International Journal of Radiation Oncology biology • physics

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Physics Contribution

Feasibility of Gold Fiducial Markers as a Surrogate for Gross Tumor Volume Position in Image-Guided Radiation Therapy of Rectal Cancer

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Received Mar 20, 2019. Accepted for publication Aug 26, 2019.

Summary

This study evaluated the feasibility of fiducials as a surrogate for gross tumor volume position in rectal cancer. Setup correction based on fiducials reduces required margins in the anterior-posterior and craniocaudal directions for a gross tumor volume boost compared with bony anatomy setup correction. Reduction of these margins

Purpose: To evaluate the feasibility of fiducial markers as a surrogate for gross tumor volume (GTV) position in image-guided radiation therapy of rectal cancer.

Methods and Materials: We analyzed 35 fiducials in 19 patients with rectal cancer who received short-course radiation therapy or long-course chemoradiation therapy. Magnetic resonance imaging examinations were performed before and after the first week of radiation therapy, and daily pre- and postirradiation cone beam computed tomography scans were acquired in the first week of radiation therapy. Between the 2 magnetic resonance imaging examinations, the fiducial displacement relative to the center of gravity of the GTV (COG_{GTV}) and the COG_{GTV} displacement relative to bony anatomy were determined. Using the cone beam computed tomography scans, inter- and intrafraction fiducial displacement relative to bony anatomy were determined.

Results: The systematic error of the fiducial displacement relative to the COG_{GTV} was 2.8, 2.4, and 4.2 mm in the left-right, anterior-posterior (AP), and craniocaudal (CC) directions, respectively. Large interfraction systematic errors of up to 8.0 mm and

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This work was supported by the Dutch Cancer Society/Alpe d'HuZes Fund (grant number UL2013-6311) and the Leiden University Fund and Nypels van der Zee Fonds (grant 3217/28-3-13/NZ). The funding sources had no involvement in the study design; the collection, analysis, and interpretation of data; the writing of the manuscript; or the decision to submit the manuscript for publication.

Disclosures: Cook Medical fiducials were provided without costs. The producers of the fiducial markers had no involvement in the study design; the collection, analysis, and interpretation of data; the writing of the manuscript; or the decision to submit the manuscript for publication.

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2019.08.052.

Int J Radiation Oncol Biol Phys, Vol. 105, No. 5, pp. 1151–1159, 2019

https://doi.org/10.1016/j.ijrobp.2019.08.052

may be higher in patients with a proximal compared with a distal tumor.

random errors up to 4.7 mm were found for COG_{GTV} and fiducial displacements relative to bony anatomy, mostly in the AP and CC directions. For tumors located in the mid and upper rectum, these errors were up to 9.4 mm (systematic) and 5.6 mm (random) compared with 4.9 mm and 2.9 mm for tumors in the lower rectum. Systematic and random errors of the intrafraction fiducial displacement relative to bony anatomy were $\leq$2.1 mm in all directions.

Conclusions: Large interfraction errors of the COG_{GTV} and the fiducials relative to bony anatomy were found. Therefore, despite the observed fiducial displacement relative to the COG_{GTV}, the use of fiducials as a surrogate for GTV position reduces the required margins in the AP and CC directions for a GTV boost using image-guided radiation therapy of rectal cancer. This reduction in margin may be larger in patients with tumors located in the mid and upper rectum compared with the lower rectum.

Introduction

Neoadjuvant radiation therapy reduces local recurrence rates after surgery in patients with rectal cancer.[1-4] A pathologic complete response is observed in 15% to 25% of patients after neoadjuvant chemoradiation.[5,6] In addition, dose escalation is suggested to result in higher complete response rates, which is attractive considering the increased interest in organ preservation.[6-10]

The current clinical practice for setup correction in external beam radiation therapy of rectal cancer is based on bony anatomy using cone beam computed tomography (CBCT).[11] To ensure proper gross tumor volume (GTV) coverage in a GTV boost setting, a planning target volume (PTV) margin of 7 to 30 mm is used to accommodate delineation errors, setup errors, and inter- and intrafraction motion of the GTV.[12-16] Setup correction based on the GTV instead of bony anatomy may decrease the required PTV margins. However, this is challenging owing to the limited soft tissue contrast of CBCT.[17] Magnetic resonance–guided radiation therapy systems could be used to perform setup correction based on a direct visualization of the GTV with superior soft tissue contrast.[18] However, such systems are not widely available yet. Given that fiducial markers have been proven useful for setup correction in other tumor locations such as pancreas, esophagus, and prostate,[19-21] fiducials may be useful as a surrogate for GTV position in rectal cancer. Several studies have reported on the use of fiducials in the rectum and focus on marker visibility and migration,[22] fiducial retention and adverse events,[23,24] and the use of fiducials to aid in the delineation of the target volume.[25] However, none have investigated the potential benefit of fiducials for setup correction in radiation therapy of rectal cancer.

To use fiducials as a surrogate for the GTV, the position of the fiducials must be representative of the position of the GTV. The aim of this study was therefore to evaluate the feasibility of fiducials as a surrogate for GTV position in radiation therapy of rectal cancer.

Methods and Materials

Patients

Between July 2015 and September 2016, we included 20 patients with proven rectal adenocarcinoma who were scheduled for short-course radiation therapy (5 × 5 Gy) or long-course chemoradiation therapy (LC-CRT; 25 × 2 Gy combined with capecitabine 825 mg/m^2 twice daily on days of radiation therapy) followed by total mesorectal excision. Patients were treated in supine position. Before each radiation therapy fraction, patients were asked to void their bladder and subsequently drink 300 cm^3 of water to reproduce bladder filling.

Exclusion criteria were contraindication for fiducial insertion (coagulopathy or anticoagulantia that could not be stopped), prior pelvic irradiation, pelvic surgery or hip replacement surgery, pregnancy, a contraindication for magnetic resonance imaging (MRI), or World Health Organization performance status 3 to 4. This study was registered at the Dutch Trial Registry (REMARK study, registration no. NL4473).[26]

Fiducials

We used 4 types of fiducials, inserted in 5 patients each (Visicoil 0.5 x 5 mm and Visicoil 0.75 x 5 mm [IBA Dosimetry, GmbH, Germany], Cook 0.64 x 3.4 mm [COOK Medical, Limerick, Ireland], and Gold Anchor 0.28 x 20 mm [unfolded length][Naslund Medical AB, Sweden]). We endoscopically placed the fiducials in the tumor and mesorectum at least 1 day before the start of radiation therapy. The fiducial insertion strategy is described in Rigter et al.[24]

MRI processing

We performed 2 multiparametric MRI examinations for each patient on a Philips Achieva 1.5T, Philips Achieva 3T, Philips Achieva dStream 3T, or Philips Ingenia 3T. Details of

the scan protocol are listed in the supplementary material (available online at https://doi.org/10.1016/j.ijrobp.2019.08.052). We acquired a first MRI examination up to 2 weeks before or up to 1 week after the start of radiation therapy and a second MRI examination between 1 and 2 weeks after the start of radiation therapy. In an earlier study, we evaluated the MRI visibility of the fiducials, and we identified 17 out of 34 fiducials on the first MRI and 9 out of 30 fiducials on the second MRI.[27] The Visicoil 0.75 and the Gold Anchor were the best visible fiducials on MRI. In addition, a consensus meeting with a radiologist (EP) and a resident radiation oncologist (ER) was held to identify more fiducials for this study. We delineated the artefacts that the fiducials created on MRI on the tT2-TSE scan with help of the other available sequences. The coordinate of the center of gravity (COG) of this delineation represented the fiducial position.

The GTV was delineated on the tT2-TSE scan of both MRI examinations by 1 observer (RE) and was subsequently checked by a radiation oncologist (FP) in Oncentra (Elekta, Veenendaal, Netherlands). We registered the tT2-TSE sequence of the second MRI examination to the tT2-TSE sequence of the first MRI examination using Elastix[28] with a rigid transformation based on the bony anatomy of the pelvis and the sacrum.

We selected both ischial spines and the pubic symphysis as anatomic landmarks on the bony anatomy on the MRI examinations to assess registration accuracy. The registration accuracy was defined as the mean and standard deviation of the distances between a landmark position on the registered second MRI examination and the corresponding landmark position on the first MRI examination.

To determine the displacement of the fiducials relative to the GTV, we calculated the displacement for each fiducial relative to the center of gravity of the GTV delineation (COG_{GTV}) on the second MRI with respect to the first MRI. Subsequently, we determined the mean of means by calculating the mean displacement over all fiducials and the group systematic error by calculating the standard deviation over all fiducial displacements.[29]

To determine the interfraction GTV displacement relative to bony anatomy, we calculated the displacement of the COG_{GTV} relative to bony anatomy on the second MRI with respect to the first MRI. Subsequently, we determined the mean of means by calculating the mean displacement over all COG_{GTV} displacements and the group systematic error by calculating the standard deviation over all COG_{GTV} displacements.[29]

To test for differences in displacement between proximal and distal tumors, we calculated the interfraction COG_{GTV} displacement relative to bony anatomy on MRI separately for patients with a tumor in the mid and upper rectum (7-16 cm from anal verge) and the lower rectum (0-6 cm from anal verge).[30]

CBCT processing

During the first week of radiation therapy, we acquired daily pre- and postirradiation CBCT scans (Elekta XVI, reconstructed slice thickness 1.0 mm, pixel spacing 1.0 mm × 1.0 mm). For the patients who were treated with LC-CRT, preirradiation CBCT scans were acquired weekly after the first week of radiation therapy.

The first preirradiation CBCT scan was used as the reference scan. We registered all subsequent CBCT scans to the reference scan using Elastix with a rigid registration based on the bony anatomy of the pelvis and the sacrum.[28] The registration accuracy was assessed using the same method as described for the MRI examinations, with the promontory as an additional anatomic landmark.

We segmented fiducials on the reference and registered CBCT scans by manually selecting a point on each fiducial. A box of 12 × 12 × 12 mm was automatically created around each selected point, and a threshold that was well above the image intensities of the surrounding soft tissue was applied to segment the fiducial. The coordinate of the COG for each fiducial segmentation was used as the position for each fiducial.

The displacement of the COG of all fiducials (COG_{FID}) as a result of changes in fiducial configuration was calculated as follows. For patients with 2 or more fiducials in situ, the position of each fiducial relative to the COG_{FID} was determined on each preirradiation CBCT scan. To assess the resulting displacement of the COG_{FID}, we calculated the standard deviation of each fiducial position relative to COG_{FID} over all preirradiation CBCT scans (SD_{FID}) and subsequently calculated the standard deviation of the COG_{FID} for each patient with 2 or more fiducials in situ:

$$SD\ of\ COG_{FID} = \frac{\sqrt{SD^2_{FID_1} + SD^2_{FID_2} + , + SD^2_{FID_n}}}{n}$$

with $SD^2_{FID_1}$, $SD^2_{FID_2}$, …, $SD^2_{FID_n}$ being the squared standard deviation of a fiducial position relative to COG_{FID} over all preirradiation CBCT scans in the patient and n being the number of fiducials in the patient. Subsequently, we determined the group random error by calculating the root mean square of all the standard deviations of COG_{FID}.[29]

To determine the interfraction fiducial displacement relative to bony anatomy, we calculated the displacement of each fiducial on each preirradiation CBCT scan with respect to the reference scan. To determine the intrafraction fiducial displacement relative to bony anatomy, we calculated the displacement of each fiducial on the post-irradiation CBCT scan with respect to the preirradiation CBCT scan of the same fraction. For each fiducial, we calculated a mean displacement and corresponding standard deviation over all fractions for the inter- and intrafraction displacement in the left-right (LR), anterior-posterior (AP), and craniocaudal (CC) directions. Subsequently, we calculated for the inter- and intrafraction fiducial displacement the mean of means over all fiducials and the group systematic and random error by calculating the standard deviation of the mean displacements of all fiducials and the root mean square of the standard deviation of all fiducials.[29]

To test for differences in displacement between proximal and distal tumors, we calculated the interfraction fiducial displacement relative to bony anatomy separately for patients with a tumor in the mid and upper rectum (7-16 cm from anal verge) and the lower rectum (0-6 cm from anal verge).[30]

Treatment margins

To determine PTV margins, we quadratically added systematic and random errors of the different components to derive the combined errors for the GTV position in 3 image guidance scenarios using the Van Herk et al margin recipe.[31] For setup correction based on bony anatomy, the inter- and intrafraction displacement of the GTV relative to the bony anatomy needs to be considered. We derived the interfraction displacement relative to bony anatomy in 2 ways: first, from the COG_{GTV} displacement on MRI, and second, from the fiducial displacements on CBCT. Both were combined with the intrafraction fiducial displacement on CBCT to calculate the errors for setup correction based on bony anatomy. In a scenario of setup correction based on fiducials, we also need to consider the position uncertainty of the GTV relative to the fiducials. Therefore, we combined the fiducial displacement relative to the COG_{GTV} with the COG_{FID} displacement as a result of changes in fiducial configuration and the intrafraction fiducial displacement relative to bony anatomy on CBCT. In a scenario in which the GTV can be visualized directly for setup correction, we only used the errors of the intrafraction fiducial displacement relative to bony anatomy.

Statistical analysis

We used SPSS Statistics 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0. Armonk, NY) for statistical analysis. Because of the small sample size in this study, we used the nonparametric Mann−Whitney U test to test for differences between the mean and standard deviation of the fiducial displacements according to the distance from the anal verge.

Results

Patients and fiducials

One patient was excluded because all fiducials were inadvertently inserted in the prostate. Therefore, 19 patients were available for analysis, of whom 8 received short-course radiation therapy and 11 received LC-CRT. Patient characteristics are shown in Table 1. The fiducial retention in the REMARK study was described earlier.[24] A total of 35 fiducials in situ were available for analysis on CBCT, of which 26 fiducials were in the tumor and 9 were in the mesorectum.[27] The consensus meeting resulted in 22 identified fiducials on the first MRI and 17 identified fiducials on the second MRI. All 17 fiducials identified on the second MRI were also identified on the first MRI. Of those, 14 fiducials were inserted in the tumor and 3 fiducials were inserted in the mesorectum. Examples of a GTV delineation and a fiducial on the T2-TSE sequence of both MRI examinations and a fiducial on 2 CBCT scans is shown in Figure 1.

Imaging

Median time from the first MRI to the start of radiation therapy was 0 days (range, -5 to 12 days). Median time between the first and second MRI examination was 7 days (range, 4-21 days). For 2 patients who were treated with LC-CRT, the first MRI examination was acquired 2 days (2 fractions) and 5 days (3 fractions) after start of radiation therapy. The median delineated GTV volume was 22.8 cm^3 (range, 6.9-64.6 cm^3) for the first MRI and 15.2 cm^3 (range, 6.1-71.0 cm^3) for the second MRI. Median difference between the GTV volumes of the first and second MRI was -3.0 cm^3 (range, -26.5 to 6.4 cm^3), with a negative difference indicating a smaller volume in the second MRI. Fourteen out of 19 delineated GTV volumes were smaller on the second MRI. The MRI registration error was on average 0.0 ± 0.6 mm (LR), 0.2 ± 1.4 mm (AP), and -0.1 ± 1.3 mm (CC).

A total of 219 CBCT scans were acquired in 19 patients (range, 2-21 per patient), of which 132 were preirradiation CBCT scans in 19 patients and 87 were postirradiation CBCT scans in 17 patients. The average time between pre- and postirradiation CBCT scans was 9 ± 1 minutes. The CBCT registration error was on average -0.1 ± 0.7 mm (LR), -0.2 ± 0.9 mm (AP), and 0.0 ± 0.8 mm (CC).

Inter- and intrafraction displacement

The systematic error of the interfraction fiducial displacement relative to the COG_{GTV} was 2.8 mm (LR), 2.4 mm (AP), and 4.2 mm (CC) as shown in Table 2. The random error of the interfraction displacement of the COG_{FID} was <1 mm in all directions.

The systematic error of the COG_{GTV} displacement relative to bony anatomy was substantially larger than the systematic error of the fiducial displacement relative to bony anatomy on CBCT in the AP (7.2 mm vs 4.8 mm) and CC direction (8.0 mm vs 4.6 mm). This was mainly due to 2 patients who showed large COG_{GTV} displacements on MRI in the AP and CC directions: 15 mm and -20 mm (AP), and -16 mm and 20 mm (CC), respectively. After reviewing the MRI examinations, we observed a large difference in the amount of air in the rectum, which displaced the GTV. In one of these patients, a large difference in bladder filling was also observed. In the other 17 patients, the group systematic error of the COG_{GTV} displacement relative to bony anatomy was 4.1 mm (AP) and 5.6 mm (CC), in line with the fiducial displacement relative to bony anatomy on CBCT.

Table 1 Patient characteristics

Patient	Sex	Age (y)	cTNM	Distance from anal verge (cm)	Tx	Fiducial type	No. preirradiation CBCT scans	No. postirradiation CBCT scans	No. implanted fiducials	No. fiducials in situ at end of Tx*	No. fiducials identified on both first and second MRI*
1	M	71	T3N0M0	5	SC-RT	Visicoil 0.5	5	5	3	1	1
2	M	82	T3N0M0	0	SC-RT	Visicoil 0.5	5	4	3	2	1
3	M	63	T2N0M0	2	LC-CRT	Visicoil 0.5	10	4	3	1	0
4	M	60	T3N1M0	8	LC-CRT	Visicoil 0.5	10	4	3	3	0
5	F	60	T3N1M0	2	SC-RT	Visicoil 0.5	2	0	3	1	1
6	M	67	T3N2M0	8	LC-CRT	Visicoil 0.75	10	6	3	1	1
7	F	52	T3N1M0	8	SC-RT	Visicoil 0.75	5	0	3	2	0
8	M	75	T3N0M0	10	SC-RT	Visicoil 0.75	4	2	3	2	2
9	M	82	T2N1M0	15	SC-RT	Visicoil 0.75	5	5	3	1	1
10	M	63	T3N1M0	15	SC-RT	Visicoil 0.75	5	5	3	1	1
11	F	62	T2N1M0	11	SC-RT	COOK	5	5	3	2	0
12	M	58	T3N0M0	1	LC-CRT	COOK	-	-	4	-	-
13	M	57	T3N2M0	7	LC-CRT	COOK	10	5	4	1	1
14	F	60	T3N1M0	2	SC-RT	COOK	5	5	4	3	0
15	M	59	T3N2M0	8	LC-CRT	COOK	11	8	4	3	0
16	M	63	T3N0M0	1	LC-CRT	Gold Anchor	9	5	3	2	2
17	M	65	T3N2M0	2	LC-CRT	Gold Anchor	9	5	3	1	1
18	M	59	T2N1M0	16	SC-RT	Gold Anchor	5	5	3	2	2
19	F	61	T3N1M0	10	SC-RT	Gold Anchor	5	5	3	3	1
20	M	51	T3N0M0	2	LC-CRT	Gold Anchor	12	9	3	3	2
Total							132	87	64	35	17

Abbreviations: CBCT = cone beam computed tomography; cTNM = clinical TNM; F = female; M = male; MRI = magnetic resonance imaging; Tx = treatment schedule; SC-RT = short-course radiation therapy; LC-CRT = long-course chemoradiation therapy.
* Excludes fiducials that were inadvertently inserted in the prostate.

For the interfraction COG_{GTV} displacement relative to bony anatomy, the systematic error was 3.0 mm (LR), 8.7 mm (AP), and 9.4 mm (CC) for patients with a tumor in the mid or upper rectum, whereas it was 1.3 mm (LR), 4.7 mm (AP), and 4.9 mm (CC) for patients with a tumor in the lower rectum. Similarly, for the interfraction fiducial displacement relative to bony anatomy on CBCT, systematic and random errors were 3.8 and 3.4 mm (LR), 6.1 and 5.1 mm (AP), and 5.5 and 5.6 mm (CC), respectively, for the mid and upper group and 3.1 and 1.1 mm (LR), 1.6 and 2.3 mm (AP), and 2.8 and 2.9 mm (CC), respectively, for the lower-rectum group. The standard deviation of the interfraction fiducial displacements relative to bony anatomy was significantly higher for patients with a tumor in the mid or upper rectum compared with patients with a tumor in the lower rectum in the LR ($P < .01$), AP ($P = .03$), and CC ($P = .04$) directions. An overview of the inter- and intrafraction fiducial displacements relative to bony anatomy split according to tumor location is shown in Figure 2 and Figure 3.

Systematic and random errors of the intrafraction fiducial displacement relative to bony anatomy were $\leq$2.1 mm in all directions.

Setup correction scenarios

For setup correction based on bony anatomy, the estimated margins were 8.3 mm (LR), 19.5 mm (AP), and 21.9 mm (CC) using the COG_{GTV} displacement relative to bony anatomy and 11.3 mm (LR), 15.7 mm (AP), and 15.8 mm (CC) using the fiducial displacement relative to bony anatomy (Table 3). For setup correction based on fiducials, a reduction to 8.3 mm (LR and AP) and 12.8 mm (CC) was observed. Setup correction based on a direct visualization of the GTV would further reduce required margins to 3.0 mm (LR), 4.7 mm (AP), and 5.5 mm (CC).

Discussion

The aim of this study was to evaluate the feasibility of fiducials as a surrogate for GTV position in rectal cancer. Despite fiducial displacement relative to the COG_{GTV}, an advantage for fiducial setup correction was observed in the AP and CC directions compared with bony anatomy setup correction. Consequently, the use of fiducials in a GTV boost setting allows for more precise irradiation of the GTV and

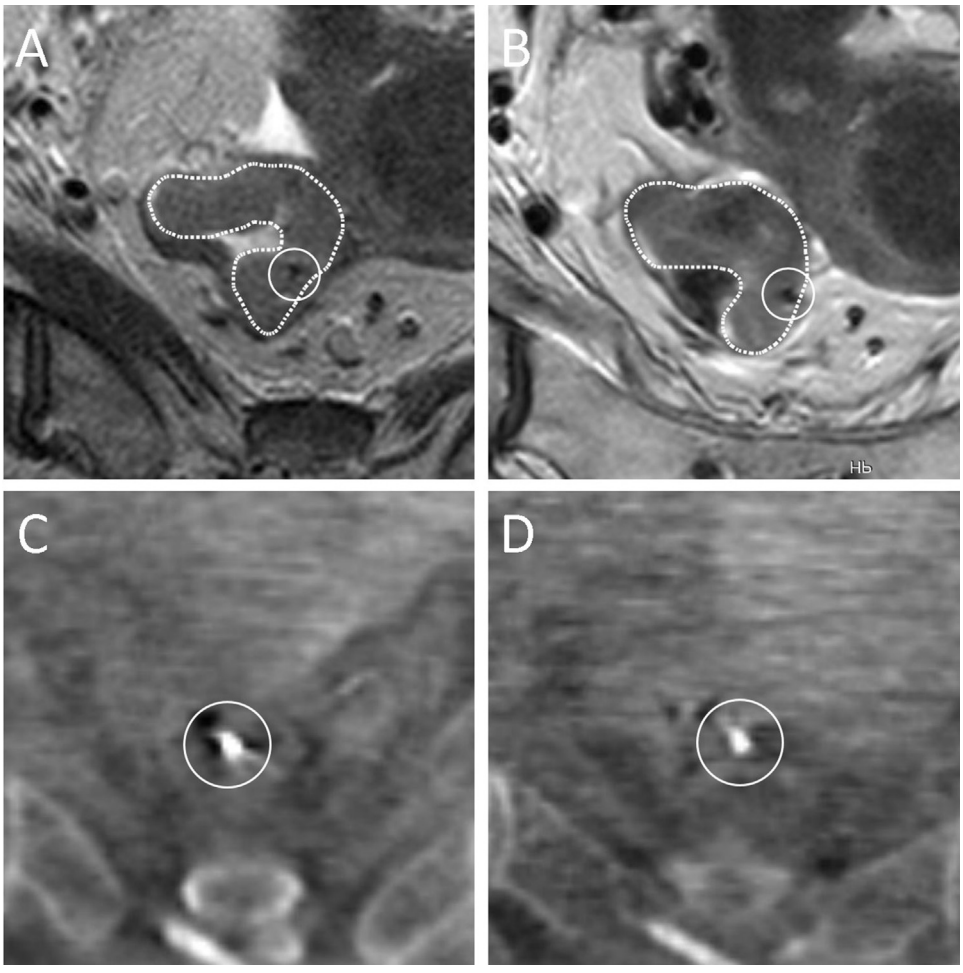

Fig. 1. (A) and (B) examples of a gross tumor volume delineation and a fiducial on the T2-TSE sequence of both magnetic resonance imaging examinations and (C) and (D) the same fiducial on 2 preirradiation cone beam computed tomography scans for patient 19.

sparing of organs at risk. More organ motion of the proximal rectum compared with the distal rectum is reported.[32-34] Although only a small number of patients were included in our study, a similar difference was observed. This suggests that the advantage of setup correction based on fiducials may be larger in patients with a proximal tumor.

The interfraction systematic error of the COG_{GTV} relative to bony anatomy, as based on MRI, was substantially larger than the systematic and random errors of the fiducial displacements on CBCT. This is mainly due to large displacement of the COG_{GTV} in 2 patients on MRI and may be explained by the absence of patient preparation before the MRI examinations. For the calculation of the displacement of the COG_{FID} as a result of changes in fiducial configuration, the COG_{FID} was used as a reference point, assuming that all fiducials contributed equally to changes in fiducial configuration.

There is an inherent inaccuracy in determining exact fiducial locations on MRI, for instance due to the asymmetrical artefacts of the fiducials.[35] With help of the other available sequences, we delineated the fiducials on the tT2-TSE scan because it had the smallest artifacts.[27] Therefore, we believe that the inaccuracy in selecting the exact fiducial location has a minor effect on the observed fiducial displacements on MRI.

In the last 2 decades, organ motion in patients with rectal cancer has been actively investigated, and most studies focus on the movement of the clinical target volume relative to bony anatomy.[11,32,33,36-38] Only a few papers have investigated the position variability of the GTV to determine the required margins for a GTV boost. Kleijnen et al studied the motion of the rectum and GTV based on repeated MRI data.[39-41] They evaluated the intra- and interfraction displacement of the GTV relative to bony anatomy on time intervals of 1 minute, 9.5 minutes, 18 minutes, and 1 to 4 days using daily MRI examinations in 16 patients. They report a required margin of around 8 mm in all directions for both the 9.5-minute and 1- to 4-day timepoints.[33] However, a direct comparison is difficult because they used a different method to calculate the displacements and corresponding margins, and they did not report the tumor location for each patient.

Furthermore, Kleijnen et al report that although setup errors based on the rectal wall were slightly reduced

Table 2 Mean of means, systematic error, and random error for the different analyses

		LR, mm	AP, mm	CC, mm	Available data	
Position uncertainty of GTV w.r.t. fiducials						
Interfraction displacement fiducials	M	−0.9	0.5	−0.2	MRI scans	26
w.r.t. COG_{GTV} (MRI)	Σ	2.8	2.4	4.2	Fiducials	17
	σ	-	-	-	Patients	13
Interfraction displacement of	M	-	-	-	CBCT scans	76
COG_{FID} as a result of changes in	Σ	-	-	-	Fiducials	27
fiducial configuration (CBCT)	σ	0.6	0.9	0.9	Patients	11
Interfraction displacement w.r.t. bony anatomy						
Interfraction displacement of	M	−0.2	0.5	−1.2	MRI scans	38
COG_{GTV} (MRI)	Σ	2.8	7.2	8.0	Patients	19
	σ	-	-	-		
Interfraction displacement of	M	0.4	−2.7	1.2	CBCT scans	132
fiducials (CBCT)	Σ	3.6	4.8	4.6	Fiducials	35
	σ	2.7	4.2	4.7	Patients	19
Intrafraction displacement w.r.t. bony anatomy						
Intrafraction displacement of	M	−0.1	−0.5	1.1	CBCT scans	87
fiducials (CBCT)	Σ	0.8	1.4	1.6	Fiducials	32
	σ	1.4	1.7	2.1	Patients	17

Abbreviations: AP = anterior-posterior; CBCT = cone beam computed tomography; CC = craniocaudal; COG = center of gravity; FID = fiducial; GTV = gross tumor volume; LR = left-right; M = mean of means; MRI = magnetic resonance imaging; Σ = systematic error; σ = random error.

compared with bony anatomy, a similar PTV margin was found. More importantly, the rectal wall could not be used as a surrogate for the GTV position because displacement of the rectal wall and the GTV along the direction of the rectal wall will not be detected owing to the absence of anatomic landmarks on the rectal wall.[40] They conclude that to further reduce uncertainties in a GTV boost setting, direct or indirect online tumor visualization is needed. In our study, we have shown that fiducials as an indirect visualization of the GTV reduces uncertainties. However, an uncertainty of the GTV position relative to the fiducials remains.

The suggested margins for setup correction based on bony anatomy as reported by Kleijnen et al[41] are lower than those in our study, especially in the AP direction. However, a direct comparison is difficult because they did not report on the tumor location or intrafraction displacement of the tumor. Brierley et al assessed the interfraction displacement of the rectum, mesorectum, and GTV relative to bony anatomy.[34] They found that GTV displacement was greatest in the CC direction, which is confirmed by the results in our study.

A limitation of the use of fiducials might be the low retention rate. In our study, a total of 64 fiducials were inserted, of which 35 fiducials were still in situ at the end of radiation therapy.[24] Furthermore, the insertion of fiducials is an invasive procedure. Previous studies on fiducial insertion in the rectum report no serious adverse

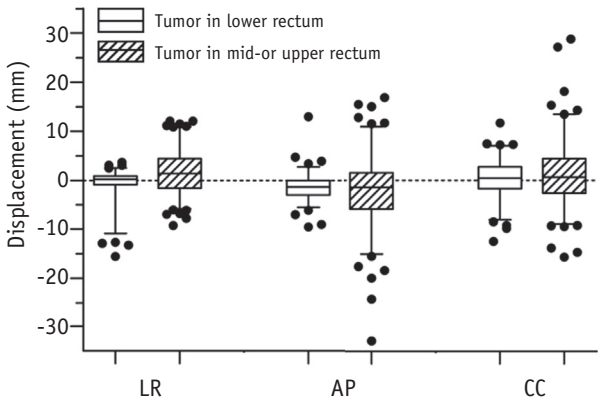

Fig. 2. Boxplots of the interfraction fiducial displacements relative to bony anatomy on cone beam computed tomography in the left-right, anterior-posterior, and craniocaudal directions, split according to tumor location.

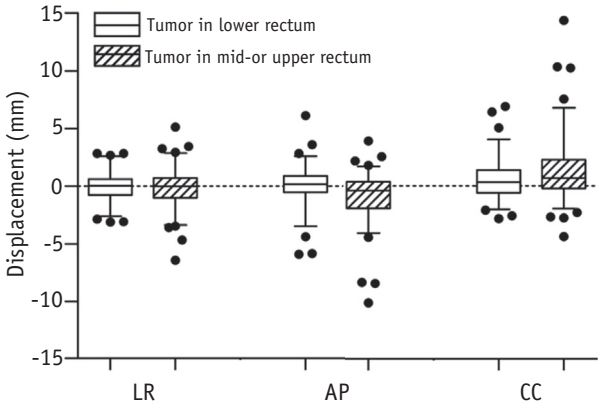

Fig. 3. Boxplots of the intrafraction fiducial displacements relative to bony anatomy on cone beam computed tomography in the left-right, anterior-posterior, and craniocaudal directions, split according to tumor location.

Table 3 Systematic error, random error, and corresponding margin for different setup correction scenarios

	LR, mm	AP, mm	CC, mm
Setup correction based on bony anatomy (COG_{GTV} MRI data)			
Σ	2.9	7.3	8.2
σ	1.4	1.7	2.1
Margin	8.3	19.5	21.9
Setup correction based on bony anatomy (fiducial CBCT data)			
Σ	3.7	5.0	4.9
σ	3.0	4.5	5.1
Margin	11.3	15.7	15.8
Setup correction based on fiducials			
Σ	2.9	2.8	4.5
σ	1.5	1.9	2.3
Margin	8.3	8.3	12.8
Setup correction based on GTV			
Σ	0.8	1.4	1.6
σ	1.4	1.7	2.1
Margin	3.0	4.7	5.5

Abbreviations: AP = anterior-posterior; CBCT = cone beam computed tomography; CC = craniocaudal; COG = center of gravity; GTV = gross tumor volume; LR = left-right; MRI = magnetic resonance imaging; Σ = systematic error; σ = random error.

events.[22,24,25] In one study, a small amount of bleeding that resolved spontaneously was reported in 1 out of 54 patients.[23]

A limitation of this study is the small number of patients. Therefore, the determined margins and the observed difference between proximal and distal tumors would need confirmation in a larger study. Because only 3 fiducials in the mesorectum were identified on both MRI examinations, no conclusions can be drawn about fiducial displacement with respect to the tumor between fiducials implanted in the tumor and the mesorectum. Furthermore, we evaluated the displacement of the fiducials relative to the GTV only for the first week of radiation therapy. If fiducials would be used for the full duration of a long-course radiation therapy schedule, the displacement of the fiducials relative to the GTV should be investigated for all 5 weeks. Owing to logistical reasons, the time between the MRI examinations differed between patients. However, the difference is mainly due to the time range of the first MRI examination relative to the start of radiation therapy. Finally, the estimated margins presented in this paper are based on the position of the fiducials and GTV and do not include other remaining errors involved in the treatment process.

Conclusions

The results of this study show that despite the observed fiducial displacement relative to the GTV, the use of fiducials as a surrogate for GTV position reduces required margins in the AP and CC directions for a GTV boost using image guided radiation therapy of rectal cancer. The reduction of required margins may be higher in patients with a proximal compared with a distal tumor. However, this needs to be confirmed in a larger study.

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