mm]
1	2.3	1.5
2	2.1	1.0
3	1.6	1.1
4	1.2	2.0
5	1.5	2.4
6	2.3	1.5
7	2.3	1.8
8	2.9	1.5
9	1.2	1.8
10	1.6	1.3
	Average: 1.9 mm	Average: 1.6 mm

Given is the average ASE of two measurements for each match and the average of ASEs of the eight weekly MRI matches.

The comparison of the CT-based match of different MRIs clearly confirms the accuracy of image fusion by mutual information (Table 2, Supplement Figure 1). Comparing the gel volumes, the differences were below or at 1% for each modality underlining these findings.

Thereafter, we studied the impact of potential distortions of 'isotropically-acquired' MR-images (Figure 2, Table 3). The deviations of the GMs were not systematically shifted in one direction i.e., a random error might be assumed. The largest deviation was measured in the 3 T MRI but was below the size of SLT. The vector shifts also indicate that the position of the GMs within the gel i.e., centrally or peripherally did not influence the spatial deviation. The markers contain 0.5% iron yet no systematic deviation could be found when comparing the three T2 TSE sequences of different scanners. We did not attempt deformable image registration due to the inherent difficulties of a spatially accurate match [16].

Visualizations of the GMs in 3 T MRI was superior to both 1.5 T MRI in all sequences due to more susceptibility artifacts resulting in a generally slightly larger volume of the fiducial, as shown in Figure 2, Table 2 which is in line with a report from Tanaka et al. [12]. Despite volume differences, the artifacts in CT or MRI did not impair contouring in both modalities. To avoid artifacts and facilitating MR-monitoring during eight weeks of EBRT we have chosen one of the smallest available GMs to reduce potential artifact on CT and MRI [17]. In the clinical setting, the artifacts were sometimes in T2 TSE images so low that the GMs could not be identified. This limitation has been described before [18]. Therefore, another sequence (R2*; available for Skyra) was employed in the clinical prospective Mbase Pro 1.0 study to facilitate the fiducial-based co-registration of T2 TSE sequences and MR adaptive IGRT (Figure 3(a–b)). In addition, we demonstrated that small GMs as used in this study were also detectable in isotropic VIBE Dixon sequences which are available for the latest MR-tomography generation (Aera, Skyra). We did not detect distortions of MRIs leading to volume underestimation compared to CT with the investigated isotropic MR sequences. Bossard et al. published another protocol using fiducials to indirectly match a diagnostic multiparametric (mp) MRI on a curved table with a planning CT via another flat table MRI [19]. In contrast to that matching algorithm we performed an additional mpMRI after insertion of the fiducials on a flat table to enable a direct image fusion of the mpMRI showing the intraprostatic lesion.

The MRI-based match of initial mpMRI (before insertion of fiducials or start of ADT) as well as the monitoring MRIs during EBRT were then performed either also by fiducials or using identical anatomic landmarks of MRI.

Our findings compare well to the results of Maspero et al. and Hamdan et al., who each used automatic GM-localization approaches and found similarly small deviations (below 2 mm) [20,21]. In contrast to this study, the authors did not evaluate the MRI sequence which is used for contouring (T2 TSE). An automatic registration method of GMs was performed but the co-registration of other sequences was not mentioned. Furthermore, Huang et al. and Walcker et al. also demonstrated deviations of less than 2 mm using MR-phantoms without gold markers [14,22]. Therefore, PTV-margins should at least cover SLT (2 mm in this study) plus an additional margin. In general, interfractional changes are well compensated by daily CBCT but margins should not be reduced too much to be large enough for intrafractional movement [23]. Engels et al. used daily IGRT plus fiducials

with tight PTV margins (minimal PTV margin: 3 mm vs. 6 mm) and reported increased recurrence rates potentially due to intrafractional displacement in the arm with 3 mm margins [24]. Intrafractional movement depends on duration of treatment i.e., duration of CBCT plus radiotherapy. Consequentially, short delivery time through VMAT (volumetric modulated arc therapy) or even FFF (flattening filter free) techniques might help to solve this problem [25] as well as tracking of the prostate [26] or other visible markers like spacers [27,28].

This study has several limitations: The prostate phantom was only scanned once in each MRI. Multiple data sets might provide a more robust result regarding spatial deviations or distortions. We deliberately used 2 mm of SLT for our planning CT and all MRI sequences, because this SLT is frequently used in RT planning routine. A lower SLT could provide even more precise information about the spatial deviations of GMs and also about the quality of the CT to MRI match of the outer contour. However, the risk of artificial movements in the clinical situation might be increased by the longer duration of MR-acquisition. Our data were derived from voxel-isotropic MRI-sequences. Therefore, our findings cannot be transferred to non-isotropic conditions.

In conclusion, this study suggests that MR-based adaptive IGRT using voxel-isotropic MR-images with a fiducial-based match is associated with low match-related inaccuracies. Consecutive matching of additional MRIs (monitoring of treatment) is feasible using the proposed workflow with uncertainties also below SLT of the MRI.

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Disclosure statement

The authors report no conflicts of interest. We mention the cooperation with Siemens Healthcare in another project (ACM, DT, DZ, KN) and as part of an internal clinical use test (ACM).

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