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Organ motion in cervix cancer

Increasing treatment accuracy for cervical cancer patients using correlations between bladder-filling change and cervix–uterus displacements: Proof of principle

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ABSTRACT

Purpose: To investigate application of pre-treatment established correlations between bladder-filling changes and cervix–uterus displacements in adaptive therapy.
Materials and methods: Thirteen cervical cancer patients participated in this prospective study. Pre-treatment, and after delivery of 40 Gy, a full bladder CT-scan was acquired, followed by voiding the bladder and acquisition of 4 other 3D scans in a 1 h period with a naturally filling bladder (variable bladder filling CT-scans, VBF-scans). For the pre-treatment VBF-scans, linear correlations between bladder volume change and displacements of the tip of the uterus (ToU) and the center of mass (CoM) of markers implanted in the fornices of the vagina relative to the full bladder planning scan were established. Prediction accuracy of these correlation models was assessed by comparison with actual displacements in CT-scans, both pre-treatment and after 40 Gy. Inter-fraction ToU and marker-CoM displacements were derived from the established correlations and twice-weekly performed in-room bladder volume measurements, using a 3D ultrasound scanner.
Results: Target displacement in VBF-scans ranged from up to 65 mm in a single direction to almost 0 mm, depending on the patient. For pre-treatment VBF-scans, the linear correlation models predicted the mean 3D position change for the ToU of 26.1 mm ± 10.8 with a residual of only 2.2 mm ± 1.7. For the marker-CoM, the 8.4 mm ± 5.3 mean positioning error was predicted with a residual of 0.9 mm ± 0.7. After 40 Gy, the mean ToU displacement was 26.8 mm ± 15.8, while prediction based on the pre-treatment correlation models yielded a mean residual error of 9.0 mm ± 3.7. Target positioning errors in the fractioned treatments were very large, especially for the ToU (−18.5 mm ± 11.2 for systematic errors in SI-direction).
Conclusions: Pre-treatment acquired VBF-scans may be used to substantially enhance treatment precision of cervical cancer patients. Application in adaptive therapy is promising and warrants further investigation. For highly conformal (IMRT) treatments, the use of a full bladder drinking protocol results in unacceptably large systematic set-up errors.

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Cervical cancer patients may be treated with IMRT to reduce often observed side effects. However, several studies have reported on the large extent and variability of internal-organ motion in these patients [1–5]. To compensate for the geometrical uncertainties, generous margins around the target volume are to be used, reducing the positive impact of IMRT [6–9].

Changes in target position and shape in cervical cancer patients may be caused by rectum- and bladder-filling changes, but may also be due to tumor shrinkage during radiotherapy [5,7–9]. Most of the published studies show that the largest impact is caused by variations in bladder filling, especially for the uterus. A common approach to limit bladder-filling changes is the use of drinking instructions, aiming at daily treatment with a full bladder. However, the efficacy of such a full bladder protocol is often limited, i.e. large inter-fraction variability in bladder volume and significant volume decreases during treatment do still occur [10]. Therefore, it is reasonable to expect considerable inter-fraction organ motion related to bladder filling variations, at least for some patients.

Existence of patient-specific correlations between cervix–uterus position/shape and bladder volume would point at a possibility to estimate at the start of each fraction the internal cervix–uterus position and shape from a measured bladder volume. A "plan of the day" could then be selected from a pre-treatment created library of plans, each designed for a different cervix–uterus position and shape, related to a bladder volume. As a first step in exploring the feasibility of such a strategy, we investigated whether pre-treatment established correlations between bladder volume and positions of two

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points of interest (POI) in the complex cervix–uterus target can be used to predict subsequent positions during fractionated treatment. To this purpose, for each patient 3D CT scans with various bladder fillings were acquired at planning and after 40 Gy dose delivery. For each CT-scan, the corresponding bladder volume was assessed with ultrasound (US). For all patients, US bladder volume measurements were also performed twice a week during fractionated treatment. These in-room measured volumes and correlations between bladder volume and POI-position, as derived from CT-scans acquired with various bladder fillings, were used to generate distributions of POI set-up deviations that occurred during the fractionated treatments.

Methods and materials

Patients and CT sessions

Thirteen patients with cervical cancer were included in this prospective study. The distribution of FIGO (International Federation of Gynaecology and Obstetrics) stages was as follows: IB: 1 patient, IIA: 3 patients, IIB: 6 patients, IIIA: 1 patient, IIIB: 1 patient, and IV: 1 patient. The patients' ages ranged from 26 to 67 years (median 49).

In accordance with our treatment protocol, all patients were treated with external beam radiotherapy (EBRT). The doses at the ICRU reference point were 46 or 50 Gy, which were delivered in 23 or 25 daily fractions of 2 Gy (4–5 weeks of full treatment course). During the last weeks of the EBRT treatment, seven patients received a boost to the primary tumor by means of brachytherapy (BT) in two sessions of 8.5 Gy. For four patients, EBRT and BT were combined with hyperthermia, and for two patients, EBRT and BT were combined with chemotherapy. In an attempt to achieve day-to-day reproducibility in bladder filling, the patients were asked to drink 500 ml of water 1 h prior to each EBRT treatment fraction. Patients were treated in prone position on a belly board and with a foot rest.

All patients had 2–6 fiducial markers implanted in the fornices of the vagina [11]. The patients had two CT-scanning sessions for acquisition of CT-scans with various bladder fillings, one at planning, the other after delivery of 40 Gy (Fig. 1). Each scan acquisition was followed by a US bladder volume measurement. During treatment, these volume measurements were also performed twice a week, immediately after dose delivery. The study was approved by the local ethics committee, and all patients provided written informed consent before entering the study.

In each of the 2 sessions per patient, 5 3D CT-scans with different bladder fillings were acquired. As for the EBRT treatment fractions (see above), patients were asked to drink 500 ml of water 1 h prior to each session. The first scan was acquired immediately at the start of a session, after positioning the patient in treatment position on the belly board. After acquisition of this scan, the patient was asked to go to the toilet to empty her bladder, and then drink another 300 ml. This was followed by acquisition of the other 4 CT scans on the belly board, acquired every 20 min while the bladder filled naturally (in the remainder of this paper, these 4 scans are designated variable bladder filling CT-scans, VBF-scans). Immediately after each acquisition, the bladder volume was measured using a portable 3-dimensional bladder US scanner (patient supine) [10]. The first CT scan in the first session (acquired 1 h after drinking 500 ml) was used as the planning CT scan for the actual patient treatment. Scans were acquired from L1 to the anus with a slice spacing of 3 mm. In total 128 3D CT-datasets were acquired. Only one patient (patient 2) could not hold her full bladder before the start of the protocol and she had to empty her bladder before the acquisition of the first CT scan. For that patient the first CT scan of the second series is missing. For another patient (patient 5) the fifth CT-scan of the first series was incomplete due to technical reasons.

Correlations between bladder volume change and ToU and marker-CoM motions

For these analyses, all acquired CT datasets in the first and the second CT sessions of a patient were first registered to the planning CT using bony anatomy of the pelvis. In this manner, bony anatomy set-up variations (translations and rotations) were to a very large extent removed, leaving mainly internal-organ motion.

The CT-scans and corresponding US bladder volumes obtained in the pre-treatment CT session were used to derive linear correlations between bladder volume changes and 3D motion of two POIs, (1) the marker-CoM, and (2) the ToU. The positions in the planning CT-scan were used as reference. In each scan, the ToU was marked in an interactive process using sagittal, axial and coronal views (all performed by a single observer, RA). The data were fitted using linear models, i.e. for each patient POI one model per direction. From this point on, the models obtained from the pre-treatment session are referred to as planning models. To investigate the potential use of these models for prediction of POI positions, we compared measured displacements of the POIs in the CT-scans of the planning session with displacements predicted by the model.

To check applicability of the established planning correlations for assessment of POI displacements during the fractionated treatment (requiring constancy of the correlations), measured POI displacements in the after 40 Gy CT-scans were compared with

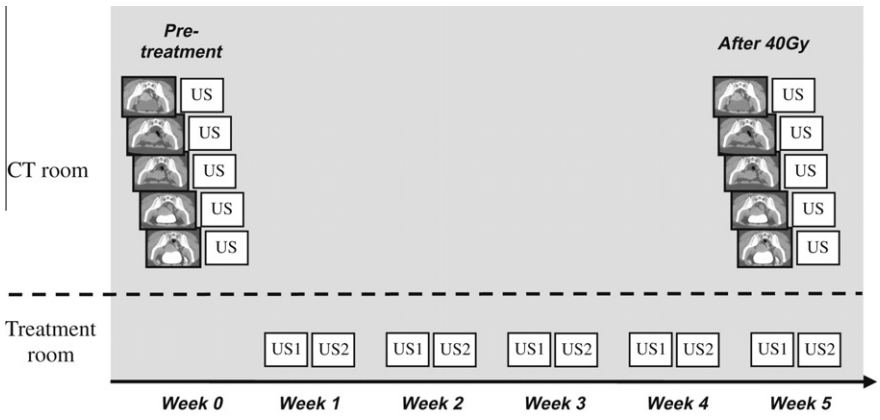

Fig. 1. Protocols for (1) acquisition of pre-treatment (week 0) and after 40 Gy (week 5) variable bladder filling CT scans + corresponding US bladder volume measurements and (2) twice weekly in-room US measurements. For both CT-scanning sessions, all CT scans were acquired in an approximately 1 h interval.

displacements predicted with the corresponding US bladder volumes and the planning models.

POI positioning errors derived from in-room measured bladder volumes

The bladder volumes obtained from the twice-weekly performed US measurements were used to establish patient-specific distributions of marker-CoM and ToU positioning errors for the fractionated treatments of the patients in this study. For each in-room measured bladder volume, POI positioning errors were estimated both using the planning correlation model and the for this purpose derived after-40-Gy model. The POI set-up error was then defined by the average of the outcome of both models. As mentioned above, in our clinical practice, a full bladder is aimed for in all fractions, like in the planning CT scan. Nonetheless, position deviations were also calculated, assuming that the planning CT-scan was acquired with a half-full or empty bladder. In these analyses, we used the half-full and empty bladder CT-scans acquired in the first CT session as virtual planning CT scans. For each (virtual) planning scan, the overall mean set-up error for the patient group, M, was calculated as the average of the per-patient mean set-up error during the fractionated treatment. The group systematic set-up error Σ was calculated as the SD of the distribution of the per-patient mean errors. Standard deviations σ, characterizing random variations around the mean errors were determined by taking averages of the patient SDs for these variations.

Uncertainty in establishing the 3D position of the tip of the uterus in a CT-scan

As markers are clearly visible in the various CT-scans, determining the marker-CoM in a scan can be done with little ambiguity. This is different for the tip of the uterus. Therefore, for 5 arbitrary patients in this study, the positions of the ToU in all 10 CT-scans were determined twice by a single observer, with a time interval of two months. The repeat measurements were performed without access to the initial data. The acquired uncertainties are relevant for interpretation of other data presented in this paper.

Results

Uncertainty in establishing the 3D position of the ToU in a CT-scan

For the twice established ToU positions in the 50 CT-scans involved in this analysis, the overall mean differences in the two observations in left–right (LR), inferior–superior (IS), and anterior–posterior (AP) directions were 0.8, 1.0, and −1.0 mm, respectively. For the same directions, the standard deviations describing the inter-patient variation in mean difference between the first and second observations were 1.4, 1.9 and 1.7 mm. The standard deviations describing the intra-patient variations were on average 4.6, 4.4, and 2.7 mm.

Correlations between bladder volume change and ToU and marker-CoM motions

The open symbols in Fig. 2 (see Supplementary data) show for each patient and each direction, observed ToU motions in VBF-scans acquired during the pre-treatment CT session. Large extents of motion were found, especially in inferior and anterior directions (up to 65 mm translation in anterior direction for patient 13 for the empty bladder scan, Fig. 2c). The degree of displacement varied widely from patient to patient. For example, patients 1 and 2 had motion ranges of only ∼5 mm in the IS direction, while patients 4 and 7 show motion ranges of over 40 mm (Fig. 2b). The closed symbols in Fig. 2 are deviations of measured displacements (open symbols) from fitted linear regression lines through the measured data points. Fig. 3 shows data as in Fig. 2, but now for the marker-CoM. Clearly, marker motion as a function of bladder volume change is generally smaller than ToU motion, but often of high clinical relevance. For all patients and all directions, predictions reduced the uncertainty in the mean ToU and marker-CoM positions. Figs. 2 and 3 are summarized in Table 1 (see Supplementary data). With prediction of ToU positions, the average patient mean displacements reduced from 1.3 mm ± 5.7 (1 SD) to 0.3 mm ± 1.1, from −13.7 mm ± 8.7 to −0.8 mm ± 1.6, and from −10.6 mm ± 16.2 to −0.3 mm ± 1.9 for the LR, IS, and AP directions, respectively (m and m_{res} in Table 1). For the marker-CoM, these reductions are from 1.2 mm ± 1.5 (1 SD) to 0.0 mm ± 0.2, from −4.0 mm ± 5.7 to −0.4 mm ± 0.7, and from −3.1 mm ± 6.3 to 0.1 mm ± 0.8. Displacement vector lengths decreased from 23.1 mm ± 10.8 to 2.2 mm ± 1.7, and from 8.4 mm ± 5.3 to 0.9 mm ± 0.7 for the ToU and marker-CoM, respectively. For almost all patients/directions the overall displacement range also reduced, with a few exemptions with a minor increase in range. For the marker-CoM, standard deviations describing deviations of measured data from the linear fits were, 0.8, 1.9 and 1.6 mm in LR, IS and AP directions, respectively. For the ToU, these standard deviations were 4.1, 5.8 and 5.0 mm.

Figs. 2 and 3 also show the slopes of the regression lines. For the ToU, the mean slopes were: 0.0 mm/100 ml (range −2.8 to 0.9) for the LR direction, 6.1 mm/100 ml (range 0.2 to +15.5) for the SI direction, and 4.7 mm/100 ml (range −3.4 to +12.1) for the AP direction. The mean slopes for the marker-CoM were −0.4 mm/100 ml (range −1.1 to +0.9) for the LR direction, 1.2 mm/100 ml (range −0.7 to +3.9) for the IS direction, and 1.5 mm/100 ml (range −1.7 to +3.0) for the AP direction. Statistically significant non-zero slopes for POI movement as a function of bladder-filling are marked in Figs. 2 and 3.

For the after 40 Gy scans, Fig. 4 shows measured ToU displacements versus displacements derived from the corresponding US bladder volume measurements and planning correlations between bladder volume and ToU motion. If the planning models would have perfectly predicted the ToU positions after 40 Gy, all points should lie on the unity lines. Certainly for large motions, position predictions based on the planning models could have substantially increased treatment precision after 40 Gy. In Fig. 4b and c, patients 1 and 11 show considerable deviations from the unity lines. Inspection of the CT-scans learned that they both had large tumor regression after 40 Gy dose delivery, probably resulting in the poor prediction accuracy. For both the ToU and marker-CoM, comparisons between measured after 40 Gy displacements with residuals after prediction with planning models are summarized in Table 2 (excluding patients 1 and 11, see above). For the ToU, the positive impact of predictions demonstrated in Fig. 4 is clearly confirmed with a reduction in mean displacement vector length from 26.8 mm ± 15.8 to 9.0 mm ± 3.7. For the marker-CoM, prediction accuracy of planning models is much smaller (Table 2b).

POI set-up deviations derived from in-room measured bladder volumes

Table 3a summarizes the estimated POI displacements as experienced by the patients in this study during their treatments (excluding patients 1 and 11, see above). As described in detail in the Material and methods, POI displacements were determined using patient-specific correlations between bladder volume change and POI motion as observed in CT scans with various bladder fillings. In agreement with our previous study [10], deviations from full bladder as in the planning scan were frequent and large. During the fractionated treatments, patient systematic set-up errors

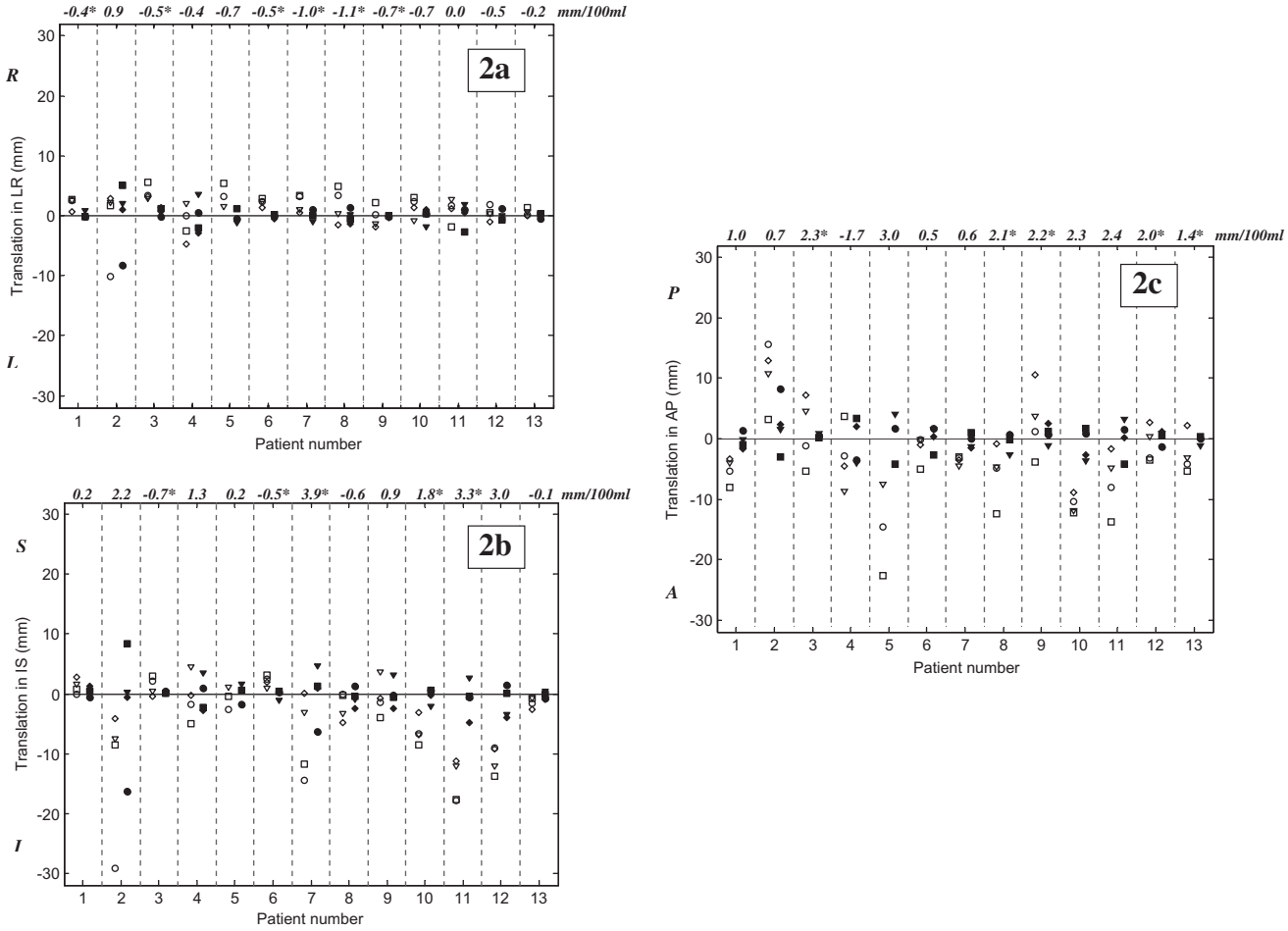

Fig. 3. Open symbols: marker-CoM displacements relative to the planning CT-scan, as measured in variable bladder filling CT-scans acquired in the planning session. Closed symbols: corresponding residual displacements after correction with the planning correlation models. The numbers above the graphs are slopes of the regression lines, * points at a slope that is statistically significant different from 0. The displacements were calculated for four different CT scans; with empty bladder (□), after 20 min (○), after 40 min (▽) and after 60 min (◇).

for the ToU were on average 18.5 and 13.7 mm in inferior and anterior directions, respectively. Among patients there were also huge variations in mean set-up error, Σ = 11.2 mm in IS direction and Σ = 17.9 mm in AP direction. On top of this, in IS and AP directions there were also large day-to-day variations in the ToU position (SD ~8 mm). Table 3b and c show POI set-up deviations while assuming that the planning CT-scan was acquired with a half full bladder or empty bladder, respectively. Clearly, the overall mean set-up errors during treatment (M) for the ToU and marker-CoM are best represented by a planning CT-scan with a half full bladder. However, also for this scan, Σ- and σ-values remain large, especially for the ToU.

Discussion

We have investigated for cervical cancer patients treated prone on a belly board, the feasibility of predicting cervix- and ToU displacements during fractionated treatments, as resulting from frequently occurring (large) inter-fraction bladder volume variations, even with a drinking protocol [10]. To exclude delineation uncertainty in cervix analyses, we used the center of mass (CoM) of markers implanted in the fornices as a surrogate for the cervix. The assumption that we had to make herein is that marker-CoM *motion* correlates with cervix *motion* (differences in absolute positions are irrelevant for the analyses). Predictions were based on established patient-specific linear correlations between bladder volume changes and displacements of these POI, as derived from the planning CT-scan and VBF-scans. For the patients in this study we also performed twice weekly bladder volume measurements using a 3D ultrasound scanner. Correlations obtained using the VBF-scans were then applied to estimate inter-fraction marker-CoM and ToU motions that actually occurred during the fractionated treatments.

The VBF-scans clearly demonstrate huge variation between patients in the extent of motion due to changes in bladder volume. Some patients did hardly demonstrate any motion, while others had motions up to 65 mm in a single direction. This observation suggests that using a CTV-PTV margin recipe that should ensure the vast majority of patients adequate tumor coverage, will for a subgroup of patients lead to highly excessive dose delivery to healthy tissues. Soon, acquisition of VBF-scans for treatment preparation will become a standard practice in our institution. These scans will then be used to individualize planning margins.

Several other studies also reported a considerable extent of internal-organ motion in cervical cancer patients [2,4,5,12], with displacements ranging from 8 mm up to 48 mm. van de Bunt et al. [9] found that the change in the rectum correlated significantly but weakly with the motion of the cervix and uterus in the AP direction. For the bladder the correlations were even weaker. We speculate that the weak correlation with bladder volume could be explained by the fact that they evaluated the relationship for the whole patient group, which weakened the correlation due

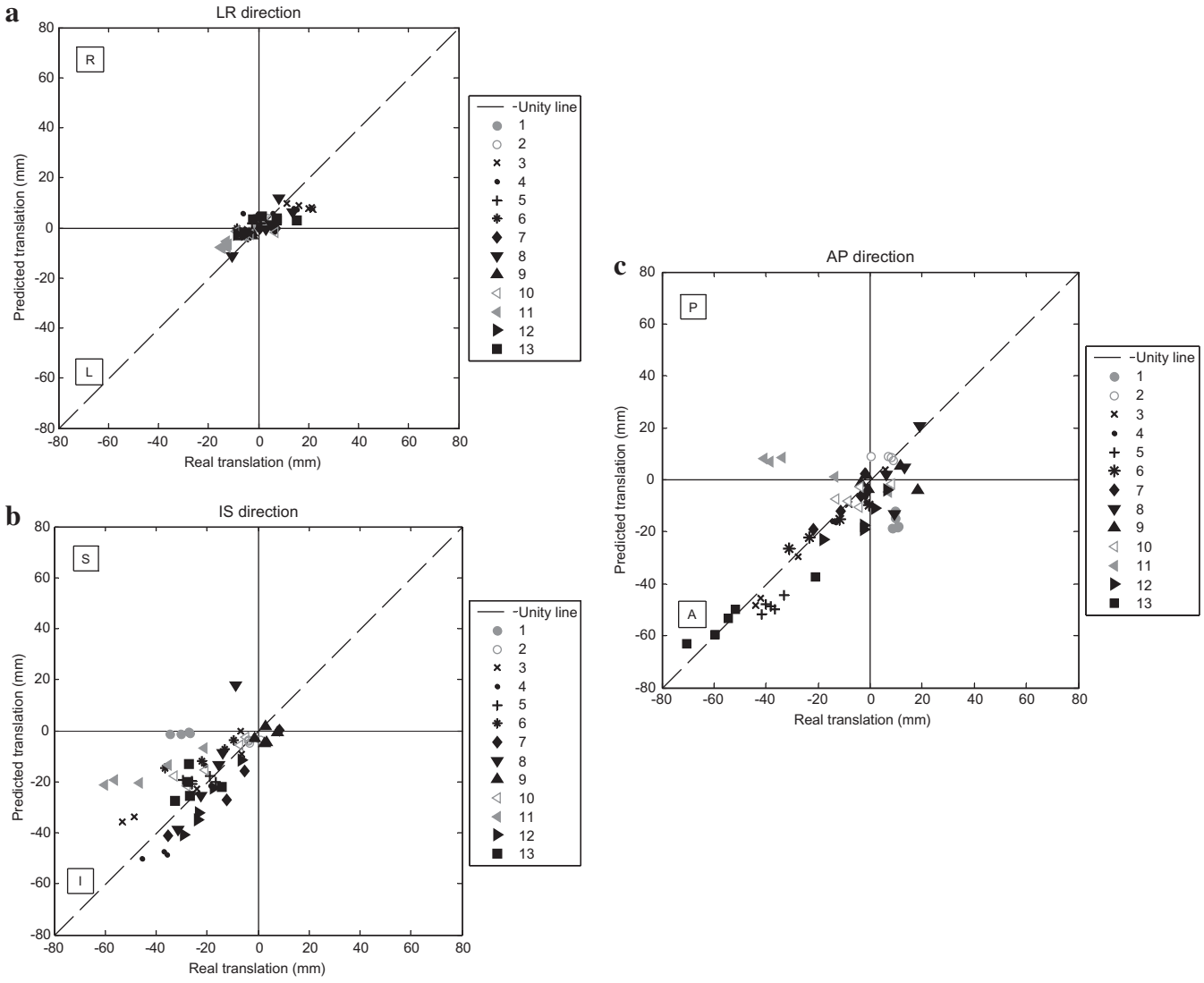

Fig. 4. Measured and predicted ToU displacements in after 40 Gy variable bladder filling CT-scans. Predictions were performed using planning correlations.

Table 2
Tip-of-uterus (a) and marker (b) displacements observed in after 40 Gy variable bladder filling CT-scans for the LR, IS and AP directions. The last 2 columns relate to vector lengths. The columns m, R, and d in (a) and (b) are descriptions of observed patient mean parameters in the variable bladder filling scans; m: patient mean displacements, R: patient mean displacement ranges, d: patient mean displacement vector lengths. MEAN = mean of means, SD = standard deviation in patient mean values, MIN and MAX are minimum and maximum patient mean parameters. Columns m_{res}, R_{res}, and d_{res} are descriptions of residual displacements after predictions with planning correlations between bladder filling and POI-displacement.

	LR				IS				AP				d	d_{res}
	m	m_{res}	R	R_{res}	m	m_{res}	R	R_{res}	m	m_{res}	R	R_{res}		
(a) Tip-of-uterus displacements (mm)														
MEAN	2.1	0.6	11.4	10.6	−17.8	−0.6	23.9	15.2	−12.2	3.9	24.4	13.2	26.8	9.0
SD	7.1	4.1	7.2	5.4	10.5	6.9	13.0	8.5	18.9	4.6	14.2	8.2	15.8	3.7
MIN	−6.6	−4.7	4.2	3.6	−31.5	−10.9	4.8	4.8	−51.4	−2.5	8.5	2.9	7.2	3.0
MAX	18.1	9.7	24.4	19.6	3.1	9.7	46.7	33.8	9.3	12.0	50.2	25.9	57.8	15.1
(b) Marker displacements (mm)														
MEAN	1.2	0.0	3.2	2.3	−2.4	1.1	5.7	4.9	−3.4	0.3	7.0	5.2	7.2	6.7
SD	2.8	2.7	2.7	1.2	4.5	6.2	4.8	2.0	5.8	3.5	3.6	2.2	4.9	3.2
MIN	−2.9	−3.8	0.7	0.5	−10.1	−9.1	0.7	2.1	−15.7	−6.5	3.5	2.7	2.1	2.8
MAX	6.8	5.3	9.1	4.5	4.6	10.0	15.7	8.5	6.1	4.8	16.8	10.3	18.7	11.4

to large inter-patient variation in this correlation. Furthermore, the measurements were spread out in time such that rectum filling changes and tumor regression additionally weakened the correlation. Another difference is that in their study the patients were scanned in supine position and not in prone using a belly board. Most other studies support our data that the greater impact on cervix–uterus motion is caused by variations in bladder filling [1,5,8].

Table 3
Marker-CoM and tip-of-uterus position errors as derived from measured in-room bladder volumes and established patient-specific correlations between bladder volume changes and displacements. (a) reference = full bladder CT-scan (clinical), (b) reference = half full bladder scan and, (c) reference = empty bladder scan.

	Markers (mm)			Tip of the uterus (mm)		
	LR	IS	AP	LR	IS	AP
(a)						
M	1.3	−3.3	−2.6	1.8	−18.5	−13.7
Σ	2.2	4.4	5.2	5.8	11.2	17.9
σ	0.8	1.4	2.6	1.9	7.7	7.1
(b)						
M	1.0	1.1	−0.5	−2.3	−4.0	1.1
Σ	3.6	7.0	4.6	5.1	12.2	9.8
σ	0.8	1.4	2.6	1.9	7.7	7.1
(c)						
M	−1.2	1.0	3.5	1.0	10.2	6.9
Σ	1.9	3.9	5.7	5.3	8.9	7.7
σ	0.8	1.4	2.6	1.9	7.7	7.1

It was demonstrated that POI displacement with bladder volume change could be well described by linear regression lines. For marker-CoM, deviations from the fitted lines were 1–2 mm (1 SD). For the ToU, the observed spread around the regression lines was substantially larger, ~5 mm (1 SD). However, repeat assessments of the 3D position of the ToU in CT-scans for a subset of patients showed an intra-patient variability of ~5 mm (1 SD). Therefore, the observed increase in spread of residual errors around linear regression lines for the ToU, as compared to the marker-CoM, does not imply larger deviations from linearity. Obviously, the increased uncertainty in establishing the 3D ToU position contributed to this observation.

As shown in Figs. 2 and 3, for many of the individual patient-directions, there was no proof that the slope of the linear correlation was statistically significant, different from zero. On the other hand, we noted that for all patient-directions, the mean residual error after correction with the derived linear correlation model was smaller than the mean of the original errors, both for the ToU and marker-CoM and also for patient-directions with slopes that were not statistically different from zero. Moreover, the reductions in mean error vector lengths for the ToU and marker-CoM (d_{res} versus d in Table 1) were highly statistically significant ($p < 0.001$, signed rank test). We believe that the difficulty in proving statistical significance for the individual patient-directions is related to the (unavoidably) small number of observations involved, i.e. 4 3D CT-scans. Based on the arguments given here and our view that correlation models have to be regularly checked during the fractionated treatments as they may become invalid due to tumor shrinkage (see below), all patients, except patients 1 and 11 with large tumor shrinkage, were included in the analyses resulting in Tables 2 and 3.

Also after 40 Gy, position predictions for the ToU based on planning correlations resulted in clinically highly significant reductions in uncertainties (not for the two patients with large tumor regression after delivery of the first 40 Gy). For marker-CoM, position prediction in after 40 Gy scans, based on planning correlations, seems less accurate. The latter finding may be related to a larger sensitivity of marker-CoM position for tumor shrinkage or for changes in rectal filling in the after 40 Gy CT session compared to the planning session.

The twice-weekly performed US bladder volume measurements revealed very large POI displacements relative to planning, especially for the ToU in the IS and AP directions, with mean errors of 18.5 mm ± 11.2 and 13.7 mm ± 17.9 in inferior and anterior directions, respectively (Table 3). This finding is in line with our previous observations of large and frequent deviations from the full bladder that is aimed for [10]. Obviously, the patient anatomy in the applied full bladder planning CT-scan is generally only a poor representation of the mean anatomy during treatment. As variations in rectal filling and other uncertainties were not included in these analyses, the full errors are even larger than those presented here. Due to the target shape, the observed large target displacements will generally not lead to severe under dosage in BEV-planned four-field box techniques. For highly conformal (IMRT) treatments with considerable bladder sparing in the planning CT-scan, great care is needed to avoid severe target under dosage in the fractionated treatment. Because of the limited reproducibility of the correlations between bladder filling and marker-CoM position after 40 Gy dose delivery (possibly related to rectal filling variations or tumor shrinkage, see above), estimations of POI positions from the in-room performed US were limited to the ToU.

The clinical potential for a substantial increase in treatment precision for cervical cancer patients by using VBF-scans to assess each individual patient, target motion with bladder volume change, has been clearly demonstrated. More work needs to be done to start clinical implementation in adaptive therapy. In ongoing investigations we focus on derivation of linear correlations for the full target surface (instead of only ToU and marker-CoM). These correlations are derived from VBF-scans, using deformable image registration [13]. With this approach it will be possible to predict the 3D target shape from a measured bladder volume. In the current stage of clinical protocol development, the idea is to divide patients in two groups, those with minor target motion with bladder volume change, and those with large motion. The former group will be treated with a reduced planning margin. For the latter, an adaptive approach is being developed, based on patient-specific libraries of treatment plans. Such a protocol should also take into account intra-fraction motion of the uterus due to the filling of the bladder. This error may be estimated for each patient separately by calculating the target displacement from the patient specific bladder in-flow rate, the patient-specific correlations between bladder volume change and motion, and the time between in-room bladder volume measurement and dose delivery. Important part of the investigations is to also include set-up uncertainties related to rectal filling variations. Here there may also be a role for the implanted fiducials that can be easily extracted in daily stereoscopic 2D or 3D kV imaging [11]. As we have observed, planning correlations can become inaccurate in case of tumor shrinkage. Therefore, clinical introduction will be accompanied by regular imaging during the fractionated treatments for validation and update of the planning correlations. Because of better soft tissue contrast, (also) these imaging studies should preferentially be done with MRI. So far we have decided to base the adaptive approach on patient-specific libraries of plans, on measured in-room bladder volumes using a 3D US bladder scanner, and on two stereoscopic planar kV images for marker detection. Alternatively, it would also be possible to daily use cone beam CT-scans to measure both the bladder volume and detect markers. This would, however, increase imaging dose delivery to the patients. In theory, a daily cone beam CT-scan could also be used to directly detect target motion followed by the selection of a treatment plan from the library of plans that was created using the VBF-scans. However, we have experienced too much variation in image quality between patients and from fraction to fraction to consider this as the most promising approach at this time. Possibly, this image quality issue could be related to the often large patient diameters at the target level and to motion in the intestines during scan acquisition.

Conclusions

Motion of the cervix–uterus due to bladder filling variations may be very large (up to 65 mm in a single direction) or almost

absent, depending on the patient. Motion ranges can be readily obtained from variable bladder filling CT-scans. Linear correlations between target point displacements and bladder volume changes, as derived from these scans, have interesting potentials in adaptive radiotherapy, with target deformations accounted for by different correlations for all target points. The current approach of using full bladder drinking instructions for planning CT-scan acquisition and for daily treatment leads to large mean systematic set-up errors in the fractioned treatments, especially for the tip of the uterus (-18.5 mm ± 11.2 in SI-direction).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2010.11.010.

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